Physical causes of dosing errors in patients receiving multi-infusion therapy

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Physical causes of dosing errors in patients receiving multi-infusion therapy

Fysische oorzaken van doseringsfouten bij patiënten behandeld met multi-infusie
(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

Introduction

BACKGROUND, OBJECTIVES AND OUTLINE

1 The needs and risks of multi-infusion

Many patients suffer from medical conditions that require the intake of pharmaceutical compounds. The delivery of these compounds to the patient can be achieved in several ways, for example, by simple oral ingestion. However, especially on the intensive care unit (ICU), the treatment of critically ill patients typically involves the simultaneous, continuous and intravenous delivery of drugs, such as vasopressors, vasodilators, analgesics, antibiotics, sedatives, fluids and parenteral nutrition.

To enable intravenous delivery, drugs are usually administered as a liquid solution. This also enables infusion technology, e.g. infusion pumps, to deliver a continuous stream of the medication to the patient. Continuous administration is required to sustain homeostasis of the drug concentration in the blood plasma. However, the intravenous administration of some of these drugs by means of infusion is challenging [1–4]. There are several reasons for this. Firstly, many critically ill patients suffer from hypotension due to serious conditions such as sepsis, which often requires the immediate administration of potent rapid- and short-acting vasoactive drugs, such as norepinephrine, dopamine and dobutamine [5,6]. Because these potent drugs typically have short plasma half-lives and small therapeutic windows, the administration to the patient has to be continuous, as well as precise and accurate. This means that even relatively short transient dosing errors, lasting only a few minutes, are likely to produce adverse effects. Several studies have, for example, reported hemodynamic instability in patients in relation to the administration of rapid-acting inotropics [7,8]. Secondly, several drugs are commonly administered through one central infusion set and catheter. This method of drugs administration, called multi-infusion [9,10], is of keen interest because it increases the complexity and therefore the likelihood of dosing errors dramatically [9–11]. Multi-infusion is necessary because vascular access is limited and the insertion of a vascular access device is challenging [12,13]. An essential difficulty is that the insertion of a vascular access device, such as a catheter or cannula, constitutes a high risk of systemic infections, notably catheter-related sepsis [14], which is potentially lethal. In other words, the number of catheter insertions has to be minimized. Even though multi-lumen catheters are often used to separate incompatible medication, these catheters are usually limited to two or three separate lumen due to the flow resistance and the limited diameter of blood vessels. Especially in neonates, blood vessels are very small. Lastly, many patients with organ dysfunction and neonates in general are not capable of handling large quantities of fluid [15,16]. As a consequence, these patient populations require drug solution that are relatively concentrated in order to reach the desired therapeutic effect at low flow rates, which can be as low as 0.1 ml/h. However, as a result, small deviation in these low flow rates yield relatively large dosing errors given the high concentration of the drug solution. Neonates, especially pre-term neonates, are considered to be one of the most challenging patient populations to treat with multi-infusion. Indeed, errors related to medication and infusion are common on the NICU (Neonatal Intensive Care Unit) [1,17]. Nevertheless, also outside of the NICU infusion technology constitutes a high risk for the patient.

Infusion technology in general is associated with one of the highest error rates of any medical technology [18–20]. Error rates related to intravenous medication administration were approximately between 49% and 81% [1,2,21], with an overrepresentation of serious complication compared to other adverse drug events (ADEs) [21,22]. A comprehensive study conducted by the U.S. Federal Drug Administration (FDA) recorded 56,000 reports of ADEs associated with infusion pumps between 2005 and 2009 [20]. Moreover, the probability of an ADE was found to increase with 3% for every additional drug administered intravenously [23]. A large proportion of the medical errors related to infusion are known to involve inevitable human factors [24] , such as, not responding to an alarm due to alarm fatigue [19], confusion and mixing up infusion lines [19,25], prescription errors [2], combining incompatible medications [21], using the wrong route of administration [3] and not clamping infusion lines during a syringe exchange [26] (see Figure 1). Moreover, as with any technology, infusion technology may malfunction or produce technological 'glitches' in certain cases, resulting in drug dosing errors [27]. Multiple studies have stressed that unknown or ambiguous factors in drug administration might cause or contribute to the occurrence of many ADEs [4,21]. Indeed, even if the infusion system is operating without any apparent problems, it was found that intrinsic physical/technical properties of infusion systems may still cause flow and dosing rate variability, which may subsequently cause adverse effects. Over the past ten years, ample evidence has been produced to support the assumption that intrinsic physical properties of the infusion hardware are, in fact, related to dosing errors [3,4,10,28–30]. It is typical that these physical effects impact the clinician's ability to achieve the intended goals of infusion therapy. Figure 1 shows the causality of common (multi-)infusion risks and the position of the risks caused by physical effects within the infusion therapy process.

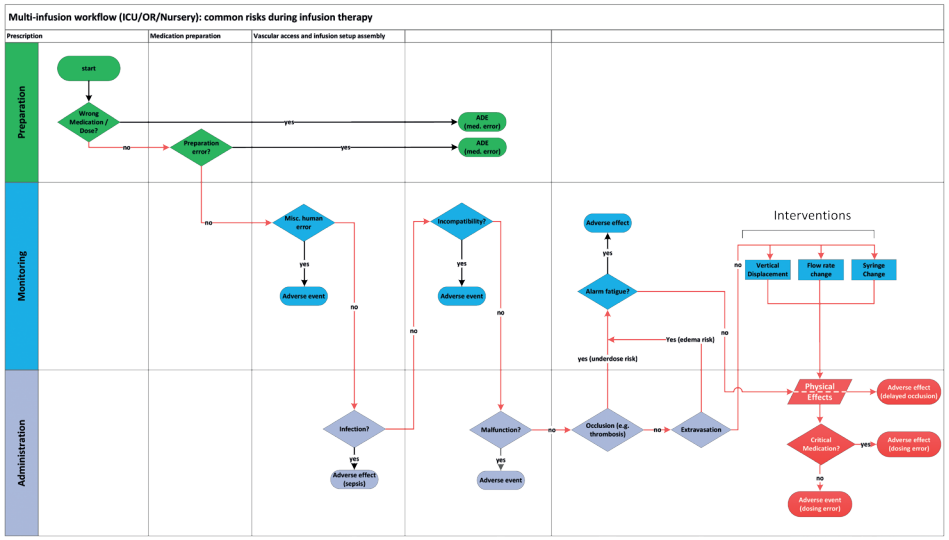

Figure 1. *Diagram showing typical risks of infusion therapy and the place of errors due to physical effects in a simplified clinical infusion therapy process. Red lines indicate a direction that may still cause dosing errors due to physical effects. Besides dosing errors, physical effects may cause a delay in triggering the pump alarm in case of, for example, an occlusion. ADE = adverse drug event.*

2 Infusion technology and dosing errors

The pumps

In order to deliver a drug solution continuously and in a controlled manner to the patient, medical pumps are used. Infusion pumps use several techniques to induce the movement of fluids. In critical care, on the ICU and OR (operation room), syringe pumps, gravity driven infusion and volumetric pumps are typically used [3]. Syringe pumps use a syringe driver that pushes the plunger of the syringe forwards, upstream towards the patient (Figure 2a). For clinicians, syringe pumps are the most accurate and precise option, especially for low flow rates. Most syringe pumps were found to produce a flow rate error of less than 5% in a laboratory setting [31]. A disadvantage of syringe pumps is the small drug reservoir. Common volumes of syringes are 10, 20 and 50 ml. These syringes deplete quickly if higher flow rates are used, compelling clinicians to frequently exchange the empty syringe for a new one, as patients may require the administration of the drug for days. Because of contamination and infection risks [32], infusion components are preferably not decoupled from the infusion setup. This is an important reason to use larger drug reservoirs for higher flow rates. Gravity driven infusion and volumetric pumps are usually equipped with much larger drug reservoirs, this is typically an infusion bag. Gravity driven infusion uses gravity as a primary mode of fluid propulsion. The difference in height between the infusion bag and the patient can assumed to be proportional to the hydrostatic pressure applied to the drug reservoir. Although this option is cheap, it is not very reliable. Volumetric pumps, sometimes also simply called “infusion pumps”, use a mechanical pump such as a peristaltic mechanism (Figure 2b). A major disadvantage

of volumetric pumps is the lower precision in short time intervals, despite the use of mechanisms such as the peristaltic technique [3,31]. Volumetric pumps and gravity driven infusion are preferably not used for high-risk medication that requires very precise administration at low flow rates. For this reason the focus of this thesis is mainly on syringe pumps.

Dosing errors

In infusion therapy the concentration of the medication (e.g. µg/ml) in the drug reservoir of the pump is often kept constant. Therefore, the dose intended to be administered during a time interval is realized by setting and, if necessary, adjusting the flow rate. A dose is delivered per unit time (dosing rate), denoted as, e.g. µg/h or µg/kg/h (adjusted for the patient's weight in kg). Consequently, if the patient receiving infusion therapy requires a different dose, the clinician changes the infusion flow rate (ml/h) of the drug solution while the concentration (mg/ml) remains unaltered (Figure 2). A dose is therefore often defined as the amount (ml) delivered after a certain time interval (the area under the curve of the flow rate). A relative dosing error is defined as the deviation (%) of the administered dose (e.g. ml or µg) from the set point value (i.e. intended dose) (eq. 1).

Dosing errors are any deviation from the intended drug dose to the patient.

$$\text{Dosing Error} = \left(\frac{\text{Administered Dose}}{\text{Intended Dose}} - 1\right) \cdot 100\% \qquad (1)$$

It is known that dosing errors occur after certain clinical interventions, such as, changes in flow rates [16], changes in physical height of a pump relative to the patient (vertical displacement) [33,34] and syringe exchanges [35]. A combination of multiple interventions and physical effects during the clinical process may result in dosing errors that are counter-intuitive (see Figure 1).

The multi-infusion system

To administer the medication from the pump into the patient, a variety of additional infusion hardware components are used, often referred to as disposables. Many of these infusion components have been associated with flow rate variability and dosing errors [36]. Examples are, syringes [30], infusion lines [37], catheters [38], cannulas [39], filters [40] and valves [41]. One of the most prominent examples of infusion hardware associated with dosing errors are multiple-in, single-out infusion sets or manifolds [9,42] (Figure 2c). If these infusion sets are used, the flows originating from all pumps, that are joined on this central infusion set, are able to interact. This principle is defined as multi-infusion. For example, if a pressure change occurs because the flow rate is changed, the parallel pumps (Figure 2c), will be influenced because the pressure change occurs in the entire multi-infusion system.

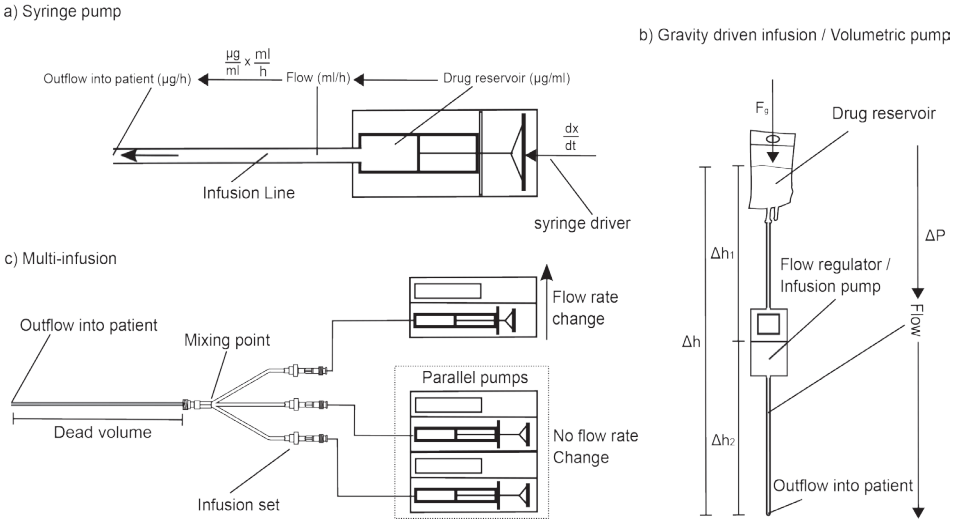

Figure 2. *Common infusion systems in critical care. (a) A syringe pump used to administer drugs to the patient is illustrated with typical units used in clinical practice. The syringe, which acts as a drug reservoir, contains a drug solution with a concentration in µg/ml. The primary mechanism that displaces the fluid is the movement of the syringe driver, which moves the plunger with a certain velocity (dx/dt). Consequently, the drug solution from the syringe is forced out of the syringe, through the infusion line, producing a flow rate in ml/h. Eventually the patient receives the drug with a certain dosing rate in µg/h. (b) A gravity driven infusion system or volumetric infusion pump. A pressure difference (ΔP) in the drug reservoir, in most cases an infusion bag, is produced by gravity (designated as F_g).The magnitude of ΔP is dependent on the difference in height between the drug reservoir, the outflow point and the density of the liquid (ρ). In case of exclusively gravity driven infusion, gravity is the primary mechanism producing the flow. If the flow regulator is simply a resistance (e.g. a clamp), the height difference between the drug reservoir and outflow point into the patient (Δh) is responsible for the flow. In other cases flow regulators, such as a drip chamber, may be used. In this case, the height difference responsible for the flow is between the flow regulator and the patient ($Δh_2$). In case of a volumetric pump, instead of gravity, the primary mechanism displacing the fluid is typically an electronic mechanism such as a peristaltic pump. (c) Multi-infusion setup. Multiple pumps are combined on one multiple-in single-out infusion set. The volume between the mixing point and the patient is defined as the dead volume. After a flow rate change was conducted, the parallel pumps are defined as the pumps combined on a common infusion set, in which no flow rate change was initiated within a certain finite timeframe.*

Another fundamental property of multi-infusion systems is the dead volume, which is defined as the volume between the mixing point and the outflow (e.g. catheter tip, see Figure 2c). Essentially, the concentrations of the drug mixture inside the dead volume, cannot be actively changed. The time to 'flush' the dead volume, i.e. renew all the fluid inside the dead volume, can be approximated using eq. 2.

$$t_{flush} = \frac{dead\ volume}{flow\ rate} \qquad (2)$$

For example, if the dead volume is one ml and the pump is set to one ml/h it takes one hour to flush the dead volume.

Fluid mechanics

Within fluid mechanics, many theories exist that describe the motion of fluid. In the scope of this thesis, it can be prospectively determined that some fundamental physical effects are negligible and, even if they occur, are very unlikely to cause clinically relevant effects. As stated, low flow rates (approximately 0.1 – 20 ml/h), typically used to administer critical drugs, are mainly considered in this thesis. With these flow rates and typical infusion tubing diameters, the flow can be considered laminar. The Hagen-Poiseuille law provides a reasonable approximation of flow in a multi-infusion system. From this law it is also known that, due to friction of the tubing walls, the fluid at the center of the infusion tubing moves faster than the fluid closer to the tubing walls. Finally, diffusion of the drug mixture may have some impact. The number of Péclet predicts negligible diffusion in the axial direction (longitudinal, along with the flow towards the patient) in most cases. However, the diffusion in radial (transversal) direction is noteworthy and causes the medication to mix over this radial plane in a certain amount of time. Moreover, due to this diffusion, particles of the solute may be transported from and to faster and slower lamina (infinitesimal streams with different velocities) [43]. A combination of these effects can be described as Aris-Taylor dispersion [43–45]. Figure 3 illustrates the flow of a drug mixture through a tube.

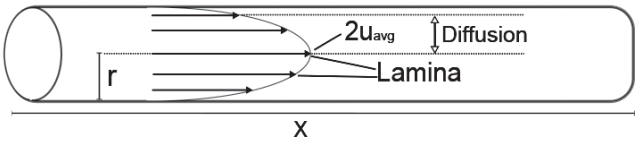

Figure 3. *Laminar flow through a tube. Where r is the radius and u_{avg} is the average flow velocity on the central longitudinal axis. It can be seen that the lamina at the center move at twice the flow velocity u_{avg}. The lamina can be considered infinitesimal streams with different velocities. The resulting concentration distribution is also affected by radial diffusion where molecules are transported from and to lamina with different flow velocities [45].*

THESIS OBJECTIVES

The general objective of this thesis is to investigate physical causes of dosing errors in patients receiving multi-infusion therapy, and the clinical consequences of these dosing errors.

More specifically, the following objectives are formulated:

1. To identify the most relevant physical causes of dosing errors in patients receiving multi-infusion therapy.
2. To characterize these dosing errors in an experimental *in vitro* setup
3. To develop a model that describes the relationship between the properties of the infusion hardware, clinical interventions and these dosing errors.
4. To investigate the (potential) clinical impact of these dosing errors.

OUTLINE

PART I: The physical perspective

In this part a more technical/physical perspective on the subject of this thesis is given, starting with a literature review in **chapter 2.1.** The aim of the review was to identify the most relevant physical phenomena causing dosing errors in multi-infusion systems. In addition to this, a general overview of the problems that may occur due to these physical phenomena was described. In **chapter 2.2** the physical and mechanical properties and characteristics of infusion hardware were investigated and how these factors relate to flow rate variability. In this thesis, we used a real-time and inline absorption spectrophotometry measurement method to investigate multi-infusion *in vitro*. The medication was mimicked with dyes (colorants). This method was previously introduced and developed in our group by R. Verdaasdonk and co-workers [46]. In **chapter 2.3** an analytical simulation model was developed to predict the quantity of dosing errors in relation to interventions and infusion hardware. Results were compared to measurements using the measurement method. In **chapter 2.4** the basic physical mechanisms were placed in a more clinical perspective in order to investigate the clinical meaning of these effects. *In vitro* measurement, as well as some basic simulation principles were used.

PART II: The clinical perspective

In this part, the methods developed in PART I were applied to clinical situations. **Chapter 3.1** is a case report describing a serious norepinephrine overdose after a syringe exchange. Subsequently, possible technical and physical causes of this incident were investigated. In **chapter 3.2** dosing errors caused by a syringe exchange were investigated. The impact of different infusion hardware and different methods of performing the syringe exchange were investigated using the simulation model and measurement method. In **chapter 3.3** an *in vivo* pilot study is presented that investigates the impact of two different infusion sets on the mean arterial blood pressure in two cohorts of neonates.

In **chapter 3.4** dosing errors due to deliberate flow rate changes in three different pumps were quantified and characterized. Finally in **chapter 4** the results of this thesis are put in broader perspective in the general discussion.

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Chapter 2

The physical perspective

Chapter 2.1

Flow variability and its physical causes in infusion technology: a systematic review of in vitro measurement and modeling studies

Biomed. Eng / Biomed. Tech 2015; 60(4):277–300

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ABSTRACT

Infusion therapy is medically and technically challenging and frequently associated with medical errors. When administering pharmaceuticals by means of infusion, dosing errors can occur due to flow rate variability. These dosing errors may lead to adverse effects. We aimed to systematically review the available biomedical literature for *in vitro* measurement and modeling studies that investigated the physical causes of flow rate variability. Special focus was given to syringe pump setups, which are typically used if very accurate drug delivery is required. We aimed to extract from literature the component with the highest mechanical compliance in syringe pump setups. We included 53 studies, six of which were theoretical models, two articles were earlier reviews of infusion literature, and 45 were *in vitro* measurement studies. Mechanical compliance, flow resistance, and dead volume of infusion systems were stated as the most important and frequently identified physical causes of flow rate variability. The syringe was indicated as the most important source of mechanical compliance in syringe pump setups (9.0×10^{-9} to 2.1×10^{-8} l/Pa). Mechanical compliance caused longer flow rate start-up times (from several minutes up to approximately 70 min) and delayed occlusion alarm times (up to 117 min).

1 INTRODUCTION

1.1 Background

Infusion technology is among the most frequent sources of technology-related medical errors [1]. Intravenous (IV) drug administration by infusion is especially challenging for critical applications because stable infusion flow rates are necessary. Variability in flow rate leads to dosing errors which may lead to adverse clinical effects. These clinical effects can be classified as either insufficient efficacy (underdosing) or increased toxicity (overdosing). There are several reasons for this. First of all, patients, especially those on the intensive care, often need very concentrated pharmaceuticals (drugs) that are delivered with flow rates as low as 0.1 ml/h to minimize excess fluid delivery [2]. Secondly, IV access sites should be limited for reasons of infection risk. Usually, only one catheter is used to deliver multiple IV drugs. Consequently, multiple pumps are combined on this single catheter, causing the flows originating from each individual pump to interact with each other due to pressure differences and mixing effects. This principle of joining multiple infusion pumps on one central line has been named multi-infusion or co-infusion and may be the source of considerable flow rate variability [3]. Thirdly, the total infusion setup consists of several components, many of which are disposable medical devices. While the syringe pumps should produce a relatively accurate flow rate, it has been suggested that the physical properties of the other components in an infusion setup may still cause an instable and seemingly unpredictable flow rate [4,5]. The flow rate is especially unpredictable after pressure changes [6]. These pressure changes appear, for example, after the pump is started, the flow rate is changed or the pump height is altered. There has been an increased awareness that flow rate variability may be responsible for medical errors associated with medical technology. Therefore, in recent years, research has been conducted to trace and assess the origin of infusion flow rate variability. Most of the studies found were *in vitro* laboratory investigations, using several measurement methods [3,5,7–12].

Nowadays, it is generally recognized that the actual drug serum concentrations in the patients involves more than the pharmacokinetics of the drug inside the patients alone. The dynamics of the infusion systems outside the patient plays a significant role in drug delivery as well [13]. Timmerman et al. [14] found three major physical causes explaining the dynamics of the infusion system: mechanical compliance, flow resistance and dead volume. Previous studies have already summarized flow rate variability studies from a clinical perspective [5] but do not elaborate about the underlying physical causes found in literature. Recently, Sherwin et al. [15] explored infusion studies and stated that the physical variables/causes that affect drug delivery in infusion systems require further exploration. In order to facilitate further research in the area of drug metrology we aim to systemically review the biomedical literature for *in vitro* measurement and modeling studies that investigated the physical causes of flow rate variability.

1.2 Mechanical compliance

Mechanical compliance (or compressibility) is described as the volume change caused by changing pressure. The underlying cause is the elasticity of the infusion components. Consequently, volume is stored due to the stretching of non-rigid infusion components as a result of the rising pressure applied by the pump. Mechanical compliance is defined according to eq. 1:

$$C = \frac{\Delta V}{\Delta P} \qquad (1)$$

where C (l/Pa) is the mechanical compliance, DV (l) is the volume increase and DP (Pa) the applied pressure difference. Pressure changes may be caused by changing the nominal flow rate. For example, relatively large pressure changes occur inside the infusion system when the pump is started from a standstill. Another possible cause of pressure change is the vertical displacement of an infusion pump. When the pump is moved up, with respect to the output, i.e. the patient, the pressure increases because the pressure produced by a water column is only dependent on its height. In case of a volumetric pump, regulated by gravity only, the flow rate will increase after increasing the height of the pump. The only limitation is caused by the flow resistance of the tubing and the viscosity of the fluid. However, in case of a syringe pump, merely a bolus (temporary increase of flow rate) is expected. Most syringe pumps simply push the plunger a certain amount per unit time forwards upstream, towards the patient, while preventing the plunger to move backwards, towards the pump. Because of the mechanical compliance, however, some amount of fluid can be stored or released if the pressure is changed. For example, when the pump moves upwards, the pressure is increased at the lower end of the system. As a result, the pressure on the syringe is decreased which causes the syringe to contract. This decrease in volume causes a small bolus. Conversely, a downwards motion causes a temporary under dosing because the syringe expands. This effect is not related to the velocity of motion during the very act of vertical displacement of the pumps, so the kinetic energy remains irrelevant. It is only the change in position (height) that matters (before and after the vertical displacement of the pump, respectively), not the vertical motion itself that is needed to implement this change in height. The time it takes for the outflow from the syringe in the pump to reach the nominal value is not only dependent on the mechanical compliance but also the flow resistance. The magnitude of the resistance is determined mainly by the diameter of infusion lines (tubing). Infusion devices with small diameters, for example, a catheter with an inner diameter of 1 mm, have a relatively high resistance, i.e. approximately 0.1 mbar per ml/h (10 Pa per ml/h). Of all the infusion components, these relatively small diameters are often found in vascular access devices, such as catheters and cannulae. Viscosity has influence on the effects of the resistance, since with more viscous liquids, the effects of resistance are expected to be more pronounced. Temperature, in turn, may alter the magnitude of the viscosity.

In the infusion setup, mechanical compliance causes deviations in flow rate changes that are opposite with respect to any flow rate change. For example, when the pump is started from a standstill, the pump requires time to reach the nominal flow rate at the catheter

tip, where the pharmaceutical enters the patient. This delay between the flow rate and the nominal flow rate is caused by mechanical compliance. Another potential danger, caused by compliance, is a delayed occlusion alarm. When an infusion line is occluded (obstructed), the pressure in the infusion system will increase. If this happens, the pumps should stop and trigger an alarm signal. However, because the pressure increase expands the infusion components first, the force transducer in the pump, usually located at the plunger in syringe pumps to measure an increase in pressure, does not measure this pressure increase until the components are not able to expand any further. In a multi-infusion situation, a flow rate change in one pump may cause flow rate deviations in the output from other pumps that are connected to the same central line or catheter. When the flow differences are relatively large, or when the central line is occluded beyond the mixing point (upstream), backflow may occur. In such a case, the liquid flows back towards a syringe or infusion bag [3,16].

1.3 Dead volume

Dead volume is a term first described in the field of infusion technology by Lovich et al. [17,18]. Dead volume is the total volume between the mixing point and the outflow into the patient at the catheter tip, also called drug reservoir, internal volume or dead space volume. When a certain drug concentration is introduced into the infusion line it travels through the dead volume into the patient. In clinical practice there is approximately one meter of distance between the patient and the pump. With the use of typical infusion lines this results in about 1.6 milliliters of dead volume. If multiple infusion pumps are combined on one central line and catheter, the dead space volume is shared between those pumps. In this case, a flow rate change in one pump introduces changes to the entire combined mixture in the central line (Figure 1). A concentration ratio of multiple medications is introduced at the mixing point, where multiple pumps are combined. This concentration ratio is based on the current flow rates produced by the pumps. For example, if pump one has a flow rate of 20 ml/h and pump two has a flow rate of 30 ml/h, then the ratio of medication originating from pump one will be 2/5 and the ratio of medication originating from pump two will be 3/5. This ratio remains unaltered between the mixing point and the patient once it is inside the tube between the mixing point and the patient at the catheter tip. Therefore, this mixing ratio administered to the patient at the catheter tip is a mixing ratio that was produced in the past. Consequently, if the nominal flow rate of pump one is increased to 30 ml/h, a new ratio of 3/6 is introduced at the mixing point, for both pump one and pump 2. However, the ratio of 2/5 and 3/5, for pump one and two, respectively, is still inside the line between mixing point and the catheter tip. This mixture, introduced in the past, will be infused with a new combined flow rate of 60 ml/h, which produces a temporary unwanted bolus until the old concentration ratio has been flushed out. The time it lasts for a concentration mixture to be flushed out of the dead volume (the dead volume time) can be calculated as: [t (s) = dead volume (l) / flow rate (l/s)], where the flow rate is the cumulative new flow rate originating from all the pumps connected to the same central line.

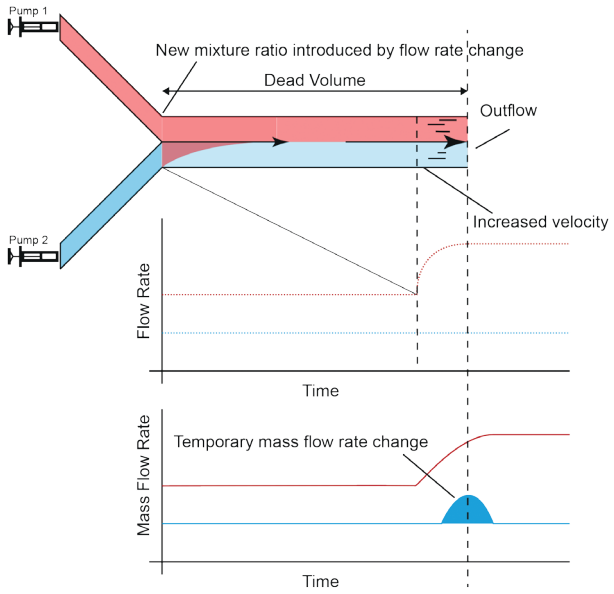

Figure 1. *Schematic explaining the effect of dead volume in a multi-infusion system. When the flow rate of the red pump is increased, an excess bolus of pharmaceuticals from the blue pump enters into the patient. This bolus occurs due to the fact that the concentration mixture within the "dead volume", which has been based on the "old" situation before the flow rate increase in the red pump, is now propelled out from the dead volume into the patient with the new increased total flow rate of the red and blue pumps.*

In practice, the phenomena of mechanical compliance, resistance and dead volume are superimposed on each other. Consequently, the pharmaceutical dose per unit time administered to the patient is not just related to the nominal flow rate; but may also be affected by the physical effects of mechanical compliance, resistance and dead volume.

1.4 Infusion components and equipment

For each study, we categorized the pumps that were used. Pumps can mostly be categorized as syringe pumps or volumetric (peristaltic) pumps. Syringe pumps are commonly used for the accurate delivery of relatively low flow rates. Volumetric pumps are used for higher flow rates. The flow in volumetric pumps can be regulated in several ways such as drip chambers or counters or peristaltic methods. These methods are generally less accurate than syringe pumps. In many cases, a combination of syringe and volumetric pumps is used, where the volumetric pump is used as a faster (i.e. higher flow rate) 'carrier' for the slower syringe pumps containing critical pharmaceuticals. For example, a volumetric pump with a high flow rate containing a NaCl solution may be used to 'push out' an older concentration ratio, produced by multiple slower pumps combined on the same central line. The volumetric pump containing the NaCl is called a carrier flow, i.e. the faster flow 'carries' the drug mixture, originating from several slower pumps, through the dead volume of the central line, between the mixing point and the patient at

the catheter tip. Moreover, because the concentrations of the critical pharmaceuticals from the slower pumps are reduced by the faster carrier flow, the impact of flow rate variability is smaller. Conversely, the dosing error will be larger if the concentration of the critical medication is higher. Consequently, the impact for the patient will be more severe. However, many patients are unable to tolerate large quantities of fluid, the use of a carrier flow is therefore not always possible.

Infusion components include stop cocks, manifolds, anti-reflux and anti-syphon valves, infusion lines (tubing), catheters, cannulae, filters and syringes. The mechanical properties of these components are associated with the physical causes described earlier.

2 METHODS

2.1 Search strategy and selection of studies

We searched for *in vitro,* i.e. laboratory studies, in Medline related to infusion flow rate variability, published between August 1994 and August 2014. Flow rate variability was considered to be any phenomenon which was measured in terms of flow rate. Common phenomena and causes of infusion flow rate variability were used as our inclusion criteria. These phenomena included: start-up and fluctuations of flow rates, back flow and dead volume. These phenomena are generally related to infusion components such as syringes, tubing, valves, catheters, etc. In addition to measurement studies we also searched for theoretical modeling studies. Figure 2 illustrates the rationale for the keywords used. The keywords were grouped as ‘effects’, ‘components’ and ‘methodology’. The keywords within each group were combined with logical OR operators. Other keywords that were attempted included: ‘compliance’, which was too generic and gave too many results. The keywords of ‘pressure’, ‘flow’ and ‘in vitro’ returned too many unwanted results as well. Flow AND variability returned insufficient results, while flow OR variability returned too many results. Metrology was not a common keyword in biomedical literature and returned no relevant additional results.

Accordingly, the following search string was used in Medline (Pubmed): (infusion) AND (flow rate OR start-up OR backflow OR dead volume) AND (infusion line OR stop cock OR syringe OR tubing OR filter OR valve OR pump OR catheter OR measuring OR model)

The following options were activated in Pubmed: ‘Full text’, ‘Abstract’, ‘English only’. Checking ‘review’ or ‘in vitro’ as a search option did not give the expected results and was not used.

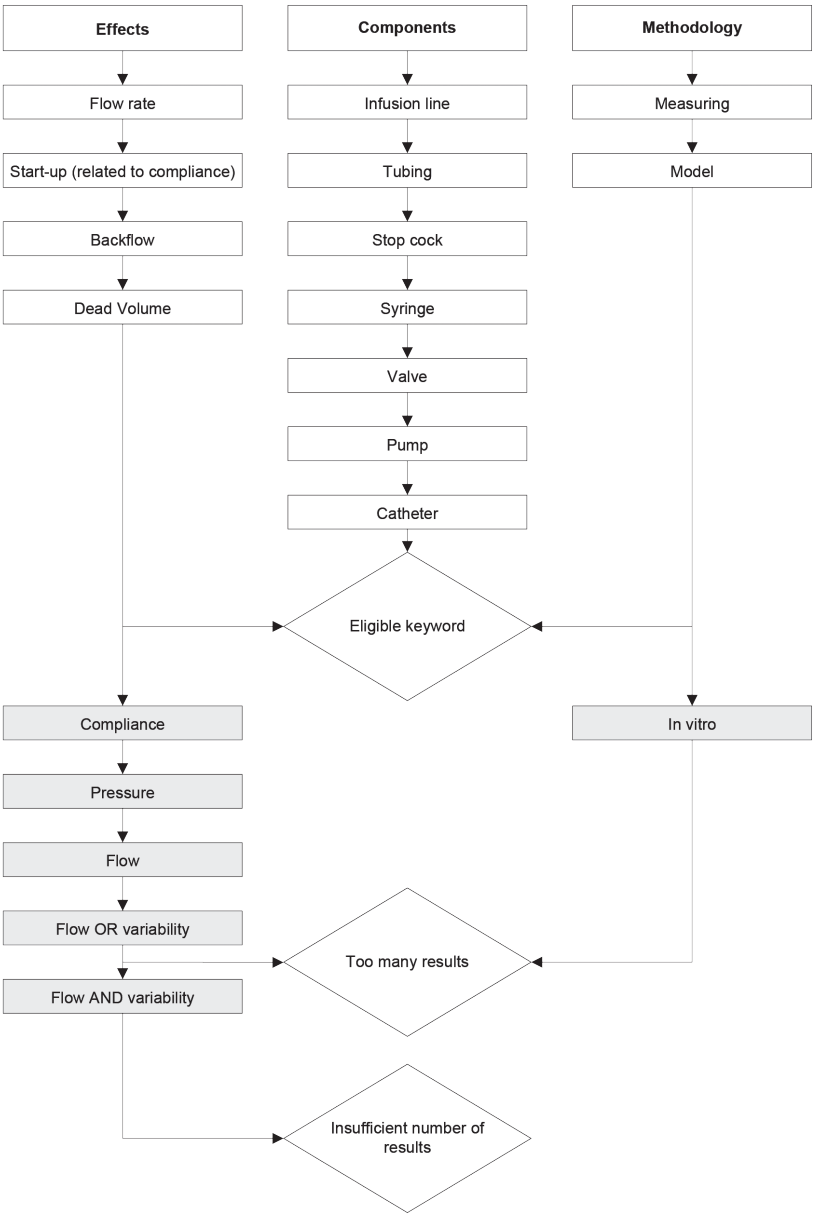

Figure 2. *Flowchart of the keywords that were either used or attempted in the search strategy. The keywords were categorized as "effect" studied, "component" studied, and "methodology" used to conduct the study.*

When reading the studies, we focused on the following four questions:

1. How are the physical effects causing flow rate variability, especially the physical causes of mechanical compliance, flow resistance and dead volume, explained?

2. Which physical effects were indicated as the most important causes of flow rate variability?
3. When the role of mechanical compliance was mentioned, which component of the infusion device chain was identified as the most compliant element?
4. What has been the purpose for theoretical modeling studies and what physical effects were studied?

Only full-text English papers with abstracts were considered. We screened titles and abstracts before reading the entire article. In case other reviews were found that investigated infusion flow variability studies, we cross-checked our results with the results of the other reviews. The condition was that all studies from these reviews matching our inclusion criteria should show up with our search query. The classification of the included studies are stated under 2.2 Data extraction. We also used a classification for the excluded studies after reading and interpreting the title. The excluded studies were categorized in one of the following categories:

In vivo: Studies concerned with the effects of infusion flow rate variability inside humans or animal subjects. **Non-flow:** Non-flow studies were all studies that were not evaluating flow rates in any way. For example, studies aimed at measuring only pressure or the assessment of non-continuous infusion were excluded. Studies evaluating the flow outside the infusion system such as the distribution to tissue were also excluded. These studies were classified as non-flow. **N/A:** Studies that we were not able to obtain. **Miscellaneous excluded studies:** Studies in which no measurement method or theoretical models were used to evaluate continuous infusion flow rate. Studies that differed entirely from the subject were also categorized as miscellaneous excluded studies.

Studies investigating the properties of drugs such as mixing and absorption by infusion components were not included.

2.2 Data extraction

From the included articles we extracted to following data:

(1) Objective. (2) Year of publication. (3) Details about the measurement method used: setup, sensitivity, sample time, etc. (4) Details about the pump used: type of infusion pump, brand. (5) Infusion disposable type, if this was specifically associated with a physical cause. (6) Nominal flow rates. (7) The physical parameters/causes that were investigated. If this was not specifically stated the physical parameters/causes were interpreted.

We classified the measurement studies according to the physical causes of flow rate variability. Measurement studies that could not specifically be classified according to a general physical cause were categorized as miscellaneous, these studies usually evaluate the performance of specific infusion pumps.

3 RESULTS

The search resulted in 1498 publications from which 1368 were excluded. From most of the excluded studies it was found that the subject differed entirely after reviewing the title. Another 29 studies were non-English and one study did not provide an abstract, these 30 studies were excluded as well. After this, we reviewed the abstracts and excluded 52 studies on the basis of the specific criteria stated before. Five studies were added after cross-checking references of the studies found (Figure 3).

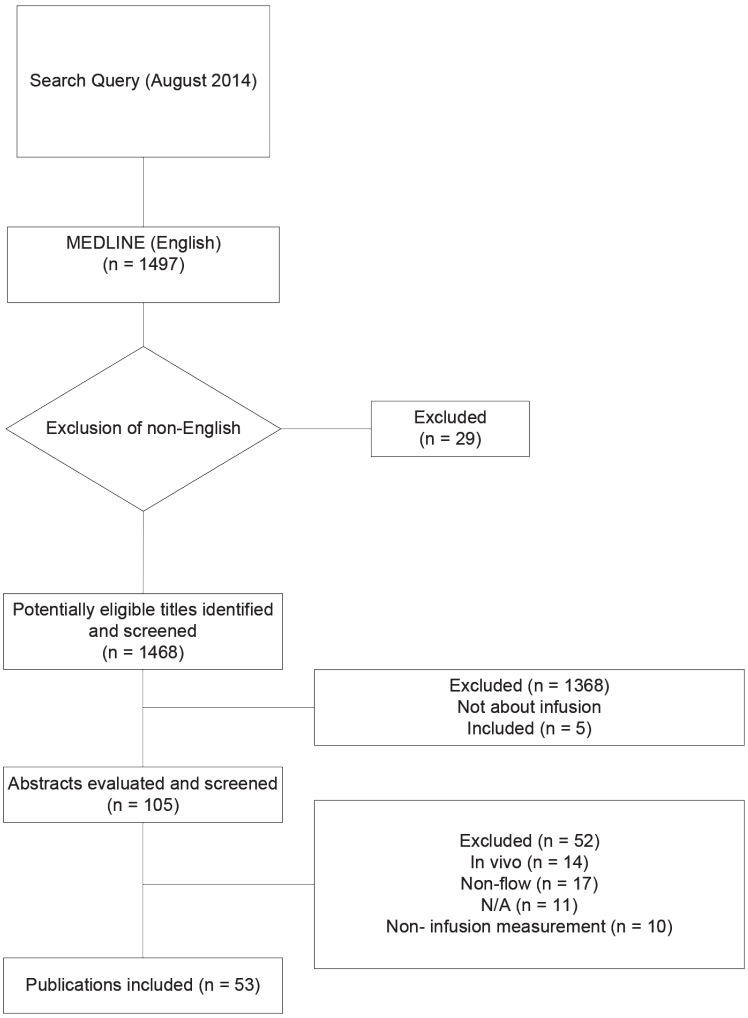

Figure 3. *Systematic review query. Fourteen in vivo studies were excluded. Seventeen studies were not about flow measurement (non-flow). Eleven studies were not available (N/A), and ten studies were not included for miscellaneous reasons. Fifty-three papers were included, of which six were theoretical modeling studies and two papers were other reviews about infusion flow rate variability.*

We included 53 studies, of which six were theoretical models, two were other reviews, and 45 were *in vitro* measurement studies. Table 1 shows a complete overview of the studies found in our review.

3.1 Study characteristics

We found several measurement methods used for investigating flow rate variability in infusion. Figure 4 shows the number of publications by year and the measurement methods that were used. Gravimetric methods were commonly used for single flows investigating flow rate start-up and mechanical compliance. Spectrometric methods were mostly used for the assessment of dead volume. Spectrometric methods include any method using a spectrometer to obtain the concentration output originating from a specific pump. Absorption spectrophotometry was common. In many cases dye analogues were used. However, we also found studies in which actual pharmaceutical concentrations were measured using similar spectrometric techniques. Further study characteristics can be found in Figure 5.

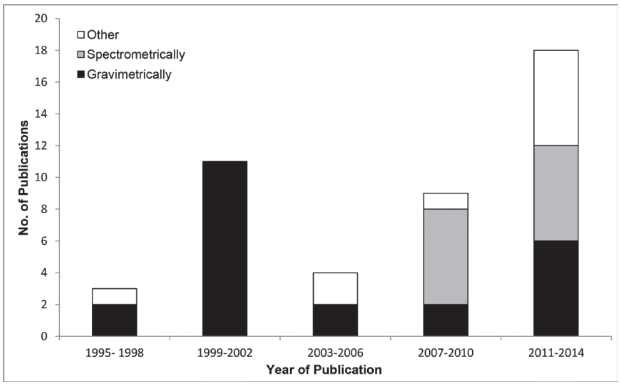

Figure 4. *Overview of measurement methods used in the included publications (n = 45). Measurement methodologies included gravimetric methods, spectrometric methods, and others.*

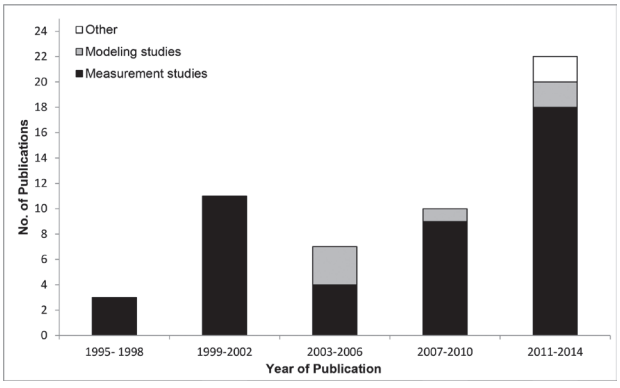

Figure 5. *Overview of study characteristics. Modeling studies that were tested using a laboratory setup were categorized as a modeling study.*

3.2 Physical causes

From the 45 measurement studies 33 explicitly investigated flow rate variability due to the physical causes of mechanical compliance, flow resistance or dead volume. The other measurement studies focused on the performance of specific infusion pumps. 15 studies primarily investigated the role of mechanical compliance caused by infusion components as a cause of flow rate variability. Of all the studies investigating the role of mechanical compliance, ten associated the mechanical compliance with syringes. Seven studies investigated the physical effect of resistance caused by infusion components. Of these studies, four explicitly stated that the physical effect of resistance was investigated. Eleven studies investigated dead volume and all studies explicitly stated that the physical effect of dead volume was investigated. Besides these major physical effects, turbulence in relation to air bubbles was mentioned as a possible source of flow variability [19]. Also temperature and viscosity of the infused liquid were indicated as factors influencing the flow rate [11,20]. Studies investigating mechanical compliance in relation to start-up time were common and mostly measured gravimetrically. Start-up or onset (time) is defined as the time required to reach the nominal flow rate or a certain pre-defined fraction of the nominal flow rate. However, dead volume studies, usually using spectrometric methods for measuring drug concentrations, became increasingly numerous during the last years.

Mechanical compliance and flow resistance

Mechanical compliance and resistance were mostly investigated in relation to start-up time. However, we have also found several studies in which compliance was specifically analyzed [6,21–24]. Neff et al. found a mechanical compliance of approximately 1.2 – 1.8 µl/mmHg (9.0×10^{-9} – 1.35×10^{-8} l/Pa) for several different pumps using an Injectomat Syringe (Fresenius, Bad Homburg, Germany) 50 ml [21]. Weiss et al. found approximately 1.24 – 1.85 µl/mmHg (9.3×10^{-9} – 1.38×10^{-8} l/Pa) for four different 50-ml syringes: CODAN Medical ApS (Rødby, Denmark), IVAC Medical Systems (San Diego, CA, USA), Becton Dickinson (Plymouth, Ireland) and Fresenius AG (Bad Homburg, Germany) [23]. We found 1.5×10^{-8} to 2.1×10^{-8} l/Pa for a B.Braun (Melsungen, Germany) 50-ml syringe using a pressure gauge and a balance [4]. Kim et al. [25] found that the syringe was the most compliant component in a syringe infusion setup and specifically stated that the mechanical compliance is located in the latex plunger of the syringe. Kim also found that the accuracy of the flow rate was not significantly improved with smaller syringes but that larger syringes delayed the time to reach an occlusion alarm from 7.4 to 84 minutes for the 10 and 60-ml syringes, respectively. The experiments were performed with the model 2001 (Medifusion, Medex Inc, Duluth, GA, USA) pump [25]. Priming the infusion set with some pressure may decrease the effects of mechanical compliance, thereby decreasing the flow rate onset time. However, a bolus may occur at start-up [26]. Neff et al., Weiss et al. and Schmidt et al. [23,27–29] evaluated start-up times gravimetrically for different syringes and syringe sizes. All stated the influence of mechanical compliance explicitly and found that smaller syringe sizes, i.e. syringes with smaller diameters and therefore smaller volumes, showed shorter onset delays and shorter ‘zero-drug delivery times’ in which there was no flow rate at all. It was found that start-up time was at least 60 minutes

with the 50-ml syringe. With the 10-mL syringe, start-up time was less than 20 minutes. However, these start-up times could not entirely be attributed to compliance, although it was attempted to remove other influences [28]. Neff et al. found between 3.6 ± 0.9 (10-ml syringe, 1.0 ml/h nominal flow rate) and 74.5 ± 26.6 (50-ml syringe, 0.1 nominal flow rate) minutes start-up time [27]. The start-up times as well as the no-flow times after lowering the pump were in correlation with the calculated mechanical compliance and the elastic nature of the plunger material [22,30]. Moreover, lower flow rates were associated with longer start-up delays [22,27,28,30].

Another cause of pressure changes in an infusion system, which exploits compliance, is the vertical displacement of the pump. This has been investigated in several studies. It was generally found that an upward motion is followed by a bolus delivery, and a downward motion is followed by temporary reduced flow output [6,7,21,24,31–33]. This effect is not related to the velocity of motion during the act of vertical displacement of the pumps. Only the difference in height between the pump and the point of outflow causes the temporary flow deviation. Infusion lines were also stated as a source of mechanical compliance [24,30]. Weiss et al. [24] evaluated gravimetrically the influence of infusion lines on mechanical compliance due to vertical displacement. The flow rate onset time, i.e. the time in which there was no flow rate, varied between 5.1 ± 1.5 and 44.0 ± 6.8 (mean ± SD) seconds, depending on the type of infusion line, after lowering the middle part of the infusion lines 70 cm below the infusion pump, at a nominal flow rate of 0.5 ml/h. The infusion lines tested were: Syringe Extension Set (IVAC Medical SYSTEMS, San Diego, CA, USA, Ref G30402M/652403), Injectomat-Line (Fresenius, Bad Homburg, Germany, Ref 9011971), Syringe Extension Set, (IVAC Medical SYSTEMS, San Diego, CA, USA, Ref G30402/652393), Syringe Extension Set and Injectomat Line PEL (Fresenius, Bad Homburg, Germany, Ref 9000951). The variation of the results showed a close correlation between the variation of the infusion line mechanical compliances, which varied between 0.48 ± 0.17 µl/mmHg ($3.6 \times 10^{-9} \pm 1.3 \times 10^{-9}$ l/Pa) and 2.15 ± 0.26 µl/mmHg ($1.6 \times 10^{-8} \pm 2.0 \times 10^{-9}$ l/Pa). These mechanical compliances were obtained using a blood pressure transducer [24]. Brotschi et al. [33] evaluated the influence a neonatal Pall in-line filter device (Pall Posidyne Neo Filter 0.2 lm, Pall AG Switzerland, Basel, Switzerland) on start-up times and flow rate irregularities during vertical displacement of the syringe pump. The experiments were performed with nominal flow rates of 0.5, 1.0 and 2.0 ml/h. The time to first drop was registered as well as the time required to reach 95 % of the nominal flow rate. For each of these end points, a comparison between using an in-line filter and not using an in-line filter was made. The values, resulting from four repeated experiments, were presented as median values, the range is denoted between parentheses. The time required to reach 95 % of the nominal flow rate (95 % time) differed significantly when using a filter and not using a filter for the nominal flow rates of 0.5 ml/h ($p = 0.02$) and 2.0 ml/h ($p = 0.003$) but not for 1.0 ml/h ($p = 0.7$). For a nominal flow rate of 0.5 ml/h the time to first drop was 355.5 (0–660) seconds without the filter and 115 (0–320) with the filter, the difference was not statistically significant. 95 % of the nominal flow rate was reached in 580 (360–870) seconds without a filter and reduced to 284 (130–650) seconds with

the filter. For a nominal flow rate of 1.0 ml/h the time to first drop was 0 (0–172) seconds without the filter and 0 (0–160) with the filter, the difference was not statistically significant. 95 % of the nominal flow rate was reached in 230 (220–350) seconds without the filter and 210 (120–520) seconds with the filter, the difference was not statistically significant. For a nominal flow rate of 2.0 ml/h the time to first drop was 0 (0) seconds without the filter and 0 (0–60) with the filter, the difference was not statistically significant. 95 % of the nominal flow rate was reached in 249.5 (153–393) seconds without the filter and 62 (0–200) seconds with the filter. It was concluded that the start-up time was reduced after introducing an in-line filter. However, the differences were diminished at higher flow rates, i.e. 1.0 and 2.0 ml/h, and the time to first drop differences were not statistically significant. The storing of fluid into the compliant disposables of a system was reduced using an in-line filter after lowering the pump. The bolus resulting from elevation of the pump was not reduced using an in-line filter. Experiments were performed gravimetrically and a thin layer of oil was used to prevent evaporation [33].

Yet another compliant element in the infusion system is air. The influence of air bubbles was gravimetrically evaluated by Davey et al. [34] at 1.0 ml/h. Davey stated that "Small air bubbles can become lodged in the pressure-sensing disc part of syringe pump delivery lines. This can give rise to serious disturbances in fluid delivery from minute to minute, but does not trigger pump alarms. Small air bubbles being delivered through non-horizontal sections of delivery line can also cause significant transient disturbances to fluid delivery. Flow rate fluctuated between 1 and 3 ml/h" [34].

Resistance was also evaluated. Angle et al. [35] measured the pressure using a pressure gauge for several Peripherally Inserted Central Catheter (PICC)-lines, a common vascular access device. The flow rate was calculated according the Poiseuille law. Flow rate capacity was related to the inner diameter. Resistance was specifically given for each PICC line ranging from approximately 0.05 to 1.5 mmHg per ml/h (7 Pa per ml/h to 200 Pa per ml/h) [35]. Non-linear resistance occurs with several types of valves to prevent backflow. It has been shown that this causes flow rate variability [3,9,12,31,36,37]. Liu et al. [37] measured the effect of using several sizes of cannulae in combination with a SmartSite Needle-Free (CareFusion, San Diego, CA, USA) anti-reflux valve on the time required to empty an infusion bag of a volumetric infusion pump. Experiments were performed under a gravity-only condition, where the bag was emptied due to gravity alone. Furthermore, a pressure infuser was used, in this case the bag was squeezed with a pressure of 0.4 bar (4×10^4 Pa). Each experiment was performed with and without an anti-reflux valve, and repeated five times. Results were presented with a 95 % confidence interval (95 % CI). For the biggest cannula (14G) a flow rate of 82 (79–86, 95 % CI) and 126 (116–135, 95 % CI) ml/min was measured with and without an anti-reflux valve, respectively, for the gravity-only condition. For the smallest cannula (20G) a flow rate of 43 (41–44, 95 % CI) and 47 (46–48, 95 % CI) ml/min was measured with and without an anti-reflux valve, respectively, for the gravity-only condition. Smaller cannulae and the presence of an anti-reflux valve delayed the emptying of the infusion bag and thus delayed the flow rate

under gravity only condition as well as with the use of a pressure infuser [37]. Weiss et al. [38] investigated different flush techniques for arterial lines and cannulae and found that, when using a syringe pump the onset time of flow rate was significantly longer than using a pressure bag system. Start-up time (zero flow time) was 0.1 ± 0.01 and 7.7 ± 0.5 minutes for the bag flush system and syringe pump, respectively [38]. Le Noel et al. [39] tested the influence of several catheters with different lengths (42 – 200 mm) and inner-diameters (0.9 – 1.6 mm) on the flow rate using a peristaltic pump. The pump contained a fluid with a viscosity similar to that of blood. Nominal flow rates of 100, 200, 300 and 400 ml/min were used. The experiments were performed according to the ISO 10555-3 standard using a gravimetric measurement setup. The study showed that these relatively high flow rates were not reached and that the error of the underestimation increased with decreasing catheter inner-diameters, longer catheter lengths and higher fluid viscosity. These findings indicate that the lower than expected flow rates were related to the flow resistance caused by the catheter [39]. Van der Eijk et al.[31] investigated the effects of three different types of check valves BBraun Infuvalve (Melsungen, Germany), Filtertek BV SyphonSafe (Co. Limerick, Ireland), BBraun BC1000 (Melsungen, Germany) on start-up time and the total delivered volume during measurement, these effects can be related to flow resistance. A thermal flow meter was used for a pump with a nominal flow rate of 0.1 ml/h. An additional pump with a nominal flow rate of 2.5 ml/h was also measured simultaneously using a Coriolis Flowmeter. The pumps were connected to a common central line with a three-way stopcock. The results were presented as mean ± SD. Start-up time was defined as reaching 75 % of the nominal flow rate. Van der Eijk found longer start-up times with check valves (up to 43.7 ± 2.7 minutes) than without check valves (27.6 ± 3.8 minutes) for the pump with a nominal flow rate of 0.1 ml/h. A lower than expected total volume delivery was found in the pump with a nominal flow rate of 2.5 ml/h. The lowest value found with a check valve was 12 ± 24 % of the expected total volume compared to 52 ± 21 % without a check valve. It can be concluded from the results that check valves may cause flow reduction [31]. Hall et al. [12] used a flow meter to observe flow rate reduction caused by three different anti-reflux valves: Protect-a-Line 3 (Vygon Ltd, Cirencester, UK), Wescott Sae-flo (Wescott Medical Ltd, Chester-le-Street, UK), B. Braun Back flow valve (B. Braun Medical, Melsungen,Germany). The experiments were performed with a volumetric pump under gravity (150 cm height difference) or an applied pressure of 0.4 bar (4×10^4 Pa) and measured using a flowmeter. In addition, the influence of two different cannulae with different diameters (16G and 20G) were investigated. Flow rate decreased for all valves with a 16-G cannula, the highest reduction was -38 % under gravity and -23 % (both with the Protect-a-Line 3) under the applied pressure. For the 20G cannula no statistically significant flow rate reductions were found [12]. McCarroll et al. [9] evaluated three anti-syphon valves: B. Braun Medical BC1000 Backcheck Valve (Melsungen, Germany) , Wescott Medical 200 cm anti-syphon set (Wescott Medical Ltd, Chester-le-Street, UK), Vygon Protect-A-Line (Vygon Ltd, Cirencester, UK) at nominal flow rates of 2, 10 and 50 ml/h, using syringe pumps. An observer recorded the time between depressing the start button and the first drop that fell from the infusion line. All

results were compared to a 'control' situation without an anti-syphon valve. The results were presented as mean ± SD. The time to first drop was longer when an anti-siphon valve was used at lower nominal flow rates. The longest time until the first drop was observed was 18.4 ± 9.26 minutes, as opposed to 3.5 ± 2.09 minutes in the control situation, with a nominal flow rate of 2 ml/h. At the higher nominal flow rates of 10 and 50 ml/h, the times to first drop were less pronounced. In these cases, none of the difference with the control group were statistically significant, except for the Wescott valve for which a start-up time of 0.6 ± 0.33 minutes was found as opposed to 0.3 ± 0.14 minutes for the control situation. Overall, all the valves performed similar within the uncertainties that were presented [9]. At low flow rates, time to first drop was significantly longer using an anti-syphon valve as opposed to the control group. At the faster rates this difference was less pronounced but still observed in some cases.

Dead volume and multi-infusion

Dead volume or internal volume has been related to central infusion lines, manifold or the entire infusion set [2,3,10,40–44]. Dead volume was also associated with vascular access devices such as catheters [17,45,46]. Lowering the dead volume was practically unanimously recommended in the literature reviewed. However, lowering the volume of tubing by reducing the diameter increases the resistance [3,17].

Dead volume is especially important for relatively low flow rates, i.e. between 0.1 – 10 ml/h. Low flow rates are typically used on the neonatal intensive care unit (NICU), because the small infants cannot tolerate large quantities of fluid [2]. Consequently, the concentrations of the pharmaceuticals are high. However, this is also the reason that small deviations can easily cause dosing errors. Therefore, there has been a focus on flow rate variability in the NICU setting [5,6,47]. However, we also found flow variability studies outside the NICU setting.

A research group led by Décaudin [3] conducted a series of studies to investigate the effects of, amongst other effects, dead volume. Décaudin et al. [3] investigated two different multiple-in, single-out infusion sets (both from Doran International, Toussieu, France) used for multi-infusion. The sets differed in length and dead volume, i.e. the volume between the mixing point and the distal end of the infusion set. In addition, the presence and position of an anti-reflux valve was varied between the tests. Depending on the access position of the infusion set (i.e. distal or proximal with respect the infusion pump) the dead volumes were between 0.046 and 8.01 ml. Drug concentration at the end of the infusion set was measured using an UV spectrometer. The mass flow rate and mass flow rate plateau (µg/min) were investigated, where the mass flow rate plateau was defined as the mean amount of drug delivered to the patient per unit time in steady state, i.e. the stage where a concentration equilibrium has been reached. A deviation in the 'drug delivery plateau' (in percentages) was evaluated, where 100 % corresponded to the expected mass flow rate plateau. It was hypothesized that values lower than 100 % were caused by backflow from the other pumps connected to the same infusion set.

In addition, the FCE (Flow Change Efficiency) was calculated. The FCE is the ratio (in percentages) of the expected delivered drug and the measured drug delivered. The 'drug delivered' is defined as the 'area under curve' of the mass flow rate during a specific time period, usually after a flow rate change was initiated. For example, if during a flow rate start-up period of 30 minutes, the mass flow rate corresponds for 100 % to the expected mass flow rate, the FCE is 100 %. Three syringe pumps with nominal flow rate between 7 and 15 ml/h and one carrier flow volumetric pump with a nominal flow rate of 50 ml/h were used. The results were presented as mean ± SD. The FCE was 53.0 % ± 15.4 % and 5.6 % ± 8.2 %, for dead volumes of 0.046 and 6.16 ml, respectively. It was therefore found that infusion sets with lower dead volume resulted in higher FCE values. This finding was true for any flow rate change. The presence of an anti-reflux valve increased the mass flow rate plateau from 92.4 % to 99.3 % of the theoretical curve of the nominal flow rate, without and with an anti-reflux valve, respectively. This showed that an anti-reflux valve reduced backflow into the tubing of another infusion pump, that was connected to the same infusion set as the infusion pump from which the fluid originated [3]. From the same group, Lannoy et al. [41] conducted a similar experiments using the same infusion sets as Decaudin et al. [3]. However, in this case the effects of carrier flow was investigated. The influence of a 10-minute carrier flow interruption, as well as two different nominal carrier flow rates of 90 and 350 ml/h were investigated. The nominal flow rates of the pump used to simulate drug delivery, noradrenaline in this case, was varied between a 'low flow' and 'high flow' regime of 7 and 65 ml/h, respectively. For the 'low flow' regimen the FCE of noradrenaline was 6.7 % ± 0.5 % and 63.5 % ± 0.8 %, for dead volumes of 6.16 and 0.046 ml, respectively, during a 10-minute period after stopping the carrier fluid. The FCE was 257.8 % ± 25.0 % and 119.9 % ± 0.6 %, for dead volumes of 6.16 and 0.046 ml, respectively, during a 10-minute period after restarting the carrier flow. For the 'high flow' regime the FCE of noradrenaline was 56.2 % ± 1.8 % and 94.7 % ± 4.4 %, for dead volumes of 6.16 and 0.046 ml, respectively, during a 10-minute period after stopping the carrier fluid. The FCE was 146.0 % ± 6.9 % and 102.2 % ± 3.7 %, respectively, for dead volumes of 6.16 and 0.046 ml during a 10-minute period after restarting the carrier flow. This is similar to the conclusion of Decaudin et al. [3] that a smaller dead volume is providing a better FCE, which means that the delivered amount of drugs is closer to the expected value [41].

In another study, Lannoy et al. [42] investigated several infusion sets with dead volumes between 6.16, 3.70, 1.85, 0.93 and 0.046 ml with and without anti-reflux valves. The drug (Noradrenaline) was set to a nominal flow rate of 7 ml/h. The nominal carrier flow rates were 35, 70 and 115 ml/h. the FCE varied between 5.6 % and 53 %, for 6.16 to 0.046 ml dead volume, respectively, during the period of the first five minutes. After 10 to 15 minutes the FCE was around 100 % for all dead volumes, so after 15 minutes the mass flow rate of noradrenaline was as expected. The FCE increased in a non-linear fashion with increasing dead volume. Anti-reflux valves improved the drug delivery (FCE) by approximately 10 % for the low carrier flow after a duration of 10 minutes from the start. It was found that flow rate variability was less for the infusion set with a low dead volume

[42]. Foinard et al. [44] evaluated a new low dead volume disposable, 150 cm extension line (Cair LGL, Civrieux d'Azergues, France) and a nine-lumen infusion device (Edelvaiss-Multiline®, Doran International, Toussieu-Lyon, France), in a similar fashion as the studies conducted by Décaudin et al. [3] and Lannoy et al. [41,42] and found a different FCE for the new disposable when increasing and decreasing the flow rate in the pump containing noradrenaline. After increasing the nominal flow rate of the noradrenaline from 7 to 14 ml/h, the FCE was 58.4 % ± 5.3 % and 84.3 % ± 5.2 % for the conventional and new infusion set, respectively. After decreasing the nominal flow rate from 7 to 14 ml/h, the FCE was 175.3 % ± 8.9 % and 108.2 % ± 4.4 % for the conventional and new infusion set, respectively [44]. It was concluded that the new disposable showed significantly less drug delivery disturbances. In the studies conducted by the group of Décaudin (including Lannoy and Foinard) [3,41,42], a balance was often used to obtain the cumulative fluid quantity at the end of the infusion setup.

Tsao et al. [2] found that dead volume in a multi-infusion setting caused flow rate variability after changing the nominal flow rate. Flow rates used were 10 ml/h for the carrier and 5 ml/h for the syringe pump containing the drug. A bolus lasting about 10 minutes of approximately 20 % above the nominal flow rate was found. A spectrometric setup was used and the medication schedule was based on a neonatal regimen. Moss et al. [43] evaluated a traditional manifold (4-stopcock Hi-Flo manifold, Arrow International, Reading, PA, USA) against a new infusion disposable 6-port Multi Line Extension Set (Summit Medical Products, Worcester, MA, USA). The new infusion disposable was specifically designed to reduce the dead volume. Experiments were performed using a carrier flow of 10 ml/h and 3 ml/h for the flow of the pump containing the model drug, results were presented as mean ± SD. The start-up time (50 % of the nominal value) of the model drug was found to be proportional to the dead volume. The shortest start-up time (3.53 ± 0.11) was found for the new disposable, the longest start-up time was found for the traditional manifold (9.21 ± 0.33) [43]. Bartels et al. [46] investigated a double lumen catheter (#AK-15402, Arrow, Reading, PA, USA) with similar flow rate and regimens as moss, using a spectrometric method. Bartels found that start-up time until the drug concentration was reached was significantly longer with lower flow rates. Also priming, i.e. filling, reduced the onset time. Lovich et al. [17] investigated the dead volume of several central venous catheters using a carrier flow of 10 and 60 ml/h and a drug flow of 3 ml/h. The time necessary to reach steady state in the mass flow rate of the model drug differed between central venous catheters. The differences were related to dead volume. However, Lovich stated that besides dead volume, vascular access sizes are distinguished by their resistance. Oualha et al. [45] evaluated delay time due to dead volume in a central venous catheter (#CS-16402, Arrow, Teleflex, PA, USA) using retrospective HPLC analysis. A dead volume time was calculated, which amounted to 6 minutes for a dead volume of 0.3 ml and a nominal flow rate of 2 ml/h. However, 100 % of the expected concentration of the drug was only reached in 15-18 minutes, which is longer than the expected time calculated on the dead volume [45].

3.3 Miscellaneous

An early study performed by Lönnqvist et al. [32] attributed a bolus followed after vertical displacement to design flaws in syringe pumps. After a change in pressure, mechanical compliance may store or release some additional fluid. In this case, a gap between the plunger and the syringe driver was indicated as a source for the flow rate variability after vertical displacement. This means that the syringe is able to move slightly forward (upstream, towards the patient) or backward (towards the pump) as a result of increasing and decreasing the height of the pump, respectively [32]. Neff et al. found a similar problem [29]. They also found that pump design caused significantly different flow rate variability during vertical displacements of several types of pumps with the same syringe [21]. Ilan et al. [48] investigated the time until an occlusion alarm was released for the Sigma 8000-plus (Sigma, Medina, NY), Graseby 3000 (Smiths Medical, Watford, Herts, United Kingdom), Baxter colleague (Baxter, Deerfield, IL), Alaris 7230B (Alaris Medical Systems, San Diego, CA) peristaltic pumps. Nominal flow rates of 2, 10 ad 100 ml/h were used. Time to occlusion alarm was 0.3 ± 0.1, 2.3 ± 0.5 and 11.7 ± 3.1 (mean ± SD) minutes for nominal flow rates of 100, 10 and 2 ml/h, respectively [48].

Levi et al. [10] evaluated a combination of low flow syringe and volumetric 'infusion' pumps for accuracy and precision using a spectrometric setup. In addition, a multiple-in/single-out stopcock array was evaluated. Levi et al. found that the infusion pump was more accurate than a 60-ml syringe pump in generating infusion rates of both 0.1 and 0.2 ml/h. Also the multiple-in/single-out stopcock array caused significant delays of at least 30 minutes, for the concentration to double after the flow rate was doubled. This was due to dead volume [10]. Neff et al. [21] investigated three different syringe pumps from two different manufacturers Fresenius (Bad Homburg, Germany) and IVAC (Medical Systems, San Diego, CA, USA) and found significant differences in zero drug delivery time between the pumps after vertical displacement while keeping the same syringe type. The zero drug delivery time varied from 2.78 ± 0.29 to 5.99 ± 1.09 minutes. Because the syringe types were kept constant, the differences in zero drug delivery time were attributed to the difference in mechanical compliance of the syringe pump itself, which varied from 1.22 ± 0.01 to 1.75 ± 0.02 µg/mmHg ($9.2 \times 10^{-9} \pm 7.5 \times 10^{-11}$ l/Pa to $1.3 \times 10^{-8} \pm 1.5 \times 10^{-10}$ l/Pa) [21]. Dönmez et al. [49] evaluated 40 syringe pumps (two types) using a variety of syringe sizes, measuring the time to reach the occlusion alarm at relatively low flow rates of 0.5 – 5.0 ml/h. Time to occlusion was longer with lower flow rates and shorter for higher flow rates, up to 117.3 ± 9.4 minutes for 0.5 ml/h and 15.0 ± 7.1 minutes for 5 ml/h (mean ± SD) . Syringe type had no statistically significant effect on the time to occlusion alarm [49]. Neff et al. [29] evaluated four syringe pumps at 1 ml/h for start-up times gravimetrically. Time to first fluid delivery, as well as time to steady state (time between first fluid delivery and reaching the nominal flow rate) were evaluated. Significant differences were found between the syringe pumps. The times to first fluid delivery ranged from 0.3 ± 0.1 to 1.1 ± 0.8 minutes, and the times to steady state ranged from 6.0 ± 3.1 to 11.1 ± 4.3 minutes after eliminating the gap in the pump by giving a bolus first. When this bolus was not given the time to first fluid delivery and the time

to steady state were 57.2 ± 28.6 and 76.3 ± 29.0 minutes, respectively [29]. Neff et al. [50] also evaluated FASTSTART-mode in the IVAC P7000 syringe pump (Alaris Medical Systems, Hampshire, UK) in a similar fashion. FASTSTART delivers an intelligent bolus to lower start-up times. "FASTSTART significantly reduced time to first delivery and times to steady state in the unprimed syringe pump infusion System". The greatest improvement was obtained after priming the pump. The time to steady state was reduced by about 50 % from 1.4 ± 1.4 to 0.7 ± 0.6 (mean ± SD) minutes. The experiments were performed gravimetrically [50]. Sarraf et al. [30] performed a benchmark test for a specific syringe pump (Graseby 3400, Marcal Medical, Millersville, MD, USA) using a TRN001 isometric transducer (Kent Scientific, Torrington, CT, USA). The isomeric transducer was used to measure a downwards force and was therefore able to measure the weight of water ejected from the syringe. 'Start-up loss' was measured. Start-up loss was defined as the difference in mass measured after 25 seconds compared to an ideal, instantaneous, start-up curve. Results were presented as mean ± SD. Sarraf found 'mass lost' between 29.8 ± 1.31 and 937.7 ± 32.36 mg, compared the ideal curve, for nominal flow rates were between 20 and 400 ml/h, respectively [30].

Miscellaneous infusion pump setups

Although the vast majority of the studies found were based on syringe or volumetric pumps in an intensive care setting, we found some studies evaluating the performance of less common types of infusion setups.

Pierce et al. [51] evaluated a drip chamber under specific conditions. Drip chambers monitor the flow rate of gravity driven volumetric pumps by counting and regulating drops, ideally independent from physical factors such as height or resistance. However, it was hypothesized that if the drip chamber was in "wide open" condition, the drops can no longer be quantified and the physical factors start to influence the flow rate. Under "wide open" conditions flow rate varied significantly as a result of changing the height of the infusion bag from 60 to 120 cm above the point of outflow. The flow rate increased with 61.2 % ± 0.01 % from 25.0 ± 0.0 to 40.3 ± 0.5 ml/min (mean ± SD) for a 14G catheter. This catheter had the largest diameter of the catheters tested. Catheter diameter size also influenced the flow rate significantly, the largest difference was 2.9-fold (95 % confidence interval, 2.84–2.96) between the 14G and 22G catheter when the pump was placed 120 cm above the point of outflow. It was not recommended to use gravity driven pumps for administration of drugs that require accurate delivery such as vasoactive drugs [51]. Kawabata et al. [11] tested the influence of temperature and viscosity on the time required to deliver the total volume of the infusion reservoir. Cancer treatment regimens were simulated, using actual cytostatic medication. Viscosity of the cytostatic medications were related to temperature. The pump evaluated was the SUREFUSER 23, which is a portable disposable infusion pump. The largest deviation was found for a total volume (volume to be delivered) of 250 ml, which was infused in 63 hours and 55 hours for 25°C and 30°C, respectively [11]. Weiss et al. [7] tested a new microvolumetric infusion pump (MVIP) at a nominal flow rate of 0.5 ml/h against a conventional Alaris Asena GH

(IVAC Medical Systems, Hampshire, United Kingdom) syringe pump gravimetrically. Time to first fluid and time until achieving 95 % of the steady state nominal flow rate value were assessed. Results were presented in mean ± SD. Time to first fluid delivery was 10.5 ± 4.1 and 10.8 ± 4.0 seconds with a low mechanical compliance 20-ml and a 10-ml syringe, respectively, for the conventional pump. For the conventional pump steady state (95 % of nominal flow) was 2.0 ± 0.8 and 12.9 ± 7.4 for the 10 and 20 ml syringe. The fastest steady state start-up was 8.8 ± 3.9 for the MVIP. It was found that the novel MVIP concept showed to eliminate most of the problems during the initial start-up. In addition, most problems during steady state flow and vertical pump displacement were improved [7]. Capes et al. [52] investigated two pumps, the Graseby MS16A (Watford, United Kingdom) syringe driver and the spring driven Springfusor 30 (Go Medical Industries Pty. Ltd. Subiaco, Australia). These pumps were used for patient controlled subcutaneous analgesia infusion. The percentage that the flow rate was within 20 % of the nominal flow rate over 35 minutes was measured. This was 91.9 % and 100 % for the Graseby and Springfusor, respectively. The percentage within 5 % of the nominal flow rate over 35 hours resulted in 58.2 ± 13.2 % and 100 % for the Graseby and Springfusor, respectively. However, the Sprinfusor deviated from +10 % to -10 % over 35 hours in an almost linear fashion. Temperature had some effect on the Springfusor. The accuracy was 100 % within the 20 % of the nominal flow rate and 97.4 ± 3.0, for 25°C and 30°C, respectively. Measurements were performed according to an adaptation of the Association for the Advancement of Medical Instrumentation (AAMI), the International Organization for Standardization (ISO), and the International Electrotechnical Commission (IEC) method [52]. Seo et al. [53] evaluated a wearable ambulatory IV infusion device (AIVD) prototype using an infrared drip chamber measurement method. The device was able to deliver flow rates between 36 and 90 ml/h with less than 10 % error [53]. Ilfeld et al. [20] tested six portable pumps for flow rate accuracy and consistency using a gravimetric setup. The pumps provided ± 15 % of the nominal rate for 18 % - 100 % of their infusion duration. Increasing the temperature by steps of 4°C had different effects on the infusion rates for each model. However, generally, the flow rates increased for each model tested, with ranges of 0 % to 33 % flow rate increase [20]. Two benchmark studies investigating elastomeric pumps were found. Mohseni et al. [54] measured the flow rate accuracy after repeated use of 10 different elastomeric pumps (BOT-802, Nanchang Biotek Medical Device Company, Nanchang, China) because erroneous delivery times of analgesia were reported after repeated use of the same elastomeric pump. To simulate the repeated use, the same elastomeric pump was refilled and re-used for three times. The flow rates were measured gravimetrically using a microset with 100 ml capacity. Significance of evaporation was considered and temperature was kept at body temperature. Elastomeric pumps tend to start higher than the nominal flow rate, this was also the case with the pumps evaluated in this study. At the start, the flow rate was about 6.75 ml/h, while the nominal flow rate was 5 ml/h. After about four hours the flow rate remained within 5.75 and 4.75 ml/h for the rest of the total infusion time of 20 hours. This profile was similar after repeated use, therefore, it was concluded that repeated use of elastomeric pumps

is safe [54]. Weisman et al. [55] evaluated five different elastomeric pumps for accuracy during a total infusion time of about 40 to 70 hours, gravimetrically. The flow rates varied typically between -30 % and +30 % of the nominal flow rate for almost all of the pumps for the total infusion time. However, the ACTion pump AMBU Inc. (Glen Burnie, Maryland, USA) was the most accurate pump as it infused within ±15 %, from the beginning to the end of investigation [55].

3.4 Theoretical modeling studies

We also found six studies that investigated flow rate variability theoretically. For Lovich et al. [8,18] the reason for modeling was to formally investigate the effects of dead volume and carrier flow. Moreover, Lovich aims to raise awareness that the dead volume is a 'drug reservoir'.

Lovich et al. [8] derived relatively simple mathematical models, a plug-flow model and a well-mixed model, to describe the flow of drugs within the dead volume. The model simulated two pumps, one carrier flow pump and one drug flow pump. In the plug-flow model, the drug and carrier flow mix instantaneously at the mixing point. In the well-mixed model, the mixture inside the dead volume is always uniform. The model was tested by measuring the concentration of a model drug using a spectrometric setup. The experimental data generally showed features of the plug-flow model as well as the well-mixed model. Lovich et al. stated that 'The models predict a lag in response time to changes in carrier or drug flow, which is proportional to the dead-volume and inversely related to the total flow rate'. Increasing the carrier flow rate caused a temporary bolus [8]. Lovich et al. [18] also used a similar approach to investigate a specific clinical case, involving the infusion of phenylephrine as a model drug. However, the model developed was generic, and describes the effects on the mass of drug delivered to the patient after flow rate interventions for any of the two pumps. Cutting off the carrier flow was found to reduce drug delivery profoundly. Moreover, after flow rate interventions disrupted the drug delivery, it was found that it took longer to reach the steady state flow rate with a large dead volume, slower carrier flow or larger stock-drug concentrations. Lovich et al. stated shat "after a change in carrier flow or drug dosing, a significant lag is possible before drug delivery achieves steady state" [18]. Murphy et al. [16] developed a mathematical model to conveniently alter infusion component parameters in order to study flow dynamics that would otherwise be difficult to observe in an *in vitro* situation. Murphy applied mechanical compliance and flow resistance. The model was compared to experimental results conducted in an earlier experiment, in which two syringe pumps were connected to a common central line. The end of the infusion line was occluded while the pumps continued to deliver fluid. This simulated the occlusion of a cannula, which may occur in clinical practice. The nominal flow rates were 10 and 1 ml/h. Although the line is occluded, 'internal flow' was possible because of the mechanical compliance of the system, in which the excess fluid is accommodated for by the expanding compliant infusion components. After the occlusion was released, the expanded infusion components typically convert the excess fluid into a bolus until the pressure inside the

system is balanced again. Mechanical compliance and resistance of the syringes and infusion lines were partly calculated and partly experimentally determined. A mechanical compliance of 0.8 x 10^{-11} m^3 / Pa (0.8 x 10^{-8} l / Pa) was found for a representative 50-ml intensive care syringe pump with an 1.5 m extension line with an internal diameter of 1.5 mm (CareFusion, San Diego, CA). After the infusion line was released, the experiment found a bolus of 0.8 ml, the simulation model predicted 0.9 ml [16]. Jayanthi et al. [19] studied the effects of cannula length. IV cannulae of sizes 14 G, 16 G, 18 G and 20G ('Venflon' Becton Dickinson, Helsingborg, Sweden). 'Stitch cutter blades' (Swann Morton Ltd., Sheffield, UK) were used to shorten the cannulae . The 20G cannula was 32 mm in length, the rest were 45 mm in length. Flow rates between approximately 90 to 400 ml/min were observed. Jayanthi stated that "Mathematical calculations performed using Hagen-Poiseuille's law predicted an increase of 40 % in flow rates when the IV cannulae were shortened by 13 mm" [19]. However, *in vitro* measurement results showed an increase of only 4 - 18 %. Jayanthi attributed the difference to turbulence. In-line air bubbles were stated as a possible cause for turbulence, although it was attempted to remove air bubbles. Measurements for the *in vitro* validation measurements were performed using an Urodyn 1000 flowmeter (Dantec, UK) [19]. Ma et al. [13] used the previous developed mathematical derivations of Lovich et al. [8,18] to analyze "continuous intravenous infusions in pediatric anesthesia" [13]. The effects of "patient weight, infusion system dead volume, drug and carrier flow rates, along with drug stock concentration and dose, on propofol and remifentanil delivery to the circulation" [13] were studied. A lag time related to dead volume and flow rate was found, the effects were the most prominent for neonates. The analysis showed the 'potential importance of factors influencing drug delivery to the patient's circulation, focusing on propofol and remifentanil administration to small patients' [13]. Levine et al. [56] constructed low-pressure and high-pressure models and compared to two difference multi-lumen stets, TIVA 3 way set with 2 anti-syphon valves and back-check valve' (Cardinal Health, Dublin, OH, USA, product number 500-003 AMS) and the 'Trifuse, 3 clave' (ICU Medical Inc, San Clemente, CA, USA, product number 011-C4290). The Cardinal consisted of three arms, the longest was 8 cm with an inner diameter of 1.68 mm. The ICU Medical also consisted of three arms of 18 cm length and an inner diameter of 1.19 mm. The experiments were performed with and without BD (BD Medical, Franklin Lakes NJ, USA) Insyte IV cannulae (14G, 16G, 18G, 20G and 22G). The hypothesis was that according to the Poiseuille equation, narrow and long multi-lumen extensions would impede the flow rate. A pressurized infusion system was tested *in vitro* by measuring the different times of a certain amount of fluid to flow into an open burette. It was found that the flows were reduced using both multi-lumen extensions by maximally 76 %, the effects were the most prominent for large cannulae. Moreover, Levine et al. advised manufacturers to provide information on the diameters with their disposables [56].

4 DISCUSSION

We found 53 studies of which six were theoretical modeling studies and 45 were *in vitro* measurement studies. From the measurement studies the majority explicitly investigated a physical cause of either mechanical compliance, flow resistance or dead volume. In the following subsections, we discuss the findings from the literature, focusing on the physical causes of flow rate variability, in the light of the four questions stated in the methods section.

4.1 Role of mechanical compliance, flow resistance and dead volume in flow rate variability

Mechanical compliance and resistance were mostly investigated in relation to start-up of the flow rate [6,22,23,27,30,57] but also in relation to a delayed occlusion alarm [48,49,58]. However, other effects affecting start-up times were also found. Lönnqvist et al. [32] attributed a bolus following after vertical displacement of the pump to design flaws in syringe pumps. Mechanical compliance was not stated as a physical cause, instead a gap between the plunger and the syringe driver was indicated as a source for the flow rate variability after vertical displacement. The disposables used were not specifically rigid and the mechanical compliance of the disposables were not given either. It remains, therefore, unclear what fraction of the delay is contributed by the gap and what fraction is contributed by the mechanical compliance. However, Neff et al. [29] found a similar design problem with a pump using non-compliant disposables. Besides pump start-up and other flow rate changes, vertical displacement causes flow rate variability due the mechanical compliance in the system. It was generally found that an upward motion is followed by a bolus, i.e. a temporary flow rate increase, and downward motion is followed by reduced flow output [6,7,24,31–33,57]

Resistance accentuates the effects of mechanical compliance; Neff et al. [27] stated that a combination of resistance and mechanical compliance may prolong start-up times. This statement is supported by modeling studies that use the RC-time as a measure for duration of the start-up effects, in which the RC-time is the product of flow resistance R and mechanical compliance C [59]. Resistance is largely related to the diameter and the length of the infusion tubing. Especially vascular access devices such as catheters are resistant. For example, Angle et al. [35] measured the pressure using a pressure gauge for several Peripherally Inserted Central Catheter (PICC) lines. PICC lines are specific central venous vascular access devices. The flow rate was calculated according the Poiseuille law, with the assumption that the PICC lines were not significantly compliant. Angle et al. found that the inner diameter of the PICC line was related to the flow capacity. Resistance was specifically given for each PICC line [35]. Le Noel et al. [39] found that the actual flow rate in a fast peristaltic infusion pump was lower than the preset nominal flow rate using different catheters with different diameters. Resistance was explicitly stated as the cause [39]. Non-linear resistance occurs with several types of valves, used to prevent backflow. It has been shown that this causes flow rate variability, usually in form of flow

rate reduction or an additional delay in start-up time [3,9,12,31,36]. McCarroll et al. [9] explicitly recognized that the valves provided a high resistance to flow. However, the resistant effects of valves is non-linear and the effects of valves on flow rate were not always recognized as resistance in all studies found.

Dead volume or internal volume was related to central infusion lines, manifold or the entire infusion set [2,3,10,40,41,43,44]. Dead volume was also associated with vascular access devices such as catheters [17,45,46]. Oualha et al. [45] found that the measured delay time due to dead volume was longer than the theoretical delay time. Oualha et al. attributed the difference to shear forces. It was also theorized that diffusion might be responsible [45]. However, it is unlikely that this has a significant impact, given the flow rate and fluid properties of the watery fluid as predicted by the number of Péclet. Moreover, other differences in the uniformity of the drug concentration in the dead volume, described earlier by Lovich et al. [8] may explain the differences found delay. Another possibility is that the compliance of the infusion setup plays a significant role. Modeling studies found that a combination of flow resistance and mechanical compliance may alter the flow rate onset. Therefore, this delay is superimposed on the dead volume effects [59]. If the setup becomes more complex it is expected that it can still be simulated by a more advanced model incorporating mechanical compliance, flow resistance and dead volume effects. This has been done to some extent [8,16,18].

Besides the major physical effects of mechanical compliance, resistance and dead volume, turbulence in relation with air bubbles was mentioned as a possible source of flow rate variability [19]. However, in most infusion applications the flows are too low. In these cases, the Reynolds number predicts that there will be no turbulence. Also temperature and viscosity of the infused liquid were found as factors influencing the flow rate [11,20,39,52]. Large temperature changes and viscous medication are not common, at least on the intensive care, where critical medications are ordinarily used. The design flaws stated earlier [29,32] are also an effect not directly related to mechanical compliance, resistance or dead volume. However, design flaws such as gaps between the syringe drivers and the syringe have been improved in the newer models of syringe pumps. Furthermore, Sarraf et al. [30] found that the start-up delays were correlated to flow rates in an asymptotic fashion which is expected from the elastic stress/strain properties of the infusion material [30].

In summary, it is likely that mechanical compliance, resistance and dead volume remain the most important physical causes of flow variability in infusion.

4.2 Components with the largest contribution to the system´s mechanical compliance

Kim et al. [58] found that the syringe was the most compliant component in a syringe infusion setup, and stated that the largest portion of the mechanical compliance is located in the latex plunger of the syringe. We also found that syringes were the most important source of mechanical compliance [4,59]

Some other sources of mechanical compliance were found too. Infusion lines were also stated as a source for mechanical compliance [24,30] as well as air bubbles [34]. Besides the syringe, the infusion lines may also act as a reservoir for fluid after lowering the pump, which causes the flow rate to reduce. Weiss et al. [24] demonstrated that some brands of infusion lines clearly contributed to the total mechanical compliance of the whole system after vertical displacement of the pump [24]. To what extent the infusion lines contribute to the entire system mechanical compliance as opposed to other components was not quantified. Air bubbles can be a relatively large source of mechanical compliance as well. However, we were not able to find a source about the regularity of significantly compliant in-line air bubbles in clinical practice. Furthermore, the pump itself was mentioned as a source of mechanical compliance [29]. Neff also found that pump design caused significantly different flow rate variability during vertical displacements of several types of pumps with the same syringe [57]. Whether this was due to mechanical compliance in the syringe driver or another problem was not specifically stated. The start-up times obtained by Weiss et al., Neff et al. and Schmidt et al. [22,27,28,60] for different syringes and syringe sizes were in correlation with the calculated mechanical compliance. Moreover, the mechanical compliance was closely related to the syringe plunger area [22]. However, it was also found that for some brands of syringes the mechanical compliance was related to the filling volume. It was concluded that some syringe walls are also compliant. Nevertheless, Weiss concluded that the plunger accounted for at least 2/3 of the mechanical compliance [60]. The correlations between syringe properties such as syringe size, plunger area and flow rate onset time demonstrated that the syringe is the most probable source of mechanical compliance in syringe pump infusion systems. The mechanical compliance values varied from 9.0×10^{-9} – 2.1×10^{-8} l/Pa [4,22,57,60]. It should be noted that the precise values of mechanical compliance that were presented are based on the entire infusion setup. However, since the syringe was found to be the most important source of mechanical compliance [26], syringes with similar volumes are eligible for inter-comparison between studies.

4.3 Theoretical models of infusion systems

We have presented the main purposes for developing theoretical models for infusion systems in the results. In addition, Ma et al. [13] stated that managing continuous drug infusion requires not only an understanding of pharmacokinetics inside the patient. It also requires an understanding of the system delivering the drug into the bloodstream outside the patient. This can be accomplished by modeling. In our opinion, another reason, not stated in literature, can be that modeling studies are able to conveniently isolate, e.g. physical effects associated with mechanical compliance, from other physical effects. This is more difficult in *in-vitro* laboratory experiments.

The studies from Lovich et al. [8,18] and Ma et al. [13] provide a straight-forward description of the dead volume effect. However, an effort was made to accommodate for different mixing effects when drug flow mixes with carrier flow at the mixing point. A plug-flow model assumed that the drug and carrier flow mix perfectly at the mixing point

and, subsequently, travels as a plug toward the patient. Conversely, a well-mixed model assumed that the concentration in the drug is uniform everywhere in the dead volume. The time required to reach steady state was three times longer in well-mixed model compared to the plug-flow model. It was found that the actual time required to reach steady state was between the boundaries defined by the plug-flow and well-mixed models [8]. It is also stated that carrier flows might introduce diffusion, for which the model was not able to accommodate. It remains controversial whether diffusion is actually a significant effect at the flow rates typically used on the intensive care or operation room. Another limitation of the model was that it was unable to account for variable carrier flow rates, while carrier pumps are often gravity driven volumetric pumps, in which the flow rates fluctuates [8,18]. Mechanical compliance and resistance of the infusion system were also not incorporated in the model used by Lovich et al. and Ma et al. [8,13,18]. It was shown that these effects do play a significant role in flow rate variability in infusion systems [14]. Conversely, Murphy et al. [16] were able to simulate the flow rate variability due to the properties of mechanical compliance and resistance of the infusion setup, but did not incorporate the dead volume effect. However, to simulate the actual resulting drug delivery of a clinically relevant infusion setup, the dead volume of the central infusion line and catheter has to be included in the model as well. The modeling studies found in this literature study typically considered a simplified two-pump multi-infusion situation. Although this makes the physical effects that were investigated comprehensible, in clinical practice, a multi-infusion setup usually consists of much more than two pumps. A model incorporating more than two pumps might therefore give useful insights in realistic clinical medication schedules.

5 CONCLUSIONS

In order to minimize the negative effects of flow rate variability, reduction of dead volume [8] and mechanical compliance [22] was recommended. However, this effect cannot be completely removed. First of all, the patient should be able to move. So some distance between the pump and the patient should be maintained, especially in the case of an incubator where the pumps are situated outside the incubator. Thus, there will always be some dead volume. Secondly, infusion lines should be flexible and therefore at least somewhat compliant. In case of completely rigid lines, vascular access devices such as catheters can easily be damaged as a result of movement. However, using more rigid and small syringes is recommended for very low flows of critical medications such as inotropics. Thirdly, shared dead volume of a multi-infusion setup cannot be avoided in every case. The diameter of a vascular access device is limited because the size of blood vessels where the catheter is inserted is limited. This is especially evident in small children such as neonates. Lowering the volume of tubing by reducing the diameter increases the resistance [35]. Consequently, flow resistance is inevitable.

The physical effects of mechanical compliance, resistance and dead volume were recognized in the predominant majority of the studies found. Moreover, it was concluded that these physical effects are the principal causes of flow rate variability in infusion. Syringes were the most important source of mechanical compliance and, therefore, the principal cause of the delayed onset of flow rate and delayed occlusion alarm times.

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Table 1. Overview of the studies found in the review.

No	Author	Measurement Method	Nominal Flow Rates	Pump Type*	Objective	Physical Cause†
1	Weisman (2014) [55]	**Gravimetrically** - Readability: 0.1 g - Repeatability 0.1 g - Sample time 1 h - Capacity 4000 g	7 - 10 ml/h	**Elastomeric pump** (five different types) ACTion Pump (Ambu, Glen Burnie, Maryland), GoBlock-SF (B. Braun, Bethlehem, Pennsylvania), ON-Q C-bloc (I-Flow, Lake Forest, California) MedFlo MultiRate (MR) (Acacia Inc, Brea,California), Infusor LV Multirate (Baxter, Round Lake, Illinois).	Pump evaluation for accuracy [55].	-
2	Mohseni (2014) [54]	**Gravimetrically** - Capacity: 100 ml	5 ml/h	**Elastomeric pump** BOT-802, Nanchang Biotek Medical Device Company, China)	Pump evaluation for accuracy after repeated use [54].	-
3	le Noel (2014) [39]	**Gravimetrically** - Sample time: 30 s	100 – 400 ml/min	**Peristaltic pump** (TGV 600; Gamidatech, Eaubonne, France)	Testing of influence of two catheters diameters using a fast infusion pump en solvent related to the blood viscosity [39].	Resistance Temperature
4	Eijk (2014) [31]	**Flowmetry** Thermal mass flowmeter Coriolis mass flowmeter - Sample time: 0.01 s	0.1 ml/h	**Syringe pump** Perfusor fm (B.Braun Melsungen, Germany)	Evaluation of check valves [31].	Resistance

5	Sarraf (2014) [30]	**TRN001 isometric transducer.** - Sample time: 0.1 s	20 – 400 ml/h	**Syringe pump** Graseby 3400 pump (Marcal Medical, Millersville, MD)	Pump benchmark and Syringe evaluation. Start-up time, update time evaluated [30].	Compliance Resistance
6	Lovich (2013) [40]	**Spectrometry** - Sample time: 60 s	3, 10 ml/h	**Syringe pump** (Medfusion 3500, Smiths Medical, Lower Pemberton, UK)	Dead volume assessment of manifold using carrier flow [40].	Dead Volume
7	Seo (2014) [53]	**Infrared drip chamber measurement / 'Measuring volume in reservoir'**	40 – 100 ml/h	A wearable ambulatory intravenous infusion device (AIVD) prototype	Pump evaluation on errors [53].	-
8	Foinard (2013) [44]	**Spectrometry** **Gravimetrically** - Readability 0.1 mg - Sample rate: 60 s (for both)	Carrier: 90 ml/h Other: 7 – 14 ml/h	**Syringe pump** (Module DPS, Fresenius, Bad Homburg, Germany) **Volumetric pump** one volumetric pump for the carrier fluid infusion (Module MVP, Fresenius, Bad Homburg, Germany)	New disposable evaluation [44].	Dead volume
9	Oualha (2014) [45]	**HPLC (retrospective measurement)**	2 – 4 ml/h	**Syringe pump** DPS, Fresenius Vial, Brezins, France)	Evaluation of dead volume in CVC [45].	Dead volume
10	Kim (2013) [26]	**Gravimetrically**	-	**Syringe pump** (PILOTE ANETHESIE 2 IS, Fresenius Vial, Le Grand Chemin, Brezins, France).	Evaluating the effect of priming on TCI (target-controlled infusion) performance [26].	Compliance

11	Medlicott (2013) [47]	**Spectroscopy** - Sample time: 5 min - Mixture: dyes	3.8, 18.7 ml/h	**Syringe pump** Colleague volumetric neonatal infusion pump, Baxter Healthcare (Auckland, New Zealand). **Volumetric pump** Graseby syringe driver (Graseby Medical, Hertfordshire, UK), T34 syringe pump (REM systems Ltd, Auckland, New Zealand) and Asena CC syringe pump (CareFusion, Auckland, New Zealand).	Simulation of gentamicin delivery to neonates [47].	-
12	Pierce (2013) [51]	**Gravimetrically** **Graduated cylinder** - Accuracy: 0.5 ml **Balance** - Accuracy: 0.01 ml	0 – 1998 ml/ min	**Volumetric pump** (Sigma Spectrum, Medina, NY)	Evaluation of drip chamber (benchmark) [51].	-
13	Liu (2013) [37]	**Time till empty**	~ 50 – 400 ml/min	**Volumetric pump**	Influence on flow rate of cannula [37].	Resistance
14	Tsao (2013) [2]	**Spectrometry** - Sample time: 1 min - Mixture: dyes	Carrier: 10 ml/h Other: 5 ml/h	**Syringe pump** Medfusion 3500 (Smiths Medical, Dublin, OH, USA)	Flow rate interaction in low flow NICU simulation [2].	Dead volume
15	Brotschi (2012) [33]	**Gravimetrically** - Sensitivity 0.1 mg - Sample time: 10 s	0.5, 1, 2 ml/h	**Syringe pump** Alaris Asena GH syringe pump (IVAC Medical Systems, Hampshire, UK)	Influence of in-line filter. Start-up time, variability, Influence of vertical pump displacement evaluated [33].	Resistance Compliance

16	Lannoy (2012) [41]	**Spectrometry** - Mixture: pharmaceuticals - Sample time: 6 s - UV spectrum **Gravimetrically**	Protocol 1: Carrier: 90 ml/h Other: 7 ml/h Protocol 2: Carrier: 350 ml/h Other: 65 ml/h	**Syringe pump** (Pilote A2; Fresenius Vial, Bre´zins, France) (accuracy 2 % of the set flow rate) **Volumetric pump** (Optima MS; Fresenius Vial, Brezins, France).	Interrupting and resuming carrier flow with an inotropic on the syringe pump [41].	Dead volume
17	Kawabata (2012) [11]	**Total volume measurement and time measurement**	~ 5 ml/h	**Elastomeric pump** Portable disposable infusion pump (SUREFUSER®A, Nipro Corporation, Osaka, Japan)	Influence of temperature and viscosity on the total volume of the drug solution in SUREFUSER®A and the duration of infusion [11].	Temperature Viscosity
18	Ellger (2011) [36]	-	0.1, 1.0 ml/h	**Syringe pump**	Test of non-return valves in preventing backflow [36].	-
19	Lannoy (2010) [42]	**Spectrometry** - Mixture: pharmaceuticals - UV spectrum **Gravimetrically**	Carrier: 35, 70, 115 ml/h Other: 7 ml/h	**Syringe pump** (Pilote A2, Fresenius Vial, Bre´zins, France) **volumetric pump** (Optima MS, Fresenius Vial, Bre´zins, France)	Testing the characteristics of several infusion sets, varying in dead volume and an anti-reflux valve [42].	Dead volume Resistance
20	Levi (2010) [10]	**Spectrometry** - Mixture: dyes - Sample time: 1 min (for the ‘infusion pump’)	Carrier: 8.0 ml/h Other: 0.1, 0.2 ml/h	**Syringe pump** Baxter, Model Automatic Syringe 50 (Baxter Inc., Deerfield, IL, USA) **Volumetric pump** Baxter Colleague 3cx (Baxter Inc.) quoted as ‘infusion pumps’.	Evaluation of syringe and volumetric pump for accuracy and precision [10].	Dead volume

21	Schmidt (2010) [28]	**Gravimetrically** - d = 0.1 mg - Sample Time: 1 min	0.4, 0.8, 1.0 ml/h	**Syringe pumps** Pump A, Terumo Terufusion Infusion Pump TE-331 (Terumo, Tokyo, Japan) Pump B, Braun Perfusor Compact (B.Braun, Melsungen, German)	Testing different syringes for start-up time [28].	Compliance Resistance
22	Moss (2009) [43]	**Spectrometry** - Mixture: dyes - Sample time: 1 min	Carrier: 10 ml/h Other: 3 ml/h	**Syringe pump** Dual channel syringe pump (Harvard Clinical Pump, Harvard Clinical Technology, South Natick, MA, USA)	Analysis of traditional stopcock manifold against a micro infusion set. Onset time evaluated [43].	Dead volume
23	Bartels (2009) [46]	**Spectrometry** - Mixture: dyes - Sample time: 1 min	Carrier: 2, 2 ml/h Other: 0.5 ml/h	**Syringe pump** dual-channel syringe pump (Harvard Clinical 2 pump, Harvard Clinical Technology, South Natick, MA).	Analysis of double lumen catheter. Onset time evaluated [46].	Dead volume
24	Decaudin (2009) [3]	**Spectrophotometric** - Mixture: pharmaceuticals - Sample time: 30 s - Recovery: 99.5 %–101.0 % - UV spectrum	Carrier: 90 ml/h Other: 15, 10, 7 ml/h	**Syringe pump** Pilote A2 (Fresenius Vial France; flow rate accuracy 1 % on drive mechanism) **Volumetric pump** 1 Lbag (Maco Pharma, Tourcoing, France).	Evaluation of infusion set length, dead volume and the presence of an anti-reflux valve [3].	Dead volume

25	Ilan (2008) [48]	**Pump occlusion alarm time**	2, 10, 100 ml/h	**Peristaltic pump** Sigma 8000-plus (Sigma, Medina, NY) Graseby 3000 (Smiths Medical, Watford, Herts, United Kingdom) Baxter colleague (Baxter, Deerfield, IL) Alaris 7230B (Alaris Medical Systems, San Diego, CA)	Analysis of occlusion: time-to-alarm in four peristaltic infusion devices [48].	-
26	Lovich (2007) [17]	**Spectrometry** - Mixture: dyes - Sample time 1 min	Carrier: 10, 60 ml/h Other: 3 ml/h	**Syringe pump** Harvard 2 Clinical Pump (Harvard Clinical Technology, South Natick, MA, USA)	Analysis of dead volume of several central venous catheters [17].	Dead volume
27	Neff (2007) [27]	**Gravimetrically** - Sensitivity: 0.1 mg	0.1, 0.5, 1 ml/h	**Syringe pump** Asena GH syringe pump (Alariss Medical Systems, Hampshire, UK)	Syringe analysis on size and architecture [27].	Compliance
28	Hall (2005) [61]	**Flowmeter** - Accuracy: 1 % The flowmeter was calibrated to a certain volume.	2.8 – 8.6 ml/h	**Volumetric pump** (Macroflex,Macro Pharma, London, UK) was connected to a blood administration set (C2071B, Baxter Healthcare Ltd, Newbury, UK)	Analysis of flow rate reduction by anti-reflux valves and cannulae [61].	Resistance
29	Davey (2005) [34]	**Gravimetrically** - Sensitivity: 0.01 mg - Sample time: 30 s	1.0 ml/h		Evaluation of influence of air bubbles on delivery [34].	Compliance
30	Dönmez (2005) [49]	**Pump occlusion alarm**	0.5, 1.0, 2.0, 5.0 ml/h	**Syringe pump** 20 JMS SP-100 and 20 JMS SP-500 (JMS, Hiroshima, Japan)	Pump bench test of occlusion alarms with different syringe sizes [49].	Compliance Resistance

31	Weiss (2004) [7]	**Gravimetrically** - Sensitivity: 0.1 mg - Sample time: 1 s	0.5 ml/h	**Microvolumetric infusion pump (MVIP)** Prototype microfluidic device using an infusion bag **Syringe pump** Alaris Asena GH syringe pump (IVAC Medical Systems, Hampshire, United Kingdom)	Influence of vertical displacement on low flows [7].	Compliance
32	Ilfeld (2002) [20]	**Gravimetrically** - Sample time: 1 min	5.0, 4.16, 4.0 ml/h	**Portable pump** (various technologies) Accufuser (McKinley Medical Wheat Ridge, CO) C-Bloc (I-Flow Corp. Lake Forest, CA) MedFlo II (MPS Acacia Brea, CA) Microject (PCA Sorenson Medical West Jordan, UT) Pain Pump (Stryker Instruments Kalamazoo, MI) Sgarlato Sgarlato Labs (Los Gatos, CA)	Test flow rate accuracy, consistency, and profiles of various portable pumps. Total time was measured and compared to the expected time of an empty pump. The tests were done at body temperature and higher temperatures [20].	Temperature Others

33	Neff (2001) [29]	**Gravimetrically** - Sensitivity 0.1 mg	1 ml/h	**Syringe pump** Braun Perfusor compact (Braun, Melsungen, Germany) IVAC P4000 Anaesthesia Syringe Pump (IVAC Corporation, Hampshire, UK) Fresenius Injectomat cp-IS (Fresenius Hemocare GmbH, Bad Homburg, Germany) Arcomed Syramed lSP6000 (Arcomed, Regensdorf, Switzerland)	Evaluation of start-up delays [29].	Pump design
34	Kern (2001) [6]	**Gravimetrically** No further specifications. Pressure was also measured.	1, 2, 3, 5, 10 ml/h	**Syringe pump** Injectomat-C (Fresenious, Oberusel, Germany) Ivac 770 (Ivac, San Diego, CA, USA) Perfusor fm (B. Braun Melsungen Medical, Melsungen, Germany)	Analysis of the effect of lowering the pump (vertical displacement) in a neonatal and adult setting [6].	Compliance
35	Weiss (2001) [38]	**Gravimetrically** - Sensitivity: 0.1 mg - Sample time: 1 s	0.5 – 1 ml/h	**Syringe pump** Fresenius Injectomat (cp-IS, Fresenius AG, Bad Homburg, Germany) Pressure flushing bag	Effects of different flush techniques of arterial line in a pediatric setting [38].	Compliance Resistance
36	Neff (2001) [50]	**Gravimetrically** - Sensitivity: 0.1 mg	1 ml/h	**Syringe pump** IVAC P7000 syringe pump (Alaris Medical Systems, Hampshire, UK)	Evaluation of FASTSTART mode in specific pump [50].	Compliance

37	Neff (2001) [57]	**Gravimetrically** - Sample time: 1 s	1 ml/h	**Syringe pumps** Fresenius Injectomat-S (Fresenius, Bad Homburg, Germany) Fresenius Injectomat-IS (Fresenius, Bad Homburg, Germany) IVAC P4000 Anaesthesia Syringe Pump (IVAC, Hampshire, UK)	Analysis of the effects of vertical displacement for different infusion pump models [57].	-
38	Weiss (2000) [22]	**Gravimetrically** - Sensitivity 0.1 mg - Sample time: 1 s	0.5, 1, 2 ml/h	**Syringe pump** IVAC syringe pump (IVAC-Alaris, IVAC Medical Systems, Hampshire, United Kingdom)	Evaluation of the effects of syringe size [22].	Compliance
39	Kim (1999) [58]	**Gravimetrically** **Time to occlusion alarm**	1 ml/h	**Syringe pump** Medfusion pump, model 2001 (Medifusion, Medex Inc, Duluth, GA, USA)	Three different syringe sizes investigated on the accuracy of delivery and the time to occlusion alarm [58].	Compliance
40	Weis (2000) [24]	**Gravimetrically** - Sensitivity 0.1 mg - Sample time: 1 s	0.5, 1, 1.5 ml/h	**Syringe pump** (Model 711±1G, IVAC, San Diego,Ca., USA)	Evaluation of infusion line compliance under influence of vertical displacement [24].	Compliance
41	Weiss (2000) [60]	**Gravimetrically** - Sensitivity 0.1 mg - Sample time: 1 s	1 ml/h	**Syringe pump** (IVAC Syringe Pump P4000, IVAC Medical Systems, Hampshire, UK)	Evaluating the effects of syringe plunger design on vertical displacement. Four syringes were evaluated [60].	Compliance

42	McCarroll (2000) [9]	**Time to first drop** (observer)	2, 10, 50 ml/h	**Syringe pump** Syringe driver IVAC P2000 (IVAC, San Diego, CA, USA)	Evaluation of the effects of anti-syphon valves on start-up time (time to first drop) [9].	Resistance
43	Capes (1997) [52]	**Gravimetrically**	0.388, 1.25 ml/h	**Syringe pump** MS16A syringe drivers (Graseby Medical. Watford. United Kingdom; serial numbers 261. 6293. and 31007) Springfusor 30 short model syringe drivers (Go Medical Industries Pty., Ltd., Subiaco, Australia)	Evaluation of a subcutaneous syringe pump accuracy [52].	-
44	Lonnqvist (1997) [32]	**Gravimetrically** - Detection limit: 10 mg - Sensitivity 10 mg	1 ml/h	**Syringe pump** BD Modular and BD Pilot C (Becton-Dickenson, Brezins, France) Perfusor Securra FT and Perfusor (FM, B. Braun, Melsungen, Germany) IVAC P 4000 (IVAC, San Diego, USA)	Vertical displacement evalutation [32].	Gap in infusion pump Compliance
45	Angle (1997) [35]	**Pressure conversion 'model'**	25, 65, 135, 270 ml/h	**Volumetric pump** (Harvard Apparatus, South Natick, MA)	Evaluation of infusion PICC lines [35].	Resistance

46	Levine (2013) [56]	***Model* and time for defined aliquots of fluid to pass into the open burette (validation)**	0 – 700 ml/ min	**Volumetric pump** (for validation)	Evaluation of multi-lumen extension resistance according to the Poiseuille equation [56].	Resistance
47	Ma (2011) [13]	***Model***	-	**-**	Using model of Lovich et al. to evaluate infusions in pediatric anesthesia [13].	Dead volume
48	Murphy (2010) [16]	***Model***	1 – 50 ml/h	**-**	Effects of volume storage after occlusion [16].	Compliance Resistance
49	Lovich (2006) [18]	***Model***	0, 1.2, 5, 10, 15, 100, 500 ml/h	-	Further investigation of dead volume and carrier flow by alternating the quantities [18].	Dead volume
50	Jayanthi (2005) [19]	***Model***		**-**	Investigating effects of cannulae length [19].	Resistance
51	51 Lovich (2005) [8]	***Model* and spectrometry (validation)**	3 – 640 ml/h	**-**	Investigating dead volume effects [8].	Dead volume
52	Sherwin (2014) [15]	***Review***	-	**-**	-	-
53	Eijk van der (2013) [5]	***Review***	-	**-**	-	-

* *Volumetric pumps includes any volumetric pump using a bag, gravity and an optional flow regulator such as peristaltic techniques.*

† *Primary cause investigated*

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Chapter 2.2

Assessment of drug delivery devices

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ABSTRACT

For critical drug delivery, it is important to have a constant and well-known infusion rate delivered by the complete infusion set-up (pump, tubing, and accessories). Therefore, various drug delivery devices and accessories were tested in this article in terms of their infusion accuracy, start-up delay, response time, and dependency on the viscosity. These measurements were performed as part of the European funded research project MeDD. The obtained results show that the infusion accuracy of the devices is flow rate and accessory depended, especially for low flow rates. Viscosity does not have a significant impact on the flow rate accuracy.

ABBREVIATIONS

EMRP, European Metrology Research Programme; EURAMET, European Association of National Metrology Institutes; GUM, Guide to the Expression of Uncertainty in Measurement; IPQ, Portuguese Institute for Quality; ISO, International Standard Organization; MeDD, Metrology for Drug Delivery; SUD, start-up delay; VSL, Dutch Metrology Institute.

1 INTRODUCTION

Drug delivery devices or infusion instruments are widely used in the clinical environment. Their main function is to provide drug therapy, nutrition, and hydration intravenously to patients. Drug delivery is used for almost all hospitalized patients and for those undergoing home care. Several international studies [1] have stated that the dosage of infused pharmaceuticals is subject to uncertainties that may compromise the patient's treatment. In infusion applications, the dosage is controlled by the flow rate of the infusion pump and a drug solution of known concentration.

In many cases, the actual flow rate is less important than the total delivered volume. However, if drugs with a very short half-life or a narrow therapeutic range need to be delivered, careful control of the actual flow rate is very important to ensure sound patient treatment. This is particularly the case if low flow rates are required, e.g., for patients who can only tolerate a limited amount of fluid intake, such as neonatal babies. For low flow rate applications, the concentration is typically higher, such that deviations in the infused rate can easily cause overdosing or underdosing. This effect underlines the importance of accurate measurement and control of low flow rates [2]. There are various examples where incidents are believed to be caused by an improper infusion rate, see, for example, [3] where various studies are cited.

The actual infusion rate is dependent on the characteristics of the medical devices used. Typically, when an infusion device is started, it takes some time before the target flow rate is reached, which is also known as the start-up delay (SUD). The SUD is related to system flexibility because the initial volume dispensed will lead to an expansion in the system. This is also known as the compliance of the system. Recent studies [4,5] show that two

known main sources of flow rate deviations are caused by the system compliance and the "push-out effect" (time delay in a multi-pump infusion set when just one of the pumps set-points are changed). This paper investigates how the compliance and the SUD depend on several factors, such as several physical parameters, drug delivery devices, and accessories.

The common infusion solutions used in hospitals are aqueous solutions of glucose ($C_6H_{12}O_6$) with a mass fraction of 5 cg/g and sodium chloride (NaCl) at 0.9 cg/g. When there is an incompatibility with the drugs to be administered or in case of hypertensive patients, sodium chloride at 0.45 cg/g is used.

The dynamic viscosity ($h_{20°C}$) and the density ($\rho_{20°C}$) of these solutions (Table 1) are similar to the ones for water, which is used as reference liquid in the calibration of the syringe pumps. However, there are some commonly applied infusion solutions, such as Hespan® and Dextran 40® from BBraun®, which are four times more viscous than water. The dynamic viscosity can be an important parameter, because it directly influences the resistance that can affect the flow rate and its error. The flow rate error will probably be

most affected during startup because higher resistance leads to a larger pressure drop which, in turn, leads to a larger volume increase and start-up delay. Furthermore, different drug(s) (solutions) have different viscosities, which make the viscosity a clinically relevant parameter. For that reason, the infusion pumps should be tested with more viscous reference liquids in order to represent the real operational conditions.

Table 1. Physical properties of the hospital infusion solutions and water.

	$h_{20°C}$ (mPa·s)	$\rho_{20°C}$ (kg/m^3)
Infusion solutions		
5 cg/g $C_6H_{12}O_6$	1,145	1017,5
0,9 cg/g NaCl	1,020	1005,3
0,45 cg/g NaCl	1,011	1001,8
Water	1,002	998,2

To meet this need, a metrological infrastructure that can be used by the health care community has since been developed within the European Metrology Research Programme (EMRP) project called “Metrology for Drug Delivery” (MeDD). This infrastructure consists of calibration facilities to determine the flow rate error for varying operating conditions, such as the viscosity, (back) pressure, and temperature (see also [6]). Furthermore, the compliance can be measured as well as the impact of accessories.

There are several types of drug delivery devices. In this work, a syringe pump. Perfusor Space from BBraun® (BBraun central office, Melsungen, Germany; BBraun Portugal, Barcarena, Portugal) was chosen to be tested using different scenarios, flow ranges, accessories, and various different liquids. In the frame of work package three of the EMRP project MeDD [2], tests were performed by the Portuguese Institute for Quality (IPQ) (Figure 1a) and VSL-Dutch Metrology Institute (Figure 1b) using the gravimetric method. Both, setups and calibration methods used are in accordance with the IEC 60601-2-24 standard [7]. The results are in good agreement with earlier studies [8–10]. However, by taking various accessories and varying operating conditions into account, this current research focuses on additional aspects.

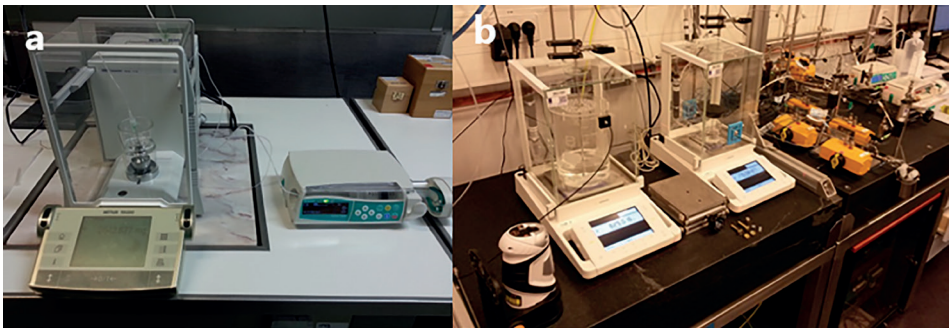

Figure 1. *IPQ setup for syringe pump calibration by gravimetric method (a) VSL setup for syringe pump calibration by gravimetric method (b)*

2 EQUIPMENT AND SCENARIOS

Three different flow rates were studied for the syringe pump: 0.5 ml/h, 2 ml/h and 10 ml/h, and for plastic disposable syringes of different volumes: 10 ml and 50 ml. Each individual test was repeated three times to determine measurement repeatability.

The accessories tested included the following: an infusion line with a length of 1.5 m BBraun®, REF 8722935), an infusion line of 5.5 m [twice a 2 m line (BBraun®, REF 8722862) and once the earlier mentioned 1.5 m], a filter (BBraun® REF 4184637), and a check valve (Icumedical, REF 011-C3302). Further, glucose aqueous solutions with different viscosities (2 mPa s and 4 mPa s) were used in addition to water. All disposables, infusion lines, filters, and so on, were replaced every day and the syringes were replaced when the plunger reached its end.

The following measuring setups (SU) have been studied:

- (SU1) Pump with a rigid syringe connected to the default connections of the micro flow setup, i.e., from the pump directly via rigid tubing and via the default dispersing needle into the measurement beaker;
- (SU2) SU1 with standard syringe;
- (SU3) Pump connected to a typical infusion line (with a length of 1.5 m) and then via the default micro flow setup into the measurement beaker (baseline);
- (SU4) SU3 with elongated infusion line (1 time 1.5 m and twice 2 m infusion lines);
- (SU5) SU2 with a filter installed;
- (SU6) SU2 with a check valve installed;
- (SU7) SU2 with a filling procedure that leads to more entrapped air in the syringe, which resembles the common practice in hospital usage;
- (SU8) SU3 with a typical catheter used in the hospitals to dispense the water in the measurement beaker.

In order to determine the impact of the viscosity on the flow rate error, SU2, SU3, and SU8 were tested with glucose aqueous solutions with different viscosities (2 mPa s and 4 mPa s). The densities of these solutions were determined by an oscillation-type density meter [11], and the nominal viscosity was established through the measured density according to the literature [12,13]. These two solutions, along with pure water, were then tested with the syringe pump at three different flow rates. Each test was carried out three times.

3 PROCEDURE

The procedure to test the infusion devices is similar to that described in [7]. In addition, the balance readings were corrected for the buoyancy forces on the measurement beaker, dispensing needle and collected water. The latter two were relative and were in the order of 0.1–0.2% (depending on the equipment used), whereas the first one depended on the stability of the environmental conditions. For low flow rates (e.g., those lower than 1 ml/h), the buoyancy correction for the measurement beaker is deemed significant. For example, for 0.5 ml/h and a temperature stability of 0.5 °C, this term can take on values up to 0.5 %.

In contrast to [7], the back pressure was approximately zero in these tests, because no flow restrictors were used. In the next phase of the project, we plan to determine the impact of the back pressure on the flow rate error, along with compliance and start up delay.

Meanwhile, the syringes were filled with degassed ultra-pure water [7] and the system was rinsed with sufficient water to ensure that there was no air in the system. The intended flow rate was programmed in the syringe pump, after which the water was collected in a vessel standing on the weighing scale. More details on the calibration facilities used can be found in [6].

3.1 Flow rate error

The relative error ε, obtained in each measurement, is calculated by the following formula:

$$\varepsilon = 100\% \frac{q_{pump} - q_{reference}}{q_{reference}} \quad (1)$$

where q_{pump} is the target flow rate (ml/h) set in the pump, and $q_{reference}$ follows from the balance measurements including corrections.

3.2 Response time and compliance

The response time and compliance were determined for setup SU2 to SU8. For the response time, both the SUD and the delay by doubling or quadrupling of the flow rate were determined. The SUD was defined as the time needed to reach 95% of the target set point after the pump was started. Equally, the delay in doubling the flow rate was defined as the time needed to reach 95% of the new set point (where the new set point was twice

the previous set point). The SUD and the delay times in doubling or quadrupling the flow rate were all based on the mass readings of the balance.

The compliance (C) (ml/bar) is given by the ratio between pressure increase (Δp) (bar) due to an applied volume increase (ΔV) (ml) during the occlusion, which is expressed as:

$$C = \frac{\Delta V}{\Delta p} \; [\mathrm{ml/bar}] \qquad (2)$$

In order to determine the compliance, an occlusion was simulated by closing a downstream valve of the pump (and accessories if used). Thereafter, we measured pressure as function of time. From the measurements, the pressure increase was defined as the maximum pressure that occurs just before the pump gave the occlusion alarm. The pressure was measured with an inline pressure sensor connected via a T-junction. The volume increase followed from the elapsed time to occlusion (response time) multiplied with the flow rate following the set point of the syringe pump. Hence, with this procedure, the compliance can be determined for all pressures that occurred before the occlusion. However, in this work the compliance was only determined for the occlusion pressure, which was approximately 0.65 barg (bar gauge) or 1.65 bara (bar absolute).

The standard ISO-7886-2 [14] describes a similar but more direct way to measure the compliance of a syringe. This is based on adding volume with another syringe and measuring the pressure in a similar fashion. Comparison of both methods revealed that they are in agreement within 30%. This may seem to be a large difference; however, considering the large spread in the measurement results this is a fair number. In this work, the former method is preferred because it offers an easy alternative to determine the flow rate error, stability, response time until occlusion, and compliance all in the same run. Furthermore, standard ISO-7886-2 only takes the compliance due to the syringes into account. The compliance of the syringe pump itself (“pusher”) as well as the accessories and infusion lines can be significant and should also be taken into account, too.

With a simulation model of the drug delivery system, the measured compliance can also be used to determine the SUD. This is because an infusion system can be seen as a network of compliant and resistive tubes. When the flows are considered as laminar, the Hagen-Poisseuille law can be used to describe the flow behavior or velocity profile. A laminar flow is a good assumption because the Reynolds number is typically well below 100. Furthermore, it can be assumed the flow is fully developed as the inner diameter is small compared to the length of the infusion lines. For now, unsteady effects due to temporal or spatial temperature gradients are neglected. The network can then be modelled using standard network theory and Laplace-transformations, from which the SUD can be determined.

3.3 Measurement uncertainty

The overall measurement uncertainty [15] can be derived from the uncertainty of the calibration facility and the standard deviation of the mean of the repetitions. The

measurement uncertainty was evaluated in this study following the Guide to the Expression of Uncertainty in Measurement (GUM) [16]. See [6] for more information on the uncertainty of the calibration facilities used. For the flow rate error, the measurement uncertainty varies between 0.5% for the higher flow rates and up to 2% for the lower flow rates. The standard deviation of the measurement results is the fundamental influencing factor on measurement uncertainty.

4 RESULTS AND DISCUSSION

In this section the results obtained for the flow error, response time and compliance are discussed.

4.1 Flow rate error

Figures 2 and 3 show the flow rate errors for the complete setup (syringe pump including accessories) for 10 ml and 50 ml syringes, respectively, and various accessories.

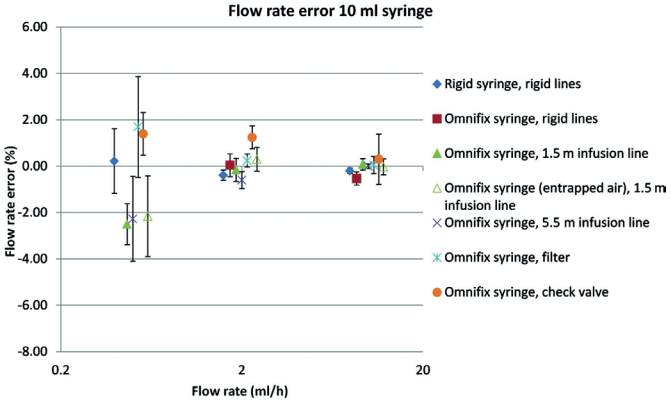

Figure 2. *Relative flow rate error as a function of the target flow rate and various accessories for a syringe volume of 10 ml (SU from 2 to 7).*

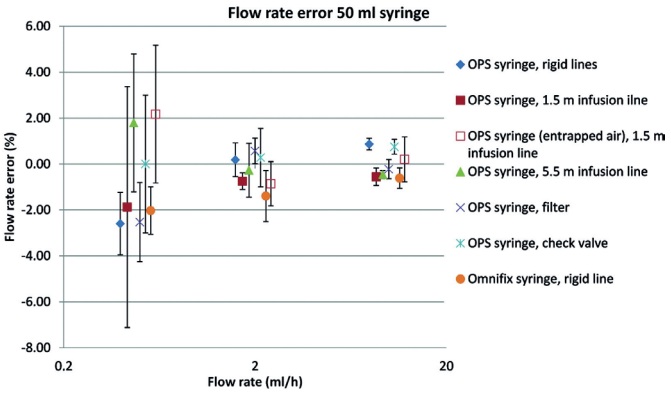

Figure 3. *Relative flow rate error as a function of the target flow rate and various accessories for a syringe volume of 50 ml (SU from 2 to 7).*

The flow rate error is determined as described in (1). In this case, a positive error indicates that the pump is delivering less than its set point (q_{pump} is larger than $q_{reference}$). Hence, a positive error should be regarded as an underestimation of the drug delivered, or the actual delivered drug is less than predicted from the set point. From these results several statements can be made, as listed below.

- The flow rate error is typically larger for decreased flow rates. This is confirmed by results one would expect, i.e., the lower flow rates are beyond the normal usage of a 50 ml syringe.
- The errors using the 50 ml syringe are generally larger than the errors that occur when using the 10 ml syringe.
- In case a filter is included, the flow rate error is shifted in the positive direction. Hence, the pump is delivering less than its set point. This can be explained by more entrapped air in the filter or by a higher flow resistance due to the filter.
- For flow rates of 2 ml/h and 10 ml/h, it can be concluded that the pump is performing within its claimed accuracy specifications of 2% [17]. However, for a flow rate of 0.5 ml/h, the same conclusion cannot be made because the uncertainty bars cross the 2% error range. Hence, it cannot be concluded (with 95% certainty) whether the pump is performing within or outside its claimed accuracy specifications.
- A larger spread of results can be found at lower flow rates. This is probably caused by varying material properties and/or dimensions of the syringes.

In Figures 4a – 4c, the flow rate error is plotted for SU2, SU3, and SU8 and for different values of the viscosity. In this context "*w*" stands for the viscosity of water, and "w2" and "w4" stand for two and four times the viscosity of water, respectively.

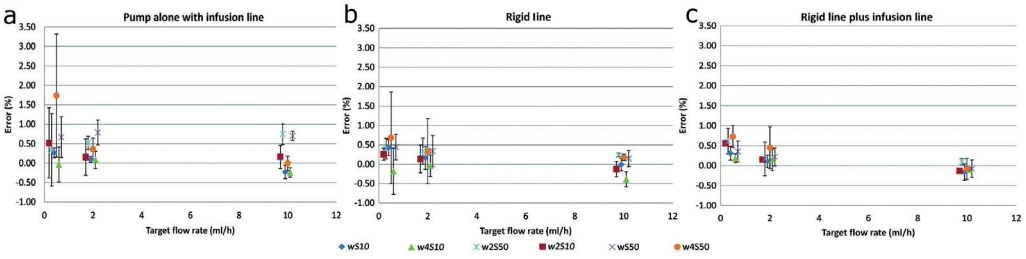

Figure 4. *Relative flow rate error as a function of the target flow rate and viscosity and SU8 (a), SU2 (b) and SU3 (c). wS10 corresponds to water using a 10 ml syringe, w2S10 corresponds to the 2 mPa s solution using a 10 ml syringe, and w4S10 corresponds to the 4 mPa s solution using a 10 ml syringe, the same is valid for the 50 ml syringe.*

From the results obtained for the syringe pump several conclusions can be made, as listed below.

- The errors using the 50 ml syringe are generally larger than the errors in the case the 10 ml syringe is used.

- There is no significant difference in the measured error when using solutions with different viscosities, except for the 50 ml syringe in SU8. In all SU for the 50 ml syringe and for the 0.5 ml/h, higher viscosity produces a higher positive error. This means that the measured flow rate is more underestimated when using *w4* solution.
- A larger spread of results can be found at lower flow rates. This is probably caused by varying material properties and/or dimensions of the syringes.
- Larger uncertainties can be found in SU8 due to the setup's larger instability caused by the flexible infusion line.

4.2 Response time and compliance

In Table 2 the compliance for various scenarios and syringe volumes is shown. The flow compliance is determined as described in (2). The larger the compliance, the larger the "elasticity" of the system and the longer the response times (SUD and delay time in doubling or quadrupling the flow rate). From these results several observations can be made, as listed below.

Table 2. Compliance for various scenarios and syringe volumes.

Scenario	10 ml syringe (ml/bar)	50 ml syringe (ml/bar)
rigid syringe	0.24	N/A
standard syringe	0.21	1.54
standard syringe, 1.5m infusion line	0.20	1.54
standard syringe, 1.5m infusion line, entrapped air	0.22	1.61
standard syringe, 5.5m infusion line	0.44	1.89
standard syringe, filter	0.52	2.10
standard syringe, check valve	0.22	1.54

- The much lower compliance for the 10 ml syringe setups confirms that the syringe has the largest impact on the overall compliance. Further, for a setup including a 10 ml syringe, adding accessories and infusion lines has a much bigger impact in the relative sense.
- For both systems, the inclusion of a filter has the greatest impact when it comes to increasing compliance. This is very likely caused by entrapped air inside the filter. Given that air is more compressible, entrapped air significantly increases the compliance of the system.

Next, the results for the SUD are shown in Figures 5 and 6. From these results, several remarks can be made, as listed below.

- In general it can be stated that, the lower the flow rate, the larger the SUD. The SUD depends on the flow rate because for a lower flow rate, it simply takes longer until the whole system is pressurized (although for the lower flow rates the resistance is slightly lower).
- A larger spread of results can be found at lower flow rates. This is probably caused by varying material properties and/or dimensions of the syringes as well as accessories.

Furthermore, it is more difficult to avoid inclusion of air when the accessories are included in the setup. As air will have a significant impact on the compliance and thus startup delay, this can also result in a larger spread.

- The measured SUD for the 50 ml syringe is comparable to that of the 10 ml syringe, which is in contrast to the measured compliance. This is probably due to the fact that compliance has been determined for the occlusion pressure (approximately 0.65 barg), whereas the required pressure increase during startup is significantly lower. Typically, the compliance increases significantly when the pressure is increased from zero to larger values (thereafter, it levels off or even decreases again). Hence, in case a theoretical model is used to determine the compliance, it is important to have determined the compliance at the right pressure.
- For both systems, the inclusion of a filter has the greatest impact when it comes to increasing the compliance and start up time. Most probably this is caused by entrapped air inside the filter.

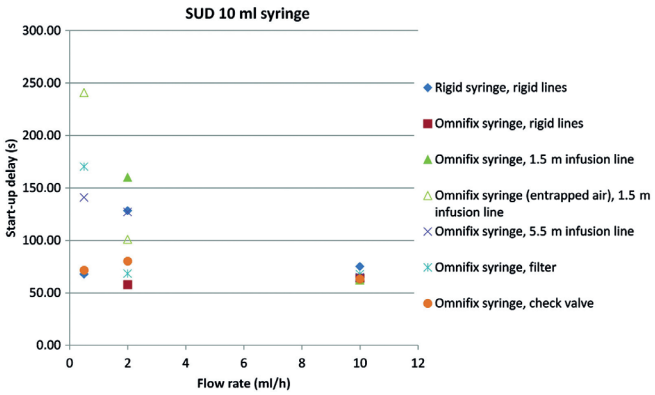

Figure 5. *SUD as a function of the target flow rate and various accessories for a syringe volume of 10 ml. Setup from 2 to 7.*

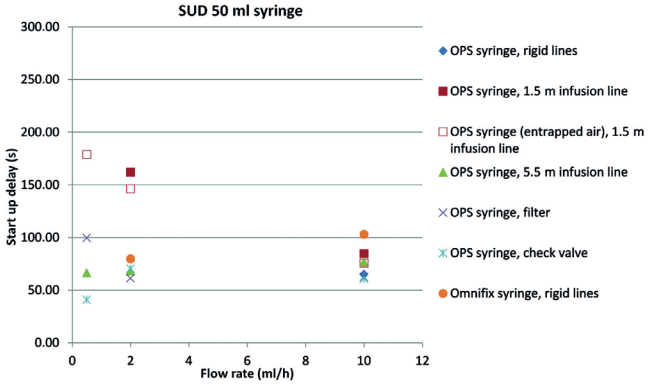

Figure 6. *SUD as a function of the target flow rate and various accessories for a syringe volume of 50 ml. Setup from 2 to 7.*

Finally, Figures 7 and 8 show the response times after doubling and quadrupling the flow rate, respectively.

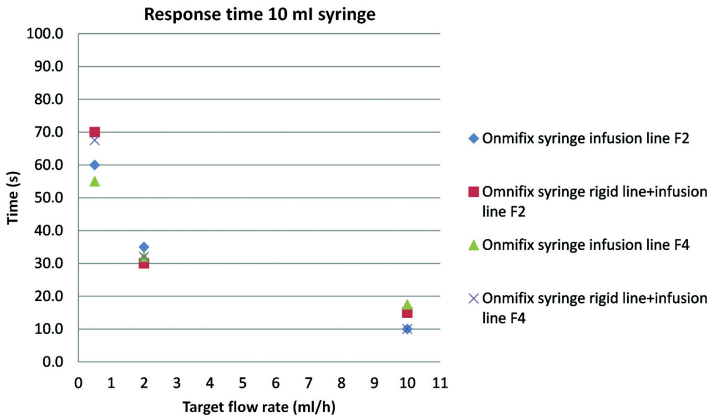

Figure 7. *Response time (time to reach 95% of the final flow rate) as a function of the target flow rate, SU 3 and 8 (F2-double flow rate, F4 quadrupled flow rate) for the syringe pump with a 10 ml syringe.*

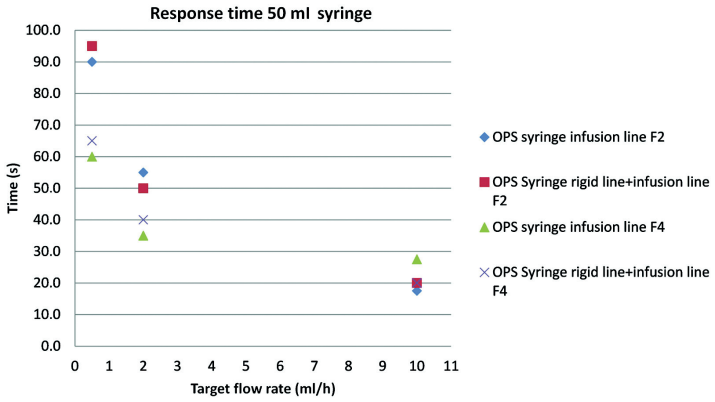

Figure 8. *Response time (time to reach 95% of the final flow rate) as a function of the target flow rate, SU 3 and 8 (F2-double flow rate, F4 quadrupled flow rate) for the syringe pump with a 50 ml syringe.*

These results are obtained for a syringe volume of 10 ml and 50 ml and setups SU8 and SU3. From these results, several observations can be made, as listed below.

- The lower the flow rate, the longer the delay time to reach a steady flow rate after doubling or quadrupling the flow. This is as expected and corresponds to the startup delay and compliance.
- For the larger syringe, it takes more time to reach steady flow than for the smaller syringe.
- The type of setup used only has some influence on the lowest flow rate where the variability of the results is larger.

5 CONCLUSIONS AND FUTURE WORK

Infusion devices must be reliable when used in drug delivery. However, the normal calibration procedure described in IEC 60601-2-24 does not take into consideration the variations when these instruments are used in field applications, e.g., usage of accessories and varying operating conditions are omitted. Furthermore, not all buoyancy corrections are taken into account. Consequently, calibrations at low flow rates may be subjected to significant uncertainties, which can then lead to undesired patient treatment.

The results obtained in this study show that the devices are sensible to variations in use, particularly at small flow rates and when using large syringes. However, the pump generally performs within its claimed accuracy specifications (i.e., the lower the flow rate, the larger the standard deviation of the results).

System compliance is an important characteristic of infusion devices, which can cause temporary flow rate variations induced by set point changes. Particularly at low flow rates, the (syringe) compliance effects are important, because the temporary deviations with respect to the intended set point values are relatively large. Regulatory authorities and hospitals should therefore consider adopting specific standards and guidelines for system compliance when using high risk medication at low flow rates.

Thus far, IPQ and VSL have tested the infusion devices for the impact of viscosity and accessories. The following research is scheduled: impact of back pressure (METAS, Switzerland), impact of temperature (CETIAT, France) and the impact of various syringes (DTI, Denmark). Furthermore, future works will include other syringe pumps and insulin pumps.

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Chapter 2.3

Analytical method for calculation of deviations from intended dosages during multi-infusion

Submitted

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ABSTRACT

In this paper, explicit expressions have been derived for the total volume, central time point, and duration of dosing errors in a multi-infusion set-up. These expressions contain hardware parameters, such as mechanical compliance of syringes, and resistances and lengths of tubes and the catheter, as variables. Our new approach uses the Z-transform to model the contents of the catheter, and after implementation in Mathematica (Wolfram), the explicit expressions were produced automatically. The relative contribution of various factors affecting the dosing errors, such as the Poiseuille mixing effect, can be discerned clearly in the structure of these expressions. Consistency of the resulting analytical expressions has been examined for limiting cases, and three types of in-vitro measurements have been performed to obtain a first experimental test of the validity of the theoretical results.

1 INTRODUCTION

If a patient needs the intravenous administration of medication, it is important for the clinician to understand the basic pharmacokinetics of these medications. However, in recent years, ample evidence has been produced [1-4], showing that physical effects related to the infusion hardware are equally important to understand [7,9]. The clinical relevance of physical effects related infusion hardware has been described in several clinical cases and in vivo studies [13-16,12]. Especially in critical care, on the ICU and the OR, where multiple medications are typically delivered through one single lumen of a thin catheter, these physical effects may cause ambiguous and counter-intuitive discrepancies between the intended dose and the dose that has been actually delivered. This is particularly true after interventions [11]; for example, fast-acting and critical inotropic drugs are often titrated, i.e. the dosing rate is altered by adjusting the flow rate ad hoc, based on the mean arterial blood pressure (MABP).

There are three major factors that can produce significant deviations from the intended medication dosage scheme that is implemented in the form of the flow rate values of the various infusion pumps as function of time: (i) the length of the catheter causes a delay in the administration of the medication into the patient, and the contents inside this line constitutes a memory in which the effects of previous pressure changes are stored. This has been called ”dead volume effect” in the literature [14,8]. Furthermore, (ii) the syringes that are used in clinical practice are far from ideal, because these syringes have a significant non-zero mechanical compliance primarily due to the compressibility of the rubber plunger inside the syringe [10]. As a result, the syringes are no ideal current sources: whenever the pump flow rate setting of one of the infusion pumps in a multi-infusion set-up is changed, the pressures inside the tubes, catheter, and most notably all other syringes change as well. This causes a change in the deformation of the compressible parts in the system, and hence a deviation from the intended flow rates. Finally, (iii) the low velocities of the fluids in catheters ensure that the flow inside these lines will be laminar (low Reynolds number), and hence exhibit a Poiseuille flow profile, in which the fluid particles near the central longitudinal axis of the catheter travel faster than fluid particles near the wall of the catheter, thus giving rise to a ”mixing effect” of its own.

Several infusion simulation studies have attempted to reinforce the importance of these problems by demonstrating the influence of the physical effects of dead volume, compliance and the Poiseuille effect on drug delivery in isolation. (i) There are a number of studies that describe the ”dead volume effect” in isolation from the syringe compressibility (”compliance”) effect [14]. In simple cases, calculation of the ”dead volume effect” is straightforward: If the actual volumetric flow rate u is assumed to be constant, and the internal volume V_{cath} of the single lumen of a catheter (i.e., the internal volume as measured starting from the mixing point, at which the medications from all syringes come together, up to the distal catheter tip inside the vasculature of a patient) is known, then calculation of the ”delay time” t_{delay} , i.e. the time needed for a droplet of medication to travel through the dead volume before it reaches the blood stream of the patient, is simply $t_{delay} = V_{cath}/u$.

In clinical practice, however, the situation is often more complex: the flow rate may vary during the delay time due to changes in the pump flow rate settings, and the actual flow rate also typically differs from the pump flow rate setting value temporarily, due to the effects of mechanical compliance as mentioned above (ii). These compliance effects have been studied in isolation (from the ”dead volume effect”) as well [2,3,18]. Its basic mechanism is a ”capacitor” effect, which has been quantified using the electric analog of a system containing capacitors, and the calculations of the dosing errors have been performed using the Laplace transform.

The third major factor (iii), the mixing effect due to the Poiseuille profile [19], can be described as a convolution, as will be explained in more detail in Appendix. It causes a spreading out of the dosing error in time, in which the first arrival of the dosing error occurs sooner then it would have without Poiseuille mixing effect.

As a result, due to the combination of the effects (i), (ii), and (iii) mentioned above, non-trivial deviations from the intended medication dosages scheme may occur, as will be explained below.

In an earlier paper, we have shown that the ”dead volume effect” on one hand, and syringe compliance (”capacitor”) effect on the other hand, produce opposite deviations from the pump flow rate settings in the actual drug output concentrations, making the net result hard to predict and often counterintuitive [4].

In this paper, however, we focus on the mathematical method of calculating dosing errors in multi-infusion setups in complex situations. The aim of the new method described in this paper is to obtain analytical expressions for the deviations from the intended dosages during multi-infusion that result from the combination of the effects (i) and (ii) described above. These analytical expressions contain dependencies on parameters that represent the physical variables in a multi-infusion set-up, such as: intended flow rates of the various pumps, compliances of the syringes, resistances of the various tubes, height differences within the multi-infusion set-up, etc.

As opposed to conventional numerical simulations, our objective therefore is to obtain explicit analytical expressions for these deviations, in which physical characteristics of the multi-infusion set-up are represented explicitly as variables.

The rationale underlying our objective to obtain these explicit analytical expressions is that we see the need for a tool for clinicians and medical physicist that provides understanding of the role that various physical parameters (i.e., characteristics of the multi-infusion hardware) play in the emergence of a dosing error. In order to make these roles explicit, we will use our new mathematical approach, presented in the method sections of this paper, to explicate these roles in the form of direct mathematical relationships between physical hardware parameters and dosing errors.

In order to make our new mathematical approach work, we used the computing power of a PC in an unconventional way: Instead of using a standard simulation package that produces mere numerical simulations (i.e., producing a single numerical output for each single numerical input), we used the strong symbolic calculation capabilities of the Mathematica package (Mathematica 10, Wolfram Inc., USA) to process Laplace-transforms and Z-transforms analytically. This will be explained in the method section. Furthermore, we have performed in-vitro measurements in order to verify our mathematical results experimentally.

2 METHOD: ANALYTICAL MODEL AND IN-VITRO SET-UP

To start with, we analyse the total chain of causality, from a change in the pump flow rate setting value, up to the moment that a dosing error enters the bloodstream of the patient. As has been mentioned in the introduction, it is essential to recognize that the lumen of the catheter (i.e. the internal volume C inside the catheter, starting from the mixing point M, at which the medications from all syringes come together, up to the distal tip P of the infusion line inside the vasculature of a patient) constitutes a memory in which the effects of previous changes in pump flow rate settings are stored. In the explanation of our method, we focus on a single-lumen catheter. This however can be easily extended to a multi-lumen catheter. In order to represent this memory in the mathematical model, the internal volume of the catheter C between the points M and P is divided into tiny voxels A_k, in which the index k runs from $k = 0$ at point P to $k = L$ at point M

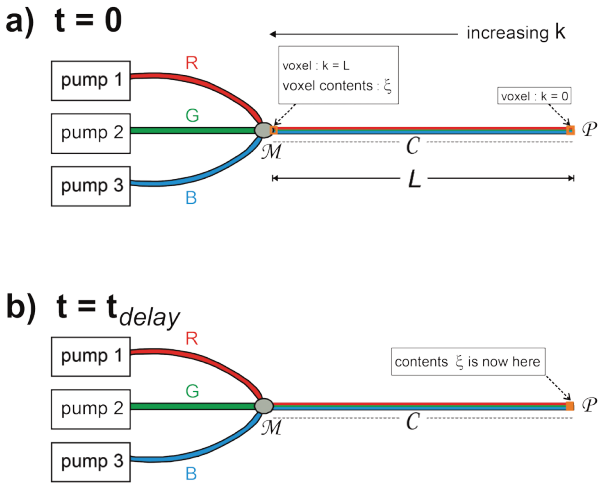

Figure 1: *Example of a general multi-infusion set-up. In this example, the number of pumps is three. The method, however, allows for any number of pumps. a) The catheter C contains a mixture of the fluids "R", "G", and "B", in which "R", "G", and "B" are the contents of syringe 1, syringe 2, and syringe 3, respectively. We consider this mixture to be completely homogeneous, despite the "stratified" rendering of the three colours in catheter C in this figure. b) Situation at $t = t_{delay}$; since t_{delay} is by definition the time needed to travel through the catheter C, the contents ξ that was inside the voxel $k = L$ (near the mixing point M) at time $t = 0$ in (a), has now reached the very tip P of the catheter at time $t = t_{delay}$, and is entering the blood stream of the patient.*

(see fig. 1), in which *L* is a very large number (which can be established by expressing the length *L* of the catheter in a small distance unit, such as e.g. millimeters). In our mathematical model, we use a general set-up containing any number of infusion pumps. For simplicity, however, we start with three pumps, in which each of these pumps contains a solution of a different medication, in which we used colours ("Red", "Green", and "Blue", or R, G, and B, respectively) to denote the three different solutions. It is important to note that the R, G, and B denote the three different solutions as stored in their respective syringes, not the medications themselves. Furthermore, in this paper, the dosing errors will be expressed as volumes of the R, G, and B solutions, instead of dosages of the medications themselves. In fig.1a, the situation directly after $t = 0$ is depicted, i.e. the point in time at which a change in pump flow rate setting value of one of the pumps takes place. As a result, the first small voxel at $k=L$ near the mixing point M is now being filled with a droplet ξ featuring a new mixing ratio between the solutions R, G, and B, resulting from the new pump flow rate setting values at t=0. The rest of the voxels inside the line C, however, contain a fluid mixture that still has the old mixing ratio corresponding to the steady-state situation before the change in pump flow rate setting value. In fig. 1b, the situation at $t = t_{delay}$ is depicted, i.e. the point in time at which this specific droplet ξ, that has been situated inside voxel $A_{k=L}$ at t=0, has now reached the distal tip of the catheter at point P at $t = t_{delay}$. Hence, at $t = t_{delay}$, the entire line C has now been filled with the new mixing ratio. The contents of voxel A_k, for any value of *k*, is described by the 3D-vector $\bar{a}_k$, in which

$$\bar{a}_k = \begin{pmatrix} a_k^{(R)} \\ a_k^{(G)} \\ a_k^{(B)} \end{pmatrix} \tag{1}$$

in which

$$\forall k : \left(a_k^{(R)} + a_k^{(G)} + a_k^{(B)} = 1 \ \wedge \ 0 \le a_k^{(R)} \le 1 \ \wedge \ 0 \le a_k^{(G)} \le 1 \ \wedge \ 0 \le a_k^{(B)} \le 1\right) \tag{2}$$

An essential point that needs to be emphasized - and that is fundamental to understanding the complexity of the dosing errors in multi-infusion set-ups - is that there are *two* points in time that affect the amount of medication that leaves the catheter at point P and enters the blood stream at a time point *t'*, in which $t' = 0+$, i.e. directly after $t = 0$. To clarify this, we first present the following equation that describes the amount of "Red" solution that enters the blood stream per second at time *t'*, i.e. the flow rate $u^{(R)}_{patient}(t')$ of the "Red" solution:

$$u^{(R)}_{patient}(t') = u_{cath}(t') \, . \, a^{(R)}_{(k=0)}(t') \tag{3}$$

in which $u_{cath}(t')$ is the flow rate (of the total mixture) inside the line C at *t'*, and $u^{(R)}_{patient}(t')$ is the specific amount (volume), per unit time, of "Red" solution that leaves the catheter C at point P and enters the blood stream of the patient at time *t'*. Furthermore, the subscript ($k = 0$) refers to the very last voxel at point P inside the catheter, i.e. the distal tip of the catheter. This specific voxel at ($k = 0$) releases its contents $\bar{a}_k=0$ directly into the

blood stream of the patient; $a^{(R)}_{(k=0)}(t')$ represents the fraction of fluid (R), i.e. the volume of solution (R) inside the voxel (k = 0) as fraction of the total volume inside the voxel (k = 0) at time t', according to eq. (1) and (2). If the "old" total flow rate inside the catheter C before t = 0 has been constant and equal to u_{old} for all t < 0, then the value of $a^{(R)}_{(k=0)}(t')$ equals:

$$a^{(R)}_{(k=0)}(t') \;=\; a^{(R)}_{(k=L)}(t^{\bullet}) \;=\; \text{fraction of R in the } \mathbf{old} \text{ mixing ratio, in which } \; t^{\bullet} = t' - V_{cath}/u_{old} \quad (4)$$

because voxel $\bar{a}_{(k=L)}(t\bullet)$ represents exactly the mixing ratio (ratio of incoming flow rates) at the mixing point M at that specific moment in time $t\bullet$, in which $t\bullet$ < 0 (i.e., in the past). If the "new" flow rate would be constant as well, and equal to u_{new} for all t > 0, then combining eq. (3) and eq. (4) yields:

$$u^{(R)}_{patient}(t') \;=\; u_{new} \cdot a^{(R)}_{(k=L)}(t^{\bullet}) \;=\; u_{new} \cdot (\text{ fraction of (R) in the } \mathbf{old} \text{ mixing ratio}) \qquad (5)$$

thus illustrating the dependency on flow rate and mixing ratio from two different points in time, i.e. the old mixing ratio in combination with the new flow rate.

This double time-dependency in eq. (5) can give rise to effects that may be unexpected to physicians, in which a temporary increase in dose rate of (R) entering the blood stream occurs, although no changes in the pump flow rate setting value of the pump of (R) has taken place. In figure 3, this "push-out" effect is explained, which has sometimes been called "dead volume" effect in the literature [14].

Due to the non-zero mechanical compliance of the syringes, however, (as mentioned at point (ii) in the introduction), the actual $u_{cath}(t)$ does not follow the changes in pump flow rate setting values immediately. The actual $u_{cath}(t)$ is a smooth function that does not follow the sharp edges, of the pump flow rate setting values as function of time, exactly. As a result, the actual flow rate $u_{cath}(t)$ in the catheter is not exactly equal to the sum of the pump flow rate setting values $u^{(R)}_{pump}(t)$, $u^{(G)}_{pump}(t)$ and $u^{(B)}_{pump}(t)$, due to the transient mechanical compliance effects that cause extra fluid to be stored in, or released from, the syringes directly after changes in pump flow rate setting values:

$$u^{(R)}_{pump}(t) + u^{(G)}_{pump}(t) + u^{(B)}_{pump}(t) \;\neq\; u_{cath}(t) \qquad (6)$$

Therefore, the general expression from which the "delay time" t_{delay} needs to be established is:

$$V_{cath} \;=\; \int_0^{t_{delay}} u_{cath}(\tau)\, d\tau \qquad (7)$$

in which u_{cath} depends on the compliance characteristics of the syringes as well.

2.1 New method for incorporating the memory effect of the catheter into an analytical model

In this paper, we will follow the following strategy to calculate dosing errors analytically (see figure 2):

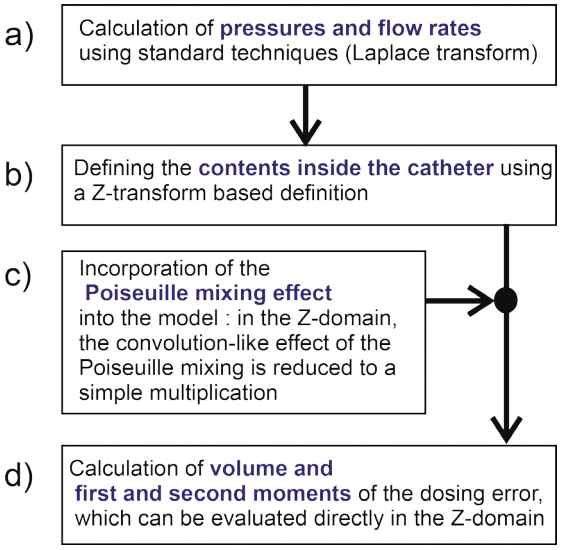

Figure 2: *Outline of the analytical method as presented in this paper. a: See subsection 2.2. b: See subsection 2.4. c: See subsection 2.5. d: See subsection 2.6.*

First, standard techniques [6] (involving the Laplace Transform) are used to calculate pressures and total flow rates (see (a) in the figure), in which the differences between the ”Red”, ”Blue” and ”Green” solutions are disregarded; i.e. in this ”color-blind” calculation, only the total flow rate inside the catheter $u_{cath}(t)$ is calculated. As a result, the flow rate entering the tube at time t and the flow rate leaving the tube (entering the blood stream) at the same time t are both equal to $u_{cath}(t)$, disregarding the different constitutions that the fluids entering, and leaving, respectively, may have in terms of the partial fluids R, G, and B.

Secondly, our new analytical method is introduced (see (b) in the figure), which enables incorporation of the ”memory effect” of the catheter into the model. In order to make the analytical approach (as opposed to already available numerical methods) possible throughout the entire calculation up to the end of point (d) in the figure, a formulation in the Z-domain (using the Z-transform, which is a discrete variant of the Laplace transform) is introduced. This new analytical method uses the results form the standard (Laplace-based) method (see (a)) as an input. This input has the from of general expressions for the various total flow rates as function of time. The Z-transform formulation in our new method (see (b)) therefore does not replace the Laplace-based method from (a), but is used after the standard method sequentially.

Third, the Z-domain formulation from (b) enables an easy, analytical, incorporation of the Poiseuille mixing effect (c) into the model, because the convolution-like nature of the Poiseuille mixing effect is reduced to a mere multiplication in the Z-domain. The mathematical details of the Poiseuille mixing effect are described in subsection 2.5.

Finally (d), we derive expressions for the volume, and the first and second moment, of the dosing error as function of hardware parameters. These moments can be calculated directly within the Z-domain. From the first and second moment, key characteristics concerning timing and duration of the dosing error are derived.

Throughout the entire process, we have relied on the strong symbolic calculation capabilities of the Mathematica package (Mathematica 10, Wolfram Inc., USA) to process Laplace-transforms and Z-transforms analytically, as can be seen in the results (section 3)

2.2 Starting point: Laplace transform and Kirchhoff's laws

In our mathematical model, all fluids are assumed to have the same viscosity. Furthermore, the small mechanical compliance of the catheter (as opposed to the significant mechanical compliance of the syringes) is neglected.

As has been mentioned above, we used standard techniques involving the Laplace Transform [6] to calculate pressures and total flow rates, in which the differences between the "Red", "Blue" and "Green" solutions are disregarded. This calculation is based on an electric circuit model that is analogous to the infusion set-up, in which current sources (the infusion pumps), resistances (infusion lines and catheter), and capacitors (mechanical compliance of the syringes) are present, and in which Kirchhoff's laws are applied on the voltages (pressures) and currents (flow rates) in the Laplace domain. The output $U_{cath}(s)$ of the calculation is the Laplace transform of the total flow rate $u_{cath}(t)$ inside the catheter. This $u_{cath}(t)$ equals the total flow rate entering the tube at time t as well as the total flow rate leaving the tube (entering the blood stream) at the same time t.

Let Γ denote the complete set of these changes in pump flow rate setting values, together with the physical hardware parameters of the set-up, which are present in the form of explicit parameters in the analytical expressions for $U_{cath}(s)$. Using the Mathematica package (Mathematica 10, Wolfram Inc, USA), we were able to perform an inverse Laplace transform in order to retrieve an analytical expression for $u_{cath}(t, \Gamma)$ from the $U_{cath}(s, \Gamma)$, in which the above mentioned hardware parameters Γ are present as explicit variables. This result is rendered in eq. (33) in the results section.

2.3 Key parameters of dosing errors

The dosing errors that are produced after changes in pump flow rate setting values in a multi-infusion set-up are of a temporary nature, i.e. the phenomena "dead volume" and "mechanical compliance" (points (i) and (ii), respectively, as mentioned in the introduction) give rise to only a temporary deviation of the actual dose rates of medications entering the blood stream of the patient from the intended dose rates (see e.g. figure 3). As a result, each of these dosing errors has the shape of a "bolus".

Let $\beta^{(R)}_{patient}(t)$ denote such a bolus-shaped dosing error, i.e. let $\beta^{(R)}_{patient}(t)$ denote the deviation from the intended partial flow rate (in this case of solution (R)), as a function of

time, in which

$$\beta^{(R)}_{patient}(t) \;=\; u^{(R)}_{patient}(t) \;-\; u^{(R)}_{pump} \tag{8}$$

Defining $t = 0$ as the moment that a change in pump flow rate setting value takes place, and defining $\beta^{(R)}(t)$ as the dosing error due to (only) this specific change in pump flow rate setting value at $t = 0$, then we have by definition:

$$\forall t < 0 \;:\; \beta^{(R)}_{patient}(t) \;=\; 0, \quad \text{and} \quad \lim_{t\to\infty} \beta^{(R)}_{patient}(t) \;=\; 0 \tag{9}$$

in agreement with the bolus-shaped nature of the dosing error $\beta^{(R)}_{patient}(t)$.

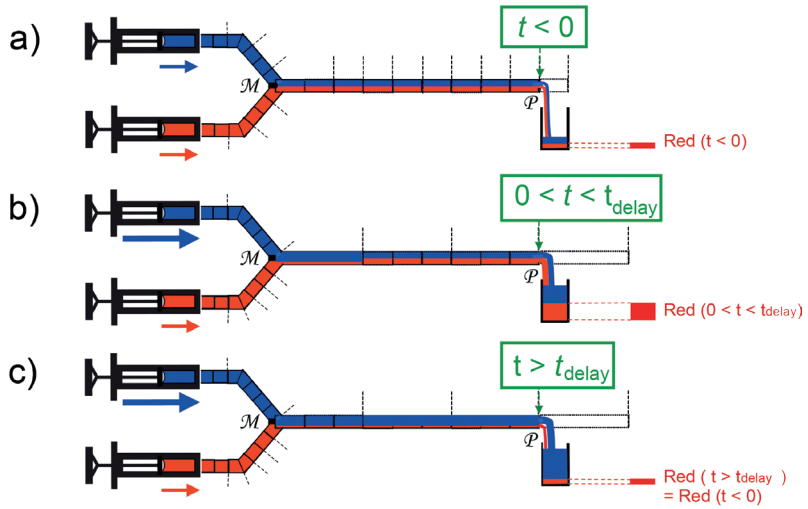

Figure 3: *Schematic, illustrating the "push-out" effect, i.e.: the temporary increase in the outflow of the "red" fluid into the patient due to an increase in speed of the "blue" pump, as is explained below. a) Two infusion pumps, filled with a "blue" and a "red" solution, respectively, produce the same flow rate, which is constant in time. The two flows are merged at the "mixing point"* M*, and subsequently travel towards point* P*, which represents the distal tip of the catheter where the fluid enters the blood stream of the patient. Since the flow rates of both pumps are equal, the catheter from point* M *to point* P *contains equal amounts of red and blue fluid, in the form of a mixture. This mixture is travelling with a flow rate that is twice the flow rate of each pump. A constant amount r of red fluid is entering the patient during each unit time interval,(illustrated by a canister at point* P *for each unit time interval). b) The same set-up, but now, at t=0, the flow rate of the "blue" pump is suddenly increased by a factor 5. As a result, after t=0, the amount of red fluid entering the patient at point* P *now temporarily equals 3r per unit time. Therefore, in (b), the "memory effect" is visible: the distal part of the catheter (near P) still contains the "old" mixing ratio corresponding to the situation before t=0. This "old" mixture is now being pushed out at the new speed; hence we dubbed this temporary increase in output of red fluid the "push-out" effect. In the literature, this effect is sometimes referred to as "dead volume" effect, or "catheter memory effect". (c) After* $t = t_{delay}$, *the amount of red fluid entering the blood stream per unit time equals r again, which equals the intended dose, just like the situation before t=0 in (a).*

There are two basic mechanisms that contribute to the dosing errors, and the effect of each of these two mechanisms is restricted to a particular time interval: During the time interval $0 < t < t_{delay}$, the dosing error entering the blood stream is caused by the push-out effect, as explained in figure 3. During the time interval $t > t_{delay}$, however, the dosing error entering the blood stream is caused by the effects of mechanical compliance.

In the following, we will use t^{POIS}_{delay} instead of t_{delay}, because, as will be demonstrated below, the Poiseuille profile of the flow affects the t_{delay}, resulting in a modified delay time that we will refer to as t^{POIS}_{delay}. Furthermore, we will consider a situation with two pumps (”Red” and ”Green”) only, and will change the flow rate setting of the ”Green” pump only (at t=0), leaving the flow rate setting of the ”Red” pump (denoted as $u^{(R)}_{pump}$constant. This does not affect the applicability of our method in more general cases. The flow rate setting of the ”Green” pump changes from $u^{(G)}_{old}$ to $u^{(G)}_{final}$ at t=0.

Calculation of the $\beta^{(R)}_{patient}(t)$ for $0 < t < t^{POIS}_{delay}$ due to the push-out effect is relatively easy, whereas calculation of the $\beta^{(R)}_{patient}(t)$ for $t > t^{POIS}_{delay}$ due to the mechanical compliance is much more complex. Therefore, we split the $\beta^{(R)}_{patient}(t)$ into two parts according to the two corresponding distinct time intervals:

$$\beta^{(R)}_{patient}(t) = \begin{cases} 0 & \text{if } t < 0 \\ \beta^{(R)}_{pushout}(t) = u^{(R)}_{pump}\frac{u^{(G)}_{final}-u^{(G)}_{old}}{u^{(G)}_{old}+u^{(R)}_{pump}} & \text{if } 0 < t < t^{POIS}_{delay} \\ \psi^{(R)}_{patient}(\tau) & \text{if } t^{POIS}_{delay} < t. \end{cases} \quad (10)$$

in which $\tau = t - t^{POIS}_{delay}$ and $\psi^{(R)}_{patient}(\tau)$ represents the effects of mechanical compliance for $t > t^{POIS}_{delay}$, and in which $\psi^{(R)}_{patient}(\tau)$ is bolus-shaped of its own:

$$\psi^{(R)}_{patient}(\tau) = 0 \text{ if } \tau < 0 \quad \wedge \quad \lim_{\tau\to\infty} \psi^{(R)}_{patient}(\tau) = 0 \quad (11)$$

In the following, we concentrate on finding analytical expressions for (the moments of) $\psi^{(R)}_{patient}(\tau)$.

2.4 Contents of the catheter without Poiseuille mixing effect

In this subsection, we derive a generic expression for the Z-Transform of the contents $\{a^{(R)}_k\}$ of the catheter, starting without incorporating the Poiseuille mixing effect for the moment.

First, let $\lambda_{tot}(t)$ denote the distance that the fluid inside the catheter has traveled as a result of the total flow rate u_{cath}, i.e.:

$$\lambda_{tot}(t) = \frac{L}{V_{cath}} \int_0^t u_{cath}(t')\, dt' \quad (12)$$

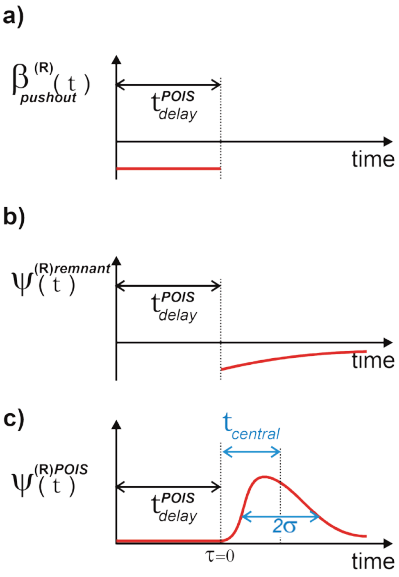

Figure 4: *Sketch of key characteristics of a dosing error distribution. The $t_{central}$ and σ are derived from the first and second moment, respectively, calculated directly in the Z-domain, without the need for an inverse Z-transform, as is explained in the text.*

Furthermore, let $u^{(R)}_{M}$ denote the actual partial flow rate of the Red fluid entering the catheter at the mixing point M.

Evidently, for some voxel *k* inside the catheter, the value of the ratio $\alpha_k^{(R)}$ reflects the $u^{(R)}_{M}(t^*)$ divided by the total flow rate $u_{cath}(t^*)$, at the time point t^* that the contents of that particular voxel entered the catheter at M, i.e.:

$$a_k^{(R)} = \frac{u_{\mathcal{M}}^{(R)}(t^*)}{u_{cath}(t^*)} \text{ in which } t^* \text{ is such that } k = \lambda(t^*) \tag{13}$$

In order to facilitate a Z-transform, we rewrite eq. (13) in the following form:

$$a_k^{(R)} = \frac{L}{V_{cath}} \int_0^{\infty} dt\, u_{\mathcal{M}}^{(R)}(t)\delta(k - \lambda_{tot}(t)) \tag{14}$$

The value of the Dirac delta $\delta(k - \lambda_{tot}(t))$ is zero everywhere, except around $t = t^*$; hence evaluation of the integral in eq. (14) shows the equivalence of eqs. (13) and (14):

$$\begin{aligned} \frac{L}{V_{cath}} \int_0^{\infty} dt\, u_{\mathcal{M}}^{(R)}(t)\delta(k - \lambda_{tot}(t)) &= \frac{L}{V_{cath}} \int_{t^*-\varepsilon}^{t^*+\varepsilon} dt\, u_{\mathcal{M}}^{(R)}(t)\delta(k - \lambda_{tot}(t)) \\ \overset{\varepsilon\to 0}{=} \frac{L}{V_{cath}} u_{\mathcal{M}}^{(R)}(t^*) \int_{t^*-\varepsilon}^{t^*+\varepsilon} dt\delta(k - \lambda_{tot}(t)) &= \frac{L}{V_{cath}} u_{\mathcal{M}}^{(R)}(t^*) \int_{k-\eta}^{k+\eta} d\lambda \left(\frac{dt}{d\lambda}\right) \delta(k - \lambda) \\ \overset{\eta\to 0}{=} \frac{L}{V_{cath}} \frac{u_{\mathcal{M}}^{(R)}(t^*)}{\left(\frac{d\lambda}{dt}\right)_{t=t^*}} &= \frac{u_{\mathcal{M}}^{(R)}(t^*)}{u_{cath}(t^*)} \end{aligned} \tag{15}$$

in which ε and η are both very close to zero.

Using the displacement rule from Z-transform theory [6], equation (14) now yields the following expression *A(z)* in the Z-domain:

$$A(z) = \frac{L}{V_{cath}} \int_0^\infty dt\, u_{\mathcal{M}}^{(R)}(t)\, z^{-\lambda_{tot}(t)} \tag{16}$$

Here it needs to be mentioned that, since the Z-transform is merely a discrete form of the Laplace transform, it would be, theoretically, possible to replace this Z-transform by yet another Laplace transform. However, for clarity, we have chosen to use the Z-transform, because it connects to the ”voxel-based” description of the contents inside the catheter in an intuitive way, and because it creates a clear distinction from the standard Laplace method used to calculate the pressures and flows that enter the mixing point M.

Similarly, we may define the basic input for the calculation of the dosing error of fluid (R) as the difference between $u_{\mathrm{M}}^{(R)}$ (i.e. the actual partial flow rate of the Red fluid entering the catheter at the mixing point M), and the intended $u^{(R)}_{pump}$ (i.e. the intended partial flow rate of the Red fluid entering the catheter at the mixing point M):

$$u_{\mathcal{M}}^{(R)diff} = u_{\mathcal{M}}^{(R)} - u_{pump}^{(R)} \tag{17}$$

yielding

$$A^{diff}(z) = \frac{L}{V_{cath}} \int_0^\infty dt\, u_{\mathcal{M}}^{(R)diff}(t)\, z^{-\lambda_{tot}(t)} \tag{18}$$

This approach now enables easy incorporation of the Poiseuille mixing effect into our model using a simple multiplication in the Z-domain, as is explained below.

2.5 Poiseuille mixing effect

The basic input for calculation of the Poiseuille mixing effect is the input from the Red line at M in the form of

$$a^{(R)diff} = \frac{u_{\mathcal{M}}^{(R)diff}}{u_{cath}} \tag{19}$$

having Z-transform *Adiff (z)* (see eq. (18)). The mixing effect due to the Poiseuille profile causes a spreading out of the dosing error in time, in which the first arrival of the dosing error occurs sooner then it would without Poiseuille mixing effect. In a Poiseuile flow, the velocity along the centerline of the tube equals two times the average velocity. This implies that, after a change in pump flow rate settings at *t=0*, the tip of the parabolic flow profile reaches point P at the end of the catheter already at $t = t_{delay}/2$. Hence, we define t^{POIS}_{delay} as: $t^{POIS}_{delay} = t_{delay}/2$. Because the Poiseuille mixing effect is a phenomenon that is created within the catheter during the very passage of the liquid through the catheter from point M to point P, an accurate description of the full extent of this effect can only be given in the form of the contents of the very last voxel at point P, just before these contents is released into bloodstream of the patient. This is illustrated in figure 5, in which the top diagram (fig 5a) shows the Poiseuille profile along the length of the catheter from point M to point P, in which the tip of the red, innermost, parabola has just finished its journey through the catheter, and is just to be released into the blood stream. Each

parabola in figure 5a constitutes a boundary between two volumes of liquid that once were subsequent, undistorted, ”regular” voxels when they entered the catheter at M. These initially flat boundaries between voxels near M are being stretched and distorted into the parabola-shaped boundaries during their travel to P.

In the Appendix, it is derived that the Poiseuille flow profile causes a mixing effect that features a simple linear relation between concentration and distance along the line from M to P (see figure 5b), which is consistent with earlier work by e.g. Taylor [28] and Hutton [29].

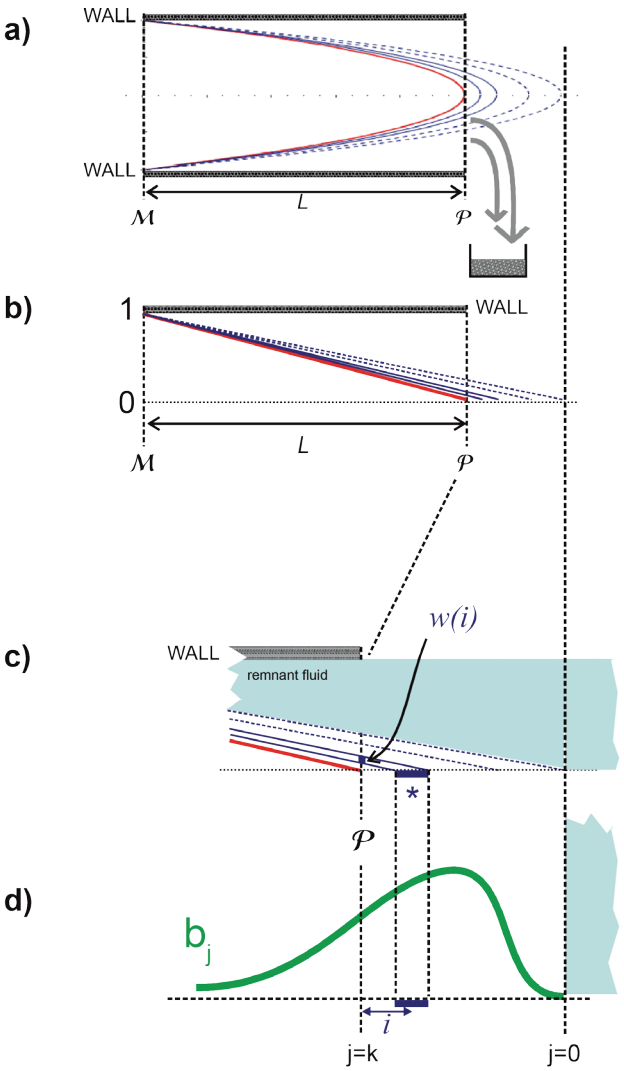

Figure 5: *Schematic representation of the Poiseuille mixing effect, as explained in the text.*

Using this simple linear relationship, the constitution of the final voxel of the catheter at P can be defined in terms of the original, undistorted, voxels that once entered the catheter at M, as is illustrated in figure 5c. For instance, the contents of the "voxel $*$", indicated by the symbol $*$, which is voxel nr. *i* counting from point P, and which is limited by two downward sloping lines and the thick blue horizontal line segment in figure 5c, contributes to the final voxel at P with weight factor *w(i)* (indicated by the small vertical thick blue line segment). On the basis of geometrical reasoning using the triangles involved (using the same small distance unit for L, i, and all other enumerations), it is clear that the weight factor *w(i)* equals:

$$w_i = \frac{L}{(i+L)^2} \tag{20}$$

Furthermore, the contents of each "voxel" *i*, with *i* running from 0 to infinity, equals that of voxel $b^{(R)}_{k-i}$, in which $b^{(R)}$ refers to the green curve in figure, which is a "stretched-out" version of the original voxels $a_j^{(R)diff}$ that entered the catheter at M, i.e. :

$$b^{(R)}_{2j} = a^{(R)diff}_j \tag{21}$$

which reflects the fact that the velocity along the centerline of the tube equals two times the average velocity. As a result, the summation of all contributions $b^{(R)}_{k-i}$ with weight factors w_i yields a (discrete) convolution, which is visible in the first term of the following equation, in which the contents of the last voxel at point P is denoted as $\psi_k^{(R)patient}$, and in which *k* refers to the position of the beginning of the green curve *b* (which shifts in time):

$$\psi_k^{(R)patient} = \underbrace{\sum_{j=0}^{k} b^{(R)}_{k-j} w_j}_{\text{convolution due to poiseuille}} + \underbrace{\frac{L}{(L+k)} \frac{u^{(R)}_{final}(u^{(G)}_{final} - u^{(G)}_{old})}{(u^{(G)}_{final} + u^{(R)}_{final})(u^{(G)}_{old} + u^{(R)}_{final})}}_{\text{remnant fluid from old mixture due to poiseuille}} \tag{22}$$

The second term in eq. (22) does not depend on the compliances and resistances in the multi-infusion set-up, but represents the remnant fluid from the old mixture due to the Poiseuille flow profile.

When calculating the first and second moment of $\psi_k^{(R)patient}$ (or $t_{central}$ and the variance σ^2 from figure 4, respectively), these moments are simply the sum of the moments of the two distinct terms in eq. (22). The moments of the second term can be calculated directly in the spatial domain (using an upper limit to the amount of fluid). For the first term, however, the Z-transform is needed, as will be explained below. Therefore, we split the $\psi_k^{(R)patient}$ according to:

$$\psi_k^{(R)patient} = \psi_k^{(R)POIS} + \psi_k^{(R)remnant} \tag{23}$$

$$\text{in which } \psi_k^{(R)POIS} = \sum_{j=0}^{k} b^{(R)}_{k-j} w_j \text{ and } \psi_k^{(R)remnant} = \frac{L}{(L+k)} \frac{u^{(R)}_{pump}(u^{(G)}_{final} - u^{(G)}_{old})}{(u^{(G)}_{final} + u^{(R)}_{pump})(u^{(G)}_{old} + u^{(R)}_{pump})}$$

and from now on will concentrate on the calculation of the first term, i.e. $\psi_k^{(R)POIS}$, only. Performing the Z-transform on $\psi_k^{(R)POIS}$ yields:

$$\sum_{j=0}^{k} b_{k-j}^{(R)} w_j \quad \overset{Ztransform}{\longmapsto} \quad B(z)W(z) \tag{24}$$

in which *B(z)* is the Z-transform of b_j, and *W(z)* is the Z-transform of w_j, which yields:

$$W(z) = 1 - L(z-1)\left(\frac{1}{z} + \frac{2^{-L}}{z^2} + \frac{3^{-L}}{z^3} + \frac{4^{-L}}{z^4} + \frac{5^{-L}}{z^5} + \cdots\right) \tag{25}$$

Since L is a large number, this constitutes a rapidly converging series for $z \approx 1$. Furthermore, since $b_{2j}^{(R)} = a_j^{(R)diff}$ (eq 21), we have $B(z) = A^{diff}(z^2)$, in which $A^{diff}(z)$ is the Z-transform of the original $a_k^{(R)diff}$, in the form in which it entered the catheter at M, before being distorted due to the Poiseuille mixing effect (see eq (18)). Therefore, in summary, we now have

$$\Psi^{(R)POIS}(z) = A^{diff}(z^2)W(z) \tag{26}$$

in which $\Psi^{(R)POIS}(z)$ is the Z-transform of $\psi^{(R)POIS}(k)$. This expression for $\Psi^{(R)POIS}(z)$, i.e. equation (26), constitutes the central equation in our method, and enables derivation of explicit expressions for the first and second moment of $\psi^{(R)POIS}(k)$ (or $t_{central}$ and σ from figure 4, respectively), *without the need* of performing an inverse Z-Transform.

2.6 Calculation of moments of the dosing error distribution after t_{delay}

We will now use the ”theorems of moments” from Z-transform theory to provide expressions for key characteristics of the $\psi^{(R)}{}_{patient}(\tau)$ that enters the patient. The zero’th moment yields:

$$\Lambda_0 = \frac{L}{V_{cath}} \int_0^\infty \left(u_{\mathcal{M}}^{(R)}(\tau) - u_{pump}^{(R)}\right) d\tau \tag{27}$$

and hence the total volume of the dosing error $\psi^{(R)}{}_{patient}(\tau)$ equals:

$$Q = \int_0^\infty \left(u_{\mathcal{M}}^{(R)}(\tau) - u_{pump}^{(R)}\right) d\tau \tag{28}$$

The first moment yields:

$$\mu = -\lim_{z\to 1}\left(z\frac{d}{dz}\Psi^{(R)POIS}(z)\right) \tag{29}$$

and hence

$$t_{central} = -\frac{V_{cath}}{\Lambda_0 L u_{final}} \lim_{z\to 1}\left(z\frac{d}{dz}\Psi^{(R)POIS}(z)\right) \tag{30}$$

Furthermore, using the second moment, the following general expression for σ is obtained, in which the typical ”duration” or ”width” of a dosing error is characterized as 2σ (see figure 4):

$$\sigma = \frac{V_{cath}}{u_{final} L}\sqrt{\frac{1}{\Lambda_0}\lim_{z\to 1}\left(z^2\frac{d^2}{dz^2}\Psi^{(R)POIS}(z) + z\frac{d}{dz}\Psi^{(R)POIS}(z)\right) - \left(\frac{\mu}{\Lambda_0}\right)^2} \tag{31}$$

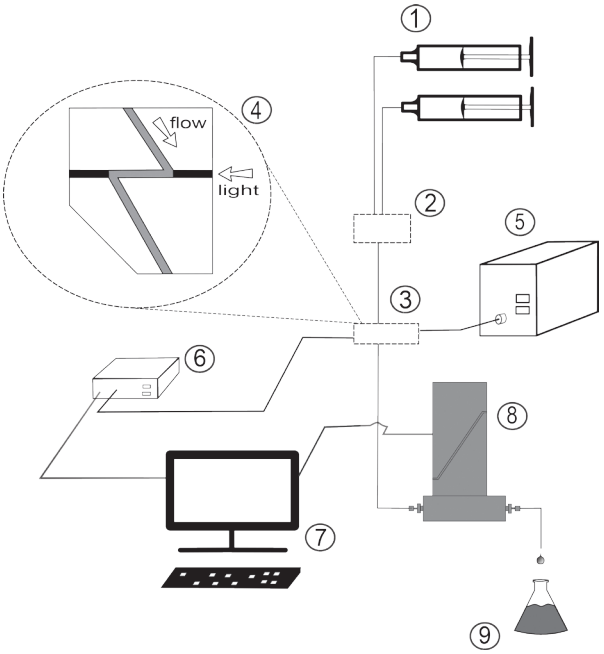

Figure 6: *Experimental setup: The syringe pumps (1) pump their contents towards a mixing point (2). From the mixing point, the fluid will flow towards a flow cell (3),(4), where the light from light source (5) is used for an absorbance measurement by the spectrometer (6). A computer will simultaneously read out the flow rates from the flow meter (8). Finally the fluid is stored inside a container (9).*

In the results section, these equations (27) to (31) will be used to produce analytical expressions for various situations. Furthermore, also in the results section, equations (27) to (31) will be evaluated for situations *without* the Poiseuille mixing effect, in which case the $\Psi^{(R)POIS}(z)$ in these equations is replaced by merely $A(z)$.

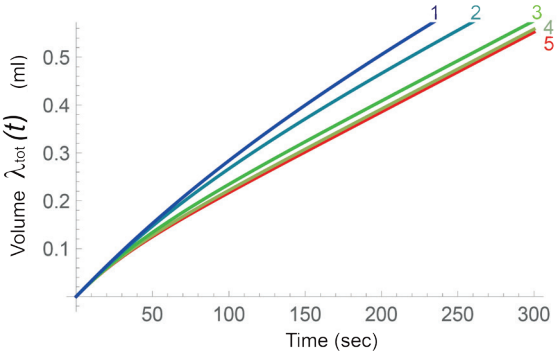

Figure 7: *Total volume $\lambda_{tot}(t)$ as function of time t for different values of the resistance R_{cath} and the mechanical compliance C_{red}, according to the theoretical model. (1): $C = C_{standard}$, $R = 3R_{standard}$. (2): $C = C_{standard}$, $R = 2R_{standard}$. (3): $C = C_{standard}$, $R = R_{standard}$. (4): $C = 0.52C_{standard}$, $R = R_{standard}$. (5): $C = 0.36C_{standard}$, $R = R_{standard}$.*

2.7 Spectrometric in-vitro set-up for feasibility tests

A schematic of the in-vitro set-up is rendered in figure 6. Two Perfusor B.braun syringe pumps (B. Braun, Melsungen AG, Germany) and 50-ml syringes (Melsungen AG, Germany) were used in the experimental setup. The syringes contained Tartrazine (TT) and Indigo Carmine (IC) solution, solved in distilled water. Each syringe was connected to an infusion line (d = 1 mm) of 200 cm (Cair LGL, France) and subsequently combined using the using a 3-needle-free Y-connector (20038E7D, Cardinal Health, Switzerland). The Y-connector outflow was connected to a flowcell (Z flowcell w/SMA 905, 10-mm pathlength, FIAlab, Seattle, WA, USA), this flowcell was also connected to a visual light spectrum (250-2500 nm) DT-1000 light source (Ocean Optics, Dunedin, FL, USA). This allowed a spectrometer QE65000 (Ocean Optics, Dunedin, FL, USA), also connected to the same flowcell, to continuously measure an absorption spectrum of the dye mixture. Concentrations of each dye were acquired from this absorption spectrum [4]. After the flow cell, the cumulative flow rate was measured using three M12p flowmeters (Bronkhorst, Ruurlo, The Netherlands). Sample time of all the measurements was 1 second.

3 RESULTS

3.1 General result from Laplace transform as a starting point

Performing the first step in the scheme rendered in figure 2, the following general expression for $u_{M}^{(R)diff}$ has been derived in the Laplace domain, using a known technique, i.e. Laplace Transform in combination with Kirchhoff laws :

$$\breve{u}_{\mathcal{M}}^{(R)diff}(s) = -\frac{C_2 u_{downstep}^{(G)} R_L}{s^2\left(C_1C_2R_LR_1 + C_1C_2R_LR_2 + C_1C_2R_1R_2\right) + s\left(C_1R_L + C_1R_1 + C_2R_L + C_2R_2\right) + 1} \tag{32}$$

in which $\breve{u}_{M}^{(R)diff}(s)$ is the Laplace transform of $u_{M}^{(R)diff}(t)$, and $u^{(G)}_{downstep}$ equals the change in pump flow rate setting of the Green pump at t=0. Meanwhile, the pump flow rate setting of the Red pump, $u^{(R)}_{pump}$ remains unchanged all the time. Using the InverseLaplaceTransform function of Mathematica, the following general expression was obtained in the time domain:

$$u_{\mathcal{M}}^{(R)diff}(t) = \frac{\left(e^{-\frac{t}{\vartheta_{first}}} - e^{-\frac{t}{\vartheta_{second}}}\right) u_{downstep}^{(G)} R_L C_2}{\sqrt{b^2 - 4ac}} \tag{33}$$

in which

$$\begin{aligned} \vartheta_{first} &= \frac{1}{2}\left(b - \sqrt{b^2 - 4ac}\right) \\ \vartheta_{second} &= \frac{1}{2}\left(b + \sqrt{b^2 - 4ac}\right) \\ a &= R_LR_1 + R_LR_2 + R_1R_2 \\ b &= C_1(R_L + R_1) + C_2(R_L + R_2) \\ c &= C_1C_2 \end{aligned} \tag{34}$$

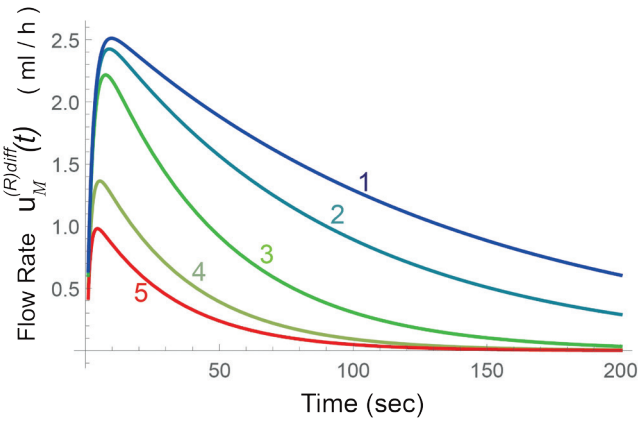

Figure 8: *Flow Rate $u_M^{(R)diff}(\tau)$ as function of time τ for different values of the resistance R_{cath} and the mechanical compliance C_{red}, according to the theoretical model. (1): $C_{red} = C_{standard}$, $R_{cath} = 3R_{standard}$. (2): $C_{red} = C_{standard}$, $R_{cath} = 2R_{standard}$. (3): $C_{red} = C_{standard}$, $R_{cath} = R_{standard}$. (4): $C_{red} = 0.52C_{standard}$, $R_{cath} = R_{standard}$. (5): $C_{red} = 0.36C_{standard}$, $R_{cath} = R_{standard}$.*

Using eq. (32), the total volume of the dosing error (i.e., the time-integral of eq. (33)) is easily calculated using the general rules for integration and for calculation of limits from Laplace transform theory. The resulting expression $Q^{(R)}_{dosingerror}(\Gamma)$, i.e. the volume of the dosing error, depends on the set of hardware parameters Γ. In this specific case, the parameter set Γ comprises of: Γ = {*Resistances, Compliances, FlowRates*}.

$$Q^{(R)}_{dosingerror}(\Gamma) = C_2 R_L u^{(G)}_{downstep} \tag{35}$$

The subtraction of two exponentially decaying functions in eq. (33) yields a characteristic bulb- shaped graph of $u_M^{(R)diff}(\tau)$ as function of the time τ; see figure 8. In this figure, eq. (33) has been evaluated for a number of parameter settings of Γ.

From the general equation, more specific and practical expressions can be derived by substituting standard values into the equation, leaving the parameters of interest as variables. The standard values for R_L, R_1, R_2, C_1, C_2, $u^{(R)}_{pump}$, $u^{(G)}_{old}$ and $u^{(G)}_{downstep}$ are rendered in Table 1.

Table 1. Standard values in simulations and in-vitro measurements

Variable	Standard value
R_L	1145 Pa/(ml/h)
R_1	23 Pa/(ml/h)
R_1	23 Pa/(ml/h)
C_1	1.5 10^{-5} ml/Pa
C_2	1.5 10^{-5} ml/Pa
$u^{(R)}_{pump}$	0.5 ml/h
$u^{(G)}_{old}$	12 ml/h
$u^{(G)}_{downstep}$	6 ml/h

3.2 Typical example: Resulting dosing error during syringe exchange

We now consider the specific case in which the ”Green” syringe is exchanged, during which the green pump is stopped and green line has been clamped (with a Kocher), but the red line is not clamped, and the settings of the red pump remain unchanged. Let $T_{restart}$ denote the time between clamping the green line and the reopening the green line, i.e. $T_{restart}$ denotes the time duration of the entire procedure of exchanging the green syringe.

During the syringe exchange time interval, the red line still oozes red fluid in undiluted form into the first voxels of the catheter directly after the mixing point M. We now consider two scenario’s within the general scenario of the syringe exchange with the green line being clamped off during the entire exchange time interval. In the first scenario, the red line is not clamped off, but the red pump is switched off (pump flow rate setting value is zero; still connected to the red line) simultaneously at the beginning of the syringe exchange procedure, and restarted to its original pump flow rate setting value at the very end of the syringe exchange procedure. In the second scenario, no actions are performed in relation to the red pump or red line at all. The first scenario entails that accumulation of undiluted red fluid directly beyond the mixing point is caused only by the compliance of the red syringe, in combination with the drop in pressure caused by the clamping of the green line. This is indicated by the text ”compliance” under the second brace in eq. 36. In the second scenario, however, the regular pumping action of the red pump (at flow rate $u^{(R)}_{pump}$) adds to the accumulation of undiluted red fluid beyond the mixing point as well (indicated by the text ”red pump on” under the first underbrace in eq. 36). As a result, in the second scenario, the total dosing error $Q^{(R)}_{dosingerror}(T_{exchange})$ is the sum of the ”compliance” and the ”red pump on” effects. See figure 12. After t_{delay}, this total dosing error is entering the blood stream of the patient within a very short time interval, due to the fact that the green pump has a high flow rate.

$$Q^{(R)}_{dosingerror}(T_{exchange}) = \underbrace{u^{(R)}_{pump} T_{exchange}}_{\text{red pump on}} + \underbrace{\frac{u^{(G)}_{downstep} R_L C_2 \left(\vartheta_{first} \left(1 - e^{-\frac{T_{exchange}}{\vartheta_{first}}} \right) - \vartheta_{second} \left(1 - e^{-\frac{T_{exchange}}{\vartheta_{second}}} \right) \right)}{\sqrt{b^2 - 4ac}}}_{\text{compliance}} \tag{36}$$

3.3 Analytical results for reducing the flow rate of the Green pump, without Poiseuille mixing effect

We now consider the more general case in which the pump flow rate setting of green pump, i.e. of the fast pump, is lowered with an amount $u^{(G)}_{downstep}$, without clamping any line. The volume $u^{(R)}_{dosingerror}$ does not depend on the specific distribution of the dosing error over time, and hence yields the same result as in eq.(35).

Here we present the general result of the calculation of the first moment of A(z) without the Poiseuille flow effect:

$$t_{central} = \frac{V_{cath}}{L} \frac{\int_0^\infty \lambda(t) u_R(t)\, dt}{u_{final} C_2 R_L u^{(G)}_{downstep}} \tag{37}$$

Applying this result to this specific case (lowering the pump flow rate setting of the green pump) yields:

$$t_{central} = b + \frac{u^{(G)}_{downstep}}{4u_{final}}\left(\sqrt{b^2-4ac} - 2C_2R_L + b + 2\frac{ac}{b}\right) \quad (38)$$

In many clinical situations we have $C_1 = C_2 = C$ and $R_1 = R_2 = R$, in which case eq.(38) reduces to:

$$t_{central} = 2C(R_L + R) + \frac{Cu^{(G)}_{downstep}(2R_L^2 + 6R_LR + 3R^2)}{4u_{final}(R_L + R)} \quad (39)$$

Applying the equation (31) from the method section to the present situation, without the Poiseuille flow effect reads:

$$\sigma = \frac{V_{cath}}{L}\frac{1}{u_{final}}\sqrt{\frac{\int_0^\infty \lambda(t)^2 u_R(t)\,dt}{C_2R_Lu^{(G)}_{downstep}} - \frac{\left(\int_0^\infty \lambda(t)u_R(t)\,dt\right)^2}{\left(C_2R_Lu^{(G)}_{downstep}\right)^2}} \quad (40)$$

Evaluation of eq. (40) yields a very long and unwieldy expression. However, as has been noted before, in many clinical situations we have $C_1 = C_2 = C$ and $R_1 = R_2 = R$, and, furthermore, for most catheters we have R « R_L. Applying these assumptions, we obtain the following result:

$$\sigma = \frac{CR_L}{2\sqrt{3}\,u_{final}}\sqrt{(u^{(G)}_{downstep})^2 + 12u^{(G)}_{downstep}u_{final} + 48(u_{final})^2} \quad (41)$$

This result will be compared with the findings from the in-vitro experiments in subsection 3.5. If, in eq. (41), the $u^{(G)}_{downstep}$ would be very small with respect to u_{final}, then this expression for σ approaches the familiar $\sigma \approx 2CR_L$.

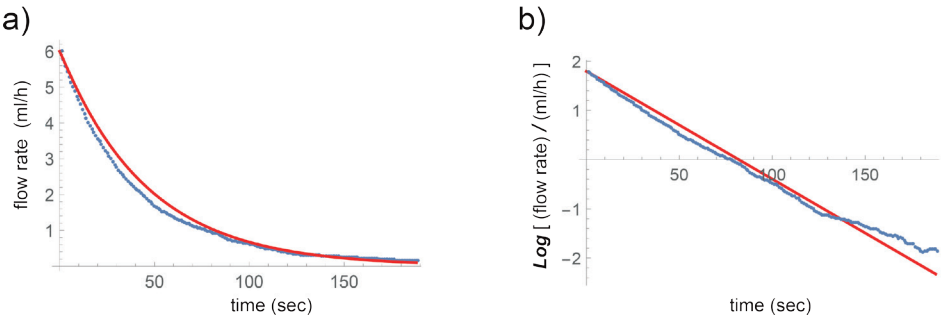

Figure 9: *Results of in-vitro experiments, in which the flow rate of the Green fluid (blue dots) is plotted as function of time, after a change in the flow rate setting of the Green pump. The predicted theoretical result of the Green fluid flow is rendered by the red line.*

3.4 Analytical results for reducing the flow rate of the Green pump, incorporating the Poiseuille mixing effect

Evaluation of equation (31) from the method section to the situation of reducing the pump flow rate setting of the green pump (still without any clamping) once more, but now substituting $\Psi^{(R)POIS}(z)$ (instead of $A(z)$) in order to incorporate the Poiseuille flow effect,

yields a very long and unwieldy expression. Therefore, again, we apply the assumptions $C_1 = C_2 = C$ and $R_1 = R_2 = R$ and $R \ll R_L$, which yields the following result:

$$\sigma^{POIS} = \frac{1}{\sqrt{3}\, u_{final}} \sqrt{C^2 R_L^2 \left((u^{(G)}_{downstep})^2 + 12 u^{(G)}_{downstep} u_{final} + 48 (u_{final})^2 \right) + 3 (V_{cath})^2} \qquad (42)$$

As can be seen in eq. (42), the strength of the contribution of the Poiseuille mixing effect to the width σ^{POIS} depends on the internal volume of the catheter V_{cath} with respect to the time CR_L in combination with the flow rates ($u^{(G)}_{downstep}$) and u_{final}; or, more precisely, on the ratio between $3(V_{cath})^2$ and $C^2 R_L^2 \left((u^{(G)}_{downstep})^2 + 12 u^{(G)}_{downstep} u_{final} + 48 (u_{final})^2 \right)$

If the catheter has a large internal volume but the time CR_L is short and the flow rates are low, then the σ^{POIS} in eq. (42) reduces to: $\sigma^{POIS} \approx V_{cath}/u_{final}$.

If, however, in eq. (42), the $u^{(G)}_{downstep}$ would be very small with respect to u_{final}, and the time CR_L would be very large and the V_{cath} would be small, then this expression for σ approaches $\sigma^{POIS} \approx 4CR_L$, which is two times larger than the $\sigma \approx 2CR_L$ that was calculated before when omitting the Poiseuille mixing effect. This factor two is a result from the fact that, in a Poiseuille flow, the velocity at the centerline of the catheter equals two times the average velocity.

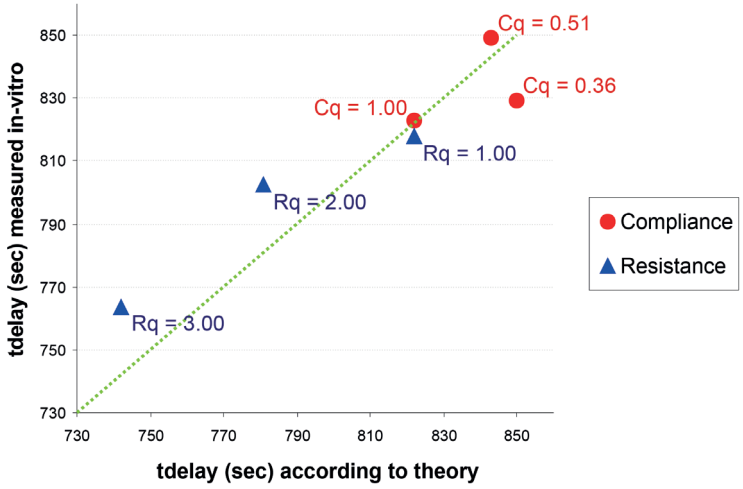

Figure 10: *Results of in-vitro experiments, in which the measured tDelay (Red dots and Blue triangles) are plotted as function of the corresponding theoretical value. Red dots: Using a syringe of 50 cc, 25 cc or 10 cc. Blue triangles: Using various resistances.*

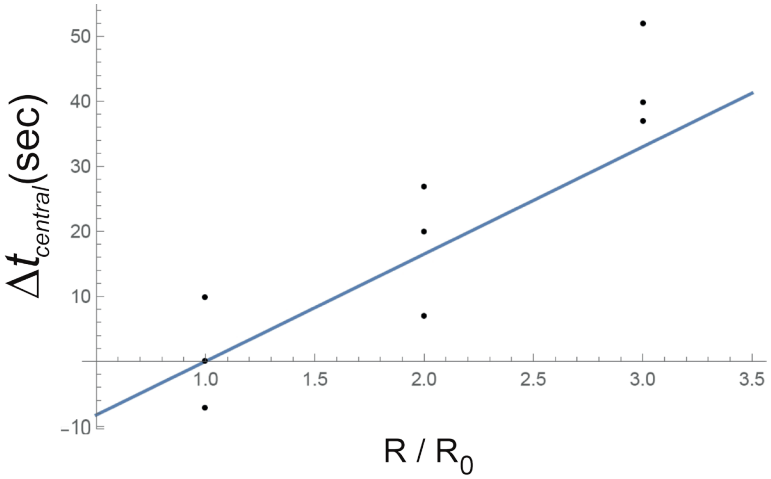

Figure 11: *Comparison of theoretical results (solid line) with the results in-vitro experiments (black dots), in which the measured $\Delta t_{central}$ is plotted as function of the value of the relative resistance R of the catheter with respect to its standard value R_0, in which $\Delta t_{central}$ is defined as the measured or caluclated value of $t_{central}$ with respect to the standard value of $t_{central}$ as calculated for R_0.*

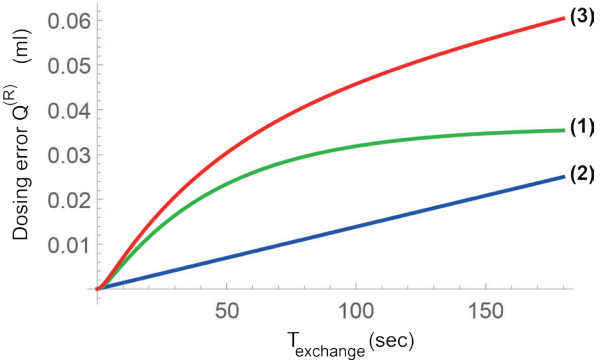

Figure 12: *Calculated total dosing error of the Red fluid as function of the time duration $T_{exchange}$ of the syringe exchange procedure, in which the green line has been fully closed (clamped) during the entire syringe exchange procedure, and in which $C_{red} = C_{standard}$, $R_{cath} = R_{standard}$. (1): Compliance effect only (see eq. 36). (2): "red pump on" effect only. (3): Compliance and "red pump on" effects combined.*

3.5 Results of in-vitro experiments, and comparison with theoretical predictions

Three types of in-vitro experiments have been performed, in order to compare theoretical results with actual measurements. These four types of experiments are:

(i) measurement of the flow rate of the Green fluid as function of time, immediately after a change in pump flow rate setting value of the green pump, corresponding to $u^{(G)}_{downstep} = 6\ ml/h$; see figure 9.

(ii) measurement of t_{delay} for a set of three different syringes and three resistances, corresponding to various values of C and RL; see figure 10.

(iii) measurement of $\Delta t_{central}$ as function of various values of the relative resistance R of the catheter with respect to its standard value R_0, in which $\Delta t_{central}$ was defined as the measured $t_{central}$ minus the standard value of tcentral for $R = R_0$. Three different values of R/R_0 have been used; and the measurement $\Delta t_{central}$ of was repeated three times for each value of R/R_0. See figure 11.

4 DISCUSSION

In this paper, explicit expressions have been derived for the total volume (Q), central time point ($t_{central}$) and "width" or "duration" (2σ) of dosing errors as function of hardware parameters such as mechanical compliance of syringes, resistance of the catheter, length of the catheter, for two general cases of a change in pump flow rate setting value in a multi-infusion set-up, as well as for a typical case of syringe change-over. After implementation of our new approach in Mathematica (Wolfram), these explicit expressions were produced automatically. In many of these expressions that were thus produced and are presented in the results section, the relative contribution of various factors affecting the dosing errors, such as the poiseuille mixing effect, can be discerned clearly in the structure of these expressions. Consistency of the resulting analytical expressions has been examined for limiting cases, and, more importantly, three types of in-vitro measurements have been performed to obtain a first experimental test of the validity of the theoretical results derived in this paper. The results from the in-vitro experiments show a reasonable to good agreement between measurements and theoretical results.

4.1 General findings from the expressions derived

In many of the resulting expressions as presented in the results section, the characteristic "time contant" $R_L C$ plays a clearly recognisable role. Furthermore, the ratio between the $u^{(G)}_{downstep}$ (the size of the change in pump flow rate setting value) and the u_{final} (the stabilized final flow rate) appears as an important factor in determining the nature of the dosing error bolus, particulary how the dosing error will spread out in time (the "width" or "duration" (2σ) of the dosing error bolus). The contribution of the Poiseuille mixing effect is clearly visible in the resulting expressions. Of particular clinical importance is the fact that the Poiseuille flow profile, once fully developed, reduces the time, that is needed for a newly administered medication to reach the patient, significantly. This may come as an unexpected effect for the clinician, as may also the fact that the value of 2σ (the "spread out") is increased at the same time. The results in this paper may help to determine the magnitude of this "spread-out" effect as function of the hardware parameters (most notably, the characteristic $R_L C$ time), and e.g. the length and resistance of the catheter.

4.2 Limitations of the method, and possible extensions

A number of limitations can be identified in our method in its present form; most apparent is the assumption that when a time interval of duration t^{POIS}_{delay} has lapsed after having changed a pump flow rate setting value, the actual flow rate has already stabilized and

reached the value u_{final}. This needs not to be true in a general case. However, using the same reasoning as presented in this paper, our method can be extended to include non-stable flow rates at $t = t^{POIS}{}_{delay}$ as well. Another limitation may arise by the fact that in our method we did not examine other elements (other than just syringes, infusion lines, catheters, and pumps) that may be present in an infusion set-up, such as a non-return valve (preventing flow back from the catheter into a line towards a pump), or filters. The non-return valves may be incorporated into the method by restricting flow rates in the catheter to positive values or zero, whereas filters may be modeled on basis of a resistance and a mechanical compliance, as indicated in the literature (e.g. [27]). Another complicating factor may be the use of high viscosity fluids in the infusion set-up. In our method, as it stands now, all fluids in the system were assumed to be of the same viscosity. Incorporation of deviating (high) viscosities into our method would entail an extension of the laminar flow profile used in this paper, because differences in viscosity of mixing liquids may produce destabilization of laminar flow. An easy, but useful, extension of our method is the incorporation of the possibility that the height at which the syringes are positioned in a set-up near the patient, is altered during the period that a patient receives medication using the multi-infusion set-up. Since a change in height may be modeled as the addition of an extra pressure source within the model during the process of infusion, this results in an extra bolus of dosing error, and, hence, in the addition of some extra terms and factors in the equations in the results section. Finally, the parabolic flow profile of a laminar flow does not come into existence instantaneously at the mixing point; it has been calculated [29] how long, c.q. what distance, it takes for the flow profile to approach the parabolic shape. All of these complicating factors need to be incorporated into the model to make it more realistic. As far as we can anticipate now, we do not expect these extra factors to be incompatible with our general approach outlined in this paper; however, further research is needed.

4.3 Potential use of the results in clinical practice

Healthcare professionals working with infusion technology in critical care have expressed the desire for a real-time tool that visualizes the multi-infusion drug therapy, e.g. continuously calculates predictions to indicate when the drugs will be entering the blood stream of the patient and in what dose. Such a tool may also visualize the causal consequences of an intervention (i.e., change in a pump flow rate setting value), before a clinician decides to proceed with such an intervention. In order to develop such a tool in the future, a fast and generic model will be necessary, combining all the relevant physical effects. The desirability of such a visualization tool, and the mathematical modeling that is a pre-requisite for the development of such a tool in the future, is what prompted us to go beyond the state-of-the-art and to develop the fully analytical method described in this paper. We envision three types of developments in which the results from this paper may be useful: (i) an interactive tool, running synchronized with the multi-infusion system on a smartphone device or on a bed-side display, e.g., next to the vital signs display monitors. Such a tool could then be used in several cases, such as inotropic titration, or to visualize the effects of a syringe changeover, or even the consequence of changing

the height of a pump during infusion. (ii) Another application of the method presented in this paper could be actual computer control of an infusion system. It has been shown that a computer-controlled pump with knowledge about the dead volume and the mixing effect within the dead volume can be useful in preventing overshoot [19]. Moreover, a control system with a feedback approach has also been attempted, where the mean arterial blood pressure was used to control the administration of a fast-acting vasodilator [21,22]. In both cases, however, increasingly complex situations and infusion setups were encountered where only the incorporation of all the interdependent physical effects, as described in this paper, would provide a sufficiently accurate prediction in order to make computer control feasible. (iii) The model can potentially also be used as an analysis and design tool, prior to investing in potential new infusion hardware. It is known that flow characteristics are influenced by valves [23,24], syringes [25], infusion lines and catheters [26], and filters [27]. By using the method from this paper, benefits of these components can be compared against potential tradeoffs.

APPENDIX: VOLUME DISTRIBUTION IN A POISEUILLE FLOW

Laminar flow produces a Poiseuille flow profile, in which the velocity u depends on the distance r to the central longitudinal axis of the catheter [5]:

$$u(r) = \frac{1}{4\eta}\frac{\Delta p}{L}(r_0^2 - r^2) \tag{43}$$

in which η is the viscosity of the fluid, $\Delta p/L$ is the pressure drop over a length L of catheter, and $2r_0$ is the diameter of the catheter.

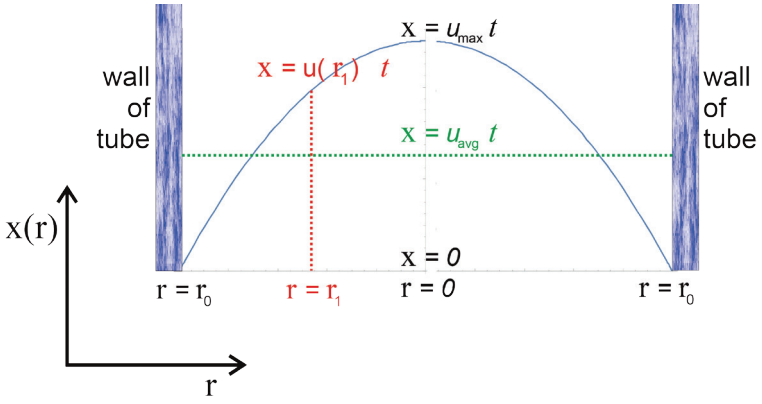

Figure 13: *Poiseulle profile in laminar flow. See text*

Furthermore, the average velocity u_{avg} equals

$$u_{avg} = \frac{r_0^2 \Delta p}{8\eta L} \tag{44}$$

and the maximum velocity (located along the central longitudinal axis of the catheter) equals

$$u_{max} = 2u_{avg} \tag{45}$$

Evidently, if thermal diffusion is left out of the model and the fluid is considered to be completely homogeneous at the mixing point M, then the length $\lambda_{max}(t)$ of the protrusion of the top of the Poiseuille profile into the catheter along the central longitudinal axis, is calculated easily by combining eq.(45) and (44):

$$\lambda_{max}(t) = tu_{max} = \frac{r_0^2 \Delta p}{4\eta L} t \tag{46}$$

Let *x* denote the position measured along the central axis along the catheter, starting with $x = 0$ at M, and let $r_{boundary}(x, t)$ denote the distance with respect to the central longitudinal axis at position *x* at time *t*, at which the boundary (parabola) is situated. Multiplying both sides of eq.(43) with *t*, yields the relation:

$$x\left(r_{boundary}\right) = \frac{1}{4\eta}\frac{\Delta p}{L}\left(r_0^2 - \left(r_{boundary}\right)^2\right) t \tag{47}$$

in which *x* is a function of $r_{boundary}$ and represents the distance that the boundary (see figure 13) has travelled in the longitudinal direction (along the length of the catheter), for a given radial position $r_{boundary}$. The relation between *x* and *r* in eq. (47) is depicted in figure 13: Conversely, solving $r_{boundary}$ from eq.(47) for all values $x \in [0, t\, u_{max}]$, we have:

$$r_{boundary}(x,t) = \sqrt{r_0^2 - \frac{4x\eta}{t\left(\frac{\Delta p}{L}\right)}} \tag{48}$$

which is depicted in figure 14.

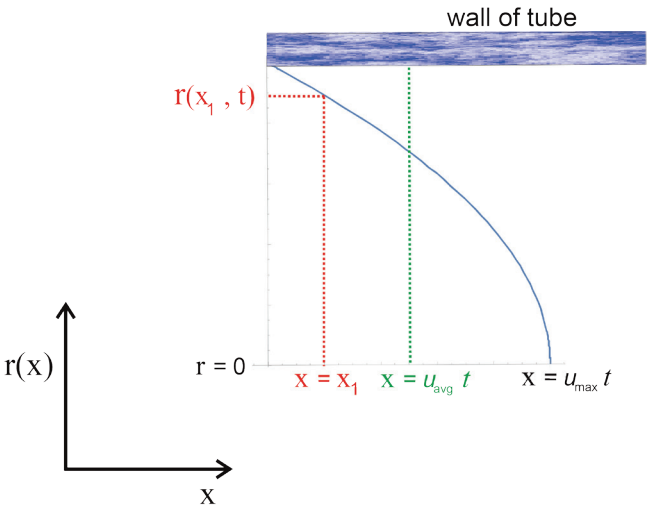

Figure 14: *Same relation as in figure 13, but now with r as function of x. Effectively, this figure results from rotating figure 13 by 90 degrees.*

In order to calculate the amount of the fluid *R* that is present inside a thin, disk-shaped, cross- sectional volume *S* of the catheter at position *x*, expressed as a fraction $f_R(x, t)$ of the total fluid in the thin volume *S*, in which the disk-shaped volume *S* is perpendicular to the central longitudinal axis of the catheter at point *x*, we need to integrate over the cross-sectional area of the catheter at point *x*, from $r = 0$ to $r = r_{boundary}(x, t)$, and divide this by the total cross-sectional area πr_0^2 :

$$f_R(x,t) = \frac{1}{\pi r_0^2}\int_0^{r_{boundary}(x,t)}\left(\int_0^{2\pi} r\,d\phi\right)dr = \frac{(r_{boundary}(x,t))^2}{r_0^2} = 1 - \frac{4x\eta}{t\left(\frac{\Delta p}{L}\right)r_0^2} \qquad (49)$$

An interesting feature of this surprisingly simple result is that, within the region of the Poiseuille profile, there is a linear relationship between *x* and $f_R(x, t)$.

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Chapter 2.4

How infusion system physical parameters cause clinically relevant dose deviations at setpoint changes

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ABSTRACT

Multi-infusion therapy, in which multiple pumps are connected to one access point, is frequently used in patient treatments. This practice is known to cause dosing errors following setpoint changes in the drug concentrations that actually enter the patients. Within the Metrology for Drug Delivery Project, we analyzed and quantified the two main physical phenomena leading to these errors: the “push-out” effect and the system mechanical compliance. We compared the dosing errors of a three-pump system with two infusion sets, both with and without anti-reflux valves, using *in vitro* spectrophotometric experiments. Additionally, computer simulations were used to study the compliance effect separately. We found a start-up time of more than 1 h, and a dosing error following a setpoint increase of another pump for the low flow rate pump, corresponding to 0.5 mg noradrenaline delivered in 8 min. We showed that the dead volume inside the tubes and syringe compliance produce opposite deviations from the setpoint values in the actual drug output concentrations, making the net result hard to predict and often counterintuitive. We conclude that metrology on compliance and push-out effects could be used by infusion device manufacturers to successfully improve drug delivery performance and relevant standards for high-risk multi-infusion applications.

1 INTRODUCTION

Drug delivery is the process of administering a pharmaceutical compound to achieve a therapeutic effect. Almost all patients who are hospitalized, and many in home care, receive intravenous medication, or in other words drugs are delivered directly in their blood stream. Infusion pumps, syringes and infusion sets are therefore amongst the most widely used medical devices in hospitals. On many occasions, several liquid therapeutic agents are administered to patients simultaneously, because vascular access sites are limited. Moreover, the procedure of inserting a catheter for high risk medications, is challenging for several reasons [1,2]. Catheter insertion is also associated with a high risk of infection, which is potentially lethal. For these reasons, multiple pumps are often combined on one catheter. This administration method is called multi-infusion. In several papers [3–5], evidence is given that in standard clinical practices multi-infusion creates unintended variations in drug dosage. Van der Eijk et al. [6] described flow rate variability at low infusion rates as a persistent problem in intravenous drug therapy for new born infants. Ethgen et al. [7] showed that unintended drug delivery changes caused by multi-infusion effects can pose threats to the adult patient as well. In standard infusion applications, the dosage is controlled by the flow rate setpoint and the drug solution of known concentration. Therefore, following the research mentioned above, this approach is not sufficient to achieve the required dosing accuracy. In particular, this is the case for potent drugs that have a very short half-life and narrow therapeutic range. In addition, if low flow rates are needed, e.g. for patients who can only tolerate a limited amount of fluid intake, the concentration of the drug to be infused will have to be increased. Consequently, deviations from intended flow rates can cause toxic concentrations in the blood more easily. The chemical and pharmacological compatibility of drugs is customarily tested as a part of pharmacologic and nursing protocols before combining two lines in a multi-infusion system. In contrast, up till now, barely any adequate description exists of customarily testing of the effect of the applied infusion system parameters on the infused drug dose. In a comprehensive review on intravenous drug delivery in neonates, Sherwin et al. [8] concluded that evaluation of infusion protocols and practices in neonatal settings is needed to give insight into unexpected therapeutic outcomes in clinical practice. The physical characteristics of the infusion system, e.g. of an infusion pump, a syringe, infusion tubing and catheter are known to contribute to dose variations.

The objective of this study is to create awareness that the actual dose that is administered to the patients' blood vessels is influenced by these physical characteristics. In the next sections, we will investigate, by combining theoretical macroscopic analysis of a syringe pump multi-infusion system with exemplary *in vitro* spectrophotometric experiments and a computer model, how a "push-out effect" and the effect of mechanical compliance in the system cause clinically relevant dosing errors. Furthermore, we will discuss why the combination of the two effects yields a result that sometimes is hard to predict. Eventually, we will explore how we can more accurately predict the actual drug dosage delivered to patients where this is clinically relevant and how and when an accurate measurement of system mechanical compliance and actual flow rates can contribute to that goal.

2 THEORETICAL CONSIDERATIONS

Clinicians relate therapy effectiveness to the drug dose delivered to the patient, which can, for example, be expressed in µg/kg/min. In a multi-infusion setup, the intended drug doses delivered to the patients are set by adjusting the flow rates of the constituent pumps. In case of syringe pumps, the parameter that is actually controlled, is the displacement of the syringe plunger. The pump software makes an internal conversion to a flow rate from the syringes. For each patient, the drug dose that needs to be administered over a certain time, the dose rate, is specified in a medication scheme. The drug dose rate is converted to a setpoint for the flow rate by multiplying it with the concentration of the drug solution in the syringe. Today's pumps typically indicate the set flow rate on a screen that is part of the pump front.

This indicated setpoint of pumps is based on a simple rule:

$$\text{Drug doses into patient} = \text{flow rates of pumps} \times \text{drug concentrations in syringes} \quad (1)$$

This equation, however, is based on two assumptions that have been shown not to hold in practice. These two assumptions are:

$$\sum_{i=1}^{N} \text{FlowRateOfPump}[i] = \text{FlowRateIntoPatient} \quad (2)$$

$$\text{DrugConcentrationsIntoInfusionLine}[t] = \text{DrugConcentrationsIntoPatient}[t] \quad (3)$$

where *t* is a point in time, *N* is the number of pumps, and i is an integer running from 1 to N.

First, in eq. (2), it is assumed that all elements in the total multi-infusion setup are infinitely stiff and mechanical compliance effects do not occur. This would imply that the sum of the flow rate setpoints of the pumps is always exactly equal to the flow rate entering the patient (eq. 2). Secondly, the concentration of the drug in the tip of the catheter, just before entering the bloodstream of the patient at time *t*, is assumed to be equal to the concentration entering the other end of the infusion setup, located outside the patient near the pumps (eq. 3).

These two assumptions are not valid in many situations, and improper use may lead to dosing errors. Instead of using equations 2 and 3, a correct formulation of the situation would be:

$$\sum_{i=1}^{N} \text{FlowRateOfPump}[i] = \text{FlowRateIntoPatient-MechanicalComplianceEffects} \quad (4)$$

$$\text{DrugConcentrationsIntoInfusionLine}[t\text{-}T] = \text{DrugConcentrationsIntoPatient}[t] \quad (5)$$

in which the mechanical compliance causes temporary effects following changes in flow rate (e.g. due to change in flow rate setpoints, or changes in height of the pumps), and *T* is an unknown delay time that depends on the history of the actual flow rates inside the catheter.

The actual drug doses delivered to the patient are therefore not only determined by the flow rates from the pumps, but by the amount of drugs stored inside the infusion system as well.

To illustrate equation 5, in Figure 1a, a simplified example is given of a multi-infusion setup schematic with two syringe pumps. The flows from the different syringes are combined via a one-piece infusion set, and from thereon continue via the central line to the patient. Finally the flow enters the patient via a catheter. When the flow rate setpoint of a pump is changed, the drug concentration entering the patient is affected by a "push-out" effect of the drug solution mixture after the mixing point. This effect is caused by the fact that the various concentrations of medications existing inside the catheter at a given moment in time *t*, reflect the history of the setpoint values of the pumps before time *t.* However, the flow rate with which this contents is pushed out of the infusion line is determined by the set-point values of moment in time *t* itself. Figure 1B shows that if the set-point value of the pump of one of the medications is increased, then the other medication, which is still present inside the infusion line, is pushed out of the infusion line into the bloodstream with increased speed, potentially causing a relevant temporary overdose. As the setpoint increases, part of the drug solution can temporarily be stored in the infusion system because of system mechanical compliance. This compliance refers to the compressibility of certain elements in the infusion set-up, primarily the plungers in the syringes. In a steady state situation, when the set-point values of the pumps have not been altered for a long time, an equilibrium exists between the line pressure and mechanical stress in the various components. When the setpoint value of one of the pumps is increased, however, the pressure is increased inside the entire multi-infusion system, causing an increased compression of the plungers. Thus, an additional amount of space is created near the plunger that is now being filled with fluid. As a result, the system mechanical compliance effect causes a delay in reaching the actual flow rate increase with respect to the set-point increase of the pump. If in a multi-infusion system the flow rates of two pumps differ greatly, the drug solution originating from the pump with the highest flow rate could even flow into the infusion line connected to another pump with a substantially lower flow rate. This phenomenon is called backflow and is known to cause dose fluctuations starting with a temporary delivery stop followed by an overdose [5,9]. Backflow can be countered by adding anti-reflux valves. However, at the same time, anti-reflux valves add to the delay of reaching the setpoint [10].

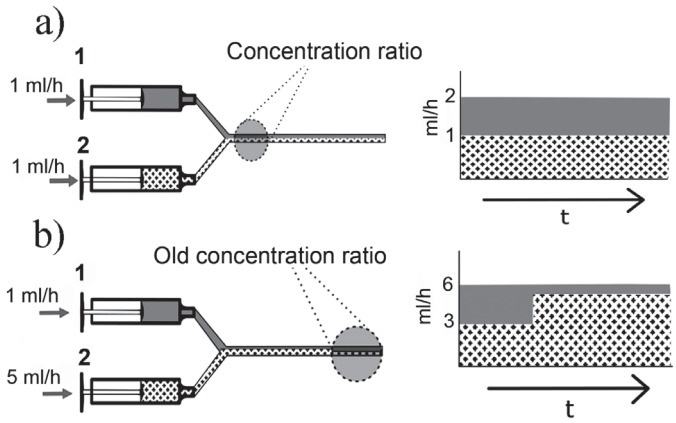

Figure 1. *Illustration of the "push-out" effect in two syringe pumps before (A) and after a setpoint change (B).*

The *purpose of this paper* is threefold: it is shown by theory and experiments that

i. both the "push-out" effect, as well as the effect of mechanical compliance can lead to substantial dosing errors, and that
ii. these dosing errors are clinically relevant, and
iii. the "push-out" effect and the effect of mechanical compliance may be of the same order of magnitude, but will be "opposite" in direction, which adds strongly to the unpredictability of the total net effect.

Furthermore, it will be corroborated that the present clinical practices, in which the push-out effect and effects due to mechanical compliance are not satisfactorily dealt with by the protocols that determine the flow rate setpoints of the pumps, possess serious risks for patients, and that action and innovation are needed.

In the following sections, we present the results of in-vitro experiments as well as predictive computer calculations, for a multi-infusion set-up using three pumps.

3 MATERIALS AND METHODS

To illustrate the push-out effect and the effect of system mechanical compliance, preliminary in vitro experiments were carried out. In the section "Start-up time measurement using *in vitro* flowmetry", the start-up characteristics of the flow rate from a single pump were investigated. In the section "Dosing deviations in a clinical medication scheme", an analysis was made of dosing deviations resulting from compliance and push-out effects in a medication scheme used in a clinical situation. The experiment was carried out both for an infusion set with and without anti-reflux valves.

3.1 Start-up time measurement using *in vitro* flowmetry

In this experiment, a Coriflow M12P Coriolis mass flowmeter (Bronkhorst, Ruurlo, the Netherlands) was used. The sample time was 1 second. A single-pump syringe pump (B.braun perfursor, Melsungen, Germany) setup was used. The syringe used was a 50-ml B.braun Omnifix syringe (Melsungen, Germany), which was filled with distilled water. The pump was connected to a 1 m-infusion (d=1 mm) line (Cair LGL, Tunisie), which was subsequently connected to the flowmeter. The nominal flow rate was 0.5 ml/h. The flowmeter measured a mass flow rate, the measured values were corrected for the density of water at the laboratory temperature of 20° C (i.e. 998.2071 kg/m3). The mean plot, resulting from the three measurement was fitted using an exponential fit. From this fit, the 95% of the start-up time, which was defined as the onset time of steady state drug delivery, as well as the 50% start-up time and the RC-time was acquired. This time period equals the resistance (pressure per volume/time) multiplied by the compliance (volume / pressure) of the entire infusion setup.

3.2 Dosing deviations in a clinical medication scheme

Two parameters were calculated to investigate whether clinically relevant dose deviations were found.

a) The start-up time in all three pumps was investigated for the standard line as well as for the octopus line with valves. The time required from T = 0 h to reach 95% as well as 50% of the steady-state flow rate was assessed (see Figure 2A).

b) The dosing error was assessed using the procedure illustrated in Figure 2B: the deviation from steady state in outflow of one drug was recorded, resulting from the increase in the flow rate setpoint value of “another” drug in another pump. The results are presented as the area under the curve (AUC) in percentages as well as in milliliters and milligrams. The exact analytical methodology is explained in the section “Data analysis”.

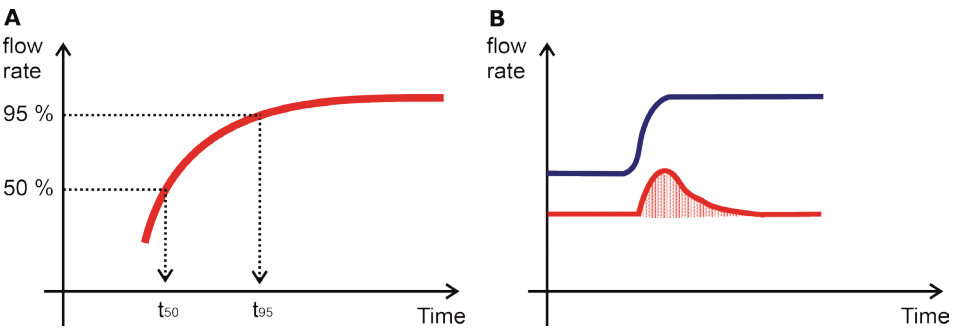

***Figure 2**. Schematic illustrating “Start-up times” (A) and “Dosing Error” (B).*

Experimental setup

In these *in vitro* experiments, we used an absorption spectrophotometric method that was developed in our group, in which multiple spectral photometric measurements

were performed simultaneously on fluids consisting of laser dyes solved in water. The purpose of the laser dyes, which mimicked the various pharmaceuticals of a medication scheme used in clinical practice, was to distinguish output concentrations. Absorption spectrophotometry allows for an accurate measurement of the concentration of the various dyes in the water when it exits inside the infusion line (at the point where it theoretically would enter the bloodstream of the patient). The setup consists of the following elements. A light source (DT-100, Ocean Optics, Dunedin, FL, USA) emits light in the visible spectrum. Subsequently, this light is guided through 200 µm optical fibers into a flow cell (FIA-Z-SMA, Ocean Optics, Dunedin, FL, USA). The flow cell was also connected to a 200-cm-long central line (2.5 mm in diameter), where the solvents from each syringe pump are joined. Consequently, the light emitted from the source passes through the solution, allowing the solvent to absorb a part of the light spectrum. The spectrum is finally analyzed by a spectrometer (QE65000, Ocean Optics, Dunedin, FL, USA). After the measurement, the solvent was guided through a line of 50 cm (1.0 mm in diameter) and released into an Erlenmeyer flask. A precision (±0.0001 g) balance (PGW 450, Adam Equipment, Danbury, CT, USA) was used to verify the total mass measurements, additionally allowing to obtain a (mass) flow rate. The sample time was 10 s.

A calibration method was needed to relate the measured absorbances to concentration values to be assessed. This calibration was performed as follows:

$$A_c = a_n \cdot C_n + b_n \qquad (6)$$

where A is an N-dimensional vector containing the absorbances at various wavelengths and n is an index running from 1 to N enumerating the various wavelengths at which the absorbances were measured. Because the number of dyes equals the number of measured wavelengths, n is the enumeration of the dyes as well. Because this was a calibration procedure, both the measured absorbances in vector A and the concentration C_n of the dye n at the point of measurement were known. From these data, the vectors a and b were retrieved (using the linear regression function in MATLAB 7.5.0 [The Mathworks, Natick, MA, USA]), which completed the calibration procedure. Subsequently, the vectors a and b were available for normal (i.e. noncalibration) measurements to solve the unknown C values from the measured A values.

Clinical situation

This experiment was based on a clinical situation that could occur in the intensive care unit, where patients received among others a combined noradrenaline and midazolam infusion therapy with an isotonic saline carrier flow. After 1 h, indicated as T = 1, the intensive care specialist decides that additional medication is needed. This drug is added to the carrier flow, setting the total flow rate from the carrier flow to 16 ml/h. An hour later (T = 2), the dose of this drug needs to be adjusted and the flow rate of this drug is raised from 8 to 17 ml/h. Finally, half an hour later, the noradrenaline is doubled after the patients' blood pressure decreases. The experiment was ended after 3 h.

The nominal flow rates of the medication schedule are listed in Table 1.

Table 1. Nominal flow rates (ml/h) of the simulated medication schedule

Time (h)	T=0	T=1	T=2	T=2,5	T=3
Pump 1 (carrier flow, NaCl and additional medication)	8	16	25	25	25
Pump 2 (midazolam1 mg/ml)	5	5	5	5	5
Pump 3 (noradrenaline 0.1 mg/ml)	2	2	2	4	4

The flow rate profiles were compared between a "standard infusion set," which consisted of a manifold (Variostop Multiple Stopcock System, Clinco Medical/Fresenius Kabi, Bad Homburg, Germany), and an "octopus infusion set" (Smartsite extension set, three-needle-free valve ports, Medica Europe, Oss, The Netherlands) with anti-reflux valves (valve-operated three-way, IMF, Dortmund/Hagen, Germany).

3.3 Data analysis

Data analysis was performed using MATLAB 7.5.0 (The Mathworks, Natick, MA, USA) for the Absorption spectrometric method of 3.2. The results from the experiment using the flowmeter of 3.1 were analyzed with Origin 9.0 (Originlab, Northampton, MA, USA)

In section 3.2, the steady-state flow rate, measured using absorption spectrophotometry, was defined as a period over which the flow rate did not change significantly. The steady-state flow rates were estimated from means over 1000 s. The artifacts in the order of one sample were ignored in any measurement. The accuracy of the mass flow measurement conducted by our precision balance was ±1 mg, which is equal to approximately ±1 µl. The results were therefore presented as three decimals at most. In case the steady-state flow rate was different before and after a dosing error, linear interpolation was used to estimate the differences between the steady state before the dosing error and the steady state after the dosing error. The AUC of this linear interpolation was subtracted from the AUC of the dosing error.

Statistical analysis

All experiments were repeated three times (n=3). A two-sample, two-tailed, t-test for unequal variances was used to investigate statistical significance for the differences in start-up times between the standard infusion set, and the octopus infusion set with valves. All the results are presented in MEAN ± SD.

3.4 Computer simulations

A basic framework for predictive computer modeling of multi-infusion output flow rate was set up by Murphy et al. [11]. We extended this model to acquire expressions for any number of pumps. In our multi-infusion network model, capacitances, resistances and flow sources are used to simulate the outflow of a realistic multi-infusion setup (See Figure 3 for an example of such a network model).

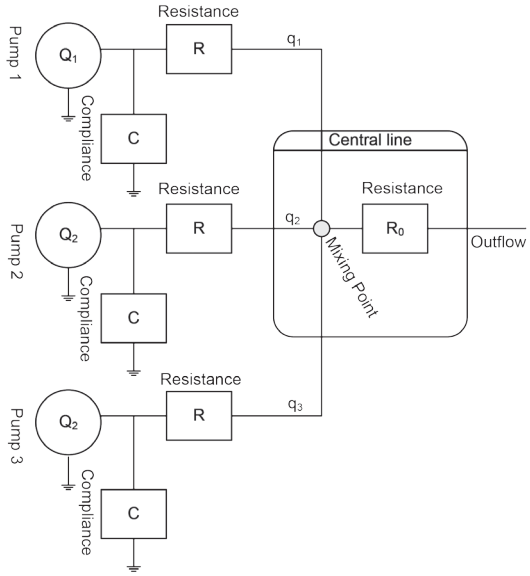

Figure 3. *Schematic representing a multi-infusion set-up with 3 pumps.*

To derive analytical expressions for the various flows in the model depicted in Figure 3, we combined Kirchhoff's laws with a Laplace transform. A realistic infusion pump can be described as a (mathematically pure) current source Q, in combination with a capacitor C that represents the compliance (compressibility) of the plunger of the syringe in the pump. Each segment of infusion line in the total setup has a resistance R. The model predicts the flow rates of the individual medications (q_1, q_2, q_3, etc.).

A great advantage of these computer simulations is that the impact of the "push-out" effect and "compliance" effect can be studied individually. In the computer simulations presented here, the effect of compliance was studied independently from other effects, because the flow rates were calculated for every point in the system, including individual flow rates from the syringes before the mixing point. Each pump is represented by the combination of a (mathematically pure) current source Q1 (or Q2 or Q3 for pumps 2 and 3, respectively) in combination with a capacitor C that represents the compliance (compressibility) of the plunger of the syringe in the pump. Each of the three pumps is connected to a mixing point by a segment of tube having a resistance R, through which the fluid flows toward the mixing point with a flow rate q_1 (or q_2 or q_3). Finally, a tube segment with resistance R_0 connects the mixing point to the outflow point (representing the point at which the infusion system releases the fluid into the bloodstream of the patient). We calculated the case for three infusion pumps. Three drug solutions were simulated in these calculations to illustrate the effect of system mechanical compliance in steady-state flows if one of the pumps alters speed suddenly. At t = 0.5 h, the flow rate setpoint of pump 1 (blue) was doubled. Furthermore, at t = 2 h, the flow rate setpoint of pump 1 was suddenly decreased to its original level.

4 RESULTS

4.1 Start-up time measurement using *in vitro* flowmetry

The effect of the system mechanical compliance on startup behavior of a single-pump setup is shown in Figure 4. It shows the start-up curve, which results purely from system mechanical compliance, for a substantial part from the syringe compliance. The effect of the system mechanical compliance therefore causes a delay of 232±28.6 s (3.9±0.5 min) in reaching 95% of the flow rate setpoint and 102±5.20 s (1.7±0.1 min) before reaching 50%. The RC time, estimated from the exponential fit, was 45.9 (0.8 min). This result confirms that the compliance effect takes place in the opposite direction with respect to the direction of the flow rate setpoint change. In Figure 4, it can be seen that, after t = 70 s, the curve can be approximated using an exponential fit. Before t = 70, the phenomena with other time constants play a part. After that, the start-up period can be approximated by a single exponential function with sufficient statistical accuracy.

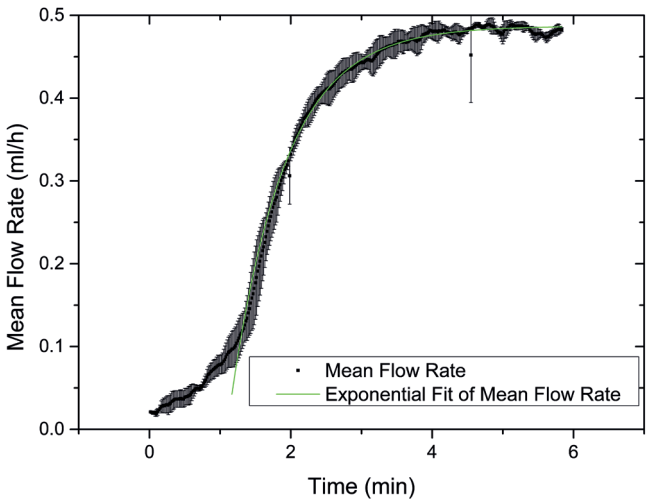

Figure 4. *Results of in vitro experiment studying the "syringe compliance" effect.*

4.2 Dosing deviations in a clinical medication scheme

A typical measurement result in the section 3.2 is rendered in Figure 5. The deviation from the flow rate setpoint is clearly visible in the green line, which shows the reaction of the midazolam solution to a change in flow rate setpoint of the carrier flow only. From Figure 5, it is clear that the deviation in the green line after approximately t = 2.0 h (the "push-out effect") takes place in the same direction as the direction of the change in flow rate setpoint in carrier flow at t = 2.0 h. The flow rate from the noradrenaline pump increases during approximately 10 min with more than 25%.

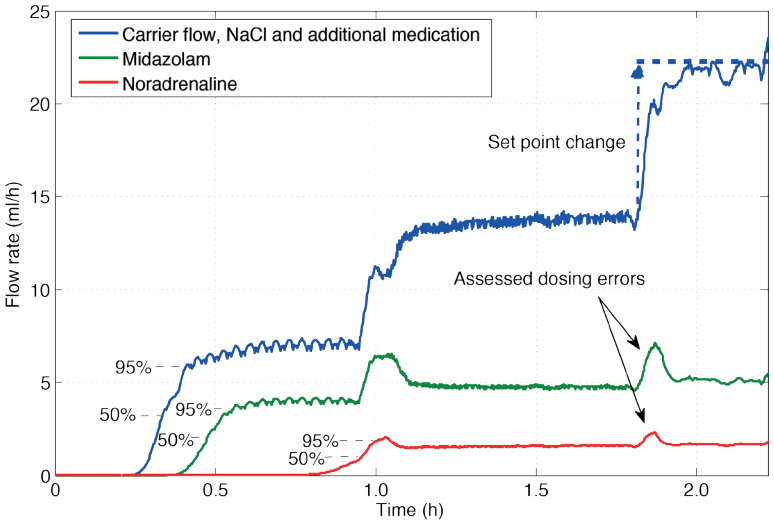

Figure 5. *Measurement results of the standard infusion set. The assessed dosing errors are indicted at the at the flow rate setpoint change. Approximate 50% and 95% startup times are also indicated.*

Start-up time measurement

Start-up delays of more than one hour were found. Table 2 lists the start-up time of the standard infusion set and the octopus infusion set with valves for all three pumps. Figure 6 shows the start-up of the standard infusion set and the octopus infusion set with valves times graphically.

Table 2. Start-up times in pumps 1-3 of the standard infusion set and the octopus infusion set with anti-reflux valves.

	Standard infusion set **Mean ± SD**	Octopus with valves **Mean ± SD**	**P value**
Start-up (95%) pump 1 (s)	1980 ± 111	1587 ± 220	0.070
Start-up (50%) pump 1 (s)	1440 ± 274	1440 ± 113	1.00
Start-up (95%) pump 2 (s)	2277 ± 307	2247 ± 32	0.88
Start-up (50%) pump 2 (s)	1943 ± 221	1877 ± 155	0.69
Start-up (95%) pump 3 (s)	3797 ± 329	4430 ± 327	0.077
Start-up (50%) pump 3 (s)	3623 ± 230	4113 ± 81	0.074

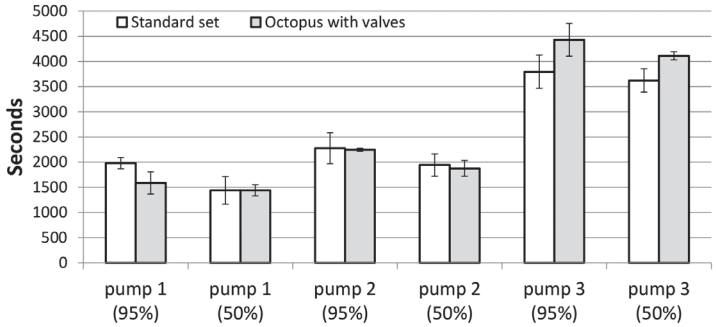

Figure 6. *Start-up times of the standard infusion set, and the octopus infusion set with anti-reflux valves.*

The start-up times found in this experiment (amounting to more than 1 h) were substantially larger than those found in the first experiment (adding to a few minutes). The largest difference found between the sets was the 50% start-up time in the noradrenaline, which was slower with the infusion set with valves. However, none of the results were statistically significant ($p < 0.05$).

Dosing errors due to "push-out" effect

Figure 7 shows the dosing errors found in pump 2 representing midazolam (a) and pump 3 representing noradrenaline (b) of the standard infusion set at T = 2.0 h following an initiated, nominal flow rate change in pump 1, representing the carrier flow. The mean AUC of the dosing errors found for midazolam was 0.16±0.03 ml, 27.5±10.4%, which lasted 483±172 s. For a 1 mg/ml midazolam solution and a standard 80 kg patient, this volume corresponds to a total additional dose of 0.16 mg midazolam in 8 min. The mean maximum dosing error of pump 2 representing midazolam was approximately 30%.

The mean AUC of the dosing errors found in pump 3, representing noradrenaline, was 0.05±0.01 ml, 23.5±8.7%, which lasted 490±156 s. This volume corresponds to a total additional dose of 0.5±0.1 µg noradrenaline in 8 min. For an 0.01 mg/ml noradrenaline solution and a standard 80 kg patient, this amounts to a total overdose of approximately 0.5 µg noradrenaline that is delivered in 8 min, which is comparable to an additional 5% of the maintenance dose (2–4 µg/min). Noradrenaline, a drug with an instantaneous effect on the heart action, is known to cause blood pressure variations upon infusion setpoint changes that can be dangerous [7,12], considering its small therapeutic width and low plasmatic half-life of approximately 2 min after intravenous administration [13].

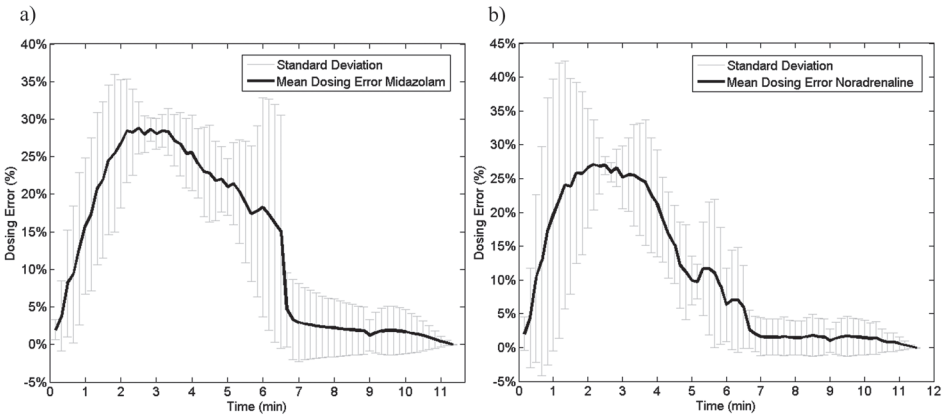

Figure 7. *Mean relative (compared to steady state) dosing errors of pump 2 representing Midazolam (a). Mean relative (compared to steady state) dosing errors of pump 3 representing Noradrenaline (b).*

4.3 Computer simulations

The results of the calculations are rendered in Figure 8. The initial values of the setpoint values of pumps 1–3 were 7, 2, and 5 ml/h, respectively. In Figure 8, the deviations in the green and red lines are caused by the "mechanical compliance" of the "red" and "green" syringes; if these compliances would have been zero, the deviations in the red and green lines would disappear.

From Figure 8, two important phenomena can be seen.

1) In all cases, the deviations from the constant setpoint values of the red and green lines take place in a direction "opposite" to the direction of the change (in setpoint value) of the blue line.
2) The depth of the dip in the red line at t = 0.5 h, with respect to the red steady-state line of 2 ml/h, is approximately 1.3 ml/h. This is equal to the depth of the dip in the green line, at the same point in time, with respect to the green steady-state line of 5 ml/h, because all syringes have the same compliance. As a result, when expressed as a percentage of the intended (setpoint) flow rate, the relative deviation caused by the dip in the red line at t = 0.5 h is much larger than the relative deviation caused by the dip in the green line at the same point in time.

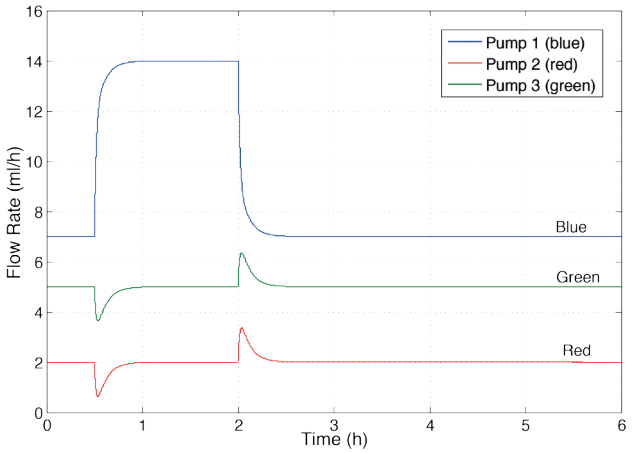

Figure 8. *Results from predictive calculations, showing calculated flow rates q1, q2, and q3 (see Figure 3).*

5 DISCUSSION

It is found, from the *in vitro* experiments, that dosing errors caused by the physical effects studied can be substantial. We found in the section "Dosing deviations in a clinical medication scheme" that a standard intervention of coupling an additional medication on the carrier flow causes an overdose in both other pumps, representing midazolam and noradrenaline. The dosing error in midazolam was 30% in more than 8 minutes. This could cause an adverse effect on the respiration. Although for at least some patients a relevant effect, the saturation of intensive care patients is intensively monitored, which would ensure that timely interventions could take place. Therefore, the most disturbing dosing error is the one found in the noradrenaline solution. This dosing error with a mean of 25% would cause the patient to experience a direct and higher increase in blood pressure than was intended by the noradrenaline medication itself. Because of the small therapeutic range and short biological half-life of noradrenaline, such an overdose could cause serious effects. Furthermore, in emergency situations in the operating room, for example, if a patient's blood pressure is falling rapidly, physicians need to act quickly. In such cases, higher flow rates, typically up to 50 ml/h, tend to be applied. When using carrier flows or multi-infusion combining high and low flow rates, the central line can become filled with a high concentration of noradrenaline or other potent drugs. If the physician is not aware of the "push-out" effect and only adjusts the noradrenaline and not the carrier flow in reaction to a blood pressure overshoot, this action can quickly lead to a dangerous and even fatal situation. Such a case was previously described by Ethgen et al. [7]. Therefore, the push-out effect is more pronounced when using high carrier flow rates or a combination of medications running with flows that greatly differ in rate. Moreover, in critical situations, the start-up times of more than 1 h for noradrenaline, as

seen in the section “Dosing deviations in a clinical medication scheme” (see Table 2), are of major clinical concern.Often in such cases, if the needed reaction in the patient fails to occur for too long due to the “push-out” effect, this can even prompt the physician to set the dose too high. From the part of the physician, however, this would be quite an intuitive action.

In the section “Start-up time measurement using *in vitro* flowmetry”, the start-up time could be approximated using a single exponential fit from 70 s onwards. The phenomenon before t = 70 s is often observed and may have several causes. A small gap between the pump and the plunger has been described [14,15] to prolong start-up time. Moreover, the friction between the plunger and the syringe wall may cause an extra resistance. The experiments show that the start-up time is a result of the combination of the mechanical compliance effects and the time delay due to the internal volume inside the infusion system. This explains the large difference in start-up times between the two experiments. The start-up time assessed in the section “Start-up time measurement using *in vitro* flowmetry” shows the effect of compliance only, typically a few minutes. Unfortunately, it is only this curve that is mandatorily measured to assess the quality of the infusion system. The start-up measurements in the section “Dosing deviations in a clinical medication scheme” show that the time delay due to the internal volume is often clinically far more relevant.

The theoretical considerations, the *in vitro* experiments and the computer simulations show that compliance is an important factor, contributing to the origin of relevant dose deviations. This is consistent with earlier studies [11,16,17]. The computer simulations show that, when the deviations are viewed as a percentage of the intended flow rate, the syringe compliance effects are particularly important at low flow rates. This underlines that, especially if low flow rates are applied, such as used in neonatology, the mechanical compliance of the syringes can significantly contribute to dosing errors, which was mentioned previously by several authors [10,18,19]. Unfortunately, the lowest flow rates are often used for the most potent drugs, such as inotropes. It is instructive to compare the magnitude of the dosing errors found from our experiments to the maximum volume displaced because of compliance effects (the compliance volume) set in standards of infusion devices, such as the NEN-ISO-7886-2 describing syringes for use in power-driven syringe pumps. In this particular standard and for a syringe of 20 ml and a typical maximum pressure of 40 kPa, the maximum compliance volume is 0.2 ml. This volume represents a 20 µg dose of our noradrenaline solution, which is clinically relevant. In many hospitals, 50 ml syringes are used as the default, even in the neonatology ward, because this practice is more efficient and reduces errors and the risk of infection that accompany syringe changes. Following the norm mentioned above, the maximum compliance volume for a 50 ml syringe is 1.2 ml. Therefore, conformation to this norm will not prevent dosing errors as large as 1.2 ml. The mechanical compliance of the syringes used is known to be dependent on several variables. In a related research [20] it is shown that the especially 50 ml syringe have the largest contribution the compliance of the complete infusion

set. The authors measured the compliance of different infusion systems components. Lucas et al. [21] found that only at low flow rates temperature influences the value of system compliance.

Many authors have stressed the necessity of placing anti-reflux valves [22] or minimizing internal volume [3,4,23]. Both 10 years ago [9] and recently [24,25], innovative connection mechanisms were invented, but have not extensively or successfully become a best practice yet. The exact reason is not known, but the fact that the difference in performance lies in the infusion system, which is not routinely measured in the standard quality measurements, might play a part. However, we think that actual application of these innovations of infusion technology, both of the pumps and the disposable infusion sets and syringes, is badly needed to really solve the problems found during multi-infusion.

No significant differences in the onset of drug delivery were found between the standard infusion set and the octopus infusion set with valves. A limitation of our experiment was that the octopus infusion set and the standard infusion line setups differed in internal volume, 1.8 ml for the standard infusion set and 1.6 ml for the octopus infusion set with valves, respectively. The measured quantities of both the start-up time and the dead volume were in agreement with the theoretical implications of the dead volume. However, the results from the infusion line with valves confirm that, in spite of the anti-reflux valves, dosing errors are still found.

Van der Eijk et al. [10] found longer start-up times with check valves (up to 43.7 ± 2.7 minutes) than without check valves (up to 27.6 ± 3.8 minutes) for a flow rate setpoint of 0.1 ml/h [10]. McCarroll et al. [19] evaluated anti-syphon valves at nominal flow rates of 2, 10 and 50 ml/h, using syringe pumps. Start-up times were longer when an anti-siphon valve was used at the lower setpoint flow rate of 2 ml/h. However, literature shows that, at the higher flow rate setpoints of 10 and 50 ml/h, start-up times differences between using a valve and not using a valve were less pronounced [19]. In fact, virtually none of the differences, using a valve and not using a valve, were statistically significant at higher flow rates [10,19]. These results are consistent with the differences found with our flow rate setpoints between 15 and 34 ml/h.

The outcome of this theoretical analysis is in agreement with the conclusion from a review on multi-infusion measurements by Snijder et al. [26]. They found that particularly system mechanical compliance and dead space volume (“push-out” effect) are often mentioned to play an important role in creating dose variations. Up until now, the typical way of dealing with these dose variations in clinical practice is to use practical solutions such as piggyback techniques [27] or quick change [28]. However, even when using these practicalities or rules of thumb, the errors unfortunately do not seem to be satisfactorily diminished.

In summary, our *in vitro* experiments and computer simulations of a three-pump multi-infusion setup show the following observations. First, the "push-out" effect produces dosing deviations (e.g. in midazolam or noradrenaline; see Figure 5) in the "same direction" as the direction of the change in flow rate setpoint (of another pump; e.g. the carrier flow). Second, the "syringe compliance effect" produces a deviation in the "opposite direction" with respect to the direction of the flow rate setpoint change. Finally, if the temporary deviations are viewed as "percentual" deviations with respect to the intended setpoint values, the (syringe) compliance effects are particularly important at "low flow rates".

As a result, the direction as well as the strength of the net total effect is highly unpredictable and often counterintuitive. This causes variations in drug delivery that are undesirable and can at times be dangerous. For example, a temporary deviation from the intended flow rate of a potent drug such as noradrenaline might cause dangerous blood pressure variations. For drugs that are intended to act quickly, be titrated to a customary dose, and intended be life-saving, this is a very unwanted situation. Therefore, to remedy this undesirable unpredictability, the amount of compressibility of notably the plungers in syringes should be reduced, especially for high-risk applications. Alternatively, the compliance can be measured to enable better predictions of the net outflow during setpoint changes, which might, in the future, be used to adapt and control the pump driver inline. Unfortunately, there are no written standards yet that give specific guidelines on the methods of ensuring a safe and sound drug delivery for (multi)infusion at high-risk applications.

At this time in Europe, the main directive concerning medical devices is the "Council Directive 93/42/EEC" (1993), including various amendments (e.g. 2000 and 2001). This directive is rather general and does not specify requirements on (the use of) drug delivery devices other than the statement that the manufacturer is responsible for an adequate flow rate accuracy and stability. The manufacturer should state the accuracy ranges. There are various written standards concerning the dosing accuracy and calibration of drug delivery devices (e.g. IEC/EN 60601-2-24). Manufacturers typically follow this written standard during the development and maintenance of their devices. However, no general standard exists on how the infusion devices should be used. Furthermore, there are no particular instructions on specific applications where accuracy counts most.

Adopting specific standards for high-risk applications would improve the reliability of the performance of the infusion system. We therefore advise to include specific requirements, into relevant standards, on the subject of syringe plunger mechanical compliance and system internal volume, for low flow rate and high-risk pharmaceutical multi-infusion applications.

6 CONCLUSIONS

In this paper, we showed that dosing errors can be studied using *in vitro* experiments based on spectroscopy and numerical modeling. The important mechanisms in multi-infusion are the “push-out” effect and system mechanical compliance. The two effects produce deviations in opposite directions with respect to each other. The *in vitro* experiments as well as computer simulations show that the direction as well as the strength of the deviations from the intended flow rates in multi-infusion are hard to predict in clinical practice and often counterintuitive. The measurements show that substantial dose deviations can occur long enough to have undesirable clinical effects, particularly when using inotropics or other potent drugs with a small therapeutic range. Where the “pushout” effect can have its most pronounced and dangerous effects when using high (carrier) flow rates, the compliance effect is most influential at low flow rates. This is confirmed in clinical case reports. From the results, we conclude that there is a need for a quantification of the impact of the compliance and “push-out” effect because these effects can cause clinically relevant dosing errors. Potentially, this quantification is required (once) for each specific (multi)infusion setup. To quantify the performance of the complete setup, there is a need for an accurate measurement of essential parameters in the multi-infusion setup, such as the mechanical compliance of the syringes. A next step would be to control the pump setpoints to deliver the required dosage to the patient. Infusion device manufacturers could thus use this metrological data to successfully improve drug delivery performance. We therefore advise to include specific requirements on compliance and system push-out effect of infusion medical devices for high-risk applications in relevant standards. In this process, the flow rate dependency of these effects for low and high flow rates should be taken into account. Thus, an increased focus and effort directed to the metrology of compressibility at low flow rates, combined with the preferential use of innovative techniques minimalizing “push-out” effects, will lead to enhanced controllability of drug delivery and consequently to better patient care.

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Chapter 3

The clinical perspective

Chapter 3.1

Hypertensive crisis during norepinephrine syringe exchange: A case report

Anesthesia & Analgesia Case Reports, accepted

The patient's family reviewed the case report and gave written permission (informed consent) for the authors to publish the case report.

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ABSTRACT

A 67 year critically-ill patient suffered from a hypertensive crisis (200 mmHg) due to a norepinephrine overdose. The overdose occurred when the clinician exchanged an almost-empty syringe and the pump repeatedly gave an error. We hypothesized that an object between the plunger and the syringe driver may have caused the exertion of too much force on the syringe. Testing this hypothesis *in vitro* showed significant peak dosing errors (up to +572%) but moderate overdose (0.07 ml, +225%) if a clamp was used, and a large overdose (0.8 ml, +2700%) if no clamp was used. Clamping and awareness is advised.

1 INTRODUCTION

Adverse events related to intravenous administration of vasoactive medication are relatively common, due to e.g. preparation and prescription errors [1]. However, many errors with vasoactive medications have been related to infusion technology [2], e.g. pump malfunctions [3]. In addition, characteristics of the infusion system may yield dosing deviations after interventions such as a syringe exchange [4], flow rate changes [5,6] and vertical displacement of the pump [7]. In this case report we describe a critical care patient receiving an accidental overdose of norepinephrine, probably caused by a pump malfunction during a syringe exchange.

2 CASE DESCRIPTION

We present a 67 year male intensive care unit (ICU) patient who unintendedly received a norepinephrine overdose and subsequently developed serious hypertension probably caused by a syringe pump malfunction.

The patient was admitted to the ICU of the University Medical Center Utrecht, the Netherlands, following a bicycle accident and presented with an out of hospital cardiac arrest (OHCA) and a high cervical (C1 and C2) paraplegia injury. The patient wished to be treated despite a poor prognosis. The patient's medical history included COPD gold I, for which he received no medication, unilateral glaucoma on the right side, treated hypertension and benign prostatic hypertrophy. Regular home medication included perindopril 8 mg per day. On the ICU the patient presented with a spinal shock causing hypotension. To treat this condition, a vasopressor, norepinephrine (0.1 mg/ml by protocol) was administered continuously (5-6 ml/h) using a syringe pump Perfusor® Space (B.Braun Perfusor, B.Braun, Melsungen, Germany) in order to achieve a maintenance dose of approximately 8-10 µg/min.

The norepinephrine was administered together with a carrier NaCl flow of 10 ml/h. Both medications were first connected to two standard 1m-infusion lines (Cair LGL, Civrieux d'Azergues, France) and, subsequently joined using an 'octopus' infusion set (CODAN Medical, Lensahn, Germany). The vascular access device used was a seven-Fr-triple-lumen catheter (Argon Careflow, Plano, TX, USA) which entered the patient at the v. femoralis. The norepinephrine and NaCl were connected to the distal lumen of the catheter, another NaCl flow (5 ml/h) was connected to the medial lumen and venous pressure measurement was performed through the proximal lumen. The syringe pumps were equipped with B.Braun Omnifix syringes (B. Braun, Melsungen, Germany) (Figure 1).

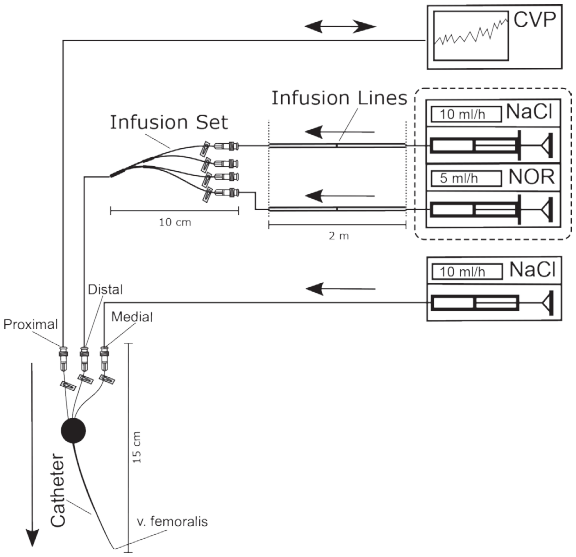

Figure 1. *Infusion setup. Within the square area indicated with the dotted lines are the NaCl and norepinephrine (NOR) pumps. Only these pumps were involved in the incident. The drugs from both these pumps were joined using an infusion set and subsequently administered to the patient using the distal lumen of a triple-lumen catheter. An additional CVP measurement and NaCl flush, respectively connected to the proximal and medial lumen of the catheter are indicated as well. The flow rates are denoted in the schematic representations of the infusion pumps. Also indicated are the flow rates during the incident, these were acquired from interviewing the nurse and, in case of the norepinephrine pump, from reading out the pump log files.*

While administering norepinephrine, the syringe pump produced an alert indicating that the syringe will be empty within ten minutes. Therefore, the clinician started a syringe exchange procedure. However, upon mounting of the new syringe, the pump signaled “repeat syringe exchange”. The full syringe was removed from the pump and placed back. The pump gave the same error message again, three times in a row. At the fourth attempt, the syringe was mounted inside a different pump, which did not signal an error. Further details about the duration of the syringe exchange procedure are unknown. Then, following restart of the infusion, the patient instantly developed a period of severe hypertension (MAP 200 mmHg, see figure 2a) lasting for several minutes, which strongly suggested that inadvertently an overdose of norepinephrine had been administered. To lower the MAP, labetalol was administered. After stabilization, ECG values were indicative for a myocardial infarction (Figure 2b), ultra sound confirmed that the anterior heart wall movement was impaired.

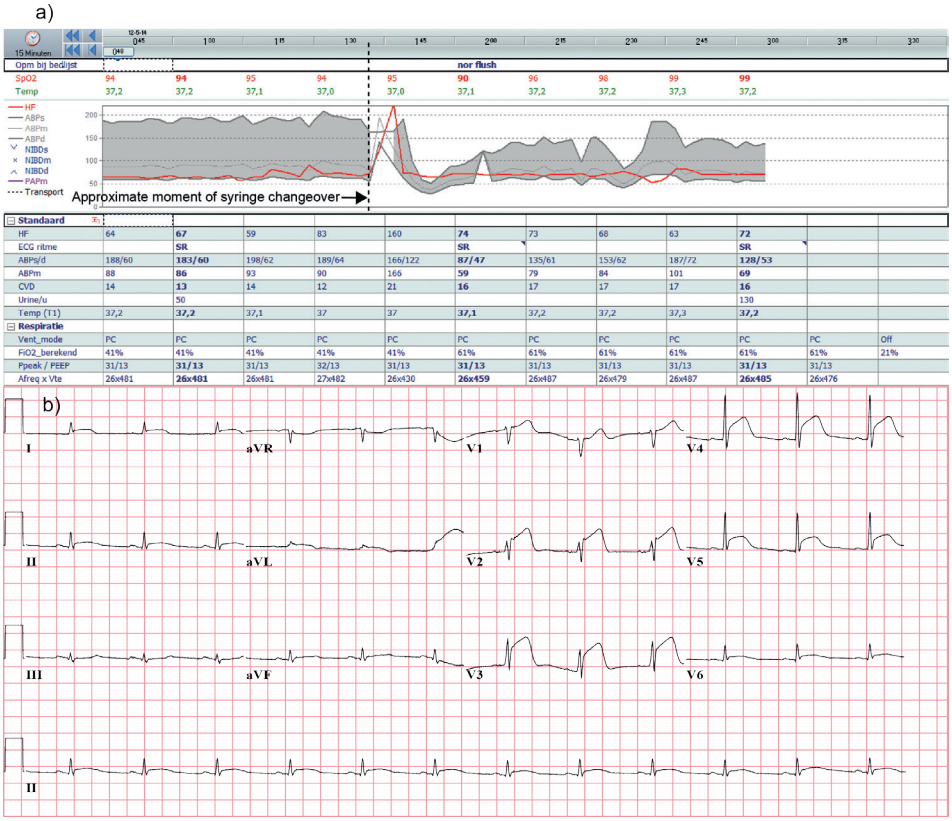

Figure 2. *Vital signs during the incident in the night from 11-05-2014 – 12-05-2014 at approximately 01:50. MABP > 200 mmHg, diastole pressure 150 mmHg, systole pressure 100 mmHg, HR > 200 bpm, (a). ECG-values approximately 10 minutes after the incident. Clearly visible ST-elevation in nodes I, II and III are indicative of myocardial infarction directly after the incident. Heart rate normalized quickly (approximately 70 bpm) (b).*

Coronary catheterization was conducted and the planned operation was postponed. Angiography showed a spastic coronary artery, which improved during the angiography procedure and the patient survived the incident. Blood test results showed a mild increase of serum troponin with a maximum of 5510 ng/l; and creatine kinase MB with a maximum of 27, indicative for myocardial cell damage. During admission the patient developed a ventilator associated pneumonia, serious pressure sores and chronic pain syndrome. After 2.5 months a decision was made, in agreement with the patient's wish, to discontinue treatment and the patient died.

3 DISCUSSION

After the incident, the pump was inspected by a maintenance engineer who found no defects, erroneous flow rate settings or other abnormalities. Moreover, none of the actions in this case report show a direct causal relationship with the apparently large epinephrine overdose. However, our investigation showed that the pump gives the reported error message if an object becomes obstructed between the syringe plunger and the syringe driver. In that case, the syringe driver exerts too much force on the syringe plunger (Figure 3). In our hypothesis, this may repeatedly have occurred causing pressure build-up in the syringe, which in turn causes too much flow and thus dosing errors upon release of the clamp, or immediately if no clamp is used.

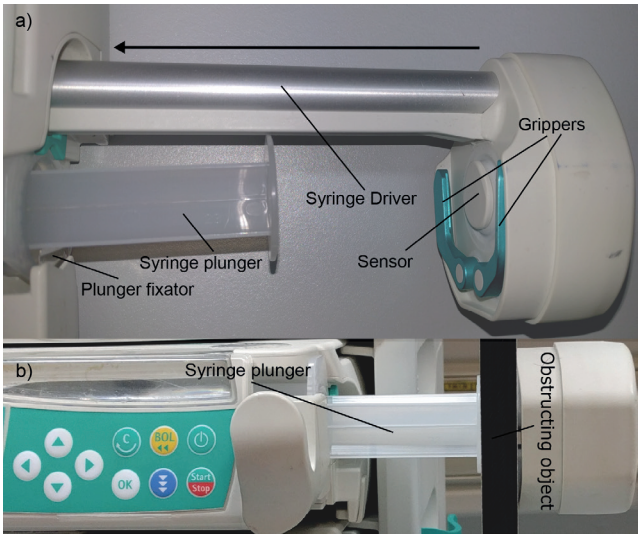

Figure 3. *Mechanism of the syringe driver of the syringe pump in the laboratory, identical to the pumps described in the case report. After the syringe is placed, the syringe plunger is fixated using a plunger fixator knife. Next, the syringe driver moves towards the syringe plunger until the sensors registers the plunger. After this, the grippers grab the syringe plunger and the plunger fixator is retracted. The grippers protrude somewhat over the sensor (a). Obstructing object allowing the syringe driver to exert force on the syringe plunger while the thickness of the grippers prevent the sensor to signal the syringe driver to halt. The syringe driver eventually does retract. However, the force exerted is large enough to cause dosing errors (b).*

3.1 Measurement setup

The plausibility of this obstruction hypothesis was tested in a laboratory setting. In order to reproduce the clinical situation in an *in vitro* experiment, the infusion setup was reduced to the hardware elements that were relevant to the norepinephrine overdose incident, see the encircled area of Figure 1. The outflow of the triple lumen catheter was submerged in 5 cm of water to simulate the venous pressure. The outflow was measured gravimetrically

using a precision (±1 mg) balance (PGW 450, Adam Equipment, Danbury, CT, USA). The sample time was 1 second.

3.2 Experiments

Firstly, the syringe exchange was performed according to the clinical protocol described earlier. To reproduce the syringe driver obstruction in a systematic manner, the grippers used to grab the plunger were deliberately obstructed with a solid 'obstructing object' between the syringe driver and the plunger (Figure 3b). Consequently, the pump signaled the error message and asked the user to repeat the syringe exchange, this procedure was repeated three times. Next, the obstructing object was removed, the syringe was mounted correctly and the clamp was released. Secondly, the experiment was repeated without the placement of a clamp. Lastly, a nominal syringe exchange, i.e. a syringe exchange without any obstruction or errors, was investigated. In each case, the period after the interventions, until the set point of the cumulative flow rates (15 ml/h) was reached again was recorded. In this period, the 'peak error' (ml/h), i.e. the highest value measured, minus the nominal value (15 ml/h), and 'excess Area Under the Curve (AUC)', i.e. the measured volume minus the nominal volume (ml), were acquired and presented. The set point cumulative flow rate (15 ml/h) or nominal volume delivered (flow rate x time), are considered 100% throughout.

The experiments were repeated 5 time (n=5). The results can be found in table 1 and are presented as mean +/- SD, An independent-Samples t-test was applied using IMB SPSS version 21 (IMB corp., Armonk, NY, USA).

Table 1. Results of experiment

	Peak Error (ml/h)	p value	AUC error (ml)	p value
Obstructed syringe change with clamp	85.8 ± 12.2 (+572%)	*** p < 0.001	0.07 ± 0.02 (+225%)	** P < 0.01
Obstructed syringe change without clamp	926 ± 65.3 (+6173%)	**** p < 0.0001	0.81 ± 0.07 (+2700%)	**** p < 0.0001
Nominal syringe change with clamp	45.5 ± 12.0 (+303%)	-	0.03 ± 0.02 (+127%)	-

The results of three interventions are shown. In each case, the nominal set point flow rate is considered 100%. The volume delivered by a flow rate of 15 ml/h during a time t is considered 100% as well. First, the syringe driver was obstructed and the infusion line clamped. The obstructed syringe driver was allowed to exert force on the plunger three times, the fourth time the syringe driver grabbed the syringe plunger properly and the infusion was continued, after this the flow rate was measured. Second, the experiment was performed without a clamp, in this case the plunger driver was again obstructed and allowed to exert force on the plunger. Because this produced an overdose immediately, the flow rate was registered during the syringe driver exerted force on the plunger. Finally, a nominal syringe exchange, according to the protocol, was reproduced in the lab, in which the pump was not obstructed and no errors or problems occured. After these three intervention, the peak error value and the excess AUC values were acquired from the flow rate data. The AUC is defined as the excess volume delivered from the point after the intervention and during the entire period that the flow rate remained larger than 15 ml/h. The p-values are comparisons of the nominal and obstructed syringe exchanges, p values smaller than 0.05 were considered statistically significant.

The results show that the syringe exchange always produced an overdose after starting the pump, even in the nominal case. However, it was found that after the pump was obstructed, a significantly larger overdose occurred. The peak error, i.e. the highest measured deviation from set point of 15 ml/h, was 85.8 (+572%) with clamp. During a short period of time (7 seconds) a 225% and 2700% overdose was infused to the patient, with and without clamp, respectively.

3.3 Advice and clinical considerations

Unexpected physiological, pharmacokinetic or –dynamic responses are unlikely as the norepinephrine was administered for several hours without any problems. It is therefore reasonable to assume that there is a causality between the syringe exchange procedure and the blood pressure incident.

The hypothetical obstruction caused clinically significant overdoses. If the syringe driver was obstructed, an additional dose of at least 2.33 (with clamp) and 27 µg (without clamp) was delivered in approximately 7 seconds. Although both these quantities exceed the maintenance dose, only the unclamped situation is likely to produce the hypertensive crisis shown in Figure 2. Moreover, clinicians should note that in these cases, a second overdose may occur because the ratio in concentration between the NaCl and the norepinephrine pump is temporarily changed at the mixing point of the infusion set, along with the flow rate deviation [6], which only occurred in the norepinephrine pump in the described case.

Although clinicians suspect that the pump may become obstructed spontaneously, albeit rarely, the authors were not able to establish proof for this nor did the authors investigate the prevalence of the malfunction. However, in clinical practice it is not unlikely that the syringe driver may indeed become obstructed by an infusion line or some other object, it is therefore important that clinicians are aware of these phenomena. Nevertheless, if the syringe after not being recognized is decoupled, the pressure build-up is in all likelihood normalized as well. Of course, infection risk should be taken into account in that case. Moreover, technical innovations such as less protruding grippers or reducing the force exerted by the syringe driver might also reduce or eliminate the effect of the described malfunction. Therefore, the norepinephrine overdose due to the technical glitch investigated in this study is deemed plausible but avoidable. Clamping the line, however, is essential. Clinicians who were treating the patient in the described case considered the possibility that line was not fully clamped. Failing to clamp the infusion line may produce an overdose for at least two reasons. First of all, free flow may occur. In such a case, the higher situated syringe empties into the patient because gravity ‘pulls’ the medication towards the patient [8]. Second, as the results showed, an obstructed syringe driver may produce an overdose of almost 1 ml if the infusion line is not clamped, despite the fact that a blade-like fixator is placed inside the plunger by the pump.

4 CONCLUSIONS

It is plausible that the norepinephrine overdose was due to the potential failure, where the syringe driver is obstructed. Partial human error is still a likely alternative explanation, especially the possibility that clamping the infusion line did not function properly, which may cause free flow. Moreover, if the line is not clamped and the pump is obstructed, the malfunction may produce a significant overdose of almost one ml. Therefore a combination of an obstructing object between the syringe driver and plunger and an unclamped line explains both the severity of the overdose and the error message of the pump described in the case report. This study therefore reinforces the importance of using a clamp during the exchange procedure. Additionally, removing the syringe from the pump each time the pump fails to start is advised. Other physical and technical errors, as well as unexpected pharmacological or physiological responses, are improbable.

ACKNOWLEDGEMENTS / ETHICS STATEMENT

This case has been reported to the Dutch Health Care Inspectorate (registered as number M1006037).

The authors would like to thank dr. R.L.M. Schoffelen for his contribution to possible explanations for the incident.

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Chapter 3.2

Impact of physical parameters on dosing errors due to a syringe exchange

Manuscript in preparation

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ABSTRACT

Introduction: Infusion therapy is challenging and dosing errors may occur due to physical phenomena related to the infusion hardware, despite the use of accurate syringe pumps. These errors typically occur after interventions, such as the exchange of a syringe. We aimed to characterize and quantify dosing errors due to a syringe exchange in relation to physical properties of infusion hardware

Methods: An analytical simulation model was used to investigate dosing errors due to three different syringe exchange mechanisms (variations). Each mechanism involved a fast syringe pump, containing a non-critical medication, and a slow syringe pump, containing a critical drug. The mechanisms were also reproduced in *in vitro* experiments to verify the simulation results. In addition, impact of syringe size, infusion set compliance, catheter diameter and the duration of the syringe exchange procedure on the quantity of the dosing errors was investigated.

Results: The syringe exchange of the slow pump resulted in an additional delay of up to 3536 seconds due to backflow. Syringe exchange of the fast pump resulted in an undiluted volume of critical drug (0.17 ml) accumulated in the infusion system, which may result in a dosing error rate of 2400%. The quantity of the dosing errors are related to the syringe exchange duration; however, impact of infusion hardware properties is generally larger. Smaller syringes, catheters with larger diameters and less compliant infusion systems in general give rise to smaller dosing errors during a syringe exchange. If both lines are clamped, additional dosing errors can be prevented.

Conclusion: Infusion hardware has a substantial impact on the dosing errors during a syringe exchange. Clamping or blocking the infusion lines using, e.g. stopcocks, on all infusion lines during a syringe exchange is essential.

1 INTRODUCTION

In critical care, almost all critically ill patients require intravenous (IV) infusion therapy. However, infusion therapy is challenging and constitutes a high potential for adverse effects [1–6]. There are several reasons for this. Many patients in critical care suffer from conditions that require the administration of critical drugs, such as, vasoactive drugs (inotropics), sedatives, analgesia etc. For example, patients on the ICU are frequently diagnosed with hypotension and require the immediate administration of vasopressors. However, these potent short- and rapid-acting inotropic drugs typically have narrow therapeutic windows and short half-lives. Consequently, vasopressors must be administered continuously, accurately and precisely. In order to meet this demand, syringe pumps are used. Another important difficulty is limited vascular access, the challenging nature of inserting a vascular access device [7] and the high risks of infection such as catheter-related sepsis [8,9]. To reduce the vascular access points to a minimum, multiple pumps are used to deliver their drugs to one central infusion set and catheter lumen. This principle is called multi-infusion [10] and is associated with significant flow rate variability and dosing errors, despite the use of syringe pumps [10–12]. Even small dosing errors in inotropics may cause hemodynamic instability, which may cause conditions such as periventricular and intraventricular hemorrhages [13]. This is especially true during clinical interventions [14]. An important example of these interventions is a syringe exchange (also called syringe changeover), i.e. the renewal of an old, empty syringe with a full new one. Syringe exchanges are frequently conducted due to the limited capacity of syringes, which is typically 10 to 50 ml. From clinical practice and laboratory investigations it is known that a syringe exchange produces relatively large dosing errors and several techniques aiming to reduce these errors have been investigated [15–19]. Argaud et al. [15] argued that operators may lack knowledge about syringe exchange mechanisms and therefore resort to poorly established empirical procedures. In a before and after intervention study they found that standardization of a syringe exchange procedure resulted in significantly less incidents [15].

Although laboratory studies have produced ample evidence that physical properties of the infusion hardware are related to dosing errors [20], the exact relationship between the syringe exchange duration, the infusion hardware and drug dosing errors remains elusive. Moreover, laboratory investigations are essentially limited to static infusion configurations, i.e. the properties of the hardware and therefore the physical parameters are either fixed or the variation is limited. Simulation studies may be able to establish this relationship better, which could help to provide a well-substantiated advice for hospital personnel.

Our objective is two-fold. First, to investigate the impact of physical parameters on dosing errors as a result of a syringe exchange in a realistic multi-infusion setup. Second, to investigate the impact on the dosing error of hypothetical situations due to a syringe exchange, in which the physical parameters of the infusion hardware, as well as syringe exchange duration time, are varied.

1.1 Theoretical simulation model

An analytical theoretical simulation model has been described previously (chapter 2.3) The model incorporates the three most important [20] physical parameters necessary to simulate an infusion system. The physical parameters are:

1. **Mechanical compliance (C)** [volume per pressure]: which occurs due to the elasticity of components, especially the syringe.
2. **Flow resistance (R)** (pressure per flow rate): which is due to the small diameters of some components, most notably the catheter.
3. **Dead volume** (volume): which is due to the inevitable volume inside the infusion lines between the mixing point and the catheter tip in the patient (see Figures 1 and 2). The time required for a drug to travel through the dead volume is denoted as T_{delay}.

In practice, the flow rates initially generated by the pumps, in turn, are influenced by the compliance and resistance. Consequently, all the variables are interdependent.

1.2 BASIC MECHANISMS THAT ARE EXPECTED TO PRODUCE DOSING ERRORS AS A RESULT OF A SYRINGE EXCHANGE

In the following subsection, three typical situations of syringe exchanges are presented that were derived from daily hospital practice. These three situations are selected on the basis that they illustrate three main types of mechanisms that, according to our hypotheses, in some cases produce dosing errors.

In all three cases, a “fast” (high flow rate) pump, syringe and infusion line *F,* filled with e.g. saline or total parenteral nutrition (TPN) and a “slow” (low flow rate) pump, syringe and infusion line *S* filled with a critical medication, e.g. dopamine or norepinephrine, are combined using a multiple-in single out infusion set. Subsequently, this set is connected to a single catheter lumen, which enters the patient’s bloodstream. The three basic syringe exchange mechanisms (A - C) are defined as follows:

Mechanism A) *Complete changeover of all syringes in the multi-infusion setup.* In this case, it is common practice to first “clamp off” all infusion lines in order to ensure that no longer any pressure or flow is conveyed from the syringes into the mixing point, as well as to prevent free flow.

Hypothesis: Clamping correctly does not allow any of the physical effects simulated in the model to produce dosing errors.

Mechanism B) *Only the “slow” syringe, connected to line S is exchanged (with a new syringe containing the same critical medication), without clamping off or stopping the “fast” infusion line and pump F.*

Hypothesis (Figure 1): It is known that due to the dead volume, medication introduced at the mixing point requires time to travel through the dead volume and reach the patient at the catheter tip; we have previously defined this time as T_{delay} (chapter 2.3). However, an additional delay (T_{extra}) may occur. Once the new syringe is installed and the infusion line is reconnected to the infusion set, an immediate pressure coming from the rest of the infusion setup, acting on the infusion line S, is introduced. It is expected that some of the fluid from pump and infusion line F ($V_{backflow}$) is therefore pumped into infusion line S. Consequently, it is expected that T_{delay} will be prolonged with an extra term T_{extra} because the fluid requires to be pumped out of the "slow" infusion line (line S) before the administration of critical drug S is reestablished.

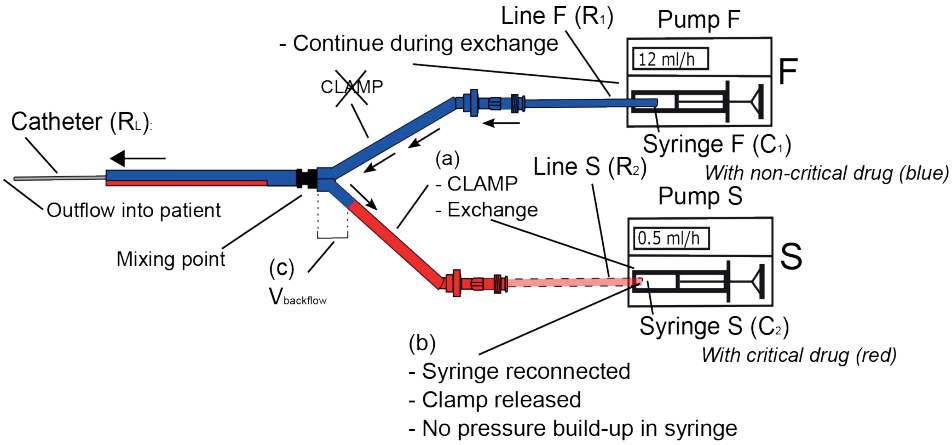

Figure 1. *Blue is the non-critical drug from the fast pump F, red is the critical drug from pump S. Mechanism explaining the extra delays caused by back flow that is facilitated by the compliance of syringe S (C_2) is illustrated. First, pump S is stopped, and the line from pump S clamped (a) while pump F continues. Once a new syringe has been mounted, the clamp is released (b), allowing the pressure coming from the rest of the system to cause the non-critical drug from pump F to be pumped beyond the mixing point into the line of pump S (c). Subsequently this extra volume $V_{backflow}$ of non-critical drugs is pumped towards the mixing point with 0.5 ml/h, thus causing an extra delay.*

Mechanism C) *In this case, only the "fast" syringe F is exchanged (again, with a new syringe containing the same fluid, e.g. TPN), without clamping off the "slow" infusion line of pump S, or stopping the "slow" pump S.*

Hypothesis (Figure 2): The fact that the critical medication from the "slow" line is still being pumped into the mixing point causes the build-up of a volume $V_{undiluted}$ inside the infusion set that consists of critical medication that is not diluted by the fluid coming from the "fast" line F. After T_{delay} it is expected that this volume of undiluted medication is administered to the patient with a much higher dosing rate (drug per unit time, e.g. µg/min) than intended. Furthermore, the fact that the pressure from the fast line is removed instantaneously upon removal of the syringe F, causes a "release" of additional critical medication from the compliant volume of the slow syringe S into the mixing point.

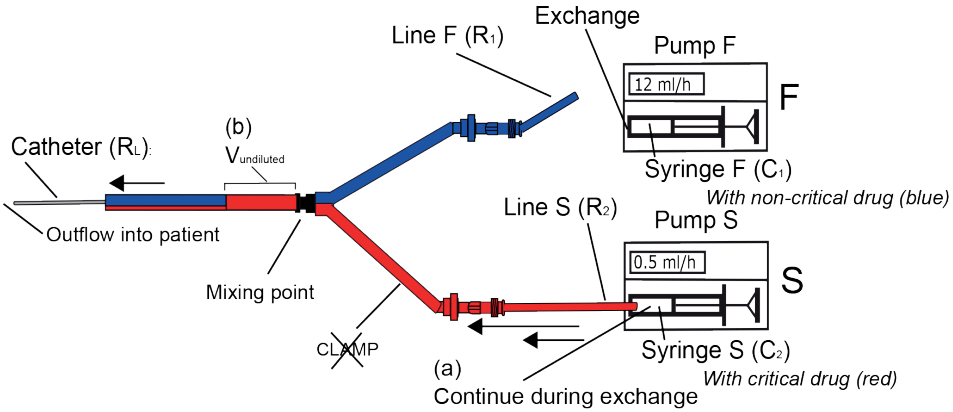

Figure 2. *Mechanism C. Blue is the non-critical drug from the fast pump F, red is the critical drug from pump S. The critical drug is poured in undiluted from beyond the mixing point, indicated as* $V_{undilted}$*. The volume of* $V_{undiluted}$ *is dependent on the resistances and compliances indicated in the schematic.*

2 METHODS

2.1 A generic clinical case

To start with, a generic NICU-case based on a patient treated on the NICU at the Wilhemina Children's Hospital, Utrecht, the Netherlands (WKZ) is described. This case was investigated in order to acquire typical parameters of a challenging case of infusion therapy. Accordingly, the infusion hardware properties and flow rates used in this case are defined as the "generic clinical case" and used for the *in vitro* experiments and simulation explained later. Because the patient suffered from hypotension, IV-treatment with dopamine was started with a flow rate of 0.5 ml/h (pump S). Multiple medications are typically co-administered with dopamine, for simplicity we defined a second pump as the total parenteral nutrition (TPN) pump with a flow rate of 12 ml/h (pump F). The pumps used were two Perfusor Bbraun syringe pumps (B.Braun, Melsungen, Germany) which were equipped with 50 ml-syringes B.Braun Omnifix (B.Braun, Melsungen, Germany). Due to drug incompatibility, a separate infusion line and catheter lumen were unavailable for both dopamine and TPN, which is why these medicine were administered together. The co-administration was achieved using a custom 173 cm central infusion set disposable (Impromediform GmbH, Lüdenscheid, Germany) (Figure 3). Both pumps were connected to the mixing point M2. Subsequently, the central infusion line was connected to the distal lumen of a 4 Fr double lumen catheter (Vygon, Ecouen, France). The catheter entered the patient through the umbilical route.

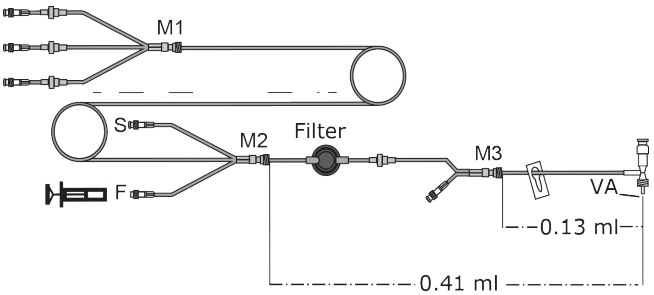

Figure 3. *Neonatal infusion set disposable (173 cm), going upstream from mixing points M1 to M3. The Luerlock connector at M1 may be used for non-critical medication, not considered in this study. M2 is used for the pumps containing the non-critical and critical medication, which are co-administered through one line, respectively indicated as F and S. M3 is used for lipids, not considered in this study. VA indicates the outflow and the location where a vascular access device, e.g. the catheter, is typically connected.*

The duration of a syringe exchange procedure varied. The protocol for syringe replacement, if it exists at all, may differ per hospital. A variation of methodologies was observed to conduct the changeover. For example, if the infusion lines were also renewed, the exchange process took longer compared to the situation in which only the syringes were exchanged. From our own time measurements on the NICU it was found that a syringe exchange procedure, performed by an experienced nurse, takes approximately 30-120 seconds.

As stated in the introduction, three typical situations of syringe exchanges are presented that were directly derived from daily hospital practice. Mechanisms B and C were selected on the basis that they illustrate two main types of mechanisms that, according to our hypotheses, produce dosing errors. Refer to Figure 4 for an overview of all syringe exchange mechanisms (A-C) and corresponding flow rates of pumps F and S.

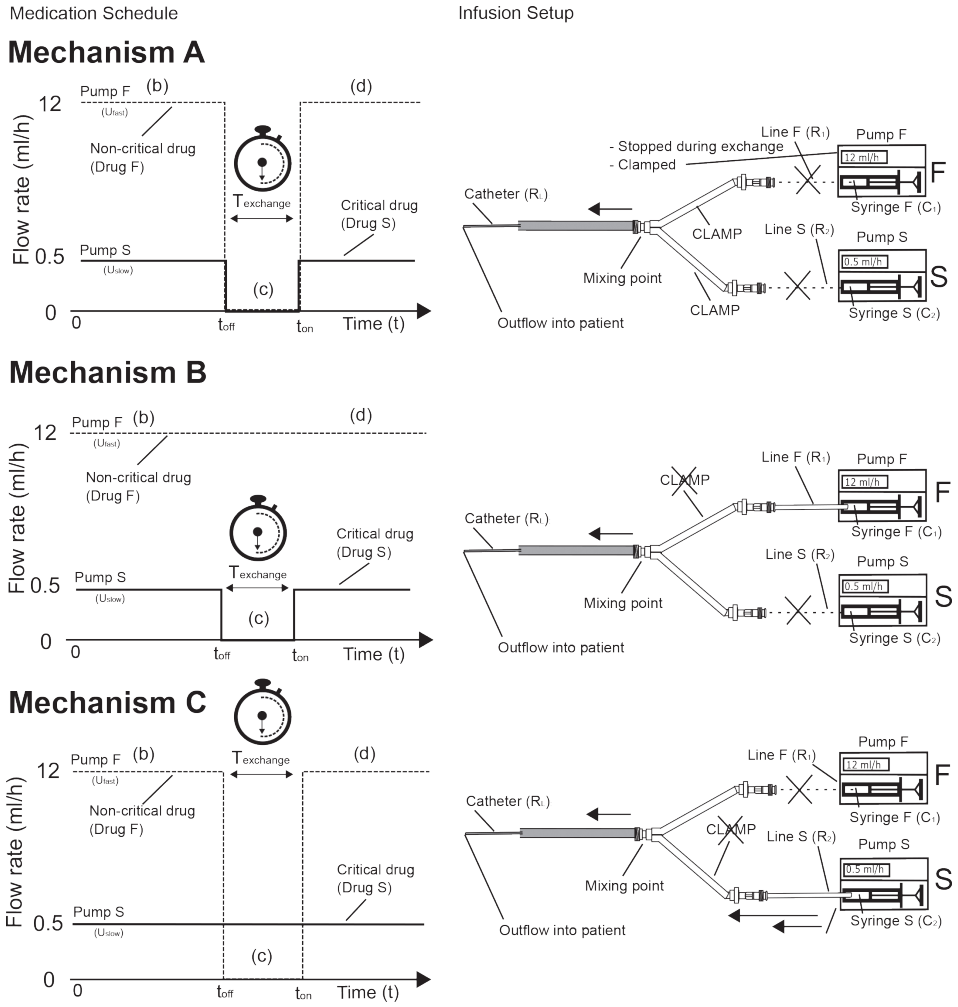

Figure 4. *Schematic of a graph representing the set-point flow rates of two pumps F and S as a function of time, for mechanisms A-C (left). The Flow rates of the fast pump F and slow pump S are 12 and 0.5 ml/h, respectively (b). The syringe exchange is performed between t_{off} and t_{on} for a period of $T_{exchange}$ (0-120 seconds), according to the description of mechanism A, in which both pumps are exchanged, mechanism B, in which the slow pump S is exchanged, and mechanism C, in which the fast pump F is exchanged (c). Next, the delivery was continued, in this period dosing errors and delays in drug delivery were observed (d). The corresponding condition of the infusion setup is represented schematically (right). Compliances C_1 and C_2 resp. of the syringes F and S and resistances (impedances) resp. of the infusion lines F (R_1) and S (R_2) are indicated. Resistance of the catheter R_L is indicated as well.*

2.2 Generic Mathematical modeling of a syringe change: multiple causes and multiple effects

The simulation model is able to predict and quantify the dosing errors and delays of drug delivery that were caused by the previously described syringe exchanges. The model also allows to gain insights about the mechanisms behind these dosing errors. Moreover, with the simulation model it is possible to quantify the dosing errors for alternative cases (and infusion setups). A variety of these combination will be simulated according to the mechanisms A-C.

Input

The dosing errors are dependent on several physical parameters, which in turn are based on the physical properties of the infusion hardware. These physical parameters are used as input parameters for the model. In the following, each input parameter will be explained.

The flow rates were according to the case described earlier (Figure 4). Next, the syringe exchange was simulated for the pumps S and/or F, according to the mechanisms A-C. In principle, a syringe exchange results in a temporary and abrupt decrease in flow rate from the set point to 0 ml/h (Figure 4). The syringe exchange duration ($T_{exchange}$) was varied according to the clinical case described earlier, it was decided to add an extra margin in order to observe possible theoretical effects. For the simulation, $T_{exchange}$ was varied between 0-240 seconds.

Varying hardware parameters within realistic boundaries

In order to investigate the influence of the physical parameters, low and high extremes for each parameter within realistic boundaries in critical care were explored. The quantities of the physical parameters were either acquired from literature, measured or calculated for this study. Table 1 lists all the physical parameters related to infusion hardware. See appendix II for the methodologies used to acquire the hardware parameters.

- Mechanical compliance (C):

Compliance is mostly related to syringes. Some syringes are more rigid, additionally, smaller syringes are known to be less compliant [21,22]. However, some of the compliance is also caused by filters, the infusion line and the pump itself [23,24]. We previously found 2.1 ml/bar (2.1 x 10^{-5} ml / pa) for a relatively compliant setup including a filter and a 50-ml B.Braun syringe (B.Braun, Melsungen, Germany), which approximately corresponds to the compliance of the generic clinical case and *in vitro* setup (explained later). The filter was estimated to have a compliance of about 0.5 ml/bar (0.5 x 10^{-5} ml / pa) [23]. For a more rigid setup with a 50-ml syringe, 1.0 – 1.5 ml/bar (1.0 – 1.5 x 10^{-5} ml / pa) was found [23]; as an intermediate value 1.5 ml/bar was therefore used. A very small compliance of 0.159 ml/bar (0.159 x 10^{-5} ml / pa) was measured for a 10-ml Plastipak syringe (Becton Dickinson, NJ, USA) syringe (appendix II). This was measured in a similar fashion as previously described [23].

- Flow resistance (R):

Resistance was mostly related to the catheters. To acquire a full range of resistive quantitates, the resistances of three catheters were acquired. The catheters were a Vygon Premicath 1-Fr (Ecouen, France), Vygon double lumen (proximal lumen used) umbilical catheter 4-Fr (Ecouen, France) and 7-Fr catheters Argon Careflow Single Lumen (Plano, TX, USA). The resistances were calculated and measured by producing a flow, with the use of a non-compliant syringe and syringe pump, Chemyx Nexus 3000 (Stafford, TX, USA) and an in-line pressure gauge SensorTechnics CTE8002AY4N and CTE8005AY4N (Berlin, Germany) (appendix II). See Table 1 for an overview of the compliance and resistance values.

Table 1. Infusion hardware input parameters, compliance, resistance and dead volume, respectively related to syringe and filter compliance, catheter resistance and the volume between the mixing point and the patient.

Compliance (ml/Pa)	Resistance (Pa per ml/h)
10-ml syringe	**1 Fr Catheter**
0.159×10^{-5}	1949
50-ml syringe	**4 Fr Catheter and flowmeter***
1.5×10^{-5} [23]	23.68
50-ml syringe (non-rigid, filter)*	**7 Fr Catheter†**
2.1×10^{-5} [23]	0.058
	in vitro* situation (4 Fr catheter + flowmeter)
	23.68 + 1121 = 1145

**Value used in the in vitro simulation based on the generic clinical case with a neonatal infusion set including a filter. †Value calculated using the Poiseuille law.*

Output

In this study, the errors following a syringe change after the pump was restarted after t_{on} (Figure 4) were investigated as a function of the input parameters, defined at the previous section. Mechanism A is not explicitly described in this section because no additional dosing errors can occur from the simulation. In **mechanism B** the quantity $\mathbf{T_{extra}}$ was acquired. This is time that the patient does not receive the critical medication due the syringe exchange, in addition to the unavoidable $\mathbf{T_{delay}}$ and $\mathbf{T_{exchange.}}$ In **mechanism C** the quantity $\mathbf{V_{undiluted}}$ was acquired. This is the amount of drug solution unintendedly not diluted by the faster pump F. The simulation results based on the multi-infusion system used in the *in vitro* experiments (explained later) are defined as the "*in vitro*".

The end point quantities of the simulation model and their dependent parameters are summarized as follows:

(1) Mechanism B: $\mathbf{T_{extra}}$ (R,C) [s] : The duration in seconds, in addition to T_{delay} and $T_{exchange}$, in which the patient does not receive the critical medication presented in seconds as a function of resistance (R) and compliance (C).

(2) Mechanism C: $\mathbf{V_{undiluted}}$ (R,C,$\mathbf{T_{exchange,}}$) [ml] : The volume in milliliters of critical undiluted

medication administered to the patient as a function of resistance (R), compliance (C) and the duration of the exchange procedure ($T_{exchange}$)

The equation that were used, were evaluated in Mathematica 10.3 Wolfram (Champaign, IL, USA). See appendix I for an overview of the equations used.

2.3 In vitro experiments

In order to validate the simulation results experimentally, the syringe exchange procedures were mimicked *in vitro* in a laboratory according to the three mechanisms A - C (Figure 4). Two different *in vitro* experiments were performed to acquire T_{extra} and $V_{undiluted}$ experimentally for mechanisms B and C, respectively. For mechanism A it was experimentally confirmed that no additional dosing errors occurred. Hardware properties and flow rates of the generic clinical case were used.

Mechanism B

In order to measure $T_{extra,}$ the cumulative flow from pumps S and F at the catheter tip was measured using a Coriolis flowmeter M12P (Bronkhorst, Ruurlo, The Netherlands). The cumulative flow rate was 12.5 ml/h in steady state prior to the syringe exchange, i.e. $U_{total}(t) = U_{fast}(t) + U_{slow}(t)$ [ml/h], where $U_{total,}$ U_{slow}, U_{fast} and t are the total flow rate, the flow rates of pumps S and F, and time, respectively. After the syringe exchange, when the syringe S is reattached, the flow rate U_{fast} of pump F (12 ml/h) remains unaltered. Consequently, any flow registered by the flow meter lower than 12 ml/h necessarily flows towards the newly attached syringe S. The time from the point where the flow rate is lower than 12 ml/h, after syringe S is reattached, until the flow rate of 12 ml/h is reached again is defined as $T_{1.}$ The total volume produced during T1 (while the total flow rate was lower than 12 ml/h) was defined as backflow ($V_{backflow}$) [ml]. Once the measured flow rate is larger than 12 ml/h again, pump S (with a set point of 0.5 ml/h), thus produces a flow rate larger than 0 ml/h and therefore pushed the volume $V_{backflow}$ of the non-critical medication (drug F), still inside line S, beyond the mixing point. From this tipping point, pump S produces a flow rate of 0 - 0.5 ml/h. Assuming that U_{fast} retains a flow rate of 12 ml the whole time, U_{slow} is obtained as: $U_{slow}(t) = U_{total}(t) - U_{fast}(t)$. The time required by U_{slow} to push $V_{backflow}$ beyond the mixing point after the tipping point is defined as T_2. Adding T_1 and T_2 together results in T_{extra}. Figure 5 illustrates this measurement principle.

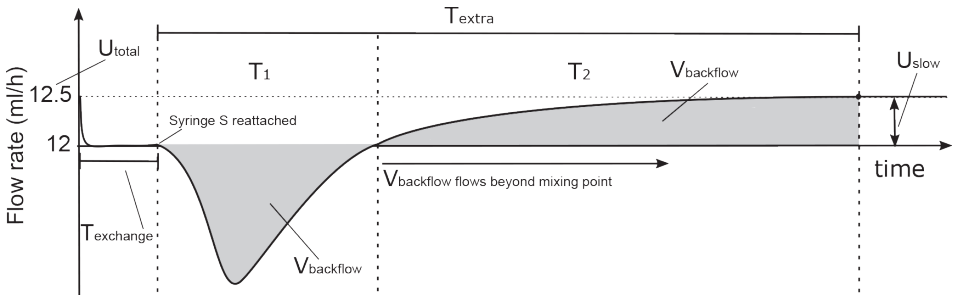

Figure 5. *Illustration of the acquisition of T_{extra}. After reattaching syringe S, flow rates lower than pump F (12 ml/h) occur because a certain volume is not flowing towards the flow meter and therefore flows towards syringe S into line S. This volume ($V_{backflow}$), is accumulated in a period T_1. After pump S has been restarted and delivers a flow rate > 0 ml/h (indicated as U_{slow} in the illustration), the same volume $V_{backflow}$ flows through the mixing in a period T_2. The time T_{extra} results from adding the periods T_1 and T_2.*

Similar to the simulation model output, the results are presented as T_{extra} in seconds.

Mechanism C

Instead of a critical and non-critical medication for pumps S and F, e.g. TPN or NaCl and Dopamine or Norepinephrine, we respectively used the dyes Indigo Carmine (20 mg/l) and Tartrazine (20 mg/l). The relevant physical properties of the dye solutions were assumed not to differ significantly from the actual drug solutions. To measure the dye concentration at the catheter tip, absorption spectrophotometry was used. This method was demonstrated before [11]. The dye concentrations at the catheter tip were measured using a QE65000 spectrometer (Ocean Optics, Dunedin, FL, USA). The cumulative flow rate was again measured using the Bronkhorst M12P flowmeter. Because both concentration and flow rate were measured, it was possible to acquire the value of $V_{undiluted}$ (error), which is defined as follows:

$$V_{undiluted}\,(error) = V_{delivered} - V_{steady\ state}$$

Where $V_{delivered}$ is the volume of drug S, delivered after the initiation of the syringe exchange procedure until steady state was reached again. $V_{steady\ state}$ is the volume delivered in the nominal situation by pump S, i.e. without dosing errors. In this case, steady state was determined as a period of 120 seconds, after the syringe exchange, in which the dosing rate fluctuated less than ±10 %. $V_{undiluted}$ (error) was used to remove systematic errors and obtain only the dosing error relative to steady state. The results of the simulation model were corrected accordingly: $V_{undiluted}\,(error) = V_{undiluted} - (U_{slow} \times T_{exchange}) = V_{undiluted} - (0.5\ ml/h \times T_{exchange})$

In this experiment, $V_{undiluted}$ (error) in milliliters, is presented as a function of the duration of the syringe exchange procedure ($T_{exchange}$). The experiment was performed with a $T_{exchange}$ of 30, 60 and 120 seconds.

The data were continuously recorded with a sample time of 1 second. The measurements were repeated three and five times (n = 3 and 5) for mechanisms B and C, respectively.

Data Analysis

The measurements were analyzed with Matlab 2014a (Mathworks, Natick, MA USA). All measurement results are presented as **mean ± SD**.

3 RESULTS

3.1 mechanism A: syringe exchange of both pumps

This mechanism did not produce any additional dosing errors or delays according to the model or in the *in vitro* experiments.

3.2 mechanism B: syringe exchange of the slow pump

Figure 6 shows an overview of the simulated results of T_{extra}. The equations used to simulate this infusion setup can be found in appendix I. T_{extra} was between 0.008 and 3536 seconds according to the simulation model. It can be seen that T_{extra} is virtually zero for the 7-Fr catheter for all of the syringes and almost one hour for the 1-Fr catheter and the 50-ml syringe with the non-rigid setup. Moreover, if smaller catheters were used, the relative impact of the syringe size/infusion set compliance, on T_{extra} increased. The generic clinical case that was reproduces in the *in vitro* experiment resulted in a T_{extra} of 1623 ± 122 seconds.

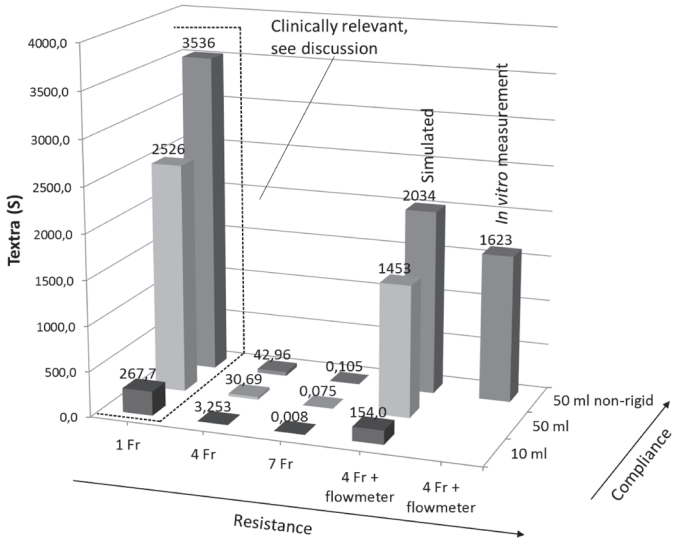

Figure 6. Extra delay time (T_{extra}) caused by the requirement to push the backflow volume ($V_{backflow}$) beyond the mixing point as a function of infusion hardware (1-7 Fr, 10-50 ml).These are the results from the computer simulation. Also indicated are the results for T_{extra} in the in vitro situation, both measured and simulated.

3.3 mechanism C: syringe exchange of the fast pump

Figure 7 shows all the results for $V_{undiluted}$ for each of the listed catheters and syringes/ infusion sets. The equations used to simulate this infusion setup can be found in appendix I. $V_{undiluted}$ was between 1.1 x 10^{-6} and 0.17 ml after a syringe exchange duration ($T_{exchange}$) of 120 seconds.

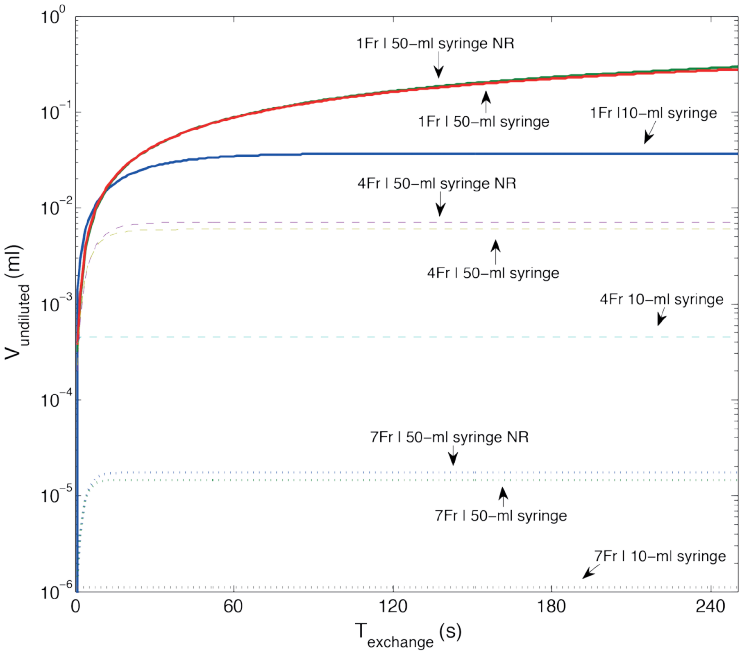

Figure 7. *Results of the computer simulation model for $V_{undiluted}$, the excess volume accumulated beyond the mixing point as a function of $T_{exchange}$, the duration of the syringe exchange. Note the logarithmic scale for the Y-axis. NR = non-rigid.*

The results of the *in vitro* experiment, which reproduced the generic clinical case, are shown in Figure 8. The simulation results, using input parameter corresponding to the *in vitro* experiment are also illustrated in Figure 8.

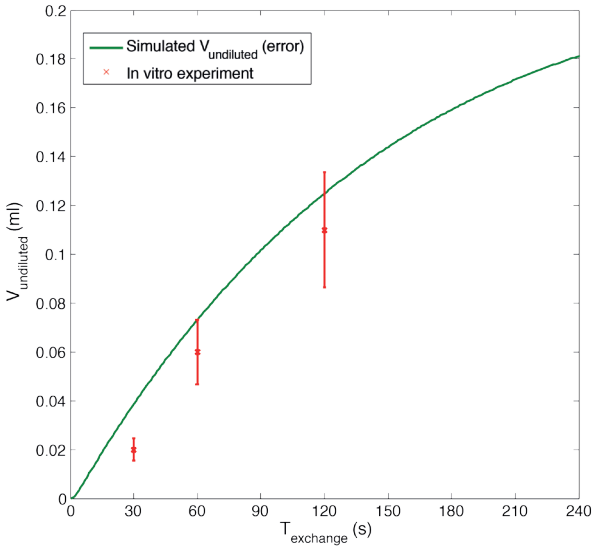

Figure 8. *Comparison of $V_{undiluted}$ (error) acquired from the in vitro experiment and the simulation model results according to the input parameters based on the in vitro experiment.*

4 DISCUSSION

The results show that each mechanism results in counter-intuitive dosing errors, which are strongly related to the mechanical and physical properties of the infusion hardware used. It was shown that if the slow pump (S) is exchanged, a significant additional delay of up to almost one hour may occur until the desired delivery of the critical medication has been reestablished. Next, it was shown that if the fast pump (F) is exchanged, a significant amount of undiluted critical drug was administered, which causes an overdose. If both infusion lines are clamped, according to mechanism A, no additional dosing errors occur. The results therefore reinforce the importance of clamping or otherwise blocking of all infusion lines during a syringe exchange. The results also show that smaller syringes and catheters with larger diameters reduce the quantity of dosing errors. Catheter diameter, however, is limited by the size of the vasculature. For example, in preterm neonates these may be very small. Smaller syringes, also have disadvantages. First of all, smaller syringe deplete faster than larger syringes and are therefore required to be replaced more often. Second, smaller syringes produce much more pressure when a similar force is introduced at the plunger in comparison to larger syringes. Among other reasons, this may pose a serious danger in case a vascular access device is inserted erroneously, such as an accidental subcutaneous position.

It is known that a syringe exchange causes errors in drugs administration. Backflow has also been studied extensively [12,25,26]. The impact of compliance on backflow was investigated in a simulation study before [27]. In that study, backflow was caused by an

occlusion in the infusion set, beyond the mixing point. Due to the compliance, a volume of fluid was allowed to accumulate. This volume which was bigger for a 50-ml syringe compared to a 10 ml-syringe. These results are thus in agreement with our study [27].

In our study a set of realistic clinical situation were assessed and simulated for a range of infusion components. We have provided a generalized overview of all the factors that impact dosing errors during a syringe exchange. These findings can be used by hospital personnel to substantiate the decisions for a syringe exchange protocol as well as the decisions for using certain infusion hardware.

4.1 Interpretation and clinical considerations

Mechanism B) Whereas clinicians and nurses will be aware of the effects of $T_{exchange}$, and hence will try to minimize the duration of the syringe exchange procedure in order to minimize $T_{exchange}$ and its effects, they might be unaware of the delay caused by T_{extra}.

From the equations generated by the model (appendix I), the mechanism behind this volume can be understood and is explained as follows. The slow syringe S was exchanged, however, no pressure built-up has been realized inside the new syringe of the slow pump S. Consequently, after the new syringe is connected to the infusion set, the direction of the least pressure will be towards this newly attached syringe. The storage of this volume is allowed because the syringe is somewhat compliant, i.e. some parts of the syringe are compressible, most notably the plunger. This, in turn, allows a volume of fluid to be pushed back from the infusion set, beyond the mixing point, into the infusion line S during the compression of the syringe connected to the line S. This small volume of fluid consists of the non-critical drug, i.e. fluid "F" (from the "fast" infusion line F) instead of the critical drug, i.e. "S" (Figure 1). Therefore it will take some time, T_{extra}, before the critical medication reaches the mixing point again, and hence the total time that no critical drug S is fed into the mixing point amounts to $T_{exchange} + T_{extra}$.

As the results show, T_{extra} is dependent on the hardware properties of the infusion system. Specifically, the amount of the backflow allowed is strongly dependent on the compliance of syringe S (C_2). This is because the compressibility of the syringe allows the fluid from the fast syringe, fluid F, to flow back in the direction of the slow syringe, syringe S (Figure 1). Therefore, smaller syringes, which are typically much less compliant, will result in less potential backflow. Moreover, the resistance of the catheter (R_L) has a substantial impact on T_{extra}, if the resistance of the catheter is low, the affinity for the fluid to flow back into syringe S is lower. These results are immediately evident from Figure 6. In fact, the results show that in the *in vitro* experiment, the problems are only clinically relevant with catheters smaller than 4 Fr. Additionally, T_{extra} is dependent on the ratio of the flow rates between the fast and the slower pump (Appendix II). In the presented generic clinical case of this simulation, the flow rates of pump S and F were 0.5 and 12 ml/h. Consequently, it takes considerably longer to push the non-critical drug F out of the infusion line S, than the time that was required to push the drug into line S.

Clinicians should also consider the dangers if the syringe is outside of the pump. In this case the plunger is not fixated, which may allow free flow to occur [28]. Moreover, during the experiments it was also found that the volume of drug F, introduced in line S due to backflow, might be even larger in this case as the plunger is simply allowed to be pushed backwards, out of the syringe. The extent of this is dependent on the pressure coming from pump F and the friction of the plunger in the syringe, which also may have a significant impact [29] and may differ per syringe type

As mentioned, besides delays caused by $T_{exchange}$ and T_{extra} there is also $T_{delay,}$ which is caused by the dead volume of the infusion set. Therefore, the (near) absence of drug S will occur only after T_{delay}, the time required for the fluid to travel through the dead volume from the mixing point to the catheter tip into the patient's blood stream. In the *in vitro* experiment, the dead volume of the infusion set was approximately 0.4 ml, resulting in a T_{delay} of approximately 193 seconds (see Appendix II). Evidently, T_{extra} was substantially larger in this case with 2034 seconds. Note that although the T_{extra} is small in the case of the 4 and 7-Fr catheter, the additional delay of T_{extra} may still amount to almost a minute, which may be unwanted in the case of, for example, a patient with severe hypotension.

During the experiments, it was empirically observed that the drug F will enter infusion line S. Drug solutions closer to the edges of the infusion line remain more unaffected by the flow of drug F, as is predicted by the model due to the 'Poiseuille-effect' (Chapter 2.3). Therefore the T_{extra} simulated and measured is a worst case scenario, in practice some critical medication may still be delivered.

Mechanism C) From the simulation results, the errors resulting from the syringe exchange of the fast syringe can be explained as follows. During the exchange of the fast pump F, the slow pump S is stopped, but not clamped. As a result, due to compliance effects, the critical drug solution from the pump S, not diluted by the fast pump F, oozes into the common line beyond the mixing point. The volume of $V_{undiluted}$ depends on the $T_{exchange}$ and many other factors, such as the initial flow (before $T_{exchange}$) of the pump F, the mechanical compliances C_1 and C_2 of syringes F and S, respectively, and the impedances R_1, R_2, and R_L of lines F, S, and the catheter, respectively (see Figure 2) (chapter 2.3).

The effects of this procedure may be even more counter-intuitive as mechanism B. Consequently, the probability that an adverse effect will occur may also be greater. From the results it is evident that the quantity of $V_{undiluted}$ is strongly dependent on the resistance and compliance. Again, with catheter-diameters larger than 4-Fr, the effects are minimal and smaller syringes also minimize the amount of $V_{undiluted}$. However, even in a situation with zero compliance and resistance, a quantity $V_{undiluted}$ will be produced if pump F is not stopped, although this amount is substantially smaller than the amount that results from the infusion system's compliance. The clinical relevance of $V_{undiluted}$ is dependent on the time required to deliver this volume to the patient, which in turn is dependent on the current flow rate. For example, if the largest measured $V_{undiluted}$ of 0.17 ml is administered with 0.5 ml/h it is, in fact, administered with the intended dosing rate in 1224 seconds.

However, in the generic clinical case, $V_{undiluted}$ was administered with a flow rate of 12.5 ml/h in 49 seconds, which means that this quantity was administered with an excess dosing rate of 2400%. It must be stated that such short dosing errors are typically clinically relevant for drugs with short onset times, e.g. noradrenaline and dopamine. In addition, a high concentration of the critical drug S, typically used for patient who cannot handle fluids, also increases the probability for an adverse event.

4.2 Limitations and future research

The spectrometer was not used in mechanism B because a higher accuracy could be achieved by using only the flowmeter. However, it should be noted that while the flow rate of pump S is increased, due to compliance and resistance effects, the flow rate of pump F could be decreased slightly, therefore impacting T_{extra} as measured in the *in vitro* experiment. Nevertheless, because the flow rate from pump F is much higher, this effect is negligible and using only the flow meter allows the acquisition of T_{extra} relatively accurately.

A discrepancy could be observed between the experimental and simulated values. All *in vitro* results were systematically underestimating the simulated results, which suggest an overestimation of the compliance of this particular infusion setup, as described in the generic clinical case. Furthermore, the experimental *in vitro* results in mechanism B did follow the expected exponential curve. We did not have the instruments available to measure the physical properties of the infusion setup in the generic clinical case in more detail, which is a likely cause for the discrepancy. Furthermore, only the results of the *in vitro* experiments using the 50 ml syringe and the non-rigid set, corresponding to a neonatal situation, were presented. The signal to noise ratio prevented us from obtaining usable results for a 10 ml syringe, which indicated that the measured quantities were too low. Obtaining usable experimental results for the smaller syringes would further validate the results of the theoretical simulation model. It is recommended to conduct these experiments with better instruments in future research.

In clinical practice, TPN or NaCl may be administered using a volumetric or gravity driven pump. These pumps do not have compliance in a similar fashion as syringes, although volumetric pumps are typically connected through compliant infusion lines in order to enable the commonly used peristaltic mechanism to operate. Typical infusion lines were shown to be compliant [24]. Since in mechanism B, T_{extra} is mostly related to the compliance of syringe S (C_2, see Figure 1) there will probably not be any substantial differences in the results. Likewise, in mechanism C, the compliance of syringe S (C_2, see Figure 2) is also the most important parameter, in combination with the resistance of the catheter. Another noteworthy point is the flow rate of pump F (12 ml/h). This was chosen to observe the effects studied in this paper with sufficient confidence in the *in vitro* experiments. The flow rate is somewhat high as the flow rate in the NICU is preferred to be kept as low as possible. The formula for T_{extra} in Appendix I can be used to calculate other flow rate combinations. In clinical practice this flow rate may also be produced by multiple pumps instead of just one syringe pump. However, in all these situations, the overall results of this study will be maintained.

5 CONCLUSION

A syringe exchange may produce dosing errors as well as substantial delay times. This may have severe implications for patient safety. The quantity of the dosing error is dependent on the exchange duration and the physical properties of the infusion hardware used, most notably the syringes and the catheter. Smaller syringes, catheters with larger inner-diameters and less compliant infusion systems in general, result in smaller dosing errors during a syringe exchange. It is recommended to consider these factors when selecting infusion hardware. By clamping all infusion lines during a syringe exchange, most of the unwanted results can be prevented or mitigated. In fact, this is more important than performing the syringe exchange procedure quickly since the extra delay due to compliance effects can be unexpectedly large, as has been shown in this study. It is therefore advised to clamp or otherwise block all infusion lines that are co-administering drugs through the same infusion set and catheter lumen as the syringe that is exchanged.

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APPENDIX I: EQUATIONS AND THEORETICAL BACKGROUND

Mechanism B

The extra time T_{extra} that emerges before the flow of the slow medication into the mixing point is restored, equals :

$$T_{extra} = R_L C_2 (u_{fast} / u_{slow})$$

Where C_2 is the mechanical compliance of the slow syringe S and R_L is the flow resistance of the catheter. U_{fast} and U_{slow} are the flow rates of pumps F and S, respectively.

Mechanism C

Dosing Error ($V_{undilluted}$) due to syringe exchange of fast pump =

$$\frac{u_{initial}\ R_L C_2 \left(\vartheta_{first} \left(1\text{-}e^{-\frac{T_{exchange}}{\vartheta_{first}}} \right) \text{-} \vartheta_{second} \left(1\text{-}e^{-\frac{T_{exchange}}{\vartheta_{second}}} \right) \right)}{\sqrt{b^2\text{-}4ac}} \qquad (1)$$

In which :

$u_{initial}$ is the initial flow rate of the syringe that was exchanged, before the syringe exchange.

$$\vartheta_{first} = \frac{1}{2}\left(b\text{-}\sqrt{b^2\text{-}4ac}\right)$$
$$\vartheta_{second} = \frac{1}{2}\left(b+\sqrt{b^2\text{-}4ac}\right)$$
$$a = R_L R_1 + R_L R_2 + R_1 R_2$$
$$b = C_1(R_L + R_1) + C_2(R_L + R_2)$$
$$c = C_1 C_2 \qquad (2)$$

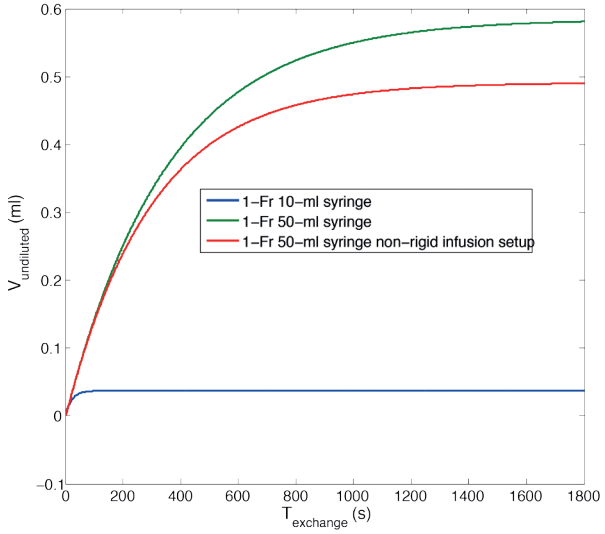

Figure 9. *$V_{undiluted}$ of a 1-Fr catheter as a function of $T_{exchange}$.*

APPENDIX II: HARDWARE PARAMETERS

Measured compliances:

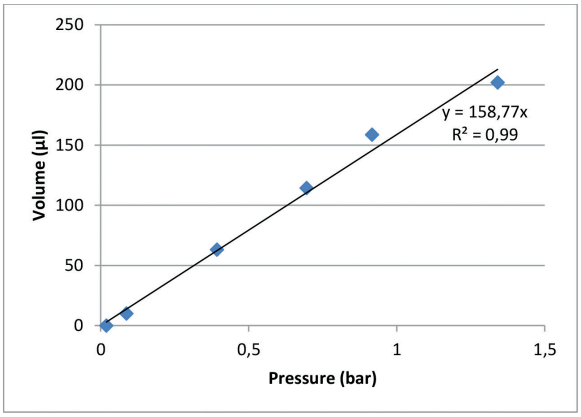

Figure 10. *Compliance of a 10-ml BD-plastipac syringe, average of 3 measurements. Pressure was measured in-line. An infusion setup with negligible compliance was used.*

Measured resistances:

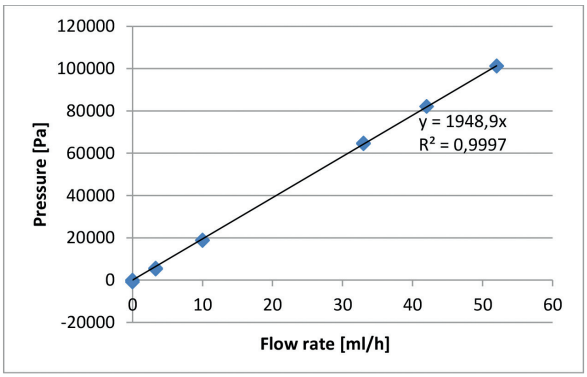

Figure 11. *Resistance of the Vygon 1Fr (Ecouen, France, 0.17 mm, REF 1261.20). Measured using a pressure guage. An infusion setup with negligible compliance was used.*

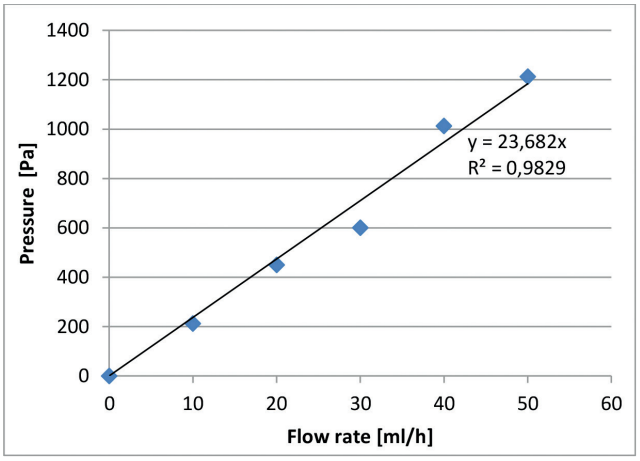

Figure 12. *Resistance of the Vygon 4Fr (Ecouen, France, diameter = 1.44 mm, REF 1272.14, double lumen), proximal lumen. Measured using a pressure gauge. An infusion setup with negligible compliance was used.*

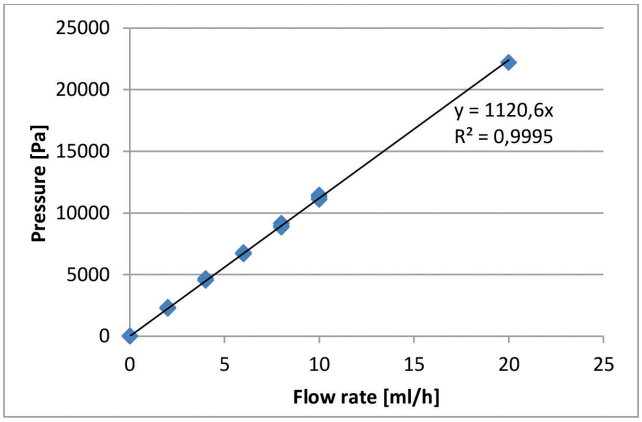

Figure 13. *Resistance of the Coriolis flowmeter M12P (Bronkhorst, Ruurlo, The Netherlands). Measured using a pressure gauge. An infusion setup with negligible compliance was used.*

Calculated resistance:

Resistance (R) for a substance similar to water was calculated for an Argon Careflow (Plano, TX, USA, REF 681706) catheter using Poiseuille's law:

$$R = \frac{\Delta P}{Q} = \frac{8\mu L}{\pi r^4} \qquad (3)$$

Where P is the pressure difference between the in- and out-flow of the catheter, Q is the volumetric flow rate, μ is the dynamic viscocity, L is the length of the catheter and r is the radius of the catheter, which resulted in a resistance of 0.058 Pa per ml/h. Note that the internal shape of lumen may impact this value.

Chapter 3.3

The effects of flow rate interventions and physical infusion setup properties on blood pressure in neonates receiving inotropic support: A pilot study

Manuscript in preparation

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ABSTRACT

Introduction: Neonates admitted to the NICU often suffer from hypotension, requiring the immediate intravenous administration of inotropics. It was hypothesized that the physical infusion setup characteristics may be related to the magnitude of the dosing errors during inotropic administration and subsequent unwanted effects in the mean arterial blood pressure (MABP). In this *in vivo* pilot study, we therefore aimed to investigate the impact of flow rate interventions and the infusion setup on MABP in neonates receiving inotropic support.

Methods: Two cohorts (A,B) of neonates treated with two different multi-infusion setups were compared. In cohort A, a chain of stopcocks was used as an infusion set. In cohort B, an infusion set with an integrated filter and anti-reflux valve was used. The impact of deliberate flow rate increases (interventions) in the inotropic pumps were investigated for the following end points: delays until a peak-MABP was reached ($MABP_{95pct}$), the time fraction that the MABP was above a desired margin ($MABP_{target}$) and an exponential fit of the increasing MABP ($MABP_{fit}$).

Results: Delays were substantial (approximately one hour) after the pump was started from a standstill but did not significantly differ between the cohorts. There were an average of 1.3 and 2.75 interventions per patient, for cohorts A and B, respectively. Overall, no substantiated differences were found in $MABP_{95pct}$, $MABP_{target}$. $MABP_{fit}$ showed that the MABP-increase was significantly steeper in cohort B. However, when starting the pump from a standstill the MABP increased and, after 40 minutes, suddenly decreased again for a limited but substantial duration in cohort B.

Conclusion: Differences between both infusion sets were limited or inconclusive. However, it can be concluded from this pilot study that the infusion hardware causes substantial delays, which has impact on the patient. The unexpected transient MABP decrease may be caused by the anti-reflux valves as well as medical reasons or a combination thereof. It is recommended to expand this pilot study in order to provide clinical advice for patient safety in relation to infusion hardware

1 INTRODUCTION

Infusion therapy constitutes a high risk for medication errors and adverse events [1–3]. Especially the administration of drugs to critically-ill preterm neonates by means of infusion is generally considered challenging and risky. Firstly, preterm infants often suffer from hypotension or even life-threatening shock [4], which may cause inadequate perfusion of tissue, establishing a risk for hypoxia [5], ischemia and periventricular leukomalacia (PVL) [6]. In order to treat hypotension, very potent fast and short acting inotropics, such as dopamine, are administered. These drugs require a continuous, accurate and precise delivery with syringe pumps. Secondly, preterm, critically-ill neonates can only tolerate limited amounts of fluid [7,8], i.e. 120-150 ml/kg/day. Therefore concentrated drug solutions have to be administered at very low flow rates, i.e. in the range of 0.1 – 5.0 ml/h. The pharmacological effects of over/underdosing in combination with the underdeveloped autoregulation in neonates may result in hemodynamic instability and cause conditions such as periventricular- and intraventricular hemorrhages (PIH) [6,9]. Finally, limited vascular access, the challenging nature of inserting a vascular access device [10], and the risks of infections, such as catheter-related sepsis [11,12], typically requires a single infusion access point connected to multiple infusion pumps to deliver these drugs. This principle is called multi-infusion [13].

Multi-infusion is associated with dosing errors [13–15]. This is largely due to the dead volume, i.e. the volume of the tubing between the mixing point in the multiple-in single-out infusion set, and the catheter tip. Dead volume, in combination with other physical effects, may cause counter-intuitive delays and dosing deviations from the intended drug dose in multi-infusion systems, despite the use of accurate syringe pumps [13,14,16–18](chapter 3.2). Because of these physical effects, it may be more difficult to titrate drugs to the desired effect by setting and adjusting the flow rate. For this reason, clinical experience led to the suggestion that using an infusion set with a large dead volume results in more interventions than an infusion set with a small dead volume. However, the exact interplay between all the relevant physical effects related to the infusion set, produces a hard to predict relationship between the physical properties of the infusion setup, the dosing errors and the clinical effect thereof (e.g. mean arterial blood pressure).

The objective of this pilot study is therefore to investigate the effect of flow rate interventions in inotropic administration as well as the possible effects of the infusion set physical properties on the mean arterial blood pressure in neonates.

2 METHODS

2.1 Setting and study population

In this study, the impact on the MABP of two different infusion sets, used to administer inotropics to neonates admitted to the 24-bed NICU of the Wilhelmina's Children's Hospital, University Medical Center Utrecht, the Netherlands, was investigated. Two cohorts of neonates admitted to the NICU, between either June – 2002 and June – 2009 (cohort A, treated with the "old infusion set") or between November 2015 and May 2016 (cohort B, treated with the "new infusion set") were established. In cohort A neonates with a gestational age (GA) less than 32 weeks were included, whereas – for practical reasons - in cohort B neonates with a gestational age less than 42 weeks were included.

The local treatment guidelines describe that inotropic administration is typically started with 5 µg/kg/min and subsequently adjusted to a dosing rate between approximately 2 and 15 µg/kg/min. There were differences in the flow rates used for the pumps containing inotropics in cohorts A and B. In cohort A, the flow rates used were 0.5, 0.75, and 1.0 ml/h. In cohort B, a range of flow rates were used between 0.1 and 1.5 ml/h. In all cases the treatment started with a flow rate of 0.5 ml/h. In this study, only dosing rate changes by changing the flow rate (interventions) were considered, not by changing the drug concentration in the syringe. An accurate documentation of the flow rate changes regarding inotropic delivery was an additional inclusion criterion. This requirement entailed the time stamp registration of these flow rate interventions in the delivery of inotropics, within a minute of accuracy. Specifically, the documentation of the timing was relevant for, 1) the moment when the pump was **started** from a standstill, and 2) the moment when the flow rate, and therefore dosing rate, was deliberately **increased**. At least two hours of MABP-data after the intervention had to be available. For all included patients gender, gestational age, and birth weight were collected.

2.2 Infusion setup

On the NICU, inotropics are typically administered by connecting multiple pumps to a multiple-in, single out infusion set, and subsequently to a catheter. In cohort A, inotropics were administered using an Alaris syringe pump (Alaris Carefusion, USA) equipped with a 50-ml BD Plastipak syringe (Becton Dickinson, NJ, USA). The patients in this cohort were treated with the "old infusion set" with monitor lines, possibly inline filters, several stopcocks ad random and where needed. A manifold was typically constructed by adding stopcocks together (Figure 1a). The point at which the pump containing the inotropics was connected varied both in time and per situation. However, in previous studies it was hypothesized that it was connected in close proximity to the patient at connection point E (Figure 1a), resulting in a much smaller dead volume of this infusion set [19] compared to the infusion set used in cohort B (described later). A needle-free access site (Carefusion, Rolle, Switzerland) was used at the point of outflow of the infusion set, to which a vascular access device, typically a four-Fr double lumen catheter (Vygon, Ecouen, France) was connected. In cohort B, inotropics were administered using a B.Braun syringe pump

(B.Braun, Melsungen, Germany) equipped with a 50-ml B.Braun Omnifix syringe (B.Braun, Melsungen, Germany). The patients in cohort B were treated with the “new infusion set”, a custom 173 cm infusion set (Impromediform GmbH, Lüdenscheid, Germany) (Figure 1b). This set included an integrated anti-reflux valve as well as a filter, and was also typically attached to a four-Fr double lumen catheter. In our NICU, total parenteral nutrition (TPN) and in some cases lipids and glucose are co-administered through the proximal catheter lumen with inotropics. The catheter entered the patient through the umbilical vascular access site. Table 1 lists the relevant properties of both infusion sets.

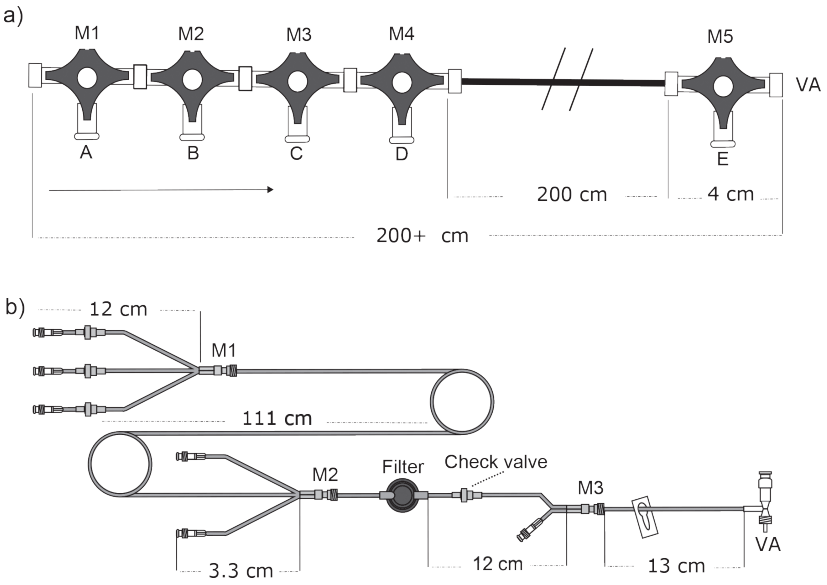

Figure 1. *Typical infusion set assembly used in cohort A, the “old infusion set”. With a manifold (A-D) used for administering miscellaneous drugs, an optional 200 cm infusion line, and finally a three-way stopcock (E). VA was typically connected to a needle-free access site that was, subsequently, connected to a catheter. Each stopcock corresponds to one mixing point (M1-M5). More interconnected stopcocks are possible. (a) Custom infusion set disposable (173 cm) used in cohort B. There are three mixing points (M1-M3). M3 is typically used for less critical medication, M2 is used for critical medications, such as dopamine, and M1 is used for lipids. Upstream, behind the filter and between M2 and M3, there is an in-line check valve. A catheter is again connect at VA (b). Parts of this Figure were adopted from van Rossum et al. [19].*

Table 1. Infusion sets specifications. Specification of the "old infusion set", used in cohort A and the "new infusion set", used in cohort B.

	Infusion set used in cohort A	**Infusion set used in cohort B**
Brand	*Manifold / Stopcocks*	*Custom (Impromediform GmbH, Lüdenscheid, Germany)*
Length (cm)	Stopcock 4 DE 200 Total ~220	Total 173
Dead volume (ml)	M5* 0.14	M3* 0.13 M2* 0.41 M1* 1.00
Anti-reflux valves	None	Integrated
Filter	Additional	Integrated filter (Pall, Washington, USA).
Stop cocks	(A-E)	None

**Volume between mixing point M5 and the outflow into the catheter for cohort A. Volume between mixing points M1-M3 into the catheter for cohort B. Inotropics may be administered through M5 for cohort A and are administered through M2 for cohort B.*

2.3 End points

For each intervention (at t=0) that was registered, a three-hour period was acquired; two hours after each intervention, "post-intervention", and one hour prior to each intervention, "pre-intervention" (Figure 2). The pre-intervention period was used as an internal control, to study the impact of an intervention within the subject (Appendix I), and for normalization of the dataset, explained later. From these data the following end points were defined:

- **$MABP_{95pct}$** of curve **(T_{post}) [minutes]**

Time until 95% of the maximum value of the MABP after an intervention (t=0) has been reached.

- **$MABP_{target}$ (T_{pre}, T_{post}) [%]**

The proportion of the time that the MABP was above the clinically desired [20,21] pre-defined target margin. This target was equal to the GA of the neonate in weeks, expressed in MABP (mmHg). If the infant's GA was above 40 weeks, the MAPB target margin was increased to 45 mmHg. The percentage is calculated as follows: 100% (T_{target} / T), where T_{target} is the time (in minutes) that the MABP was above the target margin and T is either 60 minutes (T_{pre}) or 120 minutes (T_{post}) (see Figure 2).

- **$MABP_{fit}$ (T_{post})**

A first-degree exponential fit (Trust-Region algorithm) from the point in time of the intervention (t=0) until a maximum or plateau value was reached, according to:

$$e^{bt}$$

The exponential fit characterizes the shape of the MABP-increase in response to an intervention. Only the 'steepness' is investigated, which is represented by the coefficient b [min^{-1}]. To present a more clinically meaningful quantity, the time required for the MABP to double was calculated from b as: $T_{MABP\text{-}double} = \ln(2)/b$ [min].

For the parameter b, a 95% confidence interval was calculated, t is time in seconds. The fit was calculated for normalized data ($MABP_{norm}$), explained in the data analysis section.

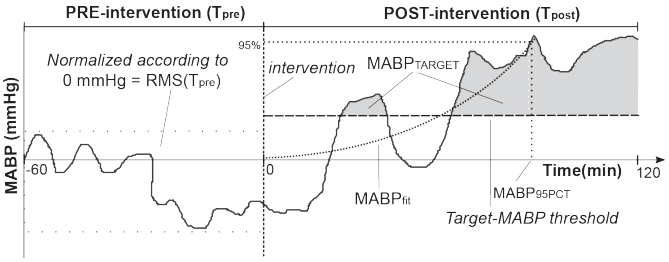

Figure 2. *Analytical methodology. Pre-intervenion (-60-0 min) and post-intervention (0-120 min) periods are shown. Indicated is the $MABP_{95pct}$ which is the time required to reach 95% of the maximum MABP-value in the post-intervention period. $MABP_{target}$ is the proportion of time above the "Target MABP threshold" line. The RMS value from the pre-intervention period is used for analytical purposes to combine all the measurements of one cohort into one graph and acquire $MABP_{fit}$, an exponential fit starting at the point in time of the "intervention" (t=0) and proceeding to the point where a maximum has been reached.*

The MABP was monitored using an arterial line inserted peripherally, in the umbilical artery or both when an umbilical arterial line was electively removed after 7 days of insertion. The vital signs were recorded with a sample frequency of 1 and 0.4 Hz for cohorts A and B, respectively. Subsequently, the data were stored in Bedbase (MTKF, UMC Utrecht, the Netherlands) and Signalbase 8.5.2 (MTKF, UMC Utrecht, the Netherlands) for offline analysis. Data of cohort A were previously gathered by Bonestroo et al. [21], the interventions "startup" and "flow increase" were retrospectively documented by van Rossum et al. [19]. These collected data and the documentation of "intervention timestamps" (i.e. the times at which the interventions in the administration of inotropic drugs were conducted), were adopted and further investigated in this study. In cohort B, the "intervention timestamps" were documented *ad hoc* by healthcare professionals treating the patient and subsequently logged into our electronic patient system Metavison (Itémedical, Tiel, the Netherlands).

2.4 Data analysis

The data from both cohorts A and B were summarized according to the investigated interventions "**startup**" and "**flow increase"**. Because the inclusion criteria did not fully match, these two groups were further subdivided according to subgroups CG1 – CG3, which were based on the following criteria

- CG1 GA < 32 weeks, dopamine interventions only
- CG2 GA < 42 weeks, dopamine interventions only
- CG3 GA < 42 weeks, dopamine and dobutamine interventions

CG1 thus corresponds entirely the inclusion criteria of the old cohort A, the other cohorts are expansions. Note that CG3 contains all data of CG2 and CG1 and thus all data. CG2 contains all data of CG1. In addition to comparing cohort A and B, defined as “hypothesis testing”, the effect of an intervention was also tested for each patient individually, defined as “within-subject testing”. This was only done for the $MABP_{target}$. See Figure 3 for the procedure in which the experimentation was conducted. In order to perform the exponential fit, the MABP-data from the cohorts were “combined” into one plot. To accomplish this, the data were normalized as follows: $MABP_{norm}(t) = MABP(t) – RMS(MABP(T_{pre}))$, where MABP(t) is the MABP at time t, and T_{pre} is the pre-intervention period. If the pre-intervention period was unavailable, the first sample of the post-intervention period was used as a substitute for $RMS(MABP(T_{pre}))$ and considered zero (0) mmHg. Subsequently, the data from cohorts A and B of the “startup” and “flow increase” interventions were averaged into one plot, by taking the mean of each synchronized and normalized data sample (appendix II).

The offline data were analyzed using Matlab 2014a (MathWorks, Natick, MA, USA). All the data were filtered using a Savitzky-Golay filter to remove noise.

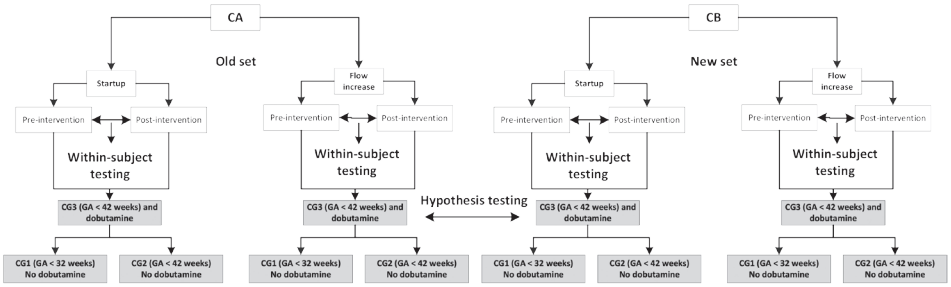

Figure 3. *Overview of the process used to conduct the experimentation. From cohorts A (CA) and B (CB) a patient was investigated for either the intervention “startup” or “flow increase”. About this intervention, a three-hour period was extracted from the MABP-data, one-hour before the intervention and two hours after the intervention. Next, several end points were calculated and several statistical tests were conducted on these end points. First, the differences between the cohorts were investigated (‘Hypothesis testing’). Next, a ‘Within-subject test’ was conducted, in order to observe the differences between het pre- and post-intervention periods, if appropriate for the end point. Finally, for the $MABP_{fit}$, the confidence intervals were compared. In each case the tests were conducted for the entire cohorts A and B, and in subgroups CG1-CG3.*

Depending on the data distribution, a Welch’s t test or Mann-Whitney U test was used to compare the end points from cohorts A and B. Within-subject testing was conducted using a paired t test. P values smaller than 0.05 were considered significant. Statistical analysis was conducted using Graphpad Prism 7.00 (Graphpad Software, Inc., San Diego, CA, USA)

3 RESULTS

3.1 Patients

Table 2. shows the patient characteristics for both cohorts A and B. The differences in gestational age and birth weight reflects the differences in inclusion criteria in cohorts A and B.

Table 2. Clinical characteristics of the patient treated with inotropics in cohorts A and B

	Cohort A (N = 15)	Cohort B (N = 9)	P-value
Gestational age (weeks)			
Median	28.2	33.9	<0.05
Range	25.9-31.4	28.3-41.3	-
Birth weight (g)			
Median	915	2635	<0.05
Range	650-2000	1180-3980	-
Gender			
	9M/5F	5M/5F	>0.05
n (%)	64.3/35.7	50.0/50.0	-

Table 3. shows the total number of times (l) a “startup” or “flow increase” intervention was performed within a cohort. The number of individual patients in which these intervention occurred are stated between brackets. In addition, the values are shown for subgroups CG1-CG3 (see data analysis), which resulted in the additional inclusion of patients and therefore additional interventions in cohort B. Note that for some patients only data of a “startup” or a “flow increase” intervention could be retrieved, which explains that the number of “startup” interventions is lower than the total number of patients in cohort A. Based on Table 3 there were an average of 1.3 “flow increase” interventions per patient in cohort A and 2.75 “flow increase” interventions per patient in cohort B (CG1).

Table 3. Number of “startup” or “flow increase” (n) interventions that occurred within cohorts A and B. The number of interventions are also shown per subgroup CG1-CG3, where CG3 contains all the interventions registered.

	Cohort A “startup” l (patients*)	**Cohort B “startup”** l (patients*)	**Cohort A “flow increase”** l (patients*)	**Cohort B “flow increase”** l (patients*)
CG1 *(Patients with GA up to 32 weeks only counting the dopamine interventions)*	l=14 (14)	l=2 (2)	l=19 (15)	l=11 (4)
CG2 *(Patients with GA up to 42 weeks only counting the dopamine interventions)*	l=14 (14)	l=5 (5)	l=19 (15)	l=20 (9)
CG3 *(ALL Patients, including dobutamine interventions)*	l=14 (14)	l=9 (7)†	l=19 (15)	l=28 (9)

**These are the number of individual patients in which the interventions occurred*

†Note the startup of dobutamine besides the startup of dopamine causes the number of startup interventions to be higher than the number of patients in subgroup CG3

3.2 Delays and target-MABP

Figures 4a and 4b show the delays for the MABP to reach a peak or plateau ($MABP_{95pct}$), for the "startup" and "flow increase" interventions, respectively. Both cohorts A and B are shown and cohort B is further subdivided into subgroups CG1 – CG3. The delays ($MABP_{95pct}$) were approximately 60 minutes, with maximums of 120 minutes. No significant differences were found between cohorts A and B.

Figures 4c and 4d show the time fraction that the MABP was above the desired target-MABP ($MABP_{target}$), after the "startup" and "flow increase" interventions, respectively. Cohort B is further subdivided into the subgroups CG1-CG3. Furthermore, the $MABP_{target}$-values for both the pre- and the post-intervention periods are shown (Figures 4c and 4d). For the "startup" intervention (Figure 4c) the time fraction that the MABP was above the target-MABP was significantly higher in cohort B for subgroups CG1 and CG2 (approx. 90%), compared to cohort A (approx. 55%). No other significant differences between the cohorts were found.

The time fraction that the MABP was above the target-MABP ($MABP_{target}$) was also compared for the pre- and post-intervention periods between themselves. This gave the following results. $MABP_{target}$ significantly increased in cohort A from approximately 20% to 55%, after the "startup" intervention ($p = 0.003^{**}$). The increase in $MABP_{target}$ of approximately 85% to 90% ($P = 0.67$) and 85% to 96% ($p=0.30$) found in cohort B, following the "startup" intervention for CG1 and CG2, respectively, were not significant. The $MAPB_{target}$ in cohort B for CG3 remained the same after the "startup" intervention with approximately 65% ($p = 0.99$), see Figure 4c. $MABP_{target}$ significantly increased from approximately 50% to 85% in cohort A ($P = 0.007^{**}$), and from approximately 85% to 95% in cohort B for both CG1 and 2 ($P = 0.005^{**}$ for both CG1 and 2) after the "flow increase" intervention. The increase in $MABP_{target}$ of approximately 75% to 80% in cohort B for CG3 following the "flow increase" intervention was not significant ($p = 0.06$), see Figure 4d.

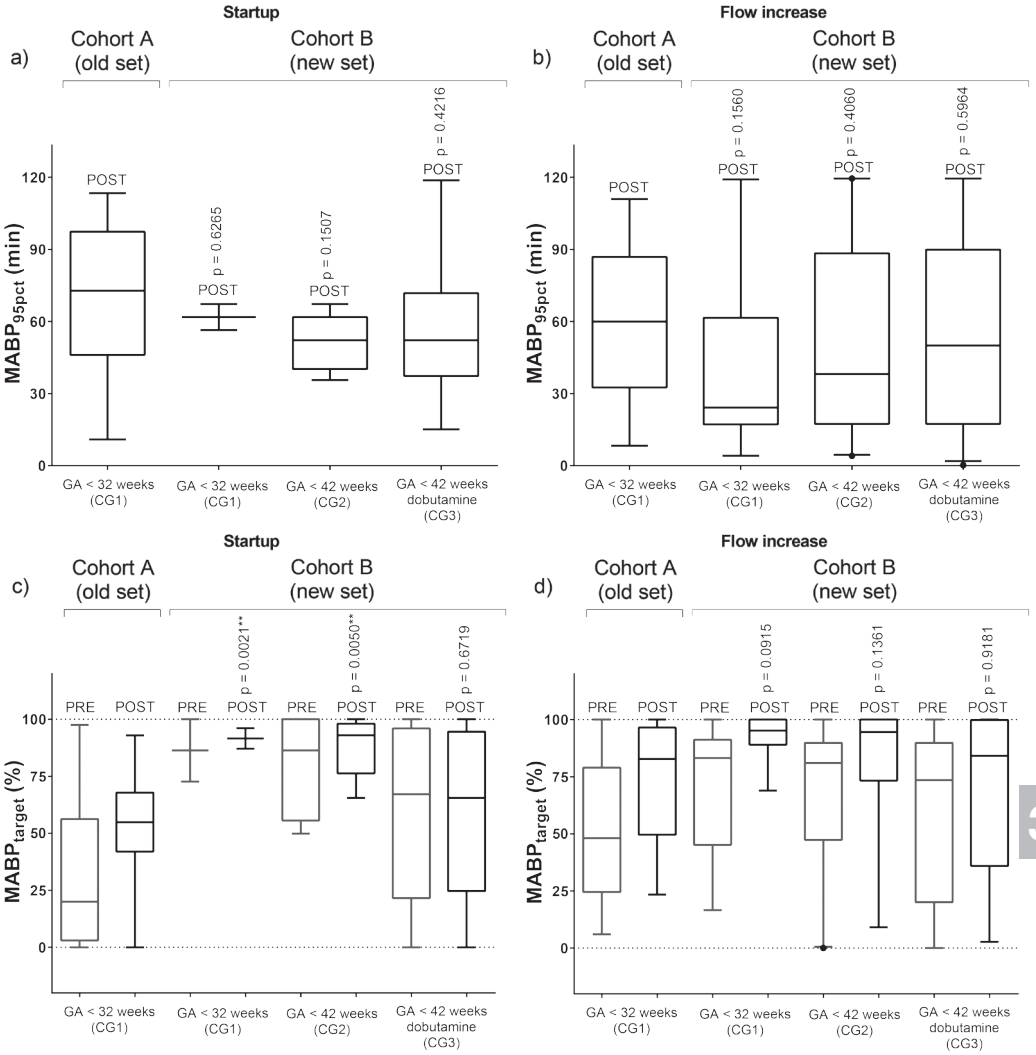

Figure 4. *Box and whiskers (5-95 percentile) plot of the results of the endpoints $MABP_{95pct}$ and $MABP_{target}$, for cohorts A and B, and subgroups CG1 – CG3. All the results are shown for the "startup" interventions (left) and the "flow increase" interventions (right). "PRE" indicates the results from the pre-intervention period, "POST" indicates the results from the post-intervention period. The p values were acquired from comparing the post-intervention values of cohort A with cohort B.*

3.3 Characteristics of the MABP-increase

Figures 5 shows the normalized and combined MABP of the cohorts A and B, fitted according to an exponential fit ($MABP_{fit}$), for the "startup" (a) and the "flow increase" (b) interventions. In all cases it can be seen that the MABP is increasing after the intervention (at t=0). In cohort B after the "startup" intervention (Figure 5a), it can be seen that the MABP decreased again after a transient MABP-increase of approximately 40 minutes (see discussion).

For the “startup” intervention, the time for the MABP to double ($T_{MABP\text{-}double}$) was 19.7 (19.4 - 20.2, 95% CI) and 9.70 (9.54 - 9.87, 95% CI) minutes for cohorts A and B, respectively. For the “flow increase” intervention, the time for the MABP to double was 16.8 (16.6 – 17.0, 95% CI) and 7.03 (6.92 – 7.13, 95% CI) minutes for cohorts A and B, respectively. In all cases the steepness of the increase of blood pressure (MABP) was significantly higher in cohort B, as indicated by the coefficient b and the $T_{MABP\text{-}double}$ that is derived from this.

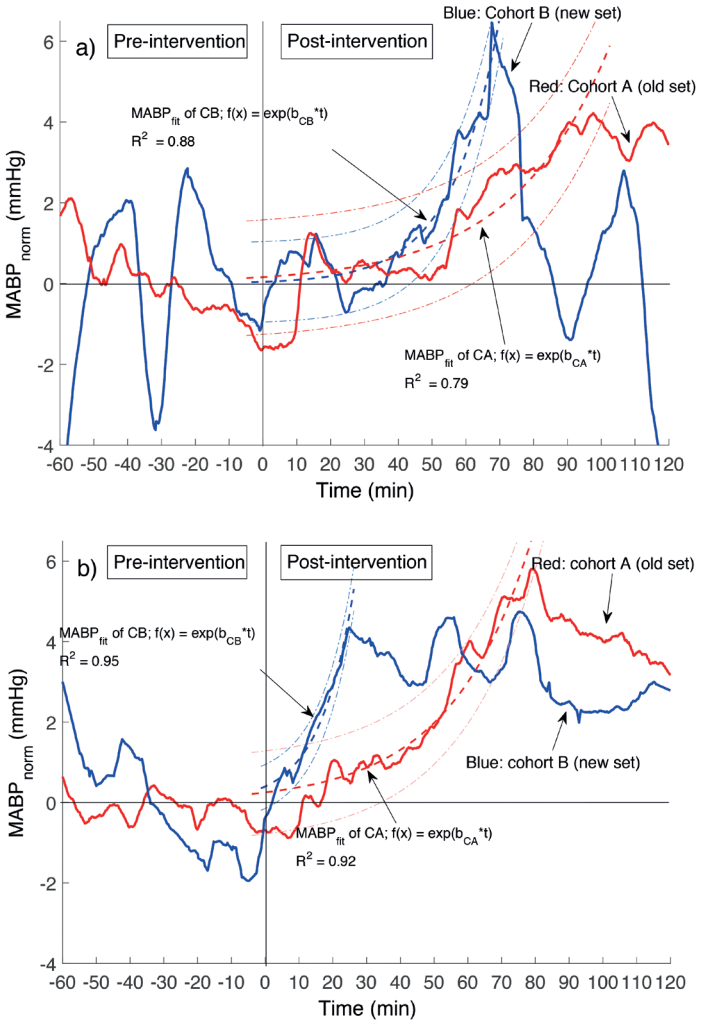

Figure 5. *Normalized and combined MABP ($MABP_{norm}$) of Cohorts A (CA, red) and B (CB, blue) for the “startup” intervention (a) and the “flow increase” intervention (b). All the data are fitted according to an exponential fit (exp(b*t)), where t is time. In all cases, subgroup CG1 was used, therefore the inclusion criteria were GA < 32 weeks and dopamine-only for both cohorts. Dotted/striped lines are the 95% confidence intervals (indicated with the same color as data to which it is fitted).*

4 DISCUSSION

The results show no significant difference between cohorts A and B in the delays until 95% of the peak MABP was reached ($MABP_{95pct}$). However, with 20 to 120 minutes, the delays were substantial. This confirms the results from *in vitro* studies [14,22] (chapter 3.4). In general, the time fraction that the blood pressure was above the target-MABP ($MABP_{target}$) was significantly higher in cohort B after the "startup" intervention, which suggests a better 'performance' in cohort B. However, this is not likely due to the infusion set because the pre- and post-intervention periods of $MABP_{target}$ were not significantly different about the "startup" intervention (appendix I). In other words, the $MABP_{target}$ was already higher prior to the "startup" intervention in cohort B. The $MABP_{fit}$ showed that the blood pressure increase in cohort B was significantly steeper. It is therefore plausible that the $MABP_{95pct}$ will be significantly smaller in cohort B if enough comparable patients are included.

One remarkable difference was found between the cohorts. In almost every instance, after the "startup" intervention, the MABP-increase decreased suddenly in cohort B (Figure 5). It was hypothesized that the new infusion set (cohort B) introduced a longer delay in comparison to the old infusion set (cohort A). It was therefore suggested that it was more difficult for pump users to titrate inotropics according to the blood pressure readings, because the intended effects occur much later than anticipated. As these delays between intervention and effect tend to be counter-intuitive, this might trigger the pump user to increase the flow rate too soon after the pump has started and no effect has been observed yet, which can eventually cause an overshoot in inotropic administration. Although the delay was not significantly longer in cohort B, as reflected by the $MABP_{95pct}$, clinicians could interpret the lower MABP after the MABP-decrease as a longer delay. Therefore, similar to an actual longer startup delay, the non-persistent MABP in cohort B might also explain the higher number of interventions found per patient in Table 3. Patient safety could be improved if the higher number of iatrogenic blood pressure variations can be avoided.

4.1 Characteristics of the MABP-increase and decrease

1) Physiological and medical explanation

Inotropic pharmacokinetics as well as the pharmacodynamics predict a direct relationship between the dosing rate of inotropics and the effects on the patient in terms of MABP. This was also shown in an *in vivo* study conducted by Lovich et al. [23]. In a swine model initiation and cessation of inotropic administration resulted in the predicted kinetics with delays of a few minutes [23]. As these delays of only a few minutes are well under the delays of approximately one hour found in this study ($MABP_{95pct}$), it can be assumed that the delays found in this study are, at least in part, due to the infusion hardware and not just the patient's physiology. Nevertheless, the inter- and intra-patient variability with regard to the responsiveness to inotropics may be large in a cohort of pre-term neonates.

Older infants may have better developed auto regulation, therefore the older infants in subgroups CG2 and CG3 may also have better auto regulation [6,9,24]. The exact impact of the limited auto regulation, however, remains uncertain. With the inclusion of the older infants, the transient increase and subsequent decrease became more prominent (Figure 6). This does suggests that this effect is not caused by the very preterm infants (GA <32 weeks), nor by the somewhat older infants (GA < 42 weeks).

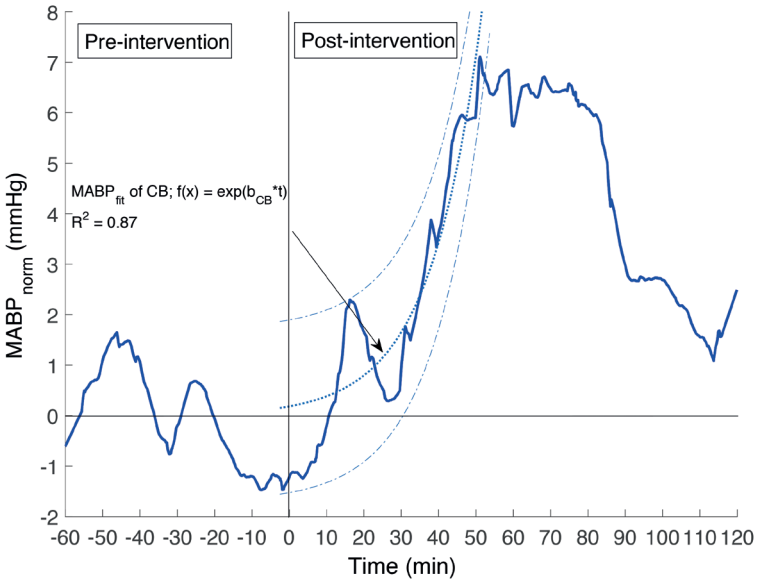

Figure 6. *Normalized and "combined" MABP ($MABP_{norm}$) of Cohorts B (CB) of subgroup CG3, for the "startup" intervention. The data are fitted according to an exponential fit (exp(b*t)), where t is time. Dotted lines are the 95% confidence interval. Coefficient b = 0.073 (0.071 – 0.075, 95% CI) min^{-1}.*

Another explanation is that the flow rate was decreased by the clinicians approximately 60 minutes after the initial intervention. This seems plausible since $MABP_{target}$ was already higher prior to the intervention (see Figure 4). However, in cohort B we also registered the flow rate decrease and no systematic flow rate decrease within an hour after the intervention was registered.

One important factor that does impact the patient's responsiveness to inotropic administration are severe illnesses such as infections. Especially systemic infections such as sepsis may cause the patient to be unresponsive to inotropic delivery. These patients may therefore substantially influence the results. A plausible explanation for the decrease of the MABP are the possible higher number of patients with systemic infections in cohort B.

2) Technical explanations

The initial hypothesis that the dead volume in the new infusion set is larger than in the old infusion set does not appear from the results. While it has been suggested that the dead volume in the old infusion system (cohort A) is smaller (~0.14 ml) than the new infusion system (cohort B) (~0.41 ml), none of the end points suggests a significant difference in dead volume. However, other physical properties of the infusion setup do provide a plausible explanation for some of the differences found, such as elasticity of infusion components. From *in vitro* studies [16,25] it was found that differences in elasticity caused a difference in steepness of flow rate changes. Therefore, the differences in steepness, as shown by $MABP_{fit}$, is suggestive of a different magnitude of elasticity (mechanical compliance) rather than a different dead volume. Moreover, flow resistance, due to narrow tubing may exaggerate the effects of the elasticity of the infusion system. The tubing in cohort A may have been narrower.

A plausible explanation for the sudden decrease in MABP may be due to the anti-reflux valve integrated in the new infusion set. It is known that anti-reflux valves introduce additional delays [26,27]. Moreover, valves require an initial pressure to open, after which the flow rate may increase suddenly. This may occur because the increasing pressure already caused the compliant syringe to expand, after opening of the valve, this overpressure may be translated in a transient overdose. Moreover, the successive opening and closing may continue for a period of time, these effects seem to be somewhat random (Appendix III).

4.2 Strengths and weaknesses

Criteria for the treatment of hypotensive infants have changed since the old cohort was collected. Criteria for the initiation of inotropic support have been tightened since the connection between hypotension and a decreased cerebral oxygenation was found to be more limited than previously thought [21]. Another reason is a change in respiratory support policy, which also reduced the need for inotropics. In order to include a sufficient number of patients it was therefore decided to introduce slightly different inclusion criteria for the new cohort B. Because of the differences between the inclusion criteria between cohorts A and B, each of the end points were also analyzed in the subgroups where the inclusion criteria were similar. This is considered a strong point. However, in retrospect, there were a lot of other parameters that may have influenced the results, which is a weak point. These parameters will be summarized in the “Advice from this pilot study” section.

A weak point was that the exact dosing rate changes in inotropics were not used in the analyses along with the interventions of “startup” and “flow increase”. Is it therefore more difficult to distinguish the impact of the pharmacology and the impact of the infusion set on the MABP.

The population size for the intervention “startup” in CG1 was too low to provide sufficient statistical power, this is a weak point. However, the number of flow rate increases were relatively larger, which enabled us to gain sufficient statistical power, which is a strong point. It should be noted, however, that some interventions occurred relatively more frequently in some patients than in other patients.

The pumps used between the studies were different, which is a weak point. However, previous studies have found differences in accuracy and precision between these pumps are small [28] and do probably not account for the differences found in this study. It also remained somewhat ambiguous how the infusion setup in cohort B was assembled exactly, this was not accurately documented but acquired by interviewing healthcare professionals and observing photographs. Moreover, contrary to the new system, the old infusion set (cohort A) also varied on a case-by-case basis, this is weak point. A well-documented description of the infusion system used to treat the patients is essential to draw hard conclusions.

4.3 Advice from this pilot study

The following recommendations can be used for the prospective design of studies aiming to investigate to influence of infusion hardware *in vivo*. In general, the patient populations should correspond better and more documentation about the treatment process is necessary. Furthermore, it is advised to:

- Establish a patient-based definition for hypertension founded on, e.g. Dionne et al. [29]. If both the target-MABP for hypo and hypertension are known, it is possible to investigate whether it is substantially more difficult to remain within a certain desired bandwidth of MABP with certain infusion hardware compared to other hardware.
- Record the times at which flow rate decrease interventions occurred instead of just the “flow increase” interventions. In combination with the definition of hypertension this might explain why the flow rate decrease is performed.
- Conduct a similar analysis on heart rate (HR) and oxygen saturation (SaO_2). Besides additional information, the clinical interpretation of these vital signs is better established compared to MABP [30,31]. Moreover, a combination of these vital signs might provide additional information such as underlying pathology. Substantial differences in these parameters may suggest that the inotropic administration is not responsible for the perceived changes in the vital signs.
- Document information about other administered medications and volume expansion as these factors might have impact on the investigated vital signs.
- Describe the infusion system used in detail, register especially dead volume, compliance and resistance. Previous studies have demonstrated methodologies on how to assess these quantities [32].
- Document the flow and dosing rates of all parenteral drugs that were administered through the same dead volume as the inotropics, within a minute of accuracy. Many pumps, such as smart pumps, are able to register the flow rates automatically.
- Document each patient that was irresponsive to inotropic administration, due to, for example, sepsis. This may be a reason for exclusion.

5 CONCLUSIONS

We found that differences in delays and achieving the target-MABP in both infusion sets were limited or inconclusive. Therefore it is difficult to make a clear distinction in the performance of both infusion sets. However, substantial delays between flow rate interventions and the intended blood pressure increase were found, which were likely related to the infusion setup. The higher number of interventions per patient in cohort B might be due to the sudden decrease in MABP after starting the pump. This sudden decrease may be caused by the anti-reflux valves as well as medical reasons such as sepsis, or a combination thereof. Compliance and resistance may be responsible for a difference in the steepness of the MABP-increase, dead volume was an unlikely explanation for this. It is feasible to investigate the impact of an infusion set on MABP. Therefore it is recommended to expand the study in order to provide advice for clinicians on how to select and construct a suitable multi-infusion setup considering patient safety.

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APPENDIX I: WITHIN-SUBJECT ANALYSIS

Table I.1 paired test pre versus post-intervention (see Appendix II for further explanation of end points)

	$MABP_{average}$ (mmhg)		$MABP_{target}$ (%)	
Cohort	**CA**	**CB**		
CG1-startup	P = 0.0026**	P = 0.6654	P = 0.0025**	P = 0.6039
CG2-startup		P = 0.2963		P = 0.0860
CG3-startup		P = 0.9922		P = 0.0917
CG1-flow increase	P = 0.0074**	P = 0.4693	P = 0.0010**	P = 0.0054**
CG2-flow increase		P = 0.0022**		P = 0.0046**
CG3-flow increase		P = 0.0551		P = 0.0575

APPENDIX II: ADDITIONAL DATA ANALYSIS

Obtaining the combined graphs for $MABP_{fit}$

$MABP_{norm}(n) = MABP(n) – RMS(MABP(T_{pre}))$, where MABP(n) is the MABP of the n_{th} sample, and T_{pre} is the pre-intervention period. $RMS(MABP(T_{pre}))$ is thus the root mean square of the pre-intervention period of a particular patient. If the pre-intervention period was unavailable, the first sample of the post-intervention period was used as a substitute for $RMS(MABP(T_{pre}))$ and considered zero (0) mmHg. Subsequently, the data were combined by taking the average of each synchronized and normalized sample (n) as follows: $MABP_{combined}(n) = MEAN(MABP_{norm,i}(n))$, where $MABP_{norm,i}(n)$ is the normalized MABP of patient i at sample n.

APPENDIX III: *IN VITRO* MEASUREMENT OF ANTI-REFLUX VALVES

To investigate whether the observed differences might be due to the infusion setup we measured the outflow of both infusion setups described in the “methods” section, by using the balance of an experimental setup, as described before [14]. From Figure 7a (new infusion set) it can be seen that the flow rate when using an anti-reflux valve is unstable, while in Figure 7b (old infusion set), the flow rate increase is stable. The reason for this unstable behavior might be explained because the valves consecutively opens and closes and opens again. Not only do these phenomena cause additional delays, the overdoses may also cause the clinician to intervene during titration because the MABP is observed to rise fast and thus interpreted as an overdose. The impact of the valve may be a possible explanation, especially in combination with resistance elements such as the filter, this may all be a plausible explanation of the variability on blood pressure found.

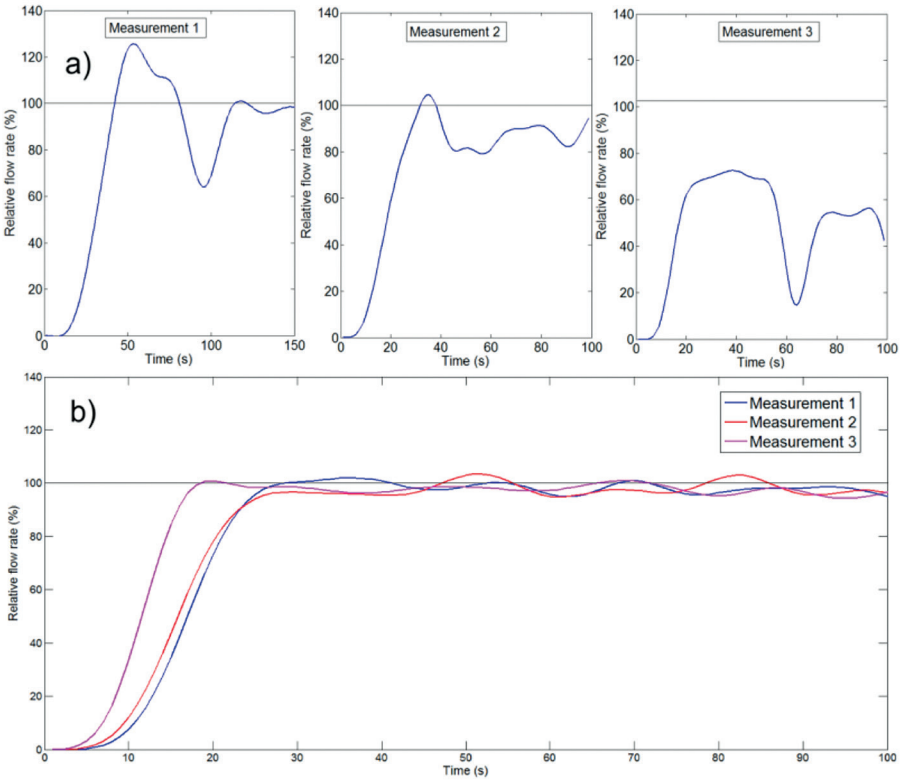

Figure 7. *Measurements of infusion set with anti-reflux valve (a) and manifold without anti-reflux valves (b). In each case 100% (indicated with a horizontal line) is the intended flow rate.*

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Chapter 3.4

Dosing errors in preterm neonates due to flow rate variability in multi-infusion syringe pump setups: An in vitro spectrophotometry study

Eur J Pharm Sci 2016; 93:56–63

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ABSTRACT

Background: Drug administration on the Neonatal Intensive Care Unit is often associated with adverse events. This may be due to dosing errors caused by multi-infusion setups. We aim to investigate these dosing errors.

Material and methods: N=3 experiment using a medication schedule, multi-infusion setup (three pumps) and disposables as applied on the NICU. In-line and real-time absorption spectrophotometry was used with dyes as substitutes for pharmaceuticals. Three flow rate changes lasting one hour were initiated. Subsequently, the possible dosing errors were estimated in the parallel pumps. In addition, startup durations, the times the flow rates required to reach steady state after significant dosing errors, as well as the total dosing error were measured.

Results: Contribution of the start-up delays to the cumulative dosing errors were the largest. However, initiated flow rate changes resulted in significant dosing errors in the parallel pumps as well. The total dosing error was not significant. The significant peak errors were between 48.2% and -32.5% at flow rate increase and decrease, respectively. Startup delays of up to 42.6 minutes were measured.

Conclusions: Applying multi-infusion while following a neonatal medication schedule may temporarily result in dosing errors, which can be relevant for fast-acting medications. Awareness may mitigate the risks.

1 INTRODUCTION

Almost all patients treated on the neonatal intensive care unit (NICU) receive intravenous (IV) infusion therapy [1]. Infusion therapy intended for NICU-patients commonly requires the continuous and simultaneous administration of multiple pharmaceuticals such as inotropics, opioids, antibiotics and sedatives. The administration of these drugs using multi-infusion to NICU-patients is challenging. For example, these little and often critically ill patients are unable to tolerate the infusion of large quantities of fluid [2]. To reduce the amount of fluid delivery but still reach the effective dose, highly concentrated mixtures are delivered at volumetric flow rates as low as 0.5 ml/h. Moreover, these mixtures frequently contain rapid-acting pharmaceuticals with short half-lives and narrow therapeutic margins requiring a stable infusion flow rate, because even a relatively small deviation in flow rate may result in clinically relevant dosing errors. Consequently, accurate motorized syringe pumps are used to meet this demand for precise and accurate drug delivery. Another risk of infusion therapy is the placement of the catheter. With each puncture and accompanying catheter insertion, the probability of systemic infections increases. The number of IV-access sites should therefore be reduced to a minimum, especially in vulnerable patients, such as very and extremely preterm neonates. As such, pharmaceuticals from multiple pumps are often combined into a single central line and catheter before entering the patient's bloodstream. This practice is known as multi-infusion or co-infusion [3,4]. Infusion technology has one of the highest rates of medical errors associated with medical technology [5]. Previous research has shown that flow rate variability is related to dead time and carrier flow [3,4,6], flow interaction between two syringe pumps [7,8] and the effects of gravity and vertical displacement [9,10]. Additionally, several publications addressed the physical effects of a variety of disposables [11–14]. Other studies have already recognized effects as a result of multi-infusion flow interaction in parallel pumps and start-up delays as plausible and possibly clinically relevant in neonatal populations [7,15–18].

In summary, the practice of multi-infusion often seems to result in flow rate variability, even when accurate syringe pumps are used. This in turn may result in clinically relevant dosing errors, which is especially true for the (preterm) neonate. Several studies have, for example, reported significant hemodynamic instability and possible adverse effects in neonates in relation to the administration of rapid-acting inotropics [19–23] and propofol [24]. Preterm neonates are known to be particularly susceptible to hemodynamic instability due to their limited ability for cerebral autoregulation in response to changing blood pressure and blood flow [22,25]. However, to our knowledge, no substantial research has been performed to quantify multi-infusion flow and dosing rate variability on the NICU.

The objective of this study is therefore to assess dosing errors due to flow rate variability in neonates as a consequence of applying a cascade of multiple infusion pumps intravenously. An absorption spectrophotometry in vitro study was conducted to simulate a multi-infusion setup and neonatal medication schedule.

2 MATERIAL AND METHODS

2.1 Experimental Setup

IV multi-infusion therapy on the NICU was simulated in a laboratory setting using three infusion pumps, each containing a dye mimicking pharmaceutical solution. The flow rate, which is linearly related to the dose at the end of the infusion line, was measured with spectrophotometry (Figure 1A). To simulate the NICU setting, the same disposables were applied in the experimental setup as are used in the daily practice of the NICU of the Wilhemina's Children Hospital of the University Medical Center Utrecht, a tertiary care academic hospital.

Three Perfusor B.braun syringe pumps (pumps 1-3) (B. Braun, Melsungen AG, Germany) and 50 ml syringes (BD Plastipak, Plymouth, Ireland) were used in the experimental setup. The pumps were connected to a 173 cm central line disposable (Impromediform GmbH, Lüdenscheid, Germany) (Figure 1B) through the two Luer-Lock access groups for medications (C1 and C2). These access groups were equipped with anti-reflux valves and, subsequently, a filter. Behind the filter there was a specific lipid access (C3) connector which was not used in the experiments. The syringe pump containing the dye solution, mimicking high-risk medication (pump 1, see Figure 1), e.g. dopamine, was connected to C2, because high-risk medications are commonly administered in close proximity to the patient. C1 was used for the pumps containing the dyes mimicking the "less"-critical medications (pumps 2 and 3), e.g. total parenteral nutrition (TPN) and glucose. The central line output was finally connected to a 4 Fr double lumen catheter (Vygon, Ecouen, France), similar to an Umbilical Venous Line used in neonates.

Catheter output concentrations, normally administered to the neonate, were continuously measured using a spectrometric setup (Figure 1A). The catheter was for this purpose connected to a flowcell (Z flow cell w/SMA 905, 10-mm pathlength, FIAlab, Seattle, WA, USA). The flowcell was connected to a spectrometer (QE65000, Ocean Optics, Dunedin, FL, USA) and a light source (DT-100, Ocean Optics, Dunedin, FL, USA) allowing the spectrometer to obtain a spectrum of the mixture driven through the flowcell. Based on calculations the dyes were expected to be fully mixed, i.e. full diffusion was expected to occur in radial direction of the infusion lines, before entering the flowcell. Finally the fluids from all pumps were collected and measured by the balance (PGW 450, Adam Equipment, Oxford, CT, USA). Both the balance and the spectrometric data were recorded by a PC (X86 32 bits, windows XP, USA) at a sample acquisition period of 10 seconds (0.1 Hz). The method described was capable to measure the flow rates originating from each specific pump, which is equivalent to the pharmaceutical dose delivered to the patient.

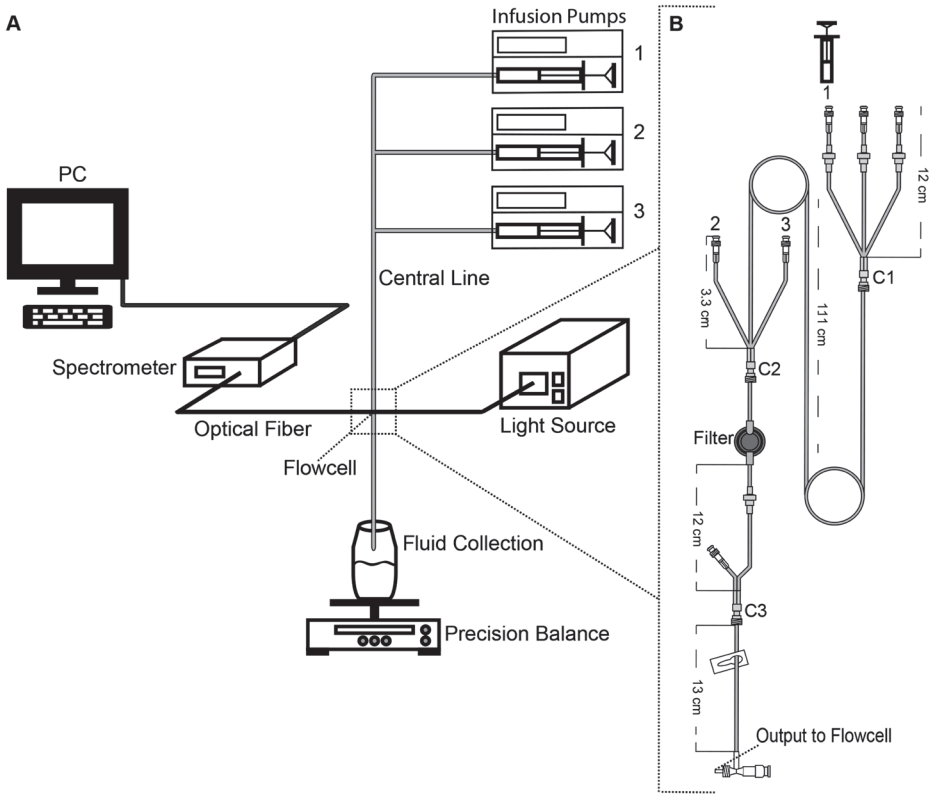

Figure 1. *Measurement setup shown schematically. The dye-filled infusion pumps were connected to the flowcell, shown at the intersection, and, subsequently, to the fluid collection after the flowcell, where the cumulative solution was measured by the precision balance. At the flowcell intersection, a light source was also connected to the same flowcell through optical fibers, which was then connected to a spectrometer. The flowcell enables the light to pass through the dye mixture, which yields an absorption spectrum. The flowcell was shielded from ambient light. The spectrometer and balance data were finally collected by a PC (**A**). 173 cm central line disposable, C1-C3 are Luer-lock connector groups, C3 is used for lipids. The flow goes from top to bottom in the drawing. Pump 1 (mimicking the critical medication) was connected to access group C2 and pumps 2 and 3 (mimicking "less"-critical medication) to C1. (**B**).*

2.2 Medication Schedule

To investigate flow rate variability (and thus dosing variability), a medication schedule was simulated in which flow rate changes were initiated and changed back for each pump (Figure 2). The total duration of the medication schedule was eight hours. Pumps 1-3 were started at flow rates of 6, 2 and 0.5 ml/h, respectively. Six flow rate changes were manually executed according to the medication schedule; first these were initiated and, next, changed back after one hour. During the flow rate changes the other two pumps, in which no flow rate change was intentionally initiated, were considered the 'parallel pumps'. The experiment was repeated three times (N=3).

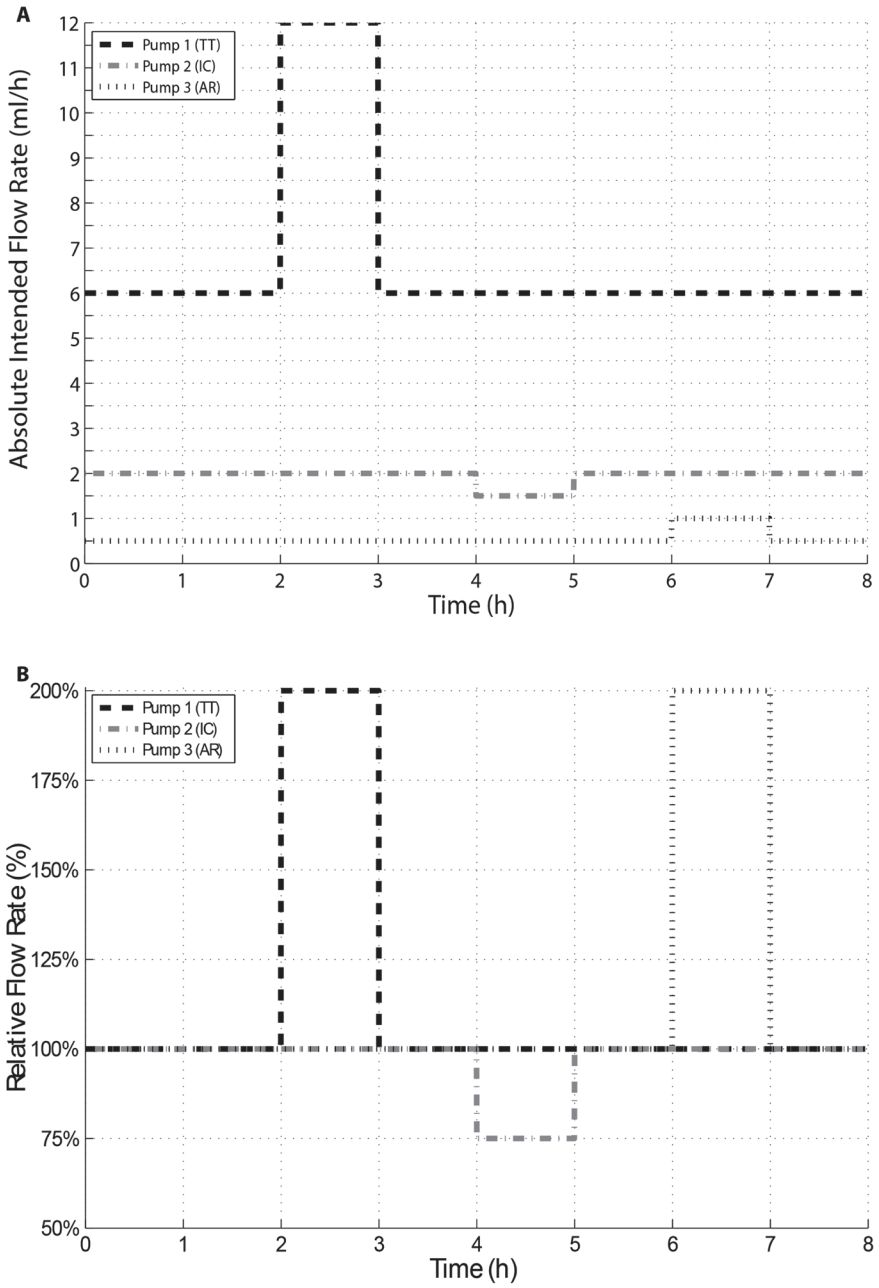

Figure 2. *Graphical representation of medication schedule set point values. Absolute intended flow rate (A) and relative flow rate changes (B). The flow rate in pump 1 was increased at t = 2h from 6.0 to 12 ml/h and back to 6.0 ml/h at t = 3h (a 100% change). Pump 2 was decreased from 2.0 to 1.5 ml/h at t = 4h and back to 2 ml/h at t = 5h (a 25% change). Pump 3 was increased from 0.5 ml/h to 1.0 ml/h at t = 6h and changed back to 0.5 ml/h at t = 7h (a 100% change). As a substitute for the pharmaceuticals Tartrazine (TT, 0.02 mg/l), Allura Red (AR, 0.1 mg/l) and Indigo Carmine (IC, 0.2 mg/l).*

Tartrazine (TT), Allura Red (AR) and Indigo Carmine (IC) laser dyes were used as substitutes for the pharmaceuticals. The dyes were selected on the basis of their distinctive absorption spectra, i.e. the overlap of the absorption spectra was minimal. Dye concentrations (Figure 2) were chosen according to the linear range agreement between concentration and absorption by which the absorption spectrum can be related to flow rate and thus the flow and dosing rate variability of each individual pump.

2.3 Dosing Errors

In clinical practice a dose is defined as the amount of a pharmaceutical administered in a certain time interval. It is usually denoted as mg or mg per kg patient weight. In infusion therapy the concentration of the pharmaceutical in the syringe pump is usually kept constant. Therefore, the dose intended to administer during a time interval is realized by setting and, if necessary, adjusting, the flow rate. This means that a dose is delivered per unit time (dosing rate), often denoted as mg/h or mg/kg/h. Consequently, if the patient receiving infusion therapy requires a different dose, the clinician changes the infusion flow rate (ml/h) of the pharmaceutical solution in a certain concentration (mg/ml). A dose was therefore defined as the amount (ml) delivered after a certain time interval (the area under the curve of the flow rate). The relative dosing error was defined as the deviation (%) of the administered dose (ml) from the set point value (i.e. intended dose). A Dosing Error (DE) can thus be described using eq. 1

$$\text{Dosing Error} = \left(\frac{\text{Administered Dose}}{\text{Intended Dose}} - 1\right) \times 100\% \quad (1)$$

Where the administered dose is the measured value and the intended dose is the set point value.

It was anticipated that dosing errors may occur in the pumps where flow rate changes were initiated, as well as the parallel pumps combined on the same central line and catheter. From each measurement the standard deviation σ (sigma) between the measured values and set point in steady state was calculated in order to distinguish dosing errors from the random error. The implications this has for the statistical significance of the data is further explained in the Data Analysis section. The following endpoints related to dosing errors were investigated (see Figure 3 for a full explanation):

1. **Total** Dosing Error: dosing error (%) during the total time T = $t_1 - t_2$ = 0 – 8h for each pump.
2. **Interval** Dosing Error: dosing error (%) during the pre-defined one hour intervals T = $t_1 - t_2$ = 2-3, 4-5, 6-7h (Figure 2), i.e. between each initiated flow rate increase and flow rate decrease.
3. **Peak Interval** Dosing Error: average dosing error (%) during the area under the curve of the peak after each flow rate change. The beginning and ending of the peak was defined by the moments that the flow rate crossed the set point ±2σ. The average dosing error was the area under the curve of the peak divided by the peak duration (defined later). Since some dosing errors in the parallel pumps were expected to be

temporary, the durations of these dosing errors were also measured. This end point was analyzed for the parallel pumps only.

4. **Startup Duration:** the duration in minutes until steady state has been reached after starting or changing the flow rate of the pumps. The startup period lasts until the set point ±2σ was crossed.
5. **Peak Duration**: the duration in minutes of a peak dosing error. Peak errors were recorded after T = 2, 3, 4, 5, 6 and 7h, i.e. after each initiated flow rate increase and flow rate decrease. The peak duration was defined by the moment that the flow rate crossed the set point ±2σ. This end point was analyzed for the parallel pumps only.

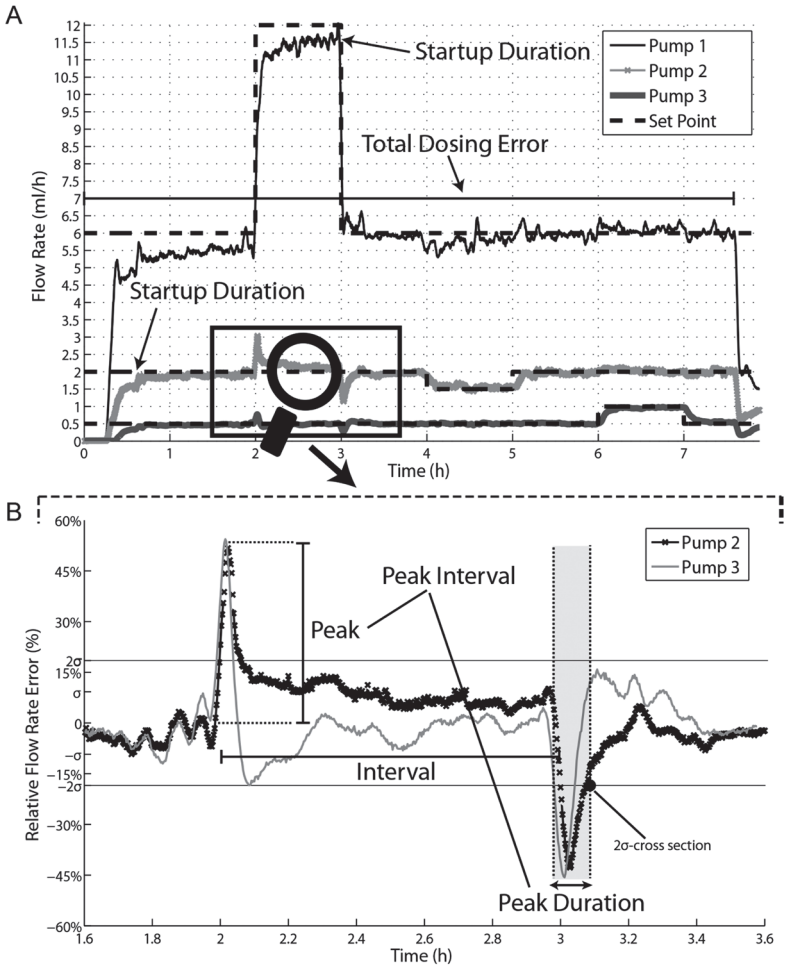

Figure 3. *Measurement of flow rates after carrying out the medication scheduled (**A**). Measurement of dosing errors between approximately t = 2 and 3h in the parallel pumps. Standard deviations (σ) are indicated as well (**B**). The endpoints of Startup, Interval, Peak interval and Total dosing errors are illustrated in the plots, the values will be given in the results.*

2.4 Data Analysis

The data were analyzed using linear regression calibration which was described earlier [26]. The method was able to acquire the concentration of each laser dye that flows through the flowcell individually in µg/h. The magnitude of the absorption peaks were related to the magnitude of the dilution of each dye. This, in turn, is proportional to the ratio of the flow rates between the pumps. Because the total volume is registered by the balance (ml), a flow rate can be obtained in [ml/h] for each pump. An additional fourth-degree Savitzky-Golay filter was used to remove a portion of the noise present in the balance data. All results are presented as averages of the three measurements.

A dosing error peak larger than 2σ ($p < 0.05$) compared to the random error was considered significant. Peak errors that were not statistically significant were discarded. Furthermore, only relative errors were investigated and presented. To analyze the spectrometric and balance data using the methods described, a program was written in Matlab 2009a 7.8.0.347 32 bits. An extensive physical and mathematical description of the method is given in Appendix I.

3 RESULTS

Statistically significant dosing errors were found as a result of flow rate variability in the simulation of IV multi-infusion therapy on the NICU (Table 1). The **total** dosing errors (-5.5 to -7.9%), measured over the entire medication schedule (Figure 2), and the **interval** dosing errors, measured over a one-hour period after the flow rate changes at t=2h, t=4h and t=6h, (-7.1% to 11.1%) were relatively small and not statistically significant.

Significant **peak** dosing errors were found in the parallel pumps, i.e. the pumps in which no flow rate change was initiated. The highest peak dosing error in the parallel pumps found was +48.2% ± 23.3% at t=2h, with a peak duration of approximately six minutes before the set point value and steady state was reached again. A similar peak of -32.5% ± 18.6% at t = 3h was found lasting approximately four minutes before the set point value and steady state was reached again. Although the peak dosing errors at t=2h and t=3h in the parallel pumps were found to be significant, the peak errors at t=4h, t=5h, t=6h and t=7h were not significant for the parallel pumps.

Startup durations of up to 43 minutes were found when starting the pumps at t=0h from a flow rate of zero ml/h. Pump 1 (set point 6 ml/h) was shown to reach the desired flow rate set point significantly faster than pumps 2 and 3 (set point 2 resp. 0.5 ml/h). When flow rates were changed at t=2h - t=7h, the duration until the set point was reached was up to 8.4 minutes. Similar to the startup at t=0h, the faster pumps consistently reached the desired set point values earlier than the slower pumps.

Table 1. Dosing errors results of investigated endpoint

Initiated flow rate change (ml/h)	Parallel Pumps (no change)	Dosing Errors (%)						Duration (min)	
		Total	p value	Interval	p value	Peak Interval[a]	p value	Startup	Peak Duration[a]
Pump 1 (0 - 6)		-7.40	0.48	-	-	-	-	22.8	-
Pump 2 (0 - 0.5)		-5.45	0.60	-	-	-	-	30.6	-
Pump 3 (0 - 2)		-7.94	0.44	-	-	-	-	42.6	-
Pump 1 (6 - 12)		-	-	-7.05	0.50	-	-	2.20	-
	Pump 2	-	-	11.1	0.29	39.1	4.22E-6‡	-	5.70
	Pump 3	-	-	2.48	0.81	39.7	1.23E-4†	-	3.30
Pump 1 (12 - 6)		-	-	-	-	-	-	3.00	-
	Pump 2	-	-	-	-	-31.2	0.0021**	-	3.80
	Pump 3	-	-	-	-	-35.5	0.0019**	-	3.60
Pump 2 (2 – 1.5)		-	-	7.65	0.46	-	-	4.10	-
	Pump 1	-	-	-3.74	0.72	N/A	N/A	-	N/A
	Pump 3	-	-	-0.83	0.94	N/A	N/A	-	N/A
Pump 2 (1.5 – 2)		-	-	-	-	-	-	3.48	-
	Pump 1	-	-	-	-	N/A	N/A	-	N/A
	Pump 3	-	-	-	-	N/A	N/A	-	N/A
Pump 3 (0.5 - 1)		-	-	-7.10	0.50	-	-	7.32	-
	Pump 1	-	-	-2.03	0.85	N/A	N/A	-	N/A
	Pump 2	-	-	4.24	0.68	N/A	N/A	-	N/A
Pump 3 (1 – 0.5)		-	-	-	-	-	-	8.40	-
	Pump 1	-	-	-	-	N/A	N/A	-	N/A
	Pump 2	-	-	-	-	N/A	N/A	-	N/A

The flow rates in pumps 1-3 were changed three times and, subsequently, changed back another three times, resulting in a total of six changes. During these changes the interval dosing errors were registered as well as the total dosing errors during the entire measurement. The changes resulted in dosing errors in the parallel pumps and the pumps in which the flow rate was initiated. The peaks of these dosing errors are listed. All the errors were temporary. The startup duration denotes the delay before the set point is reached for the pumps in which the flow rate changes were initiated. The Peak Duration states the time delay until the peak dosing errors in the parallel pumps reached the set point. The p values of all dosing errors are listed. Non-significant peak intervals could not be distinguished from noise in the data.

** $p < 0.05$; ** $p < 0.01$; † $p < 0.001$; ‡ $p < 0.0001$; [a] N/A = peak was not observed*

The initial startup contributed 91.8%, 83.7% and 74.1% to the total dosing errors for pumps 1-3, respectively. Excluding the initial startup, pumps 2 and 3 contributed resp. 66.2% and 26.5% to the total dosing error as parallel pumps, at t=2h and t=3h. The contributions to the total dosing error due to startup delays were 33.8% and 73.5%, resp. for pumps 2-3 at t=4h and t=5h and t=6h and t=7h in this case. In terms of duration, 56% and 31% were resp. due to the dosing errors in the parallel pumps for pumps 2 and 3, at t=1h and 2h (initial startup excluded).

4 DISCUSSION

The results indicate that - after changing the flow rate in one pump - clinicians should consider the possibility of an unintended short-term over- or under-dosing of medication in pumps combined to the same central line or catheter as the pump that was changed. The largest part of the total dosing errors were caused by the initial startup. Furthermore, the results show that, if the flow rate changes are larger, the contribution of the parallel pumps to the total dosing error of those flow rate changes are larger. Besides the dosing errors in de parallel pumps, clinicians should be aware of substantial startup durations after the pumps are started or the flow rates are deliberately changed. These long startup delays typically occur in the pumps containing critical medications such as inotropics, which are often required by extremely and very preterm neonates with hypotension immediately.

4.1 Underlying physics and consequences for disposables

We previously explained three physical effects: dead volume, compliance and resistance. These effects were also found in biomedical literature [3,4,27].

Dead volume is the volume between the mixing point and the patient at the catheter or infusion needle tip. The dead volume causes a temporary mass flow rate change in the parallel pumps, due to the 'push-out' effect [28]. Due to this effect, a temporary overdose or under-dose occurs in the parallel pumps after a flow rate increase or decrease, respectively. When the dead volume of a central infusion line is smaller, it is expected that the dosing errors shown in this study will be smaller as well. It is therefore advised to use disposables with small internal volumes [29]. Inside the dead volume mixing effects are of interest. With the flow rates and infusion lines used in this study, a laminar flow is expected, with no relevant diffusion in the axial, i.e. longitudinal, direction. However, full diffusion in radial direction should occur before entering the patient. Moreover, because the viscosity is close to water, the friction that the infusion line wall is exerting on the fluid is expected to cause an additional concentration gradient as the drug solution moves along the length of the infusion line [4,30,31]. Dosing errors resulting from dead volume and the cessation of one pump in high flow rates pumps was demonstrated before [4,32]. Dosing errors were quantified in a two-pump low flow rate setup [7]. In this study it was demonstrated that dosing errors in a three-pump setup, using a NICU medication schedule and disposables is plausible.

The second effect, compliance, is responsible for the slow onset of the flow rates, even if the infusion lines are pre-filled. Compliance is caused by the elasticity of the infusion disposables, most notably syringes and infusion lines [14,27,33]. If the flow differences are big, it is even possible for backflow to occur due to compliance. For example, TPN has a higher flow rate and may flow back into the slower infusion line of the slower infusion pump, e.g. the dopamine pump with a flow rate of 0.5 ml/h. This may cause a substantial additional delay for the critical drug to reach the patient again. Anti-reflux valves might prevent or mitigate this effect [32], although it has been shown that anti-reflux valves, in turn, produce other problems such as longer startup times [11]. Most NICU's use specific disposable with a minimal dead volume and anti-reflux valves. The infusion line used in this study is an infusion line specifically designed for neonatal infusion therapy. However, it was shown that clinicians should be aware that dosing errors still occur.

4.2 Clinical implications

The dosing errors found may result in unintended and unexpected clinically relevant adverse events, depending on the pharmaceutical used. Therefore, the blood concentration changes were investigated for these dosing errors.

Blood concentration change (Figure 4) can be calculated using dosing errors and the duration of the dosing errors (i.e. peak durations) from Table 1 (see Appendix II), and half-lives of the pharmaceuticals used (Table 2) as input [34].

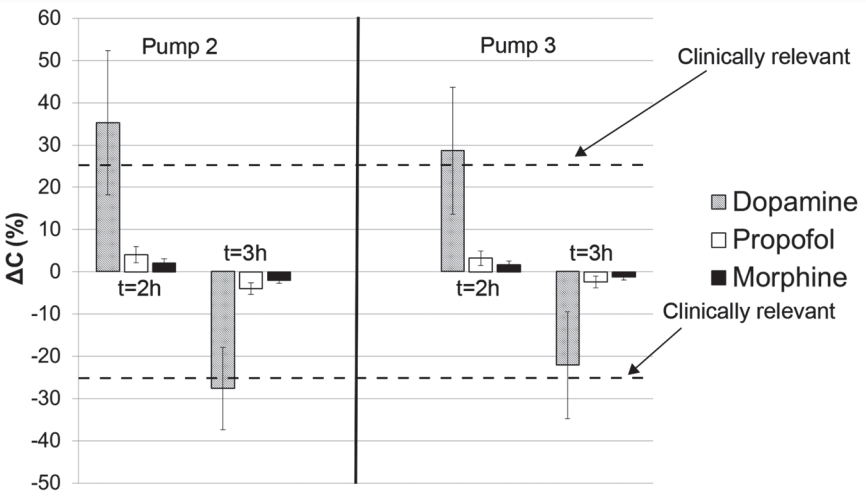

Figure 4. *Blood plasma concentration change (ΔC) of Peak Dosing Errors at t=2h and 3h for the parallel pumps 2 and 3. Illustrative medications with different half-lives, dopamine, propofol and morphine are shown. Note that the half-life may vary with gestational age (GA) and propofol is typically given as a bolus on the NICU. The dashed line at 25% indicates that the dosing errors are possibly clinically relevant*.

Table 2. Half-lives of common pharmaceuticals

Type	Common Pharmaceutical	Half-life ($t_{1/2}$)
Inotrope	Dopamine	1-2 minutes
	Dobutamine	1-2 minutes
	Noradrenaline	1-2 minutes
Anesthetic	Propofol	30 – 60 minutes
Analgesic	Morphine	2-3 hours

All the peak durations were in the order of 2-10 minutes after a peak dosing error had occurred. Even during this short duration and with the small half-lives of inotropic agents (Table 2) this still accounts for possible blood concentration overdosing of 35% ± 17 and -28% ± 10 under-dosing. It can be assumed that a 25% blood concentration change is clinically significant. Therefore, it is expected that these blood concentrations may cause adverse events for neonates. Moreover, these errors are found in the pumps of 0.5 and 2.0 ml/h, these flow rates are commonly used for high-risk pharmaceuticals such as inotropics.

For anesthetic drugs, the change in blood concentrations will be less. This might, however, still have influence on the effects of common pharmaceuticals such as Propofol, especially in the neonatal population which was found to be subject to considerable variability in pharmacokinetics [24,35]. For analgesic drugs such as opioids, with half-lives longer than one hour, the blood concentration changes were small and therefore improbable to be clinically significant for the dosing errors described in this study.

There are several adverse events associated with dosing errors in the delivery of medications such as inotropics, especially for (preterm) neonates. For example, overdosing of inotropics can cause fluctuations of blood pressure and even life-threatening hypertension [21], which may result in conditions such as peri-intraventricular hemorrhages [19,22,36]. Hypotension is a very common medical condition in preterm neonates, which may lead to insufficient perfusion of critical tissue, such as cerebral brain tissue [22,36]. Hypotension will not be treated sufficiently in case of an under-dose or when the delivery is delayed. The experiments show that the startup duration can be around 45 minutes, this is undesirable [37]. The startup duration in the fastest pump was significantly shorter. However, high flow rates are not preferred in neonates as fluid delivery should be minimized.

The faster pump typically contains Total Parenteral Nutrition (TPN), which is combined on the same central line and catheter as the pumps containing inotropics. Clinicians have to perform flow rate changes to anticipate on vital signs or to follow a regimen. Consequently, the flow rate of the TPN pump is regularly adjusted. As the results show, this may result in potential clinically relevant effects in the slower parallel pumps containing inotropics. It is therefore advised to avoid combining high-risk medications, such as inotropics,

on a single central line or catheter-lumen with other pumps. However, vascular access is very limited and challenging, especially in neonates, therefore combining multiple pumps on the same lumen cannot be avoided in many cases. It should be noted that the results are applicable to situations where the pumps may represent other combinations of medications.

From the results it can be seen that the significant dosing errors are short, while the longer interval dosing errors of one hour and the total dosing errors of eight hours are not statistically significant. Therefore, the results do not show a systematic under- or over-dosing for any medication. The results do show that, for short half-life medication such as inotropics, blood concentrations are altered with possible clinical consequences. Moreover, the startup delays will cause a delayed onset of any medication, especially when lower flow rates are used.

4.3 Strengths and limitations of the study

No actual pharmaceuticals nor realistic concentrations were used. Laser dyes were used because pharmaceuticals do not usually produce well-defined absorption peaks. Conversely, laser dyes produce absorption peaks that can be measured and analyzed using a spectrophotometric method. Laser dye solutions had to be prepared manually. A dye quantity was measured with the precision balance (Figure 1A) and diluted using a pipette with an accuracy of 1 ml. A realistic concentration for an inotropic agent in the syringe is in the order of 1-5 mg/ml, which typically produces properties similar to water in terms of viscosity and density [38]. The dye concentrations were lower and can be considered equal to the properties of water as well, hence it can be assumed there is linear relation between dye absorption and the mass flow rate of each pump. Nevertheless, the viscosity of TPN and glucose are typically different from water. This may impact delay times with relation to the compliance and resistance of the infusion system, these may increase. Moreover, TPN may be administered using a gravity-driven pump, However, the results presented in this study were mainly due to the dead volume effect, therefore the experiment is still applicable and the dosing errors are still expected to occur.

The standard deviations of the regression coefficients are relatively small, therefore the calibration method is relatively strong. However, the steady state flow rate error standard deviation was around 10% for measurement 1-3, respectively. This is a considerable error, which made it impossible to analyze the more subtle dosing errors and should therefore be considered a weak point of this study. The reason for these large standard deviation was that the balance registered a relative large amount of noise. The causes mentioned above are likely to be the reason why the initiated flow rate changes of T = 4-5h and T = 6-7h were not found to produce significant dosing errors in the parallel pumps in the measurements.

It can be seen that disposables yield substantial variance in drug delivery. From experience it was recognized that especially the syringe shows considerable variance in compliance and reliability for, amongst other effects, the startup durations, this is also supported by the literature [39]. The use of actual disposables enhanced the realistic representation of the clinical practice in this study, it is therefore considered a strength.

5 CONCLUSIONS

Significant flow rate variability was found as a result of using multi-infusion, resulting in dosing errors with potential clinical relevance for medications which are fast acting. These errors are both unwanted and unexpected during multi-infusion therapy on the NICU. This study reinforces that especially inotropics are likely to cause clinically relevant adverse events as a result of the small therapeutic ranges. Sudden changes from hypo- to hypertension are known to cause peri-intraventricular hemorrhages, which in turn may be caused by the dosing errors found in this study. Especially preterm infants, suffering from hypo- or medication-induced hypertension are at risk. It is advised to combine high risk medications delivered with comparable flow rates on one catheter lumen and to avoid doing the same with medications delivered at higher flow rates, e.g. TPN. This may not always be possible in clinical practice. Therefore, it is important that the clinician is aware of the effects shown in this study.

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APPENDIX I: ANALYTICAL METHOD

When investigating (mass) flow rate fluctuations it can simply be assumed that the dye concentrations are proportional to pharmaceutical concentrations. Table A.1 shows the dyes used

Table A.1. shows the dye name and the wavelength where maximum absorption occurs

Dye name	Absorption peak value λ (nm)
Tartrazine	425
Indigo Carmine	610
Allura Red	502

A relationship between the absorption and the concentration is established as

$$A = mc + b \tag{2}$$

Where A is the absorption or measured decrease of intensity (absorption) [factor decrease in photon count], m is the regression coefficient, c [mg/l] is the concentration to be obtained and b is the linear regression offset. b can be seen as detector noise and should be minimal. The coefficient m and offset b are obtained by calibrating the dye and finding a linear relation between the measured intensity at its peak wavelength and the concentration.

In the usual case that multiple (n) dyes are measured M is an invertible square n x n matrix, whereas b and A become vectors of length n. The concentration of c can now be calculated as

$$c = -b + M^{-1}A \tag{3}$$

Where the main diagonal of matrix M contains the peak wavelength coefficient values of each dye, while the other matrix elements position describe the coefficient of the same dye at the peak wavelength values of the other dyes. The b vector contains the arrhythmic mean of the offsets at a certain peak wavelength between all the dyes.

To visualize the process Figure 5 shows an example dye calibration.

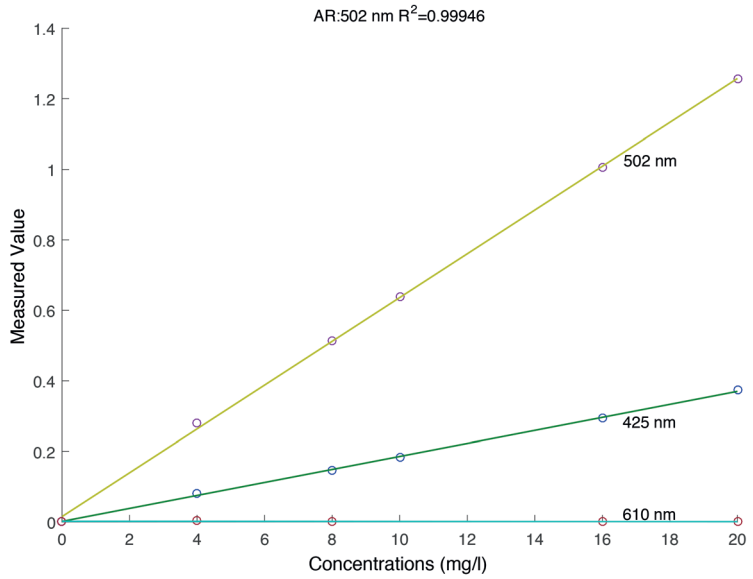


Figure 5. *Linear regression of dye Allura Red (AR). The main correlation coefficient R^2 at 502 nm was 0.999. The main regression equation at 502 nm found was y=Am+b = 0.062101x +0.015355. 502 nm is the absorption peak value of AR; 425 nm and 610 nm are the wavelengths of the peak values of the other dyes used. This calibration introduces one column in matrix M, with 502 nm on its main diagonal.*

In essence the peak value of each dye is measured and subtracted by the overlapping values of the other dyes.

It was assumed that the entire system, when activated, has a maximum built-up pressure. No additional compliance was expected to occur and therefore a unit of mechanical change in the pumps is immediately translated to a unit change of mass measured by the balance. Furthermore, the substance measured by the balance was assumed to hold the properties of water and any changes in density caused by the dyes can be neglected. By obtaining the current mass at a certain sample rate, an additional time factor was introduced. This enabled us to measure not just measure the total concentration but also the (mass) flow rate. To analyze the spectrometric and balance data using the method described we wrote a program in Matlab 2009a 7.8.0.347 32 bits.

Statistical Analysis

With normally distributed random noise, a probability density function (PDF) was calculated from each measurement. Startup and empty-syringe effects were excluded. From this PDF a standard deviation (σ) was acquired for each measurement.

P-values were acquired as:

$$1\text{-}\mathrm{Erf}\left(\frac{\sigma}{\sqrt{2}}\right) \qquad (4)$$

Where σ is the average standard deviation of a dosing error with respect to the set point. Using this method dosing errors can be distinguished from random noise.

APPENDIX II: PHARMACOLOGICAL THEORY

In case of an ordinary injection, clearance will lower the blood concentration of the drug until the drug first loses its therapeutic effects. Eventually the clearance process will completely eliminate the drug from the blood plasma. Contrary, infusion attempts to maintain a steady state of blood concentration. The time it takes to reach steady state is dependent on the pharmaceutical half-life.

The relationship between blood concentration [mg/l] and infusion rate is given by Steenhoek et al. [34].

$$C_t = \frac{R}{V_D k_e}\left(1\text{-}e^{-k_e t}\right) \qquad (5)$$

Where R is the infusion mass flow rate [mg/hour], V_d is the distribution volume [l] k_e is drug elimination rate constant [$hour^{-1}$] and t is the time [hour].

The equations essentially contains two terms, the first describing the steady state blood concentrations. As V_D and k_e are constants the blood concentration rate is directly proportional to the infusion rate. The second term is the elimination where the magnitude per unit time is determined by the elimination half-life. Accordingly, k_e can be described as

$$k_e = \frac{\ln 2}{t_{1/2}} \qquad (6)$$

Where $t_{1/2}$ is the elimination half-life [hour].

If steady state is reached and infusion is stopped the concentration can be described by

$$C_t = C_0 e^{-k_e t} \qquad (7)$$

Where C_0 is the blood concentration at the time where the infusion is discontinued.

Now a concentration difference ΔC as a result of a mass flow rate alteration $\Delta R = R_1 - R_2$ can be described as

$$\Delta C_t = C^{ss} - C_t = \frac{R_1 - R_2}{V_D k_e}\left(1 - e^{-k_e t_2}\right) \quad (8)$$

Where C^{ss} is the steady state blood concentration and t_2 is the time at which a difference in flow rate occurs and the system transcends from steady state into a change in blood concentration.

It can be seen that

$$\Delta C \propto \Delta R$$

So

$$\Delta C_t = C^{ss} - C_t = R_1 - R_2 f \rightarrow \frac{C^{ss}}{C_t} - 1 = \frac{R_1}{R_2} f - 1 = \frac{C^{ss}}{C_t} = \frac{R_1}{R_2} f$$

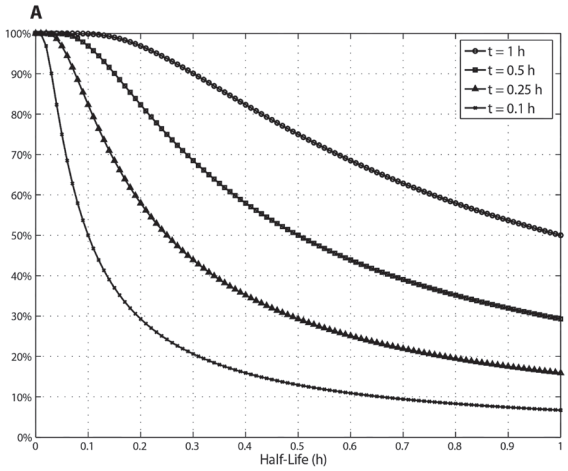
Where f is a substitution for the elimination term. Therefore, a factor change in ΔR can be translated to a factor change in ΔC. Finally a factor blood concentration change can be described as

$$\Delta C_t = \Delta R\left(1 - e^{-k_e t_2}\right) \quad (9)$$

The mutual influence of infusion lines does not necessarily cause ΔR to change abruptly and definitively as the theory assumes, therefore some new conditions need to be introduced. We separate four cases of flow rate disruption. (1) Flow rate change is permanent. (2) Flow rates that exceed the set point flow rate from steady state with long half-life times, (3) flow rates that exceed the set point flow rate from steady state with short half-life times and (4) flow rates that go below the set point flow rate from steady state. In case 1, when $t_{1/2}$ is large it can be seen that a factor change of ΔC is equal to the factor change in ΔR. In this case the maximum value of ΔC accounts for the possible occurrence of an overdose. For case 2 and 3 a new equation is introduced:

$$\Delta C_t = \frac{DE}{T_n}\left(1 - e^{-k_e t_2}\right) \quad (10)$$

Where DE is the dosing error interval of equation 1. By dividing the integral by the duration of the curve an average value is obtained. t_2 is now the duration of T_n. In case 2 the elimination term actually mitigates the possible overdose effect. In case 3, however, the elimination amplifies the possible effects of an under dose. Figure 6 shows the results of the blood concentration change as a function of pharmaceutical plasmatic half-life.



B

Common Pharmaceuticals

Type	Common pharmaceutical	Half-life ($t_{1/2}$)
Inotrope	Dopamine	1-2 minutes
	Dobutamine	1-2 minutes
	Noradrenaline	1-2 minutes
Anesthetic	Propofol	30-60 minutes
Analgesic	Morphine	2-3 hours

Figure 6. *Relation between blood plasma concentration and infusion rate as a function of half-life ($t_{1/2}$) at different times (t) (**A**). Half-lives of common pharmaceuticals (**B**).*

[33] Steenhoek A. Drugs given by intravenous infusion. University of Groningen, 1983.

Chapter 4

General discussion

Most patients on intensive care units receive intravenous infusion therapy, which is challenging for several reasons. Firstly, these critically ill patient often require the support of drugs that must be administered continuously, accurately and precisely. Syringe pumps are typically used for this purpose. Secondly, the challenging nature of vascular access [1–3], its associated risk of catheter-related infections and sepsis [4] and drug incompatibility, require that multiple drugs are co-administered through one multiple-in single out infusion set and one catheter lumen. This technique of co-administering medications is known as multi-infusion and has been associated with dosing errors [5–7] (chapters 2.1, 2.4, 3.1-3.4) caused by physical effects and possibly human interventions, despite the use of syringe pumps. A final complicating factor is that many patients, especially neonates, cannot tolerate large quantities of fluids [8,9]. For this reason the flow has to be low, which requires the drug solution to be concentrated in order to be able to administer the effective dose. From this it follows that small fluctuations in flow rate can lead to substantial dosing errors. Although it is known that the intravenous administration [10,11] and infusion technology [12,13] are associated with high error rates, the origin of these errors are not always known [14,15]. The drug dosing errors in patients receiving multi-infusion caused by physical effects are often counter-intuitive, ambiguous and are probably not always recognized.

In this thesis, we therefore aimed to investigate dosing errors due to physical causes related to multi-infusion hardware and the impact of these dosing errors on patients. More specifically, first, to identify the relevant physical causes that impacted drug administration. (1). Second, to investigate the nature and characteristics of the dosing errors by designing *in vitro* experiments according to clinical practice (2). Third, to develop a predictive simulation model in order to describe the relationship between the relevant physical properties of the infusion hardware, clinical interventions by clinicians and dosing errors (3). Finally, we aimed to investigate the clinical relevance and impact on patients of these dosing errors caused by the investigated physical effects (4).

We showed that the most important physical causes of dosing errors were mechanical compliance, flow resistance and dead volume and we found that these are related to several infusion hardware components (chapters 2.1 and 2.2) **(1)**. Furthermore, we showed that each of these physical effects were associated with several different types of errors in drug administration. First, substantial delays between the initiation of drug dosing with the infusion pump and the actual delivery of the drug into the patient's bloodstream (chapter 2.4 and 3.4) were found. Second, short-term (transient) overdosing and underdosing of drugs (chapters 2.4, 3.1 and 3.4) were found. Furthermore, it was found that these dosing errors are likely to occur in clinical practice after interventions such as a flow rate change (chapter 2.4 and 3.4) or syringe exchanges (chapters 3.1 and 3.2) **(2)**. We have developed a predictive model that estimates the timing and magnitude of the dosing errors in a specific setup of infusion hardware components after interventions (chapter 2.3). By measuring the physical properties of infusion hardware components (chapter 2.2) we were able to reproduce realistic clinical scenario's (chapter 3.2) using the model **(3)**.

Finally, we found that that physical properties of infusion hardware can have an impact on the effectiveness of the treatment (chapter 3.3) and that incidents involving infusion hardware have a severe impact on patient safety (chapter 3.1) **(4)**.

Throughout the rest of this general discussion the following four topics will be put in perspective beyond the scope of the individual chapters of this thesis

1. Measurement of multi-infusion systems *In vitro*
2. Generalizability of our findings and practical applications
3. Clinical relevance of dosing errors
4. Medication errors and patient safety in broader perspective

Each of these topics will be concluded with both clinical advice and recommendations for future research.

1 MEASUREMENT OF MULTI-INFUSION SYSTEMS IN VITRO

Measurement of flow and dosing rates in infusion systems may be accomplished by measuring the volumetric or mass flow rate or the concentration of a solved substance. The concentration of a solved substance, e.g. a drug, is directly related to the dosing rate. An important requirement for the measurement instruments used is the capability to measure low flows, e.g. 0.1 – 20 ml/h. In the future this may be even lower, as ever lower flow administration rates in many critically-ill patients with organ failure are desirable. With this prospect, our colleagues have developed standards and techniques for the measurement of flow rates as low as 1800 nl/h within the Metrology for Drug Delivery (MeDD) / European metrology research programme (EMRP) [16–18].

We found that technical developments and standards have produced syringe pumps that are becoming increasingly accurate and reliable (chapters 2.1 and 2.2). Nevertheless, as dosing errors in infusion persist, one of the main conclusions of this thesis is that an important part of these errors are caused by the mechanics of multiple interconnected pumps (multi-infusion) and intrinsic physical/mechanical properties of infusion hardware. It is therefore important to consider the entire chain of infusion components in relation to reliability and safety. To investigate multi-infusion systems it is necessary to use measurement techniques that measure the actual dosing rate (typically µg/min), administered to the patient. From a more technical perspective it is also important to investigate and characterize the physical and mechanical properties of infusion hardware such as measuring mechanical compliances of syringes. Furthermore, it is important to calibrate the infusion system, for example, to validate the accuracy and precision of an infusion pump to traceable standards. These goals are typically achieved with flow and pressure measurement [18]. All these factors are important to guarantee a reliable drug administration process to the patient.

Throughout the thesis we have used visible light absorption spectrophotometry to acquire the concentrations of the substances at the catheter tip that would normally be

administered to the patient. This method has previously been developed in our group by Verdaasdonk and coworkers [19]. To measure a volumetric flow rate, two methods have been applied. Initially a balance (chapters 2.4, 3.1, 3.4) was used, later we mostly used flowmeters (chapters 2.3, 3.2), depending on the purpose of the measurement. In the rest of this section the strengths and limitations of the measurement methods used in this thesis, as well as the future outlook of multi-infusion measurement will be discussed.

1.1 Measuring concentration

1.1.1 Spectrometry

The absorption spectrophotometric method used in this thesis aims to translate the degree of light absorption (absorbance), at a certain wavelength, to a concentration (chapter 3.4). Instead of actual medication, drug mimicking dyes (colorants) were used. One of the limitations of this method is that the dyes can only be measured in a certain range of concentrations. Within this range there is a linear relation between the attenuation of light intensity (due to absorption) and the concentration, however, above this range hardly any difference in absorption occurs. For the dyes and light intensity used in this thesis the maximum measurable concentration was typically between 20 – 40 mg/l. A challenge of this method is that prior to the *in vitro* experiment the medication schedule, describing the exact combination of flow rates, has to be known. Based on this schedule, the dye concentration in the drug reservoir, e.g. the syringe, has to be based on the maximum and minimum flow rates used. The maximum and minimum flow rates differences describe to what degree the dye will be diluted by the flows from the other pumps. This produces some limitations. An important constraint is that it may limit the possible combination of flow rates. For instance, it is often not possible to interchange the flow rates of a much faster and a slower pump. However, in clinical practice this is also very unlikely to occur. This limitation is therefore manageable.

The second difficulty is the potential overlap of the absorption spectra of the dyes, which limits the simultaneous measurement of individual dyes in a mixture. The best result can be obtained if the absorption spectrum overlap is minimized as much as possible. Consequently, using a dye with a narrow absorption peak is also desirable. In a two-pump situation it is typically possible to find two dyes that have negligible overlap. However, limited overlap can be compensated for using algorithms. We used linear regression calibration [20] and trivial linear algebra to retrieve drug concentration in a mixture at the catheter tip (see chapter 3.4). In theory, data analysis can be performed in retrospect with more powerful methods. It was found iterative target transformation factor analysis (ITTFA) was the most powerful method in the analysis of five dyes (food colorant) in a mixture [21]. This may be beneficial if larger numbers of dyes are used. Nevertheless, in previous research conducted in our group, acceptable recovery was achieved using four dyes: Allura Red, Tartrazine, Indigo Carmine and Kiton Red, with the current measurement method [19,22]. Moreover, it can be argued that most of the dosing errors caused by physical effects that may occur clinically, can be simulated using a two-pump setup. To our knowledge, almost all *in vitro* studies aiming to investigate multi-infusion systems

reduced the problem to two pumps (chapter 2.1). We conducted a study using three pumps (Chapter 3.4). In this study, the quantity of the dosing errors found were mainly due to the flow rate differences and not to the fact that three pumps were used. There may be exceptions, such as situations in which backflow is studied and many different syringe sizes and thus compliances are used in one setup. Moreover, results from *in vitro* simulations using more than two pumps may be easier to intuitively translate to an actual clinical situation.

A final question with regard to the spectrometric technique that was not thoroughly addressed in this thesis is how the dyes compare to actual medication. Because of the low concentrations of the dyes it can be assumed that the fluid properties are similar to those of water, however, this may not always be the case for drug solutions. Instead of dyes, it is possible to measure the absorption spectra of actual drugs and relate these to a dosing rate. For example, noradrenaline concentrations were successfully retrieved using ultraviolet spectroscopy, a technique similar to the spectrometric method used in this thesis [23]. However, with noradrenaline solutions used in critical care, most of the properties relevant to the fluid mechanics in infusion systems will still be similar to those of water. Nevertheless, the molecules and molecule size of medications are different from the dye molecules. This has possible consequences for the filters commonly used in neonatal infusion sets. Some temporary adsorption (and possibly some absorption) of dyes by filters was observed. To our knowledge, the relation between dye adsorption and medication adsorption by filters is not fully understood, however, it is known that some drug solutions are adsorbed by filters [24]. Moreover, the diffusion coefficients are different for different molecules. Although the Péclet number predicts negligible axial diffusion for the typical flow rates used, the radial diffusion is significant [25] (chapter 2.3). It is, however, likely that full diffusion occurs before the drug has reached the patient in a typical infusion setup. Most drug solutions will have viscosities similar to water. However, we found drug solutions, such as Hespan® (hetastarch in sodium chloride) and Dextran®, that have viscosities of up to four times that of water (chapter 2.2). Moreover, drugs may also be co-administered with total parenteral nutrition (TPN), which, depending on the concentration, results in a viscous mixture. However, these condition can be easily replicated. We have done this in chapter 2.2, where the effects were limited. However, it would still be valuable to observe the effects of viscosity on the other *in vitro* results of this thesis as well.

1.1.2 Sampling the dye mixture

Manual samples may be taken to analyze the dye mixture [26]. However, in this thesis we used a flow cell, which allows continuous measurements with sampling frequencies only limited to the data acquisition hardware. There are, however, two limitations. First of all, the fluid has to travel through the flow cell. A certain non-zero length and thus volume (~26 µl) of this path is used by the light source to produce the absorption spectrum measured by the spectrometer. Because the dye mixture has to travel through this length, the light absorption change (dA/dt), where A is absorption and t is time, is underestimated. The

degree of which is dependent on the flow rate. For example, with a flow rate of 5 ml/h it takes about 19 seconds for the mixture to travel through the 'optical path length' of the flow cell. Because the flow rate is typically also measured, it is possible to correct for this, although on the scale of most of the effects studied in this thesis the impact is minimal. The second limitation is that the flow cell has a finite diameter and therefore impacts the flow resistance. However, this is negligible compared to most catheter diameters. Trying to minimize the flow resistance by choosing a flow cell with a higher diameter has some trade-offs. If the diameter increases, the volume that the mixture has to travel through also increases because a sufficient optical path length has to be maintained. However, a more optimal flow cell may exist.

1.2 Measuring flow

The most fundamental way to measure flow is by continuously measuring the weight of the fluid output from the infusion system using a precision balance. If a very advanced balance and laboratory is available this is arguably one of the best methods to measure flow because the measurement instrument does not influence the fluid mechanics in any way. However, the balance used in this thesis showed a relatively high amount random noise. Several methods can be used to minimize this, such as detaching the scale from the ambient atmospheric pressure and preventing evaporation with a thin layer of oil. Also post-processing techniques such as filters may be possible as high frequency data and other fast changes are typically not of interest. A very accurate way to measure flow is using a flow meter, this has been done in several studies (chapter 2.1)[27]. In this thesis, we used a coriolis flow meter. The advantage of this flow meter is the high accuracy and precision at the flow rates relevant for infusion in critical care. Moreover, the coriolis mechanism is also capable of measuring the density of the measured liquid (or gas). The apparatus is therefore not dependent on the type of liquid and the temperature, which in turn is related to density. A limitation is the relatively high flow resistance. The flow resistance (1949 Pa per ml/h) is somewhere between that of a 1Fr and 4 Fr-neonatal catheter (chapter 3.2). Because of this, the effects due to compliance are exaggerated (chapter 2.3). For example, the time required to reach 95% of a flow rate change may take several minutes longer with a high flow resistance. On the other hand, as stated the catheters used in clinical practice are also resistant to flow. In combination with the patient's venous pressure a flow meter may actually approach a real clinical situation. We have also attempted to combine two or three flow meters in a parallel setting to decrease the resistance. However, this method failed regularly due to air in one of the flow meters.

1.3 Outlook

The results presented in this thesis show that it is important to characterize the mechanical properties of infusion hardware. We have started with the assessment of drug delivery devices such as the compliance of syringes and the resistance of catheters (chapter 2.2) [28]. Moreover, the results presented in this thesis and other literature may be used as input for standards related to infusion technology (chapters 2.1 – 2.4, 3.2, 3.4). For example, the NEN-ISO-7886-2 [29] describes a maximum allowed compliance

of approximately 2 ml/bar for a syringe of ≥50 ml and how to measure this. In (chapter 3.2) it was shown that compliance allows backflow, which subsequently may cause delays in the administration of drugs of approximately one hour after a syringe exchange has been conducted. From these results it can be seen that the compliance should preferably be much smaller than 1 ml/bar. It was also shown that this goal could be reached by using a smaller syringe, which are typically less compliant. This is therefore often recommended by manufacturers. However, not the size of the syringe but mainly the compliance itself is an important parameter to consider. Moreover, it is recommended that manufacturers state the compliances of their products in datasheets. The pumps could, in theory, partly compensate for many of the compliance effects if these quantities are known. For the pump itself, the IEC/EN 60601-2-24 [30] is one of the most referred standards. However, it is important to develop a standard for the entire infusion system [31]. For example, to developing standards that set upper limits for a combination of compliances and dead volume of infusion components, in order to guarantee that the total compliance and dead volume of a generic infusion system remains within safe limits. It might also be an improvement if standards state the clinical consequences of certain technical parameters. For example, how much delay in the administration of drugs can be expected when syringes with a certain compliance are used in combination with certain catheters, and possibly even the impact on the patient of this delay. Note that non-compliant infusion component, such as glass syringes exist. However, some of these components introduce new hazards such as the need for sterilization. For other infusion components such as infusion lines it is important to retain some flexibility and also the costs are not unimportant.

1.3.1 In-line measurement and control systems

To prevent or mitigate dosing errors, it would be of interest to perform in-line measurement in actual clinical situations. In-line pressure measurement does exist, however, this is mainly used for occlusion detection and introduces an extra compliance in the infusion system. In the ideal situation the dosing rate of the drugs should be measured. In theory, a spectrometric method could be used for this purpose. However, besides very practical difficulties, such as the size, usability in the clinic and sterilization of a sensor that possibly interacts with the parenteral drug mixture, many of the difficulties that were raised in this section may become limitations. Not every drug mixture may produce absorption spectra that can easily be distinguished. Moreover, these drugs would have to appear in measurable concentration ranges. It may be feasible to simply measure if a drug has crossed a certain boundary concentration, thereby preventing an overdose. The density measurement of coriolis flow meter is not specific enough to identify drug mixtures at this point either. In any case, it is desirable for the pumps to be ‘aware’ of the drug mixture that is actually delivered to the patient. Active feedback control has the potential to prevent many of the dosing errors described in this thesis. Developing the sensor is the biggest challenge, although some first initiatives do exist [18].

1.4 Advice

- Develop standards with upper limits for compliance, preferably below 1 ml/bar for any syringe size.
- As all the physical properties of infusion hardware are interconnected it is also important to set standards for a generic infusion system as a whole in terms of compliance, resistance, dead volume and accuracy/precision of pumps, especially for critical medication. In addition, the standards could provide a more clinical perspective of the impact of parameters such as compliance, for example, in terms of delays in the administration of drugs.
- Investigate the impact of viscosity on the results found in this thesis within realistic boundaries. For example, by replacing one of the faster pumps in (chapters 3.4 and 3.2) with a pump containing a TPN or glucose solution.
- Investigate relevant drug solutions to find more on the impact on (radial) diffusion and the impact on the adsorption by filters in relation to medication-mimicking dyes.
- Use flowmeters with a flow resistance that is as low as possible for in vitro measurements of clinical situations.
- Analyze the total resistance of the infusion system and factor in the vascular pressure of the patient before conducting an in vitro experiment. If still necessary, correct for the resistance of the flowmeter and the flowcell. This can be done with the support of the model (chapters 2.3 and 3.2).

2 GENERALIZABILITY OF OUR FINDINGS AND PRACTICAL APPLICATIONS

Relationships between physical hardware properties and potential dosing errors after clinical interventions were established in this thesis. It was shown that these relationships can be used to develop a predictive model capable of simulating drug administration of a multi-infusion setup. Several studies [6,32–35] have attempted to developed such a model. To our knowledge, simulation studies have separately, i.e. in isolation, investigated the most important physical parameters of compliance [33] or dead volume effects [36,37] and for a maximum of two pumps. However, in clinical practice, all these physical effects are interdependent variables. In order to fully appreciate the clinical impact, it is necessary to simulate all the relevant physical effects of compliance, resistance as well as dead volume and the Poiseuille effect. Therefore we have developed an analytical model, incorporating all of the important physical effects in order to study clinical situations (chapters 2.1 and 3.2). Moreover, the model is capable of simulating an arbitrary number of pumps. In this subsection, the generalizability of the model will be discussed as well as its practical applications.

2.1 Generalizability of infusion hardware components

2.1.1 Pumps

In this thesis the pump is generally considered to be a perfect current source. This seems to be a realistic assumption, because problems, such as delays due to gaps between the syringe driver and the plunger, are now uncommon (chapter 2.1). In fact, syringe pumps are considered to be relatively accurate [38] and can therefore be considered ideal current (flow) sources in many cases. However, the mechanics of the electrical motor does have a measurable influence, especially at very low flow rates [28]. In this thesis we focused primarily on syringe pumps as a flow source, as these pumps are typically used to administer critical medication. However, gravity driven pumps, and pumps based on other positive displacement mechanisms, such as the so-called volumetric- or simply "infusion pumps", are still commonly used in clinical practice as well. A limitation of volumetric pumps is the limited stability of the flow rates. Over long intervals volumetric pumps are reliable, however, in short intervals these pumps show cyclic fluctuations. Gravity driven pumps, on the other hand, may experience a reduction in flow rate as they deplete [28,39,40] (chapter 2.1). Cases are known where fluctuation from the electromechanical pump behavior were related to blood pressure oscillations [41]. For these reasons it is of interest to incorporate the electromechanical properties of both syringe pumps and gravity driven pumps into the model. It is expected that this is feasible. The fluctuations produced by the pumps are typically periodic fluctuations that can be described as a sinusoids [28]. The Laplace and Z-transforms transforms of such sinusoids are trivial and readily available. Most of the physical effects studied by the model in this thesis can already be simulated for volumetric or gravity driven pumps. In most of these cases these pumps can also be reduced to ideal current sources in combination with a mechanical compliance, due to the compliant infusion lines used for gravity driven and volumetric pumps. The hydrostatic impact of height differences between the patient and the infusion bag is physically trivial as well. It may also be useful to introduce new input parameters, specific to gravity driven or volumetric pumps. This is feasible as many of the flow control/regulator devices used for gravity driven pumps have been described mathematically. Examples of these described devices are clamps and drip chambers. Clamps manage the diameter of the tubing and therefore the flow by resistance, this was described in detail for a gravity driven pump, incorporating factors such as the material used [40]. For drip chambers the variation in drop volume was also described [42].

2.1.2 Filters

Filters are used to filter particles, air and reduce infections by filtering bacteria [43,44]. Filters may act as both a flow resistance [45] and a compliant element (chapter 2.2 and 3.2). Moreover, the adsorption surface may add a significant extra volume to the infusion system [24]. All of these properties can be simulated by the model. However, as stated before, the filter membranes may also adsorb (and possibly absorb) drugs. For example, it is known that filters adsorb insulin [46]. The adsorption may be related to the type of the filter, e.g. the membrane size, its polarity, and the type of drug, i.e. the properties of the molecule [47]. The effect is typically temporary as the adsorbing surface of the filter

becomes saturated after a certain amount of the medication has been adsorbed [24]. Moreover, it should be noted that adsorption and absorption is not exclusive to filters and has also been associated with other components such as infusion tubing (infusion lines) [39,46]. In general, the current literature suggests that the effects of filters on the drug dosing rate are small and temporary and small enough for the model to still be applicable. However, it may be of interest to include the specific physical/chemical properties of the filter in the future.

2.1.3 Anti-reflux valves

Anti-reflux valves are commonly used in infusion setups to prevent several types of backflow in several different settings. The valves influence the administration. Delays in startup (onset) of the flow rate may occur and in the case of gravity driven pumps the flow rate may be lower than intended [27,48–50]. Valves are probably the most challenging infusion component to simulate, because of the non-linear resistance caused by these components. A relatively high pressure is required to open the valve, however, once the valve is opened a lower pressure is required (chapter 2.1). Moreover, the opening and closing may occur randomly and consecutively at low flow rates, especially when the pump is started from a standstill (chapter 3.3). The pressure required to open the valve is typically given by the manufacturer. The pressure inside the infusion system can be derived using the model. Using these two quantities is a good starting point for simulating valves. At higher flow rates valves have less impact and once opened, the valves are unlikely to influence the flow. To this extent the model is able to simulate infusion systems with valves. Moreover, the principle where the backflow is simply blocked as intended by an anti-reflux valve can also currently be simulated. These possibilities make the model a starting point for future improvement of commonly used in infusion systems.

2.2 Fluid mechanics and transport phenomena

In most cases the flow can be considered laminar. Gravity driven and volumetric pumps may be used for much higher flow rates. High enough, in fact, to produce a turbulent flow [51]. However, this is not of interest in the administration of critical drugs. Viscosity is a physical phenomenon that may result in clinically relevant situations and is currently not explicitly handled by the model. The impact of viscosity can be illustrated according to one of the most striking results in this thesis. In chapter 3.2 a large delay in drug administration was found, caused by a syringe exchange. For a narrow (i.e. small diameter) catheters the delay was almost an hour, for wider catheters the delay almost diminished. However, if the viscosity is higher, e.g. four times that of water (chapter 2.2), the delays may be four times as long. The model is capable simulating viscosity to this extend as resistance simply changes proportionally with the viscosity. Temperature also has some impact as viscosity and temperature are inversely proportional.

A more complex situation occurs when radial diffusion is also taken into account. Because of the Poiseuille effect (chapter 2.3), lamina along the radial (transversal) axis travel at different velocities. Due to diffusion, particles of the drug mixture may travel from

and to faster or slower lamina, this produces a more complex concentration gradient. The combination of these effects can be described according to Taylor dispersion [25]. Since full diffusion is expected to occur after a few minutes in most cases, the impact is expected to be limited, therefore incorporation into the model is not essential [52]. Finally, the impact of mixing point geometry, particularity the angle at which drugs are mixed at the mixing point, has been described [53]. If multiple solution with different viscosities are mixed, the differences in lamina velocities over the radial (transversal axis), caused by the Poiseuille effect, may influence how the drugs are mixed, which may have impact on the dosing rate of that specific drug. This may cause additional delays in some situations [53]. Mixing point geometries are not handled by the model at this point. As the Poiseuille effect can already be described the geometric formulation of these mixing substances is likely to be feasible.

2.3 Outlook

Healthcare professionals have expressed the desire for a real-time tool that visualizes the current drug mixtures inside a multi-infusion system. Using our model it is feasible to develop an interactive tool, for example, running synchronized with the multi-infusion system on a smartphone device or on a bed-side display, e.g. next to the vital signs display monitors. The tool may also predict the causal consequence of an intervention, before the clinicians decides to proceeds with this intervention. Importantly, the tool may be used as a tool for teaching pump users about the impact of the physical effects in multi-infusion systems. This might mitigate dosing errors as the pump users are able to optimize the handling of the pump in case of, for example, titration.

In the previous "*in vitro*" section, feedback control was discussed. The model may be used to enable feed-forward control in which optimal control of the pump is predicted according to model's output. A combination of both feedback and feed-forward can also be used. It has been shown that a feed forward system decreases start-up time between starting the pump and the intended dosing rate, while preventing overshoot [34]. Moreover, a control system with a feedback approach has also been attempted, where the MABP was used to control the administration of a fast-acting vasodilator [54,55]. In both cases, however, increasingly complex situations and infusion setups may be encountered where only the incorporation of all the interdependent physical effect, as described in this thesis, will provide a sufficiently accurate prediction in order to make computer control feasible.

2.4 Advice

- The background of dosing errors can be investigated with the model as well the in vitro measurement setup. By doing so, the physical mechanisms behind these dosing errors and how to deal with them can be added to clinical protocols, standards, and educational programs. The focus of these contributions may be based on the main results of this thesis. Clinical advice based on these main results may include that a bolus can occur after a flow rate change for the pumps in which no flow rate change was initiated (chapter 3.4). That the clamping of infusion lines during a

syringe exchange is essential (chapter 3.1 and 3.2), and that infusion sets with low dead volumes and compliances should be taken into consideration, especially when critical medications are used (chapters 2.1, 2.4, 3.3).
- Incorporation of methods describing the electromechanical properties of pumps in the model is feasible and advised. Including anti-reflux valves in the model is also advised as these components may have a substantial influence on drug administration.
- It is advised to add the viscosity effects as this may have impact on delay in drug delivery.
- The model may be used to visualize drug mixtures inside a multi-infusion system. This can be used as a tool to support the healthcare professional with titrating critical drugs.

3 CLINICAL RELEVANCE OF DOSING ERRORS

Although the occurrence of dosing errors which are likely caused by physical effects is supported by the clinical experiences of health care professionals, it remains essential to investigate the clinical impact of these dosing errors in actual patient populations. This is necessary, first and foremost, from a healthcare perspective. If the impact of dosing errors caused by physical mechanisms related to infusion hardware are better understood, it may be possible to optimize treatment, both by improving user knowledge and clinical treatment policy and by developing innovative technology. This goal is underlined by Sherwin et al. [24] who suggested that it is important to understand the physics of infusion systems because the clinical knowledge of pharmacokinetic behavior of intravenously administered medications in humans may not have been established independently from the infusion hardware characteristics. It is also important for innovative initiatives to improve the pumps according to the pharmacokinetics of certain high-risk drugs. However, it must first be investigated for which drugs and for which patient the dosing errors found in this thesis may potentially be clinically relevant, and how to investigate these dosing errors *in vivo*.

3.1 Relevant drugs

In an extensive review of 12084 ICU-incidents reported in the UK National Patient Safety Agency between August 2006 and February 2007, Thomas et al. [56] investigated 2428 incidents involving 355 different drugs. Morphine (207 incidents), gentamicin (190 incidents) and noradrenaline (norepinephrine) (133 incidents) were most commonly associated with incidents [56]. Not all these drugs are susceptible to the dosing errors found in this thesis. The relevant drugs are typically those with a rapid onset, short half-life, small therapeutic windows and a short durations of action [39]. It is for these drugs that the short (1-10 minutes) transient dosing errors found in this thesis (chapters 2.4, 3.1, 3.2, 3.4) are likely to be clinically relevant. Most of these drugs have a short plasma half-life as the clearance of the drug from the blood plasma is quick [42]. In order to maintain the

desired blood concentration, administration has to be continuous. Conversely, when the administration deviates, the blood plasma concentration will change in a short amount of time as well. This was also found in (chapter 3.4). For a dosing error lasting a few minutes, up to almost 50% blood concentration change was found for dopamine (short half-life), while the blood concentration for morphine (long half-life) hardly changed at all in that short amount of time. In the study by Thomas et al. [56] noradrenaline and insulin were the drugs most often associated with actual harm and these drugs were also the only drugs with short half-lives (2-5 minutes) in the top ten most reported drugs [56]. This is a good indication that drugs with short half-lives are challenging to administer properly. Moreover, it is noteworthy that the majority of noradrenaline incidents were related to 'technical failures', this indicates that problems in the administration of noradrenaline are possibly related to infusion hardware. Whether or not a change in blood concentration is likely to be clinically relevant depends on the therapeutic window (also called therapeutic index). The therapeutic window is essentially the margin between the effective dose and the toxic dose. Consequently, if the therapeutic window is small, the drug dose must be accurate in order to achieve the clinically desired effect and prevent an adverse effect.

3.1.1 Drugs that require titration

If the effect of the drug dose is hard to predict then these drugs are often 'titrated to effect'. This means that the dosing rate is changed *ad hoc* until the desired clinical outcome is reached. Many of the drugs that require both titration and continuous administration are relevant for the short-lasting dosing errors found in this thesis. The fundamental reason why titration is necessary is because inter-patient as well as the intra-patient variability can be considerably large for some drugs. This can be explained by the pharmacokinetics and pharmacodynamics (PK/PD) parameters, which are related to patient's physiology, pathology and possible interactions between drugs. For example, the PK-parameter volume of distribution (V_d) may differ substantially, especially in neonates, which has implications for the dosing rate. Also the pharmacodynamics may vary substantially, this is mostly related to compensation mechanisms such as the mechanisms necessary to regulate the glucose or blood pressure levels. Again, in neonates these mechanisms may be underdeveloped. Moreover, the gestational age of neonates may have a big impact. This could be the reason why the adverse drug event (ADE) rate was about three times higher on the NICU compared to adult ICU's [57]. All these factors make titration challenging. If, on top of this, the feedback between the observed clinical outcome and the administration of the drug is obscured by the physical properties of the infusion system, adverse effects may result from this. This was discussed in (chapter 3.3).

There are also relevant drugs with longer half-lives that require titration. An example of this is propofol [58], a sedative anesthetic. Because the medication is lipophilic, the volume of distribution is large and a large initial dose is needed to achieve a clinical effect. In clinical practice, a bolus may first be given to achieve a fast onset and 'fill' the large volume of distribution. After this, the duration of action is short, despite the long half-life. Consequently, continuous and accurate administration is required in order to

maintain the desired clinical effects. These drugs are therefore also of interest for the short transient dosing errors described in this thesis. Treatment of drugs with complex PK/PD relationships, such as propofol, may be achieved with target controlled infusion (TCI), although the problem of inter-patient variability [58] as well as the dosing errors due to physical causes remain.

Drugs intended to regulate hemodynamics in patients are typically the drugs of interest in studies aiming to investigate the clinical relevance of dosing errors caused by the physical properties of infusion systems. We (chapters 2.4, 3.2, 3.3, 3.4) and others [9,50,59] used these drugs as model drugs because the relationship between the dosing rate and its effect is fast and straight forward, and because dosing errors in these drugs are clinically relevant. This means that the plasma concentration of inotropics, such as noradrenaline, change very fast after a changing dosing rate. The effect of this concentration change on the (adrenergic) α- and β-receptors results in blood pressure and heart rate changes almost immediately as well. Most of these drugs are catecholamines, which includes noradrenalin, dopamine and dobutamine. Nitroglycerin and nitroprusside, both rapid onset and short half-life vasodilator, were also used as a model drug [34,54].

3.2 Studying dosing errors *in vivo*

To our knowledge, studies investigating the clinical impact of the dosing errors caused by the physical effects described in this thesis have been scarce. Nevertheless, *In vivo* studies in animal models, as well as some retrospective studies have recently produced evidence, supporting the hypothesis that dosing errors related to the infusion hardware result in actual, e.g. measurable physiological effects *in vivo* [60–62] (chapter 3.3).

As was explained, when aiming to investigate transient dosing errors *in vivo*, a direct and predictable relationship between administration and one or more vital signs is preferred. Moreover, it is also preferred that the parameter is quantifiable and easy to measure. For example, pain relieve and sedation as a result of remifentanil and propofol administration is more challenging to quantify than blood pressure and heart rate, although pain can indirectly be related to measurable parameter such as blood pressure and heart rate. Antibiotics, also regularly continuously administered, do not have an easy to measure clinical parameter either. All these drugs are probably clinically relevant for the dosing errors found in this thesis but more challenging to investigate than inotropics for the dosing errors in this thesis. A plausible alternative may be insulin where glucose levels can be measured.

As previously stated, an important reason to study inotropic drugs is because the dosing errors in inotropics are likely to present adverse effects. Overdosing in inotropics may lead to conditions such as tachycardia, hypertension and thus a risk of hemorrhaging. Insufficient (under) dosing may lead to the insufficient treatment of hypotension, which is associated with inadequate perfusion of tissue and again hemorrhaging [63,64]. Also the PD-effect of auto regulation plays an important part. In neonates it is suggested that this mechanism is underdeveloped and cannot deal with hypertensive and hypotensive

episodes, which may have negative consequences for brain [63,65,66]. However, the actual impact of this is controversial [67].

It should also be noted that besides the transient dosing errors that were described in this thesis, long startup delays, of up to approximately one hour, after the pump was started from a standstill, were also found due to several physical causes (chapter 3.4). This can be problematic if the pathology of the patient requires the drug immediately. For example, in some patients with hypotension it is in some cases too dangerous to administer a bolus of an inotropic drug, as the effects are hard to predict. In this case, a pump must be started with a low flow rate, which is, as stated, associated with long delays.

3.3 Advice

- In general, healthcare professionals should consider that with the use of multi-infusion, dosing errors due to physical effects can occur after interventions such as flow rate changes and the starting of the pump from a standstill. Moreover, the expected results of the interventions may be substantially delayed. Again, it is important to provide education about these principles to create awareness.
- Clinicians should consider the possibility that dosing errors due to physical effects have clinically relevant impact when administering drugs that have a rapid onset, a short durations of action and a narrow therapeutic window.
- It is recommended to accurately log and store, the used flow rates and clinical interventions simultaneously with the vital sign parameters such as mean arterial blood pressure (MABP). By conducting retrospective analysis similar to the study of (chapter 3.3), infusion therapy may be optimized.
- Drugs that have a predictable relation between the concentration change and the clinical effect are the most useful to study multi-infusion dosing errors in vivo.

4 MEDICATION ERRORS AND PATIENT SAFETY IN THE BROADER PERSPECTIVE

4.1 Errors associated with medication

Intravenous drug delivery typically starts with a physician's prescription order, after which the drug is prepared by the pharmacy to finally administer the drug to the patient. This process, which in practice may involves more intermediate steps, can be described as the "chain of drug delivery". If any errors occur within this chain of drug delivery and during the time in which the drug is effective, these errors are designated as ADEs [68]. From Figure 1 in the introduction of this thesis, it can be seen that errors may occur or originate at any point of the drug delivery chain, well before the drug is actually administered to the patient. For example, in an analysis of ADEs in 1995, hospital personnel reported a lack of timely dissemination of information as a leading cause of ADEs in patients, while 5% of the errors were related to parenteral drug administration [69]. Since then, information systems have improved. A striking example of this are smart pumps which are capable of

providing pump users with *ad hoc* information about the drugs used in the clinic [70,71]. Possibly because of these improvements, more recent studies report that ADEs are relatively more likely to occur during the administration to the patient as compared to other phases such as the prescription phase. It is in this phase that dosing errors due to physical causes related to the infusion system typically occur. Recent studies report that approximately half of the studied ADEs were associated with the administration phase, and in many cases associated with intravenous administration [12,56]. Moreover, studies published between 2001 and 2011 found that error rates related to intravenous medication administration were approximately between 50% and 80% [10,56,57], with an overrepresentation of serious complication compared to other adverse events [10,69]. Additionally, a comprehensive study in the U.S. Federal Drug Administration (FDA) recorded 56,000 reports of ADEs associated with infusion pumps between 2005 and 2009 [72]. Cheung et al. [73] investigated roughly 18000 incident reports in the Netherlands between 2006 and 2011 related to medication and found that approximately 40% of adverse events occur during the administrations phase. In contrast, reports from community pharmacies reported only 1.6% incidents related to the administration phase [73], this indicates that drug administration constitutes a much higher risk in critical care. This might, in turn, be related to the challenging nature of intravenous administration. At this point it can be stated that there is ample evidence that intravenous drug administration is challenging. However, despite incidents related to medication are amongst the most numerous in healthcare, only very rarely were physical effects in multi-infusion identified as the cause of these incident. There are several possible explanations for this, these will be discussed in the rest of this section.

4.2 Are dosing errors due to physical causes not recognized?

In general, it can be challenging to investigate the clinical relevance of multi-infusion risks using error reporting alone. We suggest that errors due to physical effects in multi-infusion systems are typically not recognized, not reported as such, and, therefore likely to be underappreciated. There are several possibilities why underreporting and, consequently, under appreciation of adverse event due to the dosing errors described in this thesis occur. First of all, it was found that terminology and classification of adverse drug events are ambiguous, non-consistent, and standards are generally lacking [68,74]. Incident reports labeled as adverse drug events, adverse drug effects and adverse effects may or may not include a wrong dose due to a wrong dosing rate. For example, a dosing error classified as a medication error may be due to prescription errors, preparation errors, faulty pump operation or dosing errors caused by physical effects. The distinction cannot be made from a report stating solely that an ADE has occurred. However, nowadays hospital personnel usually keep track of the phase in the chain of drug delivery in which the incident occurred, as was shown earlier. Nevertheless, any ambiguous cause of dosing errors, such as dosing errors due to the physical phenomena in multi-infusion systems, may simply be dismissed as an unknown or technical error. Indeed, this may the reasons why a large portion of the errors associated with infusion are simply designated as ‘unknown’ [15]. In the study conducted by Thomas et al. [56] it was found

that errors involving noradrenaline were commonly associated with 'technical failures of pumps' [56]. That some of these errors may be caused by physical effects is not unlikely, as inotropics such as noradrenaline are likely candidates for drugs associated with the dosing errors investigated in this thesis. Moreover, "rate of infusion errors" was the second-most common administration incident. A second possible reason is that the origin of the adverse events caused by physical phenomena in multi-infusion systems are, in fact, not known or fully understood by some healthcare professionals. The origin of dosing errors caused by physical effects tend to be counter-intuitive (chapters 2.3 and 3.2) and it is understandable that the clinician is unaware of the precise nature of the mechanism behind these dosing errors. For example, we described a case report (chapter 3.1) where a norepinephrine overdose was administered. *In vitro* reconstruction concluded that the pump may have produced a relatively high pressure on the syringe which, subsequently, caused the administration of the norepinephrine overdose. However, this possibility was not identified in the initial incident report. The premise that dosing errors tend not to be recognized can be further substantiated by interviewing healthcare professionals who frequently work with multi-infusion. We surveyed hospital personnel familiar with infusion therapy and infusion pumps, to identify the current practices in multi-infusion therapy [31]. There were 61 respondents. More than 80% of the pump users that answered the question stated that they were aware that dosing errors can be related to use of multi-infusion, but that the exact nature of these errors were unclear to them [31]. Co-administering multiple drugs through one central line is one of the key causes of dosing errors due to counter-intuitive physical causes (chapters 2.1 and 2.4) and evidence of this has been shown throughout this thesis. A similar conclusion can be drawn from a risk analysis that we produced by consulting a consortium of expert pump users, in the University Medical Center Utrecht [18,31]. In this risk analysis likelihood and severity of risks were analyzed. Combining these two factors in a risk matrix resulted in single risk level. In the risk analysis, "problems with multi-infusion" only ranked 8th out of 14 different identified risks. The probability was ranked two out of five and the severity was ranked four out of five. Specific risks associated with multi-infusion were described as changing the flow rate before the medication is effective in the patient, especially in inotropics. This is consistent with the situations that we investigated. For example, the challenging operation of titration according to feedback from vital signs such as the blood pressure (chapter 3.3). In other words, flow rate changes are often conducted because the medication does not seem to work, while, in fact, the medication has simply not been delivered yet to the patient because of delaying effects. Throughout this thesis we have provided ample evidence of this phenomenon, delays of up to approximately one hour were found for clinical situation reconstructed *in vitro* due to compliance, resistance, dead volume and backflow (chapters 3.4 and 3.2). Moreover, we found similar delays *in vivo* after investigating the actual rise in mean arterial blood pressure (MABP) after the start and flow rate increase of dopamine/dobutamine infusion (chapter 3.3). A third reason why dosing errors due to physical causes may not be registered as such is that the origin of these errors may have multiple causes. This means that, for example, not

clamping the infusion line was designated as simply a human error. Although this is not explicitly incorrect, we showed that due to physical phenomena such as backflow, a sizeable additional delay in the delivery of drugs may occur in an unclamped line during syringe exchange (chapter 3.2). Thus, besides being designated as “unknown”, many ADE’s may also be misidentified, either in part or in its entirety. In practice, a combination of user operation and a physical cause is typically the cause of a dosing error, this is visualized from Figure 1 in the introduction of this thesis. Again, the previously described case report in (chapter 3.1), involving a norepinephrine incident, is a good example. In this case report, a definite cause could not be found initially, however, human error was considered as a possible explanation for the incident. Although this possibility after *in vitro* analysis was still not dismissed, a possible physical cause in combination with a human intervention was found to be the most plausible explanation, while a fully technical error was also possible.

Even though a clear distinction between physical causes and other causes such as human error cannot always be made, it is important to judge and report the possibilities of physically induces dosing errors. If this is done correctly, the estimation of the error rate of physical phenomena in multi-infusion systems, and therefore its risk, can be determined with greater certainty. This might then improve the appreciation for the physical causes of dosing errors due to multi-infusion, which have the potential to reach patients. Moreover, an accurate description of the incidents that occur clinically may help to improve best practices and the development of new innovations focusing on mitigating or eliminating of dosing errors in multi-infusion systems.

4.3 Advice

- Several studies have recommenced to standardize the classification of adverse drug events [68,74]. Besides this, it is advised to pre-define classification for physical causes of adverse events.
- Educating pump users with characteristics of physical effect may also improve overall safety of patients receiving multi-infusion therapy. For example, if the effects of dead volume of the infusion set used in clinical practice are known to the healthcare professionals, titration of high risk fast acting drugs can be improved.
- Another advice that was formulated after analyzing the survey of current practices, was to appoint a super user who has a deeper knowledge of the technology involved [31]. In case of an incident, a super user may be able to help formulate the incident report more accurately and provide the necessary information about possible physical causes.

CONCLUSIONS

Dosing errors in patients receiving multi-infusion therapy are mainly caused by the physical effects of compliance, resistance and dead volume. In clinical practice, the dosing errors are typically followed after interventions such as flow rate changes, starting of the infusion pump from standstill, syringe exchanges and vertical displacement of the pump relative to the patient. The errors may occur in the pump in which the interventions was conducted as well as the other parallel pumps that co-administer medication on a common infusion set and catheter to the patient. The dosing errors caused by the interplay of all these effects can be counter-intuitive. It was shown that the dosing errors are related to physical properties of infusion hardware and can be predicted, both by modeling and *in vitro* measurements. Dosing errors due to physical causes related to infusion hardware and interventions have the potential to have measurable, clinically relevant impact in patients. Technical innovations, standards, regulations and creating awareness through education programs may mitigate the dosing errors and the clinical consequences thereof. The results of this research may therefore contribute substantially to patient safety.

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Summary
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SUMMARY

Most patients admitted to the hospital are treated with pharmaceuticals (drugs). A substantial proportion thereof has to be administered intravenously by infusion. Infusion consists of at least a vascular access device (e.g. a catheter), and often many other components, enabling healthcare professionals to administer the drug as a liquid directly into the patient's vasculature. Infusion therapy is challenging in clinical practice for several reasons. First, many critically ill patients suffer from conditions that require the administration of potent rapid- and short-acting drugs. Because these drugs often have short plasma half-lives and small therapeutic windows, the administration has to be conducted in a continuous, precise and accurate manner. Small variability in the dosing rate of these drugs may easily lead to dosing errors and adverse effects. Moreover, many patients in critical care are especially susceptible to these dosing errors because of impaired physiological counterbalancing mechanisms, which may be due to the patient's pathology as well as prematurity. To meet this demand for accurate and precise drug administration, syringe pumps are typically used. Second, patients in critical care often require the simultaneous administration of several intravenous drugs, fluids and parenteral nutrition. Due to the challenging nature of inserting a catheter, vascular access is limited. Particularly, the risk of systemic infection is associated with catheter insertions, which requires clinicians to keep the procedure of inserting a catheter to a minimum. For these reasons it is necessary to administer many of the drugs and other fluids through one multiple-in, single out infusion set and one catheter to the patient. This principle is called multi-infusion. It was shown that physical phenomena related to infusion hardware, e.g. syringes, catheters, filters and infusion lines (tubing), may cause dosing errors in infusion setups, despite the use of accurate syringe pumps. In a multi-infusion setup the probability that these dosing errors occur were found to be even higher. Moreover, the characteristics and origin of the dosing errors in multi-infusion setups are often counter-intuitive and therefore hard to predict and manage. Finally, many critically ill patients, notably neonates, cannot handle large quantities of fluid. For this reason drugs may be administered with flow rates as low as 0.1 ml/h. In order to achieve the desired therapeutic effect with low flow rates, the drug solutions have to be relatively concentrated. However, as a result, small deviation in these low flow rates yield relatively large dosing errors given the high concentration of the drug solution.

In this thesis the physical causes of dosing errors in patients receiving multi-infusion therapy and the clinical consequences of these dosing errors were investigated. This thesis consists of two parts, a physical/technical part (part I, chapter 2), and a clinical part (part II, chapter 3).

In the introductory **chapter 1**, besides a short overview of the current literature, the objective and scope of this thesis is given. It was also shown that the risks of infusion therapy in general were supported by figures from scientific literature on medical errors related to intravenous drug administration. In the second part of this chapter, the fundamental physical and technical principles of infusion systems are introduced. A concise overview is presented of common infusion hardware and components typically

used in critical care. The basic mechanisms of syringe, volumetric and gravity driven pumps are explained. The focus of this thesis is mainly on syringe pumps. Next, it is explained how the infusion flow rates (e.g. ml/h) and the dosing rate of the drug (e.g. µg/h) are related to each other. Finally, the behavior of the flow of a drug solution through a tube is described. In its most elementary form, an infusion system can be described as the flow of a solution through a tube in which physical phenomena such as pressure and flow resistance influence the eventual dosing rate.

Chapter 2.1 is a systematic literature review. The objective was to identify the most important physical parameters responsible for dosing errors in a multi-infusion setup. In addition it was investigated to which infusion components these physical phenomena were mostly related. From the included studies (n=53) it was found that mechanical compliance (elasticity of the infusion components), flow resistance and dead volume were the most important physical causes of dosing errors in multi-infusion setups. Dead volume is defined as the volume between the mixing point and the outflow into the patient (e.g. catheter tip). Compliance is mostly related to syringes, while flow resistance is mostly related to narrow catheters. In **chapter 2.2** the physical properties of several infusion hardware devices were assessed. The study was conducted in cooperation with the Metrology for Drug Delivery (MeDD) research group as part of the European Metrology Research Programme (EMRP). The flow rate errors of the pumps, compliance of infusion components and startup times were investigated. The startup time was defined as the time required for the flow rate to reach 95% of the intended flow rate. In addition, the impact of viscosity of a drug mixture was investigated. The errors of the investigated syringe pumps were relatively low (±1-4%). Startup times were approximately 50 – 250 sec, depending on the infusion setup. Measured compliances were 0.24 – 2.10 ml/bar, mostly dependent on the syringe (size) used. Lower flow rates were associated with larger flow rate errors and longer startup times. Viscosity had limited impact on the flow rate errors. **Chapter 2.3** describes a theoretical model to predict the quantity and characteristics of dosing errors in relation to interventions and infusion hardware. This was done by describing the infusion system/setup in terms of the physical parameters of compliance, resistance and dead volume. In addition, the behavior of a fluid in a tube according to the Hagen-Poiseuille law was used in the model. The quantity of the physical parameters can be acquired by assessing the infusion components of an infusion setup, as was done in chapter 2.2. This subsequently allows researchers and healthcare professionals to investigate the impact of certain interventions, such as flow rates changes, in an actual infusion setup or hypothetical infusion setups. To validate the model, flow and dosing rates after interventions in a multi-infusion setup were investigated *in vitro*. The same laboratory setup was simulated using the model and the results were compared. In general the results were in satisfactory agreement with each other. In **chapter 2.4** the most important findings of part I (chapter 2) were accumulated. These findings were used to describe some of the basic clinical implications of the results. Both measurements and simulations were conducted. The measurements were conducted according to a medication schedule from the ICU. Typical infusion setups with and without anti-reflux valves were investigated. The results showed that the dead

volume was related to dosing errors after the flow rate was intentionally changed due to the “push-out” effect. After a flow increase and decrease, this effect respectively causes a transient over- and underdosing in all the other pumps connected to the same multiple-in single-out infusion set and catheter. The quantity of these dosing errors, expressed as the percentage deviation from the intended dosing rate, were around 25% and lasted approximately 8 minutes. From calculations it was found that the dosing errors may be clinically relevant for norepinephrine (noradrenaline). The time required for the patient to receive the medication (startup time) is in this case related to the compliance, flow resistance and also the dead volume. The startup times were approximately one hour, the anti-reflux valves did not significantly impact the startup time for the flow rates in this study. However, from the literature it was found that valves may introduce an additional delay, especially for lower flow rates.

Chapter 3.1 is a case report of a patient who suffered from a hypertensive crisis due to a norepinephrine overdose. This occurred after an almost-empty syringe was exchanged and the pump repeatedly gave an error. The incident was reproduced *in vitro* to investigate the possible causes of the overdose. It was found that an object may become obstructed between the plunger of the syringe and syringe driver of the syringe pump, which causes a substantial force to be applied on the syringe plunger. This force may cause a large overdose (0.8 ml, +2700%) if the infusion line (tubing), connected to the syringe that was exchanged, is not clamped. Nevertheless, if the line was clamped an overdose still occurred as soon as the clamp is released (0.07 ml, +225%). These dosing errors were administered in approximately 7 seconds. It is advised to clamp the line, remove the syringe each time the pumps gives an error, and to raise awareness about this risk. In **chapter 3.2** the analytical simulation model of chapter 2.3 was used to investigate dosing errors due a syringe exchange in a multi-infusion setup. The simulated multi-infusion setup consisted of two pumps, a faster pump (12 ml/h) and a slower pump (0.5 ml/h), respectively containing a hypothetical non-critical and critical drug. *In vitro* measurements were conducted to validate the results. If the slow pump was exchanged, an additional delay of approximately one hour may occur before the critical drug (of the slow) pump is again delivered to the patient. This is due to backflow. If the faster pump was exchanged, an undiluted volume of the critical drug (approx. 0.17 ml for a generic infusion setup) accumulated in the infusion setup beyond the mixing point. This may result in a temporary dosing rate error of 2400% for the critical drug. The quantity of these errors are strongly related to the compliance of the syringe and the diameter (and thus resistance) of the catheter. The model was capable of explaining the mechanisms behind these dosing errors in detail. It was recommended to clamp all infusion lines during a syringe exchange. Again, the awareness of the mechanisms behind the dosing errors was also found to be very important and may mitigate the risks. **Chapter 3.3** is a clinical pilot study. The mean arterial blood pressure (MABP) of two cohorts of neonates, requiring inotropic support (dopamine and/or dobutamine), was investigated. In each of the two cohorts a different infusion setup was used. It was accurately registered when the inotropic support was started and when the flow rate of a pump containing the inotropic drug was increased. About these timestamps, MABP-data of each patient was collected

for retrospective analysis. Delays in MABP-increase and an exponential fit of the MABP-increase were acquired from the MABP data. The performance of each infusion setup was investigated according to the time fraction that the MABP was above a desired MABP-margin. The delays of reaching a peak or plateau value after the inotropic pump was started from a standstill were substantial (approx. one hour) and in accordance with literature. The differences between the infusion setups were generally not statistically significant for both the delays in MABP-increase and the performance. However, in one of the cohorts it was shown that MABP-increase was significantly steeper. This might be explained by different compliances and resistances between the infusion setups. Moreover, in one of the cohorts the MABP decreased again after an initial increase, this might be interpreted by clinicians as a failure of the MABP to increase and, subsequently, cause additional flow rate interventions. This transient decrease may be caused by anti-reflux valves. Medical/physiological explanation are also possible. It is recommended to expend this type of clinical research with larger cohorts. In **Chapter 3.4** a multi-infusion setup of three syringe pumps (0.5, 2.0 and 6 ml/h), as applied on the neonatal intensive care unit (NICU), was investigated *in vitro*. In each pump intentional flow rate changes were conducted, subsequently, the dosing errors were measured in the other pumps combined on the same multiple-in single out infusion set and catheter lumen. In addition, the startup time was also measured. Statistically significant dosing errors of 48.2% and -32.5% were found after a flow rate increase and decrease respectively. These errors can largely be explained by the "push-out effect". Larger flow rate changes caused relatively larger dosing errors in the parallel pumps. The startup time was approximately 40 minutes in each pump. If this startup time is regarded as a deviation from the flow rate set point and thus a dosing errors, the contribution of this dosing error was the largest. The dosing errors due to the flow rate changes were temporary and lasted for 2 – 8 minutes, which may be clinically relevant in the case that inotropic drugs are administered, especially for critically ill preterm neonates.

In the general discussion (**chapter 4**) the results of this thesis are placed in broader perspective. Technical aspects and possibilities for improvement of the measurement setup were discussed. For the model generalizability towards infusion hardware and situations beyond the scope of this thesis were discussed. In addition, possible innovations were also discussed. Pharmacological theory was used to investigate for which drugs the dosing errors found in this thesis are likely to be clinically relevant, and which drugs are eligible for retrospective analysis similar to chapter 3.3. Finally the relevance of the dosing errors found in this thesis were substantiated and explained in the context of published figures of adverse drug events and medical errors that involved infusion.

It was shown that the dosing errors are related to physical properties of infusion hardware and can be predicted, both by modeling and *in vitro* measurement. Moreover, dosing errors due to physical causes related to infusion hardware components may have clinical consequences. The characteristics and causes of these dosing errors may be counter-intuitive. Technical innovations, standards, regulations and creating awareness through education programs may mitigate the dosing errors and the clinical consequences thereof. The results of this research may therefore contribute to patient safety.

SAMENVATTING

Vrijwel alle patiënten die opgenomen zijn in het ziekenhuis krijgen te maken met een vorm van infusietherapie. Bij infusietherapie wordt met behulp van een infuus vocht en/of geneesmiddelen direct in de bloedbaan van de patiënt gebracht. Een infuus bestaat doorgaans uit een katheter of canule die door de huid en het bloedvat wordt geprikt waardoor direct toegang tot de bloedbaan van de patiënt wordt verkregen. Via dit infuussysteem kan vervolgens een geneesmiddel in vloeibare vorm, meestal een oplossing, worden toegediend.

In de klinische praktijk, zeker op de intensive care (IC), blijkt infusietherapie een uitdagend proces. Dit heeft een aantal redenen. Ten eerste maakt de conditie van ernstig zieke patiënten het vaak nodig om geneesmiddelen voor langere tijd continu en met een grote nauwkeurigheid toe te dienen. Kleine afwijkingen in de toedieningssnelheid leiden bij deze geneesmiddelen vaak direct tot doseerfouten welke ernstige gevolgen kunnen hebben voor de patiënt. Om medicatie gecontroleerd en nauwkeurig via het infuus in de bloedbaan van de patiënt te brengen worden meestal infuuspompen gebruikt. Deze infuuspompen gebruiken verschillende technieken om de medicatie vanuit bijvoorbeeld een injectiespuit of een infuuszak met een vooraf ingestelde stroomsnelheid (debiet/flow in volume per tijdseenheid) naar de patiënt te pompen. Een tweede reden waarom infusietherapie risicovol is, is dat ernstig zieke patiënten vaak een groot aantal geneesmiddelen tegelijk nodig hebben. In de klinische praktijk worden deze geneesmiddelen vaak vanuit meerdere pompen samengebracht op één infuusset met meerdere ingangen en één uitgang die vervolgens weer op de toedienkatheter is aangesloten. Dit principe wordt multi-infusie genoemd. Multi-infusie is noodzakelijk omdat de toegang tot de bloedbaan van de patiënt beperkt is. Een belangrijke reden hiervoor is dat het inbrengen van een katheter bij de patiënt (katheterisatie) een infectiegevaar met zich meebrengt. Deze infecties kunnen ernstige gevolgen hebben voor de patiënt. Om die reden wordt het inbrengen van katheters tot een minimum beperkt.

Behalve een katheter, infuussets en pompen bestaan multi-infusie-systemen vaak uit een variëteit aan onderdelen. Bijvoorbeeld extra infuuslijnen (slangetjes), om een bepaalde afstand tussen de patiënt en de pomp te overbruggen en/of filters die ongewenste deeltjes en bacteriën uit de medicatieoplossing filteren. Uit onderzoek blijkt dat de fysische eigenschappen gerelateerd aan deze onderdelen tijdelijke veranderingen in de stroomsnelheid en daarmee doseringsfouten tot gevolg kunnen hebben, ondanks de inzet van relatief nauwkeurige moderne pompen. Hoewel bij een enkel infuus deze doseringsfouten al op kunnen treden, blijkt dat het risico op doseringsfouten bij multi-infusie nog groter is: alle pompen en stromingen kunnen invloed op elkaar uitoefenen. Hierdoor is het vaak ook lastig te doorgronden waarom en wanneer de doseringsfouten ontstaan en hoe groot deze zijn. Ten slotte kunnen ernstig zieke patiënten en vooral neonaten (pasgeborenen) het toegediende vocht niet goed verwerken. Hierdoor is het noodzakelijk de stroomsnelheid te beperken. Om er toch voor de zorgen dat de

geneesmiddelen het gewenste effect hebben bij lage stroomsnelheden, is het noodzakelijk om deze geneesmiddelen relatief hoog te concentreren. Hieruit volgt dat zelfs relatief kleine doseringsfouten direct resulteren in grote toedieningsfouten.

In dit proefschrift is onderzocht welke fysische eigenschappen, gerelateerd aan het infuussysteem (bv. pompen, katheters, infuussets, spuiten), doseringsfouten veroorzaken en welke klinische consequenties deze doseringsfouten kunnen hebben voor patiënten.

Globaal bestaat het proefschrift uit twee delen: een meer fysisch deel I (hoofdstuk 2) en meer een klinisch deel II (hoofdstuk 3).

In **hoofdstuk 1** wordt het onderzoek geïntroduceerd. In dit hoofdstuk is beknopt uiteengezet wat er over het onderwerp bekend is en het doel en de kaders van het onderzoek worden beschreven. Ook is het risico van infusietherapie gestaafd met cijfers uit de wetenschappelijke literatuur. In het tweede gedeelte worden de technische en fysische basisprincipes van infusietechnologie uitgelegd. Er wordt een kort overzicht gegeven van de pompen en andere infusieonderdelen die doorgaans worden gebruikt in de klinische praktijk. Daarnaast is gedefinieerd hoe de stroomsnelheid, vaak simpelweg infuussnelheid genoemd (bv. aantal milliliter per uur (ml/h)), en de doseringssnelheid van de medicatie (bv. aantal microgram per uur (µg/h)) zich tot elkaar verhouden. Tot slot worden de fysische principes achter het gedrag van een stroming van een medicatieoplossing door een slangetje/buisje beschreven. In de meest elementaire vorm kan het infuussysteem beschreven worden als een stroming van een oplossing door een slang waarbij elementen zoals druk en stromingsweerstand een rol spelen.

Hoofdstuk 2.1 is een literatuuronderzoek met als doel het identificeren van de belangrijkste fysische verschijnselen die doseringsfouten kunnen veroorzaken in een multi-infusie systeem. Tevens is gekeken aan welke onderdelen van een infuussysteem deze fysische verschijnselen gerelateerd zijn. Elasticiteit van het infuussysteem (beschreven als mechanische compliantie), stromingsweerstand als gevolg van nauwe slangetjes (met name katheters) en doodvolume zijn gevonden als de belangrijkste, meest relevant fysische verschijnselen. Doodvolume is gedefinieerd als het volume aan vloeistof tussen het punt waar de medicatie uit verschillende pompen samenkomt en het punt waar dit mengsel de patiënt inloopt. Tevens blijkt uit de literatuur dat in de meeste gevallen de spuit grotendeels verantwoordelijk is voor de compliantie. In **hoofdstuk 2.2** is een aantal infusieonderdelen geanalyseerd in laboratoriumonderzoeken. Dit hoofdstuk is uitgevoerd in samenwerking met leden van de Metrology for Drug Delivery (MeDD) onderzoeksgroep in het kader van het European Metrology Research Programme (EMRP). De nauwkeurigheid in stroomsnelheid van een aantal pompen en de compliantie van onder andere infuusspuiten zijn gemeten. Tot slot is de invloed van viscositeit (stroperigheid) van potentiële medicatieoplossingen gemeten. Uit de metingen is gebleken dat de compliantie vooral een relatie heeft tot de opstarttijd: dit is de tijd die nodig is voordat de pomp medicatie toedient aan de patiënt. De gevonden opstarttijden waren enkele minuten, afhankelijk van de configuratie van het infuussysteem. Uit de metingen bleek

dat de spuitenpompen relatief nauwkeurig waren en een afwijking van plusminus vier procent hebben. Daarnaast is gebleken dat de nadelige effecten, zoals de afwijking van de pomp en opstarttijden, groter zijn bij lagere snelheden. Viscositeit bleek van beperkte invloed op de nauwkeurigheid van de stroomsnelheid die de pomp uiteindelijk leverde. In **hoofdstuk 2.3** is een theoretisch fysisch model beschreven dat is ontwikkeld om de medicatietoediening aan de patiënt te kunnen voorspellen voor een bepaald multi-infusie-systeem. Dit is mogelijk door het infuussysteem te reduceren tot de eerder genoemde fysische parameters: compliantie, weerstand en doodvolume. Ook is het gedrag van een vloeistof in een infuuslijn, zoals beschreven door de wet van Hagen-Poiseuille, meegenomen in het model. Door de fysische eigenschappen van infusiehulpmiddelen van een bestaand systeem te meten in termen van bijvoorbeeld compliantie, zoals in hoofdstuk 2.2 is gedaan, kan dit bestaande systeem worden gesimuleerd met behulp van het model. Bovendien is het daarna ook mogelijk om hypothetische systemen te simuleren. Dit stelt een onderzoeker of behandelaar vervolgens in staat om theoretische voorspellingen te doen. Zo kan bijvoorbeeld onderzocht worden wat de invloed is van een verandering van de stroomsnelheid van een pomp in een complex multi-infusie systeem. Om de validiteit van het model te onderzoeken zijn laboratoriummetingen aan een multi-infusie systeem uitgevoerd. In deze metingen zijn de stroomsnelheid en doseringssnelheid gemeten. Ditzelfde infuussysteem uit het laboratorium is vervolgens gesimuleerd in het model. De uitkomsten van het model bleken grotendeels in overeenstemming te zijn met de uitkomsten van de laboratoriummetingen. In **hoofdstuk 2.4** zijn de belangrijkste uitkomsten van deel I samengebracht en is beschreven wat de fysische principes uit de voorgaande hoofdstukken betekenen voor de klinische praktijk. Dit is gedaan door metingen en simulaties uit te voeren. Tijdens de metingen werden de pompen ingesteld aan de hand van een medicatieschema gebaseerd op de klinische praktijk van de IC. Een medicatieschema is een voorschrift voor de stroomsnelheden die in een bepaald tijdsbestek ingesteld worden op de pomp. Ook is er gekeken naar de invloed van terugslagkleppen op de opstarttijd in een infuussysteem. Terugslagkleppen worden gebruikt om ervoor te zorgen dat de vloeistof in een infuuslijn niet terug kan stromen richting de pomp. Uit de resultaten bleek dat het dode volume kan zorgen voor het “push-out-effect”, waarbij een tijdelijke onder- of overdosering kan ontstaan na het respectievelijk verlagen en verhogen van de stroomsnelheid op de pomp. De stroomsnelheid wordt vaak met opzet veranderd omdat een andere doseringssnelheid noodzakelijk is voor de behandeling van de patiënt. Uit berekeningen blijkt dat de doseringsfouten klinisch relevant kunnen zijn als bijvoorbeeld het op de IC veelgebruikte geneesmiddel noradrenaline (norepinefrine) wordt toegediend. Uit de resultaten bleek dat het dode volume ook invloed heeft op de opstarttijd. Deze opstarttijd, die in dit geval is gedefinieerd als de tijd die het duurt voordat de medicatie in de juiste doseringssnelheid aan de patiënt wordt toegediend, is gerelateerd aan zowel de compliantie, de weerstand en het dode volume. Er is geen statistisch significant verschil in opstarttijd gevonden tussen een systeem met terugslagkleppen en zonder terugslagkleppen voor het medicatieschema dat is gebruikt in dit hoofdstuk. Uit de literatuur blijkt dat terugslagkleppen echter wel een significante invloed kunnen hebben, vooral bij lage stroomsnelheden.

Hoofdstuk 3.1 is een beschrijving van een incident waarbij een patiënt een overdosering aan noradrenaline toegediend kreeg nadat de spuit in een spuitenpomp werd gewisseld met een nieuwe spuit. Een wisseling van de spuit is nodig als een spuit bijna leeg is. Tijdens het wisselen gaf de pomp om onduidelijke redenen een foutmelding waardoor de procedure meerdere keren herhaald moest worden. Nadat de situatie werd nagebootst in het laboratorium bleek dat er een object kan komen tussen de plunjer (zuiger) van de spuit en het mechanisme van de spuitenpomp dat de plunjer voort moeten duwen. Hierdoor kan tijdelijk een zeer grote kracht uitgeoefend worden op de spuit. Uit de metingen is gebleken dat door deze grote kracht er een tijdelijke grote overdosering kan ontstaan. De overdosering is vooral groot als de infuuslijn aangesloten op de spuit, niet afgeklemd wordt tijden het wisselen van de spuit. Afklemmen houdt in dat de infuuslijn dichtgeknepen wordt waardoor er geen stroming kan zijn. Vanwege deze bevindingen is het advies gegeven om altijd de infuuslijnen af te klemmen tijdens een spuitwissel en de spuit uit de pomp te halen. Dit laatste is vooral belangrijk als er een foutmelding optreedt en de spuitwissel herhaald moet worden. In **hoofdstuk 3.2** is het wisselen van een spuit in een spuitenpomp in een multi-infusie systeem, bestaande uit twee pompen, gesimuleerd. In het systeem was één pomp ingesteld op een hogere stroomsnelheid en één op een lagere stroomsnelheid. Bij het wisselen van de spuit bij de pomp met een hogere stroomsnelheid kan er een substantiële vertraging optreden voordat de medicatie uit de pomp met de lagere snelheid weer wordt toegediend aan de patiënt. Bij het wisselen van de spuit bij de pomp met een hogere stroomsnelheid kan er overdosering optreden van de medicatie uit de langzamere pomp. Ook is gebleken dat de duur van de spuitwissel van invloed was. Omdat de langzamere spuit in de klinische praktijk vaak kritieke medicatie bevat kunnen beide fenomenen klinisch relevant zijn. De kwantiteit van zowel de vertraging als de overdosering hangen sterk samen met de compliantie van vooral het type spuit en de diameter van de katheter. De fysische mechanismen hierachter zijn, met behulp van het model in hoofdstuk 2.2, in detail beschreven. Op basis van de resultaten is wederom het advies gegeven om lijnen af te klemmen tijdens het wisselen van spuiten. Tevens is het belangrijk om bij de behandelaar (artsen en verpleegkundigen) bewustzijn te creëren over de fysische mechanismen die een rol spelen bij het wisselen van spuiten. **Hoofdstuk 3.3** is een klinische pilot studie. Voor dit hoofdstuk zijn twee patiëntenpopulaties van neonaten onderzocht die behandeld werden met dopamine of dobutamine. De populaties werden ieder met verschillende multi-infusie-systemen behandeld. Er is nauwkeurig bijgehouden wanneer de dopamine en/of dobutamine pomp werd gestart en wanneer de stroomsnelheid werd verhoogd. Beide acties hebben als doel om een bloeddruk stijging teweeg te brengen. Vervolgens is retrospectief onderzocht of er een verschil in bloeddrukstijging te vinden was die verklaard kon worden op basis van de verschillende fysische eigenschappen van beide multi-infusie-systemen. Zoals de theorie voorspelde waren de opstarttijden, waarschijnlijk door de fysisch effecten compliantie, weerstand en doodvolume substantieel. De duur van deze opstarttijd was ongeveer een uur wat in overeenstemming is met eerdere metingen. Het verschil in opstarttijd tussen beide systemen was beperkt en niet statistisch significant. Uit de resultaten bleek echter dat

de stijging van de bloeddruk (de richtingscoëfficiënt) wel significant verschilde tussen beide systemen. Daarnaast bleef de bloeddrukstijging van één van de infuussets vaak niet gehandhaafd. De resultaten suggereren dat dit te maken heeft met compliantie en de aanwezigheid van terugslagkleppen. Medische verklaringen zoals infecties zijn ook mogelijk. Het verschil in prestatie van beide infuussets was beperkt en niet statistisch significant. Er wordt echter aangeraden het onderzoek voort te zetten met grotere populaties. De vertragingen tussen handelingen zoals een stroomsnelheidsverandering is een goede indicatie voor het contra-intuïtieve karakter die de fysische effecten op de uiteindelijk behandeling hebben. Dit maakt dat het direct handelen op basis van de vitale functies zoals bloeddruk en hartslag voor behandelaars vaak lastig kan zijn. In **hoofdstuk 3.4** is een multi-infusie systeem met drie pompen met ieder een andere stroomsnelheid onderzocht in het laboratorium. In alle drie de pompen werd de stroomsnelheid aangepast, dat resulteerde in tijdelijke doseringsfouten in de twee andere pompen door vooral het “push-out effect”. Ook bleek uit de resultaten dat veranderingen in de stroomsnelheid bij de snellere pompen voor relatief grotere fouten zorgden. Er werd een opstarttijd van ongeveer een 45 minuten gevonden. Verder is gebleken dat als de opstarttijden zelf ook als doseringsfouten worden gerekend, deze relatief groter waren dan de doseringsfouten geproduceerd door het “push-out effect”.

In de algemene discussie in **hoofdstuk 4** zijn de resultaten van het onderzoek in een breder perspectief geplaatst. Technische aspecten van de gebruikte meetopstelling en het simulatiemodel zijn bediscussieerd. Bij het model is specifiek gekeken of het onderzoek uit te breiden is buiten de kaders die in dit proefschrift zijn gesteld. Daarnaast is met behulp van farmacologische theorie gekeken bij welke geneesmiddelen de doseringsfouten beschreven in dit onderzoek relevant kunnen zijn en welke geneesmiddelen geschikt zijn voor verder retrospectief klinisch onderzoek. Tot slot wordt er bediscussieerd wat de resultaten betekenen voor de patiëntveiligheid en hoe de risico’s beschreven in dit onderzoek zich verhouden tot de reeds gepubliceerde cijfers over incidenten met medicatie en infusie.

Doseringsfouten door fysische effecten gerelateerd aan componenten in een multi-infusie systeem kunnen klinisch relevante gevolgen hebben. De karakteristieken en grootte van de doseringsfouten zijn te voorspellen door het gebruik van een fysisch model. De oorzaak van de doseringsfouten kunnen voor behandelaars echter contra-intuïtief zijn. Technische innovaties, standaarden, regulatie en onderwijs voor behandelaars die met multi-infusie werken kunnen de risico’s verlagen. De resultaten uit dit onderzoek kunnen daarom bijdragen aan de veiligheid van patiënten die behandeld worden met multi-infusie therapie.

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CURRICULUM VITAE

Roland Snijder (1985) obtained a master's degree in Biomedical Engineering at the University of Groningen with a specialization curriculum in the area of medical physics (medical instrumentation and imaging). In his master thesis, conducted at the University Medical Center Groningen, he investigated the effects of using computed tomography (CT) for lung cancer screening. After finishing his master thesis in 2012, Roland went on to pursue a PhD degree that same year. Roland was given the opportunity to do so at the department of Medical Technology and Clinical Physics of University Medical Center Utrecht (UMC Utrecht). Here he worked as a researcher on the multi-infusion project for dr. Annemoon Timmerman. This research was conducted within the framework of the European Metrology Research Programme (EMRP). A PhD track was outlined in cooperation with the department of clinical pharmacy. Prof. dr. Toine Egberts acted as his promotor. Roland's research focused on investigating physical causes of dosing errors in multi-infusion systems. Specifically, the aim was to investigate the origin and characteristics of these dosing errors using *in vitro* measurement methods and theoretical modeling. Moreover, the clinical relevance of these dosing errors was investigated using pharmacological theory and a retrospective clinical study. Besides the hard sciences, Roland is interested in music, philosophy, (ancient) history and politics.