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Unexpected dosing errors due to air bubbles in infusion lines with and without air filters

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Abstract: The effect of the presence of an air bubble, inside an infusion line, on the time (T_{new}) needed for a new medication to reach the patient after a syringe exchange was studied in this paper. If an air bubble escapes through an air filter, then a sudden drop in pressure occurs, causing a relaxation of the compressible part of the syringe, followed by a gradual restoration of the flow rate in the line. We modeled this phenomenon mathematically and measured it experimentally *in vitro*. In an example with a pump flow rate of 5 mL/h and an air bubble of 1 cm length inside an infusion line (diameter 1 mm) with an air filter, both theory and experiment yield an additional increase of at least 600% in delay time if a naive estimate (based on the size of the bubble alone) is replaced by a more realistic estimate incorporating compressibility. Furthermore, we show that an air bubble in a line without air filter may increase T_{new} by a factor 2, depending on the initial position of the air bubble. We conclude that an air bubble in an infusion line causes delays that may not be expected by health care professionals.

Keywords: air bubble; catheter; delay time; dosing errors; infusion.

Introduction

For many decades now, investigators and physicians have been studying the risks associated with air bubbles trapped inside infusion lines, e.g., the introduction of air embolism.

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General rules for avoiding the formation of air bubbles in infusion lines are combined with the recommendation to incorporate air filters into infusion lines [1, 2]. These air filters have been designed to let air bubbles escape from the infusion line into the environment before these bubbles could enter the patient. In this paper, however, we will show the severity of two phenomena that are largely unknown to the medical staff: (i) if air bubbles are removed from the infusion line using an air filter, then an unexpectedly large extra delay in drug delivery may be created owing to pressure effects in combination with compressibility (mechanical compliance) of syringes. Furthermore, (ii) if there is no air filter present, and hence air bubbles are not filtered out, then, after a syringe exchange putting a syringe with a new medication into the pump, the presence of even very small air bubbles may have a profound effect on the time needed for the first molecules of the new medication to arrive at the patient, owing to a distortion of the Poiseuille Flow Profile. In the following, we will first give an overview of the known effects in multi-infusion (Subsection “Theoretical Background”) that help to predict the above-mentioned phenomena (i) and (ii). Subsequently, in the Methods section, we present the methods used for the numerical simulation of phenomena (i) and (ii), as well as the *in vitro* set-up used in the experiments that were designed to test the predictions made by the numerical simulation for phenomenon (i). After presenting the results of these experiments, we discuss the clinical impact of these two phenomena, and how to avoid detrimental effects for patients.

Theoretical background

One specific feature of modern infusion set-ups is of particular interest in relation to the effects of air bubbles and air filters, viz. the fact that modern disposable syringes contain a rubber stopper that is compressible under pressure [3, 4]. It has been shown that this compressibility of the plunger gives rise to a delay in the pressure build-up (and hence the build-up of the flow velocity) in the infusion line [5], and that this delay can be calculated using equivalent electric circuits modelling [6]. For instance, if a new syringe is inserted into the pump, and, subsequently, the pump is started at $t=0$ with a set flow rate of u_{pump} , then the equivalent circuit method predicts that the actual

output flow rate $u_{\text{patient}}(t)$ that enters the bloodstream of the patient at the other end of the catheter, equals:

$$u_{\text{patient}}(t) = u_{\text{pump}} \left(1 - e^{-\frac{t}{RC}} \right) \quad (1)$$

in which R is the resistance of the combination of infusion line and catheter, and C is the mechanical compliance (compressibility) of the elastic seal ('stopper') that sits on top of the plunger in the syringe. (Strictly speaking, compression occurs in several elements, such as the elastic stopper, the barrel wall (varying with the position of the stopper), and the compliance of the pump mechanism itself. Therefore, using a single value for C may not always model a given syringe's characteristics completely. For the purpose of explaining the importance of RC -effects in relation to air bubbles and air filters, however, a single C may suffice). The product of R and C is called the RC -time (also referred to as the "time-constant"). It can be seen from equation (1) that only after $t=3RC$, i.e., after waiting a time interval that equals three times the RC -time, the flow rate $u_{\text{patient}}(t)$ entering the blood stream of the patient has reached 95% of the intended flow rate u_{pump} . It has been shown [7] that in neonatal care this is of particular clinical relevance, because the resistance R of a catheter is inversely proportional to the diameter of the catheter *to the power four*, which causes very thin catheters (taking a 1 Fr catheter as an extreme example) used in the Neonatal Intensive Care Unit (NICU) to have a remarkably large value of R , and hence a particularly long RC -time of e.g., 105 s in case of a 1 French catheter (Vygon Premicath 1-Fr (Ecouen, France)) and a 50 mL syringe (B.Braun Omnifix (B.Braun, Melsungen, Germany)), which entails that it takes over 5 min to reach 95% of the set flow rate.

The essential point that we address in this paper now is that *this same start-up phenomenon will also occur directly after an air bubble has escaped through an air filter* in the infusion set-up: an air filter in an infusion line is equipped with microscopic orifices that allows air to escape into the environment, but keeps liquids inside (called 'hydrophobic' filters). If an air bubble is present inside the infusion line near the pump, it will travel along with the fluid through the infusion line, until it reaches the air filter (see Figure 1). Once the air bubble enters the air filter, the air escapes immediately to the environment, giving rise to a *sudden pressure drop* in the part of the infusion line between the pump and the air filter, which on its turn causes the compressible part of the plunger (called the plunger stopper) of the syringe to relax into its original unpressurized state. As a result, the actual flow rate of the

fluid entering the bloodstream of the patient drops as well, and needs time to be restored. This is phenomenon (i) mentioned above, and is explained and calculated in more detail in the Method section.

In the case that an air bubble is present inside an infusion system that does *not* incorporate an air filter, a different mechanism can still take place (phenomenon (ii)): Any tiny air bubble that is still large enough to cover the whole cross-sectional area of a (thin) catheter or infusion line will prevent the development of a complete Poiseuille flow profile throughout the catheter or infusion line (see Figure 2). This will be explained in more detail in the Methods section as well.

Methods: numerical modelling

Numerical modeling of set-up *with* air filter

Any air bubble that is large enough to cover the whole cross-sectional area of an infusion line, will travel through the infusion line along with the fluid, i.e., the velocity of the air bubble equals the average speed inside the infusion line (commonly referred to as 'plug flow'). As a result, in an equivalent electric circuit, the air bubble behaves just like the rest of the current, except near the location of the air filter. For the liquid in the infusion system, the air filter behaves like a normal piece of infusion line. If an air bubble arrives at the location of the air filter, however, the air filter functions as a temporary shortcut to the environment for the duration of the air escaping through the filter. Once the entire air bubble has escaped to the environment, the air filter behaves like a normal piece of infusion line again.

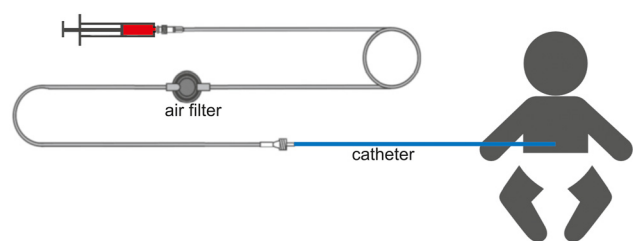


Figure 1: Schematic of syringe, infusion set with air filter, and catheter of which the distal tip ends inside the blood stream of a neonatal patient. In line with convention, the infusion line is "coiled up" between the syringe and the air filter, to indicate that the infusion line is actually much longer than depicted in this image. The initial position of the air bubble (see text) is inside the infusion line somewhere between the syringe and the air filter.

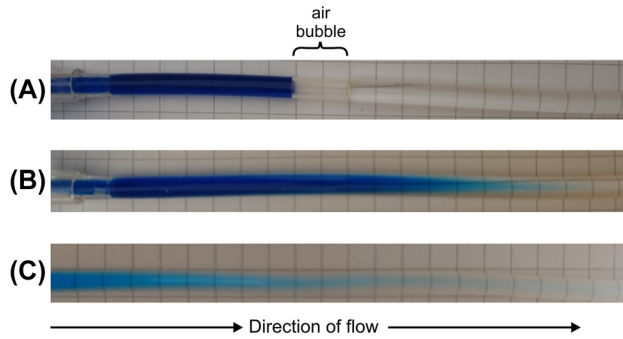


Figure 2: Photographical illustration of the effect of an air bubble in an infusion line. (A) Medication from a new syringe (blue dye in this photograph), entering the infusion line directly after a syringe exchange, is trapped behind an air bubble. The direction of the flow is from left to right in this picture. Length of the air bubble is about 1 cm. Distance between grid lines on the paper in the background is 5 mm. The “old” medication (transparent, without dye), pumped into the infusion line before the syringe exchange, is still present inside the infusion line directly next to the air bubble at the right side of the bubble. Flow rate was 20 mL/h. (B) As in (A), but now without air bubble, allowing a Poiseuille flow profile to develop. (C) As in (B), still without air bubble, but now after a longer period of time, and farther from the entrance of the infusion line, showing further development of the Poiseuille flow profile.

We have modelled this dual behaviour of the air filter as a switch (open/closed) in the equivalent electric circuit, as will be explained directly below.

In Figure 3A, the initial situation, directly after starting the pump at time $t=0$, is rendered: at the left, a schematic of the infusion set-up is shown, containing an air bubble somewhere inside the infusion line between the pump and the air filter. In clinical practice, the resistance (R_{before}) of the tubing “before” the air filter, i.e., the part of the infusion set between the syringe and the air filter, will be much lower than the resistance (R_{after}) between the air filter and the end of the catheter inside the patient, because generally the inner diameter of the catheter is much smaller than the internal diameter of the infusion line; therefore, in the equivalent electric circuit at the right of Figure 3A, we have $R_{\text{before}} < R_{\text{after}}$. The flow meter, measuring the actual flow rate entering the blood stream of the patient, is depicted by the symbol I (“current measurement”) in the equivalent circuits.

At time $t=0$, the rubber plunger of the syringe is not compressed yet, which is modelled in the equivalent electric circuit at the right of Figure 3A in the form of a capacitor that has not been charged yet. As a result, the

current travelling through the resistors R_{before} , R_{after} and the flow meter (see horizontal red arrow near R_{before} in the equivalent circuit of Figure 3A) is not fully developed yet, because a large portion of the current produced by the current source (i.e., the pump) is still flowing towards the capacitor. The air filter is behaving as being non-existent at this point in time, which is modelled in the equivalent circuit as a switch in the inconsequential “open” position. The flow $u_{\text{FM}}(t)$ measured by the flow meter (I) in Figure 3A therefore reads:

$$u_{\text{FM}}(t) = u_{\text{pump}} \left(1 - e^{-\frac{t}{(R_{\text{before}} + R_{\text{after}})C}} \right) \quad (2)$$

for t corresponding to Figure 3A

In Figure 3B, the situation is depicted in which the air bubble has still not arrived at the air filter yet, but the capacitor is now fully charged (i.e., the plunger in the syringe is fully compressed) and all the current from the current source is now flowing through the infusion line:

$$u_{\text{FM}}(t) \approx u_{\text{pump}} \text{ for } t \text{ corresponding to Figure 3B} \quad (3)$$

In Figure 3C, the air bubble has arrived at the air filter, and is escaping into the environment, causing a sudden pressure drop and loss of flow in the flow meter. In the equivalent circuit in Figure 3C, this is modelled using the switch being temporarily in the “closed” position, thus causing an electric shortcut producing the sudden loss of flow in the flow meter. Therefore, during the escape of the air bubble through the air filter, we have:

$$u_{\text{FM}}(t) \xrightarrow{\text{rapidly}} 0 \text{ for } t \text{ corresponding to Figure 3C} \quad (4)$$

because of the sudden loss of flow in the flow meter.

Furthermore, let now t^* indicate the point in time that the phase depicted in Figure 3C has ended, i.e., at $t=t^*$ the air bubble has just finished escaping through the air filter. Figure 3D depicts the situation directly after $t=t^*$, i.e., the flow needs to be built up again (analogous to the situation in Figure 3A), and therefore:

$$u_{\text{FM}}(t) = u_{\text{pump}} \left(1 - e^{-\frac{t-t^*}{(R_{\text{before}} + R_{\text{after}})C}} \right) \quad (5)$$

for t corresponding to Figure 3D

And finally, in Figure 3E, the flow has been restored again:

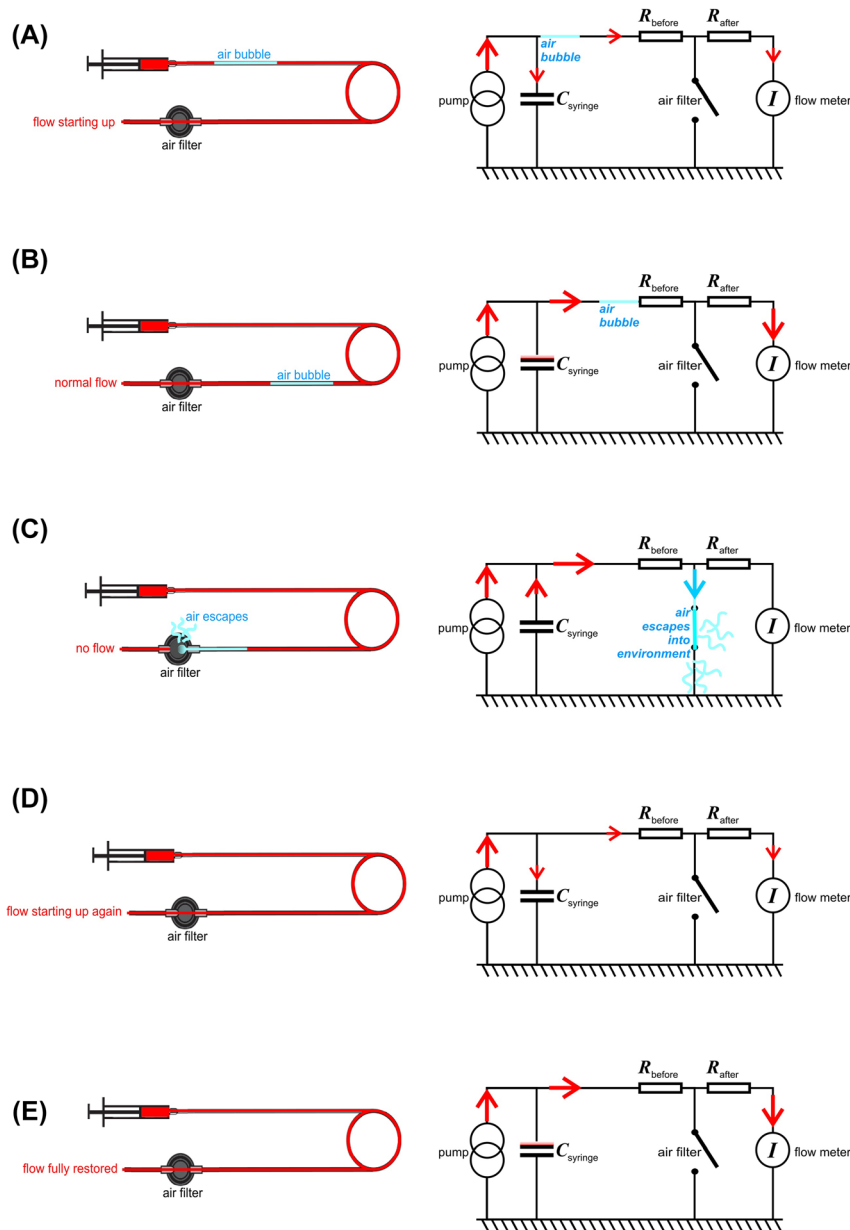


Figure 3: Schematic rendering of the various stages related to the effect of an air bubble on the actual flow rate entering the patient, in an infusion set-up containing an air filter. See text.

$$u_{\text{FM}}(t) \approx u_{\text{pump}} \text{ for } t \text{ corresponding to Figure 3E} \quad (6)$$

Numerical modeling of set-up *without* air filter

As has been mentioned before, if an air bubble is present inside an infusion system that does *not* incorporate an air filter, a different mechanism (phenomenon (ii)) will still occur, because any tiny air bubble that is still large enough to block the whole cross-sectional area of a (thin) catheter or infusion line will affect the (Poiseuille) flow profile, as is visible in Figure 2.

This phenomenon (ii) will take place on top of the obvious absence of medicinal flow into the patient during the very passage of the air bubble from the distal end of the catheter into the patient, which may already have a detrimental effect by itself.

The essential point here is that, if a syringe exchange takes place, putting a syringe containing a new medication into the pump, and starting the pump at time $t=0$, then, in the *absence* of any air bubbles, the time t_{first} needed for the first molecules of the new medication to arrive in the blood stream is approximately half the internal volume of the infusion set (V_{internal}) divided by the set flow rate (u_{pump}) of the pump:

$$t_{\text{first}} = \frac{V_{\text{internal}}}{2u_{\text{pump}}} \quad (7)$$

due to the fact that at the very centerline of the infusion line and catheter, the molecules travel at 2 times the average speed (averaged over the entire cross-sectional area).

If, however, any tiny air bubble, large enough to block the whole cross-sectional area, is present inside the infusion line directly near the entrance of the line after a syringe exchange, and the pump starts at $t=0$, then the new medication is not capable of passing through the air bubble, whereas the air bubble itself travels at the average speed (as in the case of a plug flow), leading to an arrival time t_{bubble} of the air bubble (and hence, the new medication) approximately equal to:

$$t_{\text{bubble}} = \frac{V_{\text{internal}}}{u_{\text{pump}}} \quad (8)$$

In reality, the value of t_{first} will be larger than the value calculated according to equation (7), due to the thermal diffusion (Taylor diffusion) blurring the Poiseuille flow profile, and, furthermore, the value of t_{bubble} will be smaller than calculated according to equation (8) if the air bubble is not located exactly at the beginning of the infusion line at $t=0$ but at some distance from the beginning of the infusion line near the pump, thus partially mitigating the effect of the air bubble. Furthermore, a quantity called the hydrodynamic entry length plays a role in the system. This is elaborated further in the Appendix.

Methods: *in-vitro* measurements

Experiments were conducted with the simplified setup shown in Figure 4, using a disposable infusion set from Impromediform (Impromediform GmbH, Lüdenscheld, Germany). The setup was filled with distilled water, and subsequently an air bubble was injected. The length of the air bubble was measured during the experiment using a

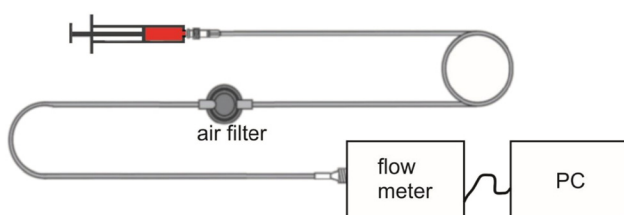


Figure 4: Simplification of the NICU infusion set containing an air filter. Adapted from Snijder et al. [7].

photocamera and a ruler. The experiment was repeated three times, using different lengths for the air bubble.

A 50 mL syringe (B.Braun Omnifix (B.Braun, Melsungen, Germany)) was attached to an infusion pump with a flow rate of 5 mL/h, and connected to an infusion line. This infusion line had a diameter of 1 mm and a length of 177.2 cm, and had a mechanical compliance that was negligible with respect to the compliance of the 50 mL B.Braun Omnifix syringe used in this experiment [7]. Generally speaking, however, the compliance of infusion lines may not be negligible, as has been shown e.g., by Batista et al. [8] for certain types of very long infusion lines. The other end of the infusion line (see Figure 4) was connected to a Coriolis mass flow meter (Cori flow M12P, Bronkhorst High-Tech BV, Ruurlo, The Netherlands). The data from the flow meter were recorded automatically by computer.

In order to facilitate comparison between measured data from the *in vitro* experiments with the results from the numerical modelling, the Resistance (R) values and the compressibility (C) values that are used in the numerical modelling (eqs (2) to (6)) are the value of C of the B.Braun Omnifix 50 mL syringe and the value of R of the Cori flow M12P Coriolis mass flow meter mentioned above, as well as the value of R of the infusion line. These values are listed in Table 1.

Results

Results of numerical modeling *with* air filter

The result of the numerical modeling of phenomenon (i) in an infusion set-up with an air filter is rendered in Figure 5. All parameter values used in the modeling yielding Figure 5 match the hardware and flow rate described in the Experimental Set-up (see Section 3) in order to facilitate comparison between the results in this section and the experimental *in vitro* results in Section 5.

Table 1: Resistance and Compressibility values of components in the *in-vitro* set-up, to be used for the numerical modelling.

Symbol	Component	Value	Unit
R_{before}	Infusion line	23.6	Pa. h/mL
$R_{\text{before}} + R_{\text{after}}$	Flow meter + infusion line	1,145	Pa. h/mL
C	Syringe (50 mL)	1.5×10^{-5}	mL/Pa
$R_{\text{before}} C$	RC-time in Figure 3C	1.27	s
$(R_{\text{before}} + R_{\text{after}}) C$	RC-time in Figure 3D	61.8	s

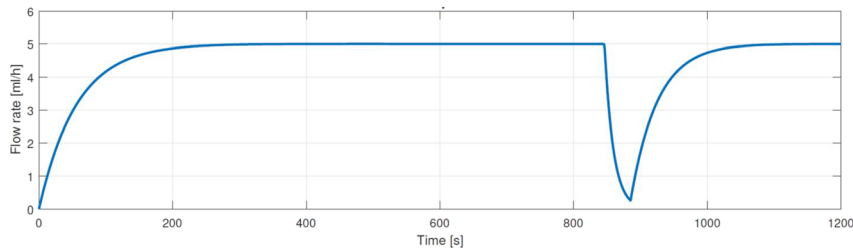


Figure 5: Results of numerical modelling of phenomenon (i), using the equivalent circuits described in Figure 3 and the values in Table 1. The flow rate (vertical axis) has been calculated as function of time, in an infusion set-up with an air filter. The pump starts at $t=0$, directly after the syringe exchange, and the air bubble escapes through the filter at approximately $t=850$ s.

Results of numerical modeling *without* air filter

For the numerical simulation of the additional delay that would be caused by a bubble *without* an air filter, an infusion line or catheter having a diameter of 1 mm and a length of 50 cm has been taken as an example. In the following, we refer to the infusion line or catheter simply as the tube. The results are rendered in Figure 6, in which “the position p of the air bubble at $t=0$ ” (i.e., the starting position of the bubble inside the tube directly after the syringe exchange when the pump is restarted), is defined with respect to the entrance point of the tube. In other words, the point on the x-axis for which $p=0$, corresponds to the situation in which an air bubble is located directly at the entrance of the tube, near the pump.

The “additional delay” is defined as the delay that would be added to the time ($t_{\text{first}} = V_{\text{internal}} / (2 u_{\text{pump}})$), see eq. (7)) already needed for the very tip of an ideal, undisturbed, Poiseuille flow to travel through the tube. For all flow rates,

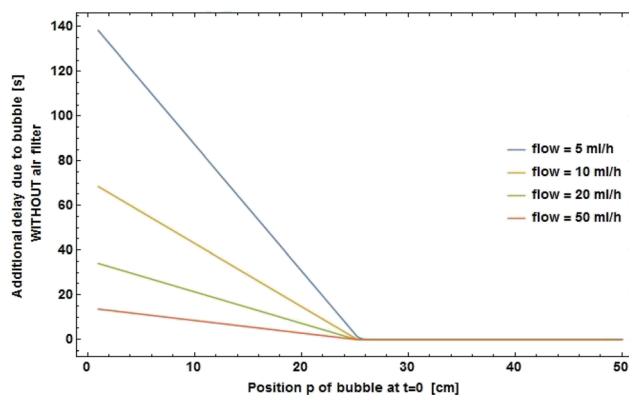


Figure 6: Results of numerical modeling, showing the additional delay (in seconds, vertical axis), due to the presence of an air bubble in an infusion system without an air filter, as function of the initial position p of the air bubble inside the tube at $t=0$. The point on the x-axis for which “position p of bubble at $t=0$ ” equals zero, corresponds to an air bubble located directly at the entrance of the tube, near the pump.

the maximal delays take place if $p=0$, i.e., the bubble is located at the entrance of the tube near the pump. The values of these maximal delays then equal $V_{\text{internal}} / (2 u_{\text{pump}})$, yielding a total delay of $V_{\text{internal}} / u_{\text{pump}}$ (see eq.(8)), because the time-of-arrival of the new medicine is then (approximately) equal to the time-of-arrival of the air bubble itself.

Results from *in vitro* setup with air filter

Figure 7 shows the results of the flow rate measurements during the passage of a bubble through an infusion line with an air filter. During the first rise in flow rate (see (a) in Figure 7, which corresponds to situation (a) in Figure 3), the

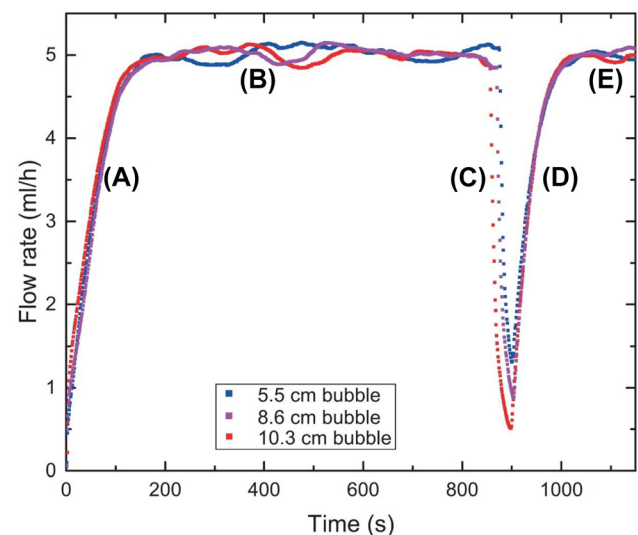


Figure 7: Output flow rates, as measured by the flow meter at the end of the infusion line (see Figure 4), during passage of air bubbles of various sizes through the air filter. The various situations indicated by (A), (B), (C), (D) and (E) correspond to the phases (A), (B), (C), (D) and (E) in Figure 3. The results are in agreement with the results of the computer simulation rendered in Figure 5.

system builds up pressure and flow rate, until a stable flow rate is reached (plateau at (b)). When the air bubble arrives at the air filter, the air from the bubble escapes into the environment through the filter, and the flow rate as measured by the flow meter drops suddenly (c).

Once the air bubble has left the system, the build-up of pressure and flow starts again (d), until a stable flow rate is reached again (plateau at (e)).

The results shown in Figure 7 are in agreement with the numerical simulations shown in Figure 5, including the fact that the time duration needed to restore the flow rate again at (d) is much longer than the time duration of the sudden pressure drop at (c) corresponding to the escape of the air bubble through the filter. This long duration of (d) may be of clinical importance because it is probably an unknown and unexpected phenomenon for many clinicians, as will be discussed in the Discussion section.

From the graphs rendered in Figure 7, we have distilled the experimental RC-times for the three different bubble sizes in both situation (a) and situation (d). The results are rendered in Table 2.

Discussion

In this paper, the effects have been studied that the presence of an air bubble inside an infusion line has on the time-of-arrival of a new medication after a syringe exchange.

For phenomenon (i), i.e., the extra delay caused by the sudden drop in pressure when the air bubble escapes into the environment through an air filter, the results from the experiment (Figure 7) seem to be in accordance with the results of the numerical simulation (Figure 5) that was based on the theoretical model described in Section 2, albeit that in Table 2 (especially concerning situation (d)) the values of the RC times from the *in vitro* experiments show deviations from the theoretical value of the RC time (61.8 s) in Table 1. In general, it will take about 3 RC times to reach 95% of the flow rate, and the time integral of the delays described in eqs.(2) and (5) amounts to exactly RC.

The overall conclusion, based on theory as well as experiment, for the case of a bubble in an infusion line *with* an air filter (phenomenon (i)) is that a delay time equal to RC will take place instead of the seemingly logical delay of $V_{\text{airbubble}}/u_{\text{pump}}$ (in which $V_{\text{airbubble}}$ is the volume of the air bubble itself) that would be expected by many health care professionals. The RC time may be much larger than $V_{\text{airbubble}}/u_{\text{pump}}$. For instance, if $u_{\text{pump}}=5$ mL/h and the bubble has a length of 1 cm and the infusion line has a diameter of 1 mm, then $V_{\text{airbubble}}/u_{\text{pump}}$ equals 5.7 s, whereas the actual delay of RC amounts to 61.8 or approximately 40 s, using the values from Table 1 or Table 2, respectively. Therefore, both the numerical modeling as the experimental results yield an additional increase of at least 600% in delay time if a naive estimate, using a (hypothetical) completely incompressible syringe ($C=0$), is replaced by RC using realistic values for R and C. It must be emphasized that in a real-life situation, additional effects may occur that have not been taken into account in the description of phenomenon (i), such as the fact that thermal diffusion of molecules has a blurring effect on the parabolic shape (the Poiseuille profile) of the progression of the new medication through the infusion line. This thermal diffusion effect gives rise to a longer travel time of the new medication than would be the case if the flow profile would not be affected by thermal diffusion.

For phenomenon (ii), i.e., the extra delay that occurs if the new medication after a syringe exchange is trapped behind an air bubble in an infusion line *without* an air filter, may range from almost zero to an increase by a factor 2. The maximum extra delay occurs if the initial position of the air bubble is at the entrance of the infusion line (or catheter) near the pump; in such a case, the new medication reaches the patient only directly after the air bubble. The air bubble itself travels merely at “plug flow speed”, yielding a total travel time of $t_{\text{bubble}}=V_{\text{internal}}/u_{\text{pump}}$ (see eq. (8)). This is visible in the results of the numerical simulation in Figure 6. Taking another example of an infusion line, having a length of 172 cm and a diameter of 3 mm, that contains an air bubble of 1 cm length but has no air filter, in combination with a flow rate of the pump of 20 mL/h, then the total time needed for the new medication to arrive at the patient varies from about 18 min to about 36 min, depending on the initial position of the air bubble in the infusion line. This discrepancy between 18 and 36 min may be unexpected for many health care professionals as well, although medications that should not be interrupted will generally be pre-flushed through the tubing, sometimes running for 1–2 h into a waste container before connecting the line to the patient initially, or using a

Table 2: RC-times for various bubble lengths.

Bubble length, cm	RC time (s) at situation (a)	RC time (s) at situation (d)
5.5	57	41
8.6	60	37
10.3	51	41

manual very high flow rate flush to fully prime the line with medication before loading into the pump.

Next to the risks associated with air bubbles as discussed above, there are additional known sources of disturbances in the flow of the medication into the patient. These sources involve generally known mechanisms such as the “push-out effect” and the compliance of syringes, infusion lines, and pumps [5, 6], but also lesser known effects such as intrinsic startup delay of the pump itself (caused by slack in the mechanism), friction of the stopper interacting with the pump mechanical compliance, as well as syringe stopper non-linear friction phenomena such as cyclical stick-slip behavior [9]. As has been mentioned above, however, many of the problems related to the “push-out effect” are best mitigated by using prime-by-pump actions before connecting the line to the patient.

We conclude that the presence of an air bubble in an infusion line may give rise to additional delay in the time-of-arrival of a new medication in a patient after a syringe exchange, and that this delay may be unexpected by the health care professional, even if an air filter is present in the infusion line. We therefore conclude furthermore that awareness of these delays is needed for health care professionals working with infusion lines, since these delays may be clinically significant in critical situations.

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Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

Appendix

If a liquid leaves the syringe and enters an infusion line, the Poiseuille flow profile is not developed instantly. Instead, it is only after travelling a certain distance, called the hydrodynamic entry length λ_{hel} , that the Poiseuille flow profile is considered to be fully developed. The value of λ_{hel} is calculated as: $\lambda_{hel} = 0.0575 Re d$, in which Re is the Reynolds number and d is the diameter of the infusion line [10]. In the numerical simulation for phenomenon (ii), i.e., without filter, this value of λ_{hel} has been incorporated into the simulation, giving rise to rounded edges, instead of sharp edges, near $p=25$ cm in Figure 6.

References

1. Brull SJ, Prielipp RC. Vascular air embolism: a silent hazard to patient safety. *J Crit Care* 2017;42:255–63.
2. Palmon SC, Moore LE, Lundberg J, Toung T. Venous air embolism: a review. *J Clin Anesth* 1997;9:251–7.
3. Weiss M, Hug MI, Neff T, Fischer J. Syringe size and flow rate affect drug delivery from syringe pumps. *Can J Anaesth* 2000;47:1031–5.
4. Schulz G, Fischer J, Neff T, Bänziger O, Weiss M. The effect of air within the infusion syringe on drug delivery of syringe pump infusion systems. *Anaesthesist* 2000;49:1018–23.
5. Timmerman AM, Snijder RA, Lucas P, Lagerweij MC, Radermacher JH, Konings MK. How physical infusion system parameters cause clinically relevant dose deviations after setpoint changes. *Biomed Tech* 2015;60:365–76.
6. Konings MK, Snijder RA, Radermacher JH, Timmerman AM. Analytical method for calculation of deviations from intended dosages during multi-infusion. *Biomed Eng Online* 2017;16:18.
7. Snijder RA, Konings MK, Van den Hoogen A, Timmerman AM. Impact of physical parameters on dosing errors due to a syringe exchange in multi-infusion therapy. *Pharm Technol Hosp Pharm* 2017;2:85–96.
8. Batista E, Almeida N, Furtado A, Filipe E, Sousa L, Martins R, et al. Assessment of drug delivery devices. *Biomed Tech* 2015;60:347–57.
9. Ong JW, Chung DC, Lin ES, Abid HA, Liew OW, Ng TW. Syringe infusion pump with absolute piston displacement control. *Rev Sci Instrum* 2019;90:076108.
10. Bergman TL, Incropera FP. Fundamentals of heat and mass transfer. Hoboken, NJ, USA: Wiley; 2011.