

*Intravascular volume after aneurysmal subarachnoid hemorrhage*

ISBN 978-90-393-5182-6

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Design and layout by Frank Boesveld, Multimedia, UMC Utrecht, the Netherlands

Printed by Gildeprint, Enschede, the Netherlands

# **Intravascular volume after aneurysmal subarachnoid hemorrhage**

*Intravasculair volume na een aneurysmatische subarachnoïdale bloeding*

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht  
op gezag van de rector magnificus, prof.dr. J.C. Stoof,  
ingevolge het besluit van het College voor Promoties  
in het openbaar te verdedigen  
op donderdag 5 november 2009 des middags te 4.15 uur

door

*Reinier Geert Hoff*

geboren op 17 september 1962 te 's Gravenhage

Promotoren: Prof. dr. C.J. Kalkman  
Prof. dr. G.J.E. Rinkel

The research described in this thesis was supported by a grant from  
ZonMw - the Netherlands Organization for Health Research and Development (grant 945-05-035).  
Financial support by ViaMedica for the publication of this theses is gratefully acknowledged.

*Aan de heer C, de heer G, mevrouw L*



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## Chapter 1

### General introduction



## General introduction

Subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm is a devastating condition. About half of the affected patients die as a result of the hemorrhage, while many of the survivors recover from the acute episode with decreased physical and mental capacity.<sup>1</sup> Delayed cerebral ischaemia (DCI) is one of the most important factors determining outcome in patients who have survived the initial hours after SAH and in whom the aneurysm has been occluded to prevent rebleeding. Although the precise pathogenesis of DCI is not clear, a variety of factors, including vasospasm of cerebral arteries, most likely contribute to an imbalance between supply (cerebral blood flow) and cerebral oxygen and glucose demand.<sup>2</sup> DCI results in neurological deterioration in about one third of patients and usually occurs 4 to 14 days after the SAH.<sup>3</sup>

Patients with SAH not only suffer neurological injury but many of them will develop dysfunctions in multiple organ systems including heart failure, pulmonary edema, disturbances in water and salt excretion and the development of a systemic inflammatory response. Such extracerebral organ dysfunction increases the risk for DCI and poor outcome.<sup>4,5</sup> Systemic circulatory disturbances, especially hypovolemia and hypotension, will compromise oxygen and glucose delivery to the brain and are seen as an important contributors to this increased risk.<sup>6-8</sup> Maintenance of a normal blood volume is therefore widely considered one of the mainstays of treatment after SAH.<sup>8-10</sup>

In an effort to augment cerebral blood flow, it has become practice in many centers around the world to increase intravascular volume status to hypervolemic levels, often in combination with induced hypertension, with or without deliberate hemodilution.<sup>9,11</sup> There are several case reports and uncontrolled studies that claimed a positive effect of this so-called 'triple-H' therapy on outcome after SAH. However the few randomized trials on prevention of DCI with 'triple-H' showed ambiguous results. At this moment there is still a lack of evidence for the efficacy of 'triple-H' or any of its constituents in the prevention and treatment of DCI.<sup>12,13</sup>

Actual measurement of the circulating blood volume is not performed in most studies on hemodynamics after SAH. Fluid therapy is typically guided by changes in clinical parameters such as heart rate, blood pressure and urine output, invasive measurements of "filling pressures" (central venous pressure; pulmonary capillary wedge pressure), or on calculated fluid balances.<sup>11,14,15</sup> However, it has repeatedly been shown that the relation between these measurements and actual blood volume is poor.<sup>16-18</sup> This raises the question whether discrepancies could exist between the presumed volume status based on such clinical criteria and the actual

measured volume status. Such a discrepancy might contribute to the ambiguity of the results of previous studies on hemodynamic augmentation after SAH.

The work presented in this thesis consists of several studies on hemodynamics after recent aneurysmal SAH, in an effort to clarify the relation between the presumed and actual condition of the systemic circulation, and thereby to find a way to improve hemodynamic management.

## Outline of the thesis

In *chapter 2* the existing information on measured blood volume after recent SAH is reviewed. In *chapter 3* we present a prospective observational study on the efficacy of fluid administration based on regular evaluation of the fluid balance in maintaining a normal blood volume after SAH. In *chapter 4* we studied the ability of nursing staff to predict hypo- or hypervolemia, based on their interpretation of available hemodynamic data. In *chapter 5* data are presented on a prospective controlled study, in which fluid management guided by daily measurements of circulating blood volume was compared to conventional fluid balance guided fluid therapy, to assess the effect on the incidence of hypovolemia after SAH. *Chapter 6* describes differences in hemodynamic parameters between patients with or without neurogenic pulmonary edema after SAH. In *chapter 7* we studied the relationship between serum brain natriuretic peptide (BNP) and hypovolemia or hyponatremia after SAH. *Chapter 8* describes a retrospective study on the incidence and severity of intra-operative hypotension during aneurysm clipping and its effect on outcome. In *chapter 9* we discuss the implications of the studies described in this thesis on patient care and on future research.

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## Chapter 2

# Blood volume after aneurysmal subarachnoid hemorrhage: a systematic review

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## Abstract

*Introduction* Achieving normovolemia or hypervolemia is widely seen as an important part of treatment after aneurysmal subarachnoid hemorrhage (SAH). Actual blood volume after SAH is however rarely measured. We performed a systematic review of the literature on measured blood volume after SAH. Objectives were to obtain an overview on available knowledge on blood volume after SAH, and to assess its relation with hemodynamic therapy and delayed cerebral ischemia (DCI).

*Methods* We searched MEDLINE and EMBASE databases for relevant articles published between May 1965 and December 2007. Studies were included if blood volume (or plasma/red cell volume) was measured in any way in patients with aneurysmal SAH. We collected data on study characteristics, hemodynamic therapy, results on blood volume after SAH, the relation between blood volume and DCI, and complications of blood volume measurement.

*Results* We included 19 studies, totaling 549 patients with SAH. In the 16 studies presenting data on numbers of volume measurements, a total of 904 measurements was performed (red cell volume n=237; plasma volume n=467; circulating blood volume n=200) in 403 patients. Several studies observed a reduction in blood volume, especially during the first days after the SAH. Patients developing DCI may be more often hypovolemic than patients without DCI. Interpretation of data is severely hampered because of methodological problems in many of the included studies.

*Conclusion* Further studies are necessary to elucidate developments in volume status after SAH, the influence of hemodynamic therapy, and the relationship between volume status and DCI. At present there is not enough scientific evidence to present an advice on fluid management after SAH.



## **Introduction**

An adequate blood volume, which is the sum of red cell volume and plasma volume, is essential to maintain cardiac output and tissue perfusion.<sup>1</sup> Hypovolemia is seen as an important contributor to delayed cerebral ischemia (DCI) and poor outcome after aneurysmal subarachnoid hemorrhage (SAH).<sup>2-4</sup> For thirty years, attempts have been made to maintain normovolemia or to obtain a hypervolemic state to reduce the risk of DCI after SAH.<sup>5-7</sup> However, in most studies on hemodynamics after SAH, blood volume is not actually measured. In these studies an impression on volume status is obtained from the interpretation of several clinical parameters, such as heart rate, arterial and central venous pressures, urine production and biochemical analyses. Although these parameters are regularly used to guide fluid therapy in clinical practice as well as during research, the association between these parameters and measured blood volume is poor.<sup>8-10</sup>

The only reliable assessment of blood volume is based on actual measurement of the blood volume or its constituents.<sup>11</sup> Red cell volume can be measured with the use of radio-isotope-labeled red cells, and plasma volume can be determined with radio-isotope-labeled human serum albumin. Total blood volume can be calculated as the sum of red cell and plasma volumes, or by using one of these measurements together with the measured hematocrit. Total circulating blood volume can also be measured by means of dye densitometry. These techniques have been described elsewhere.<sup>11,12</sup>

We aimed to review the current knowledge on measured blood volume in patients with recent aneurysmal SAH, to assess the effects of hemodynamic therapy on volume status after SAH, and to assess the relationship between hypovolemia and the development of DCI.

## Methods

A study was eligible for inclusion in the present review if the studied population contained patients with aneurysmal SAH and some form of measurement was performed of circulating blood volume, or red cell volume, or plasma volume. We searched MEDLINE and EMBASE databases for relevant articles published between May 1965 and December 2007 using MESH-headings in the following search strategy:

```
{(intracranial aneurysm) OR (subarachnoid hemorrhage)}  
AND  
{(blood volume) OR (plasma volume) OR (erythrocyte volume) OR (red cell volume)}.
```

We limited the search to human studies and to articles published in the English language. The studies identified with this search strategy were divided into the categories 'not relevant' and 'possibly relevant' on the basis of the title of the article. A study was considered 'not relevant' if that study evidently did not concern patients with aneurysmal SAH or did not concern systemic hemodynamics in any way. The abstracts of all 'possibly relevant' articles were reviewed to find out if measurement of blood volume (or plasma/red cell volume) was used in any way in a population including patients with aneurysmal subarachnoid hemorrhage. If this was the case, these studies were included in the review. If the use of volume measurement was not clear from the abstract, or there was no abstract available, the original publications were read in full to clarify the use of a blood volume measurement technique. Publications in which blood volume was discussed but not measured were not included. The reference lists from all included articles and from reviews were hand-searched for any relevant articles not yet identified by the database searches.

We collected from all included studies data on study design, patient population, method of volume measurement, number of volume measurements, fluid therapy, blood pressure regulation, results on blood volume after SAH, the incidence of DCI, the relation between blood volume and DCI, and complications of blood volume measurement.

## Results

Search of MEDLINE database with the aforementioned strategy yielded 619 results. Of these, 478 studies were considered 'not relevant' on the basis of the title. These were mostly studies concerning traumatic brain injury and studies on the volume of subarachnoid blood visible on CT-scan or MRI. Of the remaining studies, 47 were considered 'not relevant' after reading the abstract or full length article; 39 were narrative reviews on any aspect of hemodynamics after SAH; 36 were studies on hemodynamics after SAH in which blood volume was not measured. In 18 studies a form of blood volume measurement was performed in patients after SAH.<sup>2,3,13-28</sup> These studies were included for the review. In one study, blood volume was measured in a group of critically ill patients, one of whom had a SAH.<sup>29</sup> Data from this SAH patient were not provided separately from the data on the other patients; this study was therefore excluded from the review. Search of EMBASE yielded no other relevant study. By hand-searching the reference lists, one other relevant publication was identified.<sup>30</sup>

The 19 included studies contained 7 case series, published between 1981 and 1992, on a total of 98 patients. There were 9 case control studies, published between 1979 and 2003, on 278 patients. In 7 of these case control studies, patients after SAH were compared to non-SAH patients. In two of the case control studies, different treatment regimes were compared in patients after SAH. There were 3 randomized clinical trials (RCT) included, dating from 1989, 1998 en 2000. One of the RCT's studied fludrocortisone treatment; the other two compared different fluid policies after SAH.

### *Study characteristics*

Extracted data from the 19 studies are presented in *Table 1*. One of the case control studies described patient data, part of which had already been presented in a previous study.<sup>25,27</sup> The same situation exists for two of the RCT's.<sup>24,26</sup> Results of these articles on the same study population were combined in this review.

The included studies reported on a total of 549 patients (mean number of patients per study 32; range 2-98 patients). In the 16 studies presenting data on numbers of volume measurements, a total of 904 measurements was performed (mean number of measurements per study 60; range 7-200 measurements) in 403 patients. In one study, describing two patients, 15 blood volume measurements were performed per patient.<sup>20</sup> In the other studies the mean number of measurements per patient was 1.8 (range 1-4).

### ***Blood volume measurement after SAH***

Red cell volume was measured with the use of radio-isotope-labeled red cells in 7 out of 19 included studies.<sup>2,3,17,20,24,26,30</sup> A total of 237 measurements was performed in 142 patients after SAH. In 4 of the early studies totaling 58 patients, published between 1979 and 1987, a reduction in red cell volume was found, with mean red cell volume varying from 18 to 25 ml/kg, while reference values varied from 25 to 35 ml/kg.<sup>2,3,17,30</sup> As far as can be deduced from the little information provided on hemodynamic therapy, the patients in these 4 studies had low fluid intakes (1.5 to 2 liters per day). One case-series described a reduction in red cell volume after surgery, prior to neurological deterioration in one of two patients.<sup>20</sup> One study in 82 patients, described in two articles published in 1998 and 2000, found no difference in red cell volume between SAH patients treated with a normovolemic or a hypervolemic fluid policy.<sup>24,26</sup> Red cell volume varied in these patients from  $19 \pm 5$  ml/kg on day 0 to  $17 \pm 5$  ml/kg on days 3-6 after inclusion (no reference values provided). These patients were treated with ample fluid supplementation to maintain a predefined level of central venous pressure or pulmonary capillary wedge pressure.

Plasma volume was measured with radio-iodinated human serum albumin in 13 studies.<sup>2,13-23,30</sup> A total of 467 plasma volume measurements was performed in 246 patients. One study provided no data on the number of plasma volume measurements.<sup>23</sup> Four studies provided the actual values of plasma volume measurements.<sup>2,16,17,30</sup> In 3 of these studies (33 patients with 42 measurements) with very limited information on fluid therapy, mean plasma volume after SAH ranged from 35 to 38 ml/kg, and was not statistically significant different from non-SAH control patients.<sup>2,17,30</sup> One of these studies found that plasma volume increased with a hemodynamic treatment with induced hypertension and albumin administration, compared to a treatment policy without albumin.<sup>16</sup> One study described a progressive decline in plasma volume preceding DCI in one patient with daily administration of a diuretic.<sup>20</sup> Four studies described a plasma volume reduction of more than 10%, in 19 to 52% of patients after SAH, without providing plasma volume values.<sup>15,18,19,21</sup> Three of these studies applied a fluid intake of at least 3 liters per day, following previous reports on the association of low blood volume with DCI.<sup>18,19,21</sup> A non-specified reduction in plasma volume following SAH was described by two studies.<sup>13,23</sup> One was a case series on 3 patients without information on fluid policy.<sup>13</sup> The other was a study comparing patients (without DCI) with a restricted fluid policy with patients (with DCI) with induced hypertension and ample fluid administration.<sup>23</sup>

One study calculated total blood volume on the basis of measured plasma volume (no values of plasma volume provided), showing a reduction in blood volume in preoperative patients 1-3 weeks after SAH, compared to reference values.<sup>14</sup>

Circulating blood volume was measured with pulse dye densitometry in 3 studies that together reported on 98 patients after SAH.<sup>25,27,28</sup> Only one of these studies provided data on the number of measurements.<sup>28</sup> Mean circulating blood volume values were statistically significant decreased on day 2-3 after SAH ( $63 \pm 12$  ml/kg) compared to control patients ( $73 \pm 11$  ml/kg) in two articles on the same population.<sup>25,27</sup> After this initial reduction, circulating blood volume returned to normal values in the first week after SAH.<sup>28</sup>

### *Influence of hemodynamic therapy on blood volume*

Comprehensive data on fluid therapy, blood pressure regulation and other treatments that potentially affect blood volume were provided in only 6 out of 19 included studies.<sup>16,19,22-24,26</sup> Eight studies provided limited data.<sup>2,3,15,17,18,20,21,28</sup> In 5 studies there was no information on hemodynamic management.<sup>13,14,25,27,30</sup> Those studies providing data on fluid management show that patients had been treated according to very different regimes, ranging from IV fluids on maintenance basis only, via supplementary infusion of smaller or larger amounts of crystalloids or plasma expanders, to different forms of triple H therapy (hemodilution, hypertension, hypervolemia) with use of inotropic and vasopressor support. Induced hypertension was used in 5 studies.<sup>16,22-24,26</sup> Fluid intake was increased to prevent or treat delayed cerebral ischemia in 6 studies.<sup>16,19,22-24,26</sup> The amount of administered fluids varied from 1.5 to 10.0 liters per day.

One study in 19 patients found that large fluid suppletion, guided by daily fluid balances, prevented a decrease in plasma volume.<sup>22</sup> In a later RCT in 82 patients, fluid suppletion guided by venous filling pressures was not effective in the prevention of a decrease in calculated total blood volume.<sup>24,26</sup> One study in 24 patients found that plasma volume increased with a hemodynamic treatment with induced hypertension and albumin administration, compared to a treatment policy without albumin.<sup>16</sup> One study compared triple H therapy in patients with DCI with a fluid restricted treatment policy in patients without DCI.<sup>23</sup> This study described a positive effect of triple H therapy on plasma volume.

In 7 studies, blood volume measurements in patients after SAH were compared to measurements in non-SAH controls.<sup>2,3,17,25,27,28,30</sup> These control patients had a diversity of non-SAH illnesses, some had bed rest, others were ambulant outpatients (*table 1*). None of these studies provided data on hemodynamic management in control group patients.

**Table 1**  
*Overview of previous studies on blood volume after SAH*

First Author	Year	Study Design	Population	N of volume measurements in SAH patients	Method of volume measurement	Fluid therapy & blood pressure regulation	Results
Maroon <sup>2</sup>	1979	Case control	15 pts after SAH & 6 non-SAH pts without bed rest (controls)	24 RCV 24 PV	<sup>51</sup> Cr-labelled autologous erythrocytes (RCV) Radioiodinated human serum albumin (PV)	After SAH: bedrest; no fluid restriction; at least 2 liters of fluids per day; dexamethason Therapy controls: data not provided	Pts after SAH had reduced RCV compared to controls Pts after SAH had increased ADH levels Poor relation between blood volume and Ht
Kudo <sup>13</sup>	1981	Case series	3 pts after SAH	8	Radioiodinated human serum albumin (PV)	Data not provided	Pts had low PV when DCI developed and recovery of deficit after volume supplementation
Nelson <sup>30</sup>	1981	Case control	8 pts with hyponatremia after SAH & 4 pts with hyponatremia after other neurosurgical illness & 6 pts without bed rest for elective surgery	8 RCV 8 PV	<sup>51</sup> Cr-labelled autologous erythrocytes (RCV) Radioiodinated human serum albumin (PV)	No restriction of fluid intake, no diuretics	10/12 pts with hyponatremia had a decreased blood volume, 2/12 had an increased blood volume compared to controls

Rudehill <sup>14</sup>	1983	Case series	7 pts after SAH on operating room	7	<sup>125</sup> I- Radioiodinated human serum albumin (PV)	Data not provided	Pre-operative PV after SAH was lower than normal values
Solomon <sup>3</sup>	1984	Case control	25 pts after SAH & 11 non-SAH pts	31	<sup>51</sup> Cr-labelled autologous erythrocytes (RCV)	Not standardised IV fluids on maintenance basis (1800 ml/day) only	Female pts after SAH had lower RCV than control pts Pts with DCI had a higher incidence of decreased RCV
Wijdicks <sup>15</sup>	1985	Case series	21 pts after SAH	42	<sup>131</sup> I- Radioiodinated human serum albumin (PV)	Minimal fluid intake 1500 ml/day, no restriction of fluid intake	11/21 pts had a decrease in PV of >10% Hyponatremia after SAH is associated with a decrease in PV Hyponatremia after SAH is associated with a negative sodium balance
Ishiguro <sup>16</sup>	1987	Case control	24 pts after SAH and clipping, with (n=16) or without (n=8) supplemental albumin	44	Radioiodinated human serum albumin (PV)	Induced hypertension with dopamine in all pts Dextran 500 ml every day in all patients 16 pts received 200 ml albumin 25% each day and 8 pts did not	Pts treated with albumin had higher PV than control pts Control patients had already increased PV No relation found between CVP and fluid balance, nor between CVP and CBV
Nelson <sup>17</sup>	1987	Case control	10 pts after SAH & 10 pts with bed rest after neck/back disease & 20 ambulant out-patients with polycythaemia	10 RCV 10 PV	<sup>51</sup> Cr-labelled autologous erythrocytes (RCV) <sup>121</sup> I- Radioiodinated human serum albumin (PV)	5 pts after SAH with GCS<12 received supplementary infusion of 1.5-2 liters per day Data not provided for the other pts in the study	Pts after SAH have a non-significantly lower total blood volume than controls with bedrest Pts after SAH have a significantly lower total blood volume than their predicted value

First Author	Year	Study Design	Population	N of volume measurements in SAH patients	Method of volume measurement	Fluid therapy & blood pressure regulation	Results
Wijdicks <sup>18</sup>	1988	Case series	21 pts after SAH	42	<sup>131</sup> I- Radioiodinated human serum albumin (PV)	Fluid intake > 3 liters per day Fludrocortisone 2dd0.2 mg	Fludrocortisone reduced frequency and severity of hypovolemia after SAH Hyponatremia was associated with PV reduction
Hasan <sup>19</sup>	1989	RCT	91 pts after SAH, with (n=46) or without (n=45) fludrocortisone	193	<sup>125</sup> I- or <sup>131</sup> I- Radioiodinated human serum albumin (PV)	Fluid intake 3 liters per day, 500cc extra for each temp. degree above 38; no antihypertensive drugs; extra fluids when DCI occurred; 46 pts received fludrocortisone 2dd0.2 mg, 45 pts did not (controls)	50% of pts after SAH had a negative sodium balance; Fludrocortisone reduced the incidence of a negative sodium balance but had no effect on the fluid balance Negative sodium balance was associated with a decreased PV and a negative fluid balance Fludrocortisone had no significant influence on PV after 6 or 12 days PV reduction > 10% in 30% of patients
Brazenor <sup>20</sup>	1990	Case series	2 pts after SAH	30 RCV 30 PV	<sup>99</sup> Tc- labelled autologous erythrocytes (RCV) <sup>113</sup> In- Radioiodinated human serum albumin (PV)	> 3 liters intake received per day, fluid balance guided	RCV decreased prior to neurological deterioration CVP, PCWP, heart rate or blood pressure did not reflect the state of CBV or PV



Nelson <sup>21</sup>	1991	Case series	25 pts after SAH	25	<p><sup>125</sup>I- Radioiodinated human serum albumin (PV) Tritiated water (Total Body Water)</p>	<p>Minimum fluid intake 3 liters per day</p>	<p>9/25 pts were hypovolemic (PV &gt;10% decrease) in the first 4 days after SAH Hypovolemia was associated with higher WFNS CT-scan features indicative of raised intracranial pressure occurred more commonly in hypovolemic pts</p>
Diringer <sup>22</sup>	1992	Case series	19 pts after SAH	34	<p><sup>125</sup>I- Radioiodinated human serum albumin (PV)</p>	<p>Fluid intake on average 5.5 liters per day in pts without DCI, 10.0 liters per day in pts with DCI, adjusted to keep the fluid balance positive; hyponatremia corrected with NaCl; induced hypertension &amp; hypervolemia when DCI developed</p>	<p>Excessive fluid supplementation prevented a decrease in PV after SAH (6% had PV &gt; 10% reduced) Excessive fluid supplementation did not prevent hyponatremia, this occurred in 32% of pts DCI developed in 47% of pts</p>
Moq <sup>23</sup>	1995	Case control	98 pts after SAH and early surgery, with (n=51) or without DCI (n=47)	Data not provided	<p><sup>99</sup>Tc- Radioiodinated human serum albumin (PV)</p>	<p>47 pts without DCI received a total fluid intake &lt;3 liters per day 51 pts with DCI were treated with hypervolemic hemodilution with albumin 0.5 l/day &amp; dextran 0.5 l/day, total fluid intake 4-5 l/day; vasopressin to keep the fluid balance positive; sodium supplementation when hyponatremia developed; blood pressure elevation by fluids or vasopressors</p>	<p>Most pts developed hypovolemia on day 5-7 after SAH Triple-H therapy was effective in raising PV in pts with DCI</p>

First Author	Year	Study Design	Population	N of volume measurements in SAH patients	Method of volume measurement	Fluid therapy & blood pressure regulation	Results
Sato <sup>25</sup> Nakagawa <sup>27</sup>	1999 2002	Case control	14 pts in very acute phase after SAH 34 pts after SAH & 20 neurosurgical pts	Data not provided	ICG Pulse Dye Densitometry (CBV)	Data not provided	CBV decreased in the first days after SAH and increased in the following days No complications related to the CBV-measurement by ICG Pulse Dye Densitometry
Mayer <sup>24</sup> Lennihan <sup>26</sup>	1998 2000	RCT	82 pts after SAH, in normovolemic (n=41) or hypervolemic (n=41) group	134	<sup>51</sup> Cr-labelled autologous erythrocytes (RCV)	41 pts in a normovolemia group received IV infusion of 2 l/day, with 250 ml of albumin 5% when CVP <5 or PCWP <7 41 pts in a hypervolemia group received IV infusion of 2 l/day, with 250 ml of albumin 5% when CVP <8 or PCWP <14 When DCI developed pts from the normovolemia group were made hypervolemic & blood pressure was raised	No difference in DCI, fluid balance, sodium balance, blood volume or complications between the 2 groups No difference in global cerebral flow between the 2 groups No difference in complications (of fluid management) between the 2 groups No significant difference in blood volume decrease (31% of hypervolemic pts had a reduction of calculated PV of more than 10% vs. 43 pts of normovolemic pts)

Kasuya <sup>28</sup>	2003	Case control	50 pts after SAH & 21 other neurosurgical pts	200	ICG Pulse Dye Densitometry (CBV)	<p>Pts after SAH had fluid intake depending on their caloric needs; supplied by parenteral feeding;</p> <p>CBV was decreased on day 2-3 compared to controls and increased in the following days</p> <p>CBV could not be predicted with 'routine' hemodynamic measurement techniques</p> <p>hyponatremia was corrected with sodium;</p> <p>Pts with higher WFNS had a higher incidence of low CBV</p> <p>SAH pts were treated with nicardipine intracranially.</p> <p>Data not provided for the other pts in the study</p>
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ADH = anti diuretic hormone; CBV = circulating blood volume; CVP= central venous pressure; DCI = delayed cerebral ischemia; GCS = Glasgow Coma Scale; Ht = hematocrit; ICG = indocyanine green; N = number; PCWP = pulmonary capillary wedge pressure; Pts = patients; PV = plasma volume; RCT = randomized controlled trial; RCV = red cell volume; SAH = subarachnoid hemorrhage; Triple-H therapy: hypervolemia, hemodilution & hypertension; WFNS = world federation of neurological surgeons grading scale

Repeated measurements of plasma volume were used to guide fluid therapy in one case-series of three patients who developed DCI after SAH.<sup>13</sup> Fluid therapy was guided by the fluid balance in 3 studies<sup>20,22,23</sup>, by filling pressures in 2 studies<sup>24,26</sup>, by caloric needs in one study<sup>28</sup>, and adjusted on the basis of the body temperature in one study.<sup>19</sup> In 11 studies no information on the guidance of fluid therapy was provided.<sup>2,3,14-18,21,25,27,30</sup> There were no studies comparing the use of blood volume measurement to the use of other parameters to guide volume management. There were also no studies in which blood volume measurement was used to ascertain that normovolemia was maintained after SAH.

### ***Blood volume and Delayed Cerebral Ischemia***

Six studies, with a total of 131 included patients, reported on the relationship between blood volume and DCI after SAH.<sup>3,13,20,22,24,26</sup> Two of these studies were very small case series (2 and 3 patients), in which a reduction in red cell volume and in plasma volume was observed prior to the development of DCI.<sup>3,13,20</sup> One case control study found that 6 out of 7 patients with DCI (symptomatic vasospasm) had a decreased red cell volume, while only one out of 8 patients with asymptomatic vasospasm after SAH had a decreased measured volume.<sup>3</sup>

Three other studies (totaling 101 patients) did not show a relation between blood volume and DCI.<sup>22,24,26</sup> In one of these studies, patients were treated with large fluid intakes (on average 5.5 l/day for patients without DCI; 10.0 l/day for patients with DCI). With this fluid policy, a reduction in blood volume was observed infrequently (in 6% of patients). The incidence of DCI (47%) was not reduced in this study, in comparison to previous studies on DCI. Two articles presented data on the same study.<sup>24,26</sup> In this RCT there was no difference in the incidence of DCI (20%) between patients treated with fluid policies aimed at either normovolemia or hypervolemia.

### ***Complications of blood volume measurement***

One report stated that there were no complications related to the blood volume measurements.<sup>27</sup> The other 18 studies provided no information on complications.

## Discussion

Interpretation of the data from the studies included in this review is severely hampered because of methodological problems. These studies often described small numbers of patients after SAH, with single or few measurements of blood volume in each patient. Control group patients appeared to be quite dissimilar from the often severely ill SAH patients. None or very little information on hemodynamic therapy is supplied in many of the reports, either for SAH patients or for control group patients. Goals of hemodynamic therapy were often unclear, as was the way fluid therapy was guided. The described treatment regimes differed to such an extent that no conclusions can be drawn regarding their effect on volume status.

Several studies in our review observed a reduction in red cell volume, plasma volume or circulating blood volume after SAH, especially during the first days after the hemorrhage. There is also an indication that patients developing DCI are more often hypovolemic than patients without DCI. These results have strongly influenced the ideas on treatment after SAH and maintenance of a normal or raised blood volume is nowadays widely seen as an important part of treatment after aneurysmal SAH.<sup>6,31</sup> Hypervolemia is often used as a constituent of triple H therapy, to prevent or treat DCI after SAH.<sup>32,33</sup> However, a positive effect of triple H therapy on DCI and outcome has not been ascertained.<sup>33,34</sup> Whether prevention of hypovolemia is effective to prevent DCI is also uncertain.

A Cochrane review on volume expansion therapy after SAH identified two RCT's that studied this subject, and found no improvement in outcome nor in the occurrence of DCI.<sup>7,26,31</sup> Actual blood volume was measured in only one of the studies included in the Cochrane review.<sup>26</sup> That study found no difference in measured blood volume between patients with either a normovolemic or hypervolemic fluid regime, guided by venous filling pressures. Apparently, the hypervolemic volume status that was aimed for was not consistently reached. A poor relationship between cardiac filling pressures, fluid balance, and measured blood volume was noted in several studies included in the present review.<sup>16,18,20,24,26</sup> This raises serious doubt whether fluid management after SAH can be adequately guided by cardiac filling pressures or fluid balances to maintain volume status. Repeated measurements of blood volume to guide decisions on fluid therapy were only used once.<sup>13</sup> It is not known whether blood volume guided fluid therapy results in better maintenance of volume status and less DCI after SAH.

As an objective of this review was to obtain an overview on available knowledge on blood volume after SAH, we included all studies in which a form of blood volume measurement was used in patients after SAH. This resulted in diversity in included

studies, ranging from small case series to RCT's. We did not limit the review to studies of high methodological quality. We did not attempt a meta-analysis on the available data because of the variations in medical treatment in the different studies.

The results of the present review show there are still many uncertainties about volume status after SAH, the influence of hemodynamic therapy, and the relationship between volume status and DCI. To elucidate these issues, further studies are needed. Preferably studies should be performed in larger patient groups, with multiple measurements of blood volume in each patient. Results of blood volume measurements will always be influenced by the (hemodynamic) treatment applied. Different fluid strategies could be compared as to their effects on blood volume. It is uncertain whether a fluid policy can be adequately guided by fluid balances or venous filling pressures. To ascertain that the intended volume status (normovolemia or hypervolemia) is indeed achieved, repeated blood volume measurements could be used to guide fluid therapy. Next the effect of sustained normovolemia or hypervolemia on DCI and outcome could be studied. At present there is not enough evidence to present a reliable advice on fluid management after SAH.

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## Chapter 3

### Fluid balance and blood volume measurement after aneurysmal subarachnoid hemorrhage

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*Neurocritical Care* 2008; 8: 391-397

## Abstract

*Introduction* Patients with aneurysmal subarachnoid hemorrhage (SAH) are at risk for circulatory volume depletion, which is a risk factor for delayed cerebral ischemia. In a prospective observational study we assessed the effectiveness of fluid administration based on regular evaluation of the fluid balance in maintaining normovolemia.

*Methods* Fifty patients with aneurysmal SAH were included and were treated according to a standard protocol aimed at maintaining normovolemia. Fluid intake was adjusted on the basis of the fluid balance, which was calculated at 6 hour intervals. Circulating blood volume (CBV) was measured by means of pulse dye densitometry on alternating days during the first two weeks after SAH.

*Results* Of 265 CBV measurements, 138 (52 %) were in the normovolaemic range of 60-80 ml/kg; 76 (29 %) indicated hypovolemia with CBV < 60 ml/kg; and 51 (19 %) indicated hypervolemia with CBV > 80 ml/kg. There was no association between CBV and daily fluid balance (regression coefficient  $\beta = -0.32$ ; 95% CI: -1.81 to 1.17) or between CBV and a cumulative fluid balance, adjusted for insensible loss through perspiration and respiration ( $\beta = 0.20$ ; 95% CI: -0.31 to 0.72).

*Conclusion* Calculations of fluid balance do not provide adequate information on actual circulating blood volume after SAH, as measured by Pulse Dye Densitometry. This raises doubt whether fluid management guided by fluid balances is effective in maintaining normovolemia.

## **Introduction**

Aneurysmal subarachnoid hemorrhage (SAH) carries a poor prognosis. In patients who have survived the initial hours after SAH and in whom the aneurysm has been occluded, delayed cerebral ischaemia (DCI) is an important cause of poor outcome. DCI occurs in approximately one third of patients and starts usually 4 to 10 days after the SAH.<sup>1</sup> On admission, predictors for the occurrence of DCI are a depressed level of consciousness and the amount of extravasated blood on the initial CT scan. During the clinical course patients with SAH have a high tendency to develop hypovolemia, which is another risk factor for the development of DCI.<sup>2</sup> Therefore an important goal in the management of patients with SAH is maintaining normovolemia or achieving hypervolemia. However, circulatory volume is difficult to assess on clinical or biochemical grounds.<sup>3</sup> Measuring the so-called filling pressures (central venous pressure, pulmonary capillary wedge pressure) can yield information on the quality of the circulation, but there is a poor relationship between measured pressures and volume.<sup>4;5</sup> Moreover, the necessary central venous lines for measuring these pressures carry their own risk.<sup>6;7</sup>

In many centres, fluid management after SAH is aimed at normovolemia and is guided by calculations of the daily fluid balance of the patient. We performed a prospective observational study to assess if this strategy can maintain a normal circulating blood volume.

## Methods

Approval of the medical ethics committee was obtained. Patients admitted to the UMC Utrecht within 48 hours after aneurysmal subarachnoid hemorrhage of 18 years or older were eligible for inclusion. Eligible patients were asked for participation with written informed consent. If patients had a disturbed level of consciousness, their nearest relatives were asked for consent. Patients were not eligible if death appeared imminent on admission. Patients with accompanying head injury, pregnancy, severe liver- or kidney failure, a known allergy for the indicator dye, or with SAH from causes other than aneurysmal rupture, were excluded.

### *Fluid management protocol*

All patients were treated according to the standard SAH-protocol of the UMC Utrecht. The goal of fluid management was to maintain normovolemia. At admission, each patient was started on intravenous infusion of 3 liters normal saline a day, next to oral intake as desired by the patient. Intravenous fluid administration was adjusted on the basis of the fluid balance, calculated at 6 hour intervals, by subtracting urinary volume from total oral and intravenous intake. The aim was to keep the daily fluid balance at 750 ml positive, to compensate for insensible fluid loss through perspiration and respiration. When the patient developed fever (for more than 6 hours), which increases insensible loss, the desired level for the daily fluid balance was raised by 500 ml for each degree Celsius above 37 degrees. If the desired level for the fluid balance could not be reached, a colloid (Gelofusine) was added (maximum 2 liters/day). If the desired level was still not achieved, the infusion of normal saline was increased. There was no maximum set for the amount of saline that could be administered. When the fluid balance showed a higher than desired level, the infusion of intravenous fluids was decreased. If there were clinical signs of volume overload e.g. pulmonary oedema, a diuretic (furosemide) could be administered. Oral nimodipine 60 mg q. 4h. was started in all patients.

Daily fluid intake, fluid excretion and fluid balance for each patient during the first two weeks after the SAH were collected in the study database.

### *Measurement of blood volume*

Circulating blood volume was measured by means of Pulse Dye Densitometry (PDD) on alternating days, for a total of six times during the first two weeks after the SAH.

PDD is a technique developed in Japan by Nihon Kohden Corporation.<sup>8</sup> PDD uses pulse spectrophotometry, as developed for pulse oximetry, for measurement of dye concentration. A sensor is placed on a finger or nostril of the patient. Ten milligrams of the dye indocyanine green (ICG) (SERB Laboratoires Pharmaceutiques, Paris, France) is injected into a peripheral or central vein. Continuous spectrophotometric measurement of dye concentration results in a dye densitogram. Extrapolation of the initial dye concentration regression line in the dye densitogram to the moment of injection of the dye yields the concentration of the dye directly after administration when no elimination has taken place. Dividing the amount of injected dye by this dye concentration immediately at injection gives the value for circulating blood volume.

### ***Definitions***

Normal values for circulating blood volume were defined as a measured circulating blood volume of 60–80 ml per kg body weight.<sup>9;10</sup> Hypovolemia was defined as a circulating blood volume of less than 60 ml/kg, severe hypovolemia as less than 50 ml/kg, and hypervolemia as a blood volume of more than 80 ml/kg.

Delayed cerebral ischemia (DCI) was defined as a decrease in level of consciousness of at least two points on the Glasgow Coma Scale for at least three hours, the appearance of a focal neurological deficit, or both, after exclusion of rebleeding, hydrocephalus, infection or of metabolic causes for deterioration. Adverse effects of ICG administration were defined as any change in clinical condition, directly following or possibly related to, the intravenous injection of the dye. Adverse effects were categorized as minor (e.g. pain on injection, itching, nausea, decrease in mean blood pressure of more than 20 mmHg) or major (any change in condition requiring treatment).

The clinical condition on admission was classified according to the World Federation of Neurosurgical Surgeons scale.<sup>11</sup> Neurological outcome was assessed at 3 months after the SAH with the Glasgow Outcome Scale.<sup>12</sup>

All data were collected prospectively on a daily basis. Medical and nursing staffs were not informed on the results of the measurements of the circulating blood volume. The investigators performing the measurements were not involved in the care for the included patients.

### ***Statistical analysis***

Data on CBV and fluid intake, fluid excretion and fluid balance were grouped into 2 day periods. We analyzed for differences in CBV, fluid intake, fluid excretion and

fluid balance between periods using Friedman's ANOVA for non-normally distributed data in related groups. To analyze the CBV changes on an individual level, we calculated the 'normal' blood volumes for all patients using the formula of the International Committee for Standardization in Haematology.<sup>13</sup> Each CBV measurement was compared to the normal value of the particular patient and then expressed as percentage increase or decrease of this normal value (CBV deviation). An adjusted fluid balance was calculated by subtracting from the daily fluid balance a volume of 750 ml and the compensation for a rise in temperature. The cumulative adjusted fluid balance was the daily total of all previous daily adjusted fluid balances for a patient.

A scatter plot was drawn for CBV and fluid balance, for CBV and cumulative adjusted fluid balance, as well as for CBV deviation and cumulative adjusted fluid balance; the relationships were described with the regression coefficients and corresponding 95% confidence intervals from linear regression analysis. A relative risk was calculated with its corresponding 95 % confidence interval to describe the relationship between severe hypovolemia and the occurrence of DCI, and between a negative cumulative adjusted fluid balance and DCI.



## Results

Fifty patients were entered in the study between May 2003 and April 2004. Patient characteristics are listed in *table 1*. Ten patients died during the clinical course and therefore did not complete the study period. None of the patients withdrew consent during the study.

**Table 1**  
*Patient characteristics*

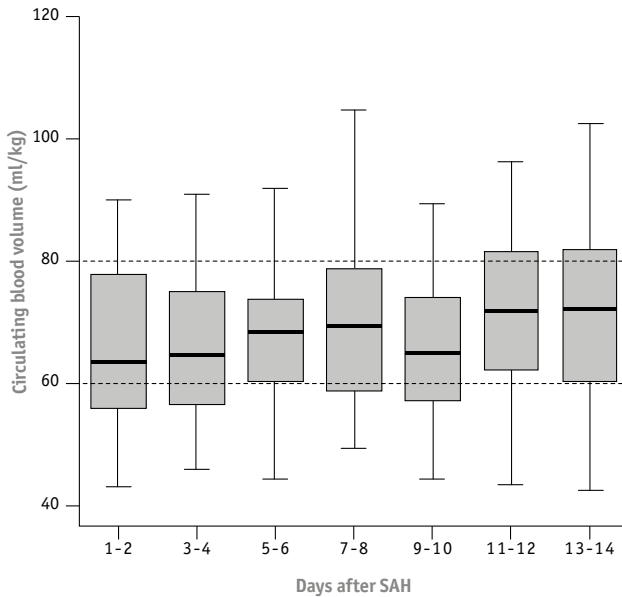
<b>Number of patients</b>	50
<b>Women</b>	37 (74 %)
<b>Age in years (SD)</b>	54 (15)
<b>Admission WFNS-grade</b>	
I	24 (48 %)
II	7 (14 %)
III	2 (4 %)
IV	12 (24 %)
V	5 (10 %)
<b>Location of aneurysm</b>	
Anterior	21 (42 %)
Carotid	12 (24 %)
Middle	10 (20 %)
Posterior	7 (14 %)
<b>Glasgow Outcome Scale at 3 months</b>	
1	10 (20 %)
2	0 (0 %)
3	3 (6 %)
4	9 (18 %)
5	28 (56 %)

SD = Standard Deviation

WFNS = World Federation of Neurological Surgeons

A total of 265 measurements of circulating blood volume (CBV) was performed, with a mean CBV of 68 ml/kg (+/- 13 ml/kg). Of these 265 measurements, 76 (29 %) were in the hypovolaemic range, 138 (52 %) in the normovolaemic range, and 51 (19 %) in the hypervolaemic range. Of all patients, 31 (62 %) had at least one

measurement in the hypovolaemic range. Eleven patients (22 %) had measurements in the severe hypovolaemic range, most of which (14 out of 18 measurements, in 9 patients) occurred in the first week after SAH. Twenty-one patients (42 %) had at least one measurement in the hypervolaemic range, most of which (30 out of 51 measurements) in the second week after SAH. Distribution of the CBV values according to the number of days after the SAH is shown in *figure 1*.



**Figure 1**

*Box plot of circulating blood volume (ml/kg) at different time periods after subarachnoid hemorrhage (SAH). Indicated are median values, interquartile range and spreading. Normal values for circulating blood volume are between 60 and 80 ml/kg.*

Mean CBV in the first period was 65 ml/kg (+/- 13 ml/kg). There was an increase over the intermediate periods to a mean CBV on day 13-14 of 71 ml/kg (+/-15 ml/kg) with a mean difference of 3.9 ml/kg (95 % CI: -3.7 to 11.6).

After 3 of the 265 dye injections (1.1 %), patients experienced local pain or itching at the site of IV administration of the dye for a few seconds. There were no other minor or major adverse effects.

A total of 656 daily fluid balances was collected. Mean daily fluid balance was 571 ml positive (+/- 998 ml). In *table 2*, the mean fluid intake, fluid excretion and fluid balance for the different periods after the SAH are presented. Over the first 14 days

after SAH, daily fluid intake as well as fluid excretion increased, while fluid balance declined (mean difference first to last period -0.71 liter; 95% CI: -0.27 to -1.1).

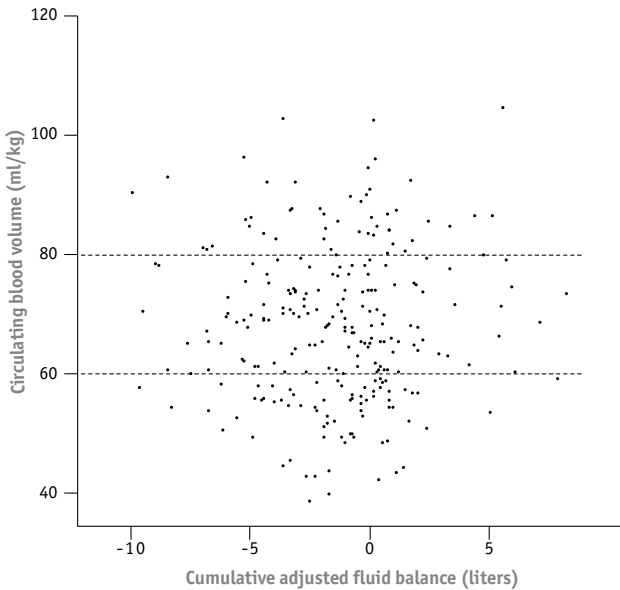
**Table 2**

*Daily fluid balance after subarachnoid hemorrhage*

Period	day 1-2	day 3-4	day 5-6	day 7-8	day 9-10	day 11-12	day 13-14
Fluid intake	3.3 (1.1)	4.1 (1.0)	4.9 (1.1)	5.1 (1.2)	5.2 (1.4)	5.2 (1.7)	5.1 (1.5)
Fluid excretion	2.3 (0.8)	3.6 (1.3)	4.2 (1.2)	4.4 (1.5)	4.8 (1.5)	4.8 (1.8)	4.8 (1.8)
Fluid balance	+1.1 (0.8)	+0.5 (0.9)	+0.7 (0.9)	+0.6 (0.7)	+0.4 (0.6)	+0.4 (0.6)	+0.3 (0.8)

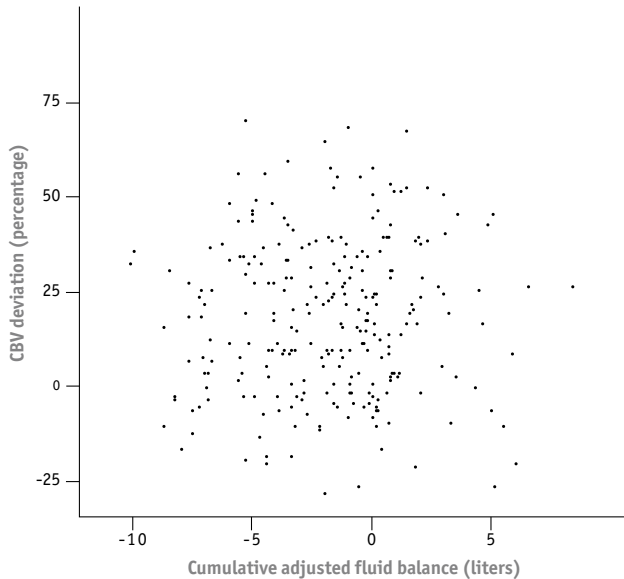
Presented are mean values in liters with standard deviation

There was no correlation between daily fluid balance and CBV (regression coefficient  $\beta = -0.32$ ; 95% CI: -1.81 to 1.17) or between the cumulative adjusted fluid balance and CBV ( $\beta = 0.20$ ; 95% CI: -0.31 to 0.72) (*figure 2*) or between the cumulative adjusted fluid balance and CBV deviation ( $\beta = 0.19$ ; 95% CI: -0.60 to 0.98) (*figure 3*).



**Figure 2**

*Scatter plot of cumulative adjusted fluid balance (liters) and circulating blood volume (ml/kg). Cumulative adjusted fluid balance is the daily total of all previous daily fluid balances, adjusted for insensible loss. Normal values for circulating blood volume are between 60 and 80 ml/kg.*



**Figure 3**

*Scatter plot of cumulative adjusted fluid balance (liters) and circulating blood volume (CBV) deviation (in percentage of individual normal CBV). Cumulative adjusted fluid balance is the daily total of all previous daily fluid balances, adjusted for insensible loss.*

DCI occurred in 24 patients (48%). Of the 9 patients with at least one measurement of CBV in the severe hypovolaemic range in the first week after SAH, 7 patients (78%) developed DCI. Of the 41 patients without severe hypovolemia in the first week, 17 (42%) developed DCI. The relative risk for DCI with severe hypovolemia in first week was 1.9 (95% CI: 1.1 to 3.1). Two patients had one measurement of CBV in the severe hypovolaemic range in the second week after SAH only. These two patients did not develop DCI. For all 11 patients with one or more severe hypovolaemic periods the relative risk for DCI was 1.5 (95% CI: 0.8 to 2.6). A negative value of the cumulative adjusted fluid balance on any day during the first 2 weeks after SAH was not associated with DCI. Twenty two patients (44%) had one or more days in the first week after SAH with a cumulative adjusted fluid balance being more than 2 liters negative. Ten of these patients developed DCI. The relative risk for DCI was 0.91 (95% CI: 0.51 to 1.6). Fourteen patients (28%) had a cumulative adjusted fluid balance of more than 3 liters negative in the first week; the relative risk for DCI was 0.68 (95% CI: 0.31 to 1.5).

## Discussion

The results of this prospective observational study indicate that fluid balances do not provide adequate information on actual circulating blood volume in patients with SAH, as measured by Pulse Dye Densitometry. This raises doubt whether fluid management based on fluid balances is effective in maintaining normovolemia.

An adequate blood volume in the cardiovascular system is essential to maintain cardiac output and tissue perfusion.<sup>10;14</sup> We defined normovolemia as a measured circulating blood volume of 60-80 ml/kg body weight, in accordance with previous studies where a value of approximately 70 ml/kg for adults was used.<sup>9;10</sup> However, this definition of “normal blood volume” is a simplification. Normal blood volume varies depending on age (elder patients have smaller blood volumes), sex (women have smaller blood volumes), and stature (obese patients have a smaller blood volume on a per kg basis than lean patients).<sup>13</sup> Furthermore, little is known about the changes in blood volume that occur as a result of illness or therapy.<sup>14</sup> For this reason, we used wide margins (60-80 ml/kg) in our definition of normovolemia. Even with these margins, one of every three measurements in our study was found to be hypovolaemic, and one of every five hypervolaemic. The absence of an association between fluid balance or cumulative adjusted fluid balance on the one hand, and measured blood volume or CBV deviation on the other hand, was not influenced by our definition of normovolemia. This absence of association further underscores the inadequacy of the management of circulating blood volume on the basis of the fluid balance only.

We used Pulse Dye Densitometry for sequential measurement of the circulating blood volume. This relatively new technique has been validated in comparison with the standard isotope-dilution techniques for measurement of blood volume in a number of small patient series.<sup>8;9;15-18</sup> Pulse Dye Densitometry is minimally invasive, does not need radioactive tracers, is easy to perform at the bedside, and has a low risk of adverse effects. Because of rapid hepatic elimination of the dye (within 10-15 minutes), measurements can be repeated after a short time period, in contrast with the isotope-dilution techniques. A disadvantage is that the pulse-spectrophotometric signal can be distorted by movement or by inadequate tissue perfusion. For this reason, in some patients the measurement had to be repeated after half an hour or longer to get reliable results. In one patient in our study, measurements in the second week were not possible due to persistent unrest.

Several investigators have measured blood volume after SAH. Studies from the seventies and eighties of the previous century showed a reduction in red cell volume, plasma volume and total circulating blood volume.<sup>2;19;20</sup> In these studies, fluid

intake was deliberately kept low or data on fluid intake were not provided. Because later studies showed an association between hypovolemia and hyponatraemia, and between hypovolemia and DCI, it became common practice to increase the fluid intake after SAH.<sup>21</sup> Aim was to maintain normovolemia or even achieve hypervolemia.<sup>22</sup> In the present study, large fluid intakes were used in an effort to keep the fluid balance positive, but nevertheless measured blood volume was frequently in the hypovolaemic range. In a previous study on the impact of large volume infusion on intravascular volume in 19 patients after SAH, blood volumes were measured on the day of admission and after 7-10 days and no hypovolemia was observed.<sup>23</sup> In our study, most hypovolaemic measurements were observed in the first week after SAH, which might explain the apparently discrepant findings. In a randomized controlled trial on the effects of a hypervolaemic versus a normovolaemic treatment protocol, blood volume was measured twice in the first week after SAH, and a decrease in volume of more than 10 % occurred in about a third of the patients in both study groups.<sup>5</sup> A reduction in blood volume during the first days after SAH has been observed in other studies using Pulse Dye Densitometry, but none of these studies provided quantitative data on fluid management.<sup>24-26</sup>

In the present study fluid balance was used as a guide for fluid administration. Over the first two weeks after SAH, the fluid supply was increased considerably but this was offset by an increase in urine excretion, resulting in a progressive decline of the fluid balance. This was accompanied by a small (non-significant) increase in mean circulating blood volume. Severe hypovolemia was most often observed during the first week after SAH when actually fluid balance was higher than in the second week. An explanation might be found in the occurrence of a systemic inflammatory response syndrome (SIRS) during the first days after SAH.<sup>27</sup> SIRS leads to capillary leakage and interstitial edema, with loss of fluid from the blood vessels. The resulting fluid retention by the kidneys reduces fluid excretion and thereby can lead to an increase in positive value of the fluid balance. This in turn leads the treating physicians to reduce fluid intake, which could then aggravate circulatory volume depletion. When the SIRS diminishes after some days, the interstitial edema disappears with reuptake of fluid in the circulation, which leads to an increase in blood volume and thereby an increase in urine production. The resulting negative fluid balance then leads the treating physicians to, inappropriately, increase fluid intake.

A number of limitations of this study should be mentioned. Although we assessed circulating blood volume without informing the treating physicians, treatment may have been influenced by the fact that the treating physicians were aware that measurements of blood volume were performed. This may have resulted in extra attention for fluid management. However, in spite of this, we found a high frequency of

hypovolemia. We evaluated changes in blood volume and fluid balance at a group level, not at the level of an individual patient. The small increase in CBV together with a less positive fluid balance over time we observed at group level may have been different for an individual patient.

Previous studies found an incidence of DCI of 20 tot 50 %.<sup>23;28</sup> The incidence of DCI we observed (48%) was at the high end of this spectrum. DCI was defined as a clinical condition. In the UMC Utrecht, transcranial Doppler (TCD) or cerebral angiography are not routinely used to screen for vasospasm because of the poor relation between signs of vasospasm and actual neurological deficits.<sup>29-31</sup> We did not deem CT-scan evidence of brain infarction as a necessary factor for diagnosing DCI. Symptoms of DCI are seen when blood supply does not meet the demand of the brain tissue; whether brain infarction eventually develops as a result of DCI depends on a variety of factors.<sup>32</sup> We found a significant association between hypovolemia and DCI, but we did not control for other factors, known to be associated with DCI. A negative value of the cumulative adjusted fluid balance was not associated with DCI.

Our study population had the typical characteristics for patients after SAH. However, the study population was too small to assess whether specific subgroups of patients were at a higher risk for volume depletion or for deviations in the fluid balance.

Calculations of fluid balance do not provide adequate information on circulating blood volume in patients with SAH, as measured by Pulse Dye Densitometry. Whether fluid management guided by fluid balances is effective in maintaining normovolemia is uncertain. Our study did not answer the question if it is actually possible to maintain normovolemia in the first weeks after SAH. And it remains to be assessed if consistently maintained normovolemia will result in better neurological outcome.

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## Chapter 4

### Nurses' prediction of volume status after aneurysmal subarachnoid hemorrhage: a prospective cohort study

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*Critical Care 2008, 12: R153 (1-5)*

## Abstract

*Introduction* Patients after aneurysmal subarachnoid hemorrhage (SAH) often have derangements in blood volume, contributing to poor outcome. To guide fluid management, a regular assessment of the volume status has to be made. We studied the ability of nursing staff to predict hypo- or hypervolemia, based on their interpretation of available hemodynamic data.

*Methods* In a prospective cohort study ICU- and Medium Care Unit (MCU) nurses, currently treating patients with recent SAH, were asked to predict the present volume status. For their assessment they could use all available hemodynamic parameters (e.g. heart rate, blood pressure, fluid balance). The nurses' assessments were compared with the actual circulating blood volume (CBV) as measured daily with pulse dye densitometry during the first 10 days after SAH. Normovolemia was defined as a CBV of 60–80 ml per kg body weight; hypovolemia as  $CBV < 60$  ml/kg; severe hypovolemia as  $CBV < 50$  ml/kg; and hypervolemia as  $CBV > 80$  ml/kg.

*Results* A total of 350 combinations of volume predictions and CBV measurements was obtained, in 43 patients. The nurses' prediction of hypovolemia had a sensitivity of 0.10 (95%CI: 0.06–0.16) and a positive predictive value of 0.37 (0.23–0.53) for actual hypovolemia. The prediction of hypervolemia had a sensitivity of 0.06 (0.01–0.16) and a positive predictive value of 0.06 (0.02–0.19) for actual hypervolemia. Mean CBV was significantly lower in instances considered hypervolemic than in instances considered normovolemic.

*Conclusion* The assessment of the hemodynamic condition in patients with SAH by ICU- or MCU-nurses does not adequately predict hypo- or hypervolemia as measured with pulse dye densitometry. Fluid therapy after SAH may have to be guided by more advanced techniques than the interpretation of usual hemodynamic parameters.

## **Introduction**

Patients with aneurysmal subarachnoid hemorrhage (SAH) often have derangements in blood volume.<sup>1</sup> Hypovolemia in these patients is associated with a higher risk of delayed cerebral ischemia, whereas hypervolemia increases the risk of pulmonary edema and cardiac failure.<sup>2</sup> Fluid management after SAH is therefore aimed at maintaining normovolemia.<sup>3</sup> To guide fluid management, a regular and accurate assessment of the current volume status has to be made, and such assessments are usually based on the available hemodynamic data. In our experience, nurses are often involved in these assessments and in the decisions on fluid management. We studied the ability of nursing staff to adequately predict hypo- or hypervolemia in patients with SAH.

## Materials and methods

We performed a prospective cohort study in patients admitted within 72 hours after aneurysmal SAH. The study setting was the 30-bed general Intensive Care Unit (ICU; 150 nurses) and the 7-bed neurological Medium Care Unit (MCU; 18 nurses) of the University Medical Center Utrecht. The hospital has a case load of around 150 SAH patients per year. Patients with SAH in good or reasonable clinical condition (WFNS grade 1-3) were mostly admitted to the MCU, patients in poorer condition (WFNS grade 4-5) were admitted to the ICU, as were patients in need of artificial ventilation or inotropic support.

The Medical Ethics Research Committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from the patients or, in case of impaired consciousness, from legal representatives. The study period was day 1 to day 10 after the SAH. Patients were treated according to current standard therapy, aimed at early treatment of the aneurysm by coiling or clipping and maintenance of normal vital functions. The goal of fluid management was to maintain normovolemia. Fluid administration was adjusted on the basis of the fluid balance, calculated at 6 hour intervals, by subtracting urinary volume from total oral and intravenous intake. The aim was to keep the daily fluid balance at 750 ml positive, to compensate for insensible fluid loss through perspiration and respiration. When the patient developed a fever (for more than 6 hours) the desired level for the daily fluid balance was increased by 500 ml for each degree Celsius above 37 degrees to allow for increased insensible loss.

Nurses could participate in the study if they had finished their supplementary training as ICU or MCU nurse. They were asked to complete a brief questionnaire, indicating their opinion on current volume status as hypo-, normo-, or hypervolemic. Nurses were allowed to use all available parameters to form their opinion but were to refrain from consulting other nurses or doctors. The parameters the nurses used included heart rate, arterial and central venous blood pressure, fluid balance, urine production and the presence of edema. On each day during the study period, only one questionnaire could be filled in by each individual nurse for the one patient whom this nurse was taking care of on that day. The questionnaire was linked to the patient but no data on individual nurses were collected, to ensure anonymity of the nurses and thereby removing any fear that data could be used for individual quality control. The nurses were not informed on the accuracy of their predictions.

Circulating blood volume (CBV) was measured daily with pulse dye densitometry (PDD), a bed-side dye dilution technique that was previously validated and has been used before in patients after SAH.<sup>4-6</sup> Normovolemia was defined as a meas-

ured CBV of 60-80 ml per kg body weight, hypovolemia as  $CBV < 60$  ml/kg, severe hypovolemia as  $CBV < 50$  ml/kg, and hypervolemia as  $CBV > 80$  ml/kg.<sup>7-9</sup>

We compared the nurses' prediction of the volume status with the actual CBV. We considered the combinations of the nurses' predictions with the measured CBV values (denoted further on as 'instances') to be independent observations because different nurses assessed volume status at different days.

For analysis we compared mean CBV between instances that were considered hypo-, normo- or hypervolemic and calculated mean differences with corresponding 95% confidence intervals taking normovolemia as reference. We calculated the prior probability, sensitivity, specificity, positive and negative predictive value (with their corresponding 95% confidence intervals) for the prediction of hypo- or hypervolemia. Prior probability was defined as the number of instances with the condition (hypo- or hypervolemia) present, as proportion of the total number of instances. Sensitivity was the probability that the prediction was positive (hypo- or hypervolemia present) if the predicted condition was actually present. Specificity was the probability that the prediction was negative (no hypo- or no hypervolemia) if the condition was absent. Positive predictive value was the probability for any particular positive prediction (hypo- or hypervolemia present) that it was correct (true positive). Negative predictive value was the probability for any particular negative prediction (no hypo- or no hypervolemia) that the condition was indeed absent (true negative).

Calculations were made with VassarStats: Website for Statistical Computations.<sup>10</sup> These calculations were made for all instances combined, and separately for instances in the absence or presence of artificial ventilation or inotropics.

## Results

Between January 2006 and June 2007 nurses' questionnaires were collected on 43 patients. Clinical characteristics are provided in *table 1*. The study period of 10 days was completed by 38 patients (88%); 3 patients died within the study period, one patient withdrew consent, and one patient was transferred to another hospital.

**Table 1**  
*Patient characteristics*

<b>Number of patients</b>	43
<b>Women</b>	32 (74 %)
<b>Age in years (mean <math>\pm</math> SD)</b>	56.6 $\pm$ 14.0
<b>Clinical condition on admission</b>	
WFNS-1	22 (51 %)
WFNS-2	6 (14 %)
WFNS-3	4 (9 %)
WFNS-4	9 (21 %)
WFNS-5	2 (5 %)
<b>Treatment of the aneurysm</b>	
Coiling	27 (63 %)
Clipping	13 (30 %)
<b>Outcome at 3 months after SAH</b>	
mRS-0	2 (5 %)
mRS-1	10 (23 %)
mRS-2	8 (19 %)
mRS-3	10 (23 %)
mRS-4	0 (0 %)
mRS-5	5 (12 %)
dead	8 (19 %)

SD = Standard Deviation

WFNS = World Federation of Neurological Surgeons grading scale

mRS = modified Rankin Scale

A total of 350 combinations of a filled-in questionnaire and a CBV measurement was obtained. CBV varied considerably in individual patients. None of the 43 included patients had all measurements in the normovolemic range (60-80 ml/kg). Twelve



patients (28%) had blood volume measurements during the study period spread over the hypo-, normo-, and hypervolemic range. Fifteen patients (35%) had measurements in both the hypo- and normovolemic range; 9 patients (21%) had measurements in both the normo- and hypervolemic range; 7 patients (16%) had only measurements indicating hypovolemia. Also the predictions by the nurses of volume status varied considerably on consecutive days. In only 9 patients (21%) normovolemia was considered present by the nurses on all measurement days.

*Table 2* presents a comparison of mean CBV for the instances classified by the nurses as hypo-, normo- or hypervolemic. If nurses predicted hypervolemia, mean CBV was 8.4 ml/kg (95% CI: 3.7 to 13.1) lower than if they predicted normovolemia. There was no significant difference in mean CBV between hypovolemic or normovolemic predictions.

**Table 2**

*Predicted volume status and measured CBV*

Predicted volume status	Number of predictions (%)	CBV (ml/kg) (mean $\pm$ SD)
Hypovolemia	41 (12%)	66.9 $\pm$ 16.9
Normovolemia	262 (75%)	65.0 $\pm$ 15.2
Hypervolemia	47 (13%)	56.6 $\pm$ 14.3

CBV = circulating blood volume

SD = standard deviation

CI = confidence interval

*Table 3* presents the test characteristics for the nurses' predictions of hypo- or hypervolemia. Of 41 hypovolemic predictions, measured CBV was in 15 instances in the hypovolemic range (< 60 ml/kg) and was in 6 instances severe hypovolemic (CBV < 50 ml/kg). Of the 309 instances with predicted normo- or hypervolemia, 139 had measured hypovolemia and 57 of these had severe hypovolemia. Of the 47 hypervolemic predictions, 3 had measured hypervolemia. Of the 303 predictions of normo- or hypovolemia, measured CBV was in the hypervolemic range in 51 instances.

In 47 instances (13%) artificial ventilation was used and in 32 instances (9%) inotropics. For instances with or without artificial ventilation, and with or without inotropics, there were no essential differences in sensitivity, specificity or predictive values for the nurses' predictions.

**Table 3***Predictive values*

<b>Predicted hypovolemia and measured hypovolemia (CBV &lt; 60 ml/kg)</b>	
Prior probability	0.44 (0.39 – 0.49)
Sensitivity	0.10 (0.06 – 0.16)
Specificity	0.87 (0.81 – 0.91)
Positive predictive value	0.37 (0.23 – 0.53)
Negative predictive value	0.55 (0.49 – 0.61)
<b>Predicted hypovolemia and measured severe hypovolemia (CBV &lt; 50 ml/kg)</b>	
Prior probability	0.18 (0.14 – 0.23)
Sensitivity	0.10 (0.04 – 0.20)
Specificity	0.88 (0.83 – 0.91)
Positive predictive value	0.15 (0.06 – 0.30)
Negative predictive value	0.82 (0.77 – 0.86)
<b>Predicted hypervolemia and measured hypervolemia (CBV &gt; 80 ml/kg)</b>	
Prior probability	0.15 (0.12 – 0.20)
Sensitivity	0.06 (0.01 – 0.16)
Specificity	0.85 (0.80 – 0.89)
Positive predictive value	0.06 (0.02 – 0.19)
Negative predictive value	0.83 (0.78 – 0.87)

Values are presented with corresponding 95% confidence interval

## Discussion

The interpretation of the volume status by ICU- or MCU nurses does not correspond with the actual presence of hypo- or hypervolemia in patients with SAH. Deviations from normovolemia occurred frequently but most instances were not recognized as such, which resulted in a very low sensitivity of the predictions. The positive predictive values of the nurses' predictions were even slightly lower than the prior probabilities of (severe) hypovolemia or hypervolemia. If hypervolemia was predicted, in fact a statistically significant lower CBV was found than if normo- or hypovolemia was predicted. In most instances no (severe) hypovolemia or hypervolemia was present. Therefore a negative prediction (no hypovolemia; no hypervolemia) was usually correct, resulting in higher values for specificity and also higher negative predictive values.

Assessment of the patient's condition is a fundamental part of critical care nursing and optimizing the hemodynamic situation can be seen as a team-effort.<sup>11</sup> One of the important factors determining quality of the circulation is the amount of circulating blood.<sup>8</sup> We defined normovolemia as a measured CBV of 60-80 ml/kg body weight, in accordance with previous studies where a value of approximately 70 ml/kg for adults was found.<sup>5,7-9</sup> This definition of "normal blood volume" is a simplification as blood volume varies depending on age, sex, and build. Furthermore, the changes in blood volume that occur in critical illness are understood incompletely.<sup>12</sup> Therefore we used fairly wide margins (60-80 ml/kg) in our definition of normovolemia and defined the threshold for severe hypovolemia (< 50 ml/kg) in accordance with the level that was previously shown to be associated with an increased risk of secondary ischemia after SAH.<sup>13</sup>

None of the clinical signs normally used to monitor the circulation (e.g. arterial or venous pressure) has a consistent relation with fluid responsiveness or with measured blood volume.<sup>14</sup> Dynamic indicators such as pulse pressure variation may have a better relation with fluid responsiveness in critically ill patients, but the relation with blood volume is not yet clear.<sup>15</sup> Blood volume itself, albeit an important determinant of preload, is only one of the factors determining the adequacy of tissue perfusion. To evaluate the current volume status, many hemodynamic parameters must be taken into consideration together and seen in the context of the overall clinical condition.<sup>16</sup> This interpretation remains therefore quite difficult, as is underscored by our results.

A limitation of our study is that the 350 combinations of CBV measurements and nurses' predictions were obtained from 43 patients. In each patient multiple CBV measurements were made, albeit on different days, and therefore these are not independent measurements in a strict sense. However, for practical purposes we

considered the combinations of these daily measurements with the nurses' predictions to be independent observations because of the large variation in measured blood volume in individual patients on consecutive days, the large number of nurses who made the predictions and the large variation in the predictions that were made.

We did not collect data on the nurses' motivations for predicting hypo- or hypervolemia. Most nurses have ample experience with this patient category because our hospital has a relatively large annual load of patients after SAH. We cannot explain with any certainty the large discrepancy between the prediction and the actually measured CBV. An explanation might be that as patients had a fluid policy based on fluid balances, a more positive fluid balance may have been seen as an indication for hypervolemia. In a previous study on CBV after SAH the relation between fluid balance and CBV was actually very poor.<sup>13</sup> Furthermore we can not ascertain if the observed low predictive values are the result of a poor correlation between hemodynamic parameters available to the nurses and measured blood volume or by poor interpretation of these parameters by the nurses. We did not study if the treating physicians were more accurate in their predictions.

## Conclusion

Hypovolemia and hypervolemia occurred frequently after SAH but were often not recognized as such. The nurses' predictions of current volume status do not seem sufficiently reliable to serve as a basis for therapeutic decisions. More advanced techniques for bedside assessment of volume status may be indicated for optimizing volume status in patients with SAH.

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## Chapter 5

### **Blood volume measurement to guide fluid therapy after aneurysmal subarachnoid hemorrhage: a prospective controlled study**

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*Stroke* 2009; 40: 2575-2577

## Abstract

**Background** Conventional parameters used to guide fluid therapy after aneurysmal subarachnoid hemorrhage (SAH) are poorly related to circulating blood volume. In a prospective controlled study we assessed whether fluid management guided by daily measurements of circulating blood volume (CBV) reduces the incidence of severe hypovolemia compared to conventional fluid balance guided fluid therapy.

**Methods** We used Pulse Dye Densitometry to measure CBV daily in 102 patients during the first ten days after SAH. Fluid management was based on CBV measurements in the intervention group (n=54) and on fluid balance in the control group (n=48). Severe hypovolemia was defined as CBV <50 ml/kg.

**Results** In the intervention group 6.7% of CBV measurements were in the severe hypovolemic range and in the control group 17.1% (mean weighted difference 7.7%; 95%CI:1.4-13.9%). In the intervention group 21 patients (39%) had one or more measurements with severe hypovolemia versus 26 (54%) of the controls (RR 0.7; 95%CI:0.5-1.1).

**Conclusion** Guiding fluid management on daily measurements of circulating blood volume reduces the incidence of severe hypovolemia after SAH. The effects on neurological outcome should be studied.



## **Introduction**

Hypovolemia after aneurysmal subarachnoid hemorrhage (SAH) increases the risk of delayed cerebral ischemia (DCI).<sup>1,2</sup> DCI occurs in 30-40% of patients, usually 4-10 days after the hemorrhage, and is a major contributor to poor outcome.<sup>3</sup> Fluid management after SAH is usually guided on clinical parameters as heart rate, arterial and central venous blood pressures, pulmonary capillary wedge pressure, fluid balance or serum sodium concentration. These parameters have a poor relation with actual measured blood volume.<sup>2,4-6</sup> In a prospective controlled study named Optimizing circulating blood volume after aneurysmal subarachnoid hemorrhage (Optica), we assessed whether fluid management guided by daily measurements of circulating blood volume results in less hypovolemia after SAH than conventional fluid balance guided fluid therapy.

## Methods

### *Study Population*

The Medical Ethics Research Committee of the UMC Utrecht approved the study and written informed consent was obtained. Patients were eligible if admitted to the UMC Utrecht within 72 hours after SAH. Patients with accompanying head injury, pregnancy, liver- or kidney failure, an allergy for the indicator dye, or with imminent death on admission were excluded. The study period was day 1-10 after the onset of SAH.

### *Study Design*

The study was performed in three sequential cohorts of patients: first a control group (25% of patients), then an intervention group (50% of patients), and finally again a control group (25% of patients). We measured CBV daily in all included patients by means of Pulse Dye Densitometry (PDD) with the dye indocyanine green (ICG). This technique was previously validated and used in patients after SAH.<sup>2,6,7</sup> CBV values were classified as normal (60-80ml/kg), moderate hypovolemic (50-60ml/kg), severe hypovolemic (< 50ml/kg) or hypervolemic (> 80ml/kg).<sup>6,8</sup>

The goal of fluid management was to maintain normovolemia. At admission, an infusion of 3 liters normal saline per day was installed, in addition to oral intake as desired by the patient.

In the control groups, intravenous fluid administration was adjusted on the basis of the fluid balance, calculated every 6 hours, by subtracting urinary volume from total oral and intravenous intake. The aim was to keep the daily fluid balance at 750ml positive, compensating for insensible fluid loss. With fever, the desired level for the daily fluid balance was increased by 500ml for each degree above 37° Celsius. In both control periods, treating physicians and nurses were not informed on the results of CBV measurements.

In the intervention group fluid management was guided by daily CBV measurements. The treating medical team was informed daily on the outcome of CBV measurements. When CBV was outside the normovolemic range, the team was advised to adjust fluid management according to a standardized intervention protocol.

Central venous pressure was not routinely monitored in WFNS grade I and II patients. If DCI developed, fluid management was continued according to treatment allocation; no intentional hypervolemia or hemodilution was used. Induced hypertension could be applied.

Adverse effects of the administration of ICG were defined as any change in clinical condition, directly following or possibly related to, the intravenous injection of the dye. Adverse effects were categorized as minor (e.g. pain on injection, itching, nausea) or major (any change in condition requiring treatment).

### ***Outcome measurements***

Primary outcome was the occurrence of severe hypovolemia. Secondary outcomes included daily fluid intake, -excretion and -balance, and the clinical diagnosis of DCI (after excluding other causes of neurological deterioration with CT and appropriate laboratory examinations) or pulmonary edema or the use of inotropics on any day during the study period.

### ***Statistical Analysis***

Proportions of patients were compared in terms of risk ratios (RR) and differences in continuous variables were reported as mean differences, each with corresponding 95% confidence interval (CI). Because in each patient multiple CBV measurements were performed, we used weighted linear regression for comparison of 'per patient mean' values, with the inverse of the standard error of the 'per patient mean' taken as weight.

## Results

Between January 2006 and June 2007, 182 patients with aneurysmal SAH were admitted to the UMC Utrecht. Of these, 104 patients were included of whom two died from rebleeding before the first CBV measurement. Thus 102 patients received the allocated treatment (intervention  $n = 54$ ; controls  $n = 48$ ). Enrollment and allocation are presented in *Figure 1*.

Patient characteristics and outcome measurements were comparable for both control periods and data from these periods are combined (*Table 1*).

A total of 894 measurements of CBV was performed (intervention  $n = 475$ ; controls  $n = 419$ ). On average there were  $8.8 \pm 2.0$  measurements per patient in the intervention group and  $8.7 \pm 1.9$  in the control group. *Figure 2* presents the results of CBV measurements, divided into the four categories of volume status. In the intervention group on average 6.7% of the CBV measurements showed severe hypovolemia as compared with 17.1% in controls (mean weighted difference 7.7%; 95%CI:1.4 to 13.9%).

In the intervention group 21 patients (39%) had one or more measurements with severe hypovolemia during the entire 10-day study period versus 26 (54%) of the controls (RR 0.7; 95%CI:0.5 to 1.1).

Secondary outcomes are presented in *table 2*. Patients in the intervention group had on average a higher fluid intake and higher fluid excretion than control patients, resulting in a similar fluid balance for both treatment groups. DCI occurred less frequently in the intervention group patients, while the clinical diagnosis of pulmonary edema was made more often and inotropic support was more frequently used in this patient group. These differences did not reach statistical significance.

There were no serious adverse events related to CBV measurements. In 7% of the measurements patients experienced a brief cold or burning sensation at the site of injection of the ICG dye. Three patients complained of a strange taste in the mouth after injection of the dye, four patients had a transient warm feeling. In 1.2% of the measurements no value of CBV could be obtained because of movement of the patient or inadequate tissue perfusion.

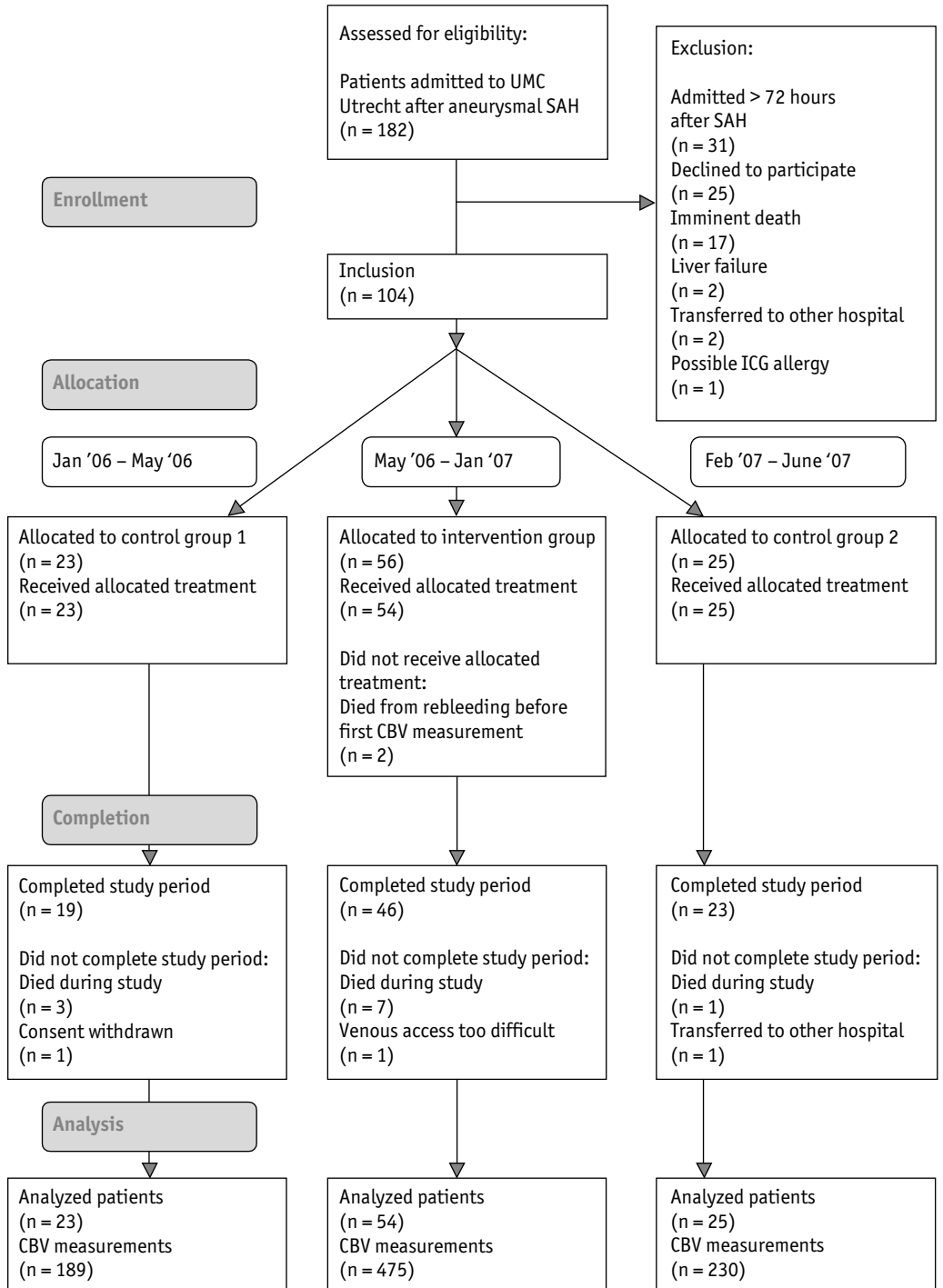


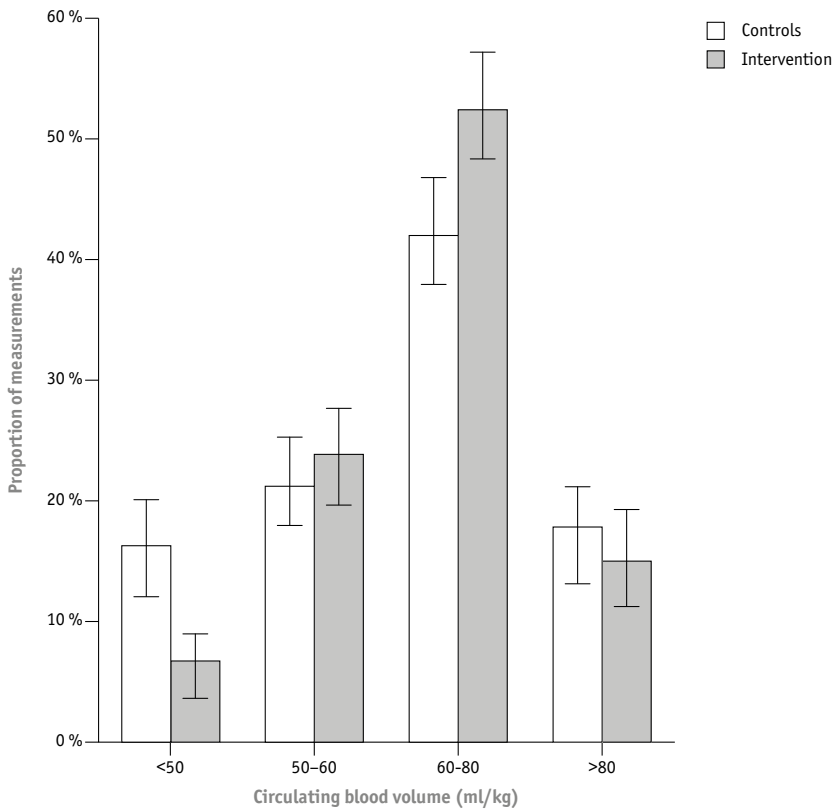
Figure 1

**Table 1**  
Patient characteristics

	Intervention	Controls
<b>Number of patients</b>	54	48
<b>Women</b>	42 (78%)	36 (75%)
<b>Age (years, mean <math>\pm</math> SD)</b>	58 $\pm$ 15	56 $\pm$ 14
<b>Length (cm, mean <math>\pm</math> SD)</b>	171 $\pm$ 9	172 $\pm$ 10
<b>Weight (kg, mean <math>\pm</math> SD)</b>	74 $\pm$ 14	77 $\pm$ 18
<b>Aneurysm location</b>		
Anterior cerebral artery	23 (43%)	22 (46%)
Carotid artery	15 (28%)	11 (23%)
Middle cerebral artery	9 (17%)	8 (17%)
Posterior cerebral artery	7 (13%)	7 (15%)
<b>WFNS grade on admission</b>		
I	22 (41%)	25 (52%)
II	12 (22%)	6 (13%)
III	3 (6%)	4 (8%)
IV	8 (15%)	10 (21%)
V	9 (17%)	3 (6%)
<b>Aneurysm treatment</b>		
Coiling	28 (52%)	32 (67%)
Clipping	18 (33%)	13 (27%)
<b>Modified Rankin Scale at 3 months</b>		
0	1 (2%)	2 (4%)
1	21 (39%)	12 (25%)
2	13 (24%)	10 (21%)
3	2 (4%)	10 (21%)
4	5 (9%)	0 (0%)
5	2 (4%)	5 (10%)
dead	10 (19%)	9 (19%)

Data are numbers with percentages or means with standard deviations

SD = standard deviation; WFNS = World Federation of Neurological Surgeons



**Figure 2**

*Circulating blood volume (CBV) measurements in 4 categories.*

*CBV values were classified as normal (60-80ml/kg), moderate hypovolemic (50-60ml/kg), severe hypovolemic (< 50ml/kg) or hypervolemic (> 80ml/kg).*

*Error bars indicate 95 % Confidence Interval.*

**Table 2**  
*Secondary outcome measurements*

	<b>Intervention</b> n = 54	<b>Controls</b> n = 48	<b>Mean difference (95%CI)</b> or <b>Risk Ratio (95%CI)</b>
Fluid intake (l/day)	5.2 (1.0)	4.7 (1.1)	MD 0.8 (0.3–1.2)
Fluid excretion (l/day)	4.2 (1.3)	3.9 (1.3)	MD 0.6 (0.1–1.1)
Fluid balance (l/day)	+1.0 (0.8)	+0.8 (0.5)	MD 0.1 (-0.1–0.4)
DCI	18 (33%)	19 (40%)	RR 0.8 (0.5–1.4)
Pulmonary edema	12 (22%)	5 (10%)	RR 2.1 (0.8–5.6)
Inotropic support	20 (37%)	11 (23%)	RR 1.6 (0.9–3.0)

Presented are mean values in liters per day (with standard deviation) of daily fluid intake/excretion/balance, and number of patients (with proportions) of newly diagnosed DCI or pulmonary edema or use of inotropic support on any day during the study period.

n = number of patients; CI = confidence interval; l/day = liters per day;

DCI = delayed cerebral ischemia; RR = risk ratio; MD = mean difference



## Discussion

Fluid management guided by daily CBV measurements improves volume status after SAH compared with conventional fluid balance guided therapy. The proportion of measurements indicating severe hypovolemia was more than halved in the intervention group, whereas the proportion of measurements in the hypervolemic range did not increase.

Previous studies on measured CBV repeatedly demonstrated hypovolemia after SAH and associations between hypovolemia, DCI and poor outcome.<sup>1,4,9</sup> In these studies fluid therapy was guided by conventional hemodynamic parameters. We found, with CBV-guided fluid therapy, a statistically significant reduction in severe hypovolemia but the incidence of DCI did not decrease to the same extent. Possible explanations are limited power to study DCI and its dependency on other factors such as the severity of vasospasm and global ischemia during the initial event.<sup>3,10</sup>

We defined normovolemia (60-80ml/kg) in accordance with previous studies but this is a simplification.<sup>2,8,11</sup> Firstly, CBV varies with age, sex, and stature. These variables showed no difference between control and intervention groups. Secondly, the changes in CBV that occur as a result of illness are incompletely understood.<sup>8</sup> Therefore we conservatively used wide margins in our definition of normovolemia.

A limitation is that DCI and pulmonary edema were clinical diagnoses made by the treating physicians, who may have been biased by their knowledge on treatment allocation. We do not routinely use transcranial doppler because of its suboptimal sensitivity for actual neurological deficits.<sup>10</sup>

Pulmonary edema was considered present more often in the intervention group, albeit not statistically significant. However, there was no increase in measured hypervolemia in the intervention group and no difference in fluid balance between both treatment groups.

## Conclusion

Guiding fluid management on daily CBV measurements results in less hypovolemia after SAH. Whether this will lead to improved neurological outcome remains to be studied. The effects on the extra-cranial circulation must be taken into account in future studies.

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## Chapter 6

### **Pulmonary edema and blood volume after aneurysmal subarachnoid hemorrhage: a prospective observational study**

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## Abstract

**Background** Pulmonary edema (PED) is a severe complication after aneurysmal subarachnoid hemorrhage (SAH). PED is often treated with diuretics and a reduction in fluid intake, but this may cause intravascular volume depletion, which is associated with secondary ischemia after SAH. We prospectively studied intravascular volume in SAH patients with and without PED.

**Methods** Circulating blood volume (CBV) was determined daily during the first ten days after SAH, by means of Pulse Dye Densitometry. CBV of 60-80 ml/kg was considered normal. PED was diagnosed on clinical signs and characteristic bilateral pulmonary infiltrates on the chest X-ray. We compared CBV, cardiac index and fluid balance between patients with or without PED with weighted linear regression, taken into account only measurements from the first day after SAH through the day on which PED was diagnosed. Differences were adjusted for age, bodyweight and clinical condition.

**Results** A total of 102 patients was included, 17 of whom developed PED after a mean of 4 days after SAH. Patients developing PED had lower mean CBV (56.6 ml/kg) than those without PED (66.8 ml/kg). Mean difference in CBV was -11.3 ml/kg (95%CI: -16.5 to -6.1), adjusted mean difference -8.0 ml/kg (95%CI: -14.0 to -2.0). After adjusting, there were no differences in cardiac index or fluid balance between patients with or without PED.

**Conclusion** SAH patients developing pulmonary edema have a lower blood volume than those without PED and are hypovolemic. Measures taken to counteract pulmonary edema must be balanced against the risk of worsening hypovolemia.

## **Introduction**

Pulmonary edema (PED) is a severe complication in patients with a subarachnoid hemorrhage (SAH) from rupture of an intracranial aneurysm.<sup>1,2</sup> PED can result in severe hypoxemia and thus contribute to cerebral hypoxia in a brain that is already vulnerable to secondary injury. PED thereby increases the risk of poor outcome.<sup>2,3</sup>

Next to well known causes of PED as cardiac failure or inflammatory reactions in the pulmonary tissue (e.g. in sepsis), PED after SAH can have a neurogenic origin. Neurogenic PED is defined as an increase in interstitial and alveolar lung fluid occurring as a direct consequence of an acute central nervous system injury. In the pathophysiology of neurogenic PED both hemodynamic and inflammatory mechanisms are involved.<sup>1,4</sup> An acute rise in intracranial pressure, accompanied by global ischemia of the brain, leads to a massive sympathetic discharge with a marked rise in pulmonary hydrostatic pressure, followed by a fluid shift from the pulmonary capillaries into the lung tissue. Inflammatory responses in the brain and the lungs induce capillary leakage. Furthermore the supraphysiologic sympathetic stimulation may provoke cardiac dysfunctions with rhythm and conduction disturbances and mechanical pump failure, which contribute to the formation of PED.

Management of PED after SAH is centered on the traditional treatment strategies for cardiac failure induced pulmonary edema, such as a reduction in preload and afterload and the use of inotropics.<sup>1,4,5</sup> A reduction in preload, by administration of diuretics and by a reduction in fluid intake, carries a risk of intravascular volume depletion. Patients after SAH already have a high risk of hypovolemia, and hypovolemia is associated with delayed cerebral ischemia and with poor outcome.<sup>6,7</sup> The avoidance of hypovolemia by ample fluid intake and, in some cases, the induction of hypervolemia are therefore mainstays of treatment after SAH.<sup>8</sup> To adequately guide fluid management, an accurate knowledge on volume status is required. We assessed intravascular volume in patients after SAH and compared it between patients who did or did not develop PED.

## Methods

### *Study Design and Setting*

We performed a prospective observational study in the UMC Utrecht, as a substudy of the 'Optica' study (Optimizing circulating blood volume after aneurysmal subarachnoid hemorrhage). In that prospective controlled study, fluid management guided by daily measurements of circulating blood volume was compared with a fluid policy based on regular evaluations of the fluid balance, to assess its effect on the incidence of hypovolemia.<sup>9</sup>

The study period was day 1-10 after the onset of SAH. The Medical Ethics Review Committee of the UMC Utrecht approved the study and written informed consent was obtained.

### *Study Population*

Patients were eligible if admitted to the UMC Utrecht within 72 hours after aneurysmal SAH. Patients with accompanying head injury, pregnancy, liver or kidney failure, an allergy for the indicator dye indocyanine green, or with imminent death on admission were excluded. Patient data on demographic and clinical variables were collected prospectively. The clinical condition on admission was classified according to the World Federation of Neurological Surgeons scale.<sup>10</sup> Delayed cerebral ischemia (DCI) was defined as a decrease in level of consciousness of at least two points on the Glasgow Coma Scale, the appearance of a focal neurological deficit, or both, for at least three hours, after exclusion of rebleeding, hydrocephalus, infection or metabolic causes for the deterioration.<sup>11</sup> Neurological outcome was assessed with the modified Rankin scale at 3 months after the SAH by a research nurse not involved in patient management.<sup>12</sup>

### *Treatment*

Patients were treated according to a standard SAH protocol. The goal of fluid therapy was to maintain normovolemia. The guidance of fluid therapy depended on treatment allocation for the parent Optica study. In the control group, fluid administration was adjusted on the basis of the fluid balance, calculated every 6 hours, by subtracting urinary volume from total oral and intravenous intake. The aim was to keep the daily fluid balance at 750ml positive, to compensate for insensible fluid loss. In the intervention group, fluid management was adjusted on the basis of daily blood volume measurements, in an effort to keep blood volume inside the



normovolemic range. Central venous pressure was not routinely monitored in patients with good or reasonable neurological condition (WFNS grade I and II). Oral nimodipine 60 mg q. 4 h. was started in all patients. If signs of delayed cerebral ischemia developed, fluid management was continued according to treatment allocation; no intentional hypervolemia or hemodilution was used, but induced hypertension could be applied.

### ***Outcomes***

A diagnosis of PED was made by the treating physicians and the consulting radiologists, based on clinical signs (dyspnea, tachypnea, basal pulmonary crackles, presence of frothy sputum, hypoxemia) in combination with characteristic bilateral pulmonary infiltrates on the chest X-ray.<sup>4</sup> Presence of pneumonia excluded a diagnosis of PED.

Blood volume and cardiac output were measured daily in all included patients by means of Pulse Dye Densitometry (PDD). This dye dilution technique uses pulse spectrophotometry, as developed for pulse oximetry, for measurement of the concentration of an injected dye (indocyanine green). PDD was previously validated, showing good accuracy in measured blood volume, and was used before in patients after SAH.<sup>7,13</sup> A measured blood volume of 60 to 80 ml/kg was classified as normal, as was a cardiac index of 2.5 to 4 l/min/m<sup>2</sup>.<sup>14</sup>

### ***Data Analysis***

We calculated individual 'per-patient-mean-blood-volume' values for all patients developing pulmonary edema, taken into consideration only the blood volume measurements from the first day after SAH through the day on which pulmonary edema was diagnosed for the first time in that patient. We calculated the median number of days after SAH after which pulmonary edema was diagnosed. We then assessed the 'per-patient-mean-blood-volume' values for patients *not* developing pulmonary edema, based on the measurements made till this median number of days after SAH. To compare mean values between patients with and without pulmonary edema we took into account that in each patient multiple blood volume measurements were performed during the study period. Therefore we used weighted linear regression for comparison of 'per-patient-mean' values, in which the inverse of the standard error of the 'per patient mean' was taken as weight. A similar analysis was used for comparison of cardiac index and fluid balance in all patients, to compare measurements of patients with pulmonary edema between intervention and control groups of the Optica study, and to compare measurements in patients

developing PED on the first day after SAH or on later days. Results are presented as mean differences with corresponding 95% confidence intervals. Differences were adjusted for age, bodyweight and WFNS grade on admission. We compared the proportion of patients with pulmonary edema between the intervention and control groups in terms of risk ratio (RR) with 95% confidence interval. The same analysis was used to compare the use of diuretics in patients that did or did not develop PED in the following days.

## Results

### *Patient enrollment*

Between January 2006 and June 2007, 182 patients with aneurysmal SAH were admitted to the UMC Utrecht. Of these, 104 patients were included, two of whom died from rebleeding before the first blood volume measurement (*Figure 1*). Baseline characteristics of patients with or without PED are listed in *Table 1*. Patients who developed PED were older and more often admitted in a poor clinical condition. There was no difference in baseline characteristics between patients from the intervention and the control groups.

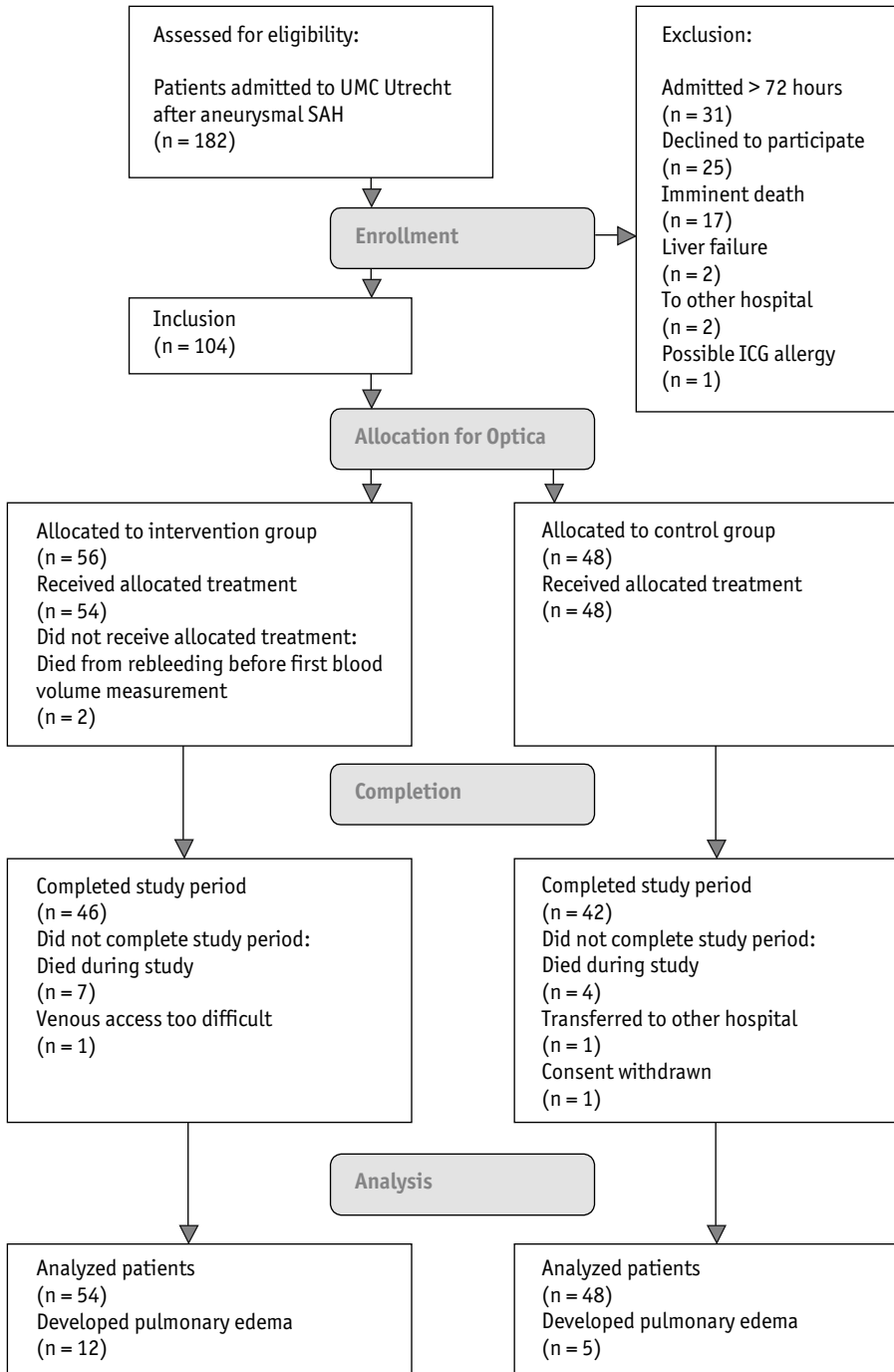


Figure 1

**Table 1**  
Patient characteristics

	Pulmonary edema	No pulmonary edema
<b>Number of patients</b>	17	85
<b>Women</b>	14 (82%)	64 (75%)
<b>Age (years, mean <math>\pm</math> SD)</b>	66 $\pm$ 14	55 $\pm$ 14
<b>Length (cm, mean <math>\pm</math> SD)</b>	170 $\pm$ 8	171 $\pm$ 10
<b>Weight (kg, mean <math>\pm</math> SD)</b>	79 $\pm$ 13	75 $\pm$ 17
<b>Aneurysm location</b>		
Anterior cerebral artery	7 (41%)	38 (45%)
Carotid artery	6 (35%)	20 (24%)
Middle cerebral artery	2 (12%)	15 (18%)
Posterior circulation	2 (12%)	12 (14%)
<b>WFNS grade on admission</b>		
I	5 (29%)	42 (49%)
II	5 (29%)	13 (15%)
III	0 (0%)	7 (8%)
IV	4 (24%)	14 (17%)
V	3 (18%)	9 (11%)
<b>Aneurysm treatment</b>		
Coiling	10 (59%)	50 (59%)
Clipping	3 (18%)	28 (33%)
<b>Delayed cerebral ischemia</b>	9 (53%)	27 (32%)
<b>Modified Rankin Scale at 3 months</b>		
0	0 (0%)	3 (4%)
1	3 (18%)	30 (35%)
2	4 (24%)	19 (22%)
3	3 (18%)	9 (11%)
4	2 (12%)	3 (4%)
5	2 (12%)	5 (6%)
dead	3 (18%)	16 (19%)

Data are numbers with percentages or means with standard deviations

SD = standard deviation WFNS = World Federation of Neurological Surgeons

## Outcome measurements

Pulmonary edema was diagnosed after a mean of 4.4 days (95% CI: 3.0 to 5.9) after SAH. Calculated differences in blood volume, cardiac index and fluid balance between patients with or without PED are presented in *Table 2*. Mean blood volume of patients with PED was in the hypovolemic range, while mean blood volume of patients without PED was in the normal range. After adjusting for age, weight and WFNS grade, blood volumes remained lower in patients with PED, while cardiac index and fluid balance did not differ statistically significant between patients with or without PED. There was no difference in mean CBV between patients with PED diagnosed early (day 1 after SAH) or later (day 2 to 10).

**Table 2**

*Calculated differences in outcome measurements*

Pulmonary edema				
	diagnosed n = 17	not diagnosed n = 85	mean difference	adjusted mean difference
<b>Blood volume</b>	56.6 (52.3 to 60.8)	66.8 (64.1 to 69.4)	-11.3 (-16.5 to -6.1)	-8.0 (-14.0 to -2.0)
<b>Cardiac index</b>	2.6 (2.2 to 2.9)	3.2 (3.1 to 3.4)	-0.5 (-0.9 to -0.1)	-0.3 (-0.7 to 0.1)
<b>Fluid balance</b>	+1.6 (1.0 to 2.2)	+1.1 (0.9 to 1.3)	+0.2 (-0.2 to 0.7)	+0.1 (-0.4 to 0.6)

Presented are mean values with 95% confidence interval of blood volume (ml/kg), cardiac index (l/min/m<sup>2</sup>) and fluid balance (l/day). Differences between patients with or without pulmonary edema are adjusted for age, weight, and WFNS grade on admission.

n = number of patients

PED was diagnosed in 17 (17%) of the 102 evaluated patients. It occurred in 12 (22%) of the 54 patients in the intervention group and in 5 (10%) out of the 48 patients in the control group (RR 2.1; 95% CI: 0.8 to 5.6). A comparison in determinants between both groups is provided in *Table 3*. The mean blood volume of the patients with PED in the intervention group was slightly higher than that in the control group, but still in the hypovolemic range. Diuretics were used in 7 of 85 patients without PED (8%) and in 11 of 17 patients (65%) with PED, in the days before PED was diagnosed (RR 7.9; 95% CI: 3.6 to 17.3).

**Table 3**

Comparison between patients with pulmonary edema from intervention and control groups of the Optica study

	intervention group n= 12	control group n = 5	adjusted mean difference	mean difference
<b>Blood volume</b>	58.2 (53.4 to 63.0)	52.0 (39.2 to 64.8)	7.9 (0.7 to 15.1)	9.1 (-0.9 to 19.1)
<b>Cardiac index</b>	2.5 (2.1 to 2.8)	2.9 (1.4 to 4.4)	-0.5 (-1.3 to 0.2)	-0.2 (-1.1 to 0.7)
<b>Fluid balance</b>	+1.9 (1.4 to 2.5)	+0.7 (-1.0 to 2.5)	+1.2 (0.1 to 2.3)	+1.2 (-0.2 to 2.6)

Presented are mean values with 95% confidence interval of blood volume (ml/kg), cardiac index (l/min/m<sup>2</sup>) and fluid balance (l/day). Differences between patients from intervention or control group are adjusted for age, weight, and WFNS grade on admission.

n = number of patients

## Discussion

Our results show that PED after SAH is accompanied by a strong decrease in blood volume. Patients with PED had a mean blood volume in the hypovolemic range in the days preceding the diagnosis of PED. Patients that developed PED more often had diuretics prescribed by the treating physicians in the days before the diagnosis of PED was made. Cardiac index tended to be somewhat lower and fluid balance somewhat more positive in patients with PED but these differences were no longer statistically significant after adjusting for age, weight and clinical condition. Calculations were based on measurements obtained in the time period from the day after SAH until the day PED was diagnosed, so these results were not influenced by any therapeutic measures initiated by the treating physicians to counteract the pulmonary edema.

We were unable to find any previous studies in which blood volume was actually measured in patients with pulmonary edema, neither in patients with a cardiac origin of the edema (by systolic or diastolic pump failure), nor in patients with non-cardiogenic edema (by increased pulmonary capillary permeability). Central venous pressure and pulmonary capillary occlusion pressure are often used in patients with pulmonary edema to be informed on volume status.<sup>15</sup> However, there is no clear relation between these pressures and the presence of neurogenic pulmonary edema, or between these pressures and measured blood volume.<sup>5,16,17</sup> Patients in the present study developing PED were older and more often admitted in a poor clinical condition, which is in agreement with previous studies.<sup>4</sup>

It was previously noticed that neurogenic PED develops earlier in patients with a normal systemic circulating volume, compared to hypovolemic patients.<sup>1,18</sup> Patients in the Optica intervention group more often had blood volumes in the normovolemic range than control group patients.<sup>9</sup> The present analysis showed that intervention group patients tended to be at increased risk of PED and that patients in the intervention group developing PED tended to have a more positive fluid balance and a higher (but still reduced) mean blood volume. Interpretation of these differences has to be made with caution because of the small number of patients in this comparison. However, this might indicate that measures to prevent hypovolemia after SAH lead to an increased risk of PED.

In neurogenic PED both cardiac and noncardiac factors result in a fluid shift from the vascular system to the lung tissue. This fluid shift from the circulation is a plausible explanation for the reduction in blood volume that we observed in patients who developed pulmonary edema. An additional explanation might be that the inflammatory mechanism in neurogenic PED is part of a systemic inflammatory



response syndrome (SIRS), with capillary leakage throughout the body.<sup>19</sup> The cardiac index was slightly lower in patients with PED than in those without, but not to such an extent to indicate cardiac failure. This may be explained by cardiac dysfunction often accompanying PED. Alternatively, the preexisting hypovolemia may have led to a decrease in cardiac filling and thereby to a reduction in cardiac index. Since we did not perform serial echocardiography, we were unable to make this distinction. Diuretics were used more often in patients that in later days developed PED. We did not collect information on the motives for the use of diuretics, but most likely the treating medical team was under the impression that these patients were hypervolemic, even before signs of PED became evident. A reason might have been that the fluid balance was strongly positive or peripheral edema was present, as both could be the case in a patient with SIRS. A previous study found no association between the fluid balance and actual measured blood volume.<sup>20</sup>

A limitation of our study is that the diagnosis of PED was based on clinical criteria in combination with chest X-ray findings. The physicians responsible for patient care were not blinded for treatment allocation. This may have contributed to an increase of PED diagnosed in the intervention group, because some clinicians believed that patients in the intervention group were at increased risk for hypervolemia and pulmonary edema. We did not routinely monitor central venous pressure or pulmonary capillary wedge pressure in these patients, because of the poor relation between these pressures and actual volume status. We did not categorize the severity of edema. Less severe instances of pulmonary edema may have escaped detection, as extravascular lung water must increase by more than 30% for edema to be visible on a chest X-ray.<sup>15</sup> Another limitation concerns the definition of normal blood volume. Previous studies found "normal" blood volume values in adults of approximately 70 ml/kg.<sup>7,14</sup> However, the changes in blood volume that occur as a result of illness or therapy are incompletely understood.<sup>21</sup> For this reason we used wide margins in our definition of normovolemia (60 - 80 ml/kg). Even with these large margins, patients developing PED fell outside this range and were considered hypovolemic.

Patients with PED after SAH must be considered at high risk of delayed cerebral ischemia due to hypovolemia. This renders fluid management in these patients especially difficult. Measures aimed at relieving pulmonary congestion and improving oxygenation (e.g. preload reduction) might increase hypovolemia, whereas measures to improve volume status might worsen pulmonary edema and possible hypoxemia. Both hypovolemia and hypoxemia are extremely deleterious for the recently injured brain. To balance these potentially conflicting goals, clinicians might consider refraining from measures that reduce preload and instead use early (non-invasive) positive pressure ventilation to maintain oxygenation. This might allow

administration of additional fluid to maintain normovolemia without a further decrease in arterial oxygen saturation. The effects of such a treatment policy on circulation, ventilation and neurological outcome need to be formally studied.

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## Chapter 7

### BNP and blood volume after subarachnoid hemorrhage

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*In preparation*

## Abstract

**Introduction** Hyponatremia occurs often after aneurysmal subarachnoid hemorrhage (SAH). It is in most cases caused by cerebral salt wasting, with hypovolemia, or by the syndrome of inappropriate ADH secretion, with normo- or hypervolemia (non-hypovolemia). We investigated whether brain natriuretic peptide (BNP) can differentiate between hypovolemic and non-hypovolemic hyponatremia.

**Methods** In 58 SAH patients, we daily measured serum BNP and sodium concentrations, and circulating blood volume by means of pulse dye densitometry, during the initial 10 days. For each patient, mean BNP concentrations were calculated until occurrence of hyponatremia ( $\text{Na} < 135 \text{ mmol/L}$ ), severe hyponatremia ( $\text{Na} < 130 \text{ mmol/L}$ ), hypovolemia (blood volume  $< 60 \text{ ml/kg}$ ), and severe hypovolemia (blood volume  $< 50 \text{ ml/kg}$ ). In patients without an event, mean BNP concentrations were calculated until the median day of that particular event. Odds Ratio's (OR) for high versus low mean BNP concentrations (dichotomized on median values per event) were calculated for the occurrence of each event and adjusted for relevant baseline characteristics.

**Results** Hyponatremia occurred in 37 (64%) patients, severe hypovolemia in 24 (41%) patients. Patients with high mean BNP more often had severe hypovolemia (OR 3.8, 95%CI 1.1-13.4). High BNP was not statistically significant associated with hyponatremia or severe hyponatremia.

**Conclusion** High BNP concentrations can not be used to differentiate between hypovolemic and non-hypovolemia hyponatremia after SAH. Repeated measurements of blood volume may play a role in the differentiation between SIADH and CSW.



## **Introduction**

In patients with aneurysmal subarachnoid hemorrhage (SAH), hyponatremia occurs in one third of patients and has been associated with the occurrence of delayed cerebral ischemia (DCI).<sup>1,2</sup> Most common causes of hyponatremia after SAH and other neurological emergencies are the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW).<sup>3,4</sup> In SIADH, there is an excessive release of ADH without a physiological stimulus like increased serum osmolality or arterial blood volume depletion. This results in impaired water excretion with normal sodium excretion. Patients with SIADH are normo- or hypervolemic (non-hypovolemic) and treatment consists of reducing fluid intake. In CSW, patients are volume-depleted and the high urine sodium concentration is due to urinary sodium wasting, not volume expansion. Therapy is opposite to the therapy of SIADH and consists of sodium and fluid replacement. The primary feature to differentiate between the two syndromes is volume status, but circulatory volume status is difficult to assess on clinical or biochemical grounds so far.<sup>3,5</sup>

The cause of urinary sodium wasting in CSW is still under discussion, but brain natriuretic peptide (BNP) has been postulated as an initiating factor.<sup>6</sup> BNP is a hormone primarily produced in the left cardiac ventricle in response to cardiac wall stretch that causes diuresis through a direct natriuretic action, increased cardiac output, and decreased aldosterone levels. In small series with SAH patients, plasma concentrations of BNP were elevated.<sup>6-8</sup> The reason for the elevated BNP concentrations is still unclear. High BNP levels after SAH have been associated with hyponatremia and the occurrence of DCI.<sup>7,8</sup>

The aim of the current study was to assess whether BNP concentrations can differentiate between hypovolemic hyponatremia, as seen in CSW, and non-hypovolemic hyponatremia, as seen in SIADH.

## Methods

### *Patients*

We studied patients who participated in the Optica study (Optimizing circulating blood volume after aneurysmal subarachnoid hemorrhage) between August 2006 and June 2007.<sup>9</sup> The objective of that study was to assess the efficacy in maintaining normovolemia with a strategy that tailors fluid management according to regular measurement of the circulating blood volume in patients with SAH. Inclusion criteria of the Optica study were 1) aneurysmal SAH; 2) admittance to our hospital within 3 days after the SAH, 3) age above 18 years, 4) informed consent obtained. The diagnosis of aneurysmal SAH was based on the presence of subarachnoid blood on CT-scan in combination with demonstration of an aneurysm on CT-angiography or conventional angiography. For the present study, patients were excluded when no regular BNP measurements were performed due to logistic problems, or when they were previously diagnosed with congestive heart failure, as these patients are assumed to have elevated BNP concentrations prior to the SAH. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

All patients were treated according to a standard protocol, including bed rest until aneurysm treatment, nimodipine 6 x 60 mg orally and a fluid policy aiming at normovolemia. Steroids, mannitol, antidiuretics or anti-fibrinolytics were not used. We recorded age (dichotomized at median value), gender and clinical condition at admission assessed by means of the WFNS score.<sup>10</sup> A WFNS score of 4-5 was considered as poor clinical condition at admission.

Serum BNP and sodium concentrations, and circulating blood volume were measured daily for the first 10 days after the SAH. For BNP measurements, EDTA plasma samples were collected in plastic collection tubes and BNP concentrations were determined with a microparticle immunoassay technique (8K28 ARCHITECT BNP Reagent Kit). Hyponatremia was defined as any sodium measurement < 135 mmol/L, and severe hyponatremia as any measurement < 130 mmol/L.

Circulating blood volume (CBV) was measured by means of pulse dye densitometry (PDD).<sup>11,12</sup> With this technique, the concentration of the dye indocyanine green is measured after injection of the dye in a peripheral vein. By dividing the amount of dye by the dye concentration, CBV is calculated. CBV < 60 ml/kg was defined as hypovolemia and CBV < 50 ml/kg as severe hypovolemia. PDD was previously validated and used before in patients after SAH.<sup>11-13</sup>

Hyponatremia was divided into hypovolemic or non-hypovolemic hyponatremia, based on CBV measurements. If more days of hyponatremia yielded different CBV

categories, mean CBV during those days determined the type of hyponatremia. DCI was defined as a decrease in level of consciousness of at least two points on the Glasgow Coma Scale for at least 3 h, the appearance of a focal neurological deficit, or both, after exclusion of rebleeding, hydrocephalus, infection, or of metabolic causes for deterioration. Poor outcome was defined as a modified Rankin score  $\geq 4$  at 3 months after the SAH.<sup>14</sup>

### ***Data analysis***

The relationship between high BNP concentrations and the occurrence of hyponatremia or hypovolemia was studied with logistic regression analysis. In patients with hyponatremia, the mean BNP concentration until the occurrence of hyponatremia was calculated. We recorded the median day of onset of hyponatremia. In patients without hyponatremia, the mean BNP concentration until this day was calculated and used for comparison. The same approach was used for the outcome hypovolemia. For each event, mean BNP concentrations were dichotomized on their median values and introduced in the regression analysis as high BNP (i.e. mean BNP above median mean BNP in the particular analysis) versus low BNP (i.e. mean BNP below median mean BNP in the particular analysis). Odds ratio's (OR) for high versus low BNP were calculated for hypovolemia and hyponatremia. In addition, we studied the outcomes severe hypovolemia and severe hyponatremia. To study whether BNP concentrations were related to the occurrence of hypovolemia in patients with hyponatremia, we calculated OR's for high versus low BNP concentration until the onset of the hypovolemic hyponatremia. OR's were adjusted for age, sex and clinical condition on admission.

## Results

Between August 2006 and June 2007, 61 SAH patients were included in the Optica study. Three patients were excluded because no BNP measurements were performed. There were no patients with a history of congestive heart failure. *Table 1* shows the baseline characteristics of the 58 included patients. BNP levels differed greatly between patients; some patients had BNP levels between 1 and 40 pmol/L, while it varied between 100 and 400 pmol/L in others.

**Table 1**

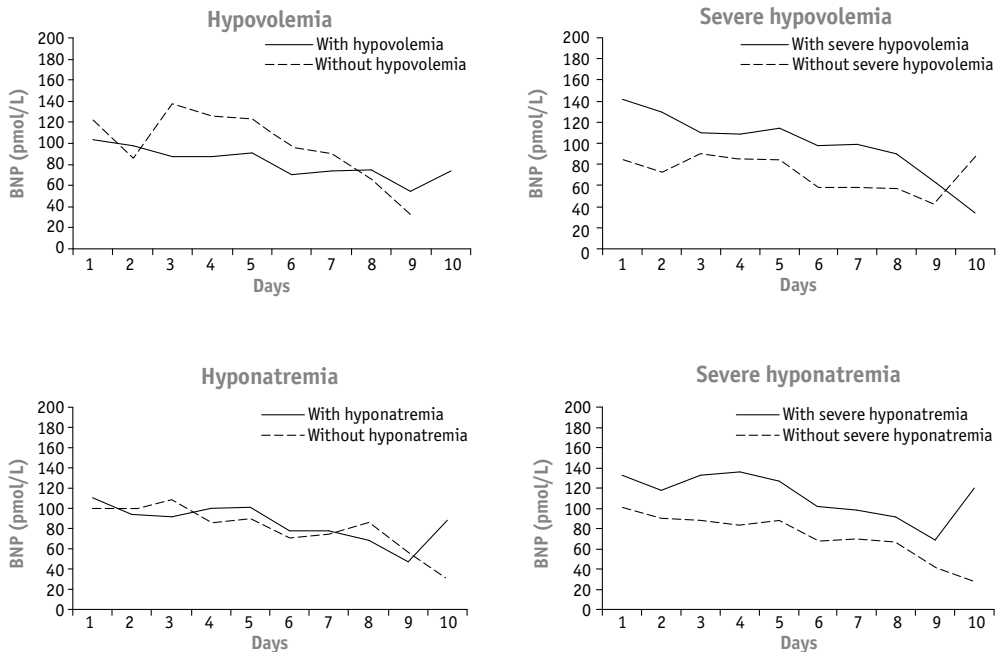
*Baseline characteristics and outcomes of included patients*

	n (%)
Mean age (SD)	59 ( $\pm 15$ )
Female	48 (83%)
Poor clinical condition at admission	15 (26%)
Mean admission BNP in pmole/L (SD)	103 ( $\pm 88$ )
Mean BNP day 1-10 in pmole/L (SD)	88 ( $\pm 88$ )
At least 1 episode of hypovolemia	47 (81%)
At least 1 episode of severe hypovolemia	24 (41%)
At least 1 episode of hyponatremia	37 (64%)
Hypovolemic hyponatremia	14 (24%)
Non-hypovolemic hyponatremia	23 (40%)
At least 1 episode of severe hyponatremia	12 (21%)
Hypovolemic hyponatremia	2 (3%)
Non-hypovolemic hyponatremia	10 (17%)
Delayed cerebral ischemia	18 (31%)
Poor outcome at 3 months	19 (33%)
Death at 3 months	9 (16%)

n = number of patients; SD = standard deviation

### ***BNP, hypovolemia and hyponatremia***

Hyponatremia occurred in 37 (64%) patients with a median day of onset on day four, and severe hyponatremia in 12 (21%) patients after a median of six days. Hypovolemia occurred in 47 (81%) patients after a median of two days, and severe hypovolemia in 24 (41%) patients after a median of three days. *Figure 1* shows the course of BNP concentrations during the initial ten days after the hemorrhage for patients with and without (severe) hypovolemia and (severe) hyponatremia.



**Figure 1**

Daily mean BNP concentrations for patients with and without hypovolemia, hyponatremia, severe hypovolemia and severe hyponatremia from day 1 to 10 after the SAH.

Patients with a high BNP until the day of the event (or median day of the event in patients without this event) had a higher risk to develop severe hypovolemia than patients with a low BNP (adjusted OR 3.8, 95% CI 1.1-13.4). The adjusted OR for developing hypovolemia, hyponatremia or severe hyponatremia did not show statistically significant differences between patients with high or low BNP (table 2).

**Table 2***Crude and adjusted OR's for high mean BNP compared to low mean BNP concentrations*

	High BNP n (%)	Low BNP n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Hypovolemia	23 (79%)	24 (83%)	1.0 (0.2-3.8)	1.8 (0.3-9.2)
Severe hypovolemia	17 (59%)	7 (24%)	4.5 (1.4-14)	3.8 (1.1-13)
Hyponatremia	18 (62%)	19 (66%)	0.9 (0.3-2.5)	0.7 (0.2-2.4)
Severe hyponatremia	8 (28%)	4 (14%)	2.4 (0.6-9.0)	2.5 (0.6-11)

Total number of patients was 58, number of patients with high BNP was 29,  
number of patients with low BNP was 29.

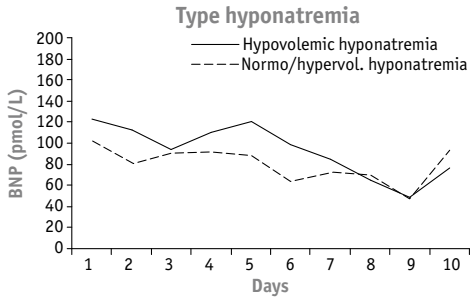
Adjusted for age, sex and clinical condition on admission

OR = odds ratio; BNP = brain natriuretic peptide; n = number of patients;

CI = confidence interval

### ***BNP and hypovolemic versus non-hypovolemic hyponatremia***

Of the 37 patients with hyponatremia, 14 (38%) were hypovolemic and 23 (62%) non-hypovolemic. In the 12 patients with severe hyponatremia, two (17%) were hypovolemic and ten (83%) non-hypovolemic (*table 1*). *Figure 2* shows the course of BNP concentration for patients with hypovolemic hyponatremia versus patients with non-hypovolemic hyponatremia. In patients with hyponatremia, the adjusted OR for the occurrence of hypovolemic hyponatremia was 1.4 (95% CI 0.3-6.4) for a high BNP concentration until the day of the event. Among patients with severe hyponatremia, only two patients had hypovolemic hyponatremia, who both fell into the high BNP group, thus no corresponding OR could be calculated.



**Figure 2**

*Mean BNP concentrations for patients with hypovolemic hyponatremia and patients with non-hypovolemic hyponatremia from day 1-10 after SAH.*

## Discussion

High BNP concentrations are related to the occurrence of severe hypovolemia but not to (severe) hyponatremia. In patients with hyponatremia, BNP concentrations could not differentiate between presence and absence of hypovolemia

We measured actual CBV. This enabled us to distinguish between hypovolemic hyponatremia, as seen in CSW, and non-hypovolemic hyponatremia, as seen in SIADH. In other studies that studied the relationship between BNP and volume status after SAH, the diagnosis of hypovolemia was based on indirect indicators of volume status such as urine output, urinary sodium excretion or fluid balance. We could not find studies in patients with SAH, in which serial BNP measurements were correlated serial CBV measurements.

Our finding that elevated BNP concentrations are associated with severe hypovolemia is consistent with previous reports.<sup>6,8</sup> However, we found no unequivocal association between BNP and hyponatremia, unlike these other studies.

BNP could not differentiate between the presence and absence of hypovolemia in the subset of patients with hyponatremia, while our hypothesis was that BNP would be higher in patients with hypovolemic hyponatremia. For patients with severe hypovolemic hyponatremia, the numbers were very small and no conclusions can be made. A possible explanation for the lack of a predictive value of BNP is that volume overload in itself could trigger BNP release due to increased left ventricular wall stretch, as BNP is also elevated in congestive heart failure patients. However, a recent study found no relation between elevated BNP levels after SAH and left ventricular filling pressures, measured by echocardiography.<sup>15</sup> Another explanation might be that increasing fluid intake prevented the occurrence of hypovolemia even at high BNP levels. Patients in our study were treated with a fluid policy aimed at maintaining normovolemia. All patients started with a 3 L saline infusion per day, to prevent the occurrence of hypovolemia. Patients still experienced hypovolemic periods frequently, which were treated by increasing fluid intake, to achieve normovolemia.

Several reports found CSW to be the most common cause of hyponatremia after intracranial disease, including SAH.<sup>6,16</sup> In our study population, non-hypovolemic hyponatremia, as seen in SIADH, is more common than hypovolemic hyponatremia, as seen in CSW. This is in accordance with another recent study that used single blood volume measurements to differentiate between SIADH and CSW in neurological patients with hyponatremia.<sup>17</sup> Different fluid policies may have resulted in these diverse results.



A limitation of our study is that we did not collect data on sodium intake and sodium excretion. As the mechanism behind the role of BNP in salt wasting is increased sodium secretion, the relationship between BNP and sodium balance might have added useful information. Furthermore, we did not perform serial echocardiography. Although there were no patients with a history of cardiac failure included, we can not rule out that some patients may have had chronic cardiac abnormalities with already increased BNP levels before they were admitted with SAH.

In clinical practice, BNP measurements are not useful to distinguish between hypovolemic hyponatremia and non-hypovolemic hyponatremia. As volume status is difficult to assess on clinical grounds, repeated measurements of blood volume may play a role in the differentiation between SIADH and CSW.

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## Chapter 8

### Hypotension in anesthetized patients during aneurysm clipping: not as bad as expected?

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*Acta Anaesthesiol Scand* 2008; 52 (8): 1006-1011

## Abstract

*Introduction* Patients with aneurysmal subarachnoid hemorrhage (SAH) often have disturbed autoregulation of cerebral blood flow. A reduction in systemic blood pressure during surgery may therefore lead to delayed cerebral ischemia (DCI). To assess the incidence and severity of intraoperative hypotension, we performed a retrospective cohort study in 164 patients with recent SAH and surgical clipping of the aneurysm.

*Methods* Intraoperative hypotension was defined in three levels of severity, as a decrease in mean arterial pressure ( $\Delta$ MAP) of more than 30%, 40% or 50% compared with the preoperative pressure. For each patient the total amount of time with intraoperative hypotension was retrieved. Logistic regression analysis was performed to study the relation between intraoperative hypotension and the occurrence of DCI and poor outcome.

*Results* A period with  $\Delta$ MAP > 30% occurred in 128 patients (78%) with a median duration of this period of 105 minutes (25-75<sup>th</sup> percentile 50-171 minutes).  $\Delta$ MAP > 40% occurred in 88 patients (54%) and  $\Delta$ MAP > 50% occurred in 22 patients (13%). In univariate analysis,  $\Delta$ MAP > 50% was associated with poor outcome. After adjusting for age and WFNS-grade, the association with poor outcome was no longer statistically significant (OR 1.018; 95% CI 0.996 to 1.041).

*Conclusion* Hypotension during surgical clipping of intracranial aneurysms occurred frequently. In our study population of patients mostly in good clinical condition, hypotension was not confirmed as an independent risk factor for DCI or poor outcome. Anesthesia may have had a cerebral protective effect.

## **Introduction**

Patients with aneurysmal subarachnoid hemorrhage (SAH) are at risk for delayed cerebral ischemia (DCI) during the first weeks after the hemorrhage. DCI is related to vasospasm of the cerebral arteries, which may impair brain tissue oxygenation, but vasospasm is neither a necessary nor a sufficient factor to explain the development of ischemia. One third of patients with vasospasm will not develop DCI and one third of patients with DCI have no vasospasm.<sup>1</sup> Other factors that can decrease brain tissue oxygenation include hydrocephalus, cerebral edema and circulatory or respiratory failure.<sup>2</sup> After SAH, cerebral autoregulation is often disturbed. Therefore cerebral blood flow might become pressure-dependent, which increases the risk for cerebral ischemia during episodes of decreased blood pressure.<sup>3</sup> Indeed, intentionally induced hypotension during clipping was associated with poor outcome.<sup>4</sup> Deliberate, or controlled, hypotension used to be favoured to facilitate dissection of the aneurysm and to minimize the risk of perioperative rupture. Today, many centres avoid deliberate hypotension in fear of increasing the risk of cerebral ischemia.<sup>5,6</sup> However, most general anesthetics reduce blood pressure by a decrease in peripheral vascular resistance or cardiac output.

We hypothesized that unintended hypotension occurs frequently during surgery for aneurysm clipping as a result of anesthesia. The purpose of this study was to assess the severity and duration of intraoperative hypotension in patients undergoing aneurysm clipping after SAH. In addition, we looked for a relationship between hypotension and the development of DCI and poor outcome.

## Methods

### *Subjects*

Patients were retrieved from a prospectively collected database of all patients with SAH admitted to the UMC Utrecht. Inclusion criteria for the present study were: a) admission from January 1999 through June 2002; b) SAH from a ruptured cerebral aneurysm; c) surgical clipping of the ruptured aneurysm within three weeks of the hemorrhage, while patients are most at risk for DCI; d) age above 18. Patients were excluded if the records were not complete or reliable preoperative blood pressures could not be obtained. The clinical condition on admission was graded by means of the World Federation of Neurological Surgeons (WFNS) grading scale.<sup>7</sup> All patients were treated according to a standardized protocol aimed at maintaining normovolemia, normo-oxygenation, normoglycemia and normothermia. Nimodipine was administered to all patients (60 mg PO q4h). Hypertension was accepted unless there were signs of cardiac or renal failure.

Patients who developed a hydrocephalus were treated on the basis of their clinical condition. If there was no neurological deterioration, a wait and see policy was followed. When a decrease in consciousness occurred, patients were preferably treated by lumbar puncture or with an external lumbar drain. Only in case of frank intraventricular hemorrhage with obstruction of one of the ventricles, an external ventricular drain was placed.

According to national regulations in the Netherlands no informed consent is needed if data collected for reasons of treatment of patients are used for research, as long as patients can not be traced back from the data in the publication.

### *Anesthesia technique*

After preoxygenation anesthesia was induced with propofol (2-3 mg/kg) or etomidate (0.2-0.3 mg/kg), sufentanil (0.2-0.6 µg/kg) and atracurium (0.5 mg/kg). Lidocaine (1 mg/kg) was often administered to decrease the hemodynamic response to intubation. Anesthesia was maintained by continuous infusion of propofol (4-10 mg/kg/h) and atracurium (0.3 mg/kg/h) and intermittent administration of sufentanil. Ventilation was controlled with a mixture of oxygen and air or oxygen and nitrous oxide and PetCO<sub>2</sub> was maintained in the range between 30 and 40 mmHg. A central venous line was placed in a subclavian or jugular vein and an intra-arterial catheter was positioned in a radial artery for continuous on-line monitoring of arterial blood pressure.

There was no protocol aiming at predefined targets of blood pressure during aneurysm surgery. Management of blood pressure was left to the judgment of the



anesthesiologist and the neurosurgeon. Transient episodes of hypotension were typically treated with bolus doses of either ephedrine (2.5-5 mg) or phenylephrine (50-100 µg). Some anesthesiologists used continuous infusion of phenylephrine to maintain blood pressure. Specific vasodilators to decrease blood pressure were not used. Normothermia was maintained during surgery.

### ***Surgical technique***

Clipping of the aneurysm was preferably performed in the early phase (0-4 days) after the SAH because of the increased risk of DCI in the intermediate phase (day 5-10).<sup>2</sup> For patients in a poor clinical condition, surgery was often postponed till after day 10 (late phase, day 10-21). Almost all patients were operated using the pterial approach with proximal vascular control.

### ***Blood pressure data and outcome assessment***

Systemic blood pressure was measured non-invasively on the day before operation (at least every 4 hours), in the operation room before induction, and during anesthesia. Continuous invasive blood pressure measurements during anesthesia were recorded every minute in a database with dedicated anesthesia record keeper software. All results of non-invasive measurements were collected from the patients file and the anesthesia record. Results of invasive measurements were assessed at ten-minute intervals, from 15 minutes after induction until the propofol infusion was discontinued or the patient was transferred to the Intensive Care Unit. Blood pressure data are reported as mean values with standard deviation (SD).

Intraoperative hypotension was defined in three levels of severity, as a decrease in mean arterial blood pressure ( $\Delta$ MAP) during surgery of more than 30%, 40% or 50% compared with the preoperative pressure ( $\Delta$ MAP >30%,  $\Delta$ MAP >40%,  $\Delta$ MAP >50%).

Mean preoperative blood pressure was calculated as the average of the measurements on the day before operation and the pre-induction blood pressure.

The difference between the mean preoperative blood pressure and the intraoperative blood pressure for each ten-minute interval was calculated and then expressed as a percentage of the mean preoperative blood pressure. Each episode with a  $\Delta$ MAP of more than 30, 40, and 50% was recorded. For each patient the total amount of time (in minutes) with a  $\Delta$ MAP of more than 30, 40 and 50% was retrieved.

Mean operative blood pressure was the average of all ten-minute recordings during surgery.

DCI was defined as development of any focal neurological signs, deterioration in the level of consciousness, or both, after surgery, with exclusion of rebleeding, hydrocephalus, metabolic disturbances or other non-neurological causes of clinical deterioration.<sup>8</sup>

Three months after the hemorrhage, a research nurse assessed outcome during a telephone interview by means of the Glasgow Outcome Scale (GOS).<sup>9</sup> A poor outcome was defined as a GOS of 1, 2 or 3 (dead, persistent vegetative state or severe disability), a good outcome as a GOS of 4 or 5 (moderate disability or good recovery). DCI and outcome were both assessed without prior knowledge on the  $\Delta$ MAP of the included patients.

### *Statistical analysis*

We compared mean duration of surgery, mean preoperative blood pressure and mean operative blood pressure between the patients with and without DCI by means of Students' t-test. The same analysis was performed between patients with poor or good outcome. Univariate logistic regression analysis was used to study the relation between the duration of periods with  $\Delta$ MAP > 30%,  $\Delta$ MAP > 40%, and  $\Delta$ MAP > 50%, and the occurrence of DCI or poor outcome. In a multivariate analysis we adjusted for patient age and clinical condition (WFNS) as known factors associated with poor outcome.<sup>2</sup> Patients who had surgery early (0-4 days) were compared with those operated on in the intermediate (5-10 days) or late phase (11-21 days) after the SAH.

## Results

During the study period a total of 246 patients with SAH underwent surgical clipping of the symptomatic aneurysm. Of these, 41 patients did not fulfil the inclusion criteria as they did not have surgery during the first three weeks after the SAH. For 30 patients no complete medical records could be retrieved; in another 11 patients no reliable pre-operative blood pressure could be obtained because patients were deeply sedated and ventilated from admission to operation. The resulting 164 patients were included in the present study. Baseline characteristics of the included and not-included patients are listed in *table 1*.

The occurrence of intraoperative hypotension of different severity ( $\Delta\text{MAP} > 30\%$ ,  $\Delta\text{MAP} > 40\%$ ,  $\Delta\text{MAP} > 50\%$ ) is indicated together with the odds ratios for DCI and poor outcome in *table 2*. In univariate analysis, only periods of  $\Delta\text{MAP} > 50\%$  were positively associated with poor outcome. After adjusting for patient age and WFNS-grade, the odds ratio for poor outcome per minute of  $\Delta\text{MAP} > 50\%$  was 1.018 (95 % CI: 0.996 to 1.041).

Mean duration of surgery was similar for patients with or without DCI ( $252 \pm 110$  minutes vs.  $237 \pm 86$  minutes;  $p=0.333$ ), and for patients with poor or good outcome ( $254 \pm 104$  minutes vs.  $238 \pm 91$  minutes;  $p=0.407$ ). Mean preoperative blood pressure showed no significant difference for patients with or without DCI ( $109 \pm 16$  mmHg vs.  $106 \pm 13$  mmHg;  $p=0.283$ ) neither for patients with poor or good outcome ( $109 \pm 16$  mmHg vs.  $106 \pm 14$  mmHg;  $p=0.374$ ). Also mean operative blood pressure was similar for patients with or without DCI ( $82 \pm 12$  mmHg vs.  $78 \pm 10$  mmHg;  $p=0.074$ ) and for patients with poor or good outcome ( $77 \pm 9$  mmHg vs.  $80 \pm 11$  mmHg;  $p=0.165$ ).

We assessed whether timing of surgery made a difference in severity or duration of the hypotensive periods, but no such difference was found. Neither was there a significant relation between hypotension and DCI or outcome in any of the three groups based on timing of surgery.

**Table 1**  
*Patient Characteristics*

	included	not-included
<b>Number of patients</b>	164	82
<b>Women</b>	65 %	70 %
<b>Age in years (SD)</b>	54 (13)	52 (12)
<b>Admission WFNS-grade</b>		
I	55 %	34 %
II	26 %	21 %
III	8 %	8 %
IV	6 %	22 %
V	5 %	15 %
<b>Localisation of aneurysm</b>		
anterior	55 %	34 %
carotid	19 %	32 %
media	22 %	21 %
posterior	4 %	13 %
Poor outcome (GOS 1,2,3)	17 %	31 %
Delayed Cerebral Ischemia	27 %	
<b>Timing of surgery (days after SAH)</b>		
early (0-4 days)	49 %	
intermediate (5-10 days)	14 %	
late (11-21 days)	37 %	
Duration of surgery in minutes (SD)	241 (93)	
Preoperative mean blood pressure in mmHg (SD)	107 (14)	
Operative mean blood pressure in mmHg (SD)	79 (11)	

Values are relative frequency or mean with standard deviation (SD)

WFNS = World Federation of Neurological Surgeons

GOS = Glasgow Outcome Scale; SAH = Subarachnoid Hemorrhage

**Table 2**  
*Intraoperative Hypotension during Aneurysm Clipping*

	Number of patients (%)	Median duration (25-75 <sup>th</sup> % <sub>oo</sub> )	Odds ratio for DCI	95% CI	Odds ratio for poor outcome	95% CI
ΔMAP > 30%	128 (78%)	105 minutes (50-171)	1.000	0.996 – 1.004	1.003	0.999 – 1.008
ΔMAP > 40%	88 (54%)	40 minutes (13-70)	1.001	0.993 – 1.008	1.003	0.994 – 1.011
ΔMAP > 50%	22 (13%)	11 minutes (10-30)	1.014	0.993 – 1.035	1.025	1.003 – 1.047

ΔMAP = Decrease in Mean Arterial blood Pressure;

DCI = Delayed Cerebral Ischemia;

CI = Confidence Interval

Odds ratios are expressed per minute duration of blood pressure decrease, e.g. 1 minute duration of ΔMAP > 50% increases the crude odds for DCI with a factor 1.014; a 5 minute period increases the crude odds for DCI with a factor  $(1.014)^5 = 1.072$ , with a corresponding widening of the confidence interval

## Discussion

Intraoperative hypotension with a decrease in mean arterial pressure of more than 30 or more than 40% occurred in a majority of patients during anesthesia for aneurysm clipping. These hypotensive periods were generally of long duration. Periods with ΔMAP > 50% occurred in a minority of patients and were shorter. In our study population we found no association between hypotension and DCI or poor outcome.

The hypotensive periods we observed were most likely caused by the anesthetics. Most anesthetic agents reduce blood pressure by a decrease in systemic vascular resistance or by a negative inotropic effect.<sup>6</sup> The magnitude of this reduction in blood pressure is, among other factors, influenced by the choice and dosing of the specific agent and by the condition of the heart, blood vessels and volume status of the patient. This reduction in blood pressure can be augmented by positive pressure ventilation and by placing the patient in a position with an elevated upper part of the body during surgery.

While hypotension was not induced intentionally, it may have been consciously accepted, with the idea of facilitating dissection and clipping. Because all data on blood pressure were collected retrospectively and our study was designed after the

study period, the anesthesiologist treating the patient at the time of the operation was not biased by the study in the management of the blood pressure. In a large randomized controlled trial of hypothermia during surgery for intracranial aneurysms, intentional hypotension was used in 5% of patients in the control group and unintended hypotension was said to occur in only 3%.<sup>10</sup> Unintended hypotension was defined as any instance where mean arterial pressure was less than 60 mmHg for more than 15 consecutive minutes. Because this was a rigidly controlled trial, strict blood pressure management by the anesthesiologists may have led to a low incidence of unintended hypotension.

Despite large decreases in blood pressure observed in our patients, hypotension was not an independent predictor for cerebral ischemia or poor outcome. Chang and colleagues, in a retrospective study on 84 patients with SAH, observed intraoperative hypotension, defined as systolic blood pressure below 90 mmHg for more than 15 minutes, in 40% of the patients.<sup>4</sup> In that study hypotension was intentionally induced with various vasoactive drugs, and hypotension was associated with symptomatic vasospasm and with poor outcome. In our study hypotension according to the definition of Chang and colleagues was present in 19% of the patients, and even when this definition was used we found no association between hypotension and DCI or poor outcome. The difference in results might be explained by a difference between intentionally induced hypotension and nonintentional hypotension. Nonintentional hypotension, as caused by the vasoactive effects of the anesthetic drugs, is related to deeper levels of anesthesia. In our study, anesthesia itself may have protected the brain from ischemic damage.<sup>11</sup> We used propofol for maintenance of anesthesia. Propofol inhibits synaptic activity and thereby reduces cerebral metabolism and cerebral blood flow.<sup>12</sup> Furthermore propofol acts as a direct scavenger of free oxygen radicals and inhibits lipid peroxidation.<sup>13</sup> These mechanisms have been associated with cerebral protection in several animal studies on cerebral ischemia.<sup>14</sup> However the possible neuroprotective effect of propofol under clinical conditions is not yet clear.

Another difference with the previous study concerns the clinical condition on admission of the patients. A poor clinical condition is a known risk factor for cerebral ischemia and for poor outcome.<sup>15</sup> In the previous study a poor clinical condition on admission (WFNS IV & V) was present in 46% of patients.<sup>4</sup> In our study only 11% of patients had a poor condition. Patients with a poor clinical condition on admission experienced longer periods of severe intraoperative hypotension than patients with a good condition. At the same time, these patients are most at risk for cerebral hypoperfusion because of impaired cerebral vascular autoregulation.<sup>16</sup> After adjusting for age and WFNS-grade, intraoperative hypotension was not an independent risk factor for DCI or poor outcome in our study. However, an increased

tendency for intraoperative hypotension and cerebral hypoperfusion might actually be a contributing factor to the poor prognosis of patients with poor clinical condition on admission.

A limitation of our study is found in patient selection. The comparison of baseline characteristics of included and not-included patients shows important differences. Included patients were in general in a better clinical condition than not-included patients and had therefore a relatively low risk for disturbances of autoregulation and DCI.<sup>16</sup> We only studied patients in whom surgical clipping of the aneurysm was performed within the first 3 weeks. Patients arriving at the hospital in very poor neurological condition or suffering severe medical comorbidity are often operated in a later phase and are subsequently not included. This kind of patient selection towards patients in good clinical condition is often encountered in studies evaluating therapeutic measures, as therapies are usually offered only to patients who may benefit from treatment. Furthermore, some patients could not be included because no reliable blood pressure data could be obtained, because of deep sedation. Deep sedation is mostly used for patients in poor clinical condition and exclusion of these patients may have contributed to patient selection.

Only half of our patients had surgery in the early phase after SAH. Early operation is performed to prevent early rebleeding but is also a risk factor for DCI.<sup>17</sup> In the patients with early operation, as in the other patients, we found no association between hypotension and DCI or poor outcome.

The retrospective design of our study had the advantage of not biasing the treating physicians; however, because of this design we were not able to collect information on the rationale of the anesthesiologists and neurosurgeons for accepting or treating a certain level of hypotension. Another limitation of the retrospective design is that in a number of patients no complete medical records could be retrieved.

DCI was defined as a clinical condition. We did not use transcranial Doppler (TCD) to screen for vasospasm because of the poor relation with actual neurological deficits.<sup>1</sup> Overall, 83% of the patients in our study population had a favourable outcome. This is comparable to the results of other studies on large numbers of patients after aneurysm surgery.<sup>10;18</sup> However, the Glasgow Outcome Scale we used to assess neurological outcome is possibly too crude a methodology to identify small differences in good grade patients.

In the present study, hypotension during surgical clipping of intracranial aneurysms occurred frequently and for long periods of time. Our study population was in a relatively good clinical condition and as such, at a low risk for cerebral hypoperfusion. Furthermore anesthesia itself may have had a cerebral protective effect. We


could not confirm intraoperative hypotension as an independent risk factor for DCI or poor outcome. However, the safety limits for intraoperative blood pressure are yet to be defined.



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## Chapter 9

### General discussion

## General discussion

Normal is not simple. Current therapy after aneurysmal subarachnoid hemorrhage focuses on the maintenance of 'normal' hemodynamic parameters. The justification for current SAH management protocols is that circulatory disturbances, especially hypovolemia and hypotension, increase the risk of delayed cerebral ischemia and poor outcome. However, the results of the studies presented in this thesis show that 'normal' parameters are not that easy to achieve or to maintain.

Guiding fluid management on regular calculations of the fluid balance did not result in consistent maintenance of normovolemia (*chapter 3*). Adjusting fluid management on the basis of the nurses' interpretation of the current volume status was not helpful in maintaining normovolemia, as most instances of hypo- or hypervolemia were not recognized as such (*chapter 4*). Just as fluid balance and the nurses' interpretation could not adequately indicate the volume status, BNP concentration could not differentiate between hypovolemia or normo-/hypervolemia in hyponatremic patients after SAH (*chapter 7*). Guiding fluid management on daily measurements of circulating blood volume did significantly reduce the incidence of severe hypovolemia. Even so, severe hypovolemia still occurred frequently in the studied population (*chapter 5*).

A reason for the high rate of hypovolemia, as well as for the discrepancies that we and other authors have observed between various hemodynamic parameters and measured blood volume, might be that the effects of a subarachnoid hemorrhage are not limited to the brain. Rupture of a cerebral aneurysm causes a subarachnoid hemorrhage that instantaneously increases intracranial pressures, often to levels sufficient to cause global cerebral ischemia. This leads to a massive reflex sympathetic discharge which results in a marked increase in blood pressure and pulmonary hydrostatic pressure and may provoke cardiac dysfunction.<sup>1</sup> This acute reaction is followed by inflammatory processes in the brain and in the rest of the body, leading to a systemic inflammatory response syndrome (SIRS).<sup>2,3</sup> Most patients develop multiple organ dysfunction after SAH which increases the risk of a poor outcome.<sup>2,4</sup> Sympathetic discharge and inflammation can result in the development of pulmonary edema with a loss of fluid from the circulation into the lung tissue. This corresponds with our finding that patients developing pulmonary edema had a decreasing blood volume over the days until the diagnosis was made (*chapter 6*). The presence of peripheral edema, often encountered in SIRS, might even be interpreted wrongly as a sign of volume overload by the treating nurses (*chapter 4*).

The body reacts to changes in volume status with compensatory mechanisms. Loss of fluid to the lungs and other tissues as part of SIRS during the first days after SAH triggers the kidneys to decrease urinary output. This results in a more positive fluid

balance, which could lead the treating physicians to reduce fluid intake, thereby aggravating circulatory volume depletion (*chapter 3*). Furthermore, the cutaneous and splanchnic circulatory beds act as a volume buffer. In reaction to a reduction in blood volume, vasoconstriction in these circulatory beds results in a shift of blood to the larger blood vessels and in a centralization of blood flow to the most vital organs (heart, lungs, brain). Vasodilatation in the splanchnic vascular beds and in the skin increases venous capacitance and thereby enables the body to accommodate an increase in blood volume.<sup>5,6</sup> These mechanisms maintain the arterial blood pressure and the so called venous filling pressures of the vascular system, the central venous pressure (CVP) and the pulmonary capillary wedge pressure (PCWP), at a normal level during moderate shifts in volume status. The compensatory mechanisms result in a poor relationship between measured pressures and measured volume, as was also shown after SAH.<sup>7-11</sup> A volume depleted patient with a highly activated sympathetic system can even have increased filling pressures. Although clinical signs of hypovolemia may be all but absent in the compensated state, the compensatory mechanisms itself decrease tissue perfusion in large areas of the body. This may lead to exaggerated inflammatory and immune responses, that contribute to the onset of multiple organ dysfunction.<sup>6</sup>

At the same time as the reactions of the body to the subarachnoid hemorrhage become manifest, the initiation of medical treatment will also influence the systemic circulation. All patients in the studies from this thesis were treated with fluid policies aiming at normovolemia. Fairly large amounts of fluids were administered. This might be a reason that cerebral salt wasting as a cause of hyponatremia was observed less frequently in our patients than in patients from earlier studies with often restricted fluid intake (*chapters 2 & 7*). Anesthesia during surgical aneurysm clipping resulted in prolonged decreases in blood pressure, which could possibly endanger cerebral blood flow. However, we were unable to find a relationship between low intraoperative blood pressures and an increased rate of severe hypovolemia (*chapter 8*). While guidance of fluid therapy based on daily measurements of blood volume decreased the incidence of severe hypovolemia, an increased incidence of pulmonary edema was observed (*chapters 5 & 6*). This illustrates that hemodynamic therapy after SAH can have serious side-effects.

Hemodynamic therapy after SAH, with its focus on maintenance of normal parameters, is meant to decrease the incidence of DCI. There are few previous studies on blood volume after SAH showing a relation between DCI and volume status (*chapter 2*). We found that guiding fluid management on daily measurements of circulating blood volume reduced the rate of severe hypovolemia significantly, accompanied by a small (not statistically significant) reduction in the risk of DCI (*chapter 5*). Whether sustained normovolemia will lead to a decrease in the risk of DCI is still an unanswered question.

## Implications for patient care and future research

Optimizing systemic circulation after SAH is a difficult task. Repeated measurements of circulating blood volume can be used to guide fluid therapy, thereby reducing the incidence of severe hypovolemia. The pulse dye densitometry technique can easily be used by trained nurses or physicians. However as yet we did not show a positive effect on DCI or outcome. This could be studied in a larger population of SAH patients, preferably in several SAH treatment centers. This will necessitate prior agreement on the uniform treatment of these patients and the availability of a bedside blood volume measurement technique on a daily basis.

An important question is whether any specific blood volume is optimal for a particular patient at a specific moment. In a patient developing pulmonary edema after SAH, a positive effect on outcome of an increased blood volume might be offset by a negative effect of hypoxemia. We do not know if a patient with heart failure needs the same blood volume as a patient with good cardiac function. The same question arises in the management of arterial blood pressure. Many patients have an elevated blood pressure immediately after SAH. This may be considered a protective response to maintain cerebral perfusion. However, should we maintain blood pressure during anesthesia at this elevated level or is a lower level, more in accordance with the patients 'normal' blood pressure just as adequate, or perhaps even better?

Furthermore, blood volume and blood pressure are just two, albeit important, parameters of systemic circulation. The patient with an aneurysmal subarachnoid hemorrhage should be considered as having a multiple organ disorder. This complicates the already difficult interplay between blood volume, blood pressure, cardiac contractility and vasoconstriction, that together determine the adequacy of the systemic circulation in providing tissue oxygenation and energy supply.<sup>5</sup>

To gain more insight in hemodynamics after SAH, it is necessary to study not only relatively static factors such as blood volume but also more dynamic factors. Examples of such dynamic variables are a change in cerebral perfusion (or cardiac performance, or oxygenation) in response to an increase in (measured) intravascular volume. Different hemodynamic management strategies could then be compared and the effect on outcome assessed.

Treatment after SAH should not be focused on a single organ (the brain), but should take into consideration the functioning of the other organs as well. The neurologist, the neurosurgeon, the anesthesiologist, the intensivist, the cardiologist, the radiologist, the nurse in the ICU or in the Stroke Unit, while treating the same patient will all tend to focus on different aspects of care. A coordinated multidisciplinary approach, in research as well as in patient care, seems most appropriate to

increase our understanding of the complex interplay of pathophysiological mechanisms. This, in turn, should help us to design new evidence-based treatment strategies that will improve patient outcome.

Ultimate goal would be to get the patient in a normal condition again.

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## Summary



## Summary

### ***Chapter 1 – General introduction***

A subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm is a devastating disorder with an often poor prognosis. The occurrence of delayed cerebral ischemia (DCI) is one of the most important factors determining outcome in patients who have survived the first hours after the hemorrhage. Hypotension and hypovolemia have been associated with an increased risk for DCI after SAH. To reduce the incidence of DCI, therapy is generally focused on maintenance of normovolemia or hypervolemia, sometimes in combination with induced hypertension and hemodilution. However there is still a lack of supporting evidence for the efficacy of this treatment. The aim of the research presented in this thesis was to study the relation between the presumed and the actual condition of the systemic circulation and thereby find a way to improve hemodynamic management after aneurysmal SAH.

### ***Chapter 2 – Blood volume after aneurysmal subarachnoid hemorrhage***

In most studies on hemodynamic management after SAH the actual amount of circulating blood is not measured. An interpretation of the current volume status is obtained on the basis of other hemodynamic parameters that however have a poor relation with actual measured volume. To obtain an overview on available knowledge on blood volume after recent SAH, we identified previous research reports describing studies in which blood volume was measured. Several of these previous studies observed a reduction in red cell volume, plasma volume or circulating blood volume after SAH, especially in the first week after SAH. Interpretation of the data from these studies is hampered because none or very little information on hemodynamic therapy is supplied in many of the reports. Those studies providing data on therapy show that very different regimes have been followed, further complicating the interpretation. There is an indication that patients developing DCI after SAH are more often hypovolemic than patients without DCI. Whether prevention of hypovolemia is effective in the prevention of DCI is not ascertained.

### ***Chapter 3 – Fluid balance and blood volume after aneurysmal SAH***

Fluid therapy after SAH is often guided on regular calculations of the fluid balance, based on meticulous registration of all fluid intake and fluid output. In a prospective observational study we assessed the effectiveness of this fluid policy in maintaining normovolemia. A total of 50 patients with recent aneurysmal SAH was included. Fluid intake was adjusted on the basis of the fluid balance calculated at 6-h

intervals. Circulating blood volume (CBV) was measured with pulse dye densitometry (PDD) on alternating days during the first two weeks after SAH. Normovolemia was defined as CBV 60-80 ml/kg. Hypovolemia (CBV < 60 ml/kg) was present in 76 (29%) of 265 CBV measurements and occurred in 31 (62%) patients. Eleven patients (22%) had measurements indicating severe hypovolemia (CBV < 50 ml/kg). We found no association between CBV and the daily fluid balance or between CBV and a cumulative fluid balance, adjusted for insensible loss through perspiration and respiration. The fluid balance does not seem an adequate guide for fluid management.

#### ***Chapter 4 – Nurses' prediction of volume status after aneurysmal SAH***

To guide fluid management after SAH, a regular and accurate assessment of the current volume status has to be made. Such assessments are usually based on the available hemodynamic data as heart rate, blood pressure, urine production, skin temperature, central venous pressure and capillary wedge pressure. Nurses are often involved in these assessments and in the decisions on fluid management. We asked ICU- and Medium Care Unit nurses, currently treating patients with recent SAH, to predict the present volume status as hypo-, normo- or hypervolemic. These assessments were compared with the actual CBV, that was measured daily with PDD during the first ten days after SAH. The results showed that deviations from normovolemia occurred frequently in these patients but that most instances were not recognized as such, which resulted in a very low sensitivity of the predictions. If hypervolemia was predicted, in fact a significant lower CBV was present than if normo- or hypovolemia was predicted. The nurses' prediction seems not a good measure for current volume status.

#### ***Chapter 5 – Blood volume measurement to guide fluid therapy after SAH***

In a prospective controlled study in patients with recent SAH we assessed whether fluid management guided by daily measurements of CBV reduces the incidence of severe hypovolemia, compared to conventional fluid balance guided fluid therapy. CBV was measured daily in 102 patients during the first 10 days after SAH. In the intervention group (n=54), with fluid management guided by CBV, less measurements were in the severe hypovolemic range (6.7% versus 17.1%) and a smaller part of patients had measurements indicating severe hypovolemia (39% versus 54%). Guiding fluid management on daily measurements of CBV reduces the incidence of severe hypovolemia, but severe hypovolemia still occurs.

### ***Chapter 6 – Pulmonary edema and blood volume after SAH***

Pulmonary edema (PE) is a severe complication after SAH. PE is often seen as a sign of hypervolemia and treated as such with diuretics, inotropics and a reduction in fluid intake. We prospectively studied CBV, fluid balance and cardiac index in SAH patients and compared it between patients who did or did not develop PE. The results showed that patients developing PE had actually a lower mean CBV than those without PE and had CBV measurements in the hypovolemic range (CBV < 60 ml/kg). Patients with fluid management guided by daily measurements of CBV were at a somewhat increased risk for the development of PE compared to patients with conventional fluid balance guided therapy. Patients with PE after SAH must be considered as hypovolemic and measures taken to counteract the pulmonary edema must be balanced against the risk of worsening hypovolemia.

### ***Chapter 7 – BNP and blood volume after SAH***

Hyponatremia occurs frequently after SAH. An important cause is so called cerebral salt wasting (CSW), where urinary loss of sodium and water is increased in a reaction to a cerebral event. Increased release of brain natriuretic peptide (BNP) is seen as a possible trigger for CSW. Patients with CSW tend to become hypovolemic. Hyponatremia can alternatively be part of the syndrome of inappropriate ADH secretion (SIADH), where increased secretion of antidiuretic hormone leads to water retention. SIADH patients have normal or slightly increased blood volumes. Fluid therapy in CSW (fluid suppletion) is opposite to fluid therapy in SIADH (fluid restriction). In 58 patients after SAH we studied the relation between BNP concentrations and the occurrence of hypovolemia, and hyponatremia. Patients with a high BNP had an increased risk to develop severe hypovolemia. However a high BNP was not associated with hyponatremia and BNP concentration could not be used to differentiate between hypovolemic hyponatremia (CSW) and normo-/hypervolemic hyponatremia (SIADH). In our population patients developing hyponatremia were in most cases (62%) normo-/hypervolemic.

### ***Chapter 8 – Hypotension in anesthetized patients during aneurysm clipping***

After SAH, cerebral autoregulation is often disturbed. Therefore cerebral blood flow might become pressure dependent, which increases the risk for cerebral ischemia during episodes of decreased blood pressure. Intentional hypotension was previously used to facilitate dissection of the aneurysm, but has been associated with poor outcome and nowadays is avoided in most centers. We hypothesized that unintended hypotension as a result of anesthesia still occurs frequently and studied retrospectively the severity and duration of intra-operative hypotension in 164 patients undergoing aneurysm clipping after SAH. We found that most patients had

a reduction in mean arterial blood pressure ( MAP) of more than 30% or 40% compared to preoperative levels and that these reductions lasted for prolonged periods. A reduction of more than 50% occurred in 13% of patients and lasted on average 11 minutes. In this population of patients in a comparatively good clinical condition we found no association between intra-operative hypotension and DCI or poor outcome.

### ***Chapter 9 – General discussion***

Results from the studies in this thesis show that normal hemodynamic parameters are not easy to achieve or to maintain. A probable cause is that SAH results in multiple organ dysfunctions and a systemic inflammatory response syndrome (SIRS). A coordinated multidisciplinary approach of the SAH patient would be appropriate, in research as well as in patient care. Future research on hemodynamics after SAH should take into account the effect of therapeutic measures on extracerebral organs as well as on cerebral blood flow. Different strategies could then be compared and the effect on outcome assessed. This could lead to a more personalized treatment of the patient after SAH. Ultimate goal would be to get the patient in a normal condition again.



## Samenvatting



### ***Hoofdstuk 1 – Inleiding***

Een subarachnoïdale bloeding (SAB) uit een gebarsten aneurysma van de hersenslagaders is een zeer ernstige aandoening met veelal een sombere prognose. Bij patiënten die de eerste uren na de bloeding overleven, wordt de mate van uiteindelijk herstel voor een belangrijk deel bepaald door het al dan niet optreden van een doorbloedingsstoornis van de hersenen met secundaire hersenschade als gevolg. Een lage bloeddruk en een krappe vullingstoestand verhogen het risico op het optreden van een dergelijke doorbloedingsstoornis. Om het risico te verkleinen wordt bij de behandeling vaak gestreefd naar het handhaven van een normale of ruime vullingstoestand van de bloedvaten, soms in combinatie met een verhoging van de bloeddruk en bloedverdunding. Het inschatten van de vullingstoestand is echter niet eenvoudig. Doel van het in dit proefschrift beschreven onderzoek was om de relatie te bestuderen tussen de veronderstelde en de werkelijke vullingstoestand en om daarmee te proberen een methode te vinden om de behandeling na een SAB te verbeteren.

### ***Hoofdstuk 2 – Bloed volume na een aneurysmatische SAB***

In de meeste studies naar de vullingstoestand na een SAB wordt de actuele hoeveelheid bloed in de vaten niet gemeten. Een interpretatie van de vullingstoestand wordt meestal verkregen op basis van diverse andere parameters van de bloedsomloop, waarvan echter bekend is dat deze geen goede relatie hebben met het werkelijke circulerende bloed volume. Om een overzicht te krijgen van de beschikbare kennis over het bloed volume na een SAB werden door ons de eerdere studies geïdentificeerd waarin het bloed volume na een SAB daadwerkelijk werd gemeten. Het afnemen in de hoeveelheid circulerende rode bloed cellen, de hoeveelheid bloedplasma of het totale circulerende bloed volume werd in diverse van deze studies beschreven, vooral in de eerste week na de SAB. Deze onderzoeksresultaten zijn lastig te interpreteren doordat in veel van deze studies weinig of geen informatie werd verstrekt over de behandeling, gericht op de bloedsomloop. In de studies waarin wel informatie over de behandeling werd verstrekt, blijken zeer diverse behandelwijzen te zijn gevolgd, waardoor de interpretatie verder wordt bemoeilijkt. Er zijn aanwijzingen dat patiënten die een doorbloedingsstoornis van de hersenen krijgen na een SAB vaker een ondervulling van de bloedsomloop hebben dan patiënten zonder deze doorbloedingsstoornis. Of het voorkomen van deze ondervulling effectief is om een doorbloedingsstoornis te voorkomen is niet vastgesteld.

### ***Hoofdstuk 3 – Vochtbalans en bloedvolume na een aneurysmatische SAB***

Het vochtbeleid na een SAB wordt vaak gestuurd door regelmatige berekening van de vochtbalans, gebaseerd op een zorgvuldige registratie van al het vocht dat wordt



toegediend en wordt uitgescheiden. Wij onderzochten in een prospectieve observationele studie bij dit vochtbeleid de effectiviteit in het handhaven van een normale vullingstoestand. Vijftig patiënten met een recente aneurysmatische SAB werden geïnccludeerd. De vochttoediening werd aangepast op basis van de vochtbalans, die elke 6 uur werd berekend. Het circulerend bloed volume (CBV) werd gemeten met behulp van pulse dye densitometry (PDD) op alternerende dagen gedurende de eerste twee weken na de SAB. Een normale vullingstoestand werd gedefiniëerd als een CBV van 60-80 ml/kg. Ondervulling (CBV < 60 ml/kg) was aanwezig in 76 (29%) van de 265 CBV metingen en trad op bij 31 (62%) patiënten. Bij elf patiënten (22%) toonden de metingen de aanwezigheid van een ernstige ondervulling (< 50 ml/kg). Wij vonden geen verband tussen CBV en de dagelijkse vochtbalans, noch tussen CBV en een cumulatieve vochtbalans, geadjusteerd voor vochtverlies bij transpiratie en bij de ademhaling. De vochtbalans lijkt geen adequate gids voor het vochtbeleid na een SAB.

#### ***Hoofdstuk 4 – Voorspelling van de vullingstoestand na een SAB door verpleegkundigen***

Om het vochtbeleid na een SAB te sturen moet een regelmatige en accurate inschatting van de vullingstoestand worden gemaakt. Deze inschattingen zijn meestal gebaseerd op diverse indicatoren van de bloedsomloop zoals de hart frequentie, de bloeddruk, de urine productie, de huid temperatuur, de centraal veneuze druk en de wedge druk. Verpleegkundigen zijn vaak betrokken bij deze inschattingen en bij de beslissingen in het vochtbeleid. Wij vroegen aan Intensive Care en Medium Care verpleegkundigen, die op dat moment de zorg hadden voor patiënten met een recente SAB, om de actuele vullingstoestand in te schatten als ondervuld, normaal gevuld of overvuld. Deze inschattingen werden vergeleken met het actuele CBV, dat dagelijks werd gemeten middels PDD gedurende de eerste 10 dagen na de SAB. Hierbij bleek dat afwijkingen van een normale vullingstoestand veel voorkwamen bij deze patiënten, maar meestal niet als zodanig werden herkend. De voorspellingen van de verpleegkundigen hadden dan ook een zeer lage sensitiviteit. Op dagen dat een overvulling werd voorspeld door de verpleegkundige, was in feite een lager CBV aanwezig dan op dagen dat een normale of lage vullingstoestand werd vermoed. De voorspelling door verpleegkundigen blijkt geen goede maat voor de werkelijk aanwezige vullingstoestand.

#### ***Hoofdstuk 5 – Bloed volume metingen als gids voor het vochtbeleid na een SAB***

Wij onderzochten in een prospectieve gecontroleerde studie in patiënten met een recente SAB of een vochtbeleid, gestuurd op dagelijkse metingen van het CBV, de incidentie van ernstige ondervulling verminderd, in vergelijking tot een conventio-

neel vochtbeleid, gestuurd op de vochtbalans. CBV werd dagelijks gemeten in 102 patiënten gedurende de eerste 10 dagen na de SAB. In de interventie groep (n=54), met het vochtbeleid gestuurd door het CBV, toonden minder metingen ernstige ondervulling (6.7% versus 17.1%) en trad ernstige ondervulling op bij een kleiner deel van de patiënten (39% versus 54%). Het sturen van het vochtbeleid op dagelijkse metingen van het CBV reduceert de frequentie van voorkomen van ernstige ondervulling, maar desondanks treed ernstige ondervulling nog steeds op.

### ***Hoofdstuk 6 – Longoedeem en bloed volume na een SAB***

Longoedeem is een ernstige complicatie na een SAB. Longoedeem wordt vaak geïnterpreteerd als een teken van overvulling en als zodanig behandeld met diuretica (plasmiddelen), inotropica (medicijnen om de knijpkracht van het hart te versterken) en met een verminderde vochttoediening. In een prospectieve studie hebben wij het CBV, de vochtbalans en de cardiac index (maat voor de pompfunctie van het hart) gemeten en de meetwaarden vergeleken tussen patiënten die al dan niet longoedeem ontwikkelden na een SAB. Hierbij bleken patiënten met longoedeem een lager CBV te hebben in de dagen totdat de diagnose werd gesteld, dan patiënten waarbij geen longoedeem optrad. Patiënten met longoedeem waren meestal ondervuld. Patiënten waarbij het vochtbeleid werd gestuurd op dagelijkse metingen hadden een licht verhoogd risico op het ontwikkelen van longoedeem, vergeleken met patiënten met het vochtbeleid gestuurd op basis van de vochtbalans. Bij het nemen van maatregelen om het longoedeem te bestrijden moet rekening gehouden worden met het risico van het verder verergeren van de ondervulling.

### ***Hoofdstuk 7 – BNP en bloed volume na een SAB***

Hyponatriaemie (verlaagd natrium zout in het bloed) komt vaak voor na een SAB. Een belangrijke oorzaak is “cerebral salt wasting” (CSW), waarbij het verlies van natrium en water bij de urine toeneemt in reactie op een acute aandoening van de hersenen. Een toename in afgifte van brain natriuretic peptide (BNP) wordt gezien als een mogelijke initiator voor CSW. Patiënten met CSW neigen naar ondervulling. Een andere oorzaak van hyponatriaemie is het “syndrome of inappropriate ADH secretion” (SIADH), waarbij een toegenomen afgifte van antidiuretisch hormoon leidt tot water retentie in het lichaam. Patiënten met een SIADH hebben een normaal of licht verhoogd bloed volume. Het vochtbeleid bij CSW (vochttoediening) is tegengesteld aan dat bij SIADH (vochtbeperking). Wij bestudeerden bij 58 patiënten na SAB de relatie tussen de BNP concentratie en het optreden van ondervulling en hyponatriaemie. Patiënten met een verhoogd BNP hadden een verhoogd risico om ernstig ondervuld te raken. Een verhoogd BNP was echter niet geassocieerd met hyponatriaemie en de BNP concentratie was niet bruikbaar om te differentiëren

tussen een hyponatraëmie met ondervulling (CSW) en een hyponatraëmie met een normale of ruime vullingstoestand (SIADH). In onze studie populatie hadden de patiënten met een hyponatraëmie na SAB in een meerderheid van de gevallen (62%) een normale tot ruime vullingstoestand.

### ***Hoofdstuk 8 – Verlaagde bloeddruk in patiënten onder anesthesie bij het clippen van een cerebraal aneurysma***

De autoregulatie van de bloedvaten in de hersenen is na een SAB vaak verstoord. Hierbij kan de doorbloeding van de hersenen dan druk-afhankelijk worden. Hierdoor neemt het risico toe op een doorbloedingsstoornis van de hersenen tijdens periodes met een verlaagde bloeddruk. In het verleden werd de bloeddruk met opzet verlaagd tijdens operaties om het clippen van het aneurysma te vereenvoudigen, maar dit gebeurt op de meeste plaatsen niet meer omdat dit beleid is geassocieerd met een verslechtering van de uitkomst. Wij veronderstelden dat een onbedoelde bloeddrukdaling als gevolg van de anesthesie frequent voorkomt. We onderzochten retrospectief de ernst en de duur van bloeddrukdaling in 164 patiënten tijdens de anesthesie voor het clippen van een cerebraal aneurysma na een SAB. De meeste patiënten bleken tijdens de operatie gedurende lange tijd een vermindering in de gemiddelde arteriële bloeddruk te hebben van 30% of 40% ten opzichte van voor de operatie. Een daling van meer dan 50% trad slechts bij een minderheid van de patiënten op (13%) en duurde kort, gemiddeld 11 minuten. In onze onderzoekspopulatie, die bestond uit patiënten in een verhoudingsgewijs goede klinische conditie, vonden we geen verband tussen de bloeddrukdaling tijdens de operatie en het optreden van een doorbloedingsstoornis in het brein of een slechte uitkomst.

### ***Hoofdstuk 9 – Algemene beschouwing***

De resultaten van de verschillende studies besproken in dit proefschrift laten zien dat het niet eenvoudig is om de vullingstoestand "normaal" te houden. Een mogelijke oorzaak hiervoor is dat een SAB veelal gepaard gaat aan een systemische onstekingsreactie en functiestoornissen ontstaan van alle organen in het lichaam. Een gecoördineerde multidisciplinaire benadering van de SAB patiënt lijkt hier op zijn plaats, zowel bij het onderzoek als bij de patiëntenzorg. Bij verder onderzoek naar de bloedsomloop na een SAB moet rekening worden gehouden met de invloed van therapeutische maatregelen op de verschillende orgaansystemen en op de doorbloeding van de hersenen. Verschillende behandelwijzen kunnen dan beter met elkaar worden vergeleken en de invloed op de uitkomst worden bepaald. Hiermee zou de behandeling van de SAB patiënt meer op het individu kunnen worden gericht. Het uiteindelijke doel zou zijn de patiënt weer in een normale conditie te krijgen.



## Dankwoord

11 september 2013

Beste ouders,

Beste kinderen,

Beste docenten,

Beste vrienden,

Beste familie,

Beste collega's,

Beste kennissen,

Beste mensen,

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Dit proefschrift is opgedragen aan de heer C, de heer G en mevrouw L, een drietal van de patiënten waarbij ik de afgelopen jaren een bijdrage heb mogen leveren aan de behandeling toen zij een tijd ernstig ziek waren. Bij de zorg voor de kritisch zieke patiënt zijn inzet en betrokkenheid altijd de moeite waard, hoe het ook afloopt.

De diverse onderzoeken die ten grondslag liggen aan dit proefschrift zijn het resultaat van een langdurige samenwerking tussen vele personen van diverse achtergronden. Het onderwerp van dit proefschrift behoort niet toe aan een specifieke medische discipline maar ligt in een gebied tussen de anesthesiologie, de cardiologie, de intensive care, de neurochirurgie en de neurologie. Inbreng vanuit deze disciplines was dan ook onontbeerlijk. Slechts een beperkt aantal mensen kan ik hier met name noemen om te bedanken voor hun steun.

Prof. dr. CJ Kalkman, beste Cor, je hebt mij geïnspireerd om onderzoek te doen, op een terrein dat nauw aansloot bij mijn klinisch werk. Ik heb geleerd van je analytische blik en kwam jouw kamer altijd uit met meer vragen dan ik had toen ik er in ging. Je leerde me om te focussen, ook wanneer dit jou zelf niet altijd goed uitkwam. Dank voor de steun en het vertrouwen.

Prof. dr. GJE Rinkel, beste Gabriël, je was voor mij niet alleen promotor maar vaak ook copromotor, ondanks je steeds drukke agenda altijd bereid om mee te denken en op een onmogelijk tijdstip mijn geschriften van (vele) opmerkingen te voorzien. Ik dank je ook voor je bereidheid om je te begeven in de black box, die de IC en de operatiekamer voor veel neurologen zijn.

Prof. dr. A Algra, beste Ale, voor alle studies in dit proefschrift heb jij de methodologische en statistische onderbouwing geleverd. Jouw gecombineerde kennis van neurologie en epidemiologie is goud waard. Danzij je geduldige uitleg was ik in staat om iets te begrijpen van wat je me probeerde bij te brengen.

Prof. dr. JTA Knappe, beste Hans, als mijn opleider in de anesthesiologie gaf je al vroeg de gelegenheid me te ontwikkelen en verantwoordelijkheid te dragen op de gebieden die mijn bijzondere interesse hadden. En zoals een waar opleider betaamt was je er steeds als ik je nodig had. Dank.

Dr. GW van Dijk, beste Gert, als gewaardeerde klinische collega en als beoogd copromotor coachte je me door de eerste fase van dit onderzoeksproject. Jouw vertrek naar Nijmegen maakte hieraan een vroegtijdig einde maar een essentiële bijdrage had je al geleverd. Dank je.

BJI Schinkel-Veldkamp en EM Sluis, beste Joanna en Etiënne, al jaren hebben jullie met me samengewerkt, eerst als gedreven IC-verpleegkundigen en later als evenzeer gedreven onderzoeksverpleegkundigen. Een groot deel van de data in deze studies is door jullie verzameld, regelmatig ook buiten de reguliere werktijd. Ik ben vereerd dat jullie me nu ook als paranimf terzijde willen staan.

Walter van den Bergh, Ivo van der Bilt, Wolfgang Buhre, Olaf Cremer, Sanne Dorhout Mees, Diederik van Dijk, Wilton van Klei, Remco Minkhorst, Joep Scholten, Arjen Slooter, Anne Marie de Smet, Bon Verweij, Eric de Waal, collegae onderzoekers, dank voor de regelmatige discussies die wij voerden, de hulp bij vormgeving van figuren en al jullie heldere (en soms troebele) inzichten.

Veel te veel personen om op te noemen, maar de inzet van de verpleegkundigen, arts-assistenten, fellows en stafleden van de afdelingen anesthesiologie, intensive care, neurochirurgie en neurologie was elementair bij de zorg voor de patiënten na een SAB, voor het uitvoeren van de diverse onderzoeken en bij het verkrijgen van de gegevens. Zo ook de activiteiten van de medewerkers van het trialbureau van de afdeling neurologie. Daarbij kwam nog de inzet van de medewerkers van het secretariaat en het bedrijfsbureau van de Divisie Perioperatieve zorg en Spoedeisende hulp, onontbeerlijk om al het papierwerk en de financiering rond te krijgen. Bedankt.

Gerrit-Jan Noordergraaf en Henk Parmentier, voor mij loopt er een rechte lijn van acute hulpverlening, via de anesthesiologie en de intensive care, naar dit proefschrift. Dank voor de samenwerking en de vriendschap.

Ineke, Renske, Veerle en Marije, jullie zijn de leukste meiden van de hele wereld! Dank voor jullie aanwezigheid, de steun, het geduld en alle bijzondere momenten.





## Curriculum vitae



## Curriculum vitae

Reinier Hoff was born in 's-Gravenhage on September 17, 1962. After graduating from the Gymnasium B at the Maurick college (Vught) in 1981, he studied medicine at the Utrecht University. He developed an interest in emergency medicine. Together with two student-colleagues, the three of them active members of the Dutch Red Cross, he organized a course in emergency medicine for first year medical students that would be part of the official curriculum for more than a decade. These activities resulted in publication of a handbook on emergency medicine and in an award from the Utrecht University.

After obtaining his university degree in medicine in 1988, he worked for half a year as a university teacher in the Department of Resuscitation and Clinical Toxicology after which he continued his study. In 1990 he obtained his medical degree and then worked as a resident in cardiology and internal medicine at Ziekenhuis Velp, followed in 1991 by a residency at the Cardiothoracic Intensive Care Unit at hospital De Weezenlanden (Zwolle). From July 1992 onwards he worked as a resident in the Department of Anesthesiology at the UMC Utrecht, where his specialist training in anesthesiology started in January 1994 (chair: Prof. dr. JTA Knape). In July 1998 he started subspecialty training in Intensive Care at the UMC Utrecht (chair: Prof. dr. TJF Savelkoul). He registered as an anesthesiologist in January 1999 and as an intensivist in January 2000. He worked in the Neuro Intensive Care Unit from 2000 till 2005, and then in the Intensive Care Center of the UMC Utrecht till April 2008. In 2002 he started the research described in this thesis at the Department of Anesthesiology (promotor: Prof. dr. CJ Kalkman) in cooperation with the Department of Neurology (promotor: Prof. dr. GJE Rinkel).

From April 2008 onwards, he works as an anesthesiologist in the Division of Perioperative & Emergency Care of the UMC Utrecht, with a special interest in neuro-anesthesia, postoperative care, and teaching. He is a medical advisor to broeder de Vries Dutch Medical Services. Reinier Hoff married Ineke Bernink in 1993. They have three daughters: Renske (1994), Veerle (1996) and Marije (1999).

## List of publications



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## List of abbreviations

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ADH	Antidiuretic hormone
BNP	Brain natriuretic peptide
CBV	Circulating blood volume
CI	Confidence interval
CSW	Cerebral salt wasting
CVP	Central venous pressure
DCI	Delayed cerebral ischemia
$\Delta$ MAP	Difference in mean arterial blood pressure
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
Ht	Hematocrit
ICG	Indocyanine green
ICU	Intensive care unit
MAP	Mean arterial blood pressure
MCU	Medium care unit
OPTICA	Optimizing circulating blood volume after aneurysmal SAH
OR	Odds ratio
PCWP	Pulmonary capillary wedge pressure
PDD	Pulse dye densitometry
PED	Pulmonary edema
PO	Per os
PV	Plasma volume
RCT	Randomized controlled trial
RCV	Red cell volume
RR	Risk ratio
SAH	Subarachnoid hemorrhage
SD	Standard deviation
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SIRS	Systemic inflammatory response syndrome
TCD	Transcranial doppler
Triple H	Hypertension, hypervolemia, hemodilution
UMC	University Medical Center
WFNS	World federation of neurological surgeons grading scale



