Extracerebral Organ Dysfunction and Sleep Disorders in Subarachnoid Hemorrhage.

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Extracerebral Organ Dysfunction and Sleep Disorders in Subarachnoid Hemorrhage

Extracerebrale orgaan disfunctie en slaapstoornissen na een subarachnoïdale bloeding (met een samenvatting in het Nederlands)

Proefschrift

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Aan Martijn, Jeroen en Nynke

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Chapter 1

General Introduction

Subarachnoid hemorrhage (SAH), mostly caused by aneurysms, is a devastating event. The case-fatality is approximately 50% overall (including pre-hospital deaths) and one third of survivors remains dependent on help for activities on daily living.[1] The incidence of SAH is six to ten cases per 100 000 patient years.[1] Advances in treatment and prevention of complications have occurred, but these have led to only modest improvement in overall outcome.[2]

Cardiac injury and pulmonary edema occurring after acute neurological injury have been recognized for more than a century. These cardiac and pulmonary complications can lead to a disturbed oxygenation of the brain and thereby contribute to poor outcome in these patients. Despite their importance and frequent occurrence, little attention has been devoted to prevention and reversal of these medical complications after aneurysmal SAH. Research and clinical resources have focused on other major causes of death following SAH such as direct pressure effects of the initial bleed, rebleeding and delayed cerebral ischemia (DCI).

Cardiac and pulmonary complications are the most common extracerebral complications, but also an inflammatory response and metabolic derangements occur frequently after SAH. [3,4,5] It is not clear which patients with SAH will develop important cardiac and respiratory complications.

This thesis focuses on the occurrence of extracerebral organ dysfunction and the additional value of markers of these medical complications in prognosticating the occurrence of DCI or poor outcome.

In Chapter 1 we give an overview of the most common extracranial complications in patients with subarachnoid hemorrhage and describe their impact on delayed cerebral ischemia and outcome. Myocardial damage expressed by serum markers of myocardial necrosis (cardiac Troponin I) can lead to frequently seen complications as ECG abnormalities, disturbances in cardiac output or cardiac contractility or the occurrence of pulmonary edema.

In chapter 2 we hypothesized that electrocardiographic (ECG) repolarization abnormalities, as a marker of cardiac dysfunction, may be related to the development of delayed cerebral ischemia (DCI). We investigated the relation of these ECG abnormalities to the occurrence of DCI and assessed the additional value of ECG characteristics to established prognosticators for clinical outcome (clinical condition on admission, age and amount of extravasated blood).

Cardiac troponin I (cTnI) is a specific and highly sensitive marker of cardiac injury and is frequently elevated after SAH. Despite the direct link between SAH and cardiac injury, it is not clear whether elevated cTnI levels on admission independently predict secondary cardiac or pulmonary complications and outcome. We investigated the additional value of cTnI in predicting cardiac or pulmonary complications and outcome in patients with SAH (Chapter 3). In chapter 4 we investigated if cTnI adversely affects cardiac performance or the occurrence of pulmonary edema measured by single transpulmonary thermodilution. Transpulmonary thermodilution with the PiCCO system enables assessment of cardiac output and cardiac contractility (cardiac function index) in combination with early identification of pulmonary edema (elevated extravascular lung water). Pulmonary edema frequently occurs after SAH. Usually it is diagnosed by chest X-ray in combination with oxygenation disturbances.

In addition to cardiac and pulmonary complications, inflammatory response syndrome and metabolic derangement are frequently seen. This inflammatory response and laboratory assessments such as hypernatremia and leucocytosis have been linked to poor outcome. These clinical and laboratory parameters are part of a frequently used severity of illness score in the intensive care unit, the simplified acute physiology score (SAPS II). We studied the prognostic value of the SAPS II in patients with SAH for the occurrence of DCI and clinical outcome (Chapter 5).
Many patients who have survived an episode of SAH remain dependent for activities in daily living. Patients who are independent are often considered to have a 'good outcome'. We assessed clinical outcome (by means of the Rankin scale) at three months follow up in all our studies in this thesis. Many of the patients who are independent have a reduced quality of life (QoL). The reasons for this reduction in quality of life have not yet been determined. During long term follow up, patients who have had a SAH frequently complain of lack of initiative, falling asleep during daily activities, fatigue, irritability, loss of interests, and lack of concentration. Similar problems during daytime are often seen in patients with disorders of sleep and wake. In addition to our investigations on prognostic factors for outcome and secondary complications we studied the frequency and severity of disorders of sleep and wake and their relation to the Quality of Life in patients who have survived an episode of SAH (Chapter 6).
In the general discussion (Chapter 7), we review the main conclusions drawn from the studies in this thesis, and describe the implications of these studies for future patient care and research.

References

1. van Gijn J, Rinkel GJ. Subarachnoid hemorrhage: diagnosis, causes and management. Brain 2001;124:249-278.
2. Hop JW, Rinkel GJE, Algra A, van Gijn J. Case-Fatality Rates and Functional Outcome After Subarachnoid Hemorrhage: A Systematic Review. Stroke 1997;28:660-664.
3. Yoshimoto Y, Tanaka Y, Hoya K. Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. Stroke 2001;32:1989-1993.
4. Solenski NJ, Haley EC, Kassell NF, et al. Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007-1015.
5. Macmillan CSA, Grant IS, Andrews PJD. Pulmonary and cardiac sequelae of subarachnoid hemorrhage: time for active management? Intensive Care Med 2002;28:1012-1023.

Chapter 2

Extracerebral organ dysfunction in the acute stage after aneurysmal subarachnoid hemorrhage. The effect on outcome and delayed cerebral ischemia. Review

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Introduction

In patients with aneurysmal subarachnoid hemorrhage (SAH) rebleeding is an important cause of morbidity and case fatality in addition to the initial bleed.[1] Earlier treatment has reduced the influence of a rebleeding on outcome. However, even after early occlusion of the aneurysm many patients still deteriorate. Delayed cerebral ischemia (DCI) and hydrocephalus are important intracranial secondary complications. Extracranial complications often occur after SAH and some are related to the occurrence of DCI or poor outcome. Cardiac and pulmonary complications are the most common complications, but also an inflammatory response and metabolic derangements are frequently described after SAH. These extracranial complications are directly related to the extent of the initial hemorrhage and some are related to neurological complications and outcome. Also composite scores expressing organ dysfunction have been related to poor outcome.[2,3] Most of the physiologic derangements follow a sudden and sustained increase in systemic catecholamines. This autonomic instability can lead to organ dysfunction, hypoxemia, hyperglycemia or an inflammatory syndrome with the release of toxic cytokines.

Our aim is to give an overview of the most common extracranial complications in patients with SAH. We performed a literature search over the period 1980 till July 2004. We searched the Medline Database to identify all studies investigating extracranial complications in patients with SAH. Electronic search terms included subarachnoid h(a)emorrhage, (pulmonary) complications, pulmonary edema, (cardiac) complications, extracerebral organ dysfunction, left ventricular dysfunction, echocardiographic, troponin I, SIRS, metabolic, sodium, hyponatremia, hypernatremia, potassium, hypokalemia, hypomagnesemia, leucocytosis, hyperglycemia, delayed cerebral ischemia (DCI) and outcome. Reference lists of identified studies were searched for further studies. We focus on the frequency and effects on outcome and the occurrence of DCI or pulmonary and cardiac complications, systemic inflammation and metabolic derangement. When possible we expressed these effects of extracranial organ dysfunction on DCI and outcome as relative risks (RRs). We also discus some aspects of the presumed pathogenesis

Pulmonary complications

Six studies assessed the frequency, types and impact of pulmonary complications in patients with SAH. In 3 of these studies the pulmonary complications were part of extracerebral organ dysfunction. (Table 1) Pulmonary complications are the most frequently seen medical complications in SAH patients. These complications include pneumonia, aspiration, and pulmonary edema. Oxygenation disturbances are seen in 43% to 92% in patients with SAH. Severe oxygenation disturbances (PaO2/FiO2 ratio < 150) were found in 20% of patients. Oxygenation deficits in the acute stage of SAH most often result from pulmonary edema. The differential diagnosis of the pulmonary complications is often difficult. Invariably, aspiration is the initial diagnosis, but when the symptoms and chest radiographic abnormalities resolve within 24 to 48 hours, neurogenic pulmonary edema is suspected. In patients with aspiration the abnormalities on chest X-ray are more often unilateral and usually in dependent portions of the lungs.

Table 1. Frequency of pulmonary complications after SAH and their effect on outcome

Ref	N=	Definition of pulmonary complications	Frequency	Clinical Outcome measurement RR(95%CI)	DCI
15	70	AAgradient > 100mmHg	80%	Significant effect LOS; (Length of hospital stay was doubled)	0.9 (0.7-1.1)
22	305	All pulmonary complications	22%	Poor outcome (GOS I,II,III): 2.0 (1.3-3.1)	1.7 (1.2-2.4)
		NPE	2%	Case fatality: 1.6 (0.8-3.2)	
*18**	457	All pulmonary complications	NPE:23% Pneumonia: 22%	Most common nonneurologic cause of Case fatality	X
20	242	PaO2/ FiO2 < 150 (also mean PaO2/FiO2)	19%	Significant effect (χ^2 test) of lowest and mean PaO2/FiO2 ratio on death or severe disability(6mns)	X
*2**	413	AA gradient > 125mmHg	43%	Death or severe disability(3mns): 2.9 (2.2-3.9)	X
21	207	PaO2/FiO2 < 300	82%	Independent effect of highest LIS score on poor outcome (GOS I,II,III) †	X
		Severe lung injury (LIS score > 2.5)	17%		

AA: alveolar-arterial oxygen difference; DCI: Delayed cerebral ischemia; GOS: Glasgow Outcome Scale; LIS: Lung injury score; LOS: Length of hospital stay; NPE: neurogenic pulmonary edema

**prospective*

†LIS score: combination score of Chest Xray findings, PaO2/FiO2 ratio and amount of PEEP

Pulmonary edema

Stress failure with raised capillary pressure resulting in the development of a hydrostatic form of pulmonary edema is an important factor in neurogenic pulmonary edema.[4] At high pressures even disruption of the capillary endothelium or alveolar epithelium, or both will occur with the development of a high permeability type of pulmonary edema. In other words there is a progression from hydrostatic to high permeability edema as the capillary pressure is increased.[5,6,7,8] High pressure pulmonary edema seems to be not the only mechanism in NPE. Left ventricular failure was held for the mechanism in a study with 20 patients with NPE.[9] This is in agreement with most of the case reports describing increased pulmonary wedge pressures (77%) most often in combination with a reduced cardiac output (CO) or reduced left ventricular function (92%).[7,8,10,11,12,13,14] In some patients with impaired oxygenation no evidence for high permeability edema or cardiac failure is found. In these patients the oxygenation disturbances may result from extravascular lung water (EVLW) causing a less fulminant form of pulmonary edema.[15] EVLW correlated well with hypoxemia in a study with mainly intracerebral hemorrhage patients and 4 SAH patients.[16]

In a clinico-pathological study of 78 patients who had died from SAH, 55(71%) had a pathological diagnosis of pulmonary edema.[17] Of these 55 patients, 18 (31%) also had a clinical diagnosis of pulmonary edema. In this study before the era of CT, 63% of patients had also intracerebral hemorrhage in addition to SAH. In two observational studies with consecutive SAH patients (one prospective), pulmonary edema was seen in 20-25% of patients during the first two weeks of hospitalization.[15,18] The development of pulmonary edema is most frequently seen within the first 7 days after onset of the SAH. There seem to be two different patterns for the development of edema. An acute pattern occurring in minutes to hours after the insult, often in association with hemodynamic instability, and a presentation several days after the precipitating event.[11,13] The highest frequency is around day 3.[18] Pulmonary edema was found more often in patients with a poor clinical condition on admission, higher age, larger amount of extravasated blood, and in the days around surgery.[18,19] Also pulmonary edema can be caused by aggressive fluid loading, especially in those patients who develop left ventricular failure in the acute stage of SAH.
Oxygenation disturbances were related to the clinical condition on admission (Table 1). On admission both patients in good and poor clinical condition can have oxygenation disturbances.[20,21] Only patients with a poor clinical condition seem to deteriorate from pulmonary edema during hospitalization.

Pulmonary complications in relation to neurological complications and outcome

Six studies totaling 1694 patients with aneurysmal SAH describe pulmonary complications in relation to outcome. Two studies also investigated the relation between these pulmonary complications and the occurrence of delayed cerebral ischemia. One of the prospective studies observed the patients of the placebo arm of a large randomized controlled trial

of a calcium antagonist. Four studies used multivariate analyses to investigate the effect of pulmonary complications in relation to established prognosticators on outcome.

Delayed cerebral ischemia

Two retrospective studies studied the relation of pulmonary complications to the occurrence of vasospasm. In one study an independent effect of pulmonary edema on DCI was found (RR 1.67; 95%CI 1.16-2.39).[22] The other study found no significant relation of oxygenation disturbances on angiographic vasospasm.[15]

Outcome

In one prospective study with 413 patients determining the effect that acute physiologic derangements have on outcome, hypoxemia was the strongest predictor of death or severe disability.[2] In another prospective study pulmonary complications were the most common non-neurological cause of death. These pulmonary complications were responsible for 50% of all deaths from medical complications.[18] All but one study showed a significant effect of hypoxemia on the occurrence of poor outcome (table 1), even when only oxygenation disturbances within the first 24 hours were taken into account.[2,15,18,20,21,22]

Cardiac complications

Evidence of possible myocardial damage in SAH patients is supported by necropsy studies, serum markers of myocardial necrosis, and echocardiography. This myocardial damage can lead to frequently seen complications as cardiac arrhythmias, other electrocardiographic (ECG) abnormalities, hypotension or pulmonary edema. Possibly this can affect the occurrence of neurological complications, poor outcome or both. Hypotension and arrhythmia are frequently observed clinical cardiac problems in the acute stage of SAH. In combination with the occurrence of respiratory problems, intensive monitoring is required in the first days after SAH. Echocardiographic studies, ECG studies and cardiac enzyme studies are used to describe the frequency of myocardial complications. In the era of CT scanning 8 studies described echocardiographic abnormalities, mostly in relation to ECG disturbances. In two of these studies also hemodynamic performance parameters were investigated. In addition to these 8 studies, 5 other studies described echocardiographic left ventricular wall motion abnormalities or reduced left ventricular ejection fraction (EF) in relation to an elevated serum marker of myocardial damage (troponin I). Four of these troponin I (cTnI) studies used prospective data collection. In this review we focused on echocardiographic myocardial dysfunction and the relation of this dysfunction with DCI and poor outcome. Also the frequency of rhythm disturbances and the relation of ECG and cTnI abnormalities to echocardiographic dysfunction are described.

The most likely cause of cardiac dysfunction after SAH is excessive catecholamine release.[23] In a clinicopathological study on 54 SAH patients with SAH, hypothalamic and myocardial

lesions were found in 42.[24] In this study there was a correlation between these hypothalamic and myocardial lesions and varying pulse rates and blood pressures. In most patients there was evidence on pathological examination of contraction band necrosis as a cause of stress failure.[24,25] These microscopic structures (contraction bands) in the heart muscle, appear like bands of dead tissue of the muscle cells. The presence of any necrosis decreases the heart's ability to conduct electricity normally and to pump normally.[26] This neurogenic pump failure caused by dramatic increases in cardiac sympathetic drive[27], has also been mentioned a stunned myocardium, a state with reversible wall motion abnormalities or reduced left ventricular ejection fraction. These cardiac wall motion abnormalities usually do not correlate with the coronary vascular distribution on ECG, which also suggest a neurogenic mechanism.[23,28] In contrast to myocardial infarction normal coronary arteries were demonstrated in all 17 patients studied by autopsy or coronary angiography in SAH patients.[28,29,30,31,32,33,34,35,36] Diffuse ECG changes not consistent with a specific coronary artery distribution argues against CAD as the underlying cause. The diagnosis of SAH should be considered in those patients who are admitted to the coronary care unit because of the suspicion of myocardial infarction without a typical myocardial enzyme release pattern, but complain about a severe headache. This is also true for patients that are admitted to the coronary care unit because of brief loss of consciousness with a period of cardiopulmonary arrest without an evident cardiac cause.

Echocardiographic studies

The frequency of echocardiographic abnormalities was described in 13 studies and occurred in 159/2057 (8%) of SAH patients.[23,28,29,33,37,38,39,40,41] In four of these studies a consecutive series of patients was examined by means of echocardiography, irrespective of their clinical condition or ECG findings. In these 4 studies (3 with prospective data collection) left ventricular dysfunction was found in 92 of the 779 patients (12%).[23,33,40,41] In these studies left ventricular dysfunction was classified as left ventricular wall motion abnormalities or a reduced left ventricular ejection fraction or both. Profound myocardial dysfunction presenting within a few hours of the initial hemorrhage with a severely disturbed cardiac index and left ventricular ejection fraction (usually <40%) was found in 3% of patients and described in 15 patients in case reports, including one case series of 4 patients.[11,30,31,32,39,42,43,44,45] Patients in poor clinical condition were more likely to develop echocardiographic abnormalities [46] (Table 2). This relation is less clear for the amount of blood on CT and age. Female gender appears to be a strong risk factor for the occurrence of myocardial dysfunction. A higher risk of cardiac dysfunction for women was also found in a pathological study: in this study the relative risk for women was 7.4 (95% CI 1.1-49.2) compared to men.[24] In 50 patients repeated echocardiographic evaluations were described. In all these patients the echocardiographic myocardial dysfunction was normalized or improved.

Table 2. Echocardiographic abnormalities (Wall motion and/ or reduced ejection fraction) in relation with clinical features (female sex, admission HH and Fisher score), outcome and the occurrence of delayed cerebral ischemia (DCI).

Ref	N=	Frequency of echocardiographic abnormalities	RR(95%CI) Women	Poor clinical condition on admission	Large amount subarachnoid hemorrhage	Poor outcome	DCI
33*	13	4/13 (31%)	2.3 (1.1-4.7)	Yes	x	6.75 (0.98-46.6)ɣ	x
23	715	67/715 (9%)	1.3 (1.1-1.5)	Yes	No	x	x
37^	41	4/41 (10%)	x	12.0 (4.1-35.5)	x	18.5 (2.1-162) €	x
38^	72	9/72 (13%)	1.7 (1.4-2.0)	2.3 (1.8-3.1)	2.0 (1.4-2.9)	x	2.1 (1.2-3.8)J

**prospective*

^Recruitment criterion of reference 37 was not specified. All patients had an aneurysm and echocardiographic examination; 10 patients did not bleed. In reference 38 all SAH patients were selected that also had echocardiographic examination and a pulmonary artery catheter was placed

€ case fatality ɣ dependency

J Also cardiac index is an independent prognosticator for the occurrence of DCI

Cardiac Troponin I

Cardiac troponin I (cTnI), a relative new marker of myocardial injury, is a regulatory protein highly specific for the cardiac muscle. With cTnI it is possible to detect myocardial cell damage that is undetectable by conventional enzyme methods, with high sensitivity and specificity.[47] It is difficult to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction by cTnI. Myocardial dysfunction caused by myocardial infarction usually causes higher cTnI values then neurogenic dysfunction. Elevated cTnI values less than 2.8 ng/ml in patients with ejection fractions less than 40% were consistent with neurogenic cardiac dysfunction in one study.[39] So in SAH patient's cTnI levels even slightly above detection levels can give serious cardiac depression. Six studies totaling 775 (range 10-413) patients studied cTnI in SAH patients.[2,39,40,41,46,48] Three of these studies examined the predictive value of changes in cTnI for myocardial dysfunction. In these studies an elevated level of cTnI was found in 20-34% of patients on admission. Elevated cTnI was a good indicator of left ventricular wall motion abnormalities and left ventricular ejection fraction abnormalities.[46] The sensitivity of cTnI in the detection of echocardiographic left ventricular dysfunction was found to be 100%, the specificity around 90%.[40,41] Also patients with an elevated cTnI are more likely to manifest clinical evidence of left ventricular dysfunction.[41] Poor neurologic condition as assessed by means of the HH, female sex, larger body surface area and left ventricular mass index, lower systolic blood pressure, higher heart rate, higher phenylephrine dose and a shorter time from SAH symptom onset were independent predictors of cTnI release.[41,46] This is not in agreement with a prospective study with 43 patients that defined a cTnI level of ≥ 1.4 μg/L as abnormal and found no effect of the clinical condition at admission and the cTnI level.[40] In one study QTc prolongation was mentioned

a prognosticator for cTnI elevation.[49] Data on the relation of ST-T wave abnormalities and cTnI in 4 studies are inconsistent.[40,41,48,49]
Because cTnI is strongly related to cardiac dysfunction, we think that all patients with an elevated cTnI need more secure hemodynamic monitoring. Coronary angiography seems not necessary because no coronary abnormalities have been found in SAH patients. As the risk of cardiac death is very low in SAH patients the presence of neurocardiogenic injury should not affect aneurysm treatment decisions.

ECG

Five studies totaling 181 (range 13-57) patients, studied the relation of ECG changes and echocardiographic myocardial dysfunction.[29,33,34,37,48] In one study echocardiographic examination was performed in 4/47 patients based on elevated cTnI levels. Forty of 138 patients with echocardiographic examination had echocardiographic abnormalities. Three of these studies found T wave inversion as predictor of left ventricular abnormalities (Table 3). QTc dispersion and ST segment elevation in the acute stage of SAH were related to transient cardiac dysfunction in one study each. One study found no clear relation between ECG disturbances and cardiac dysfunction.[37] In this study only 4 patients had echocardiographic abnormalities and the mean time between ictus and ECG was 7.9 days and echocardiograms were obtained even a mean time of 2.8 days later. In a study on 457 patients, severe life-threatening arrhythmias occurred in 5%. The peak occurrence was on day 2 and 3.[18] In this study the frequency of cardiac arrhythmias was increased on the day of, or the day after, aneurysm surgery. In a study using Holter, life threatening arrhythmias occurred in 3 of 70 patients (4%), and serious cardiac rhythm disturbances in 19 (27%) of patients.[50]

Table 3. Twave inversion in relation to echocardiographic abnormalities

Ref	N=	Frequency of T wave inversion	Frequency of echocardiographic abnormalities	Twave;RR (95% CI)
33	13	5/13 (38%)	4/13 (31%)	9.0 (1.1-4.7)
34	57	12/57 (21%)	5/57 (9%)	7.4 (3.7-14.8)
48	47	17/47 (36%)	3/4*	3.1 (2.0-4.8)

** 4/47 patients had echocardiographic examinations*

Hemodynamic profiles

In one retrospective study on 72 patients echocardiographic wall motion abnormalities and myocardial enzyme release were related with impaired left ventricular performance after SAH. Cardiac output reduction from neurogenic cardiac injury in this study increased the risk of cerebral ischemia related to vasospasm.[38] The cerebral blood flow was related with cardiac output. An increase in cerebral blood flow was associated with an increase in the cardiac output.[51]

Relation of cardiac complications with outcome and DCI

Left ventricular dysfunction

Of the 8 studies using echocardiographic examinations in SAH patients, only 1 studied the relation of these abnormalities with the occurrence of delayed cerebral ischemia and 2 studied the relation with a poor outcome (Table 2). Only one of these studies assessed cardiovascular hemodynamic performance as a risk factor for delayed ischemia.[38] In this study delayed cerebral ischemia occurred in 6 of 9 patients (67%) with echocardiographic abnormal wall motion and in 20 of 63 patients (32%) without echocardiographic abnormal wall motion. Patients with echocardiographic abnormal wall motion therefore have a two times (95% CI 1.2 to 3.8) greater risk of delayed cerebral ischemia than patients without (Table 2).

At this moment there is no obvious evidence that echocardiographic abnormalities are related to outcome. Patients with echocardiographic abnormalities seem to prognosticate the occurrence of DCI.

Cardiac Troponin I

Six studies investigated the effects of cTnI in SAH patients. Three of these studied the relation between an elevated cTnI on delayed cerebral ischemia or poor outcome (Table 4). Only in the largest prospective study with 413 patients, cTnI was significantly associated with death of severe disability in univariate analysis, but not in multivariate analysis.

Table 4. Abnormal cTnI in relation with poor outcome and DCI

Ref	N=	prospective	recruitment	Poor outcome (ADL dependent)	DCI
41	39	yes	SAH	X	1.8 (0.9-3.6)
40	43	yes	SAH	1.3 (0.9-1.9)	1.2 (0.6-2.4)
2	413	yes	SAH	2.4 (1.7-3.4)	X

SIRS and metabolic derangement

Catecholamines, released from the primary ictus in SAH can lead to the occurrence of a systemic inflammatory response (SIRS) and electrolyte disturbances. Almost all studies described a relation between these metabolic abnormalities and the severity of SAH, assessed by clinical condition on admission and the amount of blood on CT. SIRS was seen in 54% of SAH patients admitted within 3 days after SAH and was an independent predictor for poor outcome.[52] Among the four individual SIRS criteria, heart rate, respiration rate, white blood cell count and also fever have been mentioned as significant outcome predictors.[52,53] Also SIRS seems to carry an increased risk of subsequent intracranial complications, such as vasospasm as well as systemic complications. Most of extracerebral complications (77%) were

related to the presence of SIRS.[20] In a recent study, a SAH physiologic derangement score was a better prognosticator for poor outcome than SIRS.[2] A combination of oxygenation disturbances, mean arterial blood pressure, serum bicarbonate and glucose (SAH physiologic derangement score) was independently associated with death or severe disability. Serum creatinine, bilirubine and lowest platelet count during ICU admission have also been found as predictors of poor outcome in univariate analysis in a study on 242 patients.[20] Table 5 lists the relation of the most frequently seen metabolic abnormalities in SAH on delayed cerebral ischemia and poor outcome.

A slight *hyperglycemia* (>5.8mmol/L; 104 mg/dl) is seen at admission in almost all patients. A concentration of > 9.0 mmol/L (162 mg/dl) is seen in 67% and a level > 13 mmol/L (234 mg/dl) in 21% at admission.[54] In case of serial measurements a level > 12 mmol/L (216 mg/dl) was seen in 46%.[55] From admission through day 10, glucose levels remained higher for patients with poor clinical outcome than for patients with good clinical outcome on each day.[56] The admission blood glucose and also glucose levels during ICU stay seems to be a significant predictor for outcome and delayed cerebral ischemia.[2,54,55,56,58] In four studies hyperglycemia was an independent predictor of poor outcome. One study found an independent effect on the occurrence of DCI (see table 5). Glucose levels at admission were associated with the severity of the SAH.[54,56,57,58] Also *hypomagnesemia* at admission is related with large amounts of extravasated blood, poor clinical condition on admission, and longer duration of unconsciousness at onset. Hypomagnesemia at admission did not contribute to the prediction of outcome or delayed cerebral ischemia in multivariate analysis.[59] Hypomagnesemia during days 2 and 12 after SAH independently predict the occurrence of delayed cerebral ischemia in this study. A low serum *potassium* occurs in approximately half the patients with SAH.[60] It is believed that hypokalemia in SAH is caused by the catecholamine surge. This catecholamine surge causes excessive activation of the sodium/ potassium-ATPase as a result of ß2-adrenergic receptor stimulation. The activation of the sodium/ potassium-ATPase results in trafficking of potassium ions from extracellular to intracellular spaces.[61] In resuscitated SAH patients a lower serum potassium concentration is found than in heart attack or asphyxia patients, despite the presence of severe metabolic acidosis.[62] This may indicate that the amounts of catecholamines released into the systemic circulation of SAH patients are higher than in heart attack or asphyxia. The relation of serum potassium on outcome and delayed cerebral ischemia has only been investigated in one retrospective study without consecutive data collection in operated patients between 1971 and 1987.[63] In this study changes in potassium had no obvious relationship to case fatality or delayed cerebral ischemia.

A high proportion of patients develop *hypernatremia* or *hyponatremia* after aneurysmal SAH. Hypernatremia is found in 12% during the first 3 days and in 19% during the entire clinical course. Hyponatremia is found in 19% and in 30-40% during the entire clinical course.[64,65] Severe hyponatremia 120-124 mmol/L is seen in 4%.[66] This hyponatremia is most frequently seen 6-7 days after SAH onset.[65,67] Hyponatremia in SAH is associated with a decrease in plasma volume in most patients. In patients with no SAH, hyponatremia is usually caused by the syndrome of inappropriate antidiuretic hormone secretion or

iatrogenic fluid overloading. In SAH patients natriuresis and hyponatremia reflect salt wasting and not inappropriate secretion of antidiuretic hormone.[67] Fluid restriction to correct hyponatremia increased the risk for delayed cerebral ischemia.[66] The largest study investigating the effect of sodium abnormalities on outcome was done before 1980.[68] In this study without consecutive data collection hypernatremia was related to case fatality. Also a combination of sodium abnormalities or polyuria, or both was related to the occurrence of angiographic vasospasm (RR1.5; 95%CI 1.3-1.8). The only study stratifying for the severity of SAH found a significant effect of hypernatremia on death or severe disability, but no independent relation between hypernatremia or hyponatremia and symptomatic vasospasm and no relation between hyponatremia and poor outcome.[64] *Leucocytosis* is usually regarded as non-specific indicator of infection or inflammation. It has been considered reflecting a stress situation with increased catecholamine activity also.[24] Leucocytosis, incorporated in the diagnosis SIRS, is seen slightly in fairly all patients with SAH. A leukocyte count > 20 x 10^9/L is seen in 16% of patients and significantly related to the occurrence of a poor outcome. Those with a leukocyte count > 20 x 10^9/L regardless of the clinical condition on admission (11/38 patients with a leucocyte count > 20 x 10^9/L had a Hunt and Hess of I-III), had virtually no chance of a good outcome.[69,70] The degree of leucocytes is an adverse prognostic factor for both case fatality and the development of cerebral ischemia in other studies also. Monitoring leukocyte count may allow early diagnosis for the occurrence of DCI for all days after SAH.[71]

SAH causes a sympathetic nervous activation with massive catecholamine release.[74] This catecholamine release might be the link between the initial ictus and some of the systemic complications after SAH. In patients with emotional stress, catecholamine release has been found to be linked to the occurrence of myocardial stunning.[73] Catecholamine stress may also cause high pressure pulmonary edema, myocardial myocytolysis, stress hyperglycemia, hypokalemia and leucocytosis.[4,24,61] Catecholamine concentrations are no independent predictors for poor outcome after subarachnoid hemorrhage if clinical condition on admission, amount of extravasated blood and age are taken into account.[75] This further adds to the suggestion that catecholamines are the link between the severity of the initial SAH and occurrence of systemic complications. However, other factors must be involved too in the development of systemic complications, because serial measurements of catecholamines concentrations could not be linked to the occurrence of electrocardiographic abnormalities during the clinical course after SAH.[75]

Table 5. Metabolic derangement and the effect on outcome and the occurrence of delayed cerebral ischemia

Ref	N=	Admission or serial values		Outcome RR(95%CI)	Definition poor outcome (date follow up)		DCI RR(95%CI)	Multi-variate analysis	Independent predictor
Hyperglycemia									
56	337^	Both		Yes (mean)	GOS1,2,3;(3mns)		X	Yes	No
54	99	Admission		1.4(1.0-1.8) 2.4(1.4-3.9)	GOS1,2,3;(>6mns) Case fatality		X	Yes	Yes
58	616^	Both	Admis Admis Day3-7 Day3-7	1.5(1.1-2.1) 2.5(1.5-4.2) 1.9(1.5-2.5) 2.2(1.5-3.3)	GOS1,2,3,4 GOS1,2,3;(3mns) GOS1,2,3,4 GOS1,2,3;(3mns)		X	Yes	Yes
55	244	Serial		2.6(1.9-3.7) 2.3(1.1-4.9)	GOS2,3(6mns) Case fatality	Univariate multivariate	1.7(0.9-3.0) 1.9(1.04-3.6)	Yes	Yes; both
2	413*	Admission		2.3(1.8-2.9)	GOS1,2,3(3mns)		X	Yes	Yes
57	70	Admission		7.1(3.0-16.6)	Death or severe deficit		X	X	
81	161	Admission		Yes (mean)	GOS1,2,3(1mns)		X	No	
Sodium									
64	298^	Admission (incl day3)	Hypo Hyper	1.6(1.1-2.5) 2.0(1.4-2.8)	GOS1,2,3;(3mns)	Hypo Hyper	1.2(.08-1.7) 1.3(0.96-1.9)	Yes	Yes; hypernatremia and outcome
82	208	Serial	Hypo	1.3(0.4-3.9)	Case fatality caused by DCI		2.0(1.1-3.6)	X	
66	134^	Serial	Hypo	1.4(0.6-3.1)Y	Case fatality caused by DCI		2.9(1.8-4.6)Y	X	
68	1000	Serial	Hypo Hyper	2.4(1.2-5.1) 6.1(3.5-10.9)	Case fatality		X	X	
63	173	Serial		No	Case fatality		No (mean)	X	
Hypomagnesemia									
59	107*	Both	Admis	1.5(1.1-2.1)	GOS1,2,3;(3mns)	Days2-12	2.0(0.9-4.3)	Yes	Yes; hypomagnesemia and DCI between day 2-12
Leucocytosis									
83	224	Serial		X			Yes	Yes	Yes
84	103	Serial		X		Day 3-14	Yes	X	
69	60	Admission	>12.000 >20.000	12.8(1.8-92.6) 9.1(3.8-21.5)	Case fatality		Yes	X	
71	173	Serial		Yes (mean and >15.000)	Case fatality		No obvious	X	
85	47	Admission		X			No	X	
70	171	Admission		2.9(2.2-3.8)	Case fatality		X	X	

DCI: Delayed Cerebral Ischemia
** prospective*
^ used prospective database
Y 26/44 had been treated with fluid restriction

Severity of illness scores, such as the APACHE II score are frequently used at the ICU. These scores include metabolic derangement, systemic inflammation, pulmonary and cardiac parameters and can predict the occurrence of an unfavorable neurologic outcome after SAH.[3,20] These scores offer an important insight into the acute and widespread systemic physiologic derangement that occurs in SAH with the initial 24 hours and point to potential therapeutic targets that may influence outcome.

Studies to test antihyperglycemic treatment in patients with SAH may be worthwhile. Intensive monitoring and treatment of blood glucose using insulin protocols improves blood glucose control and reduces morbidity and mortality in critically ill patients.[76,77]These positive effects on outcome of insulin protocols have been found in a heterogeneous population of critically ill patients. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for patients with SAH has to be investigated in future studies. The objectives of the treatment of hyponatremia in SAH are volume replacement and maintenance of a positive salt balance. Water and salt supplementation is the most commonly reported method.[78] In case of severe hypokalemia or hypomagnesemia, potassium or magnesium should be replaced either intravenously or orally. Prophylactic management with high dose magnesium sulfate therapy following SAH is under study in clinical trials.[72,79,80]

In case of pulmonary edema or oxygenation disturbances intensive monitoring is required for appropriate therapy. Inotropic medication and sometimes diuretics are needed in forward failure. Positive end-expiratory pressure is mandatory in neurogenic pulmonary edema without cardiac depression.

The frequency of cardiac arrhythmias, which include ventricular fibrillation and other arrhythmias impairing circulation warrant continuous rhythm monitoring to enable prompt treatment in SAH patients, at least for the first few days after the hemorrhage.[50] Also paroxysmal atrial fibrillation in SAH patients may need antiarrhythmic therapy. No general recommendations for the management of patients with SAH and cardiac dysfunction exist. In case of clinical relevant cardiac dysfunction (hypotension, pulmonary edema or acute ischemic changes on ECG), echocardiographic examination and invasive hemodynamic monitoring has been suggested.[34,43]

Conclusion

Pulmonary and cardiac complications, systemic inflammation and metabolic derangement are frequently seen after SAH. Most extracerebral organ dysfunctions are related to the extent of hemorrhage expressed as the clinical condition on admission and the amount of blood on CT. Hypoxemia, hyperglycemia, leucocytosis and hypernatremia are independently related to a poor outcome. Hypomagnesemia between days 2 and 12 and cardiac dysfunction are related to the occurrence of delayed cerebral ischemia. Echocardiographic abnormalities and reduced cardiac output seems to prognosticate the occurrence of DCI. There is less information about the effect of NPE on outcome and DCI or oxygenation disturbances on DCI. Almost no information exists about the prognostic information of echocardiographic left ventricular dysfunction on outcome. The effect of pulmonary edema and cardiac

complications in the first days after SAH on neurologic complications and outcome have to be investigated in new prospective studies, assessing consecutive SAH patients and adjusting for clinical condition on admission, gender and amount of blood on CT. Also prognosticating outcome with combined physiologic health scores in the acute stage of SAH needs further research. With this new prognostic information, management strategies can be tailored to those patients who are at high risk of delayed cerebral ischemia and poor outcome.

References

1 Kassel NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The international cooperative study on the timing of aneurysm surgery. Part1: Overall management results. J Neurosurg 1990;73:18-36.

2 Claassen J, Vu A, Kreiter KT, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832-838.

3 Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. Stroke 2002;33:1225-1232.

4 West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries in the intensive care setting. Schweiz Med Wochenschr 1992;122:751-757.

5 Smith WS, Matthay MA. Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema. Chest 1997;111:1326-1333.

6 Fein A, Grossman RF, Jones JG, et al. The value of edema fluid protein measurement in patients with pulmonary edema. Am J Med 1979;67:32-38.

7 Sprung CL, Rackow EC, Fein IA, Jacob AI, Isikoff SK. The spectrum of pulmonary edema: differentiation of cardiogenic, intermediate,and noncardiogenic forms of pulmonary edema. Am Rev Respir Dis 1981 Dec;124:718-22.

8 Fein IA, Rackow EC. Neurogenic pulmonary edema. Chest 1982;81:318-320.

9 Deehan SC, Grant IS. Haemodynamic changes in neurogenic pulmonary oedema: effect of dobutamine. Intensive Care Med 1996;22:672-676.

10 Schell AR, Shenoy MM,Friedman SA, Patel AR. Pulmonary edema associated with subarachnoid hemorrhage. Evidence for a cardiogenic origin. Arch Intern Med 1987;147:591-592.

11 Parr MJ, Finfer SR, Morgan MK. Reversible cardiogenic shock complicating subarachnoid hemorrhage. BMJ 1996;313:681-683.

12 McGrath RB, Kuerbitz C. Hemodynamics in subarachnoid hemorrhage. Crit Care Med 1989;17:381.

13 Mayer SA, Fink ME, Homma S, et al. Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. Neurology 1994;44:815-820.

14 Yabumoto M, Kuriyama T, Iwamoto M, Kinoshita T. Neurogenic pulmonary edema associated with ruptured intracranial aneurysm:case report. Neurosurgery 1986;19:300-304.

15 Vespa PM, Bleck TP. Neurogenic pulmonary edema and other mechanisms of impaired oxygenation after aneurysmal subarachnoid hemorrhage. Neurocritical Care 2004;1:157-170.

16 Touho H, Karasawa J, Shishido H, Yamada K, Yamazaki Y. Neurogenic pulmonary edema in the acute stage of hemorrhagic cerebrovascular disease. Neurosurgery 1989;25:762-768.
17 Weir BK. Pulmonary edema following fatal aneurysm rupture. J Neurosurg 1978;49:502-507.
18 Solenski NJ, Haley EC, Kassell NF, et al. Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007-1015.
19 Ochiai H, Yamakawa Y, Kubota E. Deformation of the ventrolateral medulla oblongata by subarachnoid hemorrhage from ruptured vertebral artery aneurysms causes neurogenic pulmonary edema. Neurol Med Chir (Tokyo) 2001;41:529-535.
20 Gruber A, Reinprecht A, Illievich UM, et al. Extracerebral organ dysfunction and neurologic outcome after aneurysmal subarachnoid hemorrhage. Crit Care Med 1999;27:505-514.
21 Gruber A, Reinprecht A, Gőrzer H. Pulmonary function and radiographic abnormalities related to neurological outcome after aneurysmal subarachnoid hemorrhage. J Neurosurg 1998;88:28-37.
22 Friedman JA, Pichelmann MA, Piepgras DG. Pulmonary complications of aneurysmal subarachnoid hemorrhage. Neurosurgery 2003;52:1025-1032.
23 Sato K, Masuda T, Izumi T. Subarachnoid hemorrhage and myocardial damage clinical and experimental studies. Jpn Heart J. 1999;40:683-701.
24 Doshi R, Neil-Dwyer GA. A clinicopathologic study of patients following a subarachnoid hemorrhage. J Neurosurg 1980;52:295-301.
25 Sato K, Masuda T, Kikuno T. Left ventricular asynergy and myocardial necrosis accompanied by subarachnoid hemorrhage: contribution of neurogenic pulmonary edema. J Cardiol 1990;20:359-67.
26 Karch SB, Billingham ME. Myocardial contraction bands revisited. Human pathology. 1986;17:9-13.
27 Masuda T, Sato K, Yamamoto S, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. Stroke. 2002;33:1671-1676.
28 Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. J Am Soc Echocardiogr 2000;13:774-9.
29 Kuroiwa T, Morita H, Tanabe H, Ohta T. Significance of ST segment elevation in electrocardiograms in patients with ruptured cerebral aneurysms. Acta Neurochir (Wien) 1995;133:141-6.
30 Jain R, Deveikis J, Thompson BG. Management of patients with stunned myocardium associated with subarachnoid hemorrhage. AJNR Am J Neuroradiol 2004;25:126-129.
31 Soman P, Senior R. Severe ventricular dysfunction secondary to subarachnoid hemorrhage. Clin Cardiol. 1997;20:402-403.
32 Pinto RJ, Goyal V, Sharma S, Bhagwati SN. Transient myocardial dysfunction in a patient with subarachnoid hemorrhage. Int J Cardiol. 1994;46:289-291.
33 Pollick C, Cujec B, Parker S, Tator C. Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study. J Am Coll Cardiol 1988;12:600-605.
34 Mayer SA, LiMandri G, Sherman D, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 1995;83:889-896.

35 Yuki K, Kodama Y, Onda J, Emoto K, Morimoto T, Uozumi T. Coronary vasospasm following subarachnoid hemorrhage as a cause of stunned myocardium. Case report. J Neurosurg 1991;75:308-311.

36 Yamaguchi T, Shimizu Y, Ono N, et al. A case of subarachnoid hemorrhage with electrocardiographic and echocardiographic changes simulating transmural myocardial infarction. Jpn J Med 1991;30:142-145.

37 Davies KR, Gelb AW, Manninen PH, Boughner DR, Bisnaire D. Cardiac function in aneurysmal subarachnoid hemorrhage: a study of electrocardiographic and echocardiographic abnormalities. Br J Anaesth. 1991;67:58-63.

38 Mayer SA, Lin J, Homma S, et al. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. Stroke 1999 Apr;30:780-786.

39 Bulsara KR, McGirt MJ, Liao L, et al. Use of peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:524-528.

40 Deibert E, Barzilai B, Braverman AC, et al. Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage. J Neurosurg 2003;98:741-746.

41 Parekh N, Venkatesh B, Cross D, et al. Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. J Am Coll Cardiol 2000;36:1328-1335.

42 Handlin LR, Kindred LH, Beauchamp GD,Vacek JL, Rowe SK. Reversible left ventricular dysfunction after subarachnoid hemorrhage. Am Heart J 1993;126:235-240.

43 Sakka SG, Huettemann E, Reinhart K. Acute left ventricular dysfunction and subarachnoid hemorrhage. J Neurosurg Anesthesiol 1999;11:209-213.

44 Yoshikawa D, Hara T, Takahashi K, Morita T, Goto F. An association between QTc prolongation and left ventricular hypokinesis during sequential episodes of subarachnoid hemorrhage. Anesth Analg 1999;89:962-4.

45 Donaldson JW, Pritz MB. Myocardial stunning secondary to aneurysmal subarachnoid hemorrhage. Surg Neurol 2001;55:12-16.

46 Tung P, Kopelnik A, Banki N, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. Stroke 2004;35:548-553.

47 Adams JED, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I. A marker with high specificity for cariac injury. Circulation 1993;88:101-106.

48 Horowitz MB, Willet D, Keffer J. The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 1998;140:87-93.

49 Sommargren CE. Electrocardiographic repolarization abnormalities in subarachnoid hemorrhage. Journal of electrocardiology 2002 suppl;35:257-262.

50 Andreoli A, di Pasquale G, Pinelli G, Grazi P, Tognetti F, Testa C. Subarachnoid hemorrhage: Frequency and severity of cardiac arrhythmias- A survey of 70 cases studied in the acute phase. Stroke 1987;18:558-564.

51 Tone O, Tomita H, Tamaki M, Hara M, Inaji M. Correlation between cardiac output and cerebral blood flow following subarachnoid hemorrhage. Keio J Med 2000;49:A151-3.

52 Yoshimoto Y, Tanaka Y, Hoya K. Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. Stroke 2001;32:1989-1993.

53 Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage. Relationship to vasospasm and outcome. Neurology 2001;56:1299-1304.

54 Alberti O, Becker R, Benes L, Wallenfang T, Bertalanffy H. Initial hyperglycemia as an indicator of severity of the ictus in poor-grade patients with spontaneous subarachnoid hemorrhage. Clin Neurol Neurosurg 2000;102:78-83.

55 Charpentie C, Audibert G, Guillemin F, et al. Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. Stroke 1999;30:1402-1408.

56 Dorhout Mees SM, van Dijk GW, Algra A, Kempink DR, Rinkel GJ. Glucose levels and outcome after subarachnoid hemorrhage. Neurology 2003;61:1132-1133.

57 Berek K, Kiechl S, Pfausler B, Auckenthaler A, Schmutzhard E. Prognostic indices in subarachnoid hemorrhage. Lancet 1992;339:68.

58 Lanzino G, Kassell NF, Germanson T, Truskowski L, Alves W. Plasma glucose levels and outcome after aneurysmal subarachnoid hemorrhage. J Neurosurg 1993;79:885-891.

59 van den Bergh WM, Algra A, van der Sprenkel JW, Tulleken CA, Rinkel GJ. Hypomagnesemia after aneurysmal subarachnoid hemorrhage. Neurosurgery 2003;52:276-282.

60 Fukui S, Katoh H, Tsuziki N, et al. Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. Critical Care 2003;7:R7-R12

61 Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med 1983;309:1414-1419.

62 Inamasu J, Nakamura Y, Saito R, et al. Normokalemia and hyperglycemia in subarachnoid hemorrhage patients resuscitated from prehospital cardiopulmonary arrest. Resuscitation. 2002;54:255-258.

63 Disney L, Weir B, Grace M, Roberts P. Trends in blood pressure, osmolality and electrolytes after subarachnoid hemorrhage from aneurysms. Can J Neurol Sci 1989;16:299-304.

64 Qureshi AI, Suri MFK, Sung GY, et al. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002;50:749-756.

65 McGirt MJ, Blessing R, Nimjee SM, et al. Correlation of serum brain natriuretic peptide with hyponatremia and delayed ischemic neurological deficits after subarachnoid hemorrhage. Neurosurgery 2004;54:1369-1374.

66 Wijdicks EFM, Vermeulen M, Hijdra A, van Gijn J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: is fluid restriction harmful? Ann Neurol 1985;17:137-140.

67 Wijdicks EFM, Vermeulen M, ten Haaf JA, Hijdra A, Bakker WH, van Gijn J. Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm. Ann Neurol 1985;18:211-216.

68 Takaku A, Shindo K, Tanaka S, Mori T, Suzuki J. Fluid and electrolyte disturbances in patients with intracranial aneurysms. Surg Neurol 1979;11:349-356.

69 Maiuri F, Gallicchio B, Donati P, Carandente M. The blood leukocyte count and its prognostic \ significance in subarachnoid hemorrhage. J Neurosurg Sci 1987;31:45-48.

70 Parkinson D, Stephensen S. Leukocytosis and subarachnoid hemorrhage. Surg Neurol 1984;21:132-134.

71 Weir B, Disney L, Grace M, Roberts P. Daily trends in white blood cell count and temperature after subarachnoid hemorrhage from aneurysm. Neurosurgery 1989;25:161-165.

72 Veyna RS, Seyfried D, Burke DG, et al. Magnesium sulfate therapy after aneurysmal subarachnoid hemorrhage. J Neurosurg 2002;96:510-514.
73 Wittstein S, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N.Engl.J.Med. 2005;352:539-548.
74 Naredi S, Lambert G, Eden E, Zall S, Runnerstam M, Rydenhag B, Friberg P. Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke 2000;31:901-906.
75 Brouwers PJAM, Westenberg HG, van Gijn J. Noradrenaline concentrations and electrocardiographic abnormalities after aneurysmal subarachnoid hemorrhage. J Neurol Neurosurg Psychiat 1995;58:614-617.
76 Krinsley Js. Effect of an intensive glucose management protocol on the mortality of critically iss adult patients. Mayo Clin Proc. 2004;79:992-1000.
77 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359-1367.
78 Harrigan MR. Cerebral Salt Wasting Syndrome: a review. Neurosurgery 1996;38:152-160.
79 Boet R, Mee E. Magnesium sulfate in the management of patients with Fisher Grade 3 subarachnoid hemorrhage: a pilot study. Neurosurgery 2000;47:602-607.
80 van den Bergh WM, Albrecht KW, Berkelbach van der Sprenkel JW, Rinkel GJ. Magnesium therapy after aneurysmal subarachnoid hemorrhage a dose-finding study for long term treatment. Acta Neurochir (Wien) 2003;145:195-199.
81 Longstreth WT, Jr, Nelson LM, Koepsell TD, van Belle G. Clinical course of spontaneous subarachnoid hemorrhage: a population based study in King County, Washington. Neurology 1993;43:712-718
82 Hasan D, Wijdicks EF, Vermeulen M.Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. Ann Neurol 1990;27:106-108.
83 McGirt MJ, Mavropoulos JC, McGirt LY, et al. Leukocytosis as an independent risk factor for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:1222-1226.
84 Niikawa S, Hara S, Ohe N, Miwa Y, Ohkuma A. Correlation between blood parameters and symptomatic vasospasm in subarachnoid hemorrhage patients. Neurol Med Chir (Tokyo) 1997;37:881-885.
85 Spallone A, Acqui M, Pastore FS, Guidetti B. Relationship between leukocytosis and ischemic complications following aneurysmal subarachnoid hemorrhage. Surg Neurol 1987;27:253-258.

Chapter 3

ECG abnormalities in predicting secondary cerebral ischemia after subarachnoid hemorrhage

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Submitted for publication

Introduction

Electrocardiographic (ECG) repolarization changes occur in three quarters of patients with Subarachnoid Hemorrhage (SAH) irrespective of the presence or absence of previous cardiac disease.[8] Most frequent are QTc prolongation, ST segment deviation, an inverted T wave or the occurrence of an abnormal U wave. ECG abnormalities in the acute stage of SAH are usually attributed to autonomic imbalance, in particular to direct autonomic discharge to the heart or to increased levels of circulating catecholamines.[17]

The ECG changes found early after SAH have been linked to outcome in some studies investigating this relationship[2,4,7,9,10,11,12,18,20] (table 1). The pathogenesis behind this relation has not been elucidated. The initial hemorrhage frequently causes repolarization abnormalities and is associated with transient myocardial dysfunction. This myocardial dysfunction can cause arrhythmias, pulmonary edema, and hemodynamic instability, which all may contribute to secondary brain injury.[13,15,16] We hypothesized that through this pathway cardiac dysfunction may be a contributing factor in the development of DCI.

The aim of this study was to investigate the prognostic value of repolarization abnormalities observed at baseline 12-lead ECG for the occurrence of DCI in patients with SAH. Additionally we investigated whether electrocardiographic repolarization abnormalities have additional prognostic information for clinical outcome in addition to established prognosticators such as the clinical condition on admission and the amount of extravasated blood on the initial brain CT.

Table 1 Literature reporting outcome in the period with brain CT

References and Year study	No. of patients	Repolarization abnormalities	Outcome event	Outcome correlation	Details
2; 1986-1987*	61	QTc,ST↓,T↓↑,U,P↑,PR	Poor outcome and DCI	No relation individual ECG abn; cardiac ischemia adds to value of clinical criteria for predicting poor outcome.	14 > 24h of SAH admission; Stratified for GCS and blood on CT
20; 1991-1996	58	ST↑↓,T↓	In hospital all cause and cardiac mortality	Univariate relationship with combination of ECG abn; multivariately not.	
7; 1997-1999#	122	QTc,ST↑↓,T↓↑ Inverted U,Q, ECG score	In hospital mortality	QTc and ECG score most significant prognosticator in multivariate analyses	ECG score (total number of leads with Q, ST↓,T↓)
4; <1991	45	QTc,ST↑↓,T↓↑,U	In hospital mortality	No relationship	10 patients no SAH; ECG: mean 5 days after SAH
10; 1999-2000#	97	QTc,ST↑↓,T↓↑,U	In hospital death	ST↓ significant relation; OR 17.7 (95%CI:1.6-880.1)	70 (42%) missing ECG 18 of 97 no aneurysm
18; 2001-ongoing*#	100	QTc,ST↑↓,T↓,U	In hospital mortality	No relationship	Computerized ECG measurement
11; 1977-1983	100	QTc,ST↑↓,T↓↑,U,Q,PR	In hospital death and angiographic vasospasm	ST↓,QTc and Q with outcome; abnormal ECG with angiographic vasospasm	No standard CT
12; <1995 (3 years study)	70	QTc,ST↑↓,T↓↑,U,P,PR	In hospital outcome (neurological deficit) and angiographic vasospasm	No relationship	Pre operative ECG ; 25 >36 h after SAH
9; <1995 (6 years of study) #	23	ST↑	Symptomatic Vaso-spasm (no further classification)	No relationship	only 4 with vaso-spasm; All 23 had ST↑ out of 226 not specified patients

**Prospective study; #only admission ECG*

Materials and Methods

Study population

We studied a consecutive series of 148 patients with SAH who had been admitted within 4 days after onset of SAH to the Westeinde hospital in the Hague between January 2000 and July 2002. From this series we excluded 9 patients with a non-aneurysmal perimesencephalic hemorrhage, 3 patients with complete left bundle branch block and 3 patients with a history of heart disease, as well as 12 patients who had no ECG recording on the day of admission. The remaining 121 patients had an SAH with an aneurysmal pattern of hemorrhage on CT. In 28 of these patients no intra-arterial angiography had been performed because of a poor clinical condition from the outset. These 28 patients all died early during their hospital

course. In 3 other patients no aneurysm was detected in two angiographic evaluations. No patient used class I or III antiarrhytmic drug or digoxin, which may alter the cardiac repolarization. All patients were treated according to standard intensive care guidelines during at least two weeks after their hospitalization. This protocol consisted of absolute bed rest, oral nimodipine, an oral antiepileptic drug and intravenous administration of fluid aiming at normovolemia. We refrained from antihypertensive medication unless in case of extreme values or impeding end-organ failure.

Data collection

An admission 12-lead ECG of each patient was analyzed by an experienced electrocardiographer who was blinded to the patient's condition. In general, ST elevation or depression greater than 0.1 mV in limb leads or 0.2 mV in pre-cardial leads were defined as an abnormal finding. A T wave was defined as inverted if less than 0.1 mV in depth, and as peaked if greater than 1 mV. T wave abnormalities were assessed in leads I, II, aVL, aVF and V.[2-6] The occurrence of a U wave was recorded. The corrected QT (QTc) interval was calculated by Bazett's formula 1 from an average of 3 complexes in lead II and was considered abnormal if it was longer than 0.42 s in men and 0.43 s in women. Occurrences of ischemic like ECG abnormalities were also recorded. We defined ischemic like ECG abnormalities as the presence of ST depression or T wave inversion, or both in at least two leads.

The clinical condition on admission was evaluated according to the WFNS classification.[5] A dichotomy was made between good neurological condition (WFNS I,II, or III) and poor neurological condition (WFNS IV or V) on admission. The amount of subarachnoid blood was assessed according to the classification of Hijdra.[6] Subarachnoid blood in 10 cisterns or fissures and in 4 ventricles on CT was evaluated semi quantitatively as scores ranging from 0 to 3 . Each cistern, fissure or ventricle was graded separately according to the amount of extravasated blood. We calculated the total sum score of blood in the basal cisterns (range 0-30) and ventricles (range 0-12) and dichotomized these at their median value.

The outcomes of interest were the occurrence of DCI and poor clinical outcome (death or dependence). DCI was considered definite in case of a new hypodense lesion on the CT scan together with a gradual developing focal deficit, impairment of consciousness, or both in a patient with no other explanation for this event. Clinical features without hypodensities revealed by a CT scan were scored as probable DCI. In all analyses, definitive and probable DCI were combined.

Based on clinical status at 3 months after onset, we evaluated outcome according to the 5 point Rankin scale.[19] We qualified the scores 0 to 3 as good outcome and the scores 4,5 and death as poor outcome. A score of 0-3 points means that the patient is independent for activities of daily life. Rebleeding was defined as a sudden clinical deterioration with evidence of new blood on CT in comparison with a previous scan.

Data analysis

Descriptive statistics were used to report the number and type of ECG abnormalities.

We related the occurrence of DCI to baseline characteristics (WFNS, amount of blood on baseline CT and age) and to the individual ECG abnormalities (ST depression or elevation, a peaked T or T wave inversion and a U wave) of admission ECG by means of Cox proportional hazards modeling, which yields hazard ratios (HR). HRs may be interpreted as relative risks;[3] these were considered statistically significant if the 95% confidence interval (CI) did not include 1. Next we developed multivariate models with forward selection. The first model was based on WFNS, age and Hijdra score (model M1); secondly we extended it with the individual ECG abnormalities (M2). Variables were retained in the model if the corresponding p-value was < 0.10. We evaluated the discriminating power of the models with the area under the curve (AUC) of the corresponding receiver operator characteristic curve (ROC). An AUC can range from 0.50 (no discriminatory power) to 1.0 (perfect prediction). In additional analyses the combined ischemic like ECG abnormalities were entered in a third model (M3) together with the baseline characteristics and the individual ECG abnormalities. In the analyses for DCI, patients were censored at the time of rebleeding, death or at discharge.

We also looked for the relation between ECG characteristics and poor clinical outcome with logistic regression modeling, which yields crude odds ratios. For multivariate analyses a similar strategy as for the analysis of DCI was used.

Table 2 Patient characteristics

Total 121 patients		
Age		
Mean (sd)		54.7 (12.9)
Female gender n (%)		90 (74%)
WFNS at admission n(%)		
I		37 (31%)
II		26 (21%)
III		13 (11%)
IV		17 (14%)
V		28 (23%)
Hijdra score		
Cisternal score	Median (range)	18 (0-30)
Ventricular score	Median (range)	2 (0-12)
Electrocardiographic findings*		
ST elevation		10 (8%)
ST depression		17 (14%)
T wave inversion		38 (31%)
Peaked T wave		21 (17%)
QTc prolongation		16 (13%)
U wave		63 (52%)
Ischemic like ECG abnormalities		33 (27%)
Outcome events		
DCI		52 (43%)
Poor outcome		58 (48%)
Rebleeding		12 (10%)

** Some patients had more abnormalities on their ECG so total exceeds 100%.*

Results

The baseline characteristics of the included patients are listed in table 2. Twenty-five (20.7%) patients had no repolarization abnormalities at the admission electrocardiogram. The most frequent abnormalities were ST depression, T wave inversion, a peaked T wave, the presence of a U wave or QTc prolongation. A U wave was found in 52% of admission electrocardiograms.

DCI

Of the individual ECG characteristics, only ST segment depression predicted the occurrence of DCI (HR 2.4 [95%CI, 1.2-4.9]) (table 3). No other baseline characteristic or the combined ischemic like ECG changes had a statistically significant relation with DCI in univariate analysis. Because ST depression was the only variable with a statistically significant association with DCI we refrained from multivariate analyses. The AUC of the ROC for ST depression was 0.53 (95%CI 0.42-0.63).

Table 3 Predictors for the occurrence of DCI in the univariate analyses

Variable	Hazard ratio	95% CI
ST depression	2.4	1.2-4.9
ST elevation	2.1	0.7-5.7
T wave inversion	0.9	0.5-1.7
Peaked T wave	0.7	0.3-1.5
U wave	0.7	0.4-1.3
QTc prolongation	1.0	0.5-2.3
Ischemic like ECG abnormalities*	1.3	0.7-2.4
WFNS	0.7	0.4-1.4
Female sex	0.5	0.4-1.6
Age	0.99	0.97-1.01
Hijdra score		
Cisternal score > median	1.4	0.8-2.4
Ventricular score > median	1.5	0.9-2.6

** ST segment depression or T wave inversion, or both in at least two leads.*

Clinical outcome

In the univariate analyses ST elevation, ST depression, T wave inversion, a peaked T wave and the occurrence of a U wave were related to outcome (table 4). A peaked T wave and a U wave were related to a favorable outcome.

Established prognostic factors such as WFNS, age, and the amount of blood on CT (model M1) predicted the occurrence of poor outcome in this population as well. In multivariate model M1 (established prognosticators) WFNS and Hijdra score were retained, but not age (table 5). Upon extension with the individual (marginal) statistically significant ECG variables (M2) only WFNS score, Hijdra ventricular score, ST depression, a peaked T wave

and a U wave were retained in the model. In subsequent extension of this model with combined ischemic like ECG abnormalities (M3) to this model the WFNS score, Hijdra ventricular score, U wave and the combined ischemic like ECG abnormalities were retained. The AUC of the ROC for model M1 was 0.81 and that for models M2 and M3 0.84 (Figure 1).

Table 4 ECG changes and baseline clinical characteristics and their relation to poor outcome in univariate analyses

	Odds Ratio	**95% CI**
ST elevation	4.9	0.99-24.0
ST depression	10.6	2.3-48.8
T wave inversion	2.5	1.1-5.5
Peaked T wave	0.4	0.1-1.03
U wave	0.4	0.2-0.9
QTc prolongation	1.1	0.9-3.2
Ischemic like ECG abnormalities *	8.3	3.0-22.2
Age (continuous)	1.04	1.01-1.07
WFNS ≥ 4	8.1	3.4-19.0
Hijdra score		
Cisternal score above median	2.8	1.4-5.9
Ventricular score above median	8.6	3.7-19.5

** ST segment depression or T wave inversion, or both in at least two leads.*

Table 5. Multiple logistic regression on selected variables for outcome

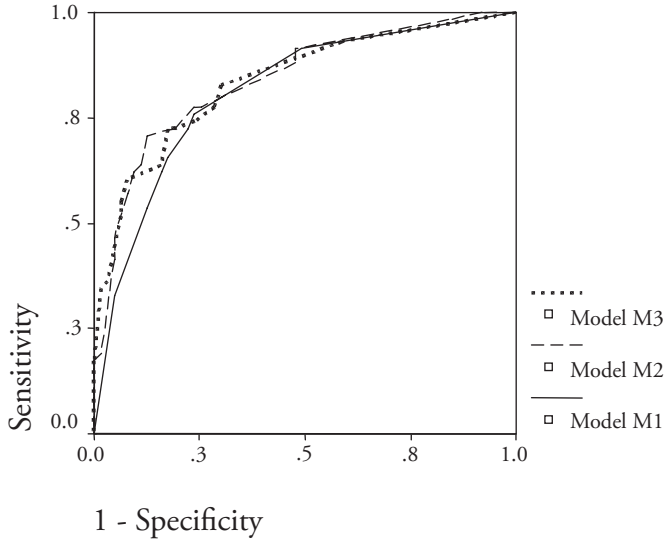
	M1		**M2**		**M3**	
Variable	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
WFNS ≥4	3.3	1.1-9.6	4.3	1.4-13.7	3.1	0.99-9.9
Hijdra score						
Cisternal score >18	2.7	1.2-6.4	-	-	-	-
Ventricular score >2	4.3	1.5-12.0	3.6	1.2-10.6	3.2	1.1-9.5
ST depression			6.2	1.2-33.7	-	-
Peaked T wave			0.3	0.1-0.9	-	-
U wave			0.4	0.2-0.98	0.4	0.1-0.9
Ischemic like ECG abnormalities					5.2	1.7-15.9
AUC of ROC	0.81	0.74-0.89	0.84	0.77-0.91	0.84	0.74-0.89

Variables were excluded from the model if the corresponding p-value was > 0.10

We found that ECG characteristics do not contribute to the prediction of DCI. Although ST depression had a statistically significant relationship with the occurrence of DCI in univariate analysis, the importance of ST depression for prognosticating DCI is negligible. Our secondary aim was prognosticating poor outcome. ST depression and in subsequent analyses a combination of ischemic ECG abnormalities appeared independent predictors

of poor outcome. The additive prognostic information of these ECG variables for poor outcome is limited.

Figure 1 ROC curves of Model M1,M2 and M3 in predicting outcome



M1: WFNS and Hijdra score

M2: WFNS, Hijdra ventricular score, ST depression, peaked T wave and U wave

M3: WFNS, Hijdra ventricular score, U wave and ischemic like abnormalities

Discussion

In the acute stage after SAH autonomic instability and an excess of catecholamines frequently lead to ECG and cardiac enzyme changes as an expression of temporary cardiac dysfunction. The electrocardiogram provides a simple tool to screen patients for cardiac dysfunction. In previous studies with SAH patients, ST elevation, T wave inversion and QTc prolongation appeared to be related with transient cardiac dysfunction,[9,14] and cardiac dysfunction has been found to be an independent prognostic factor for the occurrence of DCI.[15]

Only one study investigated the relation of serial acquired ECG abnormalities to the occurrence of DCI[2] The authors found no predictive effect of individual ECG abnormalities on DCI. Several explanations for the weak relation between ECG abnormalities and DCI may exist. Firstly, ECG abnormalities may not be sufficiently accurate markers for the identification of myocardial damage that leads to DCI. Secondly, myocardial dysfunction leading to DCI may occur in the absence of ECG changes. Thirdly, ECG abnormalities do not necessarily reflect impaired autoregulation. An impaired autoregulation in combination

with a reduced perfusion pressure and reduced cardiac output is associated with increased risk for DCI.[13]
Numerous reports have described ECG changes after SAH that are associated with poor outcome. Many of these studies were small and sometimes hampered by exclusion of many patients, and are therefore difficult to extrapolate to other series of SAH patients. Most studies (table 1) concluded that there was a relation of the clinical condition at admission or the amount of extravasated blood and the presence of ECG abnormalities. This probably explains that the additional prognostic value of ECG abnormalities to the clinical condition on admission and the amount of extravasated blood on outcome was limited in our study. Only three studies took these prognostic baseline characteristics into account.[2,7,20] These three studies, primary focusing at case fatality rates, suggested an additional effect of a combination of ischemic like ECG abnormalities to the clinical condition on admission and the amount of extravasated blood. In a retrospective cohort study with 122 patients a combination of a pathological Q wave, ST depression and T inversion was the most powerful risk factor for in hospital mortality in a multivariate model also including Hunt and Kosnik, QTc interval, age and sex.[7] The additional prognostic value of this combined ECG score was not investigated in that study.

A limitation of our study is the partly retrospective data collection. However, 75 percent of the data were prospectively acquired and we admitted all SAH patients to the ICU for at least 2 weeks with standard daily treatment. Except for 12 patients with missing ECG's a complete dataset of all other consecutive SAH patients was present. Clinical condition on admission and outcome of the 12 patients with missing ECG's were comparable with the other patients. It is unlikely that excluding these patients influenced our results importantly. A potential drawback is that the study ECG was performed not immediately in some patients but up to 4 days after SAH onset. Almost all patients (120) were admitted within 48 hours of hemorrhage and in none of the patients the DCI preceded the first study ECG.
We investigated only the admission ECG and excluded patients with already known cardiac disease. Thereby we excluded other causes of ECG changes such as medical treatment (inotropic support). In our study we took as one of the outcomes DCI, and not vasospasm. Vasospasm does not always lead to DCI or clinical features and is therefore a less relevant outcome from a clinical standpoint of view.
In addition to the prognostic effect of ST depression and ischemic like ECG abnormalities for poor outcome, the occurrence of a U wave and a peaked T wave significantly predicted a favorable outcome. No other study mentioned this protective effect of individual ECG abnormalities. We find it difficult to explain this observation.

In conclusion ST depression and ischemic like ECG abnormalities are independent predictors of a poor outcome, but the relation of these individual ECG parameters with poor outcome is not explained through the occurrence of DCI. The additional value of ECG abnormalities to baseline characteristics in prognosticating outcome appeared to be limited.

References

1 Bazett HC: An analysis of the time relationships of the heart. Heart 1920;7:353-370.

2 Brouwers PJAM, Wijdicks EFM, Hasan D, Vermeulen M, Wever EFD, Frericks H, et al: Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage. Stroke 1989;20:1162-1167.

3 Cox DR: Regression models and life-tables. J R Stat Soc.[B] 1972;34:187-202.

4 Davies KR, Gelb AW, Manninen PH, Boughner DR, Bisnaire D: Cardiac function in aneurysmal subarachnoid hemorrhage: a study of electrocardiographic and echocardiographic abnormalities. Br J Anaesth 1991;67:58-63.

5 Drake CG: Report of World Federation on Neurological Surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988;68:985-986.

6 Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J: Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke 1990;21:1156-1161.

7 Kawasaki T, Azuma A, Sawada T, Sugihara H, Kuribayashi T, Satoh M, et al : Electrocardiographic score as a predictor of mortality after subarachnoid hemorrhage. Circ J 2002;66:567-70.

8 Khechinashvili G, Asplund K: Electrocardiographic changes in patients with acute stroke: A systematic review. Cerebrovasc Dis 2002;14:67-76.

9 Kuroiwa T, Morita H, Tanabe H, Ohta T: Significance of ST segment elevation in electrocardiograms in patients with ruptured cerebral aneurysms. Acta Neurochir (Wien) 1995133:141-146.

10 Lorsheyd A, Simmers TA, Robles de Medina EO : The relationship between electrocardiographic abnormalities and location of the intracranial aneurysm in subarachnoid hemorrhage. Pacing Clin Electrophysiol 2003;26:1722-1728.

11 Maiuri F, Benvenuti D, de Chiara A, Maddalena G, Carandente M, Albi F: Electrocardiographic changes and their prognostic significance in patients with subarachnoid hemorrhage. Acta Neurol (Napoli) 1984;6:111-116.

12 Manninen PH, Ayra B, Gelb AW, Pelz D: Association between electrocardiographic abnormalities and intracranial blood in patients following acute subarachnoid hemorrhage. Journal of Neurosurg Anesthesiol 1995;7:12-16.

13 Mayer SA, Fink ME, Homma S, Sherman D, LiMandri G, Lennihan L, et al: Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. Neurology 1994;44:815-820.

14 Mayer SA, LiMandri G, Sherman D, Lennihan L, Fink ME, Solomon RA, et al : Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 1995;83:889-96.

15 Mayer SA, Lin J, Homma S, Solomon RA, Lennihan L, Sherman D, et al: Myocardial injury and left ventricular performance after subarachnoid hemorrhage. Stroke 1999;30:780-786.

16 Pollick C, Cujec B, Parker S, Tator C: Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study. J Am Coll Cardiol 1988;12:600-605.

17 Sato K, Masuda T, Izumi T: Subarachnoid hemorrhage and myocardial damage; clinical and experimental studies. Jpn Heart J 1999;40:683-701.

18 Sommargren CE, Zaroff JG, Banki N, Drew BJ: Electrocardiographic repolarization abnormalities in subarachnoid hemorrhage. Journal of Electrocardiol 2002;35; suppl: 257-262.

19 Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.

20 Zaroff JG, Rordorf GA, Newell JB, Ogilvy CS, Levinson JR: Cardiac outcome in patients with subarachnoid hemorrhage and electrocardiographic abnormalities. Neurosurgery 1999;44:34-40.

Chapter 4

Troponin I in predicting cardiac or pulmonary complications and outcome in subarachnoid hemorrhage.

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Introduction

Subarachnoid hemorrhage (SAH) from an intracranial aneurysm remains a devastating event. Approximately 30 to 50% of patients who reach the hospital alive die and another 10-20% remain dependent on help for daily activities.[1] The leading causes of death and disability are the initial or repeated bleedings, and delayed ischemic events.[2] The initial and repeated bleedings may induce extracranial sequelae, of which cardiac and pulmonary are the most frequent.[3] These cardiac and pulmonary complications related to SAH can lead to a disturbed oxygenation of the brain and thereby contribute to poor outcome in these patients. Most likely the excessive catecholamine release after SAH is the driving force of left ventricular dysfunction of the heart and pulmonary edema.[4] The severity of the brain injury is strongly related to the occurrence of these cardiac and pulmonary complications.[5] Troponin I (cTnI), a regulatory protein highly specific for the cardiac muscle, is a reliable marker of myocardial injury leading to left ventricular dysfunction.[6] An elevated cTnI level is a marker of poor prognosis in patients with unstable cardiac ischemia and also in patients with septic shock.[7,8] In recent studies 30 to 40% of patients with SAH showed increased levels of cTnI on admission.[9,10] An elevated cTnI proved to be an highly sensitive and specific marker for cardiac dysfunction in SAH patients as well.[11,12]

Despite the direct link between SAH and cardiac injury, as defined by elevated cTnI levels, it is not clear if elevated cTnI levels on admission independently predict secondary cardiac or pulmonary complications and outcome. Therefore we performed a prospective study on the additional value of cTnI to established prognosticators (clinical condition on admission, age, and amount of extravasated blood)[13,14] in predicting cardiac or pulmonary complications and outcome in patients with SAH.

Material and methods

Patients

We studied 68 patients with aneurysmal SAH who were treated in the Medical Center Haaglanden. All SAH patients are treated at our ICU for at least two weeks. The diagnosis aneurysmal SAH was based on typical history, a CT showing blood ion the basal cisterns and an aneurysm on angiography or an aneurysmal pattern of hemorrhage on CT in those patients in whom IA-angiography was not performed because of a poor clinical condition from the outset. To be included, patients had to be admitted to the intensive care unit (ICU) within 24 hours after the onset of the hemorrhage. We did not exclude patients with a history of prior cardiac disease. Only one patient with prior stable cardiac disease was included in this study. Patients were monitored in the ICU for two weeks. Three months after SAH onset a follow up visit for all patients was planned. The initial 10 patients were included non consecutively; the remaining 58 patients were included consecutively between June 2002 and February 2004.

Baseline measurements

The neurological condition on admission was assessed by means of the World Federation of Neurological Surgeons (WFNS) scale.[15] WFNS grades I, II and III were defined as a good and WFNS grades IV or V as a poor neurological condition. Because the relation of age with cardiac complications is probably non-linear, we analyzed age in tertiles. The risk implications were similar in the second and third tertile and higher than in the first tertile; we therefore dichotomized between the first and second tertile. The amount of cisternal and ventricular blood was scored according to the Hijdra score.[16] The sum scores of blood in the cisterns (range 0-30) and ventricles (range 0-12) were dichotomized at their median value. Blood samples were obtained within 24 hours of SAH onset to assess cTnI. Venous blood was collected at our emergency department and repeated later at the ICU. No serial measurements after the first 24 hour were performed for all patients in this study. Cardiac troponin I is generally undetectable in normal volunteers. It was measured using an AxSYM random access immunoanalyzer (Abbott laboratories) The lower limit of detection was 0.3 µg/L, thus abnormal values were defined as higher than 0.3 µg/L.

A chest X-ray was obtained on admission and repeated every two days during the first two weeks of hospitalization. These chest X-rays were scored by a radiologist, who was blinded to the patient's clinical information and cTnI , as follows: grade 0, no alveolar consolidation; grade 1, little alveolar consolidation; grade 2, severe alveolar consolidation; grade 3, diffuse bilateral alveolar consolidation. We qualified grades 2 and 3 as the occurrence of pulmonary edema. For each patient we continuously recorded the following data during the first two weeks of admission: heart rate and rhythm; systolic, diastolic, and mean arterial blood pressure (MAP); fraction of inspired oxygen (FiO2); and partial pressure of oxygen in arterial blood (PaO2). Pulmonary gas exchange was expressed as the PaO2/FiO2 ratio. Comparable to patients with an Adult Respiratory Distress Syndrome [17], a PaO2/FiO2 ratio

of ≤ 200 mmHg was defined as a severe disturbance of pulmonary gas exchange. The clinical pulmonary infection score (CPIS) was used in the diagnosis of pneumonia.[18] The CPIS is a combination of clinical, radiographic and microbiological criteria, with a maximum score of 12. Values of 6 or higher are considered diagnostic for pneumonia . Patients with a CPIS score of 6 or higher were excluded from the analysis regarding pulmonary edema and abnormalities in pulmonary gas exchange. A systemic inflammatory response syndrome (SIRS) was considered present when ≥ 2 of the following conditions were met: temperature of < 36 °C or > 38 °C, heart rate of > 90 bpm, respiratory rate of > 20 breaths/min or a PCO_2 < 32 mmHg, and WBC of <4000/mm3 or >12000/mm3.[19]
Cardiac rhythm disturbances (atrial fibrillation or supraventricular tachycardia) in which anti-arrhythmic therapy was needed were recorded. Inadequate cardiac performance was defined as the need for inotropic support to obtain a MAP > 65 mmHg in the first four days after admission. An admission 12-lead ECG of each patient was analyzed by an experienced electrocariographer who was blinded to the patient's condition. ST depression greater than 0.1 mV in limb leads or 0.2 mV in pre-cardial leads were defined as an abnormal finding. A T wave was defined as inverted if at least 0.1 mV in depth. T wave abnormalities were assessed in leads I, II, aVL, aVF and V^{2-6}. We defined ischemic like ECG abnormalities as the presence of ST depression or T wave inversion, or both in at least two leads. All patients received standard intensive care treatment, which included administration of oral nimodipine, an anticonvulsant agent, and intravenous fluids to maintain normovolemia. In case of hypotension nimodipine dose was reduced or even postponed before inotropic support was started. For the prevention of ventilator-associated pneumonia, all mechanical ventilated patients received selective decontamination of the digestive tract.[20] Surveillance cultures were taken on admission and subsequently every other day of oropharynx, trachea and rectum. Two blood cultures were drawn if rectal temperature exceeded 38.5 °C.

Definition of outcome events
The predefined outcomes were the occurrence of secondary cardiac or pulmonary complications and poor clinical outcome.
A cardiac or pulmonary complication was defined as the occurrence of at least one of the afore mentioned complications (pulmonary edema, abnormalities in pulmonary gas exchange, rhythm disturbances or an inadequate cardiac performance).
Poor outcome was defined as a modified Rankin Scale score of 4, 5 (i.e. dependent on activities in daily life) or death 3 months after onset.[21]

Data analysis
We related the occurrence of a cardiac or pulmonary complication to baseline characteristics (WFNS, amount of blood on baseline CT and age) and to an abnormal troponin I in univariate and multivariate analyses by means of logistic regression models, yielding crude odds ratios. In the multivariate analysis we developed a model with forward selection based on the baseline characteristics with a corresponding p-value of < 0.10 in the univariate analysis. We extended this model with data on troponin. We evaluated the discriminatory

power of the models with the area under the curve (AUC) of the corresponding receiver operator characteristic curve (ROC).[22] An AUC can range from 0.50 (no discriminatory power) to 1.0 (perfect prediction). We categorized troponin I values in tertiles to assess a possible 'dose response' effect of the troponin I values and the occurrence of a cardiac or pulmonary complication. A similar strategy was used for the analysis of poor outcome after 3 months. A secondary analysis for poor outcome and secondary complications was performed with the 58 consecutive patients (10 non consecutively patients excluded).

Results

In 35 of the 68 included patients (52%) an elevated cTnI (range 0.3-85.2) was found on admission to the ICU. The clinical characteristics of the patients are given in table 1. Signs of cardiac ischemia on ECG (presence of ST depression or T wave inversion, or both in at least two leads) occurred in 6 of 30 (20%) patients without abnormal troponin and 17 of 33 (52%) with abnormal troponin. In 5 patients the admission ECG could no longer be retrieved.

Table 1. Patient characteristics

Patients, n	68
Women, n (%)	53 (78%)
Poor condition on admission (WFNS IV-V) , n (%)	32 (47%)
Amount of extravasated blood (Hijdra score)	
Ventricular score; median (range)	3 (0-12)
Cisternal score; median (range)	20 (3-30)
Treatment of aneurysm, n (%)	
Clipping	21 (31%)
Coiling	22 (32%)
None	25 (37%)
Troponin I, median (range)	0.4 (0-85.2)
Abnormal troponin I, n (%)	35 (52%)
Outcome events n (%)	
Pulmonary edema	19 (28%)
PaO2/FiO2 ratio ≤ 200	25 (37%)
Rhythm disturbances	11 (16%)
Inadequate cardiac performance	17 (25%)
Predefined outcome n (%)	
Cardiopulmonary complications*	39 (57%)
Poor clinical outcome	40 (59%)

** (Pulmonary edema or a PaO2/FiO2 ratio ≤ 200, or the occurrence of a rhythm disturbance or an inadequate cardiac performance)*

Cardiac and pulmonary complications

An abnormal cTnI was found on admission in 16 (84%) of the 19 patients with pulmonary edema, 20 (80%) of 25 patients with disturbance of pulmonary gas exchange, 9 (82%) of 11 patients with rhythm disturbances, and 13 (76%) of 17 patients with inadequate cardiac performance. SIRS was present in 56 patients, including all 17 patients with inadequate cardiac performance. In the patients with inadequate cardiac performance no pulmonary infiltrate was detected on the Chest X-ray. In 8 of these patients blood cultures were drawn, these were positive in two patients. Both blood cultures yielded coagulase-negative staphylococci. In 24 of the remaining 29 patients with SIRS blood cultures were drawn; in four patients these were positive for coagulase-negative staphylococci.

A cardiac or pulmonary complication was seen in 10/33 patients with an undetectable cTnI and in 29/35 patients with an elevated cTnI. Two patients were be excluded from the analysis regarding pulmonary edema because of pneumonia. In four patients pulmonary infiltrates were noted on chest X-rays during their stay in the ICU. These patients had no clinical signs of pneumonia and no potential pathogen was cultured from tracheal secretions or blood (CPIS score was below 6 in all, 4 patients). These patients were included in the analysis; an additional analysis without these four patients yielded similar results.

An abnormal cTnI and a WFNS score ≥ 4 on admission predicted the occurrence of cardiac or pulmonary complications in univariate analysis (table 2). We did not find an increasing risk for complications with increasing concentrations of cTnI. Patients in the highest tertile of cTnI values (3.3-85.2) had a similar risk increase of cardiopulmonary complications (OR 11.5 [95%CI 3.0-44]) as those in the middle tertile (OR 14.1 [95%CI 2.6-76]), both in comparison with the lowest tertile. In the model with established baseline characteristics, the WFNS score and age retained in multivariate modeling (corresponding p-value was <0.10 in univariate analysis). Upon extension of this basic model with abnormal cTnI, this last variable and age > 51 years remained in the model. This result shows that cTnI is an independent prognosticator for cardiopulmonary complications. The AUC improved from 0.70 (95%CI 0.57-0.83) for the basic model to 0.83 (95%CI 0.72-0.93) with extension of cTnI (table 3). Secondary analyses for cardiopulmonary complications with the 58 consecutive patients (10 non consecutively patients excluded) produced similar results (AUC of the ROC improved from 0.68 [95% CI 0.54-0.83] for the basic model to 0.85 [95% CI 0.75-0.95] with extension of cTnI).

Table 2. Univariate analysis of predictors for cardio-pulmonary complications

Variable	Odds ratio (95%CI)
Troponin I > 0.3µg/L	11.9 (3.7-39)
WFNS ≥ 4	3.3 (1.2-9.1)
Age >51 year*	2.9 (1.0-8.6)
Amount of extravasated blood (Hijdra score)	
Ventricular score > 3	2.1 (0.8-5.8)
Cisternal score > 20	1.3 (0.5-3.6)

**dichotomized between first and second tertile*

Table 3. Multivariate analysis of predictors for cardio-pulmonary complications

	Baseline characteristics*		Baseline characteristics and an abnormal cTnI	
	OR	95% CI	OR	95% CI
WFNS ≥ 4	3.3	1.2-9.1	-	
Age > 51 year	3.0	0.98-9.2	4.1	1.1-15.8
Troponin I ≥ 0.3µg/L			14.1	3.9-51
AUC of ROC	0.70	0.57-0.83	0.83	0.72-0.93

** WFNS score, age and amount of ventricular blood; only WFNS and age(dichotomized between first and second tertile) remained in the model (p<0.10 in univariate analysis).*

Poor outcome

In the univariate analysis, both an abnormal cTnI and all established baseline characteristics were strong predictors of poor outcome (Table 4). An abnormal cTnI was an independent prognosticator for poor outcome in the multivariate model. The AUC of the ROC did not improve with extension of an abnormal cTnI (0.89; 95%CI 0.81-0.97) to the model based on these established baseline characteristics (0.86; 95%CI 0.77-0.95). We did not find an increasing risk for poor outcome with increasing tertiles of cTnI. Secondary analyses for poor outcome with the 58 consecutive patients (10 non consecutively patients excluded) produced similar results (AUC of the ROC did not improve with extension of an abnormal cTnI [0.90; 95% CI 0.82-0.98] to the model based on the established characteristics [0.88; 95% CI 0.79 -0.97]).

Table 4. Logistic Regression of predictors for poor outcome*

	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Abnormal Troponin I	3.9	1.4-11	4.7	1.1-20
WFNS ≥ 4	9.9	3.0-31	4.9	1.1-23.4
Age > 51 year	4.7	1.6-14.2	6.3	1.3-30.7
Amount of extravasated blood (Hijdra score)				
Ventricular score > 3	12.5	3.2-48	8.1	1.5-42
Cisternal score > 20	2.9	1.0-7.8	-	
AUC of ROC			0.89	0.81-0.97

* modified Rankin Scale score 4,5 or death

Discussion

An abnormal cTnI is a powerful predictor for the occurrence of pulmonary and cardiac complications in patients with aneurysmal SAH. In our series, we found a high frequency of pulmonary edema, disturbances of pulmonary gas exchange, rhythm disturbances and an inadequate cardiac performance. Abnormal cTnI was significantly related to all these complications. An elevated cTnI was also an independent prognosticator for the occurrence of a poor outcome. The additional prognostic information of troponin I for poor outcome is limited. The severity of brain injury is the leading cause of a poor outcome[2] and pulmonary and cardiac complications are less important factors for the eventual outcome. The minor importance of pulmonary and cardiac complications for eventual outcome probably explains why a factor that predicts the occurrence of pulmonary and cardiac complications does not have additional prognostic value for the eventual outcome.
In contrast to previous studies, we assessed the *additional* prognostic value of cTnI to established prognosticators for pulmonary and cardiac complications, and for clinical outcome. The proportion of patients with an elevated troponin level in our patient group is larger than in other recent studies. This larger proportion is probably explained by the large fraction of patients with a poor clinical condition on admission, the short interval between onset of SAH and blood sampling, and the large proportion of women in our study. Female sex and shorter time from SAH onset have been associated with higher levels of cTnI.[9] A possible limitation of this relative small study is that some patients were not included consecutively. We included these patients at random. An additional analysis without these patients yielded similar results; therefore we do not think that the inclusion of these patients has biased our results to an important extent.

Release of catecholamines is linked to myocardial necrosis and elevations of cardiac enzymes.[23,24] The cardiac enzyme troponin I is a specific and highly sensitive marker of cardiac

injury. The release of catecholamines can also cause pulmonary edema by means of increasing transmural pulmonary vascular pressures caused by a combination of α and β-adrenoceptor activation, and cardiac injury.[5,25] These complications are responsible for hypotension and hypoxia, two important secondary sequelae that influence outcome after acute brain injury. Although four patients might have been misclassified as having pulmonary edema and not pneumonia, this did not influence the relationship between abnormal cTnI and pulmonary edema. Also it can be argued that a decrease in MAP was related to nimodipine, a potent vasodilator, especially when give intravenously. This seems unlikely in our patients who received only oral nimodipine. Oral nimodipine has shown to decrease MAP in a minority of patients compared to intravenous administration.[26] Finally, the possibility of septic shock and not cTnI being related to a decrease in MAP should be considered. In 2 out 17 patients with inadequate performance coagulase-negative staphylococci were cultured, and in 4 patients who did not require inotropic support. Despite the fact that coagulase-negative staphylococci are posing a lower risk of developing septic shock than other organisms in the ICU, an effect on MAP cannot be excluded entirely.[27]

We found three other studies that mentioned an effect on outcome of cTnI in patients with SAH. In a study of 47 patients (8 with increased troponin I) worse clinical outcomes in patients with an elevated cTnI were suggested but statistical significance could not be demonstrated.[28] In another study comprising 43 patients worse clinical outcomes (death or discharge to nursing home) in patients with an elevated cTnI were observed (RR 1.8; 95% CI 0.7-4.8) but no statistical significance was achieved.[12] A recent study mentioned a strong association between cTnI and outcome in univariate analysis (RR 2.4; 95% CI 1.7-3.4).[10] All these results are compatible with our findings in univariate analysis that there is marked effect of cTnI on outcome. However, none of the other studies addressed its additional prognostic value with regard to poor outcome; it proved to be absent in our study. We found no other studies investigating the additional effect of an abnormal cTnI on the occurrence of cardiac and pulmonary complications.

We defined a cTnI level above 0.3μg/L as abnormal. Other investigators have shown that even minimum peak values (just above detectable level) of troponin can reflect serious cardiac dysfunction.[29] The severe cardiac dysfunction associated with only small concentrations of cTnI probably explains the lack of a 'dose dependent' effect of an elevated level of cTnI.

In conclusion, an elevated level of cTnI is an independent predictor of secondary cardiac and pulmonary complications after a SAH. Therefore cTnI can be used as a marker to identify patients who are at risk of developing cardiopulmonary complications. These patients need special attention for hemodynamic complications and could benefit from early invasive hemodynamic monitoring to guide fluid therapy and inotropic support. Further studies are needed to assess the effectiveness of early invasive monitoring in patients with elevated cTnI concentrations on admission.

References

1 Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke 1997;28:660-664.

2 Kassell NF, Torner JC, Clark Haley E, Jane JA, Adams HP, Kongable GL. The international cooperative study on the timing of aneurysm surgery. Part I: overall management results. J Neurosurg 1990;73:18-36.

3 Solenski NJ, Haley EC, Kassell NF, et al. Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007-1017.

4 Sato K, Masuda T, Izumi T. Subarachnoid hemorrhage and myocardial damage. Clinical and experimental studies. Jpn Heart J 1999;40:683-701.

5 Macmillan CSA, Grant IS, Andrews PJD. Pulmonary and cardiac sequelae of subarachnoid hemorrhage: time for active management? Intensive Care Med 2002;28:1012-1023.

6 Naredi S, Lambert G, Edén E, Zäll S, Runnerstam M, Rydenhag P. Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke 2000;31:901-906.

7 Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific Troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342-1349.

8 Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. Crit Care Med 1999;27:1775-1780.

9 Tung P, Kopelnik A, Banki N, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. Stroke 2004;35:548-553.

10 Claassen J, Vu A, Kreiter KT, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832-838.

11 Parekh N, Venkatesh B, Cross D, et al. Cardiac Troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. J Am Coll Cardiol 2000;36:1328-1335.

12 Deibert E, Barzilai B, Braverman A, et al. Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage. J Neurosurg 2003;98:741-746.

13. Kassell NF, Torner JC, Clark Haley E, Jane JA, Adams HP, Kongable GL: The international cooperative study on the timing of aneurysm surgery. Part I: overall management results. J Neurosurg 1990;73:18-36.

14. Hijdra A, van Gijn J, Nagelkerke N, Vermeulen M, van Crevel H. Prediction of delayed cerebral ischemia, rebleeding and outcome after aneurysmal subarachnoid hemorrhage. Stroke 1988;19:1250-1256.

15 Drake CG. Report of World Federation on Neurological Surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988;68:985-986.

16 Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke 1990;21:1156-1161.

17 Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-824.

18 Pugin J, Auckenthaler R, Lew DP, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991;143:1121-1129.

19 Members of the American College of Chest Physicians: American college of chest physicians/society of critical care medicine consensus conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-874.

20 Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 1984;10:185-92.

21 Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.

22 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;7:37-43.

23 Doshi R, Path MRC, Neil-Dwyer G. A clinicopathological study of patients following a subarachnoid hemorrhage. J Neurosurg 1980;52:295-301.

24 Masuda T, Sato K, Yamamoto S, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. Stroke 2002;33:1671-1676.

25 Deehan SC, Grant IS. Hemodynamic changes in neurogenic pulmonary edema: effect of dobutamine. Intensive Care Med 1996;22:672-676.

26 Porchet F, Chiolero R, de Tribolet N. Hypotensive effect of nimodipine during treatment for aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 1995;137:62-69.

27 Brun-Buisson C, Doyon F, Carlet J. Bacteremia and severe sepsis in adults: a multicenter prospective survey in ICUs and wards of 24 hospitals. French Bacteremia-Sepsis Study Group. Am J Respir Crit Care Med 1996;154:617-24.

28 Horowitz MB, Willet D, Keffer J. The use of cardiac Troponin-I (cTnI) to determine the incidence of myocardial ischemic and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. Acta Neurochir(Wien) 1998;140:87-93.

29 Bulsara KR, McGirt MJ, Liao L, et al. Use of peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:524-528.

Chapter 5

Hemodynamic monitoring by single transpulmonary thermodilution in patients with severe subarachnoid hemorrhage with and without elevated cardiac Troponin I.

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Submitted for publication

Introduction

Cardiovascular impairment and hypoxemia occurring within 24 hours of admission are independently associated with death or severe disability after subarachnoid hemorrhage (SAH).[1] Therefore it is of vital importance to detect and treat these complications in an early stage. Cardiovascular impairment, caused by a sympathetic storm in response to a rapid increase in intracranial pressure, seems to be the result of structural cardiac damage which is demonstrated by elevated levels of cardiac troponin I (cTnI) found in 20-46% of SAH patients.[2,3,4,5] In these patients with elevated cTnI, echocardiography showed reversible left ventricular wall motion abnormalities, which were associated with impaired left ventricular performance in SAH.[6] Especially these patients are at risk of developing pulmonary edema which makes them vulnerable for the development of hypoxemia.[7] The combination of reduced cardiac output and hypoxemia is a direct threat to the brain itself because it increases the risk of cerebral ischemia.

The PiCCO system (Pulsion Medical Systems, Munich, Germany) is a minimally invasive monitoring system for ICU patients based on the transpulmonary thermodilution technique with a single thermal indicator.[8,9] It provides intermittent (transpulmonary thermodilution-derived) and continuous ("pulse contour"-derived) assessments of cardiac output, estimations of cardiac preload (intrathoracic blood volume and global end-diastolic volume), cardiac contractile function (cardiac function index) and extravascular lung water(EVLW).[8] Estimates of cardiac preload derived from the PiCCO system are reliable and even more sensitive than those derived from pulmonary artery catheter-derived filling pressures.[10,11,12,13,14,15] We used the PiCCO system in a prospective observational study to assess the frequency of cardiovascular impairment and pulmonary edema. We also determined whether myocardial injury as demonstrated by elevated levels of cTnI within 48 hours after SAH adversely affects cardiac performance or the occurrence of pulmonary edema.

Materials and methods

Study population

We prospectively studied a consecutive series of patients with aneurysmal SAH admitted to the intensive care unit of the Medical Center Haaglanden (The Hague) between May 2003 and May 2004. At study entry, baseline clinical variables including age, sex, clinical condition on admission (WFNS scale)[16] and amount of blood on baseline CT (Hijdra score[17] and modified Fisher score[18]) were recorded. Eligible patients were those with a WFNS score III, IV or V, or with a modified Fisher score of > 2.

All patients were treated according to standard intensive care guidelines during a minimum of two weeks after hospitalization. Our protocol for SAH patients admitted to the ICU consists of absolute bed rest, oral nimodipine, an antiepileptic drug, fluid therapy aiming at normovolemia and refraining from antihypertensive treatment. In all patients a central venous catheter and an arterial line are inserted. In case of hypotension inotropic drugs and vasopressors are used to maintain a mean arterial pressure (MAP) > 65 mmHg.

Measurements

Continuous recording of temperature, heart rate, respiratory rate and mean arterial pressure (MAP) was performed. Serial blood samples were drawn to assess the cardiac enzyme cardiac troponin I (cTnI) on admission and on day 2. Troponin I was measured with an AxSYM random access immunoanalyzer (Abbott laboratories).

Within 24 hours of admission a 5-F themistor-tipped catheter (Pulsioncath PV2015L20A, Pulsion Medical Systems) was placed in the femoral artery and connected to the PiCCO system. Cardiac output and volumetric variables were measured with the single indicator transpulmonary thermodilution technique. Every eight hours, measurements were obtained by injections of 20 mL NaCl 0.9%, at a temperature of < 8 ° C, injected via the distal port of the central venous catheter. These measurements were repeated during the first 5 days of admission. The data provided by the PiCCO system were not used to guide therapy in our patients. Informed consent was obtained from a legal representative to perform the PiCCO measurements.

For each patient the following data were recorded: cardiac output, cardiac function index and extravascular lung water (EVLW). For inter-individual comparison, absolute values for cardiac output and EVLW were normalized as indexed by body surface area (cardiac index) and body weight (EVLWI). The cardiac function index is defined as the ratio of cardiac output to the global end-diastolic volume, and provides an estimation of the cardiac contractile function.[19] The calculations to obtain the value of EVLW, cardiac output and cardiac function index are described elsewhere.[8,19]

Definition of parameters

We defined a cardiac index < 3 l/min/ m^2 as left ventricular dysfunction. A cardiac contractile function (CFI) < 4.0 l/min was taken as measure of decreased cardiac contractility. An EVLWI > 10 ml/kg was seen as indication of pulmonary edema.[19,20,21] Abnormal cardiac troponin I levels were defined as concentrations higher than > 0.3 µg/L.

Data analysis

Descriptive statistics were used to report the number and type of hemodynamic abnormalities, the occurrence of pulmonary edema and the frequency of abnormalities in admission cardiac enzyme cTnI. We used 2x2 contingency tables to determine the relationship between cardiac enzyme abnormalities and at least one decreased mean cardiac index, cardiac contractile function or at least one increased mean EVLWI in the first 5 days of admission. Results were expressed as odds ratios (OR's) and corresponding exact 95% confidence limits.[22]

We used linear regression analysis to report differences between mean cardiac contractile function, cardiac index or EVLWI in the first 5 days of hospitalization in patients with and without an elevated cTnI at day one or two.

Results

Thirty patients fulfilled the inclusion criteria. Two patients were excluded because the hemodynamic observations did not start in the first 24 hours of admission. Baseline characteristics of the remaining 28 patients are given in table 1. Twenty four patients had an angiographically proven aneurysmal subarachnoid hemorrhage. In four other patients the diagnosis was based on an aneurysmal pattern of hemorrhage on CT scan only, because in these patients the poor clinical condition precluded angiography.

Table 1. Baseline characteristics

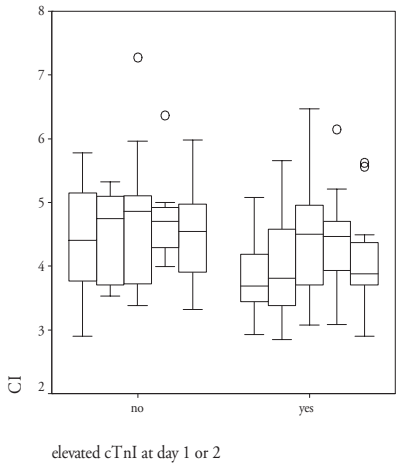
Patients; n	**28**
Women; n(%)	21 (75%)
Poor condition on admission (WFNS IV-V); n (%)	10 (36%)
Amount of extravasated blood (Hijdra score)	
Ventricular score; median (range)	3 (0-12)
Cisternal score; median (range)	22 (4-30)
Abnormal cTnI; n (%)	15 (54%)
Treatment of aneurysm*; n(%)	
Clipping	13 (46%)
Coiling	8 (29%)
None	7 (25%)
Poor clinical outcome at three months follow up (modified Rankin 4,5 or death); n (%)	16 (57%)

** All patients were treated in the first 5 days after SAH*

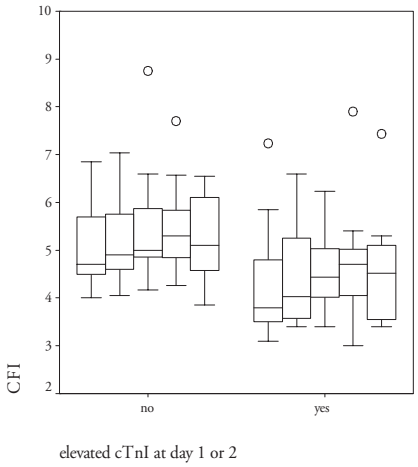
Cardiac output and cardiac contractile function

Median cardiac indices and cardiac contractile function indices during the first 5 days of hospitalization are shown in figures 1A and 1B. Six patients (21%) had a reduced mean cardiac index during at least 1 day in the first 5 days of hospitalization. Five of these patients had only 1 day with reduced cardiac index, the sixth patient a reduced cardiac index during two days. One of these 6 patients died of brain herniation, another started with hemodynamic support and the four other patients all had a spontaneous improvement of cardiac performance the next day.

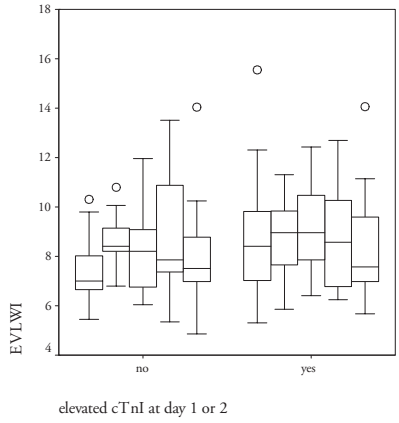
Figure 1. Relation between cTnI and the mean cardiac index (panel A), mean cardiac contractile function (panel B), and mean EVLWI (panel C) in the first 5 days of hospitalization. Data expressed as box plot with medians and interquartile ranges.



***A**. Significant difference for day 1. (p=0.028)*



***B**. Significant difference for day 3 (p= 0.043)*



***C**. No significant difference (P-values between 0.25 and 0.89)*

Circles indicate values between 1.5-fold to threefold of the whole box length.

CI: cardiac index; CFI: cardiac contractile funtion; EVLWI: extravascular lung water index

A depressed cardiac index was observed in 1/13 patients without elevated cTnI and in 5/15 patients with an elevated cTnI; the corresponding odds ratio was 6 (95%CI: 0.5 – 310). At the first day only cardiac index differed statistically significant between patients with and without elevated cTnI (figure 1A).
Ten patients (36%) had a reduced cardiac contractile function during at least 1 day in the first 5 days of hospitalization. Four of these patients also had a depressed cardiac index. In 5 patients the depressed cardiac contractile function lasted for at least 3 of the first 5 days. One of the 13 patients without elevated cTnI had a depressed cardiac contractile function as compared with 9 of 15 patients with an elevated cTnI (odds ratio 18; 95%CI:1.6 – 850). Figure 1B shows an overall trend for lower cardiac contractile function (CFI) values in patients with elevated cTnI; it attained statistical significance at day 3 only.

Pulmonary edema
Elevated values of EVLWI were recorded in 10 patients (36%). In 7 out of 10 patients this persisted for at least two days. An elevated EVLWI was seen in 3/10 patients without elevated cTnI and in 7/8 patients with an elevated cTnI; odds ratio 2.9, 95%CI:0.5 – 23. Mean extravascular lung water indices in the first 5 days of hospitalization were in general higher in patients with elevated cTnI than in those with normal cTnI (figure 1C). The differences never reached statistical significance.

Discussion

Cardiopulmonary complications were frequently observed by the PiCCO system in our SAH patients with a poor clinical condition or with large amounts of extravasated blood. Disturbed cardiac contractile function and elevated extravascular lung water occurred in about one third of the SAH patients. A depressed cardiac index was also frequently seen but was usually mild and self limiting within one day. An elevated cTnI appeared to be a good marker for the occurrence of a decreased cardiac contractile function. This is in agreement with recently performed echocardiografic studies, which have demonstrated reversible abnormalities of left ventricular contractility in SAH patients, especially in those with elevated cTnI.[2,23]

Although we observed a slight decrease in cardiac output in 6 patients, this was usually mild and followed by a swift improvement in all these patients, even in patients with elevated cTnI. This finding seems to be in contrast with some case reports and two retrospective studies, which described small series of patients with a severely disturbed cardiac output assessed by means of a pulmonary artery catheter.[6,24] In one of these studies a depressed cardiac output is mentioned as a relevant predictor for the occurrence of delayed cerebral ischemia.[6] Additional studies using single transpulmonary thermodilution are required to study the effects of these cardiac estimates on delayed cerebral ischemia and eventual outcome in SAH patients.

Pulmonary edema is a serious and common complication after SAH. Transpulmonary thermodilution enables the identification of patients with pulmonary edema (elevated EVLW) as well as the quantification of pulmonary edema and its response to therapeutic maneuvers (e.g. optimizing fluid intake, inotropic- or positive end-expiratory support).[20,25] In a study with 27 SAH patients EVLW in combination with cardiac index was used to guide triple-H therapy in addition to the conventional parameters (MAP en CVD).[26] In that study the frequency of pulmonary edema was very low compared to literature.[27] A case report concluded that monitoring volumes with the PiCCO cardiac monitor can help make clinical decisions in patients requiring hypervolemic therapy.[28] Interestingly EVLW correlated well with survival in a heterogeneous group critically ill patients.[21] The early recognition and differential diagnosis of pulmonary edema may be challenging since most common manifestations of pulmonary edema are nonspecific and usually late signs of pulmonary edema. EVLWI is an important variable for early diagnosis and treatment of pulmonary edema and may be very helpful for guiding fluid therapy.

This small study on hemodynamic alterations in SAH patients can be seen as an exploratory study using a monitoring technique for cardiac and pulmonary complications. Before it can be used as a routine in clinical practice more studies are needed on the relation between transpulmonary thermodilution parameters and delayed cerebral ischemia and clinical outcome, and on the usefulness of transpulmonary thermodilution parameters in guiding fluid and blood pressure management. Nevertheless, our preliminary study shows that this transpulmonary thermodilution technique is a promising tool in the management of SAH patients. Our study was performed in patients in a poor clinical condition or with large amounts of extravasated blood. These inclusion criteria introduce a selection bias and the proportions of patients with cardiovascular impairment and pulmonary edema can not be extrapolated to all patients with SAH. In patients in good clinical condition and less amounts of extravasated blood, elevated extravascular lung water is less likely. Another limitation is that we did not use echocardiography in addition to the transpulmonary thermodilution technique. In contrast to echocardiography, transpulmonary thermodilution is a non-operator dependent technique that can be used in all ICU patients as often as is necessary. Also transpulmonary thermodilution is a validated method in the assessment of cardiac output and cardiac contractile function (cardiac function index) in intensive care patients. The PiCCO system is a comparatively less invasive method than the traditionally used pulmonary artery catheter.

In conclusion, patients with SAH in poor clinical condition or with large amounts of extravasated blood are at risk of developing cardiopulmonary complications. We found a high frequency of cardiac contractile dysfunction, cardiac output depression and pulmonary edema in such patients. We also found that an elevated cTnI increases the risk for cardiac contractile dysfunction. Transpulmonary thermodilution technique is a promising tool for monitoring SAH patients with elevated cTnI on admission. Additional studies with extended follow-up are required to evaluate whether a therapeutic strategy taking into account cardiac

index, cardiac contractile function and EVLW can improve supportive therapy and outcome in SAH patients.

References

1 Claassen J, Vu A, Kreiter KT, Kowalski RG, Du EY, Ostapkovich N, Fitzsimmons BF, Connolly ES, Mayer SA. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med. 2004;32:832-838.

2 Tung P, Kopelnik A, Banki N, Ong K, Ko N, Lawton MT, Gress D, Drew B, Foster E, Parmley W, Zaroff J. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. Stroke. 2004;35:548-553.

3 Parekh N, Venkatesh B, Cross D, Leditschke A, Atherton J, Miles W, Winning A, Clague A, Rickard C. Cardiac Troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage. J Am Coll Cardiol. 2000;36:1328-35.

4 Mayer SA, LiMandri G, Sherman D, Lennihan L, Fink ME, Solomon RA, DiTullio M, Klebanoff LM, Beckford AR, Homma S. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg. 1995;83:889-896.

5 Sato K, Masuda T, Izumi T. Subarachnoid hemorrhage and myocardial damage. Clinical and experimental studies. Jpn Heart J. 1999;40:683-701.

6 Mayer SA, Lin J, Homma S, Solomon RA, Lennihan L, Sherman D, Fink ME, Beckford A, Klebanoff LM. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. Stroke. 1999;30:780-786.

7 Deehan SC, Grant IS. Haemodynamic changes in neurogenic pulmonary edema: effect of dobutamine. Intensive Care Med. 1996;22:672-676.

8 Sakka SG, Rűhl CC, Pfeiffer UJ, Beale R, McLuckie A, Reinhart K, Meier-Hellmann A. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution Intensive Care Med. 2000;26:180-187.

9 Goedje O, Hoeke K, Lichtwarck-Aschhoff M, Faltchauser A, Lamm P, Reichart B. Continious cardiac output by femoral thermodilution calibrated pulse contour analysis:Comparison with pulmonary arterial thermodilution. Crit Care Med. 1999;27:2407-2412.

10. Brock H, Gabriel C, Bibl D, Necek S. Monitoring intravascular volumes for postoperative volume therapy. Eur J Anaesthesiol. 2002;19:288–294.

11 Wiesenack C, Prasser C, Keyl C, Rodig G. Assessment of intrathoracic blood volume as an indicator of cardiac preload: single transpulmonary thermodilution technique versus assessment of pressure preload parameters derived from a pulmonary artery catheter. J Cardiothorac Vasc Anesth. 2001;15:584-588.

12. Godje O, Peyerl M, Seebauer T, Lamm P, Mair H, Reichart B. Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volumes as preload indicators in cardiac surgery patients. Eur J Cardiothorac Surg. 1998;13:533–539.

13. Sakka SG, Bredle DL, Reinhart K, Meier-Hellmann A. Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. J Crit Care. 1999;14:78–83.

14. Bindels AJ, van der Hoeven JG, Graafland AD, de Koning J, Meinders AE. Relationships between volume and pressure measurements and stroke volume in critically ill patients. Crit Care. 2000;4:193–199.
15. Goedje O, Seebauer T, Peyerl M, Pfeiffer UJ, Reichart B. Hemodynamic monitoring by double-indicator dilution technique in patients after orthotopic heart transplantation. Chest. 2000;118:775–781.
16 Drake CG. Report of World Federation on Neurological Surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg. 1988;68:985-986.
17 Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke. 1990;21:1156-1161.
18 Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, Connolly S, Mayer SA. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage. Stroke. 2001;32:2012-2020.
19 Combes A, Berneau JB, Luyt CE, Trouillet JL. Estimation of left ventricular systolic function by single transpulmonary thermodilution. Intensive Care Med. 2004;30:1377-1383.
20 Holm C, Tegeler J, Mayr M, Pfeiffer U, Henckel von Donnersmarck G, Műhlbauer W. Effect of crystalloid resuscitation and inhalation injury on extravascular lung water; clinical implications. Chest. 2002;121:1956-1962.
21 Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. Chest. 2002;122:2080-2086.
22 Mehta CR, Patel NR, Gray R. On computing an exact conficence interval for the common odds ratio in several 2x2 contingency tables. JASA 1985;80:969-973.
23 Deibert E, Barzilai B, Braverman AC, Farrar Edwards D, Aiyagari V, Dacey R, Diringer M. Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage. J Neurosurg 2003;98:741-746.
24 Parr MJ, Finfer SR, Morgan MK. Reversible cardiogenic shock complicating subarachnoid hemorrhage. BMJ. 1996;313:681-683.
25 Katzenelson R, Perel A, Berkenstadt H, Preisman S, Sternik L, Segal E. Accuracy of transpulmonary thermodilution versus gravimetric measurment of extravascular lung water. Crit Care Med. 2004;32:1550-1554.
26 Krayenbűhl N, Hegner T, Yonekawa Y, Keller E. Cerebral vasospasm after subarachnoid (Triple-H) therapy according to new systemic hemodynamic parameters. Acta Neurochir. 2001[Suppl] 77:247-250.
27 Vespa P, Bleck TP. Neurogenic pulmonary edema and other mechanisms of impaired oxygenation after aneurysmal subarachnoid hemorrhage. Neurocritical Care. 2004;1:157-170.
28 Segal E, Greenlee J, Hata SJ, Perel A. Monitoring intravascular volumes to direct hypertensive, hypervolemic therapy in a patient with vasospasm. J Neurosurg Anesth. 2004;16:296-298.

Chapter 6

The Simplified Acute Physiology Score (SAPS II) in predicting outcome in patients with Subarachnoid Hemorrhage

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Introduction

The case-fatality rate in patients with subarachnoid hemorrhage (SAH) still approximates 50%, and another 10-20% of patients remain dependent on help for daily activities [12]. Poor outcome can result from the initial hemorrhage and from complications such as delayed cerebral ischemia (DCI) and rebleeding. Established prognostic factors for poor outcome and for delayed cerebral ischemia are age, the clinical condition on admission and the amount of extravasated blood at the admission CT scan [15,26]. However, many patients with a poor clinical condition or large amounts of extravasated blood do not develop DCI and have a good outcome, while some patients with a good clinical condition and small amounts of extravasated blood still develop DCI. Apparently factors other than the established predictors play a role. One of these other factors might be extracerebral organ dysfunction [8]. Paraclinical parameters such as the occurrence of systemic inflammatory response syndrome (SIRS) on admission and laboratory assessments such as hypernatremia, hyperglycemia and leucocytosis have been linked to poor outcome [5,19,24,29].

These clinical and laboratory parameters are part of a frequently used severity of illness score in the intensive care unit, the simplified acute physiology score (SAPS II) [17]. SAPS II accurately predicts case fatality in stratified groups of patients [17]. SAPS II has never been tested as a generic predictor in patients with a single neurological emergency such as SAH.

We studied the prognostic value of the SAPS II in patients with SAH for occurrence of DCI and clinical outcome.

Methods.

Setting
The study was a retrospective cohort study of patients with SAH admitted to the intensive care unit (ICU) of a tertiary referral hospital between January 1, 2000 and June 2002.

Patients
We studied a consecutive series of 148 patients who had been admitted within 4 days after an SAH. Twelve patients were excluded from the study because of a non-aneurysmal perimesencephalic hemorrhage (n=9), incomplete data collection (n=2) or because the patient was moribund on admission (n=1).
The remaining 136 patients (table 1) had an SAH with an aneurysmal pattern of hemorrhage on CT. In 32 of the 136 patients intra-arterial angiography was not performed because these patients were in a poor clinical condition and died early after admission; post mortem examination was performed in one patient and revealed a ruptured aneurysm. In four patients with an aneurysmal pattern of hemorrhage no aneurysm was detected in two angiographic examinations, performed with an interval of several months.
All patients were treated according to standard intensive care guidelines during a minimum of two weeks after hospitalization. This protocol consisted of absolute bed rest, nimodipine, an antiepileptic drug, fluid therapy aiming at normovolemia and refraining from antihypertensive treatment.

Data collection.
The simplified acute physiology score (SAPS II) was calculated within 24 hours after admission to the ICU. SAPS II includes twelve physiology variables (heart rate, body temperature, white blood cell count (WBC), PaO2/FiO2 ratio, bicarbonate level, systolic blood pressure, urinary output, serum urea level, serum potassium, sodium, bilirubin level, Glasgow Coma Score, age, type of admission (scheduled surgical, unscheduled surgical, or medical) and three underlying disease variables (AIDS, hematological malignancy and metastatic cancer). The SAPS II values vary between 0 and 154. In general a high score indicates a worse prognosis. For the analysis, scores were dichotomized at the median value.

Table 1. Patient characteristics[a]

Total 136 patients	
Age	
Range	17-93
Mean	55
Sex n(%)	
Female sex	100 (73%)
SAPS II at admission	
Median (range)	27 (8-79)
8-22	47 (35%)
23-47	44 (32%)
48-79	45 (33%)
WFNS at admission n(%)	
I	40 (30%)
II	30 (22%)
III	18 (13%)
IV	19 (14%)
V	29 (21%)
Hijdra score	
Cisterns; median (range)	17 (0-30)
Ventricles; median (range)	2 (0-12)
Day of admission n(%)	
Day ictus	122 (90%)
Day one	13 (9%)
Day three	1 (1%)
SIRS criteria n(%)	
Non SIRS	38 (28%)
SIRS	98 (72%)
Treatment of aneurysm	
Surgery	57 (42%)
Coiling	37 (27%)
None	42 (31%)
Day of treatment of aneurysm, n(%)	
1-4	68 (72%)
5-10	9 (10%)
>10	17 (18%)
Hydrocephalus at admission n(%)	54 (40%)
Outcome measurements	
Rebleeding n(%)	13 (10%)
DCI	
Definite*	37 (27%)
definite and probable†	56 (41%)
Outcome	
Independent	71 (52%)
Dependent or death	65 (48%)

*aDCI, delayed cerebral ischemia; WFNS, World Federation of Neurological Surgeons; SAPS II, Simplified acute physiology score; SIRS, systemic inflammatory response syndrome, *New hypodense lesion at CT and clinical features, †Clinical features with or without new hypodense lesion at CT*

The clinical condition at admission was assessed by means of the World Federation of Neurological Surgeons (WFNS) scale [6]. A dichotomy was made between good neurological condition (WFNS I,II, or III) and poor neurological condition (WFNS IV or V) on admission. A systemic inflammatory response syndrome (SIRS) was considered present when ≥ 2 of the following conditions were met: temperature of < 36 °C or > 38 °C, heart rate of > 90 bpm, respiratory rate of > 20 breaths/min, and WBC of <4000/mm3 or >12000/mm3 [21]. From the admission CT scan the bicaudate index (BCI) was measured to assess the presence of hydrocephalus. To calculate age adjusted relative sizes, the bicaudate indices were divided by the corresponding upper limit per age group [27]. The amount of cisternal and ventricular blood was scored according to the Hijdra score [10]. The sum score of blood in the cisterns (range 0-30) and ventricles (range 0-12) were dichotomized at their median value.

The predefined outcomes were the occurrence of DCI, and poor outcome (death or dependence) 3 months after onset, as evaluated according to the modified Rankin score [28]. We qualified 0 to 3 as good outcome (independent) and 4 and 5 (dependent) together with death as poor outcome.
DCI was considered definite in case of a new hypodense lesion on the CT scan together with a gradual developing focal deficit, impairment of consciousness, or both in a patient with no other explanation for this event. Clinical features without hypodensities revealed by a CT scan were scored as probable DCI. In the analysis, we first investigated definite DCI and in a second analysis we included both definite and probable ischemia.
Rebleeding was defined as a sudden clinical deterioration with evidence of new blood on CT in comparison with a previous scan.

Data analysis
We related poor outcome after 3 months to baseline characteristics, the occurrence of SIRS and the SAPS II score during the first 24 hours of admission by means of a logistic regression model, yielding crude odds ratios. Next, we developed multivariate models with forward selection, the first was based on WFNS, age and Hijdra score (model M1), and consequently extended it with SIRS (M2) and SAPS II (M3). Variables were retained in the model if the corresponding p-value was < 0.10. We evaluated the discriminatory power of the models with the area under the curve (AUC) of the corresponding receiver operator characteristic curve (ROC) [9]. An AUC can range from 0.50 (no discriminatory power) to 1.0 (perfect prediction). In additional analyses the individual components of the SAPS II score were entered in a multivariate logistic regression model with stepwise forward selection.
Furthermore, we related the occurrence of DCI to baseline characteristics, SIRS and the total SAPS II score by means of Cox proportional hazards modeling, which yields hazard ratios (HR). HRs may be interpreted as relative risks [3]. For multivariate analysis a similar strategy as for the analysis of poor outcome was used. In the analysis for DCI, patients were censored at time of rebleeding. Finally, we categorized the SAPS II score in tertiles to further quantify the relation of SAPS II with outcome and DCI.

Results

The relation between the baseline characteristics and the SAPS II score is given in table 2.

Table 2. Relation between SAPS II score to baseline characteristics[a]

Variable	SAPS II ≤ 27 * *Median (range)*	SAPS II >27 *Median (range)*	p value
WFNS	1 (1-4)	4 (1-5)	<0.0001
Age	53 (17-82)	58 (33-93)	0.001
Hijdra score			
Cisternal score	13 (0-30)	22 (0-68)	<0.0001
Ventricular score	0 (0-9)	4 (0-12)	<0.0001
Relative Bicaudate index	0.89 (0.26-1.50)	1.10 (0.24-2.00)	0.004

a WFNS, World Federation of Neurological Surgeons scale

**27 is the median value of SAPS II in our study.*

Poor outcome

In the univariate analysis, both the SAPS II total score and WFNS score were very strong predictors of poor outcome (table 3). The relation between SAPS II and outcome was 'dose dependent': the higher the score the worse the outcome.

In multivariate model M1 WFNS and Hijdra score were retained, but not age (table 4). Upon extension with SIRS (M2) the model did not change and after entering the SAPS II score only this last variable remained in the model (M3). The AUC for models M1 and M2 was 0.81 and that for M3 0.85. From the individual variables that contribute to the overall SAPS II score heart rate, systolic blood pressure, PaO2/FiO2 ratio, serum urea level, potassium, the GCS and age had a statistically significant relationship with poor outcome in univariate analysis. In multivariate analysis PaO2/FiO2 ratio, serum urea level, age and the GCS appeared to be independent prognosticators of poor outcome (details of analyses not shown).

Table 3. Univariate analysis of predictors for death or dependence[a]

Variable	Odds Ratio (95% Confidence Interval)
SAPS II (continuous)	1.08 (1.06-1.11)*
SAPS II tertiles	
8-22	Reference
23-47	4.8 (1.8-12.9)
48-79	30.9 (9.9-96.7)
Age (continuous)†	1.04 (1.01-1.07)
Male sex	1.3 (0.6-2.8)
SIRS	4.3 (1.8-10.0)
WFNS ≥4	8.6 (3.7-19.7)
Hijdra score	
Cisternal score >17	2.3 (1.2-4.6)
Ventricular score >2	6.6 (3.1-14.0)

aWFNS, World Federation of Neurological Surgeons; SAPS II, Simplified acute physiology score; SIRS, systemic inflammatory response syndrome

** The OR needs to be interpreted as follows: for each point increase in SAPS II the risk for poor outcome increases with 8% (95%CI 6%-11%).*

† The OR needs to be interpreted as follows: for each year increase in age the risk for poor outcome increases with 4% (95%CI 1%-7%)

Table 4. Multivariate analysis of predictors for death or dependence[a]

	M1 & M2*		**M3†**	
Variable	**OR**	**95%CI**	**OR**	**95%CI**
WFNS ≥ 4	4.4	1.7-11.3	-	
Hijdra score				
Cisternal score >17	2.3	1.0-5.1	-	
Ventricular score >2	3.6	1.5-8.7	-	
SIRS	-		-	
SAPS II	-		1.08	1.06-1.12
AUC of ROC‡	0.81	0.73-0.88	0.85	0.78-0.91

aWFNS, World Federation of Neurological Surgeons; SAPS II, Simplified acute physiology score; SIRS, systemic inflammatory response syndrome.

**Model M1: WFNS and Hijdra score (age has not been retained in this model [corresponding p-value of > 0.10]).*

Model M2: Addition of SIRS into basic model M1 (WFNS and Hijdra score) yielded the same results.

† Model M3: Extension of model M2 with SAPS II (M3) resulted in a univariate model with SAPS II only.

‡ An AUC can range from 0.50 (no discriminatory power) to 1.0 (perfect prediction).

Delayed cerebral ischemia

In the univariate analysis the SAPS II score expressed as continuous variable was related to the occurrence of CT proven ischemia (OR 1.020 [95%CI 1.002-1.039]; table 5). Patients in the highest tertile of SAPS II had a significantly higher risk of DCI than those in the lowest tertile (OR 2.6; 95% CI 1.1-6.2). No other baseline characteristic had a statistically significant relationship with DCI. Because SAPS II was the only variable with a statistically significant association with DCI we refrained from multivariate analysis. The AUC of the ROC for SAPS II was 0.52 (95%CI, 0.42-0.63).

Table 5. Univariate analysis of predictors for the occurrence of delayed cerebral ischaemia[a]

Variable	Odds ratio (95%CI)
SAPS II (continuous)	1.020 (1.002-1.039) *
SAPS II tertiles	
8-22	Reference
23-47	1.8 (0.8-4.0)
48-79	2.6 (1.1-6.2)
Age (continuous)	0.99 (0.97-1.02)
Hijdra score	
Ventricular score > 2	1.9 (1.0-3.6)
Cisternal score > 17	1.1 (0.6-2.1)
WFNS ≥ 4	1.6 (0.8-3.2)
SIRS	1.9 (0.9-4.0)

aWFNS, World Federation of Neurological Surgeons; SAPS II, Simplified acute physiology score; SIRS, systemic inflammatory response syndrome

** The OR needs to be interpreted as follows: for each point increase in SAPS II the risk for DCI increases with 2%*

Discussion

In our study the SAPS II score in the first 24 hours of admission was the most powerful predictor of poor outcome in patients with SAH. It also predicted the occurrence of DCI, but less well than poor outcome. SAPS II by its own appeared to be at least as good a predictor of poor outcome than the combination of clinical condition on admission and amount of blood at the initial CT-scan.

Several individual features of the SAPS II score are associated with the risk of poor outcome after SAH. One of the most important predictors of outcome is the patient's level of consciousness on admission as expressed in the Glasgow Coma Scale (GCS) [4,26]. The GCS is the main component of the WFNS score, which probably explains why the WFNS score does not add to the SAPS II score in predicting outcome. Age is another major prognostic factor in SAH [16]. In addition to age and GCS the PaO2/FiO2 ratio

and serum urea level contributed independently to the prediction of poor outcome. The influence of the PaO2/FiO2 ratio corresponds with the frequently occurring pulmonary (neurogenic) edema or pneumonia in patients with SAH [25], and confirms our notion that extracerebral organ dysfunction plays an important role in the prognosis for patients with SAH. In a recent prospective consecutive series of 413 SAH patients, hypoxemia, metabolic acidosis, hyperglycemia and cardiovascular instability within 24 hours of admission were independently associated with death or severe disability. A physiological derangement score with these four items was superior to the physiologic subscore of the APACHE II scale in predicting outcome [2]. Other paraclinical factors related to outcome and complications mentioned in the literature are hypernatremia, high serum bilirubin, elevated creatinine and potassium level [7,8,24]. In our study low potassium level, blood pressure or heart rate out of normal range did have a predictive value for poor outcome in the univariate analysis, but not in the multivariate analysis.
Systemic complications occur more often in SAH patients with SIRS on admission than in those without [8]. All components of the SIRS criteria, heart rate, respiration rate and white blood cell count have been found as univariate predictors for poor outcome or the development of DCI [18,19,23,29]. These factors are incorporated in the SAPS II as well. The proportion of patients with SIRS on admission in our series was 72%, which is much higher than reported in other studies. This high proportion of patients with SIRS may explain why in the multivariate analysis SIRS did not add to the established prognostic factors (age, clinical condition and amount of extravasated blood). Recent studies suggest that the local inflammatory response of the brain initiated by SAH also triggers a systemic inflammatory response. Indeed, inflammatory mediators, like interleukine-1 and 6, produced in the injured brain are delivered into the systemic circulation and are linked to the occurrence of SIRS.[11,20] This suggests that SIRS with associated organ dysfunction is a primary mechanism of extracerebral organ system dysfunction and that this event contribute tangibly to outcome[8].

Inherently to a retrospective study design is incomplete retrieval of data. In our series only 2 patients had to be excluded because data could no longer be retrieved. The relative completeness of our dataset can be partly explained by the computerized data storage at our ICU. All patients with SAH admitted to our hospital are treated at the ICU for at least 2 weeks. In our study we took as one of the outcomes DCI, and not vasospasm. Vasospasm does not always lead to DCI or clinical features and is therefore a less relevant outcome from a clinical standpoint of view. We assessed outcome three months after the SAH. Functional outcome continues to improve significantly between 4 months and 18 months post-SAH [13]. So we don't know the effects on long term functional outcome of the SAPS II score.

Up to now neurosurgeons and neurologists pay little attention to the use of severity of illness scores as a predictor of morbidity and mortality. Our study convincingly shows that a scoring system including assessment of extracerebal organ function provides a better prognostication than scoring systems that include only neurological items. These results suggest that regular control of physiological items such as temperature, oxygenation, circulation parameters,

glucose, electrolyte disturbances, may lead to substantial improvement in outcome for SAH patients; however, this needs to be proven in appropriately designed treatment studies. Severity of illness scoring systems are often used in the ICU to compare selected groups for significant differences. The SAPS II score is validated in North America and Europe [14]. The SAPS II score is one of the easiest to use ICU severity of illness scoring systems and as effective for estimating the probability of mortality in ICU patients as other scores such as the APACHE II score [17]. SAPS II has thus far only been validated in mixed general medical and surgical intensive care patients [1,22].
The SAPS II score is a good predictor of outcome in SAH patients. This score may in some circumstances provide more information than specific SAH scales based on the established risk factors age, WFNS and amount of blood on CT in predicting poor outcome and the occurrence of DCI. These results have to be confirmed in a prospective study.

References

1. Agha A, Bein T, Fröhlich D, Höfler S, Krenz D, Jauch KW: Simplified acute physiology score (SAPS II) in the assessment of severity of illness in surgical intensive care patients. Chirurg 2002;73:439-442.
2. Claassen J, Vu A, Kreiter KT, Kowalski R, Du EY, Ostapkovich N, Fitzsimmons B-FM, Connolly ES: Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832-838.
3. Cox DR: Regression models and life-tables. J R Stat Soc[B] 1972;34:187-202.
4. Deruty R, Pelissou-Guyotat I, Mottolese C, Amat D, Bognar L: Level of consciousness and age as prognostic factors in aneurysmal SAH. Acta Neurochir Wien 1995;132:1-8.
5. Dorhout Mees SM, van Dijk GW, Algra A, Kempink DR, Rinkel GJ: Glucose levels and outcome after subarachnoid hemorrhage. Neurology 2003;61:1132-1133.
6. Drake CG: Report of World Federation on Neurological Surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg 1988;68:985-986.
7. Fukui S, Katoh H, Tsuzuki N, Ishihara S, Otani N, Ooigawa H, Toyooka T, Ohnuki A, Miyazawa T, Nawashiro H, Shima K: Multivariate analysis of risk factors for QT prolongation following subarachnoid hemorrhage. Critical Care 2003;7:R7-R12.
8. Gruber A, Reinprecht A, Illievich UM, Fitzgerald R, Dietrich W, Czech T, Richling B: Extracerebral organ dysfunction and neurologic outcome after aneurysmal subarachnoid hemorrhage. Crit Care Med 1999;27:505-514.
9. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;7:37-43.
10. Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J: Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke 1990;21:1156-1161.
11. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A: Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem Res 1997;22:1249-1255.
12. Hop JW, Rinkel GJ, Algra A, van Gijn J: Case-fatality rates and functional outcome after subarachnoid

hemorrhage: a systematic review. Stroke 1997;28:660-664.
13. Hop JW, Rinkel GJE, Algra A, van Gijn J: Changes in functional outcome and quality of life in patients and caregivers after aneurysmal subarachnoid hemorrhage. J Neurosurg 2001;95:957-963.
14. Junger A, Engel J, Benson M, Hartmann B, Röhrig R, Hempelmann G: Risk predictors, scoring systems and prognostic models in anesthesia and intensive care. Part II intensive care[In German]. Anästhesiol Intensivmed Notfallmed Schmerzther 2002;37:591-599.
15. Kassell NF, Torner JC, Clark Haley E, Jane JA, Adams HP, Kongable GL: The international cooperative study on the timing of aneurysm surgery. Part I: overall management results. J Neurosurg 1990;73:18-36.
16. Lagares A, Gómez PA, Lobato RD, Alén JF, Campollo J: Prognostic factors on hospital admission after spontaneous subarachnoid hemorrhage. Acta Neurochir Wien 2001;143:665-672.
17. Le Gall JR, Lemeshow S, Saulnier F: A new simplified acute physiology score (SAPS II) based on a european/north american multicenter study. JAMA 1993;270:2957-2963.
18. Maiuri F, Gallicchio B, Donati P, Carandente M: The blood leukocyte count and its prognostic significance in subarachnoid hemorrhage. J Neurosurg Sci 1987;31:45-48.
19. McGirt MJ, Mavropoulos JC, McGirt LY, Alexander MJ, Friedman AH, Laskowitz DT, Lynch JR: Leukocytosis as an independent risk factor for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:1222-1226.
20. McKeating EG, Andrews PJ, Signorini DF, Mascia L: Transcranial cytokine gradients in patients requiring intensive care after acute brain injury. Br J Anaesth 1997;78:520-523.
21. Members of the American College of Chest Physicians: American college of chest physicians/society of critical care medicine consensus conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-874.
22. Murthy JM, Meena AK, Raj Kumar S: Severity-of-illness scoring systems and models: neurological and neurosurgical intensive care units. Neurol India 2001;49:S91-94.
23. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, Rordorf G, Schwamm LH, Koroshetz WJ, McDonald CT: Fever in subarachnoid hemorrhage. Relationship to vasospasm and outcome. Neurology 2001;56:1299-1304.
24. Qureshi AI, Suri MFK, Sung GY, Straw RN, Yahia AM, Saad M, Guterman LR, Hopkins LN: Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2002;50:749-756.
25. Solenski NJ, Haley EC, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC: Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007-1017.
26. Tamargo RJ, Walter KA, Oshiro EM: Aneurysmal subarachnoid hemorrhage: prognostic features and outcomes. New Horiz 1997;5:364-375.
27. van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M, Crevel H: Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg 1985;63:355-362.
28. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.
29. Yoshimoto Y, Tanaka Y, Hoya K: Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. Stroke 2001;32:1989-1993.

Chapter 7

Disorders of sleep and wake in patients after subarachnoid hemorrhage

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Introduction

Many patients who have survived an episode of SAH remain dependent for activities in daily living, and many of those who are independent have a reduced quality of life (QoL). The reasons for this reduction in quality of life have not yet been determined. During long term follow up, patients who have had an SAH frequently complain of lack of initiative, falling asleep during daily activities, fatigue, irritability, loss of interests, and lack of concentration.[1,2] Similar problems during daytime are often seen in patients with disorders of sleep and wake. The reported problems in patients with SAH may therefore be related to sleep disturbances. Disturbed sleep is a common complaint after an ischemic stroke, but has never been investigated among SAH patients.[3] The major sleep disorder associated with ischemic stroke is sleep apnea (OSAS), but insomnia and excessive daytime sleepiness (EDS) are frequently found after ischemic stroke as well. These sleep disturbances affect QoL,[4,5] and treatment of these disorders of sleep and wake can improve QoL.[6,7]

We performed a survey of the frequency and severity of specific sleep disturbances in patients who have survived an episode of SAH. Additionally we investigated the relation between sleep disturbances or excessive daytime sleepiness and the QoL at least one year after SAH.

Methods

Patients

We studied a prospectively collected series of consecutive patients with SAH, who had been admitted to the Medical Center Haaglanden in The Hague between January 1, 2000 and December, 1 2002. All patients had extravasated blood in the basal cisterns on CT, or if CT was negative, xanthochromia of the cerebrospinal fluid. Patients with a nonaneurysmal perimesencephalic hemorrhage (distribution of blood mainly or exclusively around the mesencephalon and no aneurysm on four vessel angiography) were included but those with SAH of traumatic origin or bleeding from a vascular malformation were excluded. The clinical condition on admission was assessed by means of the World Federation of Neurological Surgeons (WFNS) scale.[8] A dichotomy was made between good (WFNS I, II, or III) and poor neurological condition (WFNS IV of V). The amount of subarachnoid blood on CT was assessed according to the classification of Hijdra.[9] The amount of blood in 10 cisterns or fissures and in 4 ventricles on CT was graded separately on a semi quantitatively scale ranging from 0 (no blood visible) to 3 (completely filled with blood). The sum scores of cisternal blood (range 0-30) and of ventricular blood (range 0-12) were dichotomized at their median value.

Measures

All patients filled out the Sleep Diagnosis Questionnaire (SDL) to explore the possibility of sleep disorders. This SDL is a questionnaire in a Likert scale fashion with the categories: 'never', 'seldom', 'sometimes', 'often', and 'very often or always'. The questionnaire is derived from the 'Sleep Diagnostic Questionnaire (SDQ).[10] The Dutch translation is validated for the Netherlands in a normal population and in a patient population with sleep disorders.[11] The 75 questions cover six dimensions of sleep (related) disorders. These dimensions are insomnia, RLS, excessive daytime sleepiness (EDS), narcolepsy, sleep disorders due to depression and sleep apnea syndrome. Per dimension a total score can be calculated from the relevant items in the questionnaire. This score ranges from 0 to 4. For our survey of the SAH patients we focused on the dimensions insomnia and EDS. A score of ≥ 3 on at least one of these two dimensions was considered as a significant indicator for a disorder of sleep and wake (severe sleep complaints). We used also the Epworth Sleepiness Score (ESS), a frequently used subjective assessment, as a second measure for daytime sleepiness. The ESS has been validated in various groups of patients.[12] The ESS is a questionnaire describing 8 situations, scored again in a Likert scale fashion of 'never','slight','moderate', and a 'high' chance of dozing during daytime. The summed scores range from 0 to 24. A score above 10 is thought to be indicative of EDS.[13]

We carried out 48 hour polysomnographic studies at home in a subset of patients. For this part of the study we asked all patients (except for patients in a nursing home) with a score of ≥ 3 on the dimensions Insomnia or EDS of the SDL. The ambulatory polysomnography (APSG) contained electroencephalography (EEG), submental electromyography (EMG) and recording of eye movements. Simultaneously, leg movements and airflow were measured

during the nights. Standard scoring systems were used.[14,15] Objective quality of sleep was monitored for an additional week by actigraphic recording as well. An actigraph has the size of a digital watch and is worn on the wrist of the subject during consecutive days and nights. It measures all activity above a certain limit.[16] Actigraphic monitoring, carried out in the patient's natural environment is a reliable and valid estimate of the sleep-wake status.[17] Furthermore, this subset of patients filled out the Dutch translation of the Beck-Depression Inventory.[18] In this inventory with 21 items a crude score of > 16 was used as indication of an accompanying depression.[19] From the data obtained as described above a final diagnosis regarding sleep disorders was defined in these patients with severe complaints of sleep.
For the assessment of measured sleep the following measurements were chosen: sleep onset latency (SOLAT, cut off point: >30min), sleep efficiency (SEI, cut off point <80%) and sleep fragmentation (>8 awakenings). As the APSG was recorded during daytime as well, naps could be assessed in detail. The one week actigraphy provided a global insight in sleep and wake for a prolonged period of time. Other intrinsic sleep disorders as OSAS and RLS/PLMD could be diagnosed through the APSG. OSAS was diagnosed if patients had an apnea-index (AHI) > 10 in combination with frequent daytime napping. The diagnosis RLS/PLMD was based on both a periodic leg movement index exceeding 10/hr and a history of RLS.

We used a modified Rankin scale to assess functional outcome. The Rankin scale is a 6-point handicap scale that focuses on restrictions in lifestyle and is validated in Dutch. A score of 0 to 3 indicates independency and a score of 4 to 5 dependency.[20] We assessed QoL by means of the SF-36, a reliable and validated questionnaire.[21] The SF-36 measures 8 health-related domains: physical functioning, role limitations because of physical or emotional health problems, bodily pain, social functioning, general mental health, vitality and general health perception. A single item is added to assess any change in health compared with 1 year before. The psychometric qualities of the Dutch version of the SF-36 have been tested in a random population sample.[22] Additionally, we applied two simple questions regarding job consequences in a Likert scale fashion ("Did you return to your previous work: yes, no, full-time or part-time") and recovery ("Do you feel that you have made a complete recovery from your SAH").

Procedure
All questionnaires were mailed to the patients at least one year after the SAH. Before sending these questionnaires we had checked with the general practitioner if patients were still alive. If patients did not respond, we first sent two reminders. Patients with a score of ≥ 3 on SDL dimensions insomnia or EDS were asked to participate in the ambulant registrations as described above. A detailed history was taken of all patients and their bed partners who participated in the ambulant registrations and all these patients were seen in our outpatient Center of Sleep and Wake Disorders to discus final diagnosis and therapy.

Data analysis

Descriptive statistics were used to report the frequency of complaints of sleep and wake. To determine the relationship between sleep disturbances (insomnia or EDS, or both) and outcome according to the Rankin scale, and sleep disturbances and the amount of blood on baseline CT, the chi-square test was used. This test was also used to study the relation between sleep disturbances and definite treatment (coiling or clipping) on the QoL. Results were expressed as Odds ratios (OR's). We analyzed the SF-36 scores of our group using the Mann-Whitney U test and expressed the differences with the normal data for the Netherlands in standard deviations from the mean in this reference group (age adjusted). The standard scores were presented as line graphs and allow comparisons between the study group and the reference population across the entire profile of the SF-36.[23]

Results

Hundred-thirty patients with SAH had been admitted during the study period. Forty-one patients died in the first year after the SAH. Of the 89 patients who were still alive one year after the SAH, six did not return the questionnaires; the remaining 83 patients completed all questionnaires. The time lapsed since the SAH ranged from 1.0 to 3.4 years (mean 1.7 years). No patient was on medication affecting sleep at time of the study. Sixteen of the 83 patients (20%) reported a complete recovery. Forty three (53%) of patients often complained of tiredness on the SF-36 list, 9 (11%) were dependent on help for daily activities and 42 (51%) had negative job consequences. (table 1). Of the six patients who declined participation 5 did not specify the reason for not responding; one was not able to fill out the QoL questionnaire because of severe neurological and cognitive deficits. The functional outcome of these 6 patients was comparable to that of the other patients, according to the outpatient Rankin scores at 6 months after SAH.

Questionnaires.

Of the 83 patients, 28 (34%; 95%CI 23-44%) had severe sleep complaints (table 2). Frequent complaints on individual questions of the SDL were difficulty falling asleep (25%; 95%CI 16-35%), difficulty returning asleep (28%; 95%CI 18-38%), and repeated awakenings (31%; 95%CI 21-42%). Complaints of snoring were noted in 35% (95%CI 24-45%) of patients. Many patients complained about poor concentration (18%; 95%CI 10-27%), deficits of memory (23%; 95%CI 14-32%) and feeling very tired (31%; 95%CI 21-42%) and had frequent daytime periods of dozing (6%; 95%CI 1-11%). Four of the 7 (57%) patients with a perimesencephalic hemorrhage had severe complaints on insomnia or excessive daytime sleepiness.

In the patients with no sleep disturbances, the mean SF-36 scores did not differ by more than 0.5 standard deviation from the scores of the reference population (Fig 1). In contrast, patients with severe sleep disturbances had a marked reduction in QoL compared with the normal population and the patients with no sleep complaints. This difference was most prominent for

the domains 'social functioning' and 'role limitations from physical or emotional problems', but statistically significant in all dimensions (p-values varied between <0.001 and 0.013). The rate of sleep disturbances was similar for patients with restrictions in activities on daily living and those without (OR 1.6; 95%CI: 0.40-6.6). Coiled patients had no significantly lower risk of having sleep disturbances than operated patients (OR 0.34; 95%CI: 0.09-1.34).

Table 1. Patient characteristics

Total 83 patients	
Age; mean (sd)	53.3 (12.1)
Women	58 (70%)
Perimesencephalic Hemorrhage	7 (8%)
WFNS at admission	
I-III	68 (82%)
IV-V	15 (18%)
Hijdra score ; median(range)	11 (0-24)
Cisternal score	0 (0-12)
Ventricular score	
Aneurysm location †	
Comm ant	26 (31%)
ICA	4 (5%)
ACM	16 (19%)
Comm post	11 (13%)
VBA	10 (12%)
Other	2 (2%)
Unknown	7 (8%)
Perimesencephalic	7 (8%)
Treatment of aneurysm	
Surgery	48 (58%)
Coiling	19 (23%)
Outcome	
Rankin score	
0	19 (24%)
1-3	54 (65%)
4-5	9 (11%)
Recovery (subjective)	
Complete recovery of SAH	
No	66 (80%)
Yes	16 (20%)
Return to previous job :	
Full-time	18 (22%)
Part-time	16 (19%)
No	26 (32%)
Not relevant*	22 (27%)
Do you feel tired‡	
Often or more	43 (53%)
Sometimes or less	39 (47%)

** For example: retired*

†Comm ant indicates anterior communicant artery; ICA, internal carotid artery; MCA, middle cerebral artery; Comm post, posterior communicant artery; VBA, vertebrobasilar artery system

‡Question in the SF-36 pertaining sleep and wake.

Table 2. The prevalence of sleep disorders in patients with SAH

Total of 83 patients	
Individual SDL questions*†	
Difficulty falling asleep	21 (25%;95%CI 16-35%)
Difficulty returning to sleep	23 (28%;95%CI 18-38%)
Awaking to early	22 (27%;95%CI 22-28%)
Repeated awakenings	26 (31%;95%CI 21-42%)
Poor concentration	15 (18%;95%CI 10-27%)
Deficits of memory	19 (23%;95%CI 14-32%)
Feeling very tired	26 (31%;95%CI 21-42%)
Complaints of snoring	29 (35%;95%CI 24-45%)
Loss of libido	22 (27%; 95%CI 17-36%)
SDL total score*	
Severe sleep complaints‡	28 (34%;95%CI 23-44%)
Insomnia	23 (28%;95%CI 18-38%)
EDS§	7 (8.5%;95%CI 2-15%)
ESS ||	5 (6%;95%CI 1-11%)

** Sleep Diagnosis Questionnaire*

† Often or very often on Likert scale

‡ Insomnia or EDS, or both; Cut-off point for Insomnia and EDS on SDL ≥3

§ EDS: excessive daytime sleepiness

|| Epworth Sleepiness Score >10

The amount of cisternal or ventricular blood was not significantly related to the existence of severe sleep disturbances (OR cisternal blood: 0.4; 95%CI: 0.1-1.6; OR ventricular blood: 0.5; 95%CI 0.2-1.3).

Polysomnography and actigraphy.

In the 28 patients with scores ≥3 on the "insomnia" and "EDS" parts of the SDL, APSG and actigraphy were planned. Two of these patients resided in a nursing home and six others declined to participate in this sub study. Thus, 20 patients participated in these objective tests of the quality of sleep and wake. None of these patients had a normal sleep. Severe sleep fragmentation, OSAS, RLS/PLMD or a combination of these disorders of sleep and wake occurred in 19 patients (95%; 95%CI 85-100%); for details see table 3. Four patients (including the one remaining patient without severe sleep fragmentation) had insomnia from inadequate sleep hygiene (staying in bed too long and daytime napping). Nine patients (45%) had a depression according to the the Beck-Depression Inventory. Only in one patient this was held for the cause of the sleep disturbance.

All studied patients and their bed partner reported that the complaints of sleep and wake started after their SAH. Four patients had no regular bed partner. Complaints of insomnia and RLS/ leg movements were not reported before the SAH. Two patients had complaints

of tiredness before their hemorrhage. This tiredness deteriorated after their bleeding. In three patients a history of snoring was unknown. One patient had severe complaint of snoring before his hemorrhage. This patient had already undergone an APSG and clinical polysomnography before the SAH because of snoring. He had no apneas before SAH but had a significant sleep apnea syndrome (AHI = 19.3) after the SAH.

Figure 1. SF-36 profile of the patients with and without sleep disturbances. Deviations from reference data are expressed in mean standard scores.

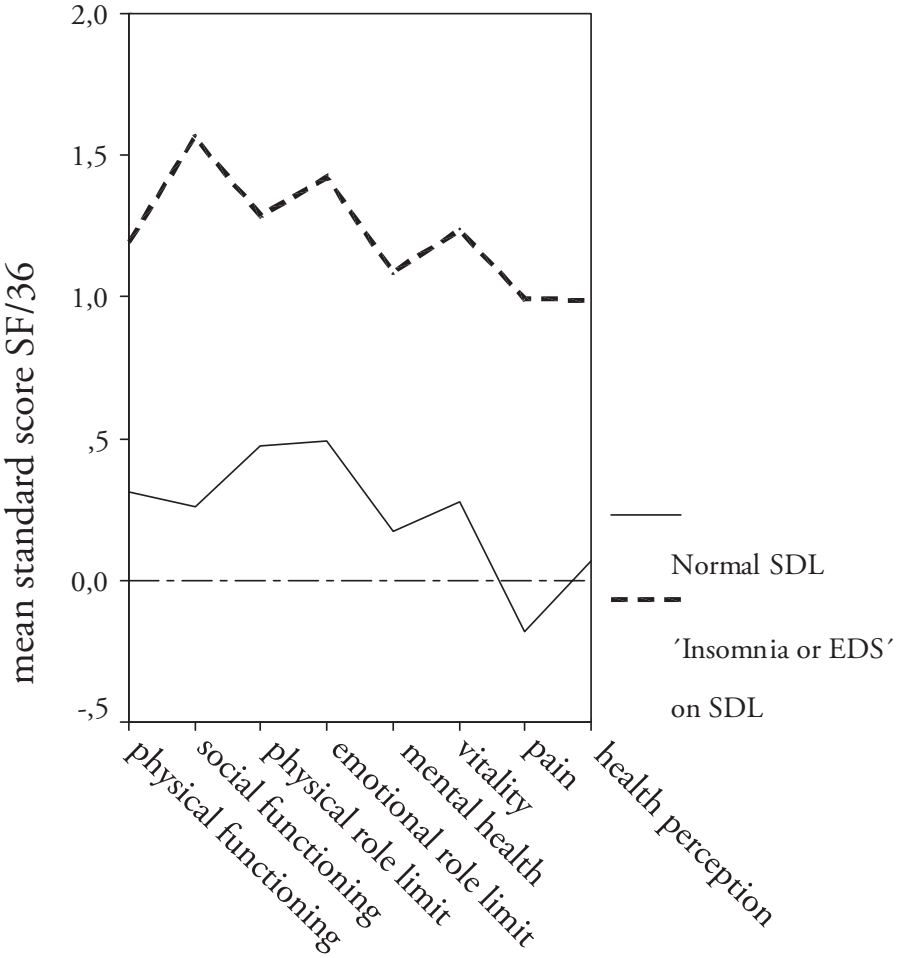

Table 3. Characteristics of polysomnographic and actigraphic monitoring

Total 20 patients*			**Cut-off point**
Diagnosis			
Sleep fragmentation	15	75%	> 8 awakenings
Disturbed sleep initation	7	35%	> 30 minutes (in at least one night)
Low sleep efficiency	11	55%	SEI <80%‡
Frequent napping	14	70%	Naps during the day
OSAS	5	25%	Apnea-index>10 and EDS
RLS/ PLMD†	5	25%	Periodic Leg movement Index>10
Inadequate Sleep hygiene	4	20%	

Some patients had more than 1 diagnosis.

** 20 patients with severe sleep complaints in SDL (Insomnia or EDS, or both)*

† Not scored in the OSAS patients

‡ SEI= sleep efficiency index

Discussion

Disorders of sleep and wake occur in one-third of patients one to three years after a SAH. Many of these patients have insomnia, excessive sleepiness during the day, or both. Patients with severe sleep disturbances often have considerably reduced QoL.

We could not find previous systematic studies of sleep disturbances in patients who have survived an episode of SAH. In only two studies sleep disturbances were mentioned sidewise. In one study, as part of a self-rating scale for the QoL, a disturbed sleep was suggested in 47% of these patients.[1] In a telephone interview asking for neurological and psychosocial outcome 4 to 7 years after SAH, 35% still experienced daytime sleepiness or fatigue and 26% experienced problems maintaining nighttime sleep.[24] These proportions are in line with those of our study. The sleep disturbances probably result in diminished concentration or memory, and daytime sleepiness, which all are often mentioned by patients after SAH. These consequences of poor sleep quality are related to the QoL which is often reduced after SAH, even in those who are independent.[23]

None of these patients with APSG studies had a normal sleep. Severe sleep fragmentation was the most frequent sleep disturbance in these studies. Also, the frequency of significant OSAS and severe RLS/ PLMD was much higher than expected on basis of data from the general population.[25,26] Both disorders can be treated. In analogy to OSAS and RLS/PLMD in the general population, it can be expected that therapy for these disorders may improve QoL.[6,7]

One of the limitations of our study is that not all patients underwent APSG. One of the 8 patients who declined APSG had RLS; five had a severely reduced SF-36 score. This reduced QoL might have been related to sleep disturbances. Our results may therefore be an underestimation of the actual proportion of patients with disturbed sleep and wake. Another limitation is that we had no control group. However, all questionnaires we used are well validated for normal and patient populations. We could compare the SF-36 score of our patient group with those of an age adjusted Dutch reference population. Moreover, we used international standardized scoring systems to qualify the stages of sleep and sleep disturbing phenomena. Although we had not systematically acquired data on sleep before the SAH, all patients and bed-partners mentioned that the sleep disturbances had started or worsened after the SAH. Depression might explain part of the sleep and wake disorders but we think that depression is not an important cause for disturbances of sleep and wake in our group of patients, because other aspects of sleep in depression (short REM sleep latency and increase amount of REM sleep) were seen in only one of our patients. We therefore think that, in analogy to many other sleep disorders, the sleep disturbance initiates the depression and not the other way around.[27]

This study may have important implications for the follow up of SAH patients. Sleep disorders after SAH are very common, often serious and are treatable. These disorders are seen in patients independently of the outcome according to the Rankin score. Our data indicate that special attention for a sleep disorder is warranted in patients complaining of daytime fatigue, restless or, nonrestorative sleep, snoring and restless legs syndrome. Treatment of these disorders of sleep and wake may be beneficial in patients who have survived an episode of SAH.

References

1. Hütter BO, Gilsbach JM, Kreitschmann I. Quality of life and cognitive deficits after subarachnoid hemorrhage. British Journal of Neurosurg. 1995;9:465-475.
2. Hermann DM, Siccoli M, Bassetti CL. Sleep-wake disorders and stroke. Schweiz Arch Neurol Psychiatr. 2003;154:369-373.
3. Leppävuori A, Pohjasvaara T, Vataja R, Kaste M, Erkinjuntti T. Insomnia in ischemic stroke patients. Cerebrovasc Dis. 2002;14:90-97.
4. Lacasse Y, Godbout C, Series F. Health-related quality of life in obstructive sleep apnoea. Eur Respir J. 2002;19:499-503.
5. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep. 1999;22;Suppl 2:S379-85.
6. Palomaki H, Berg A, Meririnne E, Kaste M, Lonnqvist R, Lehtihalm M, Lonnqvist J. Complaints of poststroke insomnia and its treatment with mianserin. Cerebrovasc Dis. 2003;15:56-62.
7. Bolitschek J, Schmeiser-Rieder A, Schobersberger R, Rosenberger A, Kunze M, Aigner K. Impact of nasal continuous positive airway pressure treatment on quality of life in patients with obstructive sleep apnoea. Eur Respir J. 1998;11:890-4.

8. Drake CG. Report of World Federation on Neurological Surgeons committee on a universal subarachnoid hemorrhage grading scale. J Neurosurg. 1988;68:985-986.
9. Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke. 1990;21:1156-1161.
10. Douglass AB, Bornstein R, Nino-Murcia G, Keenan S, Miles L, Zarcone VP Jr, Guilleminault C, Dement WC. The Sleep Disorders Questionnaire: I. Creation and multivariate structure of SDQ. Sleep. 1994;17;160-167.
11. Sweere Y, Kerkhof GA, de Weerd AW, Kamphuizen HAC, Kemp B, Schimsheimer RJ. The validity of the Dutch Sleep Disorders Questionnaire (SDQ). J Psychosom Res 1998;45:549-555.
12. John MW. Sleepiness in different situations measured by the epworth sleepiness scale. Sleep. 1994;17:703-710.
13. Bassetti C, Michael S, Chervin R, Quint D. Sleep apnea in patients with transient ischemic attack and stroke: A prospective study of 59 patients. Neurology. 1996;47:1167-1173.
14. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Brain Information Service/ Brain Research Institute, Los Angeles, 1968.
15. Recording and scoring leg movements. The Atlas Task Force. Sleep. 1993;16:748-759.
16. Sadeh A, Hauri PJ, Kripke DF, Lavie P. The role of actigraphy in the evaluation of sleep disorders. Sleep. 1995;18:288-302.
17. Sadeh A, Alster J, Urbach D, Lavie P. Actigraphically based automatic sleep wake scoring. Walidity and clinical applications. J Ambulatory Monitoring. 1989;2:209-216.
18. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-571.
19. Leentjens AF, Verhey FR, Luijckx GJ, Troost J. The validity of the Beck Depression Inventory as a screening and diagnostic instrument for depression in patients with Parkinson's disease. Movement Disorders. 2000;15:1221-1224.
20. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-607.
21. Anderson C, Laubscher S, Burns R. Validation of the Short Form 36 (SF-36) health survey questionnaire among stroke patients. Stroke. 1996;27:1812-1816.
22. van der Zee K, Sanderman R, Heyink J. De psychometrische kwaliteiten van de MOS-36 Short Form Health Survey (SF-36) in een Nederlandse populatie. Tijdschr Soc Geneesk 1993;71:183-191.
23. Hop JW, Rinkel GJE, Algra A, van Gijn J. Quality of Life in patients and partners after aneurysmal subarachnoid hemorrhage. Stroke. 1998;29:798-804.
24. Ogden JA, Utley T, Mee EW. Neurological and psychosocial outcome 4 to 7 years after subarachnoid hemorrhage; clinical study. Neurosurgery. 1997;41:25-34.
25. Neven AK, Middelkoop HAM, Kemp B, Kamphuisen HAC, Springer MP. The prevalence of clinically significant sleep apnoea syndrome in the Netherlands. Thorax 1998;53:638-642
26. Rijsman RM, Knuistingh Neven A, Graffelman AW, Kemp B, de Weerd AW. Epidemiology of restless legs in the netherlands. Eur J Neurol. 2004;11:607-611.
27. Vandeputte M, de Weerd AW. Sleep disorders and depressive feelings: a global survey with the Beck depression scale. Sleep Medicine. 2003;4:343-345.

Chapter 8

General discussion

Subarachnoid hemorrhage is a life-threatening neurological disease, most often caused by a ruptured aneurysm that requires rapid diagnosis and critical care.
During the last 20 years, attention has been focused on immediate diagnosis and treatment of the ruptured aneurysm. In addition to the initial bleeding, rebleeding is a major threat. [1]
The rate of early rebleeding within 24 hours is at least 4%, with a declining rate after day 1. Some studies report an even higher risk of an ultra early rebleeding (about 15%).[2,3,4] Earlier treatment has reduced the influence of rebleeding on outcome. Delayed cerebral ischemia (DCI) and hydrocephalus are other important intracranial complications leading to poor outcome.[1]
With advances in management strategies such as optimal timing of surgery, endovascular treatment, adequate intake of fluid, refraining from antihypertensive drugs and systematic application of nimodipine the risk of ischemic complications has reduced. The case-fatality rates decreased by approximately 0.5% per year during the last three decades.[5] Also the proportions of patients remaining independent have become larger.[5]
However, even with these advances in management strategies, many patients still deteriorate.
It is important to identify these patients at risk for secondary complications.
Age, the clinical condition at admission and the amount of extravasated blood at the admission CT scan are established prognostic factors for DCI and poor outcome.[1,6] However, many patients with a poor clinical condition or large amounts of extravasated blood do not develop DCI and have a good outcome, while some patients in good clinical condition and small amounts of extravasated blood still develop DCI. Apparently factors other than the established predictors play a role.
In this thesis we investigated the prognostic effect of frequently seen extracranial complications on outcome and DCI.

Cardiac complications
The electrocardiogram and serum cardiac troponin I level (cTnI) are simple tools to screen patients for cardiac dysfunction. Cardiac dysfunction may cause hypotension, rhythm disturbances, depressed cardiac output (total volume of blood pumped by the ventricle per minute) and pulmonary edema leading to hypoxemia of the brain. Hypoxemia is an important prognosticator for outcome (Chapter 1 and 5) and the effects on DCI have to be investigated in future research. We also have to investigate if DCI is the leading cause of poor outcome in hypoxemia. The size of the current studies (both previous and ours) precludes such analyses at this moment.

ECG abnormalities did not predict the occurrence of DCI. Several explanations for the weak relation between ECG abnormalities and DCI may exist. Firstly, ECG abnormalities may not be sufficiently accurate markers for the identification of myocardial damage that leads to DCI. Secondly, myocardial dysfunction leading to DCI may occur in the absence of ECG changes. Thirdly, ECG abnormalities do not necessarily reflect impaired autoregulation of the brain. Impaired autoregulation in combination with a reduced perfusion pressure of

the brain and reduced cardiac output might be associated with an increased risk for DCI.[7] Probably these intracranial conditions are the leading cause in the occurrence of DCI.

We also found no additional prognostic value of ECG parameters and cTnI to the established prognosticators in predicting outcome (Chapter 2 and 3). Cardiac troponin was a powerful predictor for the occurrence of clinical cardiopulmonary complications (chest X-ray pulmonary edema, abnormalities in pulmonary gas exchange, rhythm disturbances, and inadequate cardiac performance) and also for a disturbed cardiac contractility (Chapter 3 and 4). Elevated cTnI was also an independent prognosticator for the occurrence of a poor outcome but the additional prognostic information to the established prognostic factors was limited. Several factors may explain why a factor that predicts the occurrence of pulmonary and cardiac complications has no additional prognostic value for the eventual outcome.
Firstly, the severity of the initial brain injury, assessed by clinical condition and the amount of extravasated blood on CT, is the leading prognosticator for poor outcome. Most studies conclude that there is a relation between cardiopulmonary and metabolic abnormalities and the severity of SAH. Probably these cardiopulmonary complications are caused by the initial severity of bleeding and therefore the additional prognostic value to factors representing this severity of bleeding in prognosticating outcome is limited.
SAH causes sympathetic nervous activation with massive catecholamine release.[8] This catecholamine release might be the link between the initial severity of bleeding and some of the systemic complications after SAH. Catecholamines are related to myocardial stunning, high pressure pulmonary edema, stress hyperglycemia and leucocytosis.[9,10,11] This further adds to the suggestion that catecholamines are the link between the severity of the initial SAH and the occurrence of systemic complications. Catecholamine concentrations, too are no predictors for poor outcome after subarachnoid hemorrhage if the established prognosticators are taken into account.[12]
Secondly, one of the other factors explaining why cardiopulmonary complications do not contribute to the prediction of outcome might be that a local inflammatory response of the brain initiated by the SAH can trigger a systemic inflammatory response syndrome (SIRS). Indeed, inflammatory mediators, like interleukine-1 and 6, produced in the injured brain are delivered into the systemic circulation and are linked to the occurrence of SIRS.[13,14] Extracerebral organ dysfunction was frequently seen in conjunction with SIRS.[15] This suggests that SIRS with associated organ dysfunction is a primary mechanism of extracerebral organ system dysfunction and that this syndrome can contribute to outcome. Cardiopulmonary complications are only part of this syndrome. There are conflicting observations on the relation of SIRS with outcome. SIRS was related with outcome in earlier studies with retrospective data extraction in 103 and 142 SAH patients, respectively.[15,16] In one of these studies SIRS predicted outcome independent from other prognosticators.[16] A prospective observational study of 413 SAH patients, however, concluded that the additional prognostic value of SIRS for poor outcome was limited.[17] We too did not find an additional effect of SIRS to the established prognosticators on outcome. (Chapter 5).
Thirdly, we showed that the SAPS II scoring system including assessment of extracerebral

organ function independently predicts poor outcome in SAH patients (Chapter 5). Pulmonary and cardiac problems are only part of these extracerebral dysfunction and therefore the individual importance can be missed in predicting outcome.

We found cTnI to be a powerful predictor of cardiopulmonary complications (Chapter 3). We suggested that it can be used as a marker to identify patients who are at risk of cardiopulmonary complications. By measurement with single transpulmonary dilution we found a high frequency of reduced cardiac contractility or reduced cardiac output in the first 5 days after SAH, particularly in relation with elevated cTnI. The reduced cardiac output was usually mild and normalized within one day (Chapter 4). A relation of a reduced cardiac output and the occurrence of DCI was suggested in earlier research.[18] Because cTnI is strongly related to cardiac dysfunction, and cardiac dysfunction is frequently observed after SAH, we think that all patients with elevated cTnI need special attention for hemodynamic complications. These patients could benefit from early invasive monitoring. The effectiveness of guiding fluid therapy and inotropic support with these hemodynamic monitoring and the effects on outcome and DCI has to be evaluated in new trials.

Pulmonary complications

Pulmonary edema (assessed by means of extravascular lung water) was frequently observed in the first 5 days after SAH with the PiCCO system (Chapter 4). Pulmonary edema after SAH is frequently described in the literature.[19,20] In a clinicopathological study a pathological diagnosis of pulmonary edema was found in 55 patients (71%) of whom 31% had a clinical diagnosis of pulmonary edema.[21] Pulmonary edema can easily be missed clinically. The early recognition and differential diagnosis of pulmonary edema may be challenging since most common manifestations of pulmonary edema are nonspecific and usually late signs of pulmonary edema. Moreover, it has been difficult to quantify the extent of pulmonary edema based on chest radiography.[22] In some patients with impaired oxygenation no evidence for pulmonary edema or cardiac failure is found. In these patients the oxygenation disturbances may result from extravascular lung water (EVLW) causing a less fulminant form of pulmonary edema.[19] Clinical or radiological signs of pulmonary edema often do not appear before the EVLW-Index (EVLWI) doubles or triples.[23] Transpulmonary thermodilution enables the identification of patients with pulmonary edema (elevated EVLW) as well as quantification of the edema and its response to therapeutic maneuvers (e.g. optimizing fluid intake, inotropic drugs or positive end-expiratory pressure support).[24,25] The EVLW-Index is an important variable for early diagnosis and treatment of pulmonary edema and may be very helpful for guiding fluid therapy. EVLW correlates well with survival in a heterogeneous group of critically ill patients.[26] The effects on outcome and DCI of an elevated EVLWI elevation has to be investigated in a larger population of patients with SAH.

Composite scores and metabolic derangement

We used a common severity of illness score, the simplified acute physiology score (SAPS II) as predictor of outcome in patients with SAH (Chapter 5). SAPS II by its own appeared

to be at least as good a predictor of poor outcome than the combination of the established prognosticators. It also predicted the occurrence of DCI, but less well than poor outcome. In multivariate analysis of the individual SAPS II parameters: PaO2/ FiO2 ratio, serum urea level, age and the GCS appeared to be independent prognosticators of poor outcome. After exclusion of the GCS from the SAPS II score, the composite score of the remaining factors of the SAPS II score was still an independent predictor of poor outcome. Our study convincingly shows that a scoring system including assessment of extracerebal organ function provides a better prognostication than scoring systems that include only neurological items. These results suggest that regular control of physiological items such as temperature, oxygenation, circulation parameters, glucose, electrolyte disturbances, may lead to substantial improvement in outcome for SAH patients; however, this needs to be proven in appropriately designed treatment studies.

Our results demonstrate that physiological derangement is important. Multidisciplinary critical care approach using these severity of illness scoring systems for early identification of patients at risk for deterioration may be important.
The effect of using monitoring systems in identifying patients with cardiac depression or pulmonary edema and attention to potential treatment strategies of these cardiopulmonary complications may improve outcome.

Long-term outcome
Disorders of sleep and wake occur in one-third of patients one to three years after an SAH (Chapter 6). Many of these patients have insomnia, excessive sleepiness during the day, or both. Patients with severe sleep disturbances often have considerably reduced quality of life (QoL). The sleep disturbances probably result in diminished concentration or memory, fatigue, and daytime sleepiness, which all are often mentioned by patients who have recovered from an SAH. These consequences of poor sleep quality are related to the QoL which is often reduced after SAH, even in those patients who are independent.[27] In our study most important sleep disorders were all observed after SAH. The frequency of the obstructive sleep apnea syndrome (OSAS) and restless legs syndrome in combination with periodic limb movement disorder (RLS/PLMD) was much higher than expected on basis of data from the general population.[28,29] Most of these disorders of sleep and wake can be treated. In analogy to OSAS and RLS/PLMD in the general population, it can be expected that therapy for these disorders may improve QoL.[30,31] Our study may have important implications for the follow up of SAH patients. Sleep disorders after SAH are very common, often serious and are treatable. These disorders are seen in patients independently of the outcome according to the Rankin score. Treatment of these disorders of sleep and wake may be beneficial in patients who have survived an episode of SAH. In patients complaining of daytime fatigue, lack of concentration, loss of interests it is essential to determine if excessive daytime sleepiness, snoring , apnea or restless legs complaints are present. Patients with these symptoms need subsequent monitoring of sleep.

References

1. Kassel NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The international cooperative study on the timing of aneurysm surgery. Part1: Overall management results. J Neurosurg 1990;73:18-36.
2. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Koike T, and Tanaka R. Ultra-early rebleeding in spontaneous subarachnoid hemorrhage. J Neurosurg 1996;84:35-42.
3. Inagawa T. Ultra-early rebleeding within six hours after aneurysmal rupture. Surg Neurol 1994;42:130-134.
4. Ohkuma H, Tsurutani H, and Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. Stroke 2001;32:1176-1180.
5. Hop JW, Rinkel GJE, Algra A, and van Gijn J Case-Fatality Rates and Functional Outcome After Subarachnoid Hemorrhage : A Systematic Review. Stroke 1997;28:660-664.
6. Hijdra A, van Gijn J, Nagelkerke N, Vermeulen M, van Crevel H. Prediction of delayed cerebral ischemia, rebleeding and outcome after aneurysmal subarachnoid hemorrhage. Stroke 1988;19:1250-1256.
7. Mayer SA, Fink ME, Homma S, et al: Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. Neurology 1994;44:815-820.
8. Naredi S, Lambert G, Eden E, Zall S, Runnerstam M, Rydenhag B, Friberg P. Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke 2000;31:901-906.
9. West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries in the intensive care setting. Schweiz Med Wochenschr 1992;122:751-757.
10. Doshi R, Neil-Dwyer GA. A clinicopathologic study of patients following a subarachnoid hemorrhage. J Neurosurg 1980;52:295-301.
11. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med 1983;309:1414-1419.
12. Brouwers PJAM, Westenberg HG, van Gijn J. Noradrenaline concentrations and electrocardiographic abnormalities after aneurysmal subarachnoid hemorrhage. J Neurol Neurosurg Psychiat 1995;58:614-617.
13. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A: Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. Neurochem Res 1997;22:1249-1255.
14. McKeating EG, Andrews PJ, Signorini DF, Mascia L: Transcranial cytokine gradients in patients requiring intensive care after acute brain injury. Br J Anaesth 1997;78:520-523.
15. Gruber A, Reinprecht A, Illievich UM, Fitzgerald R, Dietrich W, Czech T, Richling B: Extracerebral organ dysfunction and neurologic outcome after aneurysmal subarachnoid hemorrhage. Crit Care Med 1999;27:505-514.
16. Yoshimoto Y, Tanaka Y, Hoya K: Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. Stroke 2001;32:1989-1993.
17. Claassen J, Vu A, Kreiter KT, et al. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004;32:832-838.
18. Mayer SA, Lin J, Homma S, et al. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. Stroke 1999;30:780-786.

19. Vespa PM, Bleck TP. Neurogenic pulmonary edema and other mechanisms of impaired oxygenation after aneurysmal subarachnoid hemorrhage. Neurocritical Care 2004;1:157-170.
20. Solenski NJ, Haley EC, Kassell NF, et al. Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007-1015.
21. Weir BK. Pulmonary edema following fatal aneurysm rupture. J Neurosurg 1978;49:502-507.
22. Staub NC, Hyde RW, Crandall E. NHLBI workshop summary: workshop on techniques to evaluate lung alveolar-microvascular injury. Am Rev Respir Dis. 1990;141:1071-1077.
23. Hedlund LW, Putman CE. Methods for detecting pulmonary edema. Toxicol Ind Health 1985;1:59 68.
24. Katzenelson R, Perel A, Berkenstadt H, Preisman S, Sternik L, Segal E. Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water Crit Care Med 2004;32:1550-1554.
25. Holm C, Tegeler J, Mayr M, Pfeiffer U, Henckel von Donnersmarck G, Műhlbauer W. Effect of crystalloid resuscitation and inhalation injury on extravascular lung water; clinical implications. Chest 2002;121:1956-1962.
26. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. Chest 2002;122:2080-2086.
27. Hop JW, Rinkel GJE, Algra A, van Gijn J. Quality of Life in patients and partners after aneurysmal subarachnoid hemorrhage. Stroke. 1998;29:798-804.
28. Neven AK, Middelkoop HAM, Kemp B, Kamphuisen HAC, Springer MP. The prevalence of clinically significant sleep apnoea syndrome in the Netherlands. Thorax 1998;53:638-642
29. Rijsman RM, Neven AK, Graffelman AW, Kemp B, de Weerd AW. Epidemiology of restless legs in the Netherlands. Eur J Neurol. 2004;11:607-611.
30. Palomaki H, Berg A, Meririnne E, Kaste M, Lonnqvist R, Lehtihalm M, Lonnqvist J. Complaints of poststroke insomnia and its treatment with mianserin. Cerebrovasc Dis. 2003;15:56-62.
31. Bolitschek J, Schmeiser-Rieder A, Schobersberger R, Rosenberger A, Kunze M, Aigner K. Impact of nasal continuous positive airway pressure treatment on quality of life in patients with obstructive sleep apnoea. Eur Respir J. 1998;11:890-4.

Chapter 9

Summary

Extracranial complications often occur after subarachnoid hemorrhage (SAH) and some are related to the occurrence of delayed cerebral ischemia (new hypodense lesion on the CT scan together with a gradual developing focal deficit, impairment of consciousness, or both) and poor outcome. Cardiac and pulmonary complications are the most common complications, but also an inflammatory response and metabolic derangements are frequently described after SAH. Almost all these extracranial complications are directly related to the extent of the initial hemorrhage.

In ***chapter 1*** we review the literature between 1980 and July 2004 on the most common extracranial complications and their known effects on delayed cerebral ischemia and poor outcome.

Pulmonary complications are the most frequently seen medical complications in SAH patients. Oxygenation disturbances of any severity are described in 40 to 80% of patients with SAH in three studies including 690 patients. Severe oxygenation disturbances (PaO2/FiO2 ratio <150) were found in 20% of patients in two retrospective studies with a total of 449 patients. Oxygenation deficits in the acute stage of SAH most often result from pulmonary edema. Pulmonary edema was present in 20-25% of consecutive SAH patients during the first two weeks of hospitalization. Hypoxemia is an independent predictor of death or severe disability and pulmonary complications were responsible for 50% of all deaths from medical complications. The effects of pulmonary complications on delayed cerebral ischemia are less well known.

Myocardial damage is demonstrated by post-mortem examinations after SAH, but also by serum markers of myocardial necrosis, and echocardiography. Myocardial damage can lead to ECG abnormalities, hypotension and also pulmonary edema. Electrocardiographic repolarization changes occur in three quarters of patients with SAH irrespective of the presence or absence of previous cardiac disease. Numerous reports have described ECG changes after SAH that are associated with poor outcome. The additional prognostic value to the established prognosticators has never been investigated.

Echocardiographic left ventricular wall motion abnormalities or a reduced left ventricular ejection fraction are described in about 10% of SAH patients (13 studies with 2057 patients). Profound myocardial dysfunction with a severely disturbed cardiac index and left ventricular ejection fraction (usually < 40%) was described in about 3% of patients. Echocardiographic myocardial dysfunction normalized or improved in all described patients. The risk of cardiac death is very low in SAH patients. Cardiac troponin I, a relative new marker of myocardial injury, is a regulatory protein highly specific for the cardiac muscle. It was elevated in about 20-30% of patients after SAH (775 patients). Elevated cardiac troponin I is a good indicator of echocardiographic left ventricular dysfunction. Even slightly elevated concentrations are related to serious cardiac depression. In a retrospective study, patients with echocardiographic abnormal wall motion had a two times greater risk of delayed cerebral ischemia than patients without (72 patients). The effects of echocardiographic abnormalities on outcome are not well studied. Cardiac troponin I was related with death or severe disability in univariate analysis.

Systemic inflammatory response syndrome (at least 2 of the following conditions: temperature of < 36 °C or > 38 °C, heart rate of > 90 bpm, respiratory rate of > 20 breaths/min, and WBC of <4000/mm3 or >12000/mm3) has been described in up to 50% of SAH patients and appeared to be an independent predictor for poor outcome. Systemic inflammatory response syndrome appeared to carry an increased risk of subsequent intracranial complications as well as subsequent systemic complications (242 SAH patients). A composite SAH physiologic derangement score (combination of oxygenation disturbances, mean arterial blood pressure, serum bicarbonate and glucose) was a better prognosticator for poor outcome than the existence of systemic inflammatory response syndrome.
Glucose levels were elevated (> 13mmol/L) in 21% at admission and in 46% of serial measurements. The admission blood glucose and also glucose levels during ICU stay appeared to be an independent predictor for outcome and delayed cerebral ischemia.
Hypomagnesemia during days 2 and 12 after SAH independently predicted the occurrence of delayed cerebral ischemia (107 patients). Hypomagnesemia was observed in 38% at admission and in 55% during serial measurements.
During the first 3 days after SAH *hypernatremia* was found in 12% and *hyponatremia* in 19% of patients. During the entire clinical course hyponatremia was present in 30-40%. Fluid restriction to correct hyponatremia increased the risk for delayed cerebral ischemia in a retrospective study of 134 patients and hypernatremia appeared to be significantly related to death or severe disability in the only retrospective study of 298 patients using multivariate analyses.
Severe *leucocytosis* (> 20x 10^9/L) was observed in 16% of patients. The degree of leucocytosis was described as an adverse prognostic factor for both case fatality and the development of delayed cerebral ischemia. Monitoring of the leukocyte count was suggested to quicken the diagnosis of delayed cerebral ischemia.
Severity of illness scores (such as APACHE II) combining metabolic derangement, systemic inflammation, pulmonary and cardiac parameters predicted the occurrence of an unfavorable neurological outcome after SAH.

The core of this thesis is formed by a cohort of 172 patients with aneurysmal SAH who were admitted to the ICU of the Medical Center Haaglanden between January 2000 and April 2004. All patients were treated according to standard intensive care guidelines at the ICU for at least 2 weeks. Hundred twenty one were followed prospectively and 51 by retrospective data retrieval. Their mean age was 55 (range 17-93) and 127 were female (74%). In 75 (44%) patients a surgical clip occlusion and in 45 (26%) endovascular coil placement was done to obliterate the aneurysm. In 52 (30%) patients no occlusion was performed because of a poor clinical condition from the onset. Sixty two patients (36%) had a poor neurological condition at admission. In 80 patients (46%) the outcome was poor. All studies in this thesis are based on the data of these 172 patients.
Our aim was to assess the value of extracerebral organ dysfunction and markers of these medical complications in prognosticating the occurrence of delayed cerebral ischemia or poor outcome. We also determined the frequency of this extracerebral organ dysfunction

and assessed the relation of a marker of cardiac dysfunction and the occurrence of cardiopulmonary complications. Moreover we investigated the importance of disorders of sleep and wake on the long term outcome after SAH.

Established prognosticators for outcome and the occurrence of delayed cerebral ischemia are the clinical condition at admission, age and the amount of blood on baseline CT. In ***chapters 2-6*** we evaluated the clinical condition on admission according to the WFNS classification. A dichotomy was made between good neurological condition (WFNS I, II, or III) and poor neurological condition (WFNS IV or V). The amount of subarachnoid blood was assessed according to the classification of Hijdra.
Outcome was based on the clinical status at 3 months after onset according to the Rankin scale. We qualified the scores 0 to 3 as good outcome and the scores 4, 5 and death as poor outcome. A score of 0-3 points means that the patient is independent for activities of daily life. Delayed cerebral ischemia was considered definite in case of a new hypodense lesion on the CT scan together with a gradual development of focal deficit, impairment of consciousness, or both in a patient with no other explanation for that event.
In most studies in this thesis we developed multivariate models with forward selection. Also we evaluated the discriminatory power of the models with the area under the curve of the corresponding receiver operator characteristic curve (ROC curve). An area under the curve can range from 0.50 (no discriminatory power) to 1.0 (perfect prediction).

In previous studies with SAH patients ECG characteristics appeared to be related with transient cardiac dysfunction. In ***chapter 2*** we describe a series of 121 consecutive patients with aneurysmal SAH. We related individual repolarization-like ECG changes at the admission ECG to the occurrence of delayed cerebral ischemia and to poor outcome. We used multivariate analyses and ROC curves to assess the additional prognostic value of the most important ECG characteristics to established prognosticators. Twenty-five (21%) patients had no repolarization abnormalities at the admission electrocardiogram. The most frequent abnormalities were ST depression (14%), T wave inversion (31%), a peaked T wave (17%), the presence of a U wave (52%) or QTc prolongation (13%). Also a combination of ischemic like ECG abnormalities (ST depression or T wave inversion, or both in at least two leads) was frequently seen (27%).
Of all individual ECG characteristics only ST segment depression predicted the occurrence of delayed cerebral ischemia (HR 2.4 [95%CI, 1.2-4.9]). The area under the ROC curve of ST depression for delayed cerebral ischemia was 0.53 (95%CI 0.42-0.63). These findings are in agreement with the only other study relating serial (instead of admission) acquired ECG abnormalities to the occurrence of delayed cerebral ischemia.
ST-depression and in subsequent analyses a combination of ischemic ECG abnormalities appeared independent predictors of poor outcome. The additional prognostic information of these ECG variables for poor outcome is limited. In multivariate models the area under the ROC curve improved from 0.81 to 0.84 upon extension with ECG variables of a model based on established prognosticators only.

Troponin I is a reliable marker of myocardial injury. In ***chapter 3*** we investigated the additional value of admission cardiac troponin I in predicting cardiac or pulmonary complications and outcome in patients with aneurysmatic subarachnoid hemorrhage. We prospectively studied 68 patients. An elevated cardiac troponin I was found on admission in 52%. On chest X-rays during the clinical course, pulmonary edema was seen in 28%. Pulmonary gas exchange problems (PaO2/FiO2 ratio ≤ 200) during the first two weeks of admission were found in 37% of patients. Cardiac rhythm disturbances during the clinical course (atrial fibrillation or supraventricular tachycardia) in which anti-arrhythmic therapy was needed were seen in 16% and inadequate cardiac performance (need for inotropic support to obtain a MAP >65 mmHg in the first four days after admission) was found in 25% of patients. A cardiac or pulmonary complication (at least one of the afore mentioned complications) was seen in 57% of the patients.
We related the occurrence of a cardiac or pulmonary complication to established prognosticators and to an abnormal cardiac troponin I and evaluated the additional value of an abnormal cardiac troponin I in predicting cardiac or pulmonary complications. We categorized cardiac troponin I values in tertiles to assess a possible 'dose response' effect of the cardiac troponin I.
Abnormal cardiac troponin I had a statistically significant relationship with all cardiopulmonary complications. An abnormal cardiac troponin I on admission independently predicted cardiac or pulmonary complications. Upon extension of the established prognosticators with abnormal cardiac troponin I the area under the ROC curve improved from 0.70 to 0.83. An elevated cardiac troponin I was also an independent predictor for poor outcome. The additional prognostic value of cardiac troponin I for poor outcome was limited.

In ***chapter 4*** we prospectively studied 28 patients with aneurysmal SAH who were in a poor clinical condition on admission (WFNS score III, IV or V) or had large amounts of extravasated blood (modified Fisher score >2). All patients were instrumented with a central venous catheter and an arterial line. We used the PiCCO system (a hemodynamic monitoring method combining transpulmonary thermodilution and arterial pulse contour analysis) to monitor intermittent cardiac output, cardiac contractile function (cardiac function index) and pulmonary edema (extravascular lung water[EVLW]). We assessed the frequency of cardiovascular impairment and pulmonary edema. We also determined whether myocardial injury as demonstrated by elevated levels of cardiac troponin I within 48 hours after SAH was negatively associated with cardiac performance or the occurrence of pulmonary edema. Cardiac output and extravascular lung water were normalized as indexed by body surface area (Cardiac index) and body weight (EVLWI).
Six patients (21%) had a reduced mean cardiac index < 3.0 l/min/m^2 during at least 1 day in the first 5 days of hospitalization. A depressed cardiac index was more prevalent in patients with an elevated cardiac troponin I (odds ratio (OR) 6 [95%CI 0.5-310]).
Ten patients (36%) had a reduced cardiac contractile function (cardiac function index < 4.0 l/min). In 5 patients the depressed cardiac contractile function lasted for at least 3 of

the first 5 days. A depressed cardiac contractile function was more prevalent in patients with an elevated cardiac troponin I (OR 18 [95%CI 1.6-850]).
Elevated levels of EVLWI > 10 ml/kg were found in 10 patients (36%). An elevated EVLWI was not related to the presence or absence of an elevated cardiac troponin I concentration. Mean levels of cardiac index and cardiac contractile function were in general lower in patients with an elevated cardiac troponin I but differed significantly only at the first day for CI and at day 3 for cardiac contractile function from patients with normal cardiac troponin I.
Mean EVLWI indices were in general higher in patients with elevated cardiac troponin I than in those with normal cardiac troponin I, but these differences were not statistically significant. So cardiopulmonary complications were frequently observed by the PiCCO system in patients with a poor clinical condition or with large amount of extravasated blood. An elevated cardiac troponin I appeared to be a good marker for the occurrence of a decreased cardiac contractile function.

Current prognosticators for patients with subarachnoid hemorrhage (SAH) do not take into account signs of extracerebral organ dysfunction. This may explain the only moderate predictive value of these prognosticators. In ***chapter 5*** we assessed the prognostic value of the simplified acute physiology score (SAPS II) in SAH patients. In a consecutive series of 148 patients admitted within 4 days after an SAH the SAPS II was calculated within 24 hours after admission to the ICU. The SAPS II score is one of the easiest to use ICU severity of illness scoring systems. It includes twelve physiology variables (heart rate, body temperature, white blood cell count (WBC), PaO2/FiO2 ratio, bicarbonate level, systolic blood pressure, urinary output, serum urea level, serum potassium, sodium, bilirubin level, Glasgow Coma Score, age, type of admission (scheduled surgical, unscheduled surgical, or medical) and three underlying disease variables (AIDS, hematological malignancy and metastatic cancer). We related the occurrence of delayed cerebral ischemia and poor outcome to baseline characteristics, the occurrence of a systemic inflammatory response syndrome and the SAPS II score by multivariate analysis. The effects of individual components of the SAPS II score on outcome were also evaluated. Finally we categorized the SAPS II score in tertiles to further quantify the relation of SAPS II with delayed cerebral ischemia and outcome.
SAPS II score (as continuous variable) was the only independent predictor for poor outcome (OR 1.08 [95%CI 1.06-1.11]). Patients in the highest tertile of SAPS II had a statistically significant higher risk of poor outcome than those in the lowest tertile. In multivariate analysis PaO2/ FiO2 ratio, serum urea, age and the GCS were independent prognosticators of poor outcome. SAPS II was also the only independent predictor for the occurrence of delayed cerebral ischemia (HR 1.020 [95%CI, 1.002-1.039]). The AUC for SAPS II in predicting delayed cerebral ischemia was 0.52.

In a prospectively collected consecutive series of 89 patients, 83 filled out validated and frequently used questionnaires for the assessment of disorders of sleep and wake ***(Chapter 6)***. We used the Sleep Diagnosis Questionnaire (SDL) to explore the possibility of sleep disorders. This questionnaire consists of seventy five questions covering six dimensions of

sleep (related) disorders. We focused on the dimensions insomnia and excessive daytime sleepiness. A score of ≥ 3 on at least one of these two dimensions was considered as an important indicator for a disorder of sleep and wake. We did 48 hour polysomnographic studies at home in a subset of patients. For this part of the study we invited all patients with a score of ≥3 on the dimensions insomnia or excessive daytime sleepiness of the questionnaire. We used the modified Rankin scale for functional outcome and the SF-36 to assess quality of life (QoL). We related the occurrence of severe complaints of sleep to functional outcome and to the QoL score.
Twenty eight (34%) had severe sleep complaints. Frequent complaints on individual questions of the SDL were difficulty falling asleep (25%), difficulty returning asleep (28%), and repeated awakenings (31%). Feeling very tired was noted in 31% and frequent daytime periods of dozing in 6%. Of the 83 patients, 42 (51%) had negative job consequences, 32% did not return to previous job and 19% returned for part-time.
In the patients with no sleep disturbances the mean SF-36 scores did not differ by more than 0.5 standard deviation from the scores of the healthy reference population. In contrast, the patients with severe sleep disturbances had a marked reduction in QoL, compared with the normal population and the patients with no sleep complaints. During the sleep monitoring studies in the patients with severe complaints of sleep, severe sleep fragmentation, obstructive sleep apnea syndrome, restless legs syndrome in combination with periodic leg movements during sleep or a combination of these disorders occurred in 19 of 20 patients. None of these patients had a normal sleep.

In Conclusion

ECG abnormalities did not predict the occurrence of delayed cerebral ischemia and have limited value in prognosticating poor outcome. Cardiac Troponin I is a powerful predictor for the occurrence of pulmonary and cardiac complications in patients with aneurysmal SAH. Pulmonary edema and depressed cardiac contractile function were frequently observed in the first 5 days after SAH. A depressed cardiac output was also frequently seen but usually mild and self limiting within one day. A depressed cardiac contractile function in at least one day in the first 5 days after SAH onset was more prevalent in patients with an elevated cardiac troponin I. Single transpulmonary thermodilution technique is a promising tool for monitoring SAH patients especially with elevated cardiac troponin I on admission.
The SAPS II is a useful and reliable prognosticator in SAH patients. This score may in some circumstances provide more information than specific SAH rating scales in predicting poor outcome or the occurrence of DCI. Of the individual parameters of the SAPS II score, PaO2/ FiO2 ratio, serum urea, age and the GCS were independent prognosticators of poor outcome.
Of the 83 patients who completed QoL questionnaires 9 patients (11%) had a poor outcome on the modified Rankin scale. Forty three (53%) of patients complained of tiredness and 42 (51%) had negative job consequences. In these patients disorders of sleep and wake

occurred in one-third. Patients with severe sleep disturbances often have a considerably reduced QoL.

To epitomize: extracerebral organ dysfunction is frequently seen after SAH. Grading scales incorporating signs of extracerebral organ dysfunction should be used more frequently by neurologists and neurosurgeons treating SAH patients. Cardiac troponin I can be used as marker to identify patients who are at risk of developing cardiopulmonary complications and could benefit from early invasive hemodynamic monitoring. Additional studies using single transpulmonary thermodilution are required to study the effects of cardiac and pulmonary estimates on delayed cerebral ischemia and outcome in SAH patients. Also studies with extended follow-up are required to evaluate whether a therapeutic strategy taking into account cardiac index, cardiac contractile function and extravascular lung water can improve supportive therapy and outcome. The improvement of long-term outcome should focus on attention for sleep disorders in patients complaining of daytime fatigue, restless or, nonrestorative sleep, snoring and restless legs syndrome.

Samenvatting

Een subarachnoïdale hersenbloeding (SAB) is een ernstige aandoening, die gewoonlijk door een aneurysmatische (verwijdende) vaatafwijking ontstaat. Veel mensen overlijden aan de directe gevolgen van de bloeding en een groot deel van de mensen die overleven houdt ernstige restverschijnselen. Naast de schade die direct ontstaat door de bloeding wordt een deel van de sombere afloop[1] veroorzaakt door complicaties tijdens het verblijf in het ziekenhuis. Belangrijke late complicaties zijn het optreden van een nieuwe bloeding of secundaire ischemie (neurologische uitvalsverschijnselen ten gevolge van een doorbloedingsstoornis van de hersenen, het meest tussen de vierde en tiende dag na een SAB).
Behalve deze neurologische oorzaken van een verslechtering treden er ook zeer vaak andere oorzaken van een achteruitgang op. Stoornissen in de hartfunctie en longfunctie zijn hiervan het meest voorkomend. Ook treedt er vaak een ontstekingsbeeld beeld van weefsels en organen op, soms in combinatie met ernstige ontregelingen van de stofwisseling. Deze complicaties kunnen weer een lage bloeddruk, hartritmestoornissen danwel een te laag zuurstofgehalte in het bloed veroorzaken waardoor er secundaire ischemie in de hersenen kan optreden.
Vrijwel in alle onderzoeken lijkt het optreden van deze niet-neurologische complicaties direct gerelateerd te zijn aan de ernst van de subarachnoïdale hersenbloeding.

In ***hoofdstuk 1*** wordt een overzicht gegeven van wat er in de literatuur bekend is over de frequentie van voorkomen van deze niet-neurologische complicaties en ook over hun relatie met het optreden van secundaire ischemie en de kans op een sombere afloop na de bloeding. We onderzochten hiervoor de literatuur over de periode tussen 1980 en juli 2004. Alle volgende gegevens tot aan de beschrijving van het patiënten onderzoek in het Medisch Centrum Haaglanden zijn bevindingen uit eerder literatuuronderzoek.

Complicaties van de longen zijn de meest voorkomende niet-neurologische complicaties na een SAB. Stoornissen in de oxygenatie (verzadiging met zuurstof) werden zelfs bij 40 tot 80% van de patiënten beschreven in de literatuur. Ernstige stoornissen in het zuurstofgehalte van het bloed kwamen voor bij 20% van de patiënten in de eerste twee weken van opname. De meest voorkomende oorzaak hiervan is overvulling van de longen. Dit verschijnsel werd bij 20-25% van de mensen in de eerste twee weken na een SAB beschreven in twee wetenschappelijke onderzoeken. Complicaties van de longen waren bij 50% van de patiënten de oorzaak van het overlijden door niet-neurologische complicaties na een SAB, waarbij hypoxemie (te weinig zuurstof in het bloed) een belangrijke voorspeller bleek te zijn voor het optreden van overlijden of afhankelijkheid van anderen.

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1 Voor de mate van herstel gebruikten we de Rankin-schaal. Hiermee wordt de mate van onafhankelijkheid beoordeeld, drie maanden na het optreden van de bloeding. Blijvende afhankelijkheid van anderen ofwel overlijden worden gezien als een sombere afloop.

Schade aan het hart na een SAB wordt eveneens veelvuldig beschreven. Voorbeelden hiervan zijn: schade bij pathologisch onderzoek aan hartspier, verhoging van bepaalde kenmerken in het bloed van hartschade en afwijkingen bij echocardiografisch (echografie van het hart) onderzoek. Deze schade is vaak tijdelijk van aard en leidt zelden tot overlijden ten gevolge van een cardiale (van het hart) oorzaak.
Deze schade aan het hart kan stoornissen geven in de elektrische geleiding en de pompfunctie van het hart. Dit kan ECG (hartfilm) afwijkingen en lage bloeddruk tot gevolg hebben maar bijvoorbeeld ook bijdragen aan het optreden van overvulling van de longen.
Stoornissen op het ECG kwamen voor bij ¾ van de patiënten met een SAB. Deze ECG veranderingen zouden gerelateerd zijn aan het optreden van een sombere afloop, echter de toegevoegde waarde van deze ECG veranderingen ten opzichte van de belangrijkste voorspellers van een sombere afloop is nooit onderzocht.
Echocardiografische afwijkingen werden beschreven bij 12% van deze patiënten. Ernstig echocardiografisch disfunctioneren van het hart werd bij 3% van de patiënten geconstateerd.
Cardiaal troponine I (cTnI) is een kenmerk in het bloed van schade aan het hart. Het is een specifiek eiwit voor de hartspier waarvan de waarde bij 20-34% van de mensen na een SAB verhoogd is. Ook bij de SAB is een verhoogd cTnI een goede indicator voor het krijgen van echocardiografische disfunctie. Zelfs bij minimaal verhoogde waardes kunnen er al ernstige stoornissen in de hartfunctie optreden.
Dit cTnI is gerelateerd aan een sombere afloop in enkelvoudige regressie-analyses in eerder onderzoek. De toegevoegde waarde ten opzichte van de bekende voorspellers van een slechte afloop is ook nog nooit onderzocht. Patiënten met echocardiografische afwijkingen leken een twee keer verhoogd risico te hebben op het optreden van secundaire ischemie. De effecten van deze echocardiografische afwijkingen op een sombere afloop zijn nooit goed bestudeerd.
Algehele voortdurende ontsteking (Systemic Inflammatory respons [SIRS]) treedt bij 54% van de patiënten na een SAB op en leek een onafhankelijke voorspeller voor het optreden van een sombere afloop. SIRS wordt gekarakteriseerd door de combinatie van twee of meer van de volgende symptomen: koorts of verlaagde temperatuur, versnelde hartslag, verhoogde ademhalingsfrequentie of verlaagd CO2 gehalte in het bloed, tijdelijke toe- of afname van de hoeveelheid witte bloedcellen. Ook kwamen er bij patiënten met SIRS vaker neurologische en andere niet-neurologische complicaties voor dan bij patiënten zonder SIRS. Echter een speciale SAB-score (een combinatie van een te laag zuurstofgehalte in het bloed, gemiddelde arteriële bloeddruk, bicarbonaat in het bloed en bloedsuiker) leek een betere voorspeller voor het optreden van een slechte afloop dan de aanwezigheid van SIRS.
Bloedsuikerwaardes waren bij 21% van de mensen na een SAB verhoogd en zelfs bij 46% na herhaalde metingen. Zowel waardes bij opname als bij herhaalde metingen tijdens intensieve zorg leken een belangrijke voorspeller te zijn voor het optreden van een sombere afloop en van secundaire ischemie, onafhankelijk van de bekende voorspellers van een sombere afloop.

Hypomagnesiemie (te laag magnesium gehalte in het bloed) tussen dag 2 en 12 na een SAB bleek een onafhankelijke voorspeller voor het optreden van secundaire ischemie te zijn.
Een te hoog natriumgehalte in het bloed trad tijdens de eerste 3 dagen na een SAB op bij 12% en *een te laag natriumgehalte* bij 19% van de onderzochte patiënten. Een te laag natriumgehalte werd zelfs gemeten bij 30-40% van de patiënten tijdens de hele opnameduur. Vochtbeperking gaf een verhoogde kans op het ontstaan van secundaire ischemie en een te hoog zoutgehalte in het bloed was statistisch significant gerelateerd aan een sombere afloop.
Een ernstige *verhoging van het aantal witte bloedcellen* was bij 16% van de patiënten vastgesteld. De mate van verhoging was een voorspeller van de kans op het optreden van overlijden en van secundaire ischemie. Regelmatig controle van de witte bloedcellen kan bijdragen aan een vroege herkenning van secundaire ischemie.
Scores die de ernst van ziekte kwantificeren (zoals de APACHE II) worden vaak gebruikt op de intensieve zorgafdeling. Zij combineren het optreden van ontregelingen in het bloed, kenmerken van algehele ontsteking en stoornissen in hart- en longfunctie. Deze scores lijken een bijdrage te leveren aan het voorspellen van een sombere afloop echter een speciale score ontworpen voor SAB patiënten (een combinatie van zuurstoftekort in het bloed, gemiddelde arteriële bloeddruk, bicarbonaat in het bloed en bloedsuiker) leek een betere voorspeller te zijn voor het optreden van een sombere afloop.

Beschrijving van patiënten onderzoek

In totaal zijn 172 patiënten met een aneurysmatische subarachnoïdale bloeding in de periode tussen januari 2000 en april 2004 opgenomen en gemonitord op de intensieve zorgafdeling van het Medisch Centrum Haaglanden. Al onze patiënten met een doorgemaakte SAB zijn daar twee weken behandeld overeenkomstig de standaard normen. Ze kregen absolute bedrust, nimodipine (een medicijn ter voorkoming van vaatkrampen), een medicijn tegen epilepsie, voldoende toediening van vocht via een infuus waardoor geen ondervulling ontstaat en eventuele bloeddrukverlagende medicijnen werden gestopt.
Honderdéénentwintig patiënten werden prospectief gevolgd en 51 retrospectief. De gemiddelde leeftijd was 55 jaar (range 17-93), 127 waren vrouw (74%). Van 75 (44%) werd het aneurysma geopereerd, van 45 (26%) werd het aneurysma endovasculair (via de bloedvaten) behandeld met platina coil (spiraaltje) plaatsing en bij 52 (30%) vond er geen behandeling van het aneurysma plaats, omdat de patiënt hiervoor in een te slechte conditie verkeerde. Tweeënzestig patiënten (36%) kwamen in een slechte toestand het ziekenhuis binnen en bij 80 patiënten (46%) was er een sombere afloop na 3 maanden. Alle hoofdstukken van dit proefschrift zijn gebaseerd op de gegevens van de bovenbeschreven patiënten.
Het doel van onze onderzoeken was om de waarde van niet-neurologische complicaties en bepaalde kenmerken van deze niet-neurologische problemen te onderzoeken en hun bijdrage aan het voorspellen van het optreden van cerebrale ischemie of van een sombere afloop. Het doel was ook om te kijken naar een kenmerk in het bloed van disfunctioneren van het hart

(verhoogd cTnI) en de relatie hiervan met het optreden van klinische stoornissen in hart- en longfunctie en het optreden van een sombere afloop. Hiervoor maakten we gebruik van een speciaal hemodynamisch bewakingssysteem. Ook onderzochten we het belang van het optreden van slaapstoornissen na de SAB en het effect hiervan op de kwaliteit van leven.
De belangrijkste voorspellers voor het optreden van een slechte afloop na een SAB zijn de leeftijd, de hoeveelheid bloed op de eerste CT scan van de hersenen en de klinische toestand bij opname.
Voor dit proefschrift gebruikten we een internationale schaal (WFNS) voor beoordeling van de klinische toestand van de patiënt bij opname. Van een goede toestand werd gesproken bij een WFNS score van I, II of III en van een sombere toestand bij een WFNS van IV of V.
Voor het meten van de hoeveelheid bloed op de opname scan werd de Hijdra-score gebruikt. Deze beoordeelt de hoeveelheid bloed in de belangrijke hersenvochtruimtes (range tussen 0 en 42).
Voor de mate van herstel na drie maanden gebruikten we de Rankin-schaal. Hiermee wordt de mate van onafhankelijkheid beoordeeld na het optreden van de bloeding. Blijvende afhankelijkheid van anderen ofwel overlijden worden gezien als een sombere afloop.
In de meeste onderzoeken voor dit proefschrift maakten we gebruik van stapsgewijze multiple regressie-analyses. Ook onderzochten we het onderscheidend vermogen van onze testen door het oppervlak onder de ROC-curve te berekenen. Het oppervlak onder de ROC-curve varieert tussen de 0.50 (geen onderscheidend vermogen van de test) en 1.0 (perfecte voorspelling).

Eerdere onderzoeken met SAB-patiënten beschreven relaties met ECG-afwijkingen en 'tijdelijk' slechter functioneren van het hart. In ***hoofdstuk 2*** beschrijven we 121 opeenvolgende patiënten met een aneurysmatische SAB. We onderzochten of er een relatie was tussen stoornissen op het opname ECG en het optreden van secundaire ischemie en een sombere afloop. Hiervoor gebruikten we multiple logistische regressie-analyses en bekeken we de toegevoegde waarde ten opzichte van de bekende voorspellers met ROC-curves. Vijfentwintig patiënten (21%) hadden geen afwijkingen op het ECG. Het meest frequent kwamen voor: ST-depressie (14%), T top afwijkingen (31%), QTc verlenging (13%) ofwel het optreden van een U-golf (52%). Ook een combinatie van ECG afwijkingen die duiden op zuurstoftekort van het hart (ST-depressie ofwel omkering van T golf dan wel een combinatie daarvan in tenminste 2 afleidingen) werden frequent waargenomen (27%). Van alle bekeken ECG afwijkingen had alleen ST depressie een statistisch significante relatie met het optreden van secundaire ischemie (relatief risico (RR) 2.4 [95%CI, 1.2-4.9]). De ROC-curve toonde vrijwel geen onderscheidend vermogen aan voor de voorspellende waarde van ST-depressie voor het optreden van secundaire ischemie. Het oppervlak onder de curve van de ROC was 0.53 (95%CI, 0.42-0.63). De bevinding dat er geen duidelijke bijdrage is voor ECG-afwijkingen bij het voorspellen van secundaire ischemie stemmen overeen met de bevindingen van een eerder onderzoek waarbij de relatie van seriële ECG-afwijkingen tijdens de opname en het krijgen van cerebrale ischemie is bekeken. Ondanks het feit dat ST-depressie en ook een combinatie van ECG-afwijkingen die duiden op zuurstoftekort van

het hart een onafhankelijke voorspellende relatie hebben met het optreden van een sombere afloop, is de toegevoegde waarde van deze ECG-afwijkingen ten opzichte van de bekende voorspellers beperkt. Het oppervlak onder de curven van de ROC verbeterde van 0.81 naar 0.84.

Troponine I (cTnI) is een betrouwbare voorspeller van echocardiografische schade aan het hart. In ***hoofdstuk 3*** wordt de toegevoegde voorspellende waarde weergegeven van de cTnI waarde bij opname ten opzichte van de bekende voorspellers voor het optreden van klinische stoornissen in hart- of longfunctie en van een sombere afloop. Bij deze studie volgden we 68 patiënten prospectief. Een verhoogd cTnI werd bij 52% van deze patiënten aangetroffen.
De longcomplicatie overvulling op de longfoto tijdens de opname constateerden we bij 28% en stoornissen in de gasuitwisseling in de eerste twee weken (PaO2/ FiO2 ratio ≤ 200) bij 37% van de SAB patiënten. De hartproblemen: ritmestoornissen tijdens opname (boezemfibrilleren of supraventriculaire ritmestoornissen) waarbij er medicijnen tegen ritmestoornissen gegeven moesten worden, werden bij 16% vastgesteld en 25% moest starten met inotropica (medicijnen om de samentrekkingskracht van het hart te verhogen) in de eerste 4 dagen na SAB, omdat de gemiddelde arteriële bloeddruk onder de 65 mm kwik kwam. Een combinatie van deze hart en long problemen werd vastgesteld bij 57% van de patiënten.
We beoordeelden de relatie tussen het optreden van hart en long complicaties met een verhoogd cTnI en maten de toegevoegde waarde ten opzichte van de bekende voorspellers. We maakten een driedeling in de cTnI waardes om te zoeken naar een mogelijk hoogte-gerelateerd effect van cTnI in het voorspellen van hart en long complicaties. Een verhoogd cTnI bij opname bleek een onafhankelijke voorspeller voor het optreden van hart en long complicaties tijdens de opname. Nadat cTnI werd toegevoegd aan het model met de bekende voorspellers, verbeterde de oppervlakte onder de ROC-curve van 0.70 naar 0.83. Een verhoogd cTnI bij opname was ook een onafhankelijke voorspeller van het optreden van een slechte afloop. Het toegevoegde effect hiervan ten opzichte van de bekende voorspellers van een slechte afloop was beperkt. We vonden geen hoogte gerelateerd effect van cTnI in het voorspellen van hart en long complicaties of van een slechte afloop.

In ***hoofdstuk 4*** hebben we prospectief 28 patiënten met een aneurysmatische SAB gevolgd die voldeden aan één van de volgende criteria: een slechte klinische toestand bij binnenkomst (WFNS III, IV of V) ofwel veel bloed op de CT scan. Bij al deze patiënten is volgens standaard beleid een arteriële lijn (in een slagader) en een centraal veneuze lijn (in een grote ader) op de intensieve zorg afdeling ingebracht. Met behulp van deze lijnen maakten we gebruik van het PiCCO systeem (een systeem waarbij er met behulp van een arterielijn en centraal veneuze lijn door middel van een bolus met vocht voor de longen, de longfunctie en hartfunctie berekend kan worden) om met tussenpozen de hartprestatie (de hoeveelheid bloed die het hart per minuut pompt), de contractiliteit van het hart (samentrekbaarheid) en de aanwezigheid van overvulling van de longen (EVLW) te meten. Hiermee bestudeerden we de frequentie van voorkomen van deze hart- en longstoornissen en het optreden van

overvulling van de longen in de eerste 5 dagen na het optreden van de bloeding. Ook werd onderzocht of een verhoogd cTnI (binnen 48 uur na de SAB) een negatief effect had op de functie van het hart of het optreden van overvulling van de longen. We beoordeelden de geïndexeerde waardes (gewicht voor het EVLW en lichaamsoppervlak voor de hartprestatie). Bij zes patiënten (21%) was er een verlaagde hartprestatie in ten minste 1 van de eerste 5 dagen na SAB. Vijf van deze zes hadden maar 1 dag verlaagde gemiddelde waarde. Een verlaagde hartprestatie in tenminste 1 van de eerste 5 dagen kwam vaker voor bij patiënten met een verhoogd cTnI (odds ratio (OR) 6 [95%CI 0.5-310]). Tien patiënten (36%) hadden een verlaagde contractiliteit van het hart < 4.0 l/min. Bij 5 van deze patiënten duurde de verlaging van de gemiddelde waardes minstens drie dagen. Een verlaagde contractiliteit van het hart kwam ook statistisch significant vaker voor bij mensen met een verhoogd cTnI (OR 18 [95%CI, 1.6-850]). Verhoogde waardes van EVLWI > 10ml/kg zagen we bij 10 patiënten (36%). Bij 7 van de 10 patiënten was deze verhoging minstens twee dagen aanwezig. Er was geen hemodynamisch significant verschil tussen mensen met of zonder verhoogd troponine en het optreden van een verhoogd EVLWI. Gemiddelde waardes van de hartprestatie en de contractiliteit van het hart waren over het algemeen elke dag lager bij patiënten met een verhoogd cTnI. Dit verschil was alleen op dag 1 voor de hartprestatie en dag 3 voor de contractiliteit van het hart statistisch significant verschillend. Gemiddelde waardes van EVLWI waren over het algemeen hoger bij patiënten met een verhoogd cTnI dan bij patiënten zonder verhoogd cTnI. Deze verschillen waren echter op geen enkele dag statistisch significant verschillend. Met behulp van de PiCCO metingen zagen we dus veel hart en long complicaties bij patiënten in een slechte toestand bij opname ofwel met veel bloed op de CT scan. Een verhoogde waarde van cTnI was een goede voorspeller van het optreden van een verminderde contractiekracht van het hart.

Huidige voorspellers van een slechte afloop voor patiënten met een SAB houden geen rekening met niet-neurologische complicaties. Met het toevoegen van deze niet-neurologische markers (kenmerken van orgaanziekten) zou de voorspellende waarde mogelijk nog verbeterd kunnen worden. In ***hoofdstuk 5*** onderzochten we de voorspellende waarde van de simplified acute physiology score (SAPS II) bij SAB patiënten. In een opeenvolgende serie van 148 patiënten die binnen 4 dagen na de SAB opgenomen waren, werd de SAPS II score berekend. De SAPS II score is één van de eenvoudigst te berekenen systemen om de ernst van ziekte te beoordelen bij mensen op een intensieve zorgafdeling. De SAPS II score is opgebouwd uit twaalf fysiologische variabelen (hartfrequentie, lichaamstemperatuur, aantal witte bloedcellen, PaO2/ FiO2 ratio, bicarbonaat in het bloed, systolische bloeddruk, urineproductie, bloed- ureum, kalium, natriumgehalte, bilirubine, Glasgow Coma Score, leeftijd, het type van de opname en eventuele onderliggende ziekten). We onderzochten de relatie tussen sombere afloop en de bekende voorspellers, het optreden van SIRS(algehele ontsteking), en de SAPS II score. Ook onderzochten we de toegevoegde waarde van de SAPS II score en het optreden van SIRS ten opzichte van de bekende voorspellers. Ook werd gekeken naar voorspellende waarde van de individuele variabelen van de SAPS II score. Dezelfde statistische analyses werden uitgevoerd om het effect van de SAPS II score op het

optreden van cerebrale ischemie te beoordelen. Tevens hebben we de SAPS II score in drieën gedeeld om een betere indruk te krijgen van de relatie tussen de SAPS II en het voorspellen van een sombere afloop of het optreden van secundaire ischemie.
De SAPS II score bleek de enige onafhankelijke voorspeller te zijn voor een sombere afloop. Patiënten in het hoogste tertiel (driedeling) van de SAPS II score hadden een statistisch significant hogere kans op een slechte afloop dan patiënten in het laagste tertiel. Van de individuele variabelen van de SAPS II score waren de PaO2/ FiO2 ratio, de ureum waarde in het bloed, de leeftijd en de Glasgow Coma Score onafhankelijke voorspellers voor een sombere afloop. De SAPS II score was ook een onafhankelijke voorspeller voor het optreden van secundaire ischemie. De oppervlakte onder de curve toonde hierbij vrijwel geen discriminerend vermogen aan (0.52).

In een prospectief onderzoek bij 89 patiënten stuurden 83 patiënten gevalideerde en veel gebruikte vragenlijsten terug voor het bepalen van het voorkomen van slaapstoornissen en de kwaliteit van leven na een SAB ***(Hoofdstuk 6)***. Hiervoor gebruikten we de slaapdiagnostische lijst en voor de kwaliteit van leven de SF-36. Voor de functionele uitkomst gebruikten we de Rankin score. De slaapdiagnostische lijst bestaat uit 75 vragen over 6 dimensies van slaapstoornissen. We keken vooral naar de dimensies van overmatige slaperigheid overdag en de aanwezigheid van slapeloosheid. Een score van ≥ 3 op tenminste 1 van deze dimensies werd beschouwd als een ernstig slaapstoornis. Ook werd er bij een groot deel van de mensen met een slaapstoornis een 48 uur durend ambulant polysomnografisch onderzoek verricht. We onderzochten de frequentie van voorkomen van slaapstoornissen en relateerden de aanwezigheid van een slaapstoornis aan de Rankin en de kwaliteit van leven. Dit gebeurde tenminste 1 jaar na het optreden van de SAB. Achtentwintig (34%) patiënten gaven ernstige slaapstoornissen aan. Frequent gemelde klachten waren moeilijk inslapen (25%), moeilijk opnieuw inslapen (28%) en frequent wakker worden (31%). Eenendertig procent gaf aan overdag ernstig vermoeid te zijn en 6% meldde frequent dutjes overdag te doen. Van de 83 patiënten meldden 42 (51%) dat de SAB negatieve consequenties had voor het beroep. Tweeëndertig procent kon niet terug naar de oorspronkelijke baan en 19% kon alleen weer parttime aan het werk. Bij patiënten zonder slaapstoornissen was er geen verschil in kwaliteit van leven in vergelijk met een referentie-populatie. Bij patiënten met slaapstoornissen was er echter een duidelijke verminderde kwaliteit van leven in vergelijking met de referentie populatie en in vergelijking met de mensen zonder slaapstoornissen. Bij de ambulante polysomnografie-studies van de patiënten met ernstige slaapklachten bleek er bij alle patiënten een afwijkende slaap te bestaan. Bij veel mensen was er sprake van een ernstig gefragmenteerde slaap. Obstructief slaap-apneusyndroom en periodieke beenbewegingen in de slaap in combinatie met klachten over rusteloze benen werden ook vaker gezien dan verwacht.

Samenvattend

ECG afwijkingen en een verhoogd troponine I gehalte hebben weinig aanvullende waarde bij het voorspellen van een sombere afloop. ECG afwijkingen hebben geen bijdrage bij het voorspellen van het optreden van secundaire ischemie.
Een verhoogd troponine gehalte is wel een krachtige voorspeller van het optreden van hart en long complicaties. Ook een verlaagde contractiekracht van het hart werd vaak vastgesteld in relatie met een verhoogd cTnI. Deze verlaagde contractiekracht van het hart en ook overvulling van de longen (EVLWI verhoging) werd vaak gezien in de eerste 5 dagen na een SAB. De verlaagde hartprestatie die ook frequent werd geconstateerd was vaak mild, kortdurend en herstelde meestal spontaan binnen 1 dag. De SAPS II score lijkt wel een bijdrage te leveren aan het voorspellen van een sombere afloop, maar in mindere mate aan het voorspellen van optreden van cerebrale ischemie. Van de individuele SAPS II variabelen leken zoals bekend uit de literatuur een verlaagd zuurstofgehalte in het bloed (verlaagde PaO2/FiO2 ratio), de leeftijd en de toestand bij opname maar ook de ureumwaarde in het bloed een onafhankelijk voorspellende waarde te hebben voor het optreden van een sombere afloop.
Van de patiënten die de SAB overleefd hadden, bleek 11% afhankelijk van hulp van anderen te zijn volgens de Rankin. Echter 53% klaagde nog over vermoeidheid en 51% gaf negatieve gevolgen voor het beroep aan. Bij deze patiënten bleken er vaak ernstige slaapstoornissen aanwezig te zijn. Deze slaapstoornissen kwamen onafhankelijk van de Rankin score voor en gaven een verminderde kwaliteit van leven.

Concluderend komen niet-neurologische complicaties vaak voor na het optreden van een SAB en zien we op lange termijn vaak slaapstoornissen. Om beter te kunnen voorspellen welke patiënten complicaties krijgen moet er meer rekening worden gehouden met niet-neurologische kenmerken van achteruitgang in voorspellende score systemen om de mate van ziekte te bepalen. Troponine I kan worden gebruikt als marker (kenmerk) voor mensen met een hoog risico op deze hart en long problemen. Deze mensen zouden kunnen profiteren van eerdere invasieve bewaking van hart- en longfunctie. Nieuwe onderzoeken met het PiCCO systeem om te onderzoeken welke effecten een verlaagde hartprestatie, een verlaagde contractiliteit van het hart en het optreden van overvulling bij de longen hebben op het optreden van cerebrale ischemie en het optreden van een sombere afloop zijn belangrijk. Met multidisciplinaire benadering, met meer aandacht voor deze niet-neurologische complicaties en met studies waarbij deze hart en long waarden eerder worden behandeld, zal mogelijk de uitkomst van de SAB in de toekomst verder verbeterd kunnen worden. Door bovendien tevens meer aandacht te besteden aan het zich voordoen van slaapstoornissen, zullen mogelijk de nadelige gevolgen van een SAB kunnen worden beperkt waardoor een betere kwaliteit van leven voor de betreffende patiënten mogelijk wordt.

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De komende jaren zal ik meer naar jou luisteren.
Ik ben zo blij met jou en de kinderen!

Curriculum vitae

Wouter Schuiling werd op 4 april 1968 geboren in Amsterdam. In 1986 behaalde hij het VWO diploma aan de Rijksscholengemeenschap te Amersfoort en begon hij met de studie Geneeskunde aan de Rijksuniversiteit te Groningen. Hij verrichte zijn wetenschappelijke stage in 1994 aan het Comprehensive Epilepsy Center van The Graduate Hospital te Philadelphia in de USA. In 1995 verrichte hij een keuze stage op de afdeling Interne Geneeskunde in het Medisch Centrum Leeuwarden. In augustus 1995 kreeg hij zijn artsdiploma. In 1995 begon hij als arts-assistent op de afdeling Neurologie in het Academisch Ziekenhuis Nijmegen. Na nog een jaar als arts-assistent op de afdelingen Longziekten en Interne Geneeskunde van het Canisius-Wilhelmina Ziekenhuis Nijmegen gewerkt te hebben startte zijn opleiding Neurologie (opleider: dr. J.Th.J. Tans) in 1998 in het Medisch Centrum Haaglanden, locatie Westeinde te Den Haag. Tijdens zijn opleiding in het Medisch Centrum Haaglanden startte hij met wetenschappelijk onderzoek naar de gevolgen van de Subarachnoïdale bloeding. In 2004 werd hij Neuroloog en sinds september 2004 is hij werkzaam als Neuroloog in het Medisch Centrum Leeuwarden. Hij is getrouwd met Helga Bokma en vader van drie kinderen, Martijn (2000), Jeroen (2002) en Nynke (2004).