CARDIAC ABNORMALITIES AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

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Cardiac abnormalities after aneurysmal subarachnoid hemorrhage

Cardiale dysfunctie na een aneurysmatische subarachnoïdale bloeding

(met een samenvatting in het Nederlands)

Proefschrift

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Ivo Adriaan Cornelis van der Bilt

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There is a tide in the affairs of men,
Which, taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries
On such a full sea are we now afloat,
And we must take the current when it serves,
Or lose our ventures.

Brutus, Shakespeare, Julius Ceasar IV.3 210

Dank aan alle patiënten en familieleden
die in de moeilijke tijd na een SAB
toestemming hebben gegeven voor de SEASAH studie

Contents

CHAPTER 1

General Introduction

Adapted from: van der Bilt IA, Hasan D, Rinkel GJ, Wilde AA, Visser FC. Rationale of the SEAS study: Serial Echocardiography After Subarachnoid hemorrhage, a prospective national, multicenter, multidisciplinary, cohort study to evaluate cardiac abnormalities following intracranial hemorrhage. *Neth Heart J.* 2006 Nov;14(11):366-371.

In 1902, Harvey Cushing reported that increased intracranial pressure due to cerebral tumors leads to cardiopulmonary dysfunction.[1] Since this early observation, it gradually became established that cardiac dysfunction may occur following several forms of physical,[2-5] and emotional stress.[6, 7] This dysfunction typically occurs in the absence of coronary artery disease, is mostly reversible and consists of myocardial wall motion abnormalities (WMA), electrocardiographic (ECG) changes, elevated serum markers for myocardial damage (troponin, CK-MB, BNP), and histopathological changes.[8]

The last few years, reported incidence of- and interest in this stress induced cardiomyopathy have significantly increased. Especially cases of Takotsubo cardiomyopathy (TC) have been reported rather frequently. TC is a transient stress induced myocardial dysfunction typically affecting the apex of the left ventricle, with hyperkinesia of the basal segments. This leads to dyskinesia or "ballooning" of the apex. The characteristic left ventricular angiographic or echocardiographic image has similarities with the shape of a Japanese octopus trap. In Japanese "Tako" means octopus and "Tsubo" means trap, hence the term: "Takotsubo cardiomyopathy". Other commonly used terms are apical ballooning, stress cardiomyopathy and broken heart syndrome.[6, 7] Furthermore, several authors have also reported stress induced wall motion abnormalities without the typical apical ballooning shape, but with diffuse WMA, midventricular ballooning, basal ballooning and other patterns. Typical ECG changes in stress cardiomyopathy are ST-segment changes, T wave changes, prominent U-waves and QTc prolongation.[9, 10] Transient Q-waves have also been reported.[11] In addition, arrhythmias consisting of ventricular tachycardia, ventricular fibrillation, atrial fibrillation, and atrial tachycardia have been described.[12, 13] Serum Troponin, N-terminal portion of proBrain Natriuretic Peptide (NT-pro-BNP) and CK-MB may be elevated,[14-16] as the result of cellular degradation.

Stress induced cardiomyopathy has also been reported quite frequently after aneurysmal subarachnoid hemorrhage (aSAH), a devastating neurological disease which carries a poor prognosis. An aSAH is caused by rupture of an intracranial aneurysm, causing acute sympathetic stress. Following this rupture, blood spurts into the subarachnoid space under arterial pressure, continuing until increased local or generalized intracranial pressure stops the bleeding. The annual incidence of aSAH adjusted for age and sex, is 7.8-23.0 per 100,000 population.[17] In a systematic review case fatality after aSAH was reported between 32 and 67%,[18] mainly caused by the

initial bleeding and complications such as rebleeding or delayed cerebral ischemia. Apart from neurological complications, non-neurological complications occur after aSAH, of which pulmonary and cardiac complications are the most important. To further investigate the incidence and prognostic meaning of stress cardiomyopathy in aSAH we launched a nationwide, multicenter, multidisciplinary cohort study called Serial Echocardiography After SubArachnoid Hemorrhage (S.E.A.S.A.H.).

The study objectives were: first, to assess the incidence of cardiac abnormalities, defined as ECG changes, echocardiographic systolic and diastolic function abnormalities and cardiac specific enzyme and protein elevations in patients with aSAH. Second, to determine clinical variables that may predict the occurrence of cardiac abnormalities following aSAH. Third, to assess the impact of cardiac abnormalities on outcome at 3 months.

Patients who were admitted within 72 hours after an aSAH were eligible for inclusion in the study. An aneurysm had to be confirmed by angiography or CT angiography. On admission and at 4 and 8 days after onset of symptoms cardiac evaluation was performed using echocardiography, electrocardiography and blood sampling. Clinical parameters such as medical history, neurological condition on admission (Glasgow Coma Scale (GCS),[19] World Federation of Neurosurgeons Score (WFNS),[20] amount of blood on CT-scan (Hijdra score), medication, intracranial- (delayed cerebral ischemia, rebleeding, hydrocephalus) and extracranial- or systemic complications (pulmonary edema, pneumonia, cerebral salt wasting), and type of treatment (surgical or endovascular) were obtained. Finally, outcome at 3 months by means of the Glasgow Outcome Scale (GOS) [21] was assessed.

Transthoracic echocardiography was the standard examination. All echocardiographic examinations were performed according to the American Heart Association standards. The cross sections and the segments were recorded for off-line analysis. A minimum of three heart cycles was recorded. Two investigators (independent from each other and unaware from the clinical data of the patient) analyzed the echocardiogram for assessment of global and regional left ventricular function. Diastolic function was determined using E/A ratios and pulmonary vein flow.

All ECGs were analyzed by one investigator, who was unaware of the clinical data of the patient. Criteria for the ECG abnormalities were defined according to the

guidelines of the European Society of Cardiology. A Q-wave in two contiguous leads was considered pathological when ≥ 0.03s wide and ≥ 0.1mV deep. ST deviation was considered to represent myocardial ischemia when ST elevation occurred at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads. Horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1 were also considered ischemic changes. The Cornell voltage criteria (RaVL+SV3 > 28 mm (men) or > 20 mm (women)), or Sokolow-Lyon voltage index (SV1+RV5/6) >35 mm for left ventricular hypertrophy were used.

The diagnostic brain CT-scan was used for analysis. The amount of blood in 13 individual cerebral cisterns on each CT was scored: a score of 0 = no blood; 1 = cistern partially filled with blood; and 2 = completely filled with blood. Subsequently, the sum score (ranging from 0 to 26) for each CT was calculated. A sum score greater than 13 was regarded as a "high cisternal blood score".

A neurological examination was conducted on admission, on a daily basis, and after every deterioration of clinical condition. The level of consciousness was assessed by means of the 15-point Glasgow Coma Scale.

Prognosis was defined as death or dependency using the GOS. The follow-up period was defined as the time interval between entering the study and 3 month after onset of the aSAH.

Before we conducted the SEASAH study, we first performed a meta-analysis of the available literature from 1960 to 2007 regarding cardiac dysfunction after aneurysmal subarachnoid hemorrhage. This meta-analysis can be found in **Chapter 2** of this thesis**.** As most of the included studies were of small sample size, different study design and retrospective, questions remained. Therefore, in **Chapter 3** we describe the results of the SEASAH study. In this chapter we describe the incidence and prognostic significance of cardiac abnormalities after aSAH. In **Chapter 4** we describe the time course and risk factors of the myocardial dysfunction after aSAH. We found that WMA may be present on admission or develop during the course of aSAH. In **Chapter 5** we describe a study where we found that aSAH patients with cardiac dysfunction have an impaired cerebral perfusion measured with perfusion CT. This

supports the hypothesis that aSAH patients with cardiac dysfunction have a higher risk of DCI. In **Chapter 6** we describe a histopathological study of myocardium of patients who died from aSAH. Finally, **Chapter 7** summarizes the findings of this thesis, places it into the context of current knowledge and literature and suggests direction of further research.

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CHAPTER 2

Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage

van der Bilt IAC, Hasan D, Vandertop WP, Wilde AAM,
Algra A, Visser FC, Rinkel GJE.
Neurology. 2009 Feb 17;72(7):635-42

Abstract

Impact of cardiac complications after aneurysmal subarachnoid hemorrhage (SAH) remains controversial. We performed a meta-analysis to assess whether ECG changes, myocardial damage, or echocardiographic wall motion abnormalities (WMAs), are related to death, poor outcome (death or dependency) or delayed cerebral ischemia (DCI) after SAH.

Methods: Articles on cardiac abnormalities after aneurysmal SAH that met predefined criteria, and were published between 1960 and 2007 were retrieved. We assessed quality of reports, and extracted data on patient characteristics, cardiac abnormalities, and outcome measurements. Poor outcome was defined as death or dependence by the Glasgow Outcome Scale (dichotomized at ≤ 3), or the modified Rankin scale (dichotomized at >3). If studies used another dichotomy or another outcome scale, we used the numbers of patients with poor outcome provided by the authors. We calculated pooled Relative Risks (RR) with corresponding 95% CI for the relation between cardiac abnormalities and outcome measurements.

Results: We included 25 studies (16 prospective), totaling 2690 patients (mean age 53 years; 35% men). Mortality was related with WMAs (RR:1.9), elevated troponin (RR:2.0) and BNP levels (RR:11.1), tachycardia (RR:3.9), Q waves (RR:2.9), ST-depression (RR:2.1), T-wave abnormalities (RR:1.8), and bradycardia (RR:0.6). Poor outcome was associated with elevated troponin (RR:2.3), CK-MB levels (RR:2.3), and ST-depression (RR:2.4). Occurrence of DCI was associated with WMAs (RR:2.1), elevated troponin (RR:3.2), CK-MB (RR:2.9), and BNP levels (RR:4.5) and ST-depression (RR:2.4). All RR were significant.

Conclusion: Markers for cardiac damage and dysfunction are associated with an increased risk of death, poor outcome, and DCI after SAH. Future research should establish whether these cardiac abnormalities are independent prognosticators and should be directed towards pathophysiological mechanisms and potential treatment options.

Introduction

Case fatality after aneurysmal subarachnoid hemorrhage (SAH) is reported from 30% to 50%.[1] The main causes of death are the impact of the initial bleeding and neurological complications, such as rebleeding and delayed cerebral ischemia (DCI). Apart from the neurological complications, cardiac abnormalities occur frequently after SAH. These abnormalities include ECG changes, elevated biochemical markers of myocardial damage and heart failure, and decreased left ventricular function.
We hypothesized that cardiac abnormalities following SAH are related to the occurrence of death, poor outcome, and DCI. Therefore, we performed a meta-analysis on observational studies to assess the associations of cardiac complications with death, poor outcome, and DCI following aneurysmal SAH.

Materials and Methods

Search Strategy
Three investigators (I.B., D.H., and F.V.) independently performed a systematic search for studies regarding SAH accompanied by cardiac abnormalities, published between January 1960 and January 2007, using the electronic search engine PubMed. The following keywords were used: SAH* OR SAB* OR subarachnoid haemorrhage* OR subarachnoid hemorrhage* OR subarachnoid bleed* OR subarachnoid blood* OR intracranial aneurysm* OR intracranial bleed*. All these keywords were combined with the keywords: ECG*, electrocardiographic*, electrocardiography*, echocardiography*, echocardiographic, stunning*, myocardial damage*, myocardial necrosis*, left ventricular dysfunction*, LV dysfunction*, takotsubo*, apical ballooning*, CK*, CPK*, CK-MB*, MB*, troponin, BNP*, brain natriuretic peptide*, NT-pro-BNP* in different combinations.
Reference lists were manually cross-checked for additional publications. This procedure was followed until no additional studies were found. Because many publications were more than ten years old, no efforts were made to contact authors in case of missing data.

Eligibility

Two investigators (I.B. and D.H.) assessed eligibility of studies independently. Criteria for inclusion of studies in this review were: publication after 1960 in the English, French or German language. All studies had to report on cardiac abnormalities and outcome following aneurysmal SAH. Cardiac abnormalities were defined as echocardiographic wall motion abnormalities (WMAs), diastolic dysfunction, or biochemical evidence of myocardial damage (defined as elevated troponin levels, or elevated CK-MB levels), or elevated brain natriuretic peptide levels (BNP and NT-pro-BNP), or ECG changes. SAH had to be documented by either CT scanning or cerebrospinal fluid examination. Studies with less than ten patients, case reports, and reviews were excluded.

To avoid selection bias, only studies that included consecutive patients were eligible. When a study group published more articles on the same dataset, only the report with the largest number of patients was eligible for data extraction.

Quality assessment of studies

To systematically assess the quality of the studies, we modified the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist (https://www.strobe-statement.org). Although this checklist is designed to improve the reporting of observational studies for optimal data extraction and interpretation, we used the list as a quality assessment tool. For every article, each of the 22 STROBE items was assigned a zero or one by two independent observers (I.B. and F.V.), and summed as the STROBE score. Several STROBE items consist of sub-items. These sub-items were also scored as zero or one and averaged. Disagreement was solved by direct communication between the two observers. The following items were assessed: cohort identification in title or abstract possible (item 1a), abstract informative and addressing key items (item 1b), background/rationale reported (item 2), objectives given with hypothesis (item 3), study design given (item 4), setting, locations and data collection period given (item 5), in- and exclusion criteria given and sources and methods of selection of patients given (item6a), period and methods of follow-up given (item 6b), variables of interest defined (cardiac data and outcome measures) (item 7), method of assessment of variable of interest given (item 8a), comparability of assessment methods across groups given (item 8b), sources of bias given (item 9), rationale for sample size given (item 10), statistical methods given (item 11a), missing data described (item 11b), subgroup- and sensitivity analysis given (item 11c), analysis of quantitative variables given (item 12a), continuous and grouped

analysis presented (item 12b), source of funding and role of funders presented (item 13), number of patients at each stage of the study given (14a), reasons for non-participation given (item 14b), period of recruitment defined (item 14c), baseline characteristics given (item 15a), completeness of data for each baseline variable given (item 15b), average and total amount of follow-up given (item 15c), number of outcome events presented (item 16), association between determinants and outcomes given (item 17a), categories of quantitative variables compared (item 17b), absolute outcome data given (item 17c), subgroup analysis performed (item 18), key results summarized (item 19), limitations discussed (item 20), external validity of study findings discussed (item 21), overall interpretation of the results given (item 22).

Data Extraction

The three investigators who assessed quality and eligibility reviewed the publications independently. In case of disagreement, the authors reviewed the article in question together until consensus was reached. The following data were extracted: author, year of publication, study design (prospective or retrospective), definition of inclusion and exclusion criteria, number of included patients, gender, mean age, and follow-up period. The neurological condition on admission was dichotomized as good or poor according to the scoring system used in the particular article: Hunt-Hess[2], World Federation of Neurosurgical Societies (WFNS)[3], Glasgow Coma Scale (GCS)[4], or Botterell[5]. A poor condition on admission was considered when Hunt-Hess ≥3, or WFNS ≥3, or GCS <12, or Botterell ≥3. Additionally, if an article did not use any of these scoring systems or used different criteria for poor outcome, the clinical condition reported by the authors was recorded.

As determinants we extracted the incidence of WMAs, diastolic dysfunction, elevated troponin levels, elevated (NT-pro)-BNP levels, elevated CK-MB levels, atrial fibrillation, tachycardia, bradycardia, wandering P, extrasystoles, peaked P, P mitrale, short PR interval, long PR interval, bundle branch block (BBB), pathological Q waves, ST segment depression, ST segment elevation, T wave changes (inverted or flat), U wave changes (present, inverted or prominent), left ventricular hypertrophy (LVH), and prolonged QT time. Combined ECG criteria were disregarded, because the separate ECG abnormalities may harbor different prognostic value. For outcome measurements we recorded the number of deaths from any cause, the number of patients with poor outcome, and the number of patients with DCI. Poor outcome was defined as death or dependence on activities of daily living, preferably defined by means of a handicap scale such

as the Glasgow Outcome Scale (dichotomized at ≤ 3), or the modified Rankin scale (dichotomized at >3). If studies used another dichotomy or another outcome scale, we used the numbers of patients with poor outcome provided by the authors, without adjusting to our preferred definition of poor outcome.
Several studies used different definitions of DCI. Given this heterogeneity of definitions, we recorded the number of patients with DCI as given by the authors, without adjusting these numbers to a predefined definition of DCI.

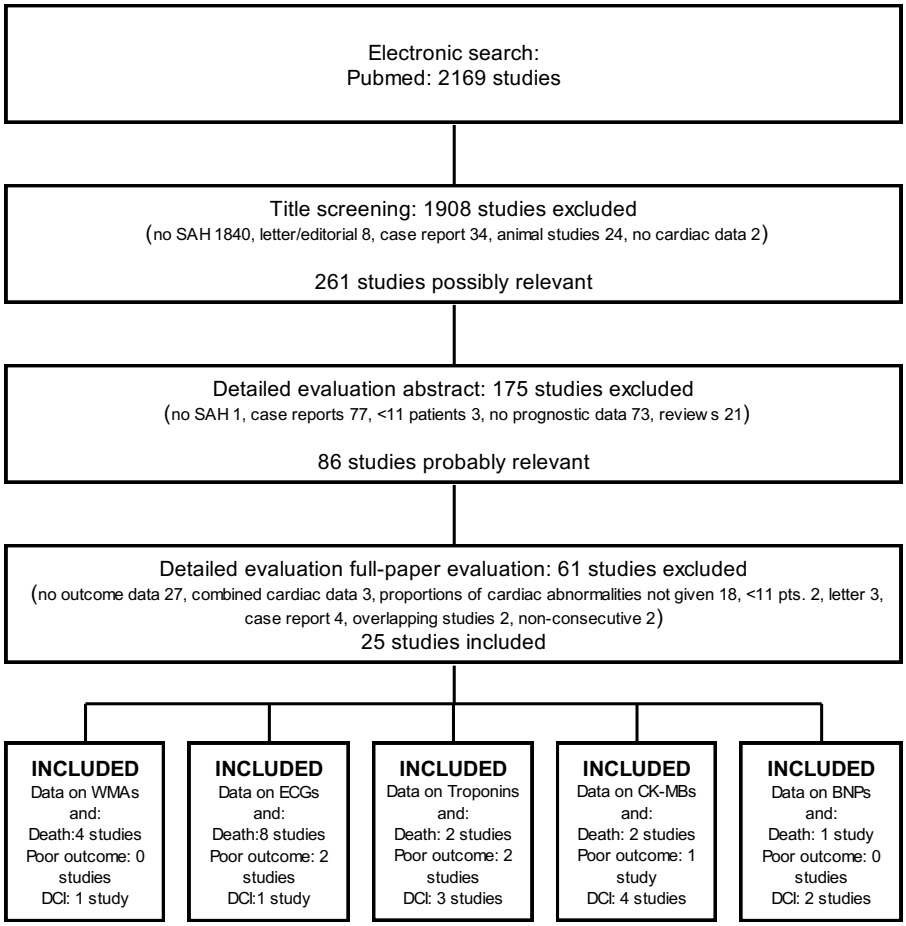
Data analysis

The relation between the three outcome measures and the 22 determinants was analyzed. The crude proportions of the extracted variables were calculated. Cross-tables were made to calculate Risk Ratios (RR) for each determinant and outcome in each article. The pooled RRs with their corresponding 95% confidence intervals (95% CI) were calculated by means of Cochrane's Review Manager 4.2. Using the same program, statistical heterogeneity of the effects was tested. This is indicated as I^2. A value greater than 50% may be considered substantial heterogeneity.[6]

Results

Study Characteristics
In the initial PubMed search 2169 studies were found that reported on cardiac abnormalities after aneurysmal SAH (figure 1).

Figure 1: Search strategy explained.



Pts: patients. WMAs: echocardiographic wall motion abnormalities, DCI: delayed cerebral ischemia, BNP: brain natriuretic peptide.

After title screening and detailed abstract evaluation, 86 studies were selected. After detailed full paper evaluation, 25 studies were included in this meta-analysis.

Baseline Characteristics

Table 1 presents the baseline characteristics of patients included in the analysis.

Table 1: Baseline characteristics of the included studies.

Reference	**Year**	*No of pts.*	*Men (%)*	*Mean age (yrs.)*	**Prospective study**	*Strobe score*	*Pts with poor condition on admission(%)*	*Follow-up period (days)*	*No. of deaths (%)*	*Pts with poor outcome (%)*	*No of pts with DCI (%)*
[31]	1965	106	46	-	+	17	-	6 months	35 (33)	-	-
[32]	1969	20	55	36	+	11	-	In-hospital	2 (10)	-	-
[33]	1976	100	-	-	-	13	48 (48)	-	38 (38)	-	-
[7]	1977	16	-	-	-	13	-	In-hospital	-	-	3 (19)
[34]	1983	17	47	53	-	11	-	-	5 (29)	-	-
[35]	1983	76	-	-	+	15	-	In-hospital	14 (18)	-	-
[20]	1986	23	48	46	+	16	6 (26)	6 months	7 (30)	-	-
[36]	1988	13	39	52	+	14	3 (23)	In-hospital	3 (23)	12 (52)	-
[8]	1989	50	52	46	-	13	26 (52)	In-hospital	-	-	20 (40)
[10]	1997	13	-	56	+	11	3 (23)	In-hospital	1 (8)	3 (23)	4 (31)
[11]	1999	72	35	51	-	20	26 (36)	In-hospital	-	-	26 (36)
[28]	1999	313	31	55	-	17	-	In-hospital	56 (18)	-	-
[9]	2000	39	39	54	+	18	14 (36)	In-hospital	5 (13)	-	16 (41)
[27]	2002	122	46	59	-	17	-	In-hospital	42 (34)	-	-
[16]	2003	43	33	55	+	14	25 (58)	In-hospital	7 (16)	27 (63)	19 (44)
[37]	2003	97	62	37	-	18	-	-	21 (22)	-	-
[12]	2003	38	45	49	+	17	14(39)*	6 months	-	-	14 (37)
[29]	2004	159	30	50	-	19	64 (40)	3 months	43 (27)	54 (34)	-
[38]	2005	223	37	54	+	17	98 (44)	In-hospital	-	-	-
[13]	2005	253	28	55	+	17	171 (68)	3 months	70 (28)	117 (46)	33 (13)
[30]	2005	68	22	-	+	17	32 (47) †	3 months	-	40 (59)	-
[39]	2006	173	32	54	+	18	-	8 days	31 (18)	-	-
[40]	2006	300	32	55	+	18	145 (48)	-	39 (13)	-	-
[14]	2006	121	26	55	+	18	58 (48)	3 months	-	58 (48)	52 (43)
[15]	2006	235	40	55	+	18	- ‡	In-hospital	38 (16)	-	18 (8)
Total		2690	35	53	16/25	Median: 17	733/1511(49)		457/2102(22)	311/670(46)	205/880(23)

Pts.:patients. Yrs: years. no: number. 2 patients missing in article, 36 patients used. †Poor outcome was defined as WFNS ≥4. ‡ baseline characteristics in study given for 300 patients, but 150 are analyzed

A total of 2690 patients were included. In the 21 studies where gender distribution was reported, the mean percentage of men was 35%. Mean age varied from 36 to 59 years, with a weighted mean of 53 years (21 studies).
Sixteen studies were prospective, nine were retrospective. The STROBE score varied from 11 to 20 with a median of 17. In 15 studies, data on the neurological condition on admission were available. The proportion of patients with a poor neurological condition on admission varied from 23% to 68%, with a mean of 49% (15 studies). The follow-up duration (for outcome assessment) varied from follow-up during hospital stay (14 studies) to six months follow-up. The proportion of patients who died during the observation period varied from 8% to 38% with a mean of 22% (18 studies). The percentage of patients with poor outcome varied from 16% to 63% with a mean of 46% (seven studies). Finally, the percentage of patients with DCI varied from 8% to 44% with a mean of 23% (ten studies). As stated earlier, the definition of DCI varied. [7]scored temporary focal neurological signs as DCI, [8,9]equated imaging signs of vasospasm with DCI, [10]used neurological deterioration with imaging evidence of spasms, [11-14] used neurological deterioration with exclusion of other causes (using CT), [15] used neurological deterioration and imaging evidence of spasms or CT evidence of infarction. [16]did not use a clear definition (clinical vasospasm).

Table 2 shows the proportions of patients with cardiac abnormalities: WMAs varied from 13% to 31% of the patients with a mean of 22% (nine studies). Diastolic dysfunction was reported in one study, in 71% of patients. Elevated troponin levels were reported in 21% to 50% of patients with a mean of 34% (six studies). CK-MB presence varied from 13% to 60% with a mean of 33% (six studies). Three studies reported elevated BNP levels, but each used different criteria for BNP elevation. Using these different criteria, elevated BNP levels were found between 9% and 100%.

Table 2: Prevalence of cardiac abnormalities.

Reference	*WMA n (%)*	*Diastolic dysfunction n(%)*	↑ *troponins n (%)*	↑ *CK-MB n (%)*	↑ *BNP n(%)*
[31]	-	-	-	-	-
[32]	-	-	-	-	-
[33]	-	-	-	-	-
[7]	-	-	-	7(44)	-
[34]	-	-	-	7(41)	-
[35]	-	-	-	-	-
[20]	-	-	-	7(30)	-
[36]	4(31)	-	-	-	-
[8]	-	-	-	30(60)	-
[10]	2(15)	-	-	-	13(100)
[11]	9(13)	-	-	15(21)	-
[28]	-	-	-	-	-
[9]	5(13)	-	8(21)	5(13)	-
[27]	-	-	-	-	-
[16]	7(16)	-	12(28)	-	-
[37]	-	-	-	-	-
[12]	-	-	-	-	17(45)*
[29]	-	-	-	-	-
[38]	-	146(71)	-	-	-
[13]	55(22)	-	126(50)	-	-
[30]	-	-	35(51)	-	-
[39]	48(28)	-	41(24)	-	-
[40]	79(26)	-	-	-	-
[14]	-		-	-	-
[15]	45(19)	-	52(22)	-	14(9) †
Total	254/1141(22)	146/223(71)	274/811(34)	71/217(33)	44/286(15)

*: BNP ratios were used. †: BNP levels > 600pg/ml was used as cut-off value.

Table 3 summarizes prevalence of any ECG abnormality that was reported in the studies. T wave changes were the most frequently observed ECG abnormality (22%), whereas pathological Q waves were present in 1%.

Relation of determinants with outcome

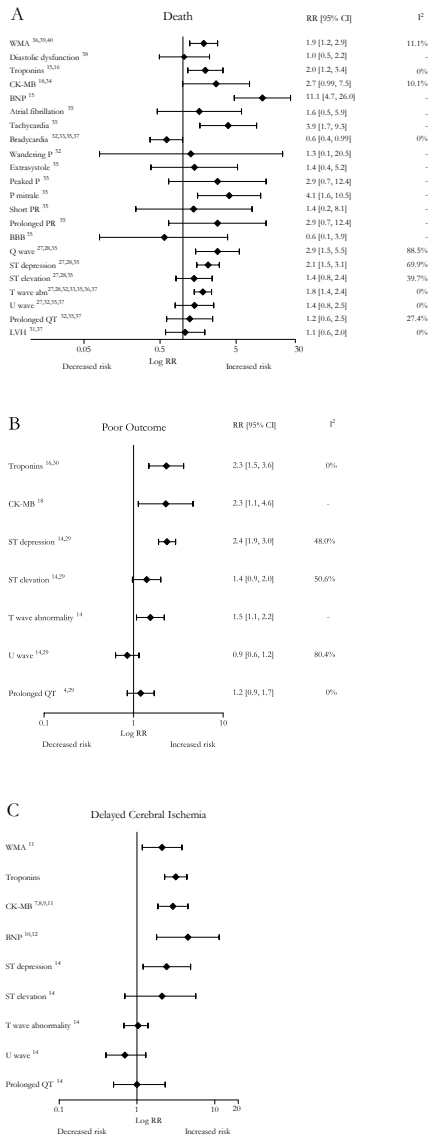
Figure 2A shows the pooled RRs and corresponding 95% CI of the defined cardiac abnormalities for death.

Table 3: Prevalence of ECG abnormalities.

Ref.	*AF n(%)*	*Tachy n(%)*	*Brady n(%)*	*Wand P n(%)*	*Extrasys n(%)*	*Peaked P n(%)*	*P mitrale n(%)*	*Short PR n(%)*	*Long PR n(%)*	*BBB n(%)*	*Path. Q n(%)*	*ST depr. n(%)*	*ST elev.n(%)*	*ΔT wave n(%)*	*ΔU wave n(%)*	*LVH n(%)*	*ΔQT n(%)*
31	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11(10)	-
32	-	-	6(30)	2(10)	-	-	-	-	-	-	0(0)	-	-	10(50)	2(10)	-	5(25)
33	-	10(10)	32(32)	-	5(5)	2(2)	-	1(1)	3(3)	12(12)	3(3)	9(9)	7(7)	34(34)	28(28)	-	21(21)
7	1(6)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35	7(9)	7(9)	21(28)	-	8(11)	2(3)	3(4)	4(5)	2(3)	9(12)	6(8)	15(20)	-	13(17)	3(4)	-	8(11)
20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36	-	-	-	-	-	-	1(8)	-	-	1(8)	1(8)	-	-	5(39)	-	-	-
8	4(8)	-	-	-	-	-	-	16(32)	-	-	-	18(36)	-	-	4(8)	-	4(8)
10	-	-	-	-	-	-	-	-	-	-	-	-	-	7(54)	-	-	2(15)
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28	-	-	4(1)	-	-	-	-	-	-	-	8(3)	13(4)	9(3)	48(15)	-	-	-
9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6(15)
27	-	-	-	-	-	-	-	-	-	-	8(7)	35(29)	10(12)	21(17)	7(6)	-	-
16	2(5)	7(16)	2(5)	-	-	-	-	-	-	9(21)	5(12)	5(12)	1(2)	11(26)	4(9)	-	5(12)
37	-	-	26(27)	-	-	-	-	-	-	-	-	5(5)	7(7)	15(16)	16(17)	27(28)	24(25)
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
29	-	9(6)	17(11)	-	-	2(1)	4(3)	-	2(1)	6(4)	16(10)	9 (6)	21(13)	32(20)	28(18)	-	36(23)
38	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-	-	-	-	17(14)	10(8)	38(31)	63(52)	-	16(13)
15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total	14/185(8)	33/378(9)	108/808(13)	2/20(10)	13/176(7)	6/335(2)	8/248(3)	21/226(9)	7/335(2)	37/391(9)	47/846(1)	126/1081(12)	65/872(7)	234/1077(22)	155/788(20)	38/203(19)	127/718(18)

AF: Atrial fibrillation. Tachy: tachycardia. Brady: Bradycardia. Wand P: Wandering P wave. Extrasys: Extrasystole. BBB: bundle branch block. Path. Q: Pathological Q wave. ST Depr.: ST segment depression. ST Elev.: ST segment elevation. ΔT wave: T wave abnormality. ΔU wave: U wave abnormality. LVH: left ventricular hypertrophy. Δ QT: prolonged QT interval.

Figure 2: Presentation of Risk Ratios (RR) for outcome measures.



Literature references for the studies used are given next to the determinants. For some determinants no I^2 is given because data are derived from one study. Panel A shows RRs for cardiac abnormalities and the occurrence of death. Panel B shows RRs for cardiac abnormalities and poor outcome. Panel C shows RRs for cardiac abnormalities and the occurrence of delayed cerebral ischemia. * indicates that these data are derived from one study that only provided Hazard ratios (HR) without raw data. Therefore, we used the HR in approximation of the RR.

Additionally, heterogeneity of the data (I^2) is presented. WMAs, elevated troponin and (NT-pro-)BNP levels, tachycardia, Q waves, ST depression and T wave abnormalities were significantly associated with an increased risk of death. Bradycardia was significantly associated with a higher chance of survival. However, Q waves and ST depression had significantly heterogeneity.
Figure 2B shows the poor outcome data. Elevated troponin and CK-MB levels and ST depression were significantly associated with poor outcome.
Figure 2C presents the pooled RRs for cardiac abnormalities on DCI. WMAs, elevated troponin, CK-MB, and (NT-pro)BNP levels and ST depression were significantly associated with an increased risk of the development of DCI. Heterogeneity for the association of DCI and troponin and BNP levels was high.

Discussion

This meta-analysis patently indicates that cardiac abnormalities after SAH are related to death, poor outcome and DCI. Although the main causes of death and poor outcome after SAH are the initial hemorrhage and neurological complications, we found that also WMAs, troponins, CK-MB, BNP, Q waves, ST depression and T wave abnormalities are associated with death and poor outcome. These markers for cardiac damage and dysfunction are often present after SAH, and are similar to those observed in ischemic heart disease, but the underlying pathophysiological mechanism is probably different.
Several mechanisms for the occurrence of cardiac complications after SAH have been suggested, but none is proven. However, a generally accepted hypothesis is that sympathetic stimulation induces catecholamine release in the myocardium, which may lead to impaired systolic and diastolic function, repolarization abnormalities, and myocardial damage.
In ischemic heart disease, QT prolongation and ST segment elevation are associated with death. Against our expectations, these ECG abnormalities were not associated with death or poor outcome in patients with SAH. Possible explanations for the lack of association are that criteria used for QT prolongation in the articles were heterogeneous and arrhythmias as a cause of death were not reported in the studies.
Bradycardia was associated with decreased risk of death. This corroborates with the results of several publications that suggest a beneficial effect of beta-blockade on outcome after SAH.[17-20] However, it is unclear whether this beneficial

effect was due to decrease of heart rate or due to systemic or neuroprotective effects of the beta-blockade. In contrast, tachycardia was associated with higher risk of death. Tachycardia may be a sign of poor hemodynamic condition or inotropic stimulation. Additionally, the presence of a P mitrale, a sign of left atrial dilatation, was associated with death. This abnormality may also represent a poor hemodynamic condition.

We also found a relation between cardiac abnormalities and DCI after SAH. DCI is a complication that occurs in around 30% of patients with SAH, usually between four to 12 days after the SAH,[21] and is an important contributor to poor outcome. In contrast to thrombo-embolic stroke, which has a sudden onset, is unifocal, and usually does not affect consciousness, DCI usually has a gradual onset with often waxing and waning focal deficits, a decreasing level of consciousness, or both, and often is multifocal. The pathogenesis of DCI has not been elucidated yet, but is often attributed to vasospasm of the intracranial arteries. However, vasospasm cannot be the only initiator of DCI, as one third of patients with severe vasospasm do not develop DCI, and one third of patients with DCI do not have vasospasm.[22] Powerful and independent predictors are the duration of loss of consciousness at time of the ictus and the total amount of extravasated blood,[23] and the occurrence of hypovolemia and hypotension.[24] Because many patients with SAH have narrowed arteries and hypovolemia, and also because autoregulation of cerebral perfusion is disturbed after SAH,[25, 26] left ventricular dysfunction may directly affect cerebral perfusion. This is a potential explanation for the finding that cardiac abnormalities are also related to DCI. With this respect, not only the presence but also the degree of the cardiac abnormality may influence outcome. This notion is supported by the finding of a linear relation between the BNP levels and vasospasm severity.[12] Additionally, the degree of troponin elevation has been associated with poor outcome.[13]

Although an association has been established, it remains unclear whether a definite causal relation exists between cardiac abnormalities and outcome after SAH. Several studies have found an independent effect of cardiac abnormalities on outcome, adjusted for clinical variables,[11, 15, 27] whereas others did not.[14, 28-30]

Caution should be perceived when interpreting these results due to shortcomings of the included studies. First, the included studies were published over a period of more than 40 years. During this period, diagnosis and treatment of SAH has improved with decreased case fatality rates,[1] possibly affecting prevalence and consequence of cardiac complications on outcome.

Second, reference values of cardiac markers were not given in all studies. Abnormal BNP levels were differently defined in the three studies that used BNP as prognosticator.

One study defined QT prolongation as more than 410 milliseconds, whereas others have used a cut-off value of more than 460 milliseconds. T wave abnormalities included both T wave inversion and T wave flattening. U waves were defined as present, greater than 1 mm or as negative U waves. Moreover, some studies did not provide criteria for abnormalities at all. This obviously might influence reported prevalence of cardiac abnormalities and influence effect of cardiac abnormalities on outcome.

Third, most studies investigated echocardiography, biochemical markers and ECG abnormalities separately. Therefore, the relative contribution and incremental prognostic value of the different cardiac abnormalities is uncertain. The combinations of several ECG abnormalities have been studied, and three studies found that the combination of different ECG abnormalities better predicts prognosis than the individual variables alone.

Fourth, as the cardiac abnormalities are reversible, with unknown time course, the timing of cardiac evaluation could influence results. Only a few of the included studies performed serial cardiac studies with predefined time intervals. The importance of the timing of cardiac investigations in relation to the outcome of SAH is highlighted in one study, in which the authors found a difference in prognostic value of elevated troponin levels on day four versus day nine after onset of SAH. LV dysfunction showed the same trend, although the criteria for LV dysfunction were different between these two days.

Fifth, the baseline characteristics of the included studies and the prevalence of the cardiac determinants and outcomes showed a large variation. Percentage of men varied from 22 to 62%, follow-up duration varied from in-hospital follow-up to six months, and poor condition on admission varied from 23 to 68%. This might indicate differences in study populations and therefore influences results.

Six, the quality of the included articles varied as reflected in the STROBE score, which varied between 11 and 20 points (out of 22 points) with a median of 17. This may also partly explain the heterogeneity of results.

Finally, the heterogeneity of the different clinical severity scores and the thresholds used to dichotomize the various scales and the timing of the assessment may be a factor.

The shortcomings of the included studies stress the need for large prospective, observational studies with clearly defined methodology, sufficient sample size, and long-term follow-up to assess whether cardiac abnormalities have independent prognostic value after SAH.

Future research should establish an independent prognostic value of cardiac abnormalities and be directed towards elucidating the pathophysiological mechanisms, and potential treatment options. In conclusion, our findings support the view that cardiac abnormalities following SAH are related to higher risk of death, poor prognosis, and DCI.

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CHAPTER 3

Cardiac dysfunction after aneurysmal subarachnoid hemorrhage: relationship with outcome

van der Bilt IAC, Hasan D, van den Brink RBA, Cramer MJM, van der Jagt M, van Kooten F, Meertens JHJM, van den Berg MP, Groen RJ, ten Cate FJ, Kamp O, Götte MJW, Horn J, Groeneveld J, Vandertop WP, Algra A, Visser FC, Wilde AAM and Rinkel GJE, on behalf of the SEASAH (Serial Echocardiography After Subarachnoid Hemorrhage) Investigators. *Neurology*. 2014 Jan 28;82(4):351-8

Abstract

Objective: To assess whether cardiac abnormalities after aneurysmal subarachnoid hemorrhage (aSAH) are associated with delayed cerebral ischemia and clinical outcome, independent from known clinical risk factors for these outcomes.

Methods: In a prospective, multicenter cohort study we performed echocardiography, electrocardiography (ECG) and measured biochemical markers for myocardial damage in patients with aSAH. Outcomes were delayed cerebral ischemia (DCI), death and poor clinical outcome (death or dependency for activities of daily life) at three months. With multivariable Poisson regression analysis we calculated risk ratios (RR) with corresponding 95% confidence intervals (CI). We used survival analysis to assess cumulative percentage of death in patients with and without echocardiographic wall motion abnormalities (WMAs).

Results: We included 301 patients with a mean age of 57 years. 70% were women. A wall motion score index ≥ 1.2 had an adjusted RR 1.2(0.9-1.6) for DCI, 1.9(1.1-3.3) for death and 1.8(1.1-3.0) for poor outcome. Midventricular WMAs had adjusted RRs 1.1(0.8-1.4) for DCI, 2.3(1.4-3.8) for death and 2.2(1.4-3.5) for poor outcome. For apical WMAs adjusted RRs were 1.3(1.1-1.7) for DCI, 1.5(0.8-2.7) for death and 1.4(0.8-2.5) for poor outcome. Elevated Troponin T levels, ST-segment changes and low voltage on the admission ECGs had a univariable association with death, but were no independent predictors for outcome.

Conclusion: WMAs are independent risk factors for clinical outcome after aSAH. This relation is partly explained by a higher risk of DCI. Further study should aim at treatment strategies for these aSAH related cardiac abnormalities to improve clinical outcome.

Introduction

Subarachnoid hemorrhage from a ruptured aneurysm (aSAH) occurs at relatively young age (mean age 55 years) and carries a poor prognosis: one third of patients die within one month and of those who survive 10-15% remains dependent.[1] Several reports have described cardiac dysfunction following aSAH, and in a meta-analysis of these studies we found that cardiac abnormalities are associated with poor outcome.[2] However, it is uncertain whether this association is independent of known clinical risk factors of poor outcome. An important prognosticator for outcome is delayed cerebral ischemia (DCI).[3] As cerebral autoregulation is disturbed after aSAH[4], impaired cardiac performance may lead to reduced cerebral blood flow (CBF), and may contribute to the development of DCI.[5]

We conducted a prospective, multicenter cohort study to assess whether cardiac abnormalities independently influence the occurrence of DCI, death and poor outcome after aSAH.

Methods:

Design:

The study was designed as a prospective, observational, multicenter cohort study in the Netherlands. The number of patients to be included was 300, which was deemed to sufficiently answer the study objectives, based on the assumption that cardiac abnormalities would occur in 20% and DCI in 30%. With these assumptions an RR of 1.5 has a 95% confidence interval of 1.1 to 2.2. In a pre-specified interim analysis after 100 patients these assumptions were confirmed. From February 2005 to March 2008, 301 patients with aSAH were enrolled. Five tertiary referral university hospitals participated.

Standard Protocol Approvals, Registrations, and Patient Consents:

The study was approved by the national ethics committee and by all participating hospitals. Written informed consent was obtained from the patient or a legal representative.

Criteria for diagnosis of aSAH:

The diagnosis of aSAH was based on clinical signs and symptoms, presence of

subarachnoid blood on computer tomography (CT) scan or xanthochromia of the cerebrospinal fluid if the CT was non-diagnostic, and by the presence of an aneurysm on conventional or CT-angiography. Patients with aSAH presenting within 72 hours of the onset of symptoms were eligible for inclusion. Patients with cardiac abnormalities prior to the aSAH (i.e. ECG or echocardiographic abnormalities after myocardial infarction, CABG or PCI) were excluded. All investigations mentioned below were performed within 24 hours after admission.

Study procedure and data collection:

Clinical data were entered in case report forms (CRF) by local investigators. Periodically, the study coordinator (IB) checked all CRFs against patients' charts and entered these in an anonymized electronic database. The following data were collected: age, sex, loss of consciousness at ictus, seizures at ictus, angina pectoris, myocardial infarction, prior coronary artery bypass graft (CABG), prior angioplasty, known hypertension, hypercholesterolemia, peripheral vascular disease, cerebrovascular events (ischemic or hemorrhagic), diabetes mellitus, current cigarette smoking, family history of coronary artery disease, drug use. The clinical condition on admission was categorized according to the World Federation of Neurosurgical Societies (WFNS) grading scale for subarachnoid hemorrhage, where a WFNS ≥ 3 was considered a poor condition on admission.[6]

CT-scan:

The amount of blood on all admission CT scans was assessed according to the Hijdra score[7] by one investigator (DH), who was unaware of the clinical condition of the patient. The amount of blood in 13 cerebral cisterns was scored from 0 (no blood) to 2 (completely filled with blood). The sum score (ranging from 0 to 26) for each CT scan was calculated.

Electrocardiography:

All ECGs were analyzed by one investigator (FV), who was unaware of the clinical data of the patient. Criteria for the ECG abnormalities were defined according to the guidelines of the European Society of Cardiology (ESC).[8] A Q-wave in two contiguous leads was considered pathological when ≥ 0.03s wide and ≥ 0.1mV deep. ST deviation was considered to represent myocardial ischemia when ST elevation occurred at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads.

Horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1 were also considered ischemic changes. The Cornell voltage criteria ($R_{aVL}+S_{V3}$ > 28 mm(men) or > 20 mm(women)), or Sokolow-Lyon voltage index ($S_{V1}+R_{V5/6}$) >35 mm for left ventricular hypertrophy were used.

Echocardiography:

Transthoracic echocardiography was performed according to the standards of the American Society of Echocardiography (ASE). Vingmed Medical Systems 7 were used, one center used a Philips Sonos 7500 for 30 examinations. For assessment of systolic function, three cardiologists (RB, MC, MG), independently from each other and unaware of the clinical data of the patients, reviewed all echocardiograms with the standard ASE 17-segment model for systolic function.[9] All segments were scored based on contractility: 0 uninterpretable, 1 normal, 2 hypokinetic, 3 akinetic, 4 dyskinetic, 5 aneurysmal. A wall motion score index (WMSI) was calculated by dividing the sum of wall motion scores by the number of visualized segments. Diastolic function was assessed measuring pulsed wave Doppler of mitral valve peak velocity of early (E) and late (A) diastolic flow, early flow deceleration time, and duration of late flow. The E/A ratio was calculated from the mean E and A of three heart cycles. Pulmonary vein systolic (Ps) and diastolic (Pd) flow velocity, and atrial reversal flow duration (Adur) were also measured. Doppler tissue imaging (DTI) of the mitral annular motion was measured for early (E') and late diastolic annular velocity and the ratio of the mitral E to the DTI E' was calculated using the septal (E/E') velocities. These parameters were then checked with the criteria on diastolic dysfunction according to the guidelines of the European Society of Cardiology.[10]

Laboratory results:

On admission, serum Troponin levels were determined, as a marker for myocardial damage. Additionally, N-terminal prohormone of B-Type Natriuretic Peptide (NT-proBNP) was measured which is a natriuretic hormone that, although first identified in the brain, is released from the heart in response to high filling pressures. Finally, Creatinine as indication of renal function was measured on admission. The upper limits of normal as defined by the local laboratory were used as reference.

Assessment of outcome: Delayed cerebral ischemia:

The study coordinator (IB) entered all episodes of clinical deterioration in an electronic database. Following this procedure, two neurologists (FK,MJ), who had access to all clinical data except the cardiac data, assessed whether these clinical deteriorations fulfilled the criteria for probable or definite DCI. Probable DCI was defined as a focal deficit or deterioration of level of consciousness not explained by rebleeding, hydrocephalus, complication from aneurysm treatment, infection, or metabolic disturbances, but without new hypodensities on a repeated CT scan. Infection was defined as fever, leucocytosis, and increased C-reactive protein, or positive cultures along with clinical signs of infection for which antibiotic treatment was started.

Definite DCI was defined as development of focal neurological signs or deterioration of the level of consciousness, or both, with evidence of cerebral infarction on CT-scan or at autopsy. Any new hypodensity on the CT scan without an obvious explanation such as neurosurgical or endovascular intervention, or perihematomal edema were scored as definite DCI even in the absence of clinical symptoms. Probable and definite DCI were taken together as one event.

Poor outcome:

Patients were contacted by phone or in the outpatient clinic three months after admission and outcome was scored according to the Modified Rankin Scale (MRS).[11] Poor outcome was defined as a MRS score > 3.

Statistical analysis:

Baseline characteristics were analyzed using descriptive statistics. Univariable risk ratios (RR) for baseline determinants and outcomes at three months (DCI, death and poor outcome) with corresponding 95% CI were calculated with Poisson regression with robust standard errors.[12, 13] For determinant-outcome combinations that yielded a significance level of 5%, multivariable adjustments were performed with Poisson regression. Adjustments are reported for those factors that changed the crude risk ratio by more than 5%. Missing values were excluded by casewise deletion. Hijdra score was dichotomized on the median, WMSI was dichotomized on one standard deviation above the median.

Additionally, we made Kaplan-Meier curves for cumulative percentages of death according to presence or absence of WMAs. Because rebleeding may increase the risk of DCI and poor outcome the chance of cardiac abnormalities, we performed a sensitivity analysis with exclusion of patients who had an episode of rebleeding after

Table 1: Baseline characteristics.

	Total	DCI	Death	Poor outcome
	(N=301)	(n=164)	(n=58)	(n=66)
Female sex	210(70%)	99(60%)	37(64%)	43(65%)
Mean age (in years)(±SD)	57(±13)	58(±13)	64(±14)	63(±14)
Coronary risk factors				
Hypertension	90(30%)	44(27%)	22(38%)	27(41%)
Hypercholesterolemia	26(9%)	13(8%)	5(9%)	5(8%)
Diabetes Mellitus	14(5%)	7(4%)	4(7%)	5(8%)
Smoking (previous and current)	115(38%)	52(32%)	15(26%)	16(24%)
Medical history				
Myocardial infarction*	8(3%)	4(2%)	1(2%)	2(3%)
Percutaneous Coronary Intervention (PCI)	7(2%)	2(1%)	0(0%)	0(0%)
Coronary Artery Bypass Graft (CABG)	4(1%)	1(1%)	0(0%)	0(0%)
Ischemic Stroke	16(5%)	8(5%)	7(12%)	7(11%)
Intracerebral Hemorrhage	7(2%)	2(1%)	1(2%)	1(2%)
Family history of cardiovascular disease	33(11%)	12(7%)	3(5%)	3(5%)
Location of aneurysm in Anterior circulation				
Anterior Communicating Artery	127(42%)	61(37%)	22(38%)	28(42%)
Anterior cerebral artery	12(4%)	6(4%)	1(2%)	1(2%)
Middle cerebral artery	61(20%)	31(19%)	13(22%)	15(23%)
Internal carotid artery	61(20%)	28(17%)	12(21%)	12(18%)
Location of aneurysm in Posterior circulation				
Posterior cerebral artery	11(4%)	5(3%)	2(3%)	2(3%)
Basilar artery	21(7%)	9(5%)	6(10%)	6(9%)
Vertebral artery	10(3%)	6(4%)	2(3%)	2(3%)
Aneurysm treatment				
Coiling	183(60%)	77(47%)	26(45%)	30(46%)
Clipping	95(31%)	58(35%)	10(17%)	14(21%)
None	25(8%)	11(7%)	22(38%)	22(33%)
Amount of blood > median (Hijdra =19 points)	142(47%)	84(51%)	35(60%)	38(58%)
Clinical condition on admission (WFNS)				
I	104(34%)	29(18%)	3(5%)	5(8%)
II	54(18%)	30(18%)	10(17%)	11(17%)
III	24(8%)	14(9%)	4(7%)	5(8%)
IV	64(21%)	40(24%)	20(35%)	23(35%)
V	57(19%)	33(20%)	21(36%)	22(33%)
Acute hydrocephalus	107(35%)	55(34%)	23(40%)	27(41%)

Baseline characteristics. N: number of patients; CABG: Coronary artery bypass graft; WFNS: World Federation of Neurosurgical Societies subarachnoid grading scale. SD: Standard Deviation; *: The patients with prior myocardial infarction, PCI or CABG that were included did not have ECG abnormalities or echocardiographic abnormalities prior to the SAH.

admission. Subanalyses were performed for patients that underwent the investigations within 48 hours of the bleed, for patients that underwent surgery or coiling and for the outcomes definite DCI, and probable and definite DCI combined.

Results

Participants:
320 patients were assessed for eligibility. Five patients were not included because no aneurysm was found; for 5 others informed consent was declined by next of kin. Nine were excluded: in 6 no cardiac examination could be performed and 3 were lost to follow-up. Finally, 301 subjects completed follow-up and were analyzed. Baseline characteristics are listed in table 1.

Cardiac data:
The prevalence of cardiac abnormalities on admission is shown in table 2.

The wall motion abnormalities did not correspond to a single coronary territory. Ten percent of patients showed hypokinesia of the apical segments with hypercontractility of the basal segments which is compatible with a Takotsubo cardiomyopathy (TTC).[14]Due to this finding, a secondary analysis was done to analyze whether WMAs occurring in the basal, midventricular or apical segments were as such associated with outcome.

Outcome data:
Probable or definite ischemia occurred in 164(54%) patients. Of these patients 146(48%) had definite DCI. The median time from aSAH onset to DCI was 3.5; IQR 4.9 days. At the end of follow up 58(19%) patients had died (median time to death 10; IQR days) and 66(22%) had a poor outcome (8 patients had MRS 4 or 5). In 57 patients cause of death was poor neurological condition, and one patient died due to cardiogenic shock. Post mortem examination in the latter patient showed a rupture of the free wall of the right ventricle and thrombotic occlusion of the right coronary artery. During the clinical course 40(16%) patients had an episode of rebleeding. Median time to rebleeding was 3.6; IQR 10.1 days. 48(51%) of patients that underwent clipping had surgery within 24 hours. 121(66%) of patients that underwent coiling had it within 24 hours. Results were essentially the same if we restricted the analyses to patients investigated within 48 hours after onset of clinical symptoms.

Table 2: Prevalence of cardiac abnormalities on admission.

Cardiac parameters	Total (n=301)	DCI (n=164)	Death (n=58)	Poor outcome (n=66)
ECG				
Heart frequency (bpm)				
<60	62(21%)	28(17%)	6(10%)	8(12%)
60<>100	212(70%)	102(62%)	29(67%)	44(67%)
>100	29(10%)	16(10%)	13(22%)	14(21%)
Pathological Q-wave present	14(5%)	8(5%)	4(7%)	5(8%)
ST depression	26(9%)	12(7%)	8(14%)	8(12%)
ST elevation	10(3%)	7(4%)	4(7%)	4(6%)
Negative T-waves	79(26%)	47(29%)	18(31%)	22(33%)
ST segment "Ischemic"	33(11%)	17(10%)	10(17%)	10(15%)
QTc prolongation	145(48%)	83(51%)	33(57%)	38(58%)
LVH – Sokolow – Lyon	56(19%)	28(17%)	11(19%)	12(18%)
Strain pattern	14(5%)	5(3%)	3(5%)	3(5%)
Low voltage	8(3%)	6(4%)	4(7%)	4(6%)
Myocardial infarction pattern	13(4%)	7(4%)	3(5%)	4(6%)
Echocardiography (N=279)				
WMSI >1.0	59(20%)	31/139(22%)	16/52(28%)	19/60(29%)
Mean WMSI (±SD)	1.1(±0.2)	1.1(±0.3)	1.2(±0.4)	1.2(±0.4)
WMAs of Basal segments	28(9%)	13/139(9%)	6/52(10%)	8/60(12%)
WMAs of Midventricular segments	46(15%)	24/139(17%)	16/52(28%)	18/60(27%)
WMAs of Apical segments	39(13%)	26/139(19%)	10/50(17%)	11/57(17%)
Diastolic dysfunction	143(47%)	71/146(49%)	33(57%)	37(56%)
Laboratory findings				
Elevated Troponin T (µg/L)*	97/261(37%)	51/117(36%)	27/48(47%)	28/55(42%)
Elevated NT-proBNP (ng/L)*	159/225(71%)	78/101(53%)	31/39(53%)	37/45(56%)
Decreased GFR (ml/min)*	66/217(30%)	29/93(20%)	13/40(22%)	14/46(21%)

N: number of patients; LVH: Left ventricular hypertrophy. WMSI: wall motion score index, WMAs: wall motion abnormalities; GFR: glomerular filtration rate; SD: Standard Deviation. *The upper and lower limits of normal as defined by the local laboratory were used as reference. In case of missing data the number of patients with available data is given after the forward slash.

Main results:

Table 3 shows the adjusted RRs for the association of WMSI ≥ 1.2 and the three outcomes. A WMSI ≥ 1.2 is associated with death and poor outcome independent of known predictors for these outcomes. As NT-proBNP was the only variable that changed the RRs > 5%, the RRs for WMSI ≥ 1.2 and outcome, adjusted for elevated NT-proBNP is also given in table 3.

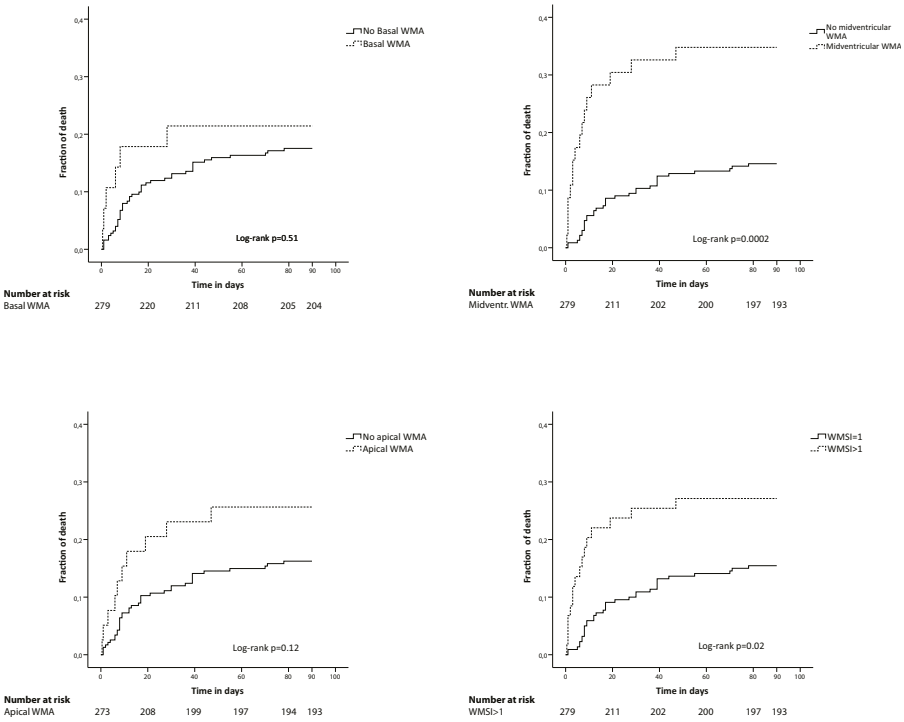
Table 3: Adjusted Risk Ratios (RR) for the three outcomes and wall motion abnormalities.

Determinants	DCI	Death	Poor outcome
WMSI > 1.1			
Crude RR	1.2(0.9-1.6)	1.9(1.1-3.4)	1.8(1.1-3.0)
Adjusted RR*	1.2(0.9-1.5)	1.9(1.1-3.3)	1.8(1.1-3.0)
Adjusted RR for NT-proBNP	1.2(0.9-1.7)	1.6(0.8-3.3)	1.6(0.8-3.0)
Basal WMAs			
Crude RR	1.0(0.7-1.4)	1.2(0.6-2.5)	1.4(0.7-2.6)
Adjusted RR*	0.9(0.7-1.4)	1.2(0.6-2.5)	1.4(0.7-2.6)
Adjusted RR for NT-proBNP	1.0(0.6-1.5)	0.8(0.3-2.5)	1.3(0.6-2.8)
Midventricular WMAs			
Crude RR	1.1(0.9-1.4)	2.3(1.4-3.7)	2.2(1.4-3.4)
Adjusted RR*	1.1(0.8-1.4)	2.3(1.4-3.8)	2.2(1.4-3.5)
Adjusted for NT-proBNP	1.1(0.8-1.5)	1.8(0.9-3.5)	1.9(1.0-3.4)
Apical WMAs			
Crude RR	1.4(1.1-1.7)	1.5(0.8-2.8)	1.4(0.7-2.6)
Adjusted RR*	1.3(1.1-1.7)	1.5(0.8-2.7)	1.4(0.8-2.5)
Adjusted for NT-proBNP	1.4(1.0-1.8)	1.4(0.6-3.2)	1.5(0.8-2.8)

Abbreviations; WMSI: wall motion score index. WMAs: wall motion abnormalities, LVH: left ventricular hypertrophy; *adjusted for WFNS, age, Hijdra score. Adjustment for elevated Troponin on admission, presence of Q-waves on ECG, low voltage on ECG, ST depression, ST elevation, Negative T-waves, prolonged QT interval (>500ms) yielded in a change of RR of < 5%.

As a secondary analysis, WMAs were subdivided in basal, midventricular and apical WMAs. Midventricular WMAs were associated with death, independent from clinical condition on admission, age or amount of blood on the CT-scan. Apical WMAs were an independent predictor for DCI. Adjustment for elevated Troponin, presence of Q-waves, low voltage, ST-segment deviation, and negative T-waves led to a change in the RR of < 5%. None of the other cardiologic determinants were associated with outcome. Diastolic dysfunction had a univariable RR for DCI of 1.0(0.8-1.2), for death of 1.5(0.9-2.3) and for poor outcome 1.4(0.9-2.2). Therefore we refrained from including diastolic dysfunction in the multivariable model. Results from the sensitivity analysis after exclusion of patients with rebleeding were comparable with those of the main analysis. Additionally, in the sensitivity analysis on patients with definite DCI only, the results are comparable to those of the main analysis. Figure 1 shows Kaplan-Meier curves for cumulative death according to presence or absence of wall motion abnormalities.

Figure 1: Fraction of death in patients with- or without WMAs.



Kaplan-Meier curves of fraction of death in patients with a wall motion score index(WMSI) > 1.0 or wall motion abnormalities in the basal, midventricular or apical segments of the heart.

Discussion

The main finding of the present study is that WMAs are a predictor for adverse clinical outcome in aSAH, independent from known clinical predictors. Since these WMAs are also an independent risk factor for the occurrence of DCI, the relation between cardiac abnormalities and outcome may therefore, at least in part, be explained by the contribution of cardiac abnormalities to the development of DCI.

We found cardiac abnormalities in a high proportion of patients; in particular prolonged QT-interval and elevated NT-proBNP. The elevated NT-proBNP, weakened the relation between wall motion abnormalities and outcome. NT-proBNP is expressed predominantly in the ventricles in response to cardiac overload.[15] This weakening of the relation between wall motion abnormalities and outcome by

NT-proBNP is therefore probably explained by the secretion of NT-proBNP by the cardiac ventricles in response to increased wall stress of the myocardium when WMAs occur after aSAH. This is supported by the finding that NT-proBNP levels in stress cardiomyopathy or TTC are elevated and correlate with catecholamine increase and severity of LV dysfunction.[16] Other studies also found an elevated NT-proBNP in patients with SAH.[17-20] However, these studies had relatively small sample size, used different cut-off values for elevated NT-proBNP, or had not defined outcome.

The cause of cardiac abnormalities after SAH cannot be answered by the present study. The generally accepted pathway is that due to massive sympathetic activation a catecholamine burst causes myocardial dysfunction by epicardial spasm, microvascular dysfunction, hyperdynamic contractility with midventricular or outflow tract obstruction, or that it is caused by direct effects of catecholamines on cardiomyocytes.[21] Myocardial ischemia is an unlikely cause of the dysfunction as myocardial perfusion was reported to be normal.[22]

Although in the univariable analysis several ST-segment changes were associated with outcome, none of the ECG parameters predicted outcome in the multivariable analyses. Possibly, ST-segment changes in aSAH are caused by changes in wall stress due to catecholaminergic stress after the aSAH. Another likely explanation is that ECG abnormalities, Troponin and NT-proBNP elevation, together with WMAs represent the same phenomenon; cardiac dysfunction after aSAH. Furthermore, we considered only the admission ECG whereas we know from earlier studies that serial ECG changes after SAH occur frequently, and have been linked to outcome.[23-25] Earlier studies found similar proportions of patients with WMAs as the present study.[26-29] However, these studies did not find a relation between WMAs and outcome, although an association with elevated troponin and outcome was reported.[30] In our study all examinations were performed within 96 hours of the aSAH, which was usually not the case in other studies. Also, our study was appropriately powered and had considerable follow-up duration.

We found that the distribution of the WMAs did not correspond with the territory of a single coronary artery, which has been described before in aSAH.[31] Some patients showed a diffusely disturbed systolic function and of the patients who had apical wall motion abnormalities, almost all also showed basal hyperdynamic contractility, consistent with a TTC. Although it has widely been accepted that TTC is a benign condition which carries an excellent prognosis[32], in our secondary analysis the patients with apical WMAs had more risk of DCI whereas midventricular WMAs were associated with death. This finding might be explained by an impaired cardiac

output in combination with disturbed cerebral autoregulation after aSAH. However, since these analyses were not part of the original protocol and sample sizes were small, these observations need further explorations. Second, we did not have hemodynamic data to support cerebral hypoperfusion. Nevertheless, as DCI is a multifactorial entity, WMAs may play a role in the pathophysiology of DCI and may, if treated, improve outcome.

Some studies have suggested that ß-sympathicomometics such as dobutamine or phosphodiesterase inhibitors such as milrinone recruit inotropic reserve in patients with aSAH.[17, 33] The aforementioned drugs could be effective in restoring myocardial function, but whether this improves outcome in patients with aSAH and WMA should be investigated.

Our study included a high number of patients with poor clinical condition compared to other studies. This might explain why we found a high proportion of patients with DCI. Another explanation for the relative high incidence of DCI lies in the criteria we used for DCI, including both clinical episodes not confirmed with new hypodensities on CT as well as any new hypodensity on CT. This definition has been proposed earlier.[34] We found a high number of patients with a rebleed. This is probably due to the inclusion of a high number of patients in whom occlusion of the aneurysm was postponed because of poor clinical condition.

As this was an observational study we could only assess associations and neither pathophysiological pathways nor therapeutic hypotheses were evaluated.

The strength of the present study is the structured, prospective, and multicenter approach with a 90 day follow-up duration. We included a representative series of patients, including a considerable proportion of patients in poor clinical condition on admission.

Cardiac abnormalities occur frequently after aSAH. Echocardiographic WMAs are associated with clinical outcome after aSAH, regardless of the severity of the aSAH. This relation may partly be explained by a higher chance of DCI.

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CHAPTER 4

Time course and risk factors for myocardial dysfunction after aneurysmal subarachnoid hemorrhage

van der Bilt IAC, Hasan D, van den Brink RBA, Cramer MJM, van der Jagt M, van Kooten F, Regtien JG, van den Berg MP, Groen RJ, ten Cate FJ, Kamp O, Götte MJW, Horn J, Girbes ARJ, Vandertop WP, Algra A, Rinkel GJE, Wilde AAM; SEASAH (Serial Echocardiography After Subarachnoid Hemorrhage) Investigators. *Neurosurgery.* 2015 Jun;76(6):700-5

Abstract

Background: Myocardial wall motion abnormalities (WMA) are independent risk factors for poor outcome in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Objective: To study the time course of WMA during the initial phase after aSAH, and to investigate which clinical, electrocardiographic or myocardial serum markers are predictors for early or late development of WMA.

Methods: In a prospective, multicenter cohort study in patients with aSAH we performed serial electrocardiography (ECG), echocardiography, and measured Troponin T and NT-proBNP. WMA present on admission were considered early WMA; those that developed during the clinical course were considered late WMA. With multivariable regression analysis we calculated odds ratios (OR) with corresponding 95% confidence intervals (CI) for clinical parameters, ECG, and myocardial serum makers with early or late occurrence of WMA.

Results: We included 301 patients (mean age 57(SD±13) years). Multivariable ORs for early WMA were: poor clinical condition 2.7(95%CI: 1.1-6.8), sinus tachycardia 5.0(1.3-19.9), ST-depression 3.7(1.02-13.1), ST-elevation 16.6 (1.5-178.9) and elevated troponin T 2.8(1.1-7.3). Multivariable ORs for late development of WMA were 6.8 (1.6-30) for myocardial infarct pattern on admission ECG and 3.4 (1.4-8.5) for elevated troponin T on admission.

Conclusions: WMA may be present on admission or develop during the course of aSAH. Poor neurological condition on admission, sinus tachycardia, ST-depression and ST-elevation at the admission ECG and elevated troponin T, are independent predictors for early WMA, a myocardial infarct pattern on the admission ECG and elevated troponin T independently predict late WMA.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a subset of stroke that occurs at young age (mean age 55 years), with an incidence of 5-20/100,000 and carries a poor prognosis: 30% of patients die within one month and of those who survive 10-15% remain dependent.[1] In patients with aSAH, myocardial wall motion abnormalities (WMA) are associated with poor outcome, independently of other well-known clinical predictors.[2-6] WMA are reported in up to 25% of patients and are usually reversible.[7-10] To early identify patients at risk for poor outcome due to cardiac dysfunction, the objective of this study was to investigate the time course of WMA after aSAH and to identify predictors for WMA using clinical parameters, ECGs and myocardial serum markers that are available on admission.

Methods

Design:

The Serial Echocardiography After SubArachnoid Hemorrhage (SEASAH) study was a prospective multicenter cohort study conducted in 5 tertiary referral centers in the Netherlands. The study design was published earlier; the major finding of the study was that WMA are associated with poor outcome independent of other clinical parameters.[6] Three hundred and one patients with aSAH were included. The Dutch national ethics committee and all local ethics committees of the participating hospitals approved the study. Written informed consent was obtained for all patients.

Criteria for diagnosis of aSAH:

The diagnosis of aSAH was based on clinical signs and symptoms, presence of subarachnoid blood on computer tomography(CT) scan or xanthochromia of the cerebrospinal fluid if the CT was non-diagnostic, and by the presence of an aneurysm on conventional or CT-angiography. Patients with aSAH presenting within 72 hours of the onset of symptoms were eligible for inclusion. Patients with known electrocardiographic or echocardiographic abnormalities were excluded.

Study procedure and data collection:

The World Federation of Neurosurgical Societies (WFNS) grading scale for subarachnoid hemorrhage was used for grading clinical condition, where a WFNS ≥ 3 was considered a poor condition.[11]

Echocardiography, ECG and testing for myocardial serum markers(N-terminal prohormone of B-Type Natriuretic Peptide (NT-proBNP) and troponin T) was performed as soon as possible after admission and 4 and 8 days after onset of symptoms. The upper limits of normal as defined by the local laboratory were used as reference.

CT-scan:

The amount of blood on the admission CT scans was assessed according to the Hijdra score[12] by one investigator (DH), who was unaware of the clinical condition of the patient or the results of the cardiologic examinations. Hydrocephalus was defined as the bicaudate index (=BCI, width of the frontal horns at the level of the foramina of Monro, divided by the corresponding diameter of the brain) on the CT, exceeding the 95th percentile for age. The upper limits are: <36 years of age, 0.16; 36-45 years, 0.17; 46-55 years, 0.18; 56-65 years, 0.19; 66-75 years, 0.20; 76-85 years, 0.21.[13]

Cardiac examinations:

The investigators who scored the echocardiograms, ECGs or blood results, were unaware of the clinical data of the patient. Criteria for the ECG abnormalities were defined according to the guidelines of the European Society of Cardiology[14] and are described earlier.[6] ST segment deviation is frequent in aSAH, but often does not represent myocardial ischemia.[15] ST deviation was considered suggestive for myocardial ischemia when ST elevation occurred at the J-point in two contiguous leads. Horizontal or down-sloping ST depression in two contiguous leads; and/or T inversion in two contiguous leads with prominent R-wave or R/S ratio >1 were also considered ischemic changes. Transthoracic echocardiography was performed according to the standards of the American Society of Echocardiography (ASE).[16] For assessment of systolic function, three cardiologists, independently from each other and unaware of the clinical data of the patients, reviewed all echocardiograms. All segments were scored based on contractility: 0 uninterpretable, 1 normal, 2 hypokinetic, 3 akinetic, 4 dyskinetic, 5 aneurysmal. A wall motion score index (WMSI) was calculated by dividing the sum of wall motion scores by the number of visualized segments. A WMSI > 1 means that WMA were present.

Statistical analysis:

Baseline characteristics were analyzed using descriptive statistics. WMSI was dichotomized on one standard deviation above the median.WMA were divided in early WMA, which were present on admission and late WMA, which were present on the echocardiograms on day 4 and/or day 8 after the onset of the aSAH but with a normal admission echocardiogram. Univariable odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated using logistic regression for baseline determinants and early and late WMA. For determinant-outcome combinations that yielded a significance level of 5% in the univariable analysis, multivariable adjustments were performed. Missing values were excluded by casewise deletion. Hijdra score was dichotomized on the median. Because rebleeding of the aneurysm may cause late WMA we performed a sensitivity analysis with exclusion of patients with a rebleed.

Results:

Participants:

Three hundred and twenty patients were assessed for eligibility. Five patients were not included because no aneurysm was found; for 5 others informed consent was declined by next of kin. Nine were excluded: in 6 no cardiac examination could be performed and 3 were lost to follow-up. Three hundred and one patients with aSAH were included and underwent the cardiac examinations. Table 1 shows the baseline characteristics.

Table 1: shows the baseline characteristics.

	N=301
Female sex	210(70%)
Mean age (in years)(±SD)	57(±13)
Coronary risk factors	
Hypertension	90(30%)
Hypercholesterolemia	26(9%)
Diabetes Mellitus	14(5%)
Smoking (previous and current)	115(38%)
Family history of CVD	33(11%)
Medical history	
Myocardial infarction*	8(3%)
PCI	7(2%)
CABG	4(1%)
Ischemic Stroke	16(5%)
Intracerebral Hemorrhage	7(2%)
Location of aneurysm in Carotid circulation	
Anterior Communicating Artery	127(42%)
Anterior cerebral artery	12(4%)
Middle cerebral artery	61(20%)
Internal carotid artery	61(20%)
Location of aneurysm in Posterior circulation	
Posterior cerebral artery	11(4%)
Basilar artery	20(7%)
Vertebral artery	9(3%)
Hijdra score >19	142(47%)
Acute hydrocephalus	107(35%)
Clinical condition on admission (WFNS)	
I	103(34%)
II	54(18%)
III	24(8%)
IV	64(21%)
V	56(19%)

Abbreviations: N: number, SD: standard deviation, WFNS: World Federation of Neurosurgical Societies. CVD: cardiovascular disease. PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft *: The patients with prior myocardial infarction, PCI or CABG who were included did not have ECG abnormalities or echocardiographic abnormalities prior to the SAH.

Cardiac abnormalities:

The prevalence of cardiac abnormalities during the study period is shown in table 2.

Table 2: shows the course of the determinants.

Cardiac parameters	**Admission n=301* (298 ECGs)**	**Day 4 n=283* (264 ECGs)**	**Day 8 n=272* (224 ECGs)**
Sinusbradycardia	41(14%)	39(15%)	18(8%)
Sinustachycardia	19(6%)	13(5%)	21(9%)
Low voltage	8(3%)	16(6%)	6(3%)
Pathologic Q wave	14(5%)	7(3%)	10(5%)
ST-depression	26(9%)	10(4%)	5(2%)
ST-elevation	10(3%)	3(1%)	3(1%)
Negative T-waves	90(30%)	134(51%)	61(27%)
Prominent U-waves	99(33%)	85(32%)	60(27%)
QTc prolongation >500ms	43(14%)	29(11%)	11(5%)
LVH on ECG	56(19%)	37(14%)	39(17%)
Strain pattern on ECG	14(5%)	11(4%)	8(4%)
Myocardial infarction pattern	13(4%)	5(2%)	9(4%)
Elevated Troponin T	97/261 (37%)	65/244(27%)	29/190(15%)
Elevated NT-proBNP	159/225 (71%)	85/207(41%)	49/150(33%)

LVH: Left ventricular hypertrophy. *The difference between the number of alive patients and the smaller number of ECGs can be explained because patients were discharged (largest effect at 8 days) or because of study logistics.

Of the individual ECG abnormalities, a prominent U-wave was the most common with a prevalence of 33% (27% on 8th day) together with negative T-waves in 30% (27% on 8th day). Twenty percent of patients had a normal ECG on admission versus 31% at the 8th day after the aSAH. Thirty seven percent had elevated troponin T on admission and 71% had elevated NT-proBNP.

Course of WMA over time:

WMA were present in 58/277 (21%) patients on admission and in 29/187(16%) of those who were still alive and not yet discharged from hospital on day 8 (26 patients had died on the 8th day after the aSAH). Of the 58 patients with WMA on admission, 14 had a normal LV function on the 8th day(see Figure 1 which demonstrates the dynamic nature of the WMA. In this figure only the patients with complete follow up (3 echocardiograms) are shown).

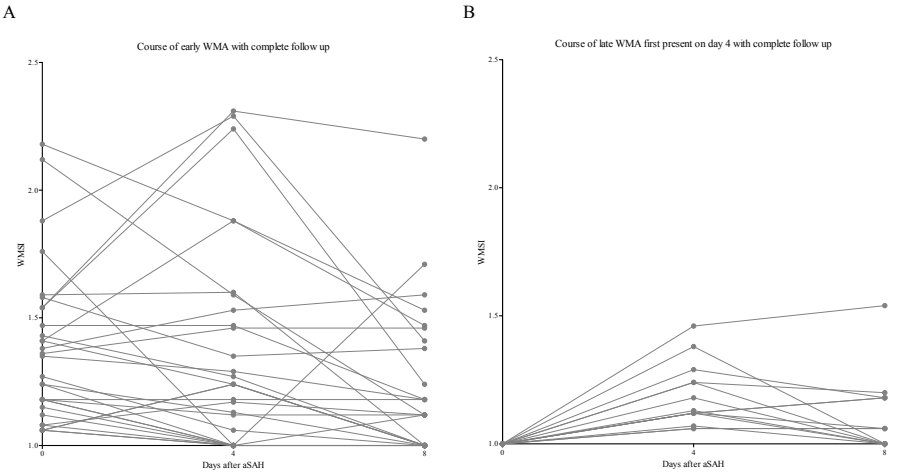

Figure 1: shows the dynamic nature of wall motion abnormalities by depicting the course of the wall motion score index (WMSI) over time. Panel A shows patients with WMSI > 1 on the admission echo. Panel B shows patients that had a normal WMSI on admission but developed a WMSI > 1 on the 4th day after the aSAH. NOTE: Only patients that completed follow-up are shown in this figure. 28 patients had WMSI>1 on admission but died or were discharged before the 4th or 8th day after the aSAH, these but are not shown in panel A.

Of the 58 patients with WMA on admission 36 had positive troponin T. Of the 16 patients with WMA on day 4 but no WMA on admission 7 had positive troponin T. Results from the sensitivity analysis after exclusion of patients with an episode of rebleeding were comparable with those of the main analysis. The WMA did not correspond to a single coronary territory. A pattern of WMA of the apical segments with hypercontractility of the basal segments, compatible with Takotsubo cardiomyopathy, was found in 25/271(9%) of patients.

Risk factors for early and delayed WMA:

Table 3 shows the univariable associations of the determinants and early and late WMA.

Table 3: shows the univariable ORs with determinants for early and late WMA.

Determinants*	Early WMA	Late WMA
Age > 50 years	1.7(0.9-3.4)	0.6(0.3-1.5)
Female sex	0.6(0.3-1.2)	0.9(0.4-2.2)
Poor WFNS	3.0(1.6-5.5)‡	1.1(0.5-2.6)
Hijdra >19	1.4(0.8-2.4)	0.9(0.4-2.2)
Acute hydrocephalus	0.6(0.3-1.1)	0.5(0.2-1.1)
Aneurysm in carotid circulation†	1.1(0.6-2.1)	1.9(0.8-4.4)
Sinusbradycardia	0.4(0.1-1.3)	0.5(0.1-2.4)
Sinustachycardia	3.3(1.3-8.9)‡	2.9(0.9-9.9)
Low voltage	3.2(0.8-11.8)	9.6(1.8-50.7) ‡
Pathologic Q wave	1.0(0.99-1.0)	1.0(0.99-1.0)
ST depression	5.8(2.4-14.4)‡	2.5(0.7-9.8)
ST elevation	31.8(3.8-264.5)‡	NE
Negative T-waves	2.4(1.3-4.8)‡	1.5(0.6-3.6)
Prominent U-waves	0.6(0.3-1.1)	1.1(0.5-2.7)
QTc prolongation > 500ms	1.7(0.8-3.7)	1.8(0.6-5.3)
LVH on ECG	0.7(0.5-1.1)	0.8(0.5-1.2)
Strain pattern on ECG	0.8(0.2-3.7)	0.9(0.1-7.8)
Myocardial infarction pattern	3.6(1.0-12.1)‡	8.0(2.0-32.2)‡
Elevated Troponin T	4.2(2.2-7.9)‡	3.9(1.6-9.7)‡
Elevated NT-proBNP	2.6(1.04-6.7)‡	1.6(0.5-5.2)
Decreased GFR	0.96(0.9-1.0)	0.99(0.9-1.1)

*The ORs of medical history (angina pectoris, myocardial infarction, prior coronary artery bypass graft(CABG), prior angioplasty, known hypertension, hypercholesterolemia, peripheral vascular disease, cerebrovascular events(ischemic or hemorrhagic), diabetes mellitus, current cigarette smoking or family history of coronary artery disease) with early and late WMA are not shown as they were not significantly associated. † includes anterior communicating artery, anterior cerebral artery, middle cerebral artery and internal carotid artery. ‡ These determinants were included in the multivariable analyses. Abbreviations: LVH: Left ventricular hypertrophy; WMA: wall motion abnormalities; GFR: glomerular filtration rate. NE: not estimable.

In the multivariable analyses (determinants marked in table 3), poor WFNS OR 2.7 (1.1-6.8), sinus tachycardia OR 5.0 (1.3-19.9), ST-depression OR 3.7 (1.02-13.1), ST-elevation OR 16.6 (1.5-178.9) and elevated troponin T OR 2.8 (1.1-7.3) predicted early WMA. Myocardial infarct pattern on the admission ECG with an OR 6.8(1.6-30) and elevated troponin T on admission with an OR 3.4 (1.4-8.5) predicted late WMA.

Discussion

WMA after aSAH may be present on admission, but can also develop during the course of the aSAH without a preceding rebleeding. Abnormal admission ECG (sinus tachycardia, ST-segment elevation or –depression) and positive troponin T are risk factors for early WMA, and a myocardial infarct pattern on the admission ECG and positive troponin T also predicts late WMA. The generally accepted hypothesis is that following the initial bleed a catecholamine release by the sympathetic nerve endings in the myocardium is responsible for the observed cardiac abnormalities.[8, 17-19] Myocardial ischemia or infarction as a cause for the abnormalities is unlikely as normal myocardial perfusion was reported after aSAH.[17] Risk factors for CAD such as smoking and hypertension were not associated with WMA in the univariable analyses, nor were the WMA associated with the perfusion territory of a single coronary artery. Nevertheless, we cannot exclude that at least in some patients the cardiac abnormalities were related to myocardial ischemia as some of the included patients, with risk factors for cardiovascular disease, may have had asymptomatic coronary artery disease (CAD). This is supported by our finding that an ECG compatible with an acute myocardial infarction predicts late WMA.

Our study is not unique in investigating prognostic significance of cardiac abnormalities after SAH. However, it distinguishes from other studies as only few studies investigated the time course of the WMA, [7, 10] and we could not find any studies that investigated risk factors for late WMA. The studies published so far have given contradicting results on the associations between troponin release, [3, 10, 20] BNP release [21] and WMA on admission. Differences in study design, definitions of determinants and outcomes, and also assay (e.g. NT-proBNP versus of BNP) might explain the discrepant findings between studies. Moreover, most of the previous studies were retrospective, monocenter, or had a smaller sample size than our study. The prospective studies that have been performed used admission determinants disregarding the dynamic nature of the WMA.

Although our study was prospective, multicenter, and used predefined definitions for the clinical determinants, it still has some potential limitations. The number of patients with late development of WMA is rather small, which limits the power for analysis on risk factors for late development of WMA. This is partly due to missing data of the last investigation, mostly because patients had died or were discharged. Another potential limitations lies in the study design as observational studies are prone for several forms of bias.[22] However, by using strict definitions for all determinants

and using liberal inclusion criteria we are confident we minimized potential bias. Another possible limitation of observational studies is the generalizability to large population cohorts. By designing this study as a multicenter national project in which the majority of the Dutch aSAH treatment centers participated, we are confident we minimized this limitation. Finally, we have no information on coronary arteries in our patients as coronary angiograms or cardiac CT scans were not routinely performed.

The potential clinical benefit of our study is that troponin T may allow us to early identify patients with a risk of developing early and late WMA. As delayed cerebral ischemia(DCI), an important prognosticator for poor outcome, usually occurs 4-7 days after the aSAH,[23] the occurrence of late WMA may play an important role in the development of DCI. However, this needs further investigation. We suggest that patients with troponin T elevation after an aSAH are closely monitored and that cardiac evaluation is performed to evaluate presence of WMA. Our data suggest that therapy aimed at restoring LV function if the troponins are increased but WMA are not (yet) present may be beneficial. However, the present study does not answer the pathophysiologic question why positive troponins are risk factors for early and late WMA. We hypothesize that cardiac abnormalities may manifest as a spectrum with some patients having ECG changes, troponin release and a severe impaired left ventricular function. Others may present with only ECG changes and they may develop troponin release or WMA in a later phase of the disease. Furthermore, we cannot exclude that treatment such as triple H therapy, Nimodipine or vasopressors also plays a role. These questions warrant more research.

Indeed, some studies have suggested that the use of ß-sympaticomimetics, phosphodiesterase inhibitors or calcium sensitizers can improve LV function.[24, 25] As calcium overload due to the sympathetic catecholamine surge is suggested to be the mechanism of the WMA,[26] these drugs should be effective in recruiting inotropic reserve. However, a drop in blood pressure and left ventricular outflow tract obstruction is reported after the use of for example dobutamine which may be especially harmful in patients with aSAH as cerebral perfusion must be optimized. Furthermore, the cardiac effects of aSAH treatment, for example administration of nimodipine, a calcium antagonist to prevent cerebral vasospasm, are also unknown. Therefore, before implementing such strategies, it is critical that large randomized clinical trials are performed to evaluate any potential therapeutic consequence of our findings.

Conclusion:

We found that WMA may be present on admission or develop during the course of aSAH. Poor neurological condition on admission, sinus tachycardia, ST-depression and ST-elevation at the admission ECG and elevated troponin T, are independent predictors for early WMA, a myocardial infarct pattern on the admission ECG and elevated troponin T independently predict late WMA. This allows the treating physicians to identify patients at higher risk, possibly influencing clinical management. More research should be directed towards treatment option of WMA after aSAH.

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CHAPTER 5

Relationship between cardiac dysfunction and cerebral perfusion in patients with aneurysmal subarachnoid hemorrhage

Cremers CH, van der Bilt IAC, van der Schaaf IC, Vergouwen MD, Dankbaar JW, Cramer MJ, Wilde AA, Rinkel GJ, Velthuis BK.
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Abstract

Introduction: Cardiac dysfunction may occur after aneurysmal subarachnoid hemorrhage (aSAH). Although it is associated with poor outcome, the pathophysiological mechanism of this association remains unclear. We investigated the relationship between cardiac function and cerebral perfusion in patients with aSAH.

Methods: We studied 72 aSAH patients admitted within 72 hours after ictus with echocardiography and cerebral CT perfusion within 24 hours after admission. Cardiac dysfunction was defined as myocardial wall motion abnormalities or positive troponin. In patients with and without cardiac dysfunction, we calculated mean perfusion (cerebral blood flow (CBF) and time to peak (TTP)) in standard regions of interest and calculated differences with 95% confidence intervals (95%CI).

Results: In 35 patients with cardiac dysfunction minimal CBF was 15.83 mL/100g/min compared to 18.59 in 37 without (difference of means: -2.76; 95%CI:-5.43 to -0.09). Maximal TTP was 26.94 seconds for patients with and 23.10 seconds for patients without cardiac dysfunction (difference of means: 3.84; 95%CI:1.63 to 6.05). Mean global CBF was 21.71 mL/100g/min for patients with cardiac dysfunction and 24.67 mL/100g/min for patients without cardiac dysfunction (-2.96; 95%CI:-6.19 to 0.27). Mean global TTP was 25.27 seconds for patients with cardiac dysfunction and 21.26 for patients without cardiac dysfunction (4.01; 95%CI:1.95 to 6.07).

Conclusion: aSAH patients with cardiac dysfunction have decreased focal and global cerebral perfusion. Further studies should evaluate whether this relation is explained by a direct effect of cardiac dysfunction on cerebral circulation or by an external determinant, such as a hypercatecholaminergic or hypometabolic state, influencing both cardiac function and cerebral perfusion.

Introduction

Cerebral perfusion can be affected shortly after aneurysmal subarachnoid hemorrhage (aSAH).[1] Cardiac dysfunction, consisting of echocardiographic wall motion abnormalities (WMAs), ECG changes and positive troponins suggestive of myocardial damage, may also occur after aSAH. The WMAs are independently associated with poor outcome after aSAH.[2] The pathophysiology behind this finding is unclear. To investigate whether the increased risk of poor functional outcome in patients with cardiac dysfunction[2] is explained by lower cerebral perfusion, a first step is to identify whether a relationship between cardiac function and cerebral perfusion exists. Therefore the aim of this study was to investigate the relationship between cardiac dysfunction and cerebral perfusion in patients with aSAH.

Methods

Design

Patients were retrieved from a prospectively collected series of aSAH patients who were admitted to the University Medical Center Utrecht between 2005 and 2008 and participated in the SEASAH (Serial Echocardiography After SubArachnoid Hemorrhage) study.[2] Patients enrolled in the SEASAH study had to be admitted within 72 hours after ictus and underwent echocardiography and blood testing within 24 hours after admission. As part of routine care in our institution all patients with aSAH undergo non-contrast CT (NCCT), CT perfusion (CTP) and CT-angiography (CTA) on admission, unless contrast contraindications exist. The SEASAH study was approved by the national and local hospital medical ethics committees. Informed consent was obtained from the patient or next of kin.

Echocardiography and troponin release

Transthoracic echocardiography was performed within 24 hours after admission. Two cardiologists, unaware of clinical and cerebral perfusion data, independently assessed the presence or absence of WMAs according to American Society of Echocardiography standards.[3] More details on the scoring of WMAs are published earlier.[2] For assessment of troponin release, the upper limits of normal as defined by the local laboratory were used as reference. Patients were dichotomized in "cardiac dysfunction" (with WMAs or positive troponins) or "no cardiac dysfunction" (no WMAs and negative troponins).

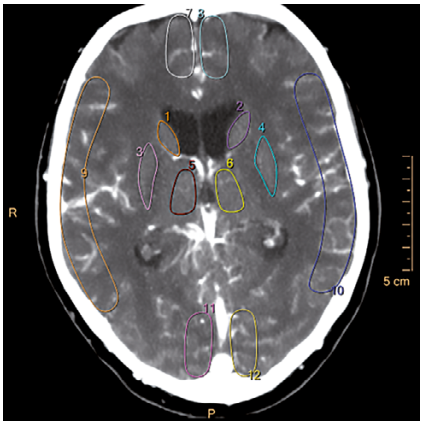
CT imaging

CT imaging was performed on 16- or 64-multidetector CT scanners (Philips Healthcare). For CTP, 40 mL of non-ionic contrast agent (lopromide, Ultravist, 300 mg iodine/mL, Schering) followed by 40 mL saline was injected intravenously at a rate of 5 mL/s. One image per 2 seconds was acquired during 60 seconds, with 512x512 matrix, 160-220 mm field-of-view, and UB filter. Scan parameters were: 16 slice, 90 kVp, 150 mAs, 8x3 mm collimation; 64 slice, 80 kVp, 150 mAs, 64x0.625 mm collimation. Depending on the multidetector type CT scanner, for the CTA scan another 60-80 mL of contrast was injected at a rate of 5 mL/s, followed by a 40 mL saline flush at a rate of 5 mL/s. Imaging was performed with: 90-120 kVp, 150–300 mAs, 512x512 matrix, 200 mm field of view, 0.9–1 mm slice thickness, and 0.45–0.5 mm reconstruction increment.

CTP post-processing

CTP maps were evaluated on a workstation (Intellispace Portal, Philips Healthcare). A tracer delay insensitive algorithm was used to calculate the perfusion maps. Twelve regions of interest (ROIs) were drawn in the peripheral (cortical) and deep (basal ganglia) flow territories of the anterior (ACA), middle (MCA) and posterior cerebral artery (PCA) (Figure 1).

Figure 1: Standard regions of interest in the peripheral (cortical) and deep (basal ganglia) flow territories of the anterior, middle and posterior cerebral artery.



Quantitative values for cerebral blood flow (CBF) and time to peak (TTP) were obtained for each ROI. We chose CBF as a measure of cerebral perfusion and TTP to represent contrast delay. The ROI with the lowest CBF value and the ROI with the highest TTP value of the 12 ROIs was selected, as this represents the brain tissue with the lowest perfusion. In addition, we calculated the mean global CBF and TTP of all the ROIs.

CTA imaging

All admission CTAs were evaluated in consensus by two experienced radiologists (IvdS, BKV). Early vasospasm was interpreted as none to mild (<25%), moderate (25-50%) or severe (>50%) arterial narrowing that could not be attributed to atherosclerosis.[4]

Analyses

In patients with and without cardiac dysfunction we compared minimal CBF and maximal TTP values on CTP to compare focal perfusion deficits and mean CBF and TTP values to compare global perfusion. Differences of means with 95% confidence intervals (95%CI) were calculated.

Results

We included 72 aSAH patients, of whom 35 had cardiac dysfunction; 11 with both WMAs and positive troponins, 5 had WMAs but negative troponins, and 19 had positive troponins and no WMAs (Table 1). Patients with cardiac dysfunction had a worse clinical condition on admission compared to patients without cardiac dysfunction. The amount of extravasated blood on admission was comparable between patients with and without cardiac dysfunction (Table 1).

Table 1: Patient characteristics

	Cardiac dysfunction (n=35)	**No cardiac dysfunction (n=37)**
Women	29 (83%)	28 (76%)
Age (mean, range)	61.9 (41.1 – 85.7)	58.1 (26.9 – 87.6)
Amount of extravasated blood (Hijdra score*) on admission (median, range)	17 (0 – 29)	19 (0 – 32)
Clinical condition (WFNS-score) on admission		
I	8 (23%)	24 (65%)
II	7 (20%)	5 (14%)
III	5 (14%)	2 (5%)
IV	7 (20%)	4 (11%)
V	8 (23%)	2 (5%)
Aneurysm location		
Internal carotid artery	3 (9%)	2 (5%)
Anterior communicating and cerebral arteries	18 (51%)	19 (51%)
Middle cerebral artery	4 (11%)	6 (16%)
Posterior communicating artery	3 (9%)	8 (22%)
Vertebrobasilar circulation**	7 (20%)	2 (5%)
Aneurysm treatment		
Clip	7 (20%)	14 (38%)
Coil	25 (71%)	23 (62%)
None	3 (9%)	0 (0%)

n = number; WFNS = World Federation of Neurological Surgeons.
* Hijdra score describes the amount of blood in the cisternal and ventricular spaces.[10]
** Including vertebral, basilar, cerebellar and posterior cerebral arteries.

Mean CBF of the ROI with the lowest value was 15.83 mL/100g/min for patients with cardiac dysfunction and 18.59 mL/100g/min for patients without cardiac dysfunction (difference of means: -2.76; 95%CI:-5.43 to -0.09). Mean global CBF was 21.71 mL/100g/min for patients with cardiac dysfunction and 24.67 mL/100g/min for patients without cardiac dysfunction (-2.96; 95%CI:-6.19 to 0.27). Mean TTP of the ROI with the highest value was 26.94 seconds for patients with and 23.10 seconds for patients without cardiac dysfunction (difference of means 3.84; 95%CI:1.63 to 6.05). Mean global TTP was 25.27 seconds for patients with cardiac dysfunction and 21.26 for patients without cardiac dysfunction (4.01; 95%CI:1.95 to 6.07) (Table 2).

Table 2: Perfusion values (with 95% confidence intervals)

	Cardiac dysfunction (n=35)				No cardiac dysfunction (n=37)
	All	WMAs and positive troponins (n=11)	WMAs only (n=5)	Positive troponins only (n=19)	
Focal perfusion					
Minimal CBF (mL/100g/min)	15.83 (14.17-17.49)	16.13 (12.22-20.03)	17.14 (10.16-24.11)	15.32 (13.30-17.34)	18.59 (16.47-20.72)
Maximal TTP (s)	26.94 (25.56-28.32)	28.39 (26.10-30.67)	24.81 (20.14-29.48)	26.66 (24.60-28.72)	23.10 (21.34-24.85)
Global perfusion					
Mean CBF (mL/100g/min)	21.71 (19.87-23.55)	22.47 (18.05-26.88)	23.03 (15.63-30.42)	20.93 (18.72-23.13)	24.67 (21.99-27.35)
Mean TTP (s)	25.27 (23.97-26.56)	26.56 (24.71-28.42)	22.98 (18.23-27.73)	25.12 (23.14-27.10)	21.26 (19.63-22.88)

n = number; WMAs = wall motion abnormalities; CBF = cerebral blood flow; TTP = time-to-peak.

Early vasospasm was seen in only two patients (2.8%) on admission CTA. One patient had severe (>50%) arterial narrowing of the right MCA bifurcation in the presence of a MCA aneurysm, substantial SAH and a large intracerebral hematoma. The lowest perfusion values were also seen in the right MCA territory. The other patient had more diffuse bilateral moderate (25-50%) narrowing of both MCA and ACA in the presence of an anterior communicating artery aneurysm. In this patient lowest perfusion values were seen in the right thalamus and the right PCA territory. Both patients with early vasospasm were in the subgroup with cardiac dysfunction, one had increased troponins and one patient had WMAs. Excluding these two patients did not change the results.

Discussion

The results of our study show that aSAH patients with cardiac dysfunction have an impaired cerebral perfusion, both on a focal and global level.

Cardiac complications following central nervous system events such as ischemic or hemorrhagic stroke, brain tumors and even emotional stress have been described extensively.[5-6] In recent years there has been increasing interest in this "heart-brain axis" and its clinical implications. Early onset cardiac and cerebral dysfunction are both related to poor outcome after aSAH.[2,7] Understanding the pathophysiology

of this early heart-brain dysfunction may have implications for preventing cerebral hypoperfusion after aSAH and therefore for better outcome.

The clinical impact of lower cerebral perfusion is not well understood, as it is unknown at what perfusion value thresholds patients develop cerebral ischemia in the context of aSAH. We could not study the influence of elevated intracranial pressure as a possible cause of cerebral hypoperfusion, as ICP measurements are not part of routine care in all aSAH patients in our hospital. Moderate to severe early vasospasm (≥25% arterial luminal narrowing) was only seen in 2 patients on CT angiography that was performed on admission in all patients.

The worse clinical condition in patients with cardiac dysfunction might therefore be explained by a lower cerebral perfusion caused by cardiac dysfunction, or by a systemic determinant that influences both cardiac dysfunction and cerebral perfusion, such as the hypercatecholaminergic response. Excessive release of norepinephrine from myocardial sympathetic nerve terminals may lead to denervation of both the myocytes and the nerve terminals and thereby to focal WMAs and cardiac dysfunction.[8] In addition, this systemic hypercatecholaminergic response might also cause dysfunction of the cerebral autoregulation and thereby lead to perfusion deficits in the brain. Other potential mechanisms underlying early cerebral hypoperfusion after aSAH are endothelial dysfunction resulting from both the initial hypoperfusion insult as well as the pro-inflammatory, pro-thrombotic and pro-vasoconstriction properties of extravasated subarachnoid blood. Another possible explanation is a hypometabolic state, which was also found to be associated with the early cerebral hypoperfusion in a PET study in SAH patients.[9]

In this study we investigated whether a relationship between cardiac function and cerebral perfusion exists in patients with aSAH. We were unable to determine whether this is a causal relationship.

Further studies need to evaluate whether cerebral hypoperfusion occurring soon after aSAH is explained by cardiac dysfunction or by an external determinant, such as a hypercatecholaminergic reaction or hypometabolic state, influencing both cardiac function and cerebral perfusion. Future studies could also investigate whether treatment of cardiac dysfunction or a systemic response, improves cerebral perfusion and thereby prognosis.

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CHAPTER 6

Myocarditis in patients with subarachnoid hemorrhage: a histopathological study

van der Bilt IAC, Vendeville JP, van de Hoef TP, Begieneman MPV, Lagrand WK, Kros JM, Wilde AAM, Rinkel GJE, Niessen HWM. J *Crit Care.* 2015 Dec 11 *epub ahead of print*.

Abstract:

Introduction: Cardiac abnormalities after subarachnoid hemorrhage (SAH) such as ECG changes, echocardiographic wall motion abnormalities and elevated troponin levels, are independently associated with a poor prognosis. They are caused by catecholaminergic stress coinciding with influx of inflammatory cells into the heart. These abnormalities could be a sign of a myocarditis, potentially giving insight in pathophysiology and treatment options. These inflammatory cells are insufficiently characterized, and it is unknown whether myocarditis is associated with SAH.

Methods: Myocardium of 25 patients who died from SAH and 18 controls was stained with antibodies identifying macrophages (CD68), lymphocytes (CD45) and neutrophil granulocytes (MPO). Myocytolysis was visualized using complement staining (C3d). CD31 was used to identify putative thrombi. We used Mann-Whitney-U testing for analysis.

Results: In the myocardium of SAH patients the amount of MPO ($p<0.005$), CD45 ($p<0.0005$), and CD68 ($p<0.0005$) positive cells was significantly higher compared to controls. Thrombi in intramyocardial arteries were found in 22 SAH patients and 1 control. Myocytolysis was found in 6 SAH patients but not in controls.

Conclusion: Myocarditis, consisting of an influx of neutrophil granulocytes, lymphocytes and macrophages, coinciding with myocytolysis and thrombi in intramyocardial arteries, occurs in patients with SAH but not in controls. These findings might explain the cardiac abnormalities after SAH, and may have implications for treatment.

Introduction

Cardiac dysfunction following subarachnoid hemorrhage (SAH), such as ECG changes, wall motion abnormalities and troponin release, occurs frequently and is associated with poor prognosis.[1] The massive sympathetic activation following the SAH leads to a catecholamine release in the myocardium which is thought to cause these cardiac abnormalities.[2] On a cellular level, catecholamine release has been associated with myocardial damage.[2-6] Literature is limited and early pathology studies that reported on myocardial cellular infiltration and myocytolysis following SAH, using immunohistochemical staining[7] , did not classify the inflammatory response nor did they specify the types of inflammatory cells in the heart. According to the Dallas criteria, myocardial infiltration of inflammatory cells and myocytolysis qualifies as a myocarditis.[8] Myocarditis after SAH has never been established but is a plausible explanation in the pathway from catecholamine release; it may explain the cardiac abnormalities and may have important clinical implications for treatment and prognosis. Therefore, the objectives of the present study were to characterize the infiltration of inflammatory cells in the heart after SAH compared to controls, to investigate whether this cellular infiltration meets criteria for the diagnosis myocarditis and to search for other myocarditis stigmata such as myocytolysis and intra-arterial thrombi.

Methods

Patients' Selection

Myocardium of patients who died from SAH between 1994 and 2004 was obtained from the departments of Pathology of the VU University Medical Center Amsterdam, the Netherlands and the Erasmus Medical Center Rotterdam, the Netherlands. The pathology databases were searched for cases in which SAH was documented as cause of death, as indicated by the clinician requesting autopsy, in concomitance with the presence of subarachnoid blood documented in the autopsy report. As a control group, myocardium of oncologic patients without cardiac involvement of the disease whom did not receive cardiotoxic chemotherapy or radiotherapy in the cardiac region was obtained. Control patients who died from a neurological disease or potentially suffered from an underlying disease associated with cardiac inflammation, e.g. sepsis, were excluded. The study was approved by and performed according to the guidelines

of the local medical ethics committee, and in accordance with the Declaration of Helsinki. Use of material for research after completion of a pathological examination is part of the patient contract in the participating hospitals.

Immunohistochemistry

The heart tissue samples of both the SAH patients and the control subjects were fixed in 4% buffered formaldehyde solution and embedded in paraffin for the preparation of 4 μm sections. Sections were then dewaxed, dehydrated, and antigen retrieval was performed by boiling in 10 mM sodium citrate buffer, pH 6.0, for 10 minutes in a microwave oven. Sections were pre-incubated with normal serum for 10 minutes. Rabbit serum was used for monoclonal antibodies; swine serum was for polyclonal antibodies. Pre-incubation was followed by incubation with primary antibodies for 1 hour.

The primary antibodies that we used are: Myeloperoxidase (MPO), mouse anti-human CD68, mouse anti-human CD45, rabbit anti-human Complement C3d and mouse anti-human CD31, all from Dako Cytomation, Denmark.

Sections were subsequently rinsed in Phosphate Buffered Saline (PBS), and incubated with a biotin-labeled secondary antibody (Rat-anti-Mouse-biotin (RαM-biotin) or Swine-anti-Rabbit-biotin (SαR-biotin)) for 30 minutes. After washing in PBS, sections were incubated with streptavidin-biotin complex/HRP (sABC/HRP) for 1 hour. After the sABC/HRP incubation, sections were rinsed with PBS, followed by visualization with 3,3'-diaminobenzidine (DAB 0.1 mg/mL, 0.02% H202). Sections were subsequently counterstained with hematoxylin, dehydrated and covered. As a control, the same staining procedure was used, but instead of primary monoclonal or polyclonal antibody, PBS was used.

Morphometric analysis

Two observers (I.B., W.L) scored the number of extravascular neutrophil granulocytes (MPO positive), lymphocytes (CD45 positive) and macrophages (CD68 positive). This was done by counting the number of positive cells within a fixed grid drawn on the microscopic slide with the specimen. To minimize inter-observer variability, some of the slides were scored on a two person multi-viewing microscope, some were done separately. Additionally a third observer, an experienced pathologist, checked samples at random. Both observers were blinded with respect to the origin of the slides (SAH versus controls). In case of significant differences in scoring results between the 2 observers, both observers examined the same myocardial slides simultaneously.

After this, consensus was achieved by the 2 observers. The number of extravascular inflammatory cells per 100 mm^2 was then calculated. Myocytolysis was defined as Complement (C3d) positivity of cardiomyocytes. Finally, the number of putative thrombi (CD31 positive) in intramyocardial arteries was scored and calculated per 100 mm^2. Myocarditis was classified according the Dallas criteria as "myocarditis": an aggregation of inflammatory cells in the myocardium coincided with areas of myocytolysis, or "borderline myocarditis": when aggregation of inflammatory cells in the myocardium was documented without myocytolysis.

Statistical analysis

Distribution of data was checked using Kolmogorov-Smirnoff analyses. After that, non-parametric testing using Mann-Whitney U was used for differences between groups. A sensitivity analysis was performed for patients with a proven aneurysm on autopsy and the patients with SAH without an aneurysm. A p-value <0.05 was considered statistically significant.

Results

Myocardial tissue samples of 25 patients were retrieved from the pathology databases. Baseline characteristics could be retrieved for 23 patients. Mean age was 59(±SD15) years of age, and 11 patients (44%) were female. In 16 patients (64%) a culprit aneurysm was reported on autopsy. Duration from hospital admission to death ranged from 2 hours to 21 days. As depicted in Figure 1, there was a large spread in the number of cells per individual patient.

Myocardial tissue of 18 control patients was used as a control group. Figure 2 shows the mean number of cells in SAH patients compared to controls. Compared to the control group, the amount of MPO, CD45, and CD68 positive cells was significantly higher in SAH patients (p<0.005 for all).

Figure 1: Number of myeloperoxidase (MPO), CD45 and CD68 positive cells per individual patient. The horizontal axis represents individual patients with SAH.

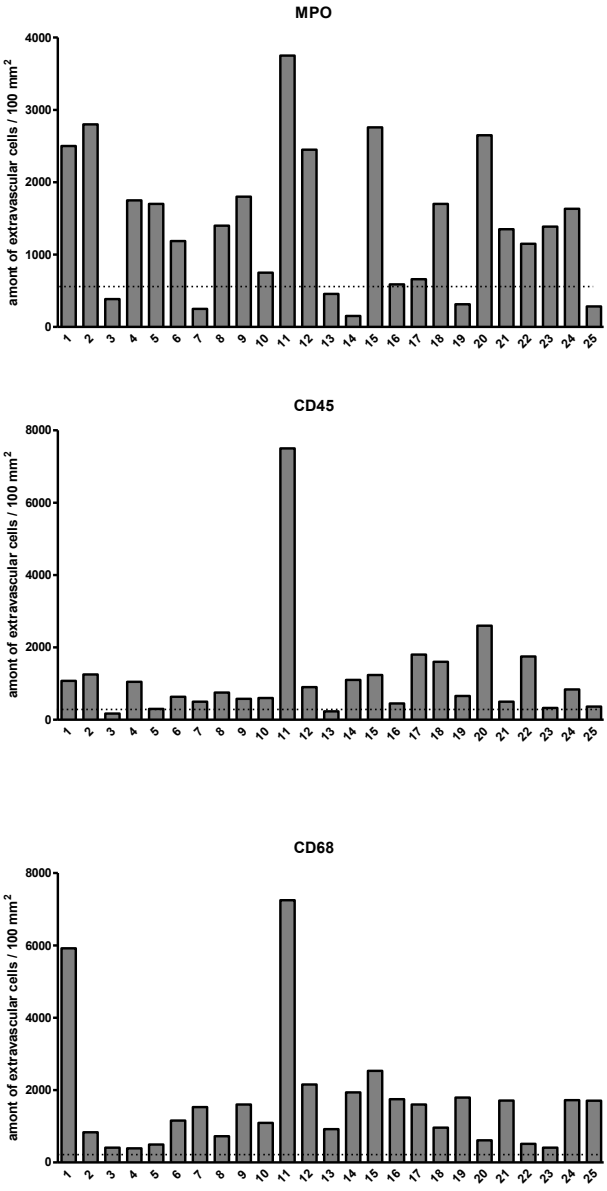
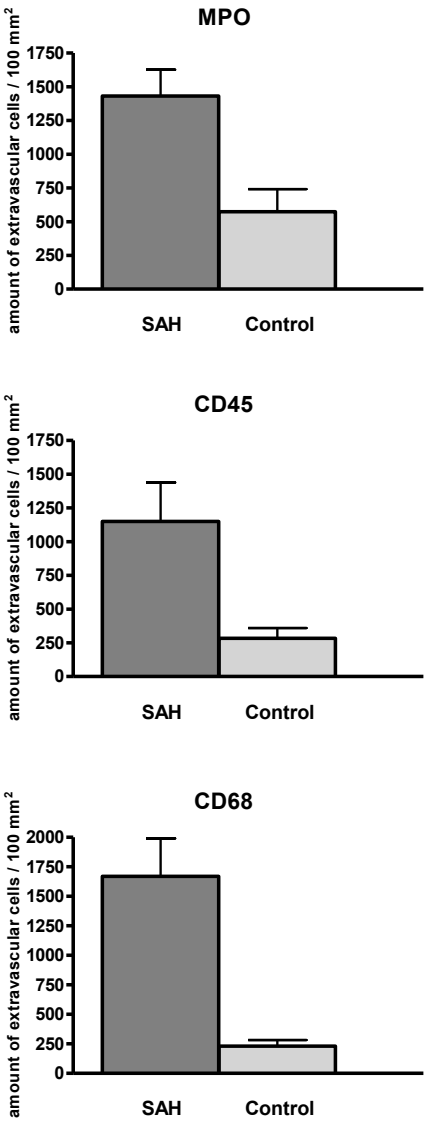


Figure 2: Mean number of myeloperoxidase (MPO), CD45 and CD68 positive cells in SAH and to controls with standard deviations. Compared to the control group, in SAH patients the amount of MPO ($p<0.005$), CD45 ($p<0.0005$), and CD68 ($p<0.0005$) positive cells was significantly higher.



In six patients with SAH (24%) spots with C3d positive cells, indicating myocytolysis, were documented, and these patients consequently fulfilled the Dallas criteria for myocarditis. In contrast, no C3d positive cells were documented in the controls. Intramyocardial thrombi were found in 22 SAH patients (88%), and in only

one control patient. Sensitivity analyses showed no difference in the number of inflammatory cells or myocytolysis in patients with- or without proven aneurysm.

Discussion

In the present autopsy study we documented an influx of neutrophil granulocytes, lymphocytes and macrophages into the myocardium of patients who died following SAH. In some this coincided with myocytolysis and thrombi in intramyocardial arteries. According to the Dallas criteria this finding suggests that patients with SAH have a borderline myocarditis and some have a myocarditis.

Although other studies have reported on myocardial cellular infiltration and myocytolysis after SAH, classification of the inflammatory cells is not described before and we could not find previous studies establishing myocarditis after SAH. Most studies focused on the myocardial cell damage after SAH, only a few studies used immunohistochemical staining methods which were not specific for the type of cell.

There is overwhelming evidence from clinical and experimental studies that catecholaminergic stress after acute cerebral lesions causes myocardial cell damage.[3, 9-16] However, influx of inflammatory cells in the myocardium was not investigated.

Intramyocardial catecholamine release by sympathetic nerve endings has been suggested as the primary source of the catecholamines, since experimental SAH studies showed no myocardial damage following SAH in sympathectomized baboons, while extensive myocardial damage was documented in adrenalectomized dogs.[17] This hypothesis is supported by the finding that cardiomyocytolysis after SAH is more prevalent in the direct surrounding of the sympathetic nerve terminals.[18]

We found evidence of thrombi in the intramyocardial arteries. It is known that myocarditis may cause vasospasm which may cause the formation of thrombi. Thrombi might cause obstruction of the microarteries thus causing myocardial infarction.[19, 20] Several other studies reported patchy subendocardial infarction after SAH, suggesting that thrombi, and likely myocarditis, were present in these cases as well.[6, 12, 21]

The clinical relevance of our study is that treatment of cardiac abnormalities after SAH may improve outcome as they are associated with poor outcome independent of other clinical parameters.[22] Our finding that myocarditis with microvascular thrombosis occurs in patients who die from SAH, has some potential clinical

implications. As treatment with inotropics, or sometimes even immunosuppressives may be beneficial in infectious myocarditis, we speculate that these treatments can be beneficial in SAH patients as well. Additionally, the myocardial microthrombosis found in this study suggests that antithrombotic therapy is an interesting treatment option in SAH patients. This suggestion is further supported by the finding that intracranial microthrombosis probably plays a role in the pathogenesis of DCI after SAH.[23] However, this is speculative and more research should be done to substantiate this.

Other conditions with acute catecholaminergic stress such as pheochromocytoma[24] or pulmonary embolism[25] have also been associated with myocarditis. Moreover, stress cardiomyopathy also known as Takotsubo cardiomyopathy, which is caused by acute sympathetic stress, has been linked to myocarditis using cardiac magnetic imaging that showed edema and late gadolinium enhancement indicating inflammation.[26] However, whether the catecholamine myocarditis is a reaction to cell damage or that catecholamines trigger another pathway (e.g. apoptosis of endothelial cells) that attracts the inflammatory cells is unknown.

Although we feel our study sufficiently shows evidence of a myocarditis in patients with SAH compared to controls, our study has shortcomings. Because we performed a retrospective search of the pathology database, detailed clinical data were unavailable to us. Because the reason of the clinician to request an autopsy was often unknown, this includes the risk of bias. Thus, we cannot draw conclusions on the proportion of SAH patients that have myocarditis. A prospective histopathology study is needed to answer these questions. Another limitation is that autopsy did not confirm the presence of an aneurysm in all patients. Brain autopsy was not performed in all patients, because it requires additional consent, which is often not given by the family if the cause of death obviously was an intracranial one. For these patients we had only information provided by the clinicians written on the autopsy form, which is often rather limited. However, if neurologists or neurosurgeons write SAH as clinical information, they usually mean SAH from an aneurysm and not traumatic SAH invariably. Given the fact that these patients had died from SAH, an aneurysm, or other arterial course of the SAH such as intracranial artery dissection is likely. Moreover, the sensitivity analysis excluding the patients without an aneurysm found similar results as in the main analysis.

Conclusion

Myocardial infiltration by macrophages, lymphocytes and neutrophil granulocytes coinciding with intramyocardial thrombi occurs frequently in patients with SAH. This indicates the presence of a myocarditis. Cardiac involvement after SAH expressed as myocarditis could explain the cardiac abnormalities observed following SAH. As cardiac abnormalities in SAH result in a worse prognosis, in consideration of the potential therapeutic and prognostic implications, further research aimed at recognition and treatment of myocarditis such as anti-inflammatory drugs, antithrombotic therapy or inotropics after SAH is warranted.

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CHAPTER 7

General Discussion

This thesis centers on the cardiac abnormalities that are associated with aneurysmal subarachnoid hemorrhage (aSAH). It is based on two observations: 1. The notion that cardiac abnormalities occur frequently after aneurysmal subarachnoid hemorrhage (aSAH) and that they might worsen clinical outcome; 2. The notion that stress cardiomyopathy, "The broken heart syndrome" or Tako-tsubo cardiomyopathy is increasingly being reported after several forms of acute physical or emotional stress and that it has striking similarities with the cardiac abnormalities observed after aSAH.

Stress induced cardiac abnormalities, which may mimic an acute coronary syndrome and predominantly occur in postmenopausal women, present with ECG changes, left ventricular dysfunction and cardiac specific serum enzyme- and protein elevation (CK-MB, Troponins, and NT-proBNP). Typically, there is absence of obstructive coronary artery disease. The characteristic echocardiographic finding is an aneurysmal apex with a hyperdynamic base, which resembles the shape of a Japanese octopus trap called Tako-tsubo (in Japanese Tako means octopus and Tsubo means trap, see figure 1), hence the name Tako-Tsubo cardiomyopathy.

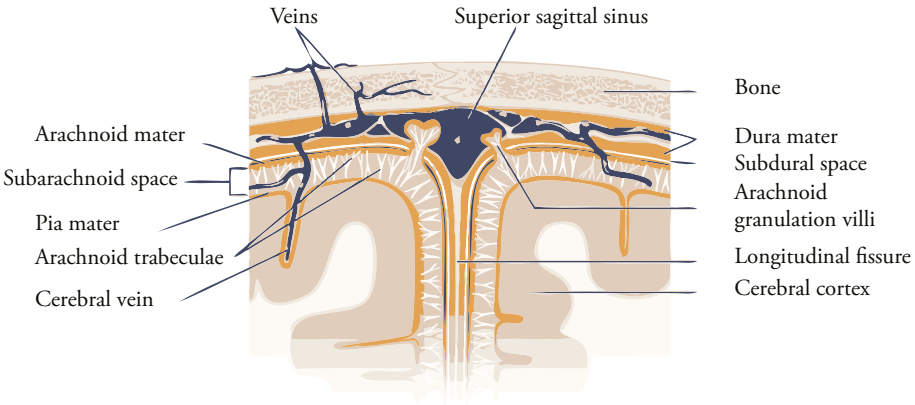
Figure 1: Japanese octopus trap or Takotsubo. The octopus swims into the pot that lies on the ocean floor with food in it. The octopus cannot swim out because of the narrow neck. Courtesy of prof. Yoshihiro Akashi, Hiroshima for providing the Takotsubo. Photo made by me.

However, other distributions of wall motion abnormalities may occur as well. These WMA are not related to the perfusion territory of a single coronary artery. The abnormalities are reversible after 1-2 weeks and prognosis is reported to be excellent. Although reports and studies on stress cardiomyopathy are rapidly expanding, not much is known about this fascinating phenomenon. It is difficult to design reliable studies and estimate the sample size in a heterogeneous patient group with unknown prevalence and incidence of the disease that is subject of study. Most reports on stress cardiomyopathy are case reports or case series. Reports on incidence, predisposing factors, pathophysiology, prognosis or treatment are scarce and equivocal. Because aSAH is a disease with a poor outcome that is often complicated by cardiac abnormalities, we decided to use aSAH as a model for acute sympathetic stress and study the incidence, clinical characteristics and impact on outcome of stress cardiomyopathy after aSAH.

Aneurysmal subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage is caused by rupture of a saccular aneurysm usually in the circle of Willis. Blood enters the subarachnoid (spider web) space under high pressure. The subarachnoid space is the anatomic space between the dura mater and the pia mater (figure 2).

Figure 2: Schematic drawing of the layers of the skull and subarachnoid space. From Wikipedia, usage under creative commons license (CMC)



This space is filled with trabeculae, giving it its spider web appearance, and contains cerebrospinal fluid. Typical symptoms of aSAH are acute onset "thunderclap" headache described as the worst headache patients have ever experienced. In the

acute phase there may be an altered- or loss of consciousness, nausea or vomiting. Coma and seizures are associated with poor outcome. The annual incidence of aSAH adjusted for age and sex, is 7.5-12.9 per 100,000 population per year. This devastating neurological disorder accounts for 22-25% of cerebrovascular deaths[1]. Improvement of medical treatment has led to an improvement of outcome in patients with aSAH[2], although the mainstay of treatment remains obliteration of the aneurysm. Postoperative care is based on optimizing cerebral oxygenation, which is dependent on oxygenation of blood, oxygen transport capacity of the blood, and cerebral perfusion. A common complication with a negative impact on outcome is delayed cerebral ischemia (DCI) which usually occurs 4-7 days after the aSAH. This may be caused by multiple factors among which are vasospasm and hydrocephalus. Cerebral perfusion may be influenced by a number of other factors, among which, importantly, are cardiac output and blood pressure. The cardiac abnormalities after aSAH are sometimes accompanied by a drop in cardiac output and blood pressure, hence influencing patients' condition and neurological outcome unfavorable. In **Chapter 2** of this thesis we describe the results of our meta-analysis on the literature. We found that reported incidence varies widely. Furthermore, we found that cardiac abnormalities may be associated with poor outcome independent of other clinical variables. However, due to the limitation of the studies, no definitive conclusions could be made. We therefore launched the consecutive and prospective cohort study Serial Echocardiography After SubArachnoid Hemorrhage (SEASAH). The results of SEASAH are described in **Chapter 3** and **Chapter 4**. Most literature focuses on electrocardiographic abnormalities and/or echocardiographic abnormalities and/or biochemical changes. We analyzed and describe these cardiac investigations separately, although they all reflect on the same disease.

Electrocardiographic Changes and Cardiac Arrhythmia's

The first report of neurogenic electrocardiographic changes following a Central Nervous System (CNS) event occurred in 1938 when Aschenbrenner and Bodechtel[3] stated that intracranial lesions may be responsible for ECG changes. Byer[4] et al, in 1947, and Burch[5] et al in 1954, found that these ECG abnormalities occur frequently in association with SAH. Since then, the majority of studies focused on ECG changes in aSAH. However, several other acute CNS events have also been reported to cause such abnormalities.[6-20]

The frequency of ECG changes in association with SAH ranges between 50% and 90%[21-25]. This large interval may largely be explained by the different monitoring

methods used in these studies and difference in study population. Brouwers et al.[21] found that all patients with aSAH, monitored with serial ECG's, had ECG abnormalities. In the same study the authors found that poor outcome in patients with aSAH was associated with fast rhythm disturbances and/or electrocardiographic signs of cardiac ischemia. Arrhythmia's occurred in 91% of patients monitored by 24 hour ECG monitoring after the onset of aSAH[26]. Common ECG changes in aSAH are sinus bradycardia (50%), ST-segment changes (50%), T-wave abnormalities (48%), prominent U-wave (44%), QT interval abnormalities (39%), signs of left ventricular hypertrophy (36%), and sinus tachycardia (20%).[21, 23, 27] Recent studies show that ECG changes after aSAH are correlated with echocardiographic abnormalities and biochemical markers of myocardial damage. Studies on the predictive value of ECG changes on impaired left ventricular systolic dysfunction are conflicting. Mayer et al.[23], in 1995, found that the presence of T waves or QT interval prolongation on any ECG was associated with 100% sensitivity and 81% specificity for echocardiographic left ventricular dysfunction. Davies et al.[22] stated 15 years earlier that ECG changes have poor relation with echocardiographic abnormalities but are related to the severity of neurological injury. The latter is confirmed in a paper of Zaroff et al.[28], who also found that ECG changes have no independent predictive value for all-cause mortality. This is in accordance with a recent retrospective study of 159 patients[29] where ST depression was found to be more common in patients with poor outcome, but ECG changes were not independently related to outcome. The electrophysiological mechanism of the ECG changes seen in SAH remains unclear. Serum magnesium levels have been proposed as a possible factor. Van den Bergh et al.[30] found that lower serum magnesium levels are related to a long QTc interval.

In our meta-analysis which is described in **Chapter 2,** we found that Q waves, ST-segment depression, and T-wave abnormalities are associated with worsened clinical outcome. However in the multivariable analysis of the SEASAH study (**Chapter 3**) we found no independent clinical association of the ECG abnormalities with outcome, which indicated that they may be used as an indicator of cardiac dysfunction only. Patients with a normal ECG did not have cardiac dysfunction (unpublished). In conclusion, ECG changes occur frequently following aSAH, are related to a more severe neurological injury, but cannot be used as an independent predictor of outcome.

Left ventricular dysfunction

In addition to the ECG abnormalities described above, left ventricular systolic dysfunction has been described in patients with aSAH. Pollick et al.[31] provided the first evidence for this in an echocardiographic study. However, as with de ECG data, epidemiological data on the occurrence of the LV dysfunction are conflicting. This may be due to the retrospective nature of most echocardiographic studies, the timing of the echocardiogram, and the difference in study population. Cardiac dysfunction not only occurs immediately after the onset of aSAH, but may also present several days after the aSAH. Pathophysiological data are lacking but this late dysfunction may be provoked by the initial aSAH as troponin may be elevated in patients with late onset dysfunction. Another possibility is that late cardiac dysfunction is caused by delayed cerebral ischemia, or recurrent bleeding ('rebleeds'). The largest prospective study to date was done by Sato et al.[32] who performed echocardiography in 715 patients with aSAH. They found left ventricular dysfunction in 9.4% of the patients. This percentage might be underestimated because the authors only included patients with echocardiographic abnormalities on presentation to hospital. Patients with a normal LV function were not included in the study thus introducing selection bias.
Another interesting observation is that the distribution of the wall motion abnormalities may vary. Typically, the apex is dyskinetic with a hyperdynamic base (typical Tako-Tsubo), but reversed Tako-Tsubo (hyperkinetic apex and akinetic base), midventricular Tako-Tsubo (hyperdynamic apex and base but hypokinetic midventricular portion of the myocardium), global hypokinesia or other segmental wall motion abnormalities have also been observed. The wall motion abnormalities usually do not correspond with the perfusion territory of one coronary artery. This makes coronary insufficiency as a cause unlikely. Furthermore, patients that underwent coronary angiograms indeed did not show any occlusion of a coronary artery. Several other studies showed that the wall motion abnormalities are reversible, thus suggesting supportive management in patients with aSAH and myocardial dysfunction. An important strength of the SEAS study is the prospective and consecutive nature and the serial echocardiography. We found that left ventricular dysfunction occurs frequently and that it is reversible. It presents at different time intervals after the onset of the aSAH and it is associated with poor outcome independent of other clinical variables (**Chapters 3 and 4**).

Myocardial damage and biochemical changes

Although many of the electrocardiographic and echocardiographic abnormalities following aSAH are typically those seen with myocardial ischemia from coronary

artery disease, pathological studies[31, 33-35] and coronary angiography[32, 36-39] have repeatedly failed to demonstrate this form of injury in such patients. In contrast to the belief that neurogenic changes on ECGs reflect purely electrical phenomena, affected patients frequently show evidence of structural cardiac damage, such as subendocardial infarctions, contraction band necrosis and myofibrillar lesions. These were first reported in the early 1960's after acute cerebral lesions.[33, 35, 40-42] Focal myocardial necrosis was seen in animals after traumatic brain injury as early as the 1970s.[43] Elrifai et al.[44] performed electron microscopy on the myocardium of dogs with experimental SAH. Individual myocardial cell lesions with a swollen and loose appearance were described. The myocardial fibers appeared distorted and separated. Remarkably an unusual infiltration of fibroblasts and macrophages were present, indicating some form of inflammation. Several other authors describe the same microscopic finding.

Biochemical markers of myocardial damage are also frequently elevated and enzyme release seems to be related with the severity of the neurological injury.[45] We found that troponins are frequently elevated, are associated with poor outcome and that positive troponins on admission predict the occurrence of left ventricular dysfunction during admission (**Chapter 4**). Furthermore, in **Chapter 6** we describe myocarditis after aSAH. Data on troponins were lacking in that study, however it is plausible that the source of the troponins after aSAH is caused by an aseptic, catecholamine induced myocarditis. Clinical presentation of myocarditis consists of ECG changes, left ventricular dysfunction and positive troponins and this is similar to the changes observed after aSAH. Future studies are needed to elucidate not only the incidence and prevalence of this phenomenon, but also the identification of possible clinical predictive variables of myocardial damage and treatment options.

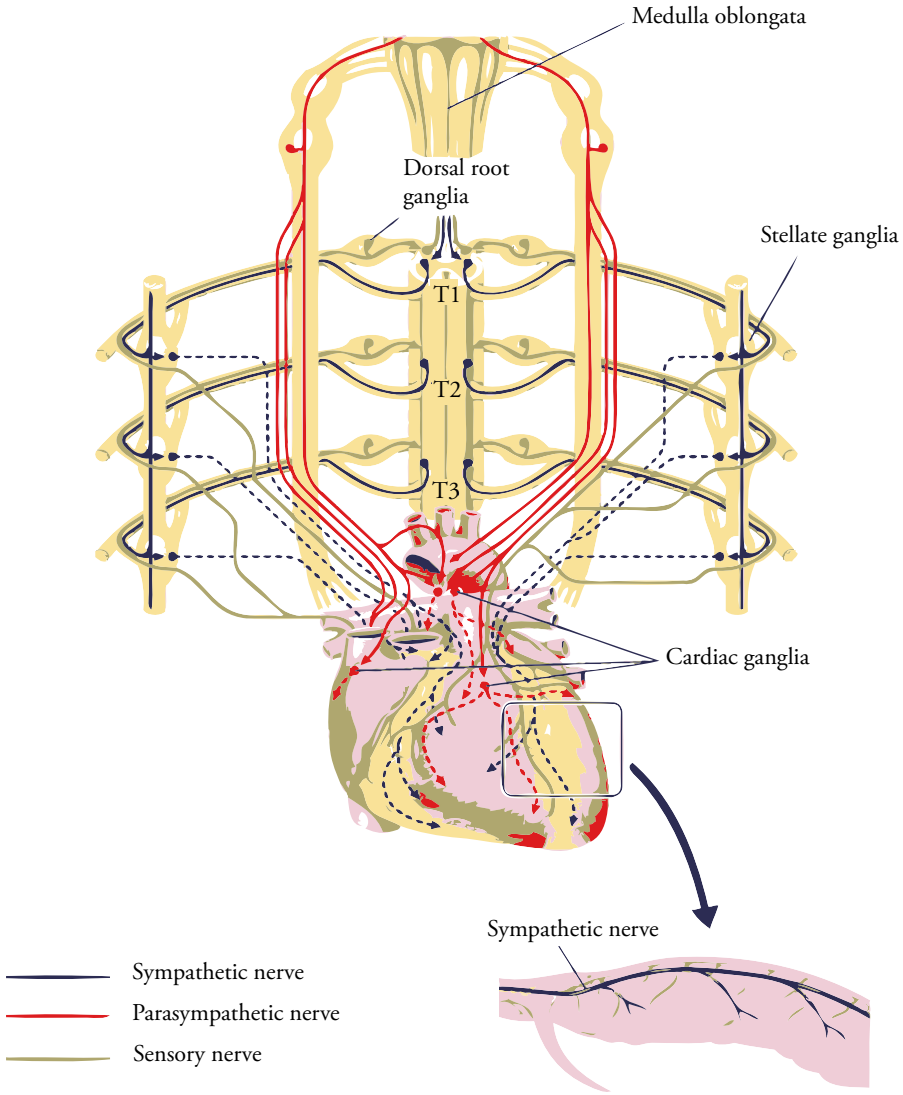
Etiology

Innervation of the heart

This thesis focusses on incidence and clinical relevance of cardiac abnormalities after aSAH, but not on pathophysiology. However, some data are available on potential etiologic factors. As already stated in the introduction of this thesis, Cushing[46] first reported that increased intracranial pressure due to cerebral tumors might lead to a substantial increase in blood pressure, a drop in heart rate, and slow irregular respiration. This is called the Cushing reflex. The Central Nervous System, consisting of a parasympathetic and a sympathetic pathway, innervates the heart through a

central autonomic network, consisting of the insular cortex, amygdala, hypothalamus, periaquaductal gray matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla (figure 3).

Figure 3: Schematic drawing of the anatomy and distribution of the cardiac nervous system. Adapted from: Kensuke Kimura et al. *Circulation Research*. 2012;110:325-336



It is known that stimulation of, epileptic seizures or stroke in particularly the insular cortex and amygdala may cause cardiac arrhythmias and other autonomic manifestations of cardiopulmonary dysfunction.[47, 48]

In addition to the cardiopulmonary control of the above described anatomical structures, the nucleus of the vagus nerve contains, among others, neurons that innervate the heart and the lungs. The preganglionic fibers of the right vagus nerve supply mostly the sinoatrial node, whereas the left vagus fibers are concentrated at the atrioventricular node. Consequently, stimulation of the right vagus influences the heart rate; the atrioventricular conduction is affected by the left vagus. Moreover, it was recently shown that parasympathetic nerve fibers innervate both atria and ventricles. The nerve density is higher on the ventricular endocardium, but nerve thickness is greater on the epicardium. The right ventricle (RV) is more densely innervated than the LV, whereas the LV endocardium is more densely innervated than the RV endocardium.[49]

The cardiac sympathetic nerves extend from the sympathetic neurons in stellate ganglia, which are located bilateral to the thoracic vertebra. Sympathetic nerve fibers project from the base of the heart into the myocardium, and are located predominantly in the subepicardium of the ventricle.

Sympathetic nervous activity is increased in patients with aSAH according to Naredi et al.[50] Plasma catecholamine concentrations are accepted as an index of sympathetic nervous activity in cardiovascular and neurological disorders and they are caused by a neurotransmitter spillover. Elrifai et al.[44] found that plasma catecholamine levels rose in their animal model with SAH and Sato et al.[32] found elevated plasma catecholamine levels in their study with patients suffering from aSAH. Increased local release of catecholamines from the local nerve endings in the heart might mediate the cardiac abnormalities following acute CNS stress. Rona et al.[51] first provided evidence that administration of high systemic doses of isoproterenol produced focal necrotic lesions in normal rat hearts. A transient severe coronary vasoconstriction causing ischemia, post ischemic left ventricle failure, and myocardial damage has been posed to be a consequence of the catecholamine release. This might cause a "neurogenic stunned myocardium", referring to the post ischemic reperfusion injury. However, Zaroff et al.[52] found no evidence of myocardial hypoperfusion in his experimental SAH study on dogs. A more plausible hypothesis is that a direct cardiotoxic effect of catecholamines leads to development of myofibrillar degeneration and subsequent myocardial dysfunction. Catecholamines may act on the ß-adrenoreceptor, inducing reversible injury through excessive cellular Ca^{2+}-influx.

Also, autopsy on hearts of cerebrally injured patients revealed massive infiltration of inflammatory cells and contraction band necrosis or coagulative myocytolysis, both signs of myofibrillar degeneration.[40, 42] Identical cardiac lesions were found in animal models with catecholamine infusion and in patients with pheochromocytoma.[53, 54] As these lesions may also be induced in adrenalectomized animals[44], but not in brain dead sympathectomized baboons[55], it is concluded that a neurogenic mechanism is plausible. Furthermore, in **Chapter 6** we describe a study that suggests a myocarditis in patients with aSAH. Myocarditis would be a plausible explanation for the cardiac abnormalities that are observed after aSAH.

Another approach to neurogenic myocardial dysfunction may be constructed using purinergic signaling. This non-adrenergic, non-cholinergic neurotransmission was discovered by Burnstock et al. in the early 1960's.[56] The neurotransmitter appeared to be extracellular Adenosine-5'-triphosphate (ATP) and was found to be an indispensable co-transmitter for the sympathetic nervous system.[57] Mammalian cells have large quantities of the ATP molecule stored in secretory and synaptic vesicles of the sympathetic nerve endings.[58] ATP in the CNS triggers pro-inflammatory reactions, predominantly by activation of the P2X7 receptor, which results in production and release of pro-inflammatory cytokines. Concomitantly with massive sympathetic activation, ATP is secreted in high quantities before being converted into extracellular adenosine. In ischemic heart disease, adenosine is known to protect the myocardium from reperfusion damage and massive infarction.[59] Adenosine acts by opening ATP dependent potassium (KATP) channels, leading to membrane hyperpolarization, shortening of the cardiac action potential, and reduction of contractility.[60, 61]

Conclusions, clinical implications and future perspectives

This thesis shows that cardiac abnormalities after aSAH occur often, that they are associated with prognosis, independently of other clinical variables, that they are transient, that they may occur days after the onset of the aSAH and disappear several days/weeks after the aSAH, and that their occurrence may be predicted using troponin. Most likely, cerebral perfusion is impaired because of cardiac dysfunction which is a possible pathway through which prognosis is influenced. Finally, catecholamine induced myocarditis seems to occur after aSAH and would be a plausible explanation for the observed cardiac abnormalities.

The observed cardiac abnormalities after aSAH show striking similarities with stress cardiomyopathy or Tako-tsubo syndrome and they are reversible. Clinical implications of this thesis are: first, it may help physicians that are confronted with

a patient with aSAH and cardiac dysfunction to better understand it and to avoid invasive investigations such as coronary angiography and associated anticoagulation because of suspected myocardial infarction. Second: potential donor hearts in neurologically injured patients could be rejected, because structural heart disease cannot be excluded. However, as stress cardiomyopathy is reversible, these hearts could be used for transplantation although data is not available. Third: this thesis helps in understanding the cardiac dysfunction after aSAH and may guide clinicians in treatment as management of patients stress cardiomyopathy after aSAH has not been established. Because of the potential reversible nature, supportive management may be sufficient. Evidence for prophylaxis is not yet provided, although α- and β-receptor blockers have been suggested. Early studies have shown a possible beneficial effect on prevention of cardiac abnormalities after aSAH. In rabbits, an α-blocker prevented death and pulmonary edema after they had been infused with epinephrine.[62] 90 patients with aSAH received orally the non-selective α-receptor blocker Phentolamine and the non-selective β-blocker Propanolol. Of the 12 patients that underwent autopsy, no myocardial lesions were found in the group that received drugs when they died. In the placebo group all patients had necrotic myocardial lesions.[63] Clinical use however, is still under discussion. Calcium antagonists, in particular nimodipine, have proven to have a beneficial effect on neurological outcome. The calcium channel blocker prevents delayed cerebral events (although incidence of vasospasm did not decrease) and improves clinical outcome, but may induce hypotension and the effect on cardiac dysfunction or myocarditis in aSAH is unclear. Furthermore, decreased cardiac output in the acute phase of aSAH may impair cerebral perfusion as is described in **Chapter 5**. Inotropic support, for example dobutamine and milrinone, has been effective in restoring cardiac function, although evidence is weak.[64, 65]

The SEASAH paper in **Chapter 3** describes the results of a prospective multicenter study in the Netherlands in third line referral university centers. Clinical meaning of our study in other settings such as different healthcare logistics or hospitals with other aSAH protocols should be interpreted with caution. Since SEASAH was an observational study and although associations could be made, sound conclusions on pathophysiology or therapeutic options should be perceived with caution.

Future studies in patients with aSAH and cardiac dysfunction should be directed towards therapeutic studies such as inotropic therapy or immunosuppressives to improve outcome. Also, further understanding of the purinergic signaling is an important topic of study. Inhibition of purinergic signaling by the administration

of nucleotides receptors (for example the ATP receptor P2X7 or the ADP receptor P2Y12) and the inhibition of the different nucleotide ecto-enzymes which leads to a decrease in tissue adenosine level may prevent or decrease the cardiac abnormalities after aSAH and perhaps also in ischemic stunning. Finally, further insights in the catecholaminergic myocarditis which is described in **Chapter 6**, are needed. By using immunohistochemistry and for example investigating presence of adhesion molecules such as ICAM and VCAM in the myocardium of patients with aSAH, our knowledge on neurogenic myocardial dysfunction will be enriched.

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Summary

Summary

Aneurysmal subarachnoid hemorrhage (aSAH), caused by rupture of an intracranial aneurysm, is a devastating neurological disease that accounts for approximately 5% of all strokes. It occurs at a relative young age (50% of patients are younger than 55 years of age), women are predominantly affected and prognosis is poor. Treatment is based primarily on aneurysm obliteration by either coiling or clipping of the aneurysm, the latter requiring craniotomy. However, during the course of the aSAH several neurological and medical complications may occur. The most important neurological complications are rebleeding of the aneurysm, hydrocephalus and delayed cerebral ischemia. Other complications are cardiac dysfunction, pulmonary dysfunction and renal dysfunction. Other common complications of a general Intensive Care Unit population such as infection, SIRS, etc. of course might also threaten this vulnerable patient group.

Of the non-neurological complications after aSAH, cardiac complications occur rather frequently and treatment options are unclear. Stress cardiomyopathy or Tako-tsubo cardiomyopathy is a fascinating phenomenon that has been described after acute stress. It is a reversible cardiac dysfunction with distinct imaging features (the echocardiographic or left ventricular angiographic image resembles a Tako-Tsubo which is a Japanese octopus trap) that is also observed after aSAH. Additionally, ECG abnormalities and biochemical changes occur. This thesis was based on the question how often cardiac dysfunction occurs in aSAH, what the clinical characteristics are and whether it influences outcome. Second we sought to further investigate Tako-Tsubo cardiomyopathy in a disease where it seemed to occur often: aSAH.

We designed a multicenter cohort study (Serial Echocardiography After Subarachnoid Hemorrhage (S.E.A.S.A.H.)) to observe the frequency of cardiac dysfunction, characteristics of the cardiac dysfunction and to investigate prognostic meaning in patients with aSAH.

In **Chapter 1** the outline of this thesis is described with an introduction and background. Furthermore we elaborate on the study design of the SEASAH study and explain the study protocol. The SEASAH was a multicenter cohort study in which serial ECG's, echocardiography and laboratory testing was performed in patients with aSAH. A follow-up took place at 3 months. Outcome was defined as death, occurrence of delayed cerebral ischemia (DCI) or poor functional status.

In **Chapter 2** the results of our meta-analysis are presented which we performed prior to conducting the SEASAH study. From this meta-analysis on literature from 1960-2007 we included 25 studies with a total of 2690 patients. We concluded that troponin and/or NT-proBNP and abnormal echocardiographic findings are associated with an increased risk of death, poor outcome, and delayed cerebral ischemia after subarachnoid hemorrhage (relative risk for death and wall motion abnormalities on echocardiography was 1.9). However, multi-variate analysis was not possible and many questions remained. So we decided to go forward with the SEASAH study.

In **Chapter 3** we describe the results of the SEASAH study. In this study we included 301 patients in which we performed serial ECGs, echocardiography and measured troponin and NT-proBNP. We performed a 3 months follow up for death, occurrence of DCI and poor outcome. We found that echocardiographic wall motion abnormalities were associated with death, DCI and poor outcome, independent of other clinical predictors for outcome. This finding was in line with the meta-analysis but answered the important question whether wall motion abnormalities were independent predictor for poor outcome. We also found that elevated troponin T levels, ST-segment changes, and low voltage on the admission ECGs had a univariable association with death but were not independent predictors for outcome.

In **Chapter 4** a sub-analysis of the SEASAH is described. Because of the reversible nature of the wall motion abnormalities we wanted to investigate the time course of WMA during the initial phase after aSAH. Furthermore we investigated which clinical, electrocardiographic or myocardial serum markers are predictors for early or late development of WMA. We found that WMA may be present on admission or develop during the course of aSAH. Poor neurological condition on admission, sinus tachycardia, ST-depression and ST-elevation at the admission ECG and elevated troponin T, are independent predictors for early WMA, a myocardial infarct pattern on the admission ECG and elevated troponin T in patients with aSAH predict late WMA independent of other clinical predictors.

In **Chapter 5** we investigated our hypothesis that cardiac dysfunction impairs cerebral perfusion and thus influences outcome. Data of cerebral CT perfusion was correlated with cardiac data from the SEASAH. We found an association between decreased cerebral blood flow in patients with impaired cardiac function compared

to patients with normal cardiac function. Although decreased autoregulation could be an explanation, pathophysiological conclusions cannot be drawn.

In **Chapter 6** we describe the results of a histopathological study. In this study we sought for evidence that the mononuclear cellular infiltration that is found in the myocardium of patients with aSAH might be a myocarditis. We compared post-mortem myocardium of patients who died from aSAH with controls. We found a markedly increase in inflammatory cells in patient with aSAH. Furthermore, we found evidence of thrombi and myocytolysis. This study supports the theory that catecholaminergic stress causes a myocarditis and gives direction to future research.

Finally, in **Chapter 7** we summarize the main conclusions of this thesis and put the findings into perspective of literature. We elaborate on available literature, put the findings of the thesis into context and describe possible etiologic factors for stress induced cardiac dysfunction. We describe clinical implications of this thesis, limitations of the studies and suggest direction for future research.

Samenvatting

Samenvatting

Een aneurysmatische subarachnoïdale bloeding (SAB) is een zeer ernstige neurologische aandoening die veroorzaakt wordt door ruptuur van een intracraniël aneurysma, een zwakke plek in een slagader. Het komt voor op een relatief jonge leeftijd (50% van de patiënten zijn jonger dan 55 jaar), vrouwen worden vaker getroffen dan mannen en de prognose is slecht. De behandeling is in eerste instantie gebaseerd op het uit de circulatie nemen van het aneurysma door "coiling" (het opvullen van het aneurysma met een soort veertje, een coil, door middel van een catheter via een bloedvat) of door "clipping" (het aanbrengen van een clip op de hals van het aneurysma via een craniotomie welke wordt uitgevoerd door de neurochirurg). Tijdens het klinische beloop van de SAB kunnen verschillende neurologische en medische complicaties optreden. De belangrijkste neurologische complicaties zijn: een recidief bloeding van het aneurysma, hydrocephalus en secundaire cerebrale ischemie (dit treedt meestal 4-7 dagen na de SAB op). Een aantal andere mogelijke complicaties zijn cardiale dysfunctie, longoedeem en nierfunctiestoornissen. Tenslotte kunnen veel voorkomende complicaties van een algemene Intensive Care populatie zoals bijvoorbeeld infectie een bedreiging vormen voor deze kwetsbare patiëntengroep. Van de niet-neurologische complicaties na SAB, komen de cardiale complicaties frequent voor, maar hoe ze te behandelen is niet duidelijk.
Stress cardiomyopathie of Takotsubo cardiomyopathie is een fascinerend fenomeen wat steeds vaker wordt beschreven. Het is vooral geassocieerd met acute emotionele stress en bestaat uit een reversibele cardiale dysfunctie (met name wandbewegingsstoornissen (WBS)) met een kenmerkend echocardiografisch of angiografisch beeld. Dit beeld lijkt op een Tako-Tsubo, een Japanse octopus val. De cardiale afwijkingen na een SAB hebben grote overeenkomsten met die van een stress cardiomyopathie.
Dit proefschrift is gebaseerd op de vraag hoe vaak cardiale disfunctie optreedt na een SAB, wat de klinische kenmerken zijn en wat het effect is op de prognose. Om dit te onderzoeken is de multicentrum cohort studie (Seriële Echocardiography na subarachnoïdale bloeding (S.E.A.S.A.H.)) ontworpen. Ten tweede wilden we stress cardiomyopathie verder onderzoeken in een ziektebeeld waar het vaak voorkomt: een aneurysmatische subarachnoïdale bloeding.

In **Hoofdstuk 1**, worden de contouren van dit proefschrift wordt beschreven, met een inleiding en een achtergrond van de literatuur. Tevens wordt de opzet van de SEASAH studie en het studieprotocol beschreven. De SEASAH was een multicenter

cohort studie waarin seriële ECG's, echocardiografie en laboratoriumtests werd uitgevoerd bij patiënten met SAB om te onderzoeken hoe vaak cardiale dysfunctie optreedt na SAB, of er klinische variabelen zijn die de dysfunctie kunnen voorspellen en of de cardiale dysfunctie een afhankelijke voorspeller is voor klinische uitkomst. Een follow-up vond plaats op 3 maanden. De primaire uitkomst werd gedefinieerd als dood, het optreden van secundaire cerebrale ischemie (DCI) of een slechte functionele status.

In **Hoofdstuk 2** worden de resultaten van de meta-analyse gepresenteerd, die voorafgaand aan de SEASAH studie werd verricht. Uit deze meta-analyse van literatuur van 1960 tot en met 2007, naar de prognostische betekenis van cardiale dysfunctie bij patiënten met een SAB, zijn 25 studies geïncludeerd met in totaal 2690 patiënten. De conclusie was dat troponine en/of NT-proBNP en abnormale echocardiografische bevindingen geassocieerd zijn met een verhoogd risico op overlijden, een slechte uitkomst, en secundaire cerebrale ischemie na een SAB (het relatieve risico op overlijden en WBS op echocardiografie was 1,9). Echter, multivariate analyse was niet mogelijk en een aantal wetenschappelijke vragen bleven onbeantwoord. Daarom werd besloten de SEASAH studie uit te voeren.

In **Hoofdstuk 3** worden de resultaten van de SEASAH studie beschreven. In deze prospectieve studie werden 301 patiënten geincludeerd die seriële ECG, echocardiografie en troponine en NT-proBNP bepalingen ondergingen. Na 3 maanden werd een follow-up uitgevoerd voor dood, het optreden van secundaire cerebrale ischemie en een slechte uitkomst. We vonden dat echocardiografische WBS geassocieerd waren met dood, secundaire cerebrale ischemie en een slechte uitkomst, onafhankelijk van andere klinische voorspellers voor deze uitkomsten. Deze bevinding was in lijn met de meta-analyse, en bevestigde de belangrijke klinische vraag of WBS onafhankelijke voorspellers zijn voor een slechte afloop. We vonden ook dat verhoogde troponine T, ST-segment veranderingen en lage QRS voltages een univariabele associatie hadden met dood, maar het waren geen onafhankelijke voorspellers voor uitkomst.

In **Hoofdstuk 4** wordt een sub-analyse van de SEASAH beschreven. Vanwege de reversibele aard van de WBS werd het tijdsverloop van WBS onderzocht tijdens de eerste fase na de SAB. Verder werd onderzocht welke klinische, elektrocardiografische of bloedwaarden voorspellers zijn voor vroeg of laat optreden van WBS. We vonden

dat WBS aanwezig kunnen zij bij opname of ze kunnen zich later ontwikkelen. Slechte neurologische conditie bij opname, sinus tachycardie, ST-depressie en ST-elevatie bij het opanme ECG en verhoogde troponine T, zijn onafhankelijke voorspellers voor het vroeg optreden van WBS, een myocard infarct patroon op het opname ECG en verhoogde troponine T bij patiënten met een SAB voorspellen het laat optreden van WBS, onafhankelijk van andere klinische voorspellers.

In **Hoofdstuk 5** onderzochten we de hypothese dat cardiale dysfunctie na een SAB cerebrale perfusie kan verminderden. De data van cerebrale CT perfusie werden gecorreleerd aan de cardiale gegevens van de SEASAH. We vonden een verband tussen verminderde bloedtoevoer naar de hersenen bij patiënten met een verminderde hartfunctie in vergelijking met patiënten met een normale hartfunctie. Verminderde autoregulatie van de cerebrale vaten zou een potentiële verklaring kunnen zijn, maar pathofysiologische conclusies kunnen niet worden getrokken uit deze studie.

In **Hoofdstuk 6** worden de resultaten van een histopathologisch onderzoek beschreven. In deze studie hebben we gezocht naar bewijs dat de mononucleaire cellulaire infiltratie die wordt gevonden in het myocardium van patiënten na een SAB aan de criteria van een myocarditis voldoet. We vergeleken post-mortem myocard van de patiënten die overleden aan een SAB met een controlegroep. We vonden een duidelijke verhoging van ontstekingscellen bij patiënten met een SAB en niet bij de controle groep. Verder vonden we trombi en myocytolysis, een andere aanwijzing voor een myocarditis. Dit onderzoek ondersteunt de theorie dat catecholaminerge stress een myocarditis kan veroorzaken en geeft richting aan toekomstig onderzoek.
Tenslotte worden in **Hoofdstuk 7** de belangrijkste conclusies van dit proefschrift samengevat en worden de resultaten in de context van de literatuur gezet. De klinische implicaties van dit proefschrift worden beschreven alsmede de beperkingen. Tenslotte wordt er een richting voor toekomstig onderzoek gesuggereerd.

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Curriculum Vitae

Curriculum Vitae

Ivo Adriaan Cornelis van der Bilt was born on august 1st. 1975 in Bergen op Zoom. He grew up in Kaatsheuvel and Berkel-Enschot and finished secondary school at the Theresialyceum in Tilburg. In 1994 he started to study Chemical Technology at the Technical University in Eindhoven but quickly decided another career would be more suitable. He was accepted for medical school at the Free University in Amsterdam in 1996 and finished his Medical Degree in 2002. From 2001-2002 he was chair of the council of interns (Co-raad). During his medical study his interest in Cardiology started. He chose a cardiovascular profile consisting of a cardiological elective (keuzevak), student internship (wetenschappelijke stage) and elective rotation (keuze co-schap). He did an extended student internship (6 months) on the Intensive Care Unit in the Dijkzigt Hospital (now Erasmus Medical Center Rotterdam) and wrote his final report on Cerebro-cardio-pulmonary interaction after aneurysmal subarachnoid hemorrhage. This paper was the basis for the SEASAH study protocol. After the student internship and before starting rotations, he was a student assistant for 6 months at the department of Anesthesiology of the Dijkzigt hospital in Rotterdam during which he wrote the SEASAH protocol, started with the study logistics and worked on several other protocols such as Xenon anesthesia and high frequency ventilation.

After his Medical Degree, he started working as a resident cardiology (AGNIO) in the Kennemer Gasthuis in Haarlem to gain clinical experience while trying to raise funds for the SEASAH study. In January 2004 he started as a resident cardiology (AGNIO) in the VU University Medical Center (VUMC) and later that year he started as a full time PhD student. Inclusion of patients in the SEASAH started in 2005. Due to funding problems in the VUMC he switched to the Academic Medical Center in 2006 where he started his training in cardiology (AIOS) in 2008.

In 2007 he co-founded the Cardionetworks Foundation. This is a non-profit NGO which launched and maintains several websites (ECGpedia.org, Echopedia.org).
From 2008 to 2010 he did his Internal Medicine residency (trainer prof. dr. P. Speelman and prof. dr. M.M. Levi). From January 2010 until May 2010 he interrupted cardiology training to finish the data inclusion of the SEASAH. From June 2010 until November 2013 he worked as a resident cardiology in the AMC with a short period of 3 months in the Tergooi Hospital in Blaricum. In November 2013 he started his differentiation year in cardiac imaging in the Heart center of the Haga Teaching

Hospital in The Hague (trainer M.J.W. Götte and B. Delemarre). He graduated as a cardiologist in October 2014.

Since December 2014 he works as a staff Cardiologist in the Haga Teaching Hospital in the Hague. He specializes in imaging and is head of the department of Echocardiography.

Since 2012 he is active within the European Society of Cardiology as a question writer and standard setter for the European Examination in General Cardiology. He was elected as a member of the ESC Education Committee 2014-2016.
His hobbies are flying and sailing. He is married with Dilia Ham and has two children, Reinout and Aletta.

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