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ORIGINAL ARTICLE

Left Ventricular Dysfunction and Cerebral Infarction from Vasospasm After Subarachnoid Hemorrhage

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Abstract

Background Although neurogenic stunned myocardium (NSM) after aneurysmal subarachnoid hemorrhage (SAH) is well described, its clinical significance remains poorly defined. We investigated the influence of left ventricular (LV) dysfunction and cerebral vasospasm on cerebral infarction, serious cardiovascular events, and functional outcome after SAH.

Methods Of the 481 patients enrolled in the University Columbia SAH Outcomes Project between 10/96 and 05/02, we analyzed a subset of 119 patients with at least one echocardiogram, serial transcranial Doppler (TCD) data, and with no prior history of cardiac disease. LV dysfunction was defined as an ejection fraction <40% on echocardiography. Infarction from vasospasm was adjudicated by the study team after comprehensive review of all clinical and imaging data. Functional outcome was assessed at 15 and 90 days with the modified Rankin Scale (mRS).

Results Eleven percent of patients had LV dysfunction ($N = 13$). Younger age, hydrocephalus, and complete filling of the quadrigeminal and fourth ventricles were associated with LV dysfunction (all $P < 0.05$). Despite a similar frequency of pre-existing hypertension, 0% of patients with LV dysfunction reported taking antihypertensive medication, compared to 35% of those without ($P = 0.009$). There was a significant association between LV dysfunction and infarction from vasospasm after

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adjusting for clinical grade, age, and peak TCD flow velocity ($P = 0.03$). Patients with LV dysfunction also had higher rates of hypotension requiring vasopressors ($P = 0.001$) and pulmonary edema ($P = 0.002$). However, there was no association between LV dysfunction and outcome at 14 days after adjustment for established prognostic variables.

Conclusions LV dysfunction after SAH increases the risk of cerebral infarction from vasospasm, hypotension, and pulmonary edema, but with aggressive ICU support does not affect short-term survival or functional outcome. Antihypertensive medication may confer cardioprotection and reduce the risk of catecholamine-mediated injury after SAH.

Keywords Subarachnoid hemorrhage · Cerebral infarction · Vasospasm · Neurogenic stunned myocardioum · Left ventricular dysfunction · Echocardiography

Introduction

Cardiac abnormalities after aneurysmal subarachnoid hemorrhage (SAH) have been described during the last 50 years or more. It has been recently found that significant emotional stressors can mimic changes seen as a result of SAH, including dynamic electrocardiogram (ECG) changes, reversible left ventricular (LV) dysfunction with hypotension and pulmonary edema, and myocardial enzyme release [1]. A central nervous system etiology has been implicated in these phenomena based on the release of local and systemic catecholamines and the characteristic pathological finding of contraction band necrosis, a unique form of catecholaine-mediated myocardial injury [1–5].

It has been estimated that up to 33% of SAH patients will have a cardiac complication within 5 days of aneurysmal rupture [6]. Important complications range from ECG changes [6–8], arrhythmias [9–12], cardiac enzyme elevations [13–15], and pulmonary edema [6, 15, 16]. Reversible cardiac wall motion abnormalities are well described based on SAH [6, 7, 13–17]. Abnormal wall motion is most often diffusive and involves multiple vascular territories of the heart [18]. Severe myocardial stunning can lead to florid cardiogenic shock and deterioration of neurological function [6, 16].

LV dysfunction may predispose SAH patients to ischemia from vasospasm by dampening the normal enhanced cardiovascular response to SAH, and by interfering with the successful implementation of hypertensive hypervolemic therapy (HHT) in response to symptomatic deterioration. We investigated the association of LV dysfunction with cerebral infarction from vasospasm, serious cardiovascular events, and functional outcome in a well-characterized subset of SAH patients with no prior cardiovascular history.

Methods

Study Population

Of the 481 consecutively admitted patients with aneurysmal SAH enrolled in the then Columbia SAH Outcomes Project between October 1996 and May 2002, we studied 119 who within the first 5 days of admission underwent echocardiography, serial transcranial Doppler (TCD) ultrasonography, and had no prior cardiac history (e.g., coronary artery disease, congestive heart failure, valvular disease, arrhythmia, myocardial infarction). Echocardiography was performed when clinical indicated on the basis of myocardial enzyme release, ECG abnormalities, or for symptoms of hypotension, congestive heart failure, chest pain, or cardiac dysrhythmia. SAH was diagnosed by computed tomogram (CT) or by xanthochromia of cerebrospinal fluid if the initial CT scan was nondiagnostic, and the presence of an aneurysm was diagnosed by angiography in all the cases. The hospital institutional review board approved this study, and written consent was obtained from each subject or an appropriate surrogate.

Clinical Management

Aneurysm repair was performed within 24 h whenever possible. All the patients received oral nimodipine. During the pre-vasospasm period, we maintained central venous pressure (CVP) between 5 and 8 mmHg using 0.9% saline solution and 5% albumin solution as needed. HHT was initiated for symptomatic vasospasm or when severe angiographic vasospasm was diagnosed in poor grade patients (Hunt-Hess 4 or 5) by increasing target CVP from 8 to 12 mmHg (or pulmonary artery diastolic pressure from 14 to 20 mmHg) and systolic blood pressure (SBP) from 180 to 220 mmHg. An external ventricular drain was placed in all the patients with depressed level of consciousness and intraventricular hemorrhage (IVH) or acute hydrocephalus. Patients with refractory symptomatic vasospasm underwent endovascular therapy including intra-arterial verapamil hydrochloride, angioplasty, or both.

Clinical and Radiological Variables

We recorded baseline demographics, social, past medical history, and symptoms at onset of hemorrhage. A neurological and general physical examination was performed by means of a study by neurointensivist at time of admission. The Glasgow Coma Scale score and Hunt-Hess scale were used to evaluate clinical status at onset [19, 20]. Admission CT scans were prospectively rated using the modified Fisher and Hijdra scales [21, 22]. Hydrocephalus was diagnosed according to the bicaudate index, with cut-points for the upper limit of normal according to decile of age [23]. CT scans were performed at the time of admission, for any change in neurologic status, and at day 15 or time of discharge, whichever came first. Lucencies were adjudicated as being due to infarction from vasospasm (the main outcome variable of interest), ictal or peri-operative infarction, retraction injury, focal cerebral edema, or other causes in weekly meetings of the study team. In selected cases, magnetic resonance imaging was performed to determine whether infarction was present. Echocardiographic findings were not taken into consideration during the adjudication process. At the conclusion of each hospital stay, all adverse events, procedures, and diagnostic studies were recorded.

TCD examinations with monitor delayed vasospasm were performed by neurosonology technicians daily or every other day during the first 2 weeks after the index SAH. Peak TCD mean flow velocity (mFV) obtained from the anterior cerebral circulation during the first 10 days after the index hemorrhage were analyzed in this study.

All the patients underwent serial ECG on admission. Cardiac troponin I (cTI) testing was performed when clinically indicated (e.g., ECG changes, hypotension, pulmonary edema, angina pectoris, cardiac dysrhythmia, or during induced hypertension). In our laboratory cTI levels >0.4 μg/l are considered abnormal.

Echocardiography

All initial echocardiographic studies were performed within 3 days of admission, and most patients underwent a repeat examination within 4–6 days after the first study. All echocardiograms were interpreted by an attending cardiologist who was blinded to the clinical status of the patient. Echocardiograms were performed using two-dimensional sector scanning, Doppler color flow mapping, and pulsed and continuous wave Doppler interrogation. Standard parasternal long axis, short axis, and apical 2- and 4-chamber views were obtained for analysis of LV dysfunction. LV ejection fraction was visually estimated and rated as normal (LVEF ≥55%) or mildly (LVEF 40–54%), moderately (LVEF 30–39%), or severely (LVEF $<30\%$) depressed. Two blinded cardiologists with expertise in echocardiography validated this LV function classification system using Simpson's biplane method and Tomtec Image Arena software (version 2.8.1) in a random sample ($N = 15$) drawn from the study population (Spearman's $R^2 = 0.855$, two-sided $P = 0.000$). All echocardiograms were also evaluated for intracardiac thrombus, and bubble studies were performed with agitated saline when clinically warranted.

Outcome Measures

The primary exposure of interest was moderate-to-severe LV dysfunction (EF $<40\%$). The primary outcome measure was cerebral infarction from vasospasm, defined as a new CT lucency developing between SAH day 3 and 21 with confirmation of vasospasm by TCD or angiography. Secondary outcome measures included hypotension (SBP <100 mmHg) requiring vasopressors, pulmonary edema (pulmonary infiltrates on chest radiography with hypoxemia [*P*/*F* ratio <300] or rales), new-onset arrhythmia (excluding sinus tachycardia or bradycardia or isolated premature ventricular contractions), and the presence of intra-cardiac thrombus. Functional outcome was assessed at 15 days with the modified Rankin Scale (mRS) [24].

Statistical Analysis

Univariate analysis was performed using Fisher's exact test, two-sided *T* tests, or the Kruskall–Wallis for non-normally distributed data. Multivariate analysis was performed with logistic regression with a removal probability of 0.2 and entry probability of 0.05 using a commercially available statistical package (SPSS v.11; Chicago, IL). Receiver operating curve (ROC) assessment was performed to assess cTI serum titers as a predictor for LV dysfunction. *P* values <0.05 were considered significant.

Results

Thirteen of the 119 study patients (11%) had moderate-to-severe LV dysfunction. Patients with LV dysfunction were significantly younger and less often used anti-hypertensive medication, despite a similar frequency of self-reported hypertension (Table 1). On admission ,CT patients with LV dysfunction were more likely to have hydrocephalus and thick clot filling the fourth ventricle or quadrigeminal cistern.

ROC assessment of peak cTI levels ($N = 69$) for the presence of LV dysfunction determined that a cutpoint of ≥10 μg/l had the greatest sensitivity (82%) and specificity (71%, area under the curve 0.79, SE 0.072, $P = 0.003$).

Patients with moderate-to-severe LV dysfunction were three times more likely to experience cerebral infarction due to vasospasm than those who did not, despite there being no difference in the frequency of symptomatic vasospasm (Table 2). Hypotension requiring pressors, pulmonary edema, and prolonged ICU and hospital length

Table 1 Admission variables associated with moderate-to-severe LV dysfunction

	LV ejection fraction		
	≥40% (*N* = 106)	<40% (*N* = 13)	*P*
Demographics and past medical history			
Male (%)	32	31	1.00
Age ≥55 years (%)	52	15	**0.017**
White (%)	48	69	0.24
Hypertension (%)	49	31	0.25
Antihypertensive medication (%)	35	0	**0.009**
SAH characteristics			
Modified Fisher scale 3 or 4 (%)[a]	70	85	0.34
Median aneurysm size (mm)	10	11	0.30
SAH completely filling either sylvian fissure (%)	76	92	0.29
SAH completely filling the suprasellar cistern (%)	73	92	0.18
SAH completely filling either ambient cistern (%)	59	85	0.13
SAH completely filling the quadrigeminal cistern (%)	36	69	**0.033**
IVH completely filling either lateral ventricle (%)	15	15	1.00
IVH completely filling the third ventricle (%)	9	23	0.13
IVH completely filling the fourth ventricle (%)	19	46	**0.036**
Hydrocephalus (%)	40	85	**0.003**
Admission clinical status			
Loss of consciousness at onset (%)	57	85	0.07
Hunt-Hess grade 3–5 (%)[b]	65	85	0.22
Median 24-h peak SBP (mmHg)	160	150	0.17

Bold indicates significant *P* values (<0.05) in univariate analysis

[a] Indicates thick cisternal blood, with or without bilateral IVH

[b] Indicates lethargy or confusion, stupor or coma

Table 2 Association of moderate-to-severe LV dysfunction with serious vascular events and functional outcome at day 15

	LV ejection fraction		*P*
	≥40% (*N* = 106)	<40% (*N* = 13)	
Cerebrovascular events			
Cerebral infarction from vasospasm (%)	13	39	**0.034**
Any cerebral infarction (%)	45	77	**0.040**
Symptomatic vasospasm (%)	25	31	0.74
Cardiovascular events			
LV thrombus (%)	2	15	0.06
Hypotension <90 mmHg requiring pressors (%)	26	77	**0.001**
Pulmonary edema (%)	31	77	**0.002**
Cardiac arrhythmia (%)	12	15	0.67
Functional outcome[a]			
15-day mRS ≥4 (%)	69	85	0.34
Length of stay			
Median ICU stay (days)	11	15	**0.006**
Median hospital stay (days)	18	28	**0.033**

Bold values indicate significant *P* values (<0.05) in univariate analysis

[a] mRS score of ≥4 indicates, death or moderate-to-severe disability (unable to walk independently or bedbound)

of stay were also associated with LV dysfunction. Although the frequency of death or moderate-to-severe disability was higher at day 15 in those with LV dysfunction, this difference were not statistically significant. In a multivariate analysis adjusting for age and Hunt-Hess grade, there was no significant relationship between the presence of LV dysfunction and death or moderate-to-severe disability (mRS 4–6) at 14 or 90 days after SAH (Table 3).

Table 4 depicts the multivariate analysis of the association between LV dysfunction and the primary outcome of interest, cerebral infarction. Age, modified Fisher score, and peak TCD mFV >180 cm/s within the first 10 days of SAH were forced into the model. LV dysfunction and peak

Table 3 Multivariate predictors of death or moderate-to-severe disability (mRS ≥4) at 14 days[a]

	Adjusted odds ratio	95% CI	*P*
Age ≥55 years	1.23	0.54–2.81	0.616
Hunt-Hess grade 3–5	2.10	0.92–4.81	0.079
LVEF <40%	2.34	0.47–11.71	0.302
Constant	3.09		0.007

[a] mRS score of ≥4 indicates, death or moderate-to-severe disability (unable to walk independently or bedbound)

Table 4 Multivariate predictors of cerebral infarction from vasospasm

	Adjusted odds ratio	95% CI	*P*
Age ≥55 years	1.33	0.42–4.16	0.630
Modified Fisher score ≥3	1.67	0.47–5.96	0.427
LVEF <40%	4.54	1.13–18.23	**0.033**
Peak TCD mFV ≥180 cm/s	3.11	1.08–8.96	**0.036**
Constant	0.34		0.007

P values refer to Wald's two-sided test. No interactions between LVEF <40% and Modified Fisher score ≥3 or Peak TCD mFV ≥180 cm/s were present

Bold *P* values are statistically significant (<0.05)

LVEF left ventricular ejection fraction, *TCD* transcranial Doppler

TCD >180 cm/s were identified as significant predictors of infarction from vasospasm.

Figure 1 depicts the probability of cerebral infarction from vasospasm according to peak TCD mFV quartile during first 10 days following SAH, stratified by LVEF. The risk of infarction was higher among patients with LV dysfunction at all TCD levels, with the highest risk occurring in those with LV dysfunction and peak TCD velocities exceeding 180 cm/s.

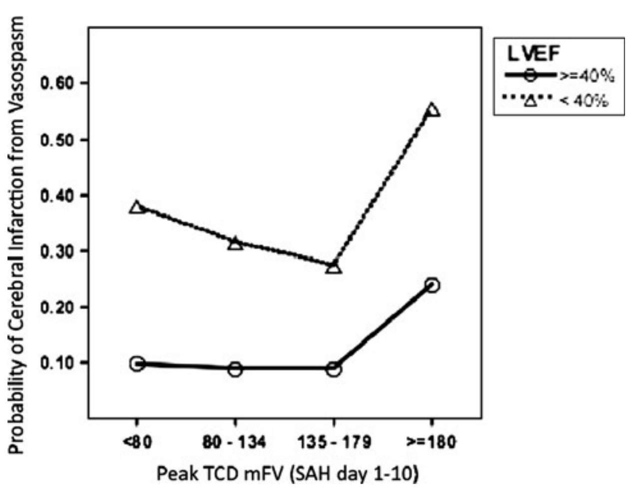

Fig. 1 Risk of cerebral infarction from vasospasm as a function of peak TCD mFV during the first 10 days after SAH, divided into quartiles. For each TCD quartile, the risk of infarction is higher when LVEF is <40%; the highest risk is among those with a peak TCD mFV >180 cm/s

Discussion

In this well-characterized subgroup of aneurysmal SAH patients considered to be at risk for neurogenic cardiac complications, LV dysfunction (defined by an ejection fraction ≤40%) occurred in 11%. A similar frequency of NSM has been reported in other series of SAH patients, ranging from 3 to 22% [13–15]. Clinical predictors of LV dysfunction included younger age, untreated hypertension, thick clot involving the fourth ventricle or quadrigeminal cistern, and acute hydrocephalus. The association with blood filling the fourth ventricle or ambient cisterns suggests a neurogenic etiology in the pathogenesis of this disorder, affecting brainstem autonomic or vasomotor centers. Tung et al. found that female sex and poor clinical grade are risk factors for NSM after SAH [17], but we were unable to confirm these associations.

It has been reported that beta-blockers attenuate troponin release after SAH [25], and that alpha- and beta-receptor polymorphisms that accentuate receptor responses to stimulation are associated with an increased risk of LV dysfunction [26]. The fact that none of our LV dysfunction patients was on antihypertensive medication at the time of their bleed, despite a 31% frequency of self-reported hypertension, is a novel observation suggesting that antihypertensive therapy may protect against NSM by reducing afterload or attenuating catecholamine-mediated injury.

A cTI level exceeding 10 µg/l was found to be optimally sensitive and specific for detecting LV dysfunction. However, because NSM can occur with cTI levels as low as 0.02 µg/l, we recommend this level as a threshold for performing screening echocardiography after SAH [13]. In an earlier study, we found that a cTI threshold of 10 µg/l identifies SAH patients in the highest quartile of troponin elevation, with a 63% positive predictive value for echocardiographic LV dysfunction, a 46% frequency of hypotension requiring IV pressors, and a 39% risk of developing pulmonary edema [13].

Our main finding is that LV dysfunction after SAH significantly increases the probability of cerebral infarction from vasospasm. In previous studies, we have found that cardiac troponin elevation and depressed post-operative cardiovascular hemodynamic performance are also risk factors for delayed cerebral ischemia after SAH [13, 27]. These findings suggest that the normal hyperdynamic pressor response to SAH protects against cerebral ischemia after SAH, and that cardiovascular decompensation due to neurogenic myocardial stunning increases this risk.

We also found that patients with LV dysfunction had a significantly higher probability of serious cardiovascular events, including pulmonary edema and hypotension requiring the use of pressors. The risk of these complications was between two- and threefold in the presence of LV dysfunction, with 77% of patients with LV dysfunction experiencing each complication. Our findings point to the problematic nature of preventing or treating symptomatic vasospasm with HHT in the presence of myocardial dysfunction. The use of fluids and pressors to maintain elevated CVP and blood pressure goals may be less likely to reach target, and may increase the frequency and severity of congestive heart failure in this group. The presence of relative hypotension, which was also associated with LV dysfunction, may also limit the use of nimodipine for vasospasm prophylaxis, further placing patients at risk for cerebral infarction.

Established predictors of symptomatic vasospasm after SAH include the presence of thick subarachnoid clot, poor clinical grade, and to a lesser extent elevated TCD flow velocities [28]. We found that LV dysfunction conferred an increased risk cerebral infarction from vasospasm across the entire range of peak TCD velocities, and that the risk was maximal when mFV exceeded 180 cm/s (Fig. 1). Patients with LV dysfunction also had a significantly greater number of infarcts from causes other than vasospasm, most commonly the so-called ictal [29] and perioperative infarcts. Impaired LV hemodynamic performance combined with cerebral autoregulatory dysfunction may increase the risk of cerebral infarction both during the acute phase of bleeding, as well as during periods of relative hypotension at the time of surgery. Mural thrombus can developing in conjunction with NSM [30], which might serve as a potential source of embolic stroke.

In the subset of high-risk patients that we studied, patients with LV dysfunction did not have significantly worse functional outcomes at 14 days than those who had LV function that was normal to mildly impaired. These findings suggest that with meticulous inotropic and pressor support, LV dysfunction does not determine outcome after SAH in the context of the many other factors that can impact on survival and recovery.

This study has several notable shortcomings. We elected to study a smaller subset of SAH patients known to be free of pre-existing cardiac disease who had complete echocardiographic, TCD, and outcome data, which represented 25% of the total SAH population treated in our ICU during the study period. As a result, subject selection bias may hamper the generalizability of our findings. The exposure of interest, LV dysfunction, is relatively uncommon. Because of this, our study may have been underpowered and unable to detect important relationships that have been noted in previous studies. We had a significant problem with loss to follow-up in this specific patient population: nearly 20% did not have 90-day functional outcome data making accurate assessment of this outcome impossible. Instead, 15-day outcomes had to be relied upon, which and may not truly represent long-term outcome in this cohort. We do not have data on the timing and relative severity of the cardiovascular and neurological complications that occurred during hospitalization. Abnormal echocardiograms were not routinely repeated, which would have allowed us to confirm the reversible nature of LV dysfunction that characterizes neurogenic stunning. The main advantage of our study design include prospective in-hospital and outcome data collection, the use of multi-observer adjudication for differentiating infarction from vasospasm from other causes of CT lucency after SAH, and the lack of important missing data for key variables in the analysis.

In conclusion, we found that among patients not having prior cardiac history, moderate-to-severe LV dysfunction after SAH is associated with an increased risk of cerebral infarction from vasospasm, and that this risk increases with the severity of vasospasm. We also found that LV dysfunction increases the risk of cardiopulmonary dysfunction (hypotension and pulmonary edema), and found a novel association between non-use of antihypertensive medication and myocardial injury. Further research is needed to develop acute cardioprotective strategies designed to minimize catecholamine-mediated myocardial injury during the acute phase of SAH.

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Conflict of interest None.

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