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The Use of Cardiac Troponin-I (cTnI) to Determine the Incidence of Myocardial Ischemia and Injury in Patients with Aneurysmal and Presumed Aneurysmal Subarachnoid Hemorrhage

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Summary

A prospective single center study was performed to determine the minimal preoperative incidence of unrecognized cardiac injury in patients suffering aneurysmal and presumed aneurysmal subarachnoid hemorrhage (SAH). When caring for such patients in the pre- and post operative period clinicians must be aware of the possibility of cardiac injury even when a history of previous cardiac symptomatology is not present.

Forty-seven consecutive patients suffering from SAH over a five-month period underwent serum measurements of the cardiac muscle marker troponin I (cTnI) immediately upon admission. Repeat studies, if possible, were done 24 hours later. EKG was performed in all patients and was available for review in 44 of the 47 cases. Echocardiography was performed in four of eight patients with elevated cTnI levels. Signs and symptoms relating to cardiac ischemia were recorded by the patients' physicians and nurses.

Eight individuals (17%) had elevations in cardiac troponin I levels. Because surgical treatment is generally carried out as soon as possible following the hemorrhage, many patients with normal troponin I levels within twenty-four hours of their hemorrhage were operated upon before a repeat enzyme could be obtained or possibly before elevations could be recorded. In addition, a number of patients were referred to our center several days post-hemorrhage at a time when marker levels may have normalized. Therefore, the 17% incidence of elevated cTnI may be an underestimate. Only two of the eight patients had clinical abnormalities in cardiac function. Four patients with elevated levels had echocardiograms, three of which were abnormal. One additional patient died of a myocardial infarction before an echocardiogram could be obtained. EKG was abnormal in six of the seven patients with elevated troponin who had tracings available for review. Recordings consistent with recent myocardial ischemia were present in four of these. Of the 39 patients with negative troponin I levels, 37 had EKG available for review. None had recordings clearly consistent with recent myocardial ischemia although 13 were suggestive of ischemic changes. None of these 39 patients had pre- or post-operative clinical changes in cardiac function. Elevations in troponin I appeared to be unrelated to the patient's Hunt and Hess grade or Fisher score although our numbers were too small to draw any meaningful conclusions.

Keywords: Troponin I; subarachnoid hemorrhage; myocardial ischemia.

Introduction

Cardiac dysfunction following aneurysmal subarachnoid hemorrhage (SAH) includes dysrhythmias, infarction, ischemia, and stunned myocardium with ventricular dysfunction. The true incidence of myocardial injury in this population however is unknown because many ischemic episodes are short-lived and subclinical. Detection using electrocardiograms (ECG) is insufficient because this modality often demonstrates ST segment and T wave changes that have not been shown to correlate with other parameters of cardiac dysfunction and injury. Cardiac enzyme studies have not been performed in an organized fashion and those studies that have been done are hampered by the fact that CK-MB levels may be elevated for reasons other than myocardial ischemia. Echocardiographic measurements, while useful for demonstrating significant cardiac dysfunction, do not demonstrate lesser levels of cardiac injury.

The measurement of cardiac troponin I (cTnI) has provided physicians with a myocardial marker that has a sensitivity for cardiac injury equal to that of CK-MB yet with greater specificity. By performing ECGs and cTnI levels in a series of 47 patients admitted with SAH we have been able to determine the minimal incidence of myocardial injury in such patients even if the level of injury was subclinical and

lacking ECG and in some cases echocardiographic evidence of cardiac dysfunction.

Methods and Patients

All patients were admitted to the neurosurgical intensive care unit. One cTnI level was drawn at admission and if possible another drawn 24 hours later if surgery had not occurred. Electrocardiograms were performed at admission and again 24 hours later. All were reviewed by a cardiologist (DW) blinded to the patients cTnI levels. Transthoracic echocardiograms were performed in 4 of 8 patients with cTnI abnormalities. The cTnI levels were performed using the Stratus II system incorporating a mass monoclonal antibody in the radial partition fluoroimmunoassay (Dade Company, Miami, FL) [3]. In a multicenter clinical trial, all patients with the diagnosis of acute myocardial infarction had a cTnI value greater than 1.5 ng/ml. The lowest detectable level was 0.4 ng/ml (Dade, unpublished data). Elevated and non-elevated subjects were compared using Fisher's exact test or the Mann-Whitney test, as appropriate.

Results

Overall Patient Population

Forty-seven consecutive patients (36 females, 11 males) with aneurysmal and presumed aneurysmal SAH were studied prospectively. Ages ranged from 27 to 85 (mean 51.7, SD = 13.6). Thirty-nine patients were white, seven were black and one was oriental. Thirty patients had cTnI levels determined within 24 hours of their hemorrhage, 7 had initial levels within 48 hours, 5 within 72 hours, 1 within 96 hours, and 4 within 144 hours. Six patients had a Hunt and Hess grade of 1, 15 had a grade of 2, and 22 had a grade of 3 (4 unknown) (mean 2.4, SD = 0.8). One patient had a Fisher score of 0, 1 had a score of 1, 5 had a score of 2, 30 had a score of 3, and 9 had a score of 4 (1 unknown) (mean 3.0, SD = 0.8). ECGs were available for 44 of the 47 patients. Fourteen studies were normal and 30 were abnormal as summarized in Table 1. ECG findings clearly consistent with recent myocardial ischemia were found in 5 patients. Patient sex and age, aneurysm location, timing of troponin level, Hunt and Hess grade, Fisher score, echocardiogram findings, and clinical cardiac function are listed in Table 1.

Elevated cTnI (Myocardial Injury) Patient Population

Eight patients had cTnI levels above 0.4 ng/ml (17% of the total study population). This group included 6 females and 2 males ranging in age from 27 to 69 (mean 45.1, SD = 13.5). All had cTnI levels determined within 24 hours of their SAH and 5 had repeat levels within 48 hours. All had ECGs at 24 and 48 hours post-SAH. Echocardiograms were performed in 4 patients, 3 of whom demonstrated wall motion abnormalities. One of these patients displayed symptoms of myocardial infarction. One patient died of cardiogenic shock before an echocardiogram could be obtained. ECGs were available for review in seven of the eight cases. One patient had a normal study while six were abnormal. Four of these were consistent with ischemia and two were considered possibly ischemic. Findings are summarized in Table 1. Clear ECG evidence for recent ischemia was seen in cases 4, 5, and 8. One patient had a Hunt and Hess grade of 1, 3 had grades of 2, and 4 had grades of 3 (mean 2.4, SD = 0.8). One patient had a Fisher score of 2, 6 had a score of 3, and 1 had a score of 4 (mean 3.0, SD = 0.5). cTnI levels ranged from 1.5–9.9. No patient had a past medical history significant for cardiac disease. Because of low population numbers, no statistical significance could be demonstrated for worse outcomes in patients with elevated cTnI although at least 50% (n = 4) demonstrated either echocardiographic motion abnormalities (n = 3) or died from myocardial ischemia (n = 1).

Non-Elevated cTnI Patient Population

Thirty-nine patients had undetectable cTnI levels (less than 0.4 ng/ml). This group included 30 females and 9 males ranging in age from 33 to 85 (mean 53.1, SD = 3.4). Twenty-two had cTnI levels determined within 24 hours, 7 within 48 hours, 5 within 72 hours, 1 within 96 hours, and 4 within 144 hours. All had ECGs at 24 and 48 hours post admission. ECGs were available for review in 37 patients. Twelve of these studies were normal. Twenty-five of the studies were abnormal with evidence suggestive of possible recent myocardial ischemia present in 13 cases. Patient 19 had ECG findings clearly indicative of ischemia. Findings are summarized in Table 1. Three patients had a Hunt and Hess grade of 2, 26 were grade 3, 9 were grade 4, and 1 was unknown (mean 2.4, SD = 0.8). One patient had a Fisher score of 0, 1 had a score of 1, 4 had a score of 2, 23 had a score of 3, 8 had a score of 4, and 2 were unknown (mean 3.0, SD = 0.8). One patient had a past medical history significant for cardiac disease. No patient in this group had cardiac complications during their admission. There was no association between elevated cTnI and

abnormal EKG ($p = .401$). Elevated and non-elevated patients did not differ on Hunt and Hess grade ($p = .846$) or Fisher score ($p = .834$).

Discussion

It has long been known that patients suffering from aneurysmal SAH have an increased incidence of cardiac abnormalities. Rhythm, repolarization, and voltage irregularities have been noted by many investigators in up to 90% of such patients [5–9, 11, 18, 19, 21, 23, 27, 28, 32, 33, 36].

When faced with the above finding it is important to determine the significance of such transient irregularities. Levine demonstrated normal postmortem myocardiums in SAH patients who had ECG findings consistent with myocardial infarction. Other investigators, however, have reported different findings. Kolin found a greater than 90% incidence of transmural myocardial damage at autopsy in eight of nine SAH patients [20]. Browers found a 100% incidence of at least one abnormal ECG in 61 individuals suffering from SAH. Of seven autopsied patients who died of cerebral complications, four had subendocardial bleeding and fibrosis [4]. Koskelo and Pollack also noted subendocardial damage at the time of autopsy in three cases of SAH [22, 27]. The clinical relevance of these findings, however, is questionable since no patients in these studies died from myocardial injury. Browers and Hersch felt that poor outcome amongst patients with more severe ECG irregularities was due to the fact that ECG abnormalities were indicators of severe intracranial disease [4, 19]. Fabinyi, Cruickshank, Pollick, and Davies agreed, feeling that myocardial injury was due to sympathetic changes and catecholamine release that concomitantly contributed to the development of intracranial vasospasm and cerebral ischemia [5–7, 13, 20, 27].

The mechanism for cardiac rhythm disturbances and myocardial injury in cases of SAH could include ischemia/infarction associated with coronary artery disease, ischemia/infarction secondary to catecholamine exposure, and sympathetic discharge and secondary changes in ventricular repolarization [35]. Doshi found that 42 of 54 patients who died following SAH had hypothalamic and myocardial necrosis, the latter of which resembled that seen with pheochromocytomas and catecholamine ingestion. Control patients with increased intracranial pressure from other causes had normal hypothalamic and cardiac studies [10]. Pollick made similar observations speculating that compromised hypothalamic circulation lead to a derangement in autonomic function [27]. Experimental studies support the theory that hypothalamic derangement can lead to ECG changes [12, 26]. Other regions whose manipulation may cause autonomic dysfunction and cardiac irregularities include the Circle of Willis, orbital frontal cortex Brodman's area 13, upper midbrain, and limbic system [8, 15, 30].

Having ascertained from published reports that many SAH patients display ECG changes and that some of these same individuals demonstrate elevations in cardiac enzymes which may portend a worse neurologic outcome because of the relationships between cardiac injury, dysrhythmia, hypothalamic injury, catecholamine release, sympathetic derangement, and vasospasm we must now determine how we can best monitor such patients to detect those at greatest risk. Dimant studied ten SAH patients. Eighty percent had abnormal ECGs. At autopsy some of these patients had subendocardial hemorrhages and focal areas of myocardial cell injury and myocytolysis which did not correlate with ECG changes. He concluded that ECG abnormalities were ubiquitous in the SAH population yet were poorly predictive of significant myocardial damage [8]. Davies came to a similar conclusion. He studied 41 SAH patients without significant history of cardiac disease. The four patients who had wall motion abnormalities on 2-D echocardiography had only minor ECG changes. Other individuals with ECG abnormalities including deeply inverted T waves had normal echocardiograms [7]. Mayer, however, felt that certain ECG changes were significant. In his study of 57 SAH patients five (8%) had wall motion abnormalities. Four of these developed hypotension and three manifested pulmonary edema within six hours of their bleed. Of these five patients all demonstrated both T wave inversions and QT prolongations. A much smaller number of patients without wall motion abnormalities exhibited similar ECG changes [24, 25]. Kono also felt certain ECG changes correlated with cardiac dysfunction. Of 12 patients with SAH, seven had ST elevations all of whom demonstrated decreased left ventricular apex wall motion in comparison to those patients without ST elevations. Motion improved in all five patients. This dysfunction followed by improvement lead to the term "neurogenic stunned myocardium" [21]. Pollick similarly studied 13 SAH patients using 2-D echocardiography and found four with wall motion abnormalities all of which devel-

Table 1

Pat	Age	Sex	Hour post SAH Troponin determined					HH Gr	Troponin		EKG findings	Echo finding	Aneurysm	Clinical cardiac findings
			24	24–48	48–72	72–96	96–144							
1	69	F	x					3	1.5		D1; QRS1, ST1	Not done	PICA	Died from post op MI
2	53	F	x	x				3	2.8	2.4	ST1; T	Not done	SUP HYP	None
3	35	M	x						2	1.8	No EKG available	Not done	PICA	None
4	57	F	x	x				1	6.0	2.8	D2; QRS2; T; ST2	Ant/lat wall akinesis; Depressed LV function	P COMM	Pre-op MI
5	27	M	x	x				3	3.8	3.4	D2; P3; T; ST3; ST4	Hypokinesis LV	?	None
6	40	F	x	x				3	9.9	7.1	ST1 detected	No abnormalities	?	None
7	40	F	x					2	1.9		Normal EKG	Not done	P COMM	None
8	40	F	x	x				2	2.8	2.1	T	Hypokinesis	PICA	None
9	44	F	x	x				2	<0.4		Normal EKG	Not done	SCA	None
10	56	F	x					3	<0.4		T	Not done	BAS TIP	None
11	79	F					x	3	<0.4		T	Not done	BAS TIP	None
12	58	F					x	3	<0.4		QRS1	Not done	P COMM	None
13	80	F	x					2	<0.4		QRS1	Not done	P COMM	None
14	49	F				x		3	<0.4		QRS4; QRS5	Not done	BAS TIP	None
15	46	F					x	2	<0.4		T	Not done	A COMM	None
16	49	F			x	x		3	<0.4		T; ST1	Not done	BAS TIP	None
17	38	F					x	3	<0.4		D2; P1; P2	Not done	BAS TIP	None
18	43	F	x	x				?	<0.4		No EKG available	Not done	MCA	None
19	52	F			x			2	<0.4		Q1; ORS5; ST3; T	Not done	SCA	Prior CABG
20	33	M		x				1	<0.4		Normal EKG	Not done	A COMM	None
21	60	F	x					3	<0.4		Normal EKG	Not done	PCA	None
22	40	M		x				1	<0.4		Normal EKG	Not done	OPH	None
23	41	F	x	x				2	<0.4		Normal EKG	Not done	PICA	None
24	39	M		x	x			2	<0.4		Normal EKG	Not done	OPH	None
25	43	F	x					3	<0.4		No EKG available	Not done	SUP HYP	None
26	54	F	x					3	<0.4		D2	Not done	A COMM	None
27	41	F		x				2	<0.4		Normal EKG	Not done	P COMM	None
28	37	F	x	x				3	<0.4		Normal EKG	Not done	?	None
29	49	M	x	x				2	<0.4		Normal EKG	Not done	P COMM	None
30	56	M	x	x				3	<0.4		Normal EKG	Not done	BAS TIP	None
31	47	F	x	x				3	<0.4		QRS1; T; ST5	Not done	PERICAL-LOSAL	None
32	85	F			x			0	<0.4		D4; P4; QRS1	Not done	PICA	Hx of CHF
33	67	F			x			3	<0.4		P2; QRS3	Not done	MCA	None
34	64	F	x					2	<0.4		ST3	Not done	A COMM	None
35	51	M		x				1	<0.4		Normal EKG	Not done	P COMM	None
36	60	M			x			1	<0.4		T	Not done	SCA	None
37	60	F	x					3	<0.4		QRS1	Not done	P COMM	None
38	56	F	x					3	<0.4		T	Not done	PICA	None
39	38	F		x				3	<0.4		Normal EKG	Not done	MCA	None
40	48	F	x					3	<0.4		T	Not done	VERT CONFL	None
41	71	M	x	x				2	<0.4		T; ST1	Not done	P COMM	None
42	76	F	x					3	<0.4		P2; QRS3; T	Not done	BAS TIP	None
43	63	F		x				3	<0.4		D4; T	Not done	ANT CHOR	None
44	52	F	x					2	<0.4		P2; QRS4	Not done	P COMM	None
45	35	F	x					3	<0.4		Normal EKG	Not done	P COMM	None
46	42	M	x					2	<0.4		P1; QRS1; T	Not done	A COMM	None
47	69	F	x					3	<0.4		ST1; T	Not done	PICA	None

(to be continued)

Table 1. *Continued*

Pat	Age	Sex	Hour post SAH Troponin determined					HH Gr	Troponin	EKG findings	Echo finding	Aneurysm	Clinical cardiac findings
			24	24–48	48–72	72–96	96–144						

EKG Abbreviations:

Dysrhythmia (D)
1 Sinus bradycardia
2 Sinus tachycardia
3 Normal sinus rhythm
4 Premature ventricular contraction

P wave changes (P)
1 Right atrial enlargement
2 Left atrial enlargement
3 Left atrial abnormality
4 First degree atrioventricular block

QRS changes (ORS)
1 Left ventricular hypertrophy
2 Left axis deviation
3 Right bundle branch block
4 Intraventricular conduction defect

T wave changes (T)

ST segment changes (ST)
1 Non-specific changes
2 Elevation

oped within the first 48 hours of their ictus. Two of these four had left ventricular apical thrombi and two developed pulmonary edema. Three of the four died due to cerebral vasospasm and of these one had evidence of subendocardial infarction. All patients without wall motion abnormalities were alive at three months. This study leads one to conclude that patients with myocardial injury are also neurologically more compromised and that ECG and echocardiographic changes do not necessarily indicate permanent cardiac injury [27].

In view of the finding that a number of patients with SAH have ECG findings consistent with myocardial injury and 2-D echocardiograms consistent with cardiac dysfunction, some investigators have studied patients using cardiac enzyme levels to help determine which patients were experiencing cardiac injury. Fabinyi studied 16 SAH patients, seven of whom had increased CK-MB. All seven developed cerebral vasospasm or other reversible neurologic deficit. He concluded that elevated CK-MB may be an indicator of cerebral ischemia and myocardial injury secondary to sympathetic dysfunction [13]. Schell described one patient with SAH and presumed neurogenic pulmonary edema. This individual also displayed elevated CK-MB, elevated pulmonary capillary wedge pressure, wall motion abnormalities, decreased left ventricular ejection fraction, and no ECG evidence of myocardial infarction. Schell concluded from this patient's findings that pulmonary edema in similar cases may be cardiogenic rather than neurogenic in origin [29].

The use of CK-MB as a marker of cardiac injury following SAH is problematic for a number of reasons. CK-MB can be elevated with skeletal muscle injury such as that occurring following a fall or seizure. The use of the ratio of CK-MB : total CK is not a very sensitive test for separating out skeletal muscle vs cardiac muscle contributions to CK-MB levels [1]. Therefore, if one wants to study the incidence of myocardial injury immediately following SAH it would be ideal to use a marker as sensitive as CK-MB but with a greater specificity. In this way there could be little argument that the incidence was skewed by elevations in isoenzyme from sources other than the heart. Cardiac troponin I is just such a marker.

While troponin I is found in cardiac and skeletal muscle, cTnI is a product of a different gene with a unique amino acid sequence. Monoclonal antibodies to cTnI have no cross reactivity with skeletal muscle forms [1]. In addition, cTnI is not expressed in neonatal skeletal muscle or in skeletal muscle after acute or chronic injury, is not found in individuals with renal failure who have elevated CK-MB, and is found at a 13 times higher concentration in myocardium than is CK-MB [17]. According to a number of studies the cardiac specificity of cTnI is 99.2% vs CK-MB which is 81–92%, total CK which is 87.4%, myoglobin which is 89%, and troponin T which is 89.8% [2, 31]. Cardiac sensitivity is equivalent to that of CK-MB. Most importantly, for a study aimed at elucidating the incidence of myocardial injury immediately following SAH, cTnI elevates to clinically significant

levels 4–8 hours following the injury and may remain elevated for 5–9 days post injury [34]. Therefore, cTnI appears to be the ideal marker for defining the true incidence of SAH associated cardiac injury. Its sensitivity rivals that of CK-MB and its specificity exceeds that of CK-MB, the previous gold standard. Finally, like CK-MB, cTnI is more sensitive and specific than ECG and echocardiography to subtle levels of myocardial injury [2].

The determination of cTnI levels in SAH patients may be important for more than just academic purposes. Myocardial injury has been correlated with neurologic outcome in such patients by numerous investigators [4, 6, 7, 13, 19, 27]. In addition, myocardial injury in critically ill patients can be an important determinant of outcome and development of complications. In a recent study of 209 critically ill patients admitted to the ICU there was a 15% overall incidence of cardiac injury as determined by cTnI levels and an 11.2% incidence in patients without a primary cardiac diagnosis. Patients with myocardial infarction were more likely than patients without a cardiac injury to be hypotensive (75 vs 49.5%), have CHF (34.4 vs 13.5%), experience arrhythmias (43.8 vs 16.7%), require mechanical ventilation (65.6 vs 26.6%), and die (40.6 vs 14.7%). Perhaps more importantly, mortality for patients with unrecognized cardiac injury was 46.7% [16]. Finally, because SAH patients are often sources for donated organs it might be useful to obtain cTnI levels to help determine the suitability of an individual's heart in terms of transplantation eligibility. Grant *et al.* demonstrated a 63% failure rate of cardiac transplantation in children when donor cTnI values exceeded 3.1 ng/ml [14].

Using cTnI, a very specific and sensitive cardiac marker for myocardial injury, we have demonstrated a minimum 17% incidence of pre-operative cardiac injury following aneurysmal and presumed aneurysmal SAH in a population of patients with a mean age of less than 60 years who have no significant past cardiac disease history. We feel that this value represents the minimal incidence because many patients were taken to surgery before repeat testing for cTnI could be performed or possibly before cTnI could reach a detectable level. In addition, a number of patients were referred to our center several days following their hemorrhage at which point in time it is possible that a marginally elevated troponin level had reverted to normal. Echocardiograms were performed in 4 of the 8 patients with elevated cTnI levels and 3 (75%) showed wall motion abnormalities. A fifth patient died of cardiogenic shock before an echocardiogram could be performed. Finally, ECG abnormalities were common in both elevated and non elevated cTnI groups, thus making ECG findings unreliable. This is especially important in view of the fact that no patients with a normal cTnI level and abnormal ECG had postoperative cardiac complications. Hunt and Hess grade and Fisher score seemed to have no correlation to the development of cardiac injury. Trends in the Glascow outcome score could not be related to the presence of elevated cTnI due to the small sample population.

Conclusion

While this study may well underestimate the incidence of myocardial injury in the aneurysmal SAH patient population, a 17% incidence should alert neurosurgeons and others who participate in the care of such patients to the possibility of cardiac dysfunction. This knowledge will hopefully aid in the care and improve the outcome in this often fragile group of patients.

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Comment

To assess the incidence of myocardial injury after aneurysmal (or presumably aneurysmal) SAH, Horowitz *et al.* have determined serum troponin I (cTnI) in 47 patients within 24 to 144 hours of SAH.

8 patients (17%) all tested within 24 hours had elevated (>0.4 ng/ml) levels of cTnI. The result is interpreted as indicating that at least 17% of patients with SAH suffer ''cardiac dysfunction''. Indeed the figures could have been different had the first determination been made within 24 hours in *all* patients.

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