Neurocardiogenic Injury in Neurovascular Disorders

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The interconnection between the central nervous system and the heart was first described by Cushing [1] at the turn of the twentieth century. Cardiac abnormalities were described thereafter, associated with various central nervous system diseases, including trauma, ischemic stroke, and intracerebral hemorrhage. Less common etiologies include tumors, electroconvulsive therapy, and central nervous system infections such as meningitis [2]. More recently, a new type of neurogenic cardiac injury was described—an emotional or physiologic stress-induced cardiomyopathy (Tako-Tsubo cardiomyopathy or transient left ventricular apical ballooning) [3–5]. Currently, hemorrhagic stroke and ischemic stroke are the best described clinical models of neurocardiogenic injury. Cardiac abnormalities after stroke include electrocardiogram (ECG) changes, cardiac arrhythmias, and myocardial injury and dysfunction.

Electrocardiogram abnormalities

Prevalence

In 1947, Byer and Toth [6] described four patients, including at least two patients with a subarachnoid bleed, whose ECG showed marked QT prolongation with large T and U waves. Subsequently, in 1954, Burch and colleagues [7] described an ECG pattern, most pronounced in the septal leads, consisting of large inverted T waves, prolonged QT intervals, and large U waves; this pattern since has been considered distinctive of cerebrovascular accidents. In the 17 abnormal ECGs reported in their study, the abnormalities were observed most frequently after a subarachnoid bleed,
followed by an intracerebral hemorrhage and an ischemic lesion. ECG abnormalities are common in stroke; their incidence ranges from 49% to 100% in different series [8–12]. ECG changes are seen more commonly in patients with intracerebral hemorrhage (60–70%) or subarachnoid hemorrhage (SAH) (40–70%) than in patients with ischemic stroke (15–40%) [13].

**QT prolongation**

The most common stroke-related ECG abnormality is QT prolongation, found in 45% to 71% of patients with SAH, 64% of patients with intracerebral hemorrhage, and 38% of patients with ischemic stroke [14–17]. QT prolongation often correlates with elevated systolic blood pressure on admission [15,16]. In the absence of hypokalemia, QT abnormalities accompanied by U wave and T wave changes are most likely due to stroke. QT prolongation may occur more commonly with right than with left hemispheric strokes because of some degree of lateralization of autonomic function [18]. Among patients with SAH, ventricular tachyarrhythmias, including sudden death and torsades de pointes, are often preceded by QT prolongation [16,18].

**Repolarization abnormalities**

ST segment changes (including ST elevations) occur in 22% to 35% of patients with ischemic stroke [19,20]. New T wave abnormalities appear in approximately 15% of patients with acute stroke, even in the absence of electrolyte disturbances or primary ischemic heart disease [19]. Inverted or flat T waves have been reported in 55% of patients with SAH [21,22]. The similarities between ECG changes resulting from acute myocardial ischemia and infarction and changes associated with SAH and ischemic stroke have led many investigators to hypothesize coexisting cardiac disease as a cause of the ECG changes. Direct evidence suggests, however, that ECG changes may occur even in patients with normal coronaries. In the series reported by Cropp and Manning [23], of the 29 patients with SAH who had ECG changes, 8 died, and of those, 5 underwent autopsy. None of the autopsied patients had epicardial coronary disease. In a study by Kono and colleagues [24], 12 patients with acute SAH and ST elevations on ECG were found to have apical wall motion abnormalities without any coronary artery stenosis or vasospasm on angiography. These findings, along with the observation that stroke-induced ECG changes are evanescent, resolving over days to months with little residuum, argue against myocardial ischemia or infarction as a cause of the ECG changes.

**Other electrocardiogram abnormalities**

New Q waves similar in morphology to those observed in acute myocardial infarction are common after acute stroke. The Q waves may be transient
or proceed through the evolutionary changes seen in myocardial infarction [15,19]. New Q waves have been identified in about 10% of patients with acute ischemic or hemorrhagic stroke [14,17]. U waves unrelated to any electrolyte abnormality are common after stroke. They may occur in isolation or with T waves and QT abnormalities. Studies found new U waves in 13% to 15% of patients with acute ischemic stroke and SAH [15,25]. U waves were distributed equally between ischemic and hemorrhagic strokes, and there was no relation between the presence of U waves and stroke mortality. The combination of U waves and QT prolongation was more common among patients with intracerebral hemorrhage and SAH [15]. One study showed that standard ECG criteria for left ventricular hypertrophy were met in 14% of patients with SAH, none of whom had a history of coronary artery disease (CAD), and 43% of whom had no history of hypertension [25].

Implication of electrocardiogram abnormalities

The data on the prognostic significance of ECG changes in SAH are inconsistent partly as a result of the fact that available studies were retrospective and had limited power to adjust for comorbid factors. One study showed that ischemic ECG abnormalities are associated with poor neurologic outcomes, but not with the all-cause mortality [26]. Kawasaki and colleagues [27] reported an ECG scoring system based on the presence of Q waves, ST depression, and inverted T waves. In their study, an ECG score of 6 or higher was a significant predictor of in-hospital mortality and adverse neurologic outcomes. Another study failed to show any association between ECG changes and adverse outcomes after SAH [28].

Management of electrocardiogram abnormalities

ECG changes usually do not require specific treatment [13]. Comparison with previous ECGs may be helpful. Apart from intensive cardiovascular monitoring, appropriate investigations should be directed at identifying other causes or contributors. The latter may require specific treatment. Prolonged QT interval can be due to hereditary long QT syndrome, hypokalemia, hypomagnesemia, and toxic effects of some antiarrhythmic (eg, quinidine, sotalol, amiodarone) or antipsychotic (eg, haloperidol) drugs. Acute myocardial infarction and hyperkalemia can produce tall T waves. Hypokalemia is the most common cause of U waves. Acute coronary ischemia can produce ST segment depression or elevation, T wave inversion, and Q waves.

Cardiac arrhythmias

Prevalence

Arrhythmias are seen in 20% to 40% of patients with ischemic stroke or intracerebral hemorrhage and in nearly 100% of patients with SAH and
may include bradycardia, supraventricular tachycardia, atrial flutter, atrial fibrillation, ectopic ventricular beats, multifocal ventricular tachycardias, torsades de pointes, ventricular flutter, and ventricular fibrillation [13]. Most arrhythmias occur within the first week after stroke [29].

In his retrospective study of 150 patients with acute stroke, Goldstein [15] found a 25% incidence of new arrhythmias compared with 3% in the control group. Of these, the most common was atrial fibrillation, occurring in 14% of patients. Ventricular arrhythmias occurred in about 5% of patients with acute stroke. Similar findings were noted by Yamour and associates [17], who also reported a correlation between the occurrence of brainstem bleeds and atrial fibrillation. Sinus bradycardia and supraventricular tachycardias were seen more commonly with traumatic frontal lobe hemorrhage (33%), whereas atrial and ventricular ectopy was seen more frequently with temporal-parietal bleeds. In patients with SAH, Stober and coworkers [30] noted sinus bradycardia in 23%, multifocal ventricular ectopy in 54%, asystolic intervals in 27%, and atrial fibrillation in 4%. In one prospective study of ischemic stroke patients, ventricular premature contractions were the most common cardiac arrhythmia, followed by atrial premature contractions, supraventricular tachycardia, and atrial fibrillation [31]. The importance of continuous ECG monitoring, especially early on in the course of SAH, was underscored by Di Pasquale and coworkers [32–34], who found that the frequency and severity of arrhythmias were significantly higher in patients studied within 48 hours of onset of SAH. In one study of the monitored patients, rhythm disturbances occurred in 35%, most commonly sinus tachycardia or bradycardia [21]. Additionally, ventricular arrhythmias, such as asystole and fibrillation, were recorded, with 5% showing a life-threatening arrhythmia [21]. In addition to the above-mentioned atrial and ventricular arrhythmias, a polymorphic ventricular tachyarrhythmia (torsades de pointes) was detected in about 4% of SAH patients; it has been shown to correlate with prolongation of the QT interval on the ECG [35,36].

**Mechanism of cardiac arrhythmias**

A significant proportion of cardiac arrhythmias occur in patients with normal cardiac function, suggesting neurogenic mechanisms. The type and location of the stroke determine the type of arrhythmia, with each cerebral hemisphere having a different influence on cardiac functions. Animal studies show that the sinoatrial node is under right-sided autonomic control, and that stimulation or inhibition of the right medulla, hypothalamus, and cerebral hemisphere exerts a greater influence on heart rate than do comparable manipulations on the left. Bradycardia and vasodepressor effects are more common with injury to the right insula, whereas tachycardia and hypertension are more common with injury of the left insular region. Supraventricular arrhythmias are more common after stimulation of the right hemisphere [18,37,38]. Because supraventricular tachycardia can be
activated by an increase in sympathetic tone, it is hypothesized that the impaired parasympathetic tone caused by right hemispheric injury is responsible for the excess in arrhythmias [16,37,38]. QT prolongation also is more common after right middle cerebral artery occlusion, explaining the higher incidence of fatal arrhythmias and sudden death after right hemispheric strokes [18,38].

Management of cardiac arrhythmias

A detailed discussion on the management of a wide range of cardiac rhythm disturbances that one can encounter in patients with acute ischemic or hemorrhagic stroke is beyond the scope of this article, and only a short overview is presented here. Importantly, patients with hemodynamically unstable bradyarrhythmias or tachyarrhythmias (supraventricular or ventricular) should be managed immediately according to advanced cardiac life support guidelines, probably in the setting of an institutional “code blue” protocol with subsequent transfer to the ICU and involvement of a cardiac team.

The following recommendations relate to a patient with stable hemodynamics and symptoms. Atrial or ventricular premature contractions generally do not require specific treatment. Therapy for sinus bradycardia or tachycardia should be aimed at correcting the underlying conditions (eg, intracranial hypertension, hyperthermia or hypothermia, hypothyroidism or hyperthyroidism, medications, anemia, pain, sepsis, anxiety). If the patient develops supraventricular tachycardia, a trial of adenosine for termination of the arrhythmia would be appropriate. An intravenous β-blocker, calcium channel blocker, or amiodarone can be used to control the heart rate in patients with atrial fibrillation or flutter and rapid ventricular response. Stable ventricular tachyarrhythmias can be managed with intravenous amiodarone or lidocaine. Any hypokalemia, hypomagnesemia, or acidosis must be corrected. Specific treatment of torsades de pointes includes intravenous magnesium. Drugs that prolong QT interval should be discontinued. In a case of hemodynamically stable bradyarrhythmias or tachyarrhythmias, more complex than sinus bradycardia or tachycardia or ectopic beats, an urgent cardiology consultation is recommended.

Myocardial injury and dysfunction

Pathologic correlates

Considerable evidence has accrued that ischemic and hemorrhagic stroke are associated with myocardial damage that does not seem to be secondary to ischemia. SAH-induced cardiac injury provides a robust example of neurocardiogenic injury and is a well-studied clinical model. Patients and animals dying after intracranial hemorrhage have been shown to develop
subendocardial lesions, presumably secondary to excessive sympathetic stimulation [39–42]. Offerhaus and Van Gool [43] showed convincingly that after intracranial hemorrhage, there was an increase in cardiac tissue catecholamines. These catecholamine-induced subendocardial lesions are known variously as contraction band necrosis, coagulative myocytolysis, or myofibrillar degeneration. Cardiac myofibrillar necrosis is histologically identical to the cardiac lesions of catecholamine infusion, “voodoo death,” hypothalamic stimulation, or reperfusion of transiently ischemic cardiac muscle [44]. The myofibrillar necrosis occurs in the vicinity of the cardiac nerves and not in the macrovascular distribution seen in patients with coronary disease [44,45]. The lesion also differs from the necrosis seen in coronary disease because it is visible within minutes of onset, and the cells die in a hypercontracted state with contraction bands, associated mononuclear infiltration, and early calcification [44,45].

Cardiac enzymes

Cardiac enzyme elevations are common in ischemic stroke and hemorrhagic stroke and provide evidence that myocardial necrosis may occur. Elevations of creatine kinase (CK) or CK-MB (isoenzyme of CK with muscle and brain subunits) level are seen in 10% to 45% of stroke patients, and there is a good correlation between elevation in CK-MB and stroke-induced ECG changes or cardiac arrhythmias [13,45]. In contrast to acute myocardial infarction, a stroke-induced increase in serum CK-MB levels occurs more slowly and peaks at a much lower value on around day 4 after stroke [46]. Cardiac troponin I elevations have been described in 20% to 25% of patients with SAH [47–49]. The degree of neurologic injury and female gender are strong predictors of myocardial necrosis after SAH (Fig. 1 and Table 1) [48]. That the severity of the initial neurologic injury (Hunt Hess grade) is a strong independent predictor of myocardial necrosis suggests a neurally mediated form of cardiac injury that occurs early in the course of SAH [49].

Left ventricular dysfunction

Global or regional left ventricular systolic dysfunction has been described after SAH with an approximate incidence of 10% to 28% [24,50,51]. Diastolic dysfunction also is common after SAH and is associated with the severity of neurologic injury and may be the cause of pulmonary edema in many patients [52]. Despite advances in diagnostic techniques of cardiac disease, the pathophysiology is unclear. A few proposed hypotheses, such as myocardial ischemia or infarction from CAD, vasospasm, and supply-demand mismatch, have not been proved. A neurogenic catecholamine-mediated mechanism of injury or “the catecholamine hypothesis” has been shown in experimental and clinical studies [53–56]. A study has shown
a link between the severity of neurologic injury and left ventricular dysfunction (Fig. 2) [57].

A study by Banki and colleagues [58] found an association between regions of contractile dysfunction and abnormalities in myocardial sympathetic innervation while showing normal perfusion. This study used a combination of echocardiography with a scintigraphic evaluation of cardiac innervation (using meta-[123I]iodobenzylguanidine [MIBG] isotope) and perfusion (using technetium sestamibi) imaging in patients with SAH. As shown in Table 2, patients with functional cardiac denervation

Table 1
Determinants of myocardial necrosis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariate</th>
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<th>Multivariate</th>
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<tr>
<td></td>
<td>OR</td>
<td>P</td>
<td>95% CI</td>
<td>OR</td>
<td>P</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (per 10-y increase)</td>
<td>1.16</td>
<td>.262</td>
<td>0.90–1.49</td>
<td>1.54</td>
<td>.112</td>
<td>0.90–2.62</td>
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<tr>
<td>Female (versus male)</td>
<td>2.98</td>
<td>.019</td>
<td>1.20–7.43</td>
<td>34.96</td>
<td>.009</td>
<td>2.47–495.01</td>
</tr>
<tr>
<td>Body surface area (per 0.2 m² increase)</td>
<td>1.03</td>
<td>.847</td>
<td>0.78–1.36</td>
<td>2.20</td>
<td>.025</td>
<td>1.11–4.39</td>
</tr>
<tr>
<td>Hunt Hess &gt; 2 (versus 1–2)</td>
<td>8.47</td>
<td>&lt;.001</td>
<td>3.43–20.92</td>
<td>6.62</td>
<td>.026</td>
<td>1.25–34.82</td>
</tr>
<tr>
<td>Systolic blood pressure (per 20 mm Hg increase)</td>
<td>0.78</td>
<td>.019</td>
<td>0.64–0.96</td>
<td>0.52</td>
<td>.007</td>
<td>0.32–0.83</td>
</tr>
<tr>
<td>Heart rate (per 10 beats/min increase)</td>
<td>1.26</td>
<td>.001</td>
<td>1.10–1.43</td>
<td>1.61</td>
<td>.005</td>
<td>1.16–2.25</td>
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<tr>
<td>Phenylephrine dose (per 50 µg/min increase)</td>
<td>1.17</td>
<td>&lt;.001</td>
<td>1.07–1.28</td>
<td>1.47</td>
<td>.010</td>
<td>1.10–1.98</td>
</tr>
<tr>
<td>LVMi (per 20 g/m² increase)</td>
<td>1.23</td>
<td>.083</td>
<td>0.97–1.55</td>
<td>1.74</td>
<td>.032</td>
<td>1.05–2.89</td>
</tr>
<tr>
<td>SAH to cTiα (per 1 day increase)</td>
<td>0.86</td>
<td>.001</td>
<td>0.78–0.94</td>
<td>0.70</td>
<td>.008</td>
<td>0.54–0.91</td>
</tr>
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Abbreviations: CI, confidence interval; LVMi, left ventricular mass index; OR, odds ratio.

a Time in days from SAH symptom onset to measurement of cardiac troponin I.

exhibited higher (worse) regional wall motion scores and more troponin release compared with patients without evidence of cardiac denervation. All study subjects had normal perfusion imaging suggesting a neurogenic mechanism of cardiac injury [58]. Fig. 3 shows normal perfusion and global denervation in a patient with SAH whose echocardiogram showed global left ventricular systolic dysfunction.

The pattern of regional wall motion abnormality seen in SAH patients differs from the typical patterns seen in coronary artery disease. There is a well-shown, unique, apical-sparing pattern in SAH patients. The most frequently affected segments in one study were the basal and midventricular portions of the anteroseptal and anterior walls and the midventricular portions of the inferoseptal and anterolateral walls [59].

Table 2

<table>
<thead>
<tr>
<th></th>
<th>H:M &gt; 1.57 (N = 19)</th>
<th>H:M &lt; 1.57 (N = 18)</th>
<th>P</th>
</tr>
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<tr>
<td>LVEF &lt; 50%</td>
<td>32%</td>
<td>61%</td>
<td>.072a</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>53 ± 15</td>
<td>51 ± 16</td>
<td>.61b</td>
</tr>
<tr>
<td>RWMS &gt; 1.0</td>
<td>47%</td>
<td>83%</td>
<td>.038c</td>
</tr>
<tr>
<td>Mean RWMS</td>
<td>1.3 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>.071b</td>
</tr>
<tr>
<td>cTi &gt; 1.0</td>
<td>16%</td>
<td>50%</td>
<td>.038c</td>
</tr>
<tr>
<td>Mean cTi</td>
<td>2.9 ± 10.2</td>
<td>5.3 ± 11.8</td>
<td>.15b</td>
</tr>
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</table>

Abbreviations: cTi, cardiac troponin I; LVEF, left ventricular ejection fraction; RWMS, regional wall motion score.

study of SAH patients showed reversibility and global and regional left ventricular dysfunction, most commonly affecting the anterior and anteroseptal walls that do not involve the apex [60]. Younger age and anterior aneurysm position were independent predictors of this pattern [61]. This apical-sparing pattern of left ventricular dysfunction argues against an obstruction or vasospasm of coronary arteries and provides indirect evidence of neurally mediated mechanism of injury. Data from Zaroff and colleagues [62] suggest that genetic polymorphisms of the adrenoceptors are associated with an increased risk of cardiac abnormalities after SAH, further supporting the hypothesis that cardiac dysfunction after SAH is a form of neurocardiogenic injury.

Neurogenic cardiac injury seems to occur during an initial “neural” phase based on clinical data and from an animal model that suggests cardiac injury occurs within hours of experimental SAH [63]. Elevated serum or
cerebrospinal fluid levels of inflammatory cytokines, including tumor necrosis factor-α, interleukin-6, interleukin-1, interleukin-1α, and interleukin-8, as well as neurohormones such as endothelin and B-type natriuretic peptide (BNP), have been described days after SAH, suggesting a second, humoral phase of neurocardiogenic injury [64]. Elevated serum, but not cerebrospinal fluid, levels of tumor necrosis factor-α receptor I and interleukin-1 receptor antagonist are associated with organ system dysfunction [65]. These humoral elements may play a crucial role in cerebral vasospasm, a common complication after SAH that causes markedly increased morbidity and mortality [66]. Whether further cardiac injury occurs during this phase is unclear. Fig. 4 shows the results of a study of 57 SAH patients suggesting that elevated serum levels of BNP are associated with cardiac injury, and that left ventricular dysfunction is indicative of injury related to neurohormonal activation [67].

Natural history

Cardiac dysfunction that occurs after SAH may normalize over time based on case reports and small studies [68–70]. The onset of left ventricular dysfunction occurs early in the course of SAH [59,61]. In the largest study to date, a regional wall motion abnormality was most likely to be present within the first 2 days [59]. The prevalence declines during days 3 to 8. In this same study, the authors showed complete or partial resolution of left ventricular dysfunction.

Fig. 4. BNP levels and cardiac outcomes. The column height indicates the mean BNP, and the error bars indicate 95% confidence intervals. Probability values indicate results of Wilcoxon rank-sum tests. cTi, cardiac troponin I > 1.0 μg/L; EF, left ventricular ejection fraction <50%; RWMA, regional wall motion abnormality. (From Tung PP, Olmsted E, Kopelnik A, et al. Plasma B-type natriuretic peptide levels are associated with early cardiac dysfunction after subarachnoid hemorrhage. Stroke 2005;36:1567–9.)
ventricular dysfunction in most patients during the acute hospitalization. There is no important difference in cardiac outcomes after surgical aneurysm clipping versus percutaneous aneurysm coiling [71]. It is unclear what risks are associated with neurocardiogenic injury after hospitalization; however, it seems that although sympathetic denervation may persist, left ventricular systolic dysfunction appears reversible over 6 months in most cases [72].

Clinical implications of myocardial injury and dysfunction

Clinical implications of neurocardiogenic injury extend beyond the observed cardiac morbidity and mortality. Several studies have shown an association between myocardial injury and dysfunction and adverse neurologic outcomes. Mayer and colleagues [73] showed that in some SAH patients, reduction of cardiac output from normally elevated levels may increase the risk of cerebral ischemia related to vasospasm. Their subsequent study showed that troponin elevation after SAH is associated with an increased risk of cardiopulmonary complications, delayed cerebral ischemia, and death or poor functional outcome at discharge [74]. Another study suggested that BNP levels are associated independently with hyponatremia and delayed ischemic neurologic deficits and predict the 2-week Glasgow Coma Scale score [75]. A study by Yarlagadda and colleagues [76] showed that elevated troponin and BNP levels are independent and strong predictors of inpatient mortality after SAH. Measurement of troponin and BNP levels and the obtaining of an echocardiogram seem justified as part of the initial management of patients with SAH.

Treatment

Pharmacologic therapy

Because the mechanism of neurogenic cardiac injury is likely catecholamine mediated, the treatment should focus on correcting or palliating the underlying neurologic process. For patients with SAH, current treatments include prevention of rebleeding with early aneurysm clipping surgery or endovascular treatment. Evidence indicates that there is no significant difference in cardiac morbidity between surgical and endovascular therapies [71]. Cerebral vasospasm may be treated with triple-H therapy (hypertension, hypervolemia, and hemodilution). Nimodipine, a dihydropyridine calcium channel blocker, is associated with improved neurologic outcomes after SAH [77–80]. Although most patients tolerate these therapies, one should be aware of the potential cardiac toxicities. Permissive or induced hypertension may improve cerebral blood flow, but increases myocardial wall stress and oxygen consumption, and hemodilution decreases oxygen delivery to the myocardium, predisposing to further injury. A more recent study found that phenylephrine is relatively ineffective in patients with low left ventricular ejection fraction (Fig. 5) [76], and some authors suggest
alternative agents with inotropic properties, such as dobutamine and milrinone [81]. In addition, deliberate hypervolemia may cause increased filling pressures leading to pulmonary edema, especially in patients with diastolic dysfunction. These therapies should not be withheld in most cases, however, given the increased morbidity and mortality of untreated vasospasm [82–84].

Given the role of excessive catecholamines as the likely cause of cardiac injury after SAH, β-blockers may have a role in providing cardioprotection if administered early in the hospital course. Only two small studies have investigated this therapy. The first study showed resolution of abnormal ECG changes associated with SAH after administration of 80 mg of propranolol [85]. The second study was a randomized, double-blinded, placebo-controlled trial of 12 patients comparing 80 mg of propranolol and 20 mg of phentolamine with placebo given within the first 48 hours [86]. Although there was no mortality benefit in the treatment group, necrotic myocardial lesions were present in all six patients who died in the placebo group, in contrast to the six patients who died in the treatment group who had no necrotic myocardial lesions. This small study suggests that β blockade may protect myocytes from the hostile environment caused by massive levels of catecholamines released from cardiac sympathetic nerve terminals after SAH. Larger studies would be helpful to determine the role of early administration of β-blockers in patients with left ventricular dysfunction after SAH.

The final step in the pathway of neurocardiac injury is hypothesized to be excessive norepinephrine within the myocardium, leading to cytosolic and intramitochondrial calcium overload resulting in contraction band necrosis [10,87,88]. To date, no trials have investigated the role of calcium channel
Blockers in SAH patients to prevent cardiac injury. Whether or not nimodipine, widely used as a cerebral protectant, also provides cardiac protection remains theoretical, and myocardial injury and dysfunction are seen commonly in clinical practice in patients treated with nimodipine.

**Cardiac catheterization**

Most patients with left ventricular dysfunction after SAH who undergo cardiac catheterization have normal epicardial coronary arteries and no evidence of vasospasm [24]. Although myocardial ischemia or infarction from CAD is an unlikely mechanism of cardiac injury in this setting, cardiac catheterization may be indicated if there is a strong clinical suspicion of plaque rupture or thrombus formation. In addition to clinical signs of heart failure, including cardiogenic pulmonary edema and hypotension, careful analysis of the ECG, assessment of cardiac function by echocardiogram, and evaluation of myocardial necrosis by cardiac markers may help determine the need for cardiac catheterization. Elevations in cardiac markers are common in neurogenic cardiac injury, but typically the levels are not as high seen in acute myocardial infarctions [89]. A close, independent relationship has been established between Hunt Hess grade and the probability of troponin release [49]. The CK-MB trend should not be used for differentiation between neurogenic injury and myocardial infarction; inconsistencies between ECG changes and location of left ventricular systolic dysfunction may be more helpful [89]. In addition, common “neurogenic” ECG changes, including T wave inversion, QTc prolongation, a shorter P-R interval, and the presence of U waves, may aid in differentiating neurogenic injury from myocardial infarction [85]. One cannot rely solely on the ECG because ST elevation may occur in neurogenic cardiac injury and mimic a transmural infarction. In the event of a rare coronary plaque rupture, percutaneous coronary intervention along with stenting may be indicated in an appropriate SAH patient. Percutaneous coronary intervention typically is followed by short-term anticoagulation using unfractionated heparin and administration of a platelet glycoprotein IIb/IIIa receptor antagonist and long-term antiplatelet therapy with aspirin and clopidogrel. This intense antithrombotic regimen is unsafe in the setting of a recently ruptured unsecured intracranial aneurysm, when the risk of spontaneous rebleeding is already high. The risk of aneurysm rebleeding is maximal during the first 24 hours, then is evenly distributed at a rate of 1% to 2% over the first 4 weeks. In a consecutive series of SAH patients, the risk of rebleeding in untreated patients was estimated to be 35% to 40% [90]. Although further studies are needed to determine the safety of percutaneous coronary intervention/stenting and anticoagulation after successful aneurysmal intervention, patients with unsecured aneurysms should not undergo any coronary intervention given the unacceptably high risk of rebleeding.

Treatment of cerebral vasospasm with triple-H therapy may reduce the delayed neurologic deficits and the significant morbidity and mortality
associated with this condition [82–84]. Because of the increased myocardial oxygen demand and decreased delivery associated with hypertension and hemodilution, this therapy may be poorly tolerated in patients with severe left ventricular dysfunction and heart failure. SAH patients with severe neurogenic cardiac injury and evidence of heart failure who cannot tolerate triple-H therapy may benefit from placement of an intra-aortic balloon pump to increase cerebral perfusion pressure in the setting of vasospasm [68,91,92].

Similar to victims of head trauma and anoxic brain injury, SAH patients may develop brain death and become potential heart donors. Many of these hearts are declined because of left ventricular dysfunction observed on preliminary transplant workup. According to the United Network for Organ Sharing in 1998, only 42% of potential donor hearts were transplanted [93]. One main reason for this low yield was left ventricular dysfunction; in 1995, 918 of 2199 potential donors were unused because of poor ventricular function [94]. Current guidelines help determine which donor hearts would have the greatest success and recommend careful evaluation and assessment of cardiac anatomy and systolic function by echocardiography and cardiac catheterization in patients who are at higher risk for CAD [95]. Because it is likely that left ventricular dysfunction after SAH is reversible and not related to CAD, initial cardiac evaluation that is often obtained under suboptimal conditions may not be an accurate reflection of the long-term left ventricular contractile function. One study showed that donor hearts with left ventricular dysfunction defined by hemodynamic criteria could be functionally resuscitated in 92% of cases, resulting in a 30% increase in donor retrieval rate [96]. Proposed guidelines that suggest evaluation during optimized conditions and more liberal criteria for cardiac catheterization, among other changes in recommendations, are being established to help increase the donor pool without compromising success after transplantation [95].

Because plaque rupture is an uncommon occurrence in SAH patients with left ventricular systolic dysfunction, cardiac catheterization usually is not indicated. The current focus of treatment should be on the underlying neurologic injury because the etiology of cardiac injury is neurogenic, and the degree of cardiac injury is related to the severity of the SAH. In the case of SAH, this includes therapies such as clipping or coiling and triple-H therapy for the treatment of vasospasm. In most cases, treatment of the cardiac injury should be supportive. β-Blockers may provide cardioprotection from the hyperadrenergic milieu around myocytes, but to date have no proven mortality benefit. In the uncommon event of an SAH patient with evidence of cardiogenic shock, a more aggressive diagnostic evaluation is recommended, including echocardiography, cardiac catheterization, and pulmonary artery catheter placement with consideration of intra-aortic balloon pump, if necessary, to maintain adequate cerebral perfusion pressure.
Cardiac evaluation of ischemic stroke patients

In contrast to SAH patients, patients with ischemic stroke are more likely to have concomitant significant heart disease [97]. A strong association between cerebrovascular disease and coronary disease has been established in numerous clinical studies. In the longitudinal Framingham Heart Study, patients with carotid bruits had a higher incidence of transient ischemic attack, stroke, myocardial infarction, and vascular death than patients without bruits, with a relative risk increase between 1.6 and 3.6. Carotid stenosis in patients with carotid bruits (n = 500) predicted cerebral and cardiac ischemic events (annual rates of 6% and 7%) [98]. In 390 patients with transient ischemic attack, the risks of myocardial infarction or sudden death (21%) and stroke (23%) were similar, although cardiac events were more likely to be fatal (63%) than stroke (16%) [99]. Hertzer and colleagues [100] found a 64% (35% severe, 28% surgically correctable) incidence of CAD by coronary angiography among 506 consecutive patients evaluated for carotid endarterectomy in small series. Thallium stress imaging also has shown significant CAD in 45% to 60% of patients with transient ischemic attack or stroke [101]. If suspicion arises, several diagnostic modalities can be used to detect significant coronary disease, including an echocardiogram, exercise or pharmacologic stress test (nuclear or echocardiographic), or coronary angiogram based on the patient’s risk level and functional status (Fig. 6).

When clinically evident CAD has been detected, several steps can be taken to improve cardiac prognosis. Management of atherosclerosis risk factors (diabetes, hyperlipidemia, hypertension, and smoking) and treatment with aspirin and a statin are of undisputed benefit, are noninvasive, and could be applied to all patients with apparent or occult CAD. β-Blockers reduce the risk for vascular events after myocardial infarction, but their role in the prevention of cardiac events in other high-risk patients with stroke is unclear. Finally, revascularization by angioplasty and

![Fig. 6. An approach to cardiac evaluation of patients with stroke. TI, thallium imaging. (From Wilterdink JL, Furie KL, Easton JD. Cardiac evaluation of stroke patients. Neurology 1998;51:S23–6; with permission.)](image-url)
coronary artery bypass grafting are beneficial for patients with symptomatic CAD, particularly patients with multivessel CAD, left main CAD, or the combination of multivessel disease and left ventricular dysfunction. Their role in improving outcome in patients with asymptomatic CAD is less clear [97].

Summary

Cardiac disturbances are diverse and frequent in the setting of stroke and are associated with adverse cardiac and neurologic outcomes. Close cardiac monitoring of stroke patients is recommended, including screening for elevated cardiac enzyme levels and echocardiographic abnormalities in high-risk patients. Treatment priority should be given to the underlying neurologic condition, even in the setting of cardiac dysfunction. Cardiac injury that occurs after SAH seems to be reversible. In contrast to SAH patients, patients with ischemic stroke are more likely to have concomitant significant heart disease. For patients who develop brain death, cardiac evaluation under optimal conditions may help increase the organ donor pool.

References


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