Cardiopulmonary Complications of Brain Injury

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Cardiac and pulmonary complications following acute neurologic injury are common and may be a cause of morbidity and mortality in this population. Examples include hypertension, arrhythmias, ventricular dysfunction, pulmonary edema, shock, and sudden death. Primary neurologic events are represented by stroke, subarachnoid hemorrhage, traumatic brain injury, epilepsy, and encephalitis and have been frequently reported. Given the high frequency of these conditions, it is important for physicians to become familiar with their pathophysiology, allowing for more prompt and appropriate treatment.

Introduction

Cardiac and pulmonary dysfunction occur frequently following acute neurologic injury and are a significant cause of morbidity and mortality in this population [1–3]. Cardiopulmonary sequelae include hypertension, arrhythmias, ventricular dysfunction, pulmonary edema, shock, and sudden death. Neurogenic cardiac and pulmonary dysfunction from stroke, subarachnoid hemorrhage (SAH), traumatic brain injury, epilepsy, and encephalitis [4–6] have all been implicated. Given the high frequency of these conditions, it is important for physicians to become familiar with their pathophysiology, allowing for more prompt and appropriate treatment.

The concept that the brain exerts influence over distant organs has been appreciated for over a century. In 1903, Cushing [7] noted the presence of arrhythmias and blood pressure abnormalities in patients with intracranial hemorrhage. Pulmonary edema following seizure activity was described by Shanahan [8] in 1908. In 1938, Aschenbrenner and Bodechtel demonstrated that electrocardiogram (ECG) changes were associated with SAH [9•]. Subsequent works have identified a pattern of neurogenic myocardial injury associated with cardiac enzyme release and normal myocardial perfusion [10–13], as well as neurogenic pulmonary edema in the setting of normal wedge pressures [14].

This review focuses on the manifestations of neurogenic influences on heart and lung function after acute brain injury and the mechanisms by which they occur. Recommendations for appropriate management of these complications are addressed.

Review of Autonomic Centers Within the Brain

The autonomic centers in the brainstem are of primary importance with regard to central nervous system (CNS) modulation of the cardiovascular and pulmonary systems. These centers have been studied extensively. Neocortical areas such as the orbitofrontal cortex, temporal pole, and cingulate gyrus also likely play a role [15]. More recently, the insular cortex, which is thought to have widespread connections to other autonomic structures throughout the brain, has been recognized as having a major influence on autonomic function [16–18]. The paleocortex (amygdala) is thought to influence the autonomic nervous system in response to different emotional states. In fact, myocardial stunning, as described in subsequent sections, has been reported following emotional stress [19•]. In 1963, Melville *et al.* [20] postulated a role of the diencephalon in autonomic control of the heart. It has since been accepted that the anterior hypothalamus shows parasympathetic activity whereas the posterior hypothalamus involves sympathetic outflow [20]. Subsequent research has shown various dysrhythmias associated with stimulation or lesions of the hypothalamus [20–23]. The mediodorsal nucleus of the thalamus has also been implicated in the modulation of autonomic functions. Brainstem medullary and supramedullary centers are involved in the afferent and efferent limbs of the autonomic nervous system as well as with integration of autonomic information from multiple levels. Afferent information from the peripheral reflex receptors (*eg*, baroreceptors, mechanoreceptors, and chemoreceptors) enter the medulla and terminate in the nucleus tractus solitarii (NTS). Some fibers from the NTS then project to the nucleus ambiguous, dorsal motor nucleus of the vagus, and intermediolateral column of the spinal cord (sympathetic preganglionic cells). Thus, reflex pathways affect the parasympathetic output from the brainstem and sympathetic outflow from the spinal cord to the sympathetic ganglion (*eg*, stellate ganglion) [24,25]. Efferent autonomic outflow from the CNS will have local

action within other organ systems (*eg*, intrinsic cardiac ganglion and cardiac beta and muscarinic receptors). Other fibers from the NTS will project to the parabrachial nucleus in the pons, which serves as a relay nucleus in the autonomic nervous system, with widespread projections to other areas [24,25].

The Neurogenic Heart

Cardiac dysfunction following brain injury is a common occurrence and includes ECG changes, arrhythmias, cardiac enzyme leaks, left ventricular dysfunction, and occasionally sudden death.

Repolarization abnormalities

Studies of patients with SAH have revealed rates of ECG changes ranging from 50% to 100% [26–28]. The most common abnormalities include ST changes, T wave inversion, and prolongation of the QT interval, although peaked T waves and U waves may also occur [29–32]. Although these findings have typically indicated myocardial ischemia, there is accumulating evidence from clinical and experimental studies that in the setting of brain injury these changes are due to diffuse myocardial damage secondary to sympathetic activation rather than cardiac hypoperfusion [33–35]. As will be discussed in the following text, there is much evidence that ECG abnormalities resulting from neurologic causes are accompanied by cardiac enzyme leaks [36], although one recent study in patients with SAH found that serum troponin I was elevated in patients with prolongation of QT interval but not ST segment changes, T wave inversion, or abnormal U waves [37]. Neurogenic ECG changes tend to be asymptomatic and normalization of repolarization occurs in association with resolution of the neurologic insult. However, more extensive neurologic injury resulting in a sustained sympathetic discharge may result in permanent ECG changes, including the development of Q waves [38].

Arrhythmia

The concept that neural activity exerts a potent influence on arrhythmogenesis has been accepted since the 1970s [39]. For example, the baroreceptor mechanism is thought to have a protective, antifibrillatory role in myocardial ischemia by maintaining a low heart rate. This is mediated through vagal nerve afferents, eventually leading to inhibition of presynaptic norepinephrine release [40,41].

Recent evidence suggests sympathetic nerve terminal sprouting and redistribution may occur after myocardial injury (*eg*, ischemia) or with age, predisposing to arrhythmias associated with dysautonomia [24]. Spectral analysis of respiratory variability has detected disorders of autonomic cardiac control in patients with epilepsy, more frequently in patients with a right hemisphere focus [42]. It is possible that sudden unexplained death in epilepsy is related to arrhythmias provoked by CNS dysfunction. Animal and human models both have suggested right insular region dominance of sympathetic innervation to the heart whereas the left insular cortex is primarily concerned with parasympathetic tone [43–46]. It has, therefore, been suggested that damage to the left insular cortex predisposes to increased cardiac sympathetic dominance and sudden cardiac death secondary to arrhythmia [47,48].

The most frequent arrhythmias following brain injury are premature ventricular complexes, sinus arrhythmia, and atrial fibrillation. Other arrhythmias including atrial flutter, ventricular tachycardia, torsades de pointe, ventricular fibrillation, and asystole have been documented [27,49–51]. In patients with SAH, rhythm disturbances were recorded in 35%, of which 5% were considered life-threatening. The majority of arrhythmias occurred within 7 days of the neurologic insult, with most occurring in the first 48 hours [52].

Neurogenic stunned myocardium

The term "neurogenic stunned myocardium" refers to neurologically mediated cardiac injury that is reversible in nature; results in myocyte enzyme release, ECG changes, and in some cases arrhythmias and left ventricular dysfunction; and that is unrelated to cardiac hypoperfusion secondary to coronary artery disease. The degree of myocardial injury as measured by creatine kinase–MB and cardiac troponins has been shown to correlate with the severity of neurologic insult [53]. Studies of SAH patients have reported the presence of elevated cardiac troponin I (> 1.0 μg/L) in up to 28% [54,55]. Examination of the hearts of animal models of stunned myocardium and those of patients at autopsy has revealed characteristic patterns of random petechial subendocardial hemorrhage and myocardial cytoplasm typified by dense eosinophilic transverse bands termed "contraction band necrosis" [10,11,32].

In 1987, Samuels [38] introduced a unifying hypothesis to explain the clinical, physiologic, biochemical, and pathologic findings that had been described in association with myocardial stunning. He proposed that excessive sympathetic discharge and catecholamine excess secondary to neurologic injury lead to prolonged opening of receptor-operated calcium channels, resulting in intense contraction of cardiac muscle, which when sustained leads to myofibrillar degeneration, reperfusion injury, and cardiac cell death [38]. This concept is boosted by the findings that similar pathologic states exist in the setting of catecholamine excess caused by non-neurological dysfunction such as pheochromocytoma [56], extreme states of emotional stress [19•], scorpion envenomation [57], and after excessive cardiac sympathetic stimulation in animals [58,59]. Furthermore, disruption of the sympathetic pathways at the level of the cervical cord [60,61] and use of catecholamine-blocking agents [23,62,63] has been found to abolish the effect of neurogenic cardiac and pulmonary injury.

Recent studies have confirmed the presence of elevated plasma levels of catecholamines and neuropeptide Y (stored and released with catecholamines in post-ganglionic sympathetic nerves) in the setting of cardiac dysfunction following sudden emotional stress [19•]. Animal models of neurogenic cardiac injury suggest that contraction band necrosis is mediated by direct release of catecholamines into the myocardium at the level of the cardiac sympathetic nerve terminals rather than from adrenal release of catecholamines into the systemic circulation [64]. Interestingly, studies of patients with SAH have revealed higher rates of myocardial injury in women [19•,65], suggesting the possibility of differences in neurogenic sympathetic activation and/or catecholamine vulnerability based on sex. Other theories attempting to explain the mechanism behind myocardial stunning include coronary spasm secondary to increased sympathetic tone [66] and sympathetically mediated microcirculatory dysfunction [67].

Decreases in left ventricular contractility leading to hypokinesia and low ejection fractions have been reported as a consequence of myocardial stunning. The characteristic pattern of abnormal wall motion (involvement of the cardiac apex and mid-portion with relative sparing of the base, termed "apical ballooning") may reflect the differential distribution of myocardial sympathetic nerve terminals [68]. In patients with SAH, left ventricular dysfunction occurs in approximately 10% of patients [65]. Decreased cardiac output from left ventricular dysfunction in the face of cerebral vasospasm may lead to increased cerebral ischemia and mortality [34]. For survivors, the wall motion abnormalities are transient and normal cardiac function usually returns [69].

Neurogenic Pulmonary Edema

Pulmonary complications such as pneumonia and pulmonary edema frequently follow acute neurologic injury [52]. The majority of clinically evident pulmonary edema is thought to be secondary to volume overload or of cardiogenic origin. However, neurogenic pulmonary edema (NPE) resulting from acute brain injury is not uncommon but remains under-diagnosed. Post-mortem studies in the 1950s and 1960s recognized pulmonary edema in approximately 50% of patients dying of acute intracranial pathology [70,71]. In 1969, a series of Vietnam casualties killed from head wounds showed most had evidence of pulmonary edema, including soldiers killed almost instantaneously [72].

The definition of NPE is generally accepted as bilateral pulmonary edema following acute brain dysfunction without associated heart failure, significant volume overload, or other obvious cause of hypoxemia. NPE has been associated with virtually any acute neurologic injury, including seizure, traumatic brain injury, intracranial hemorrhages, ischemic strokes, multiple sclerosis, tumors, and infections [73]. Recently, NPE has been described in acute, severe hypoglycemia and enterovirus encephalitis [5,74]. Onset is frequently acute (within minutes or hours of ictus) but may develop over days. A mortality rate approaching 10% has been described, although, as is the case with neurogenic stunned myocardium, if the patient survives NPE tends to resolve rapidly (commonly within 24 hours) [75].

The mechanism by which NPE occurs is controversial. In the Vietnam study, soldiers with cervical cord transaction had normal lungs, implicating sympathetic discharge as part of the pathophysiology. In 1976 Theodore and Robin [76] proposed a unifying hypothesis for NPE that is similar to the mechanism thought to underlie the neurogenic stunned myocardium. They hypothesized that the neurologic insult causes a massive sympathetic discharge, resulting in systemic vasoconstriction, hypertension, and a relative shift of intravascular volume to the lower resistance pulmonary beds. Rapid onset of transient pulmonary hypervolemia and sympathetically mediated pulmonary vasoconstriction leads to increased hydrostatic forces, causing hydrostatic pulmonary edema. They also postulated that this sudden "blast" injures pulmonary blood vessels, leading to increased pulmonary capillary permeability that persists after restoration of normal hemodynamics and cardiac function. This unifying hypothesis suggests that sampling of pulmonary edema might show fluid low in protein content (indicating a primary hydrostatic mechanism), high in protein content (indicating increased capillary permeability), or fluid with a variable amount of protein depending on when the fluid is sampled and which mechanism is predominant at the time of sampling. In fact, some subsequent studies have shown protein-rich pulmonary fluid indicating primary endothelial damage [77–79]. In recent years, it has been postulated that capillary endothelial damage is a direct consequence of local sympathetic activity.

Conversely, some recent studies have confirmed low-protein content in pulmonary fluid in the majority of patients, indicating a primarily hydrostatic mechanism. Pulmonary venoconstriction has been implicated as the main cause of increased hydrostatic pressure [80–82]. Additionally, it is thought by some researchers that transient cardiac dysfunction causing increased pulmonary artery occlusion pressure cannot be ruled out. However, it is important to note that when invasive measurements are made (*eg*, right heart catheterization), pulmonary artery occlusion pressure and cardiac index are normal shortly after the insult. Hence, neurogenic stunned myocardium is not the cause of the NPE, and in fact must be excluded when making the definitive diagnosis. Lastly, some have implicated abnormal lymphatic drainage. It is likely that NPE is multifactorial, with more than one mechanism involved.

Treatment

Cardiac and pulmonary complications following acute brain injury increase morbidity and mortality [1,52,83,84,]. Therefore, all patients presenting with intracranial pathology should have a 12-lead ECG and cardiac enzyme measurements on admission and telemetry until their neurologic condition has stabilized. There are no data to guide whether treatment of mild ECG changes improves outcome; however, treatment of the underlying neurologic insult is the most effective way of correcting the ECG abnormalities. Premature ventricular complexes do not require treatment, but if they occur with increasing frequency may signify elevated intracranial pressure and herald more serious ventricular arrhythmias. If control of intracranial pressure is difficult to obtain in a timely manner, antiarrhythmic agents may be necessary to forestall progression to life threatening arrhythmias. In the event that ventricular tachyarrhythmias or hemodynamically unstable supraventricular arrhythmias do occur, treatment with standard antiarrhythmic agents should be instituted immediately.

It is important to differentiate neurogenic stunned myocardium from cardiac ischemic injury, especially in the setting of SAH. Whereas the former is a reversible condition that will resolve with treatment of the neurologic insult, the latter may cause irreversible cardiac dysfunction and may delay crucial surgery for aneurysmal repair. Based on a retrospective study of 350 patients with SAH, Bulsara *et al*. [9•], proposed the following criteria to differentiate neurogenic stunned myocardium from ischemic cardiac dysfunction: 1) no history of cardiac problems; 2) new-onset left ventricular dysfunction (*ie*, ejection fraction less than 40%); 3) cardiac wall motion abnormalities on echocardiogram that do not correlate with the coronary vascular distribution performance on ECG; and 4) cardiac troponin levels less than 2.8 ng/mL. If doubt still exists regarding the etiology of the cardiac dysfunction, coronary angiography may be necessary.

Neurogenic pulmonary edema should be treated symptomatically, and early intubation is recommended. Treatment in general is similar to the management of cardiogenic pulmonary edema; however, the use of diuretics in SAH patients should be exercised with extreme caution, as this population requires a hypervolemic state to prevent vasospasm.

In patients who display autonomic instability, some have advocated the use of catecholamine blockers based on the observations in animal models of neurogenic sympathetic excess that they can be protective [83]. Furthermore, it has been recommended that the use of pressors and β-agonists be minimized whenever possible in the setting of stress cardiomyopathy, and to rely on mechanical circulatory support instead [19•].

Conclusions

There is substantial evidence that acute brain injury such as stroke, SAH, infection, epilepsy, and traumatic brain injury causes dysfunction of the cardiovascular and pulmonary systems. These effects can range from asymptomatic ECG changes to arrhythmias, left ventricular dysfunction, NPE, and even sudden death. The mechanism of neurogenic injury is likely mediated through excessive sympathetic discharge secondary to disruption of autonomic centers in the cerebral cortex and brainstem. Physician awareness of this phenomenon is important because early monitoring and management of end-organ dysfunction is likely to improve outcomes. Further studies are required to better elucidate mechanisms of injury and test proposed interventions, such as sympatholytics and free radical scavengers.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Silver FL, Norris JW, Lewis AJ, Hachinski VC: **Early mortality following stroke: a prospective review.** *Stroke* 1984, **15:**492–496.
2. Mayer SA, Lin J, Homma S, *et al.*: **Myocardial injury and left ventricular performance after subarachnoid hemorrhage.** *Stroke* 1999, **30:**780–786.
3. Dimant J, Grob D: **Electrocardiographic changes and myocardial damage in patients with acute cerebrovascular accidents.** *Stroke* 1977, **8:**448–455.
4. Brander L, Weinberger D, Henzen C: **Heart and brain: a case of focal myocytolysis in severe pneumococcal meningoencephalitis with review of the contemporary literature.** *Anaesth Intensive Care* 2003, **31:**202–207.
5. Prager P, Nolan M, Andrews IP: **Neurogenic pulmonary edema in enterovirus 71 encephalitis is not uniformly fatal but causes severe morbidity in survivors.** *Pediatr Crit Care Med* 2003, **4:**377–381.
6. Kantor HL, Krishnan SC: **Cardiac problems in patients with neurological disease.** *Cardiol Clin* 1995, **13:**179–208.
7. Cushing H: **The blood pressure reaction of acute cerebral compression illustrated by cases of intracranial hemorrhage.** *Am J Med Sci* 1903, **125:**1017–1044.
8. Shanahan WT: **Acute pulmonary edema as a complication of epileptic seizures.** *NY Med J* 1908, **37:**54–56.
9. • Bulsara KR, McGirt MJ, Liao L, *et al.*: **Use of the peak troponin value to differentiate myocardial infarction from reversible neurogenic left ventricular dysfunction associated with aneurysmal subarachnoid hemorrhage.** *J Neurosurg* 2003, **98:**524–528.

First study suggesting guidelines to differentiate stunned myocardium from ischemic heart disease allowing for earlier surgical intervention. However, it was based on a small set of patients and further studies are necessary.

10. Kolin A, Norris J: **Myocardial damage from acute cerebral lesions.** *Stroke* 1984, **15:**990–993.
11. Doshi R, Neil-Dwyer G: **A clinicopathological study of patients following a subarachnoid hemorrhage.** *J Neurosurg* 1980, **52:**295–301.

12. Burch GE, Sun SC, Calcolough H, *et al.*: **Acute myocardial lesions following experimentally induced intracranial hemorrhage in mice: a histologic and histochemical study.** *Arch Pathol* 1967, **84:**517–521.
13. Kono T, Morita H, Kuroiwa T, *et al.*: **Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium.** *J Am Coll Cardiol* 1994, **24:**636–639.
14. Malik AB: **Mechanism of neurogenic pulmonary edema.** *Circ Res* 1985, **57:**1–18.
15. Kenedi I, Csanda E: **Electrographic changes in response to electrical stimulation of the cerebral cortex.** *Acta Physiol Acad Sci Hung* 1959, **16:**165–170.
16. Oppenheimer M, Hopkins D: **Suprabulbar neuronal regulation of the heart.** In *Neurocardiology.* Edited by Armour JA and Ardell JL. New York: Oxford University Press; 1994:309–342.
17. Oppenheimer SM, Cechetto DF: **Cardiac chronotropic organization of the rat insular cortex.** *Brain Res* 1990, **533:**66–72.
18. Hachinski VC, Oppenheimer SM, Wilson JX, *et al.*: **Asymmetry of sympathetic consequences of experimental stroke.** *Arch Neurol* 1992, **49:**697–702.
19.• Wittstein IS, Thiemann DR, Lima JA, *et al.*: **Neurohumoral features of myocardial stunning due to sudden emotional stress.** *N Engl J Med* 2005, **352:**539–548.

This article provides evidence that myocardial stunning seen after sudden emotional stress is similar in character and mechanism to the myocardial stunning seen after neurologic injury. It provides further backbone to the theory that sympathetic discharge and not myocardial ischemia is responsible for the myocardial injury.

20. Melville KI, Blum B, Shister HE, Silver MD: **Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation.** *Am J Cardiol* 1963, **12:**781.
21. Spencer SE, Sawyer WB, Loewy AD: **L-glutamate mapping of cardioreactive areas in the rat posterior hypothalamus.** *Brain Res* 1990, **511:**149.
22. Gelsema AJ, Roe MJ, Calaresu FR: **Neurally mediated cardiovascular responses to stimulation of cell bodies in the hypothalamus of the rat.** *Brain Res* 1989, **482:**67–72.
23. Weinberg SJ, Fuster JM: **Electrocardiographic changes produced by localized hypothalamic stimulations.** *Ann Intern Med* 1960, **53:**332–334.
24. Verrier L, Antzelevitch C: **Autonomic aspects of arrhythmogenesis: the enduring and the new.** *Curr Opin Cardiol* 2004, **19:**2–11.
25. Martin H: **The hypothalamus and the regulation of endocrine and visceral functions.** In *Neuroanatomy Text and Atlas,* edn 2. Edited by Martin JH. Stamford, CT: Appleton & Lange; 1996:419–445.
26. Cropp C, Manning G: **Electrocardiographic change simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage.** *Circulation* 1960, **22:**24–27.
27. Andreoli A, di Pasquale G, Pinelli G, *et al.*: **Subarachnoid hemorrhage: frequency and severity of cardiac arrhythmias. A survey of 70 cases studied in the acute phase.** *Stroke* 1987, **18:**558–564.
28. Mayer SA, Lin J, Homma S, *et al.*: **Myocardial injury and left ventricular performance after subarachnoid hemorrhage.** *Stroke* 1999, **30:**780–786.
29. Brouwers PJ, Wijdicks EF, Hasan D, *et al.*: **Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage.** *Stroke* 1989, **20:**1162–1167.
30. Salvati M, Cosentino F, Artico M, *et al.*: **Electrocardiographic changes in subarachnoid hemorrhage secondary to cerebral aneurysm. Report of 70 cases.** *Ital J Neurol Sci* 1992, **13:**409–413.
31. Burch GE, Meyers R, Abildskov JA: **A new electrocardiogram pattern observed in cerebrovascular accidents.** *Circulation* 1954, **9:**719–723.
32. Greenhoot JA, Reichenbach DD: **Cardiac injury and subarachnoid hemorrhage. A clinical, pathological and physiological correlation.** *J Neurosurg* 1969, **30:**521–531.
33. Zaroff JG, Rordorf GA, Titus JS, *et al.*: **Regional myocardial perfusion after experimental subarachnoid hemorrhage.** *Stroke* 2000, **31:**1136–1143.
34. Jain R, Deveikis J, Thompson BG: **Management of patients with stunned myocardium associated with subarachnoid hemorrhage.** *Am J Neuroradiol* 2004, **25:**126–129.
35. Hammermeister KE, Reichenbach DD: **QRS changes, pulmonary edema and myocardial necrosis associated with subarachnoid hemorrhage.** *Am Heart J* 1969, **78:**94–100.
36. Norris JW, Hachinski VC, Myers MG, *et al.*: **Serum cardiac enzymes in stroke.** *Stroke* 1979, **10:**548–553.
37. Sommargren CE, Zaroff JG, Banki N, Drew BJ: **Electrocardiographic repolarization abnormalities in subarachnoid hemorrhage.** *J Electrocardiol* 2002, **35:**257–262.
38. Samuels MA: **Neurogenic heart disease: a unifying hypothesis.** *Am J Cardiol* 1987, **60:**15–19.
39. Lown B, Verrier R: **Neural activity and ventricular fibrillation.** *N Engl J Med* 1976, **294:**1165–1170.
40. Levy N, Blattberg B: **Effect of vagal stimulation on the overflow of norepinephrine into the coronary sinus during cardiac sympathetic nerve stimulation in the dog.** *Circ Res* 1976, **38:**81–84.
41. Kolman S, Verrier L, Lown B: **The effect of vagus nerve stimulation upon vulnerability of the canine ventricle: role of sympathetic-parasympathetic interactions.** *Circulation* 1975, **52:**578–585.
42. Massetani R, Strata G, Galli R, *et al.*: **Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability.** *Epilepsia* 1997, **38:**363–369.
43. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC: **Cardiovascular effects of human insular cortex stimulation.** *Neurology* 1992, **42:**1727–1732.
44. Tokgozoglu SL, Batur MK, Topuoglu MA, *et al.*: **Effects of stroke localization on cardiac autonomic balance and sudden death.** *Stroke* 1999, **30:**1307–1311.
45. Kulshreshtha N, Zhang ZH, Oppenheimer SM: **Effects of insular lesions on the rat baroreceptor reflex.** *Soc Neurosci Abstracts* 1996, **22:**157.
46. Oppenheimer M, Martin M, Kedem G: **Left insular cortex lesions perturb cardiac autonomic tone.** *Clin Auton Res* 1996, **6:**131–140.
47. Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF: **Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death?** *Brain Res* 1991, **550:**115–121.
48. Darbin O, Casebeer DJ, Naritoku DK: **Cardiac dysrhythmia associated with the immediate postictal state after maximal electroshock in freely moving rat.** *Epilepsia* 2002, **43:**336–341.
49. Cropp GJ, Manning GW: **Electrocardiographic changes simulating myocardial ischaemia and infarction associated with spontaneous intracranial haemorrhage.** *Circulation* 1960, **22:**25–38.
50. Shuster S: **The electrocardiogram in subarachnoid haemorrhage.** *Br Heart J* 1960, **22:**316–320.
51. Galloon S, Rees GA, Briscoe CE, *et al.*: **Prospective study of electrocardiographic changes associated with subarachnoid haemorrhage.** *BJA* 1972, **44:**511–516.
52. Solenski NJ, Haley EC, Kassell NF, *et al.*: **Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study.** *Crit Care Med* 1995, **2:**1007–1017.
53. Tung P, Kopelnik A, Banki N, *et al.*: **Predictors of neurocardiogenic injury after subarachnoid hemorrhage.** *Stroke* 2004, **35:**548–551.
54. Deibert E, Barzilai B, Braverman AC, *et al.*: **Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage.** *J Neurosurg* 2003, **98:**741–746.

55. Parekh N, Venkatesh B, Cross D, *et al.*: **Cardiac troponin I predicts myocardial dysfunction in aneurysmal subarachnoid hemorrhage.** *J Am Coll Cardiol* 2000, **36:**1328–1335.
56. Takeno Y, Eno S, Hondo T, *et al.*: **Pheochromocytoma with reversal of tako-tsubo-like transient left ventricular dysfunction: a case report.** *J Cardiol* 2004, **43:**281–287.
57. Cupo P, Jurca M, Azeedo-Marques MM, *et al.*: **Severe scorpion envenomation in Brazil. Clinical, laboratory and anatomopathological aspects.** *Rev Inst Med Trop Sao Paulo* 1994, **36:**67–76.
58. Pilati CF, Clark RS, Gilloteaux J, *et al.*: **Excessive sympathetic nervous system activity decreases myocardial contractility.** *Proc Soc Exp Biol Med* 1990, **193:**225–231.
59. Kaye MP, McDonald RH, Randall WC: **Systolic hypertension and subendocardial hemorrhages produced by electrical stimulation of the stellate ganglion.** *Circ Res* 1961, **9:**1164–1170.
60. Simmons RL, Martin AM Jr, Heisterkamp CA 3rd, Ducker TB: **Respiratory insufficiency in combat casualties. II. Pulmonary edema following head injury.** *Ann Surg* 1969, **170:**39–44.
61. Theodore J, Robin ED: **Speculations on neurogenic pulmonary edema (NPE).** *Am Rev Respir Dis* 1976, **113:**405–411.
62. Cruickshank JM, Neil-Dwyer G, Lane J: **The effect of oral propranolol upon the ECG changes occurring in subarachnoid haemorrhage.** *Cardiovasc Res* 1975, **9:**236–245.
63. Offerhaus L, van Gool J: **Electrocardiographic changes and tissue catecholamines in experimental subarachnoid haemorrhage.** *Cardiovasc Res* 1969, **3:**433–440.
64. Mertes PM, Carteaux JP, Jaboin Y, *et al.*: **Estimation of myocardial interstitial norepinephrine release after brain death using cardiac microdialysis.** *Transplantation* 1994, **57:**371–377.
65. Tung P, Kopelnik A, Banki N, *et al.*: **Predictors of neurocardiogenic injury after subarachnoid hemorrhage.** *Stroke* 2004, **35:**548–551.
66. Lacy CR, Contrada RJ, Robbins ML, *et al.*: **Coronary vasoconstriction induced by mental stress (simulated public speaking).** *Am J Cardiol* 1995, **75:**503–505.
67. Sadamatsu K, Tashiro H, Maehira N, Yamamoto K: **Coronary microvascular abnormality in the reversible systolic dysfunction observed after noncardiac disease.** *Jpn Circ J* 2000, **64:**789–792.
68. Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH: **Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury.** *J Am Soc Echocardiogr* 2000, **13:**774–779.
69. Pollick C, Cujec B, Parker S, Tator C: **Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study.** *J Am Coll Cardiol* 1988, **12:**60–605.
70. Richards P: **Pulmonary oedema and intracranial lesions.** *BMJ* 1963, **5349:**83–86.
71. Paine R, Smith J, Howard F: **Pulmonary oedema in patients dying with diseases of the central nervous system.** *JAMA* 1952, **149:**643–646.
72. Simmons RL, Martin AM, Heisterkamp CA, *et al.*: **Respiratory insufficiency in combat casualties. II. Pulmonary edema following head injury.** *Ann Surg* 1969, **170:**39–44.
73. Fontes RB, Aguiar PH, Zanetti MV, *et al.*: **Acute neurogenic pulmonary edema: case reports and literature review.** *J Neurosurg Anesthesiol* 2003, **15:**144–150.
74. Mishriki YY: **Hypoglycemia-induced neurogenic-type pulmonary edema: an underrecognized association.** *Endocr Pract* 2004, **10:**429–431.
75. Fontes RB, Aguiar PH, Zanetti MV, *et al.*: **Acute neurogenic pulmonary edema: case reports and literature review.** *J Neurosurg Anesthesiol* 2003, **15:**144–150.
76. Theodore J, Robin ED: **Speculations on neurogenic pulmonary edema.** *Am Rev Respir Dis* 1976, **113:**405–411.
77. Bowers RE, McKeen CR, Park BE, *et al.*: **Increased pulmonary vascular permeability follows intracranial hypertension in sheep.** *Am Rev Respir Dis* 1979, **119:**637–641.
78. Simon RP, Bayne LL, Tranbaugh RF, *et al.*: **Elevated pulmonary lymph flow and protein content during status epilepticus in sheep.** *J Appl Physiol* 1982, **52:**91–95.
79. McClellan MD, Dauber IM, Weil JV: **Elevated intracranial pressure increases pulmonary vascular permeability to protein.** *J Appl Physiol* 1989, **67:**1185–1191.
80. Maron MB, Dawson CA: **Pulmonary venoconstriction caused by elevated cerebrospinal fluid in the dog.** *J Appl Physiol* 1980, **49:**73–78.
81. Johnston SC, Darragh TM, Simon RP: **Postictal pulmonary edema requires pulmonary vascular pressure increases.** *Epilepsia* 1996, **37:**428–432.
82. Smith WS, Matthay MA: **Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema.** *Chest* 1997, **111:**1326–1333.
83. Cruickshank JM, Neil-Dwyer G, Degaute JP, *et al.*: **Reduction of stress/catecholamine-induced cardiac necrosis by beta 1-selective blockade.** *Lancet* 1987, **2:**585–589.
84. Sander D, Winbeck K, Klingelhofer J, *et al.*: **Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke.** *Neurology* 2001, **57:**833–838.