Stress-Induced Cardiomyopathy and Possible Link to Cerebral Executive Function: A Case Report

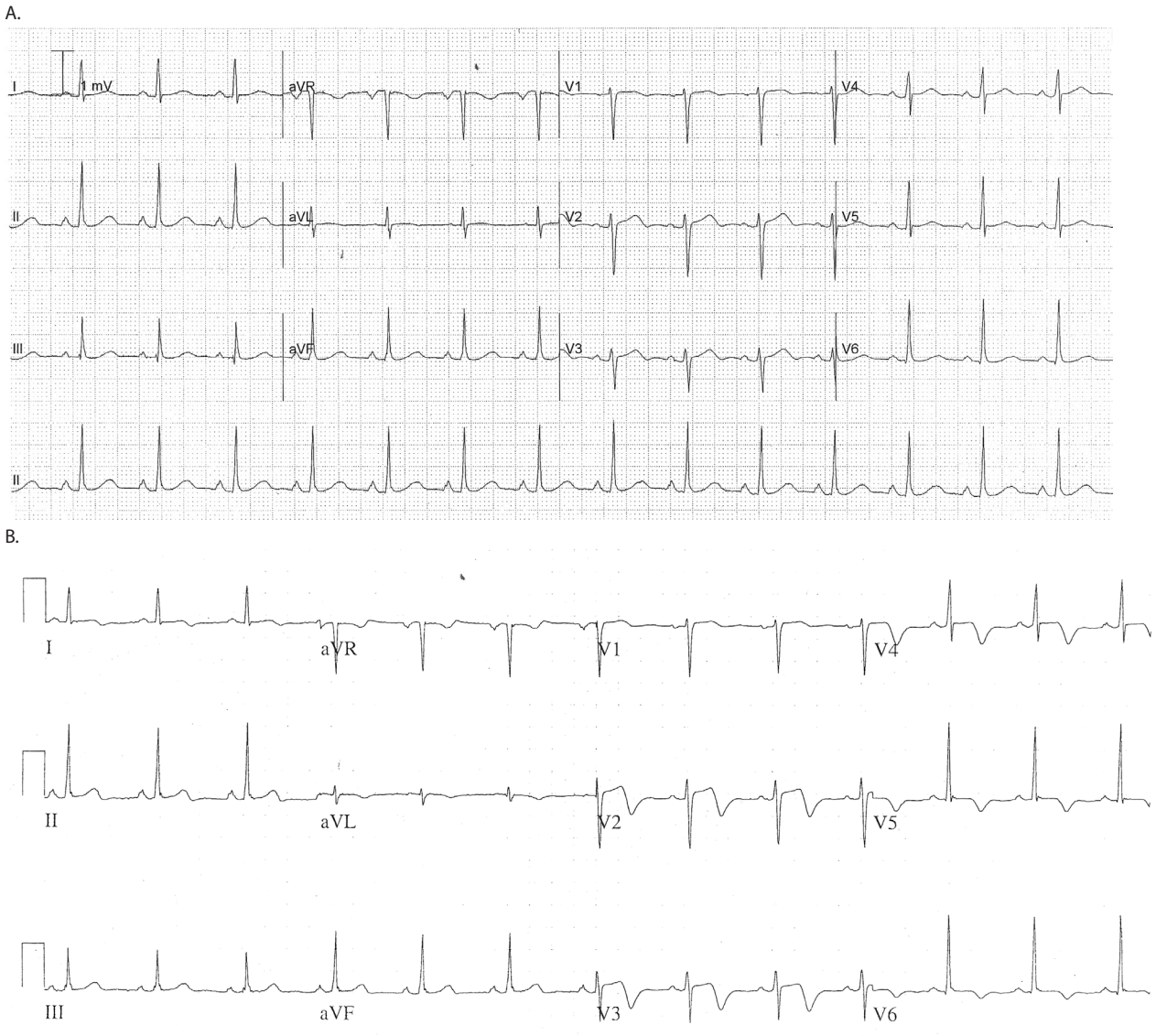
To the Editor: A complex and poorly understood relationship exists between cerebral and cardiac function.[1] Stress produces a range of physiological responses that are relevant to cardiovascular and cerebrovascular disease. Upon stress perception, the hypothalamic-pituitary-adrenocortical (HPA) and sympatho-adrenomedullary axes are activated, increasing bioavailability of cortisol, epinephrine, and norepinephrine.[2] Given the reliance of both cardiac and cerebral function on the integrity of this system, any impairment in the form of overstimulation or understimulation may manifest as cardiac and cerebrovascular pathology as illustrated in the case report below.

Case report. Ms A, a 56-year-old woman with known hypertension and hypercholesterolemia, was admitted with chest pain following an argument with a family member. She had no history of ischemic heart or neurologic disease. On presentation, she was noted to be confused.

Physical examination was unremarkable with no focal neurologic or cardiac abnormality identified. Further investigations revealed troponin T and creatine kinase peak concentrations of 1.15 μg/L (reference range, < 0.03 μg/L) and 614 U/L (reference range, < 180 U/L), respectively. Admission electrocardiogram (ECG) demonstrated sinus rhythm without ischemic changes (Figure 1). Computed tomography scan of the brain was unremarkable. She continued to experience amnesia over the first 12 hours after her admission; amnesia had resolved by the following day. An urgent neurology consultation was sought, and the diagnosis of transient global amnesia was made on the basis of the patient's clinical features.

Ms A was admitted to the coronary care unit; serial ECG monitoring showed biphasic and deep T-wave inversion over the anterolateral leads (see Figure 1). She underwent coronary angiography, which showed "smooth" coronary arteries and apical "ballooning" on left ventriculography consistent with takotsubo cardiomyopathy. Magnetic resonance imaging of the brain identified an incidental 6-mm left middle cerebral artery aneurysm with

Figure 1. A 12-Lead Electrocardiogram (A) At Admission, Showing Normal Sinus Rhythm, and (B) 15 Hours Later, Demonstrating Deep T-Wave Inversion Over Leads V2–V5 (anterolateral leads) Resembling Acute Coronary Ischemia



© 2013 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.

no associated hemorrhage or ischemia. Her final diagnoses were stress-induced (takotsubo) cardiomyopathy and transient global amnesia.

Adrenergic receptors are abundant throughout the brain,[3] myocardium,[4] and coronary arteries.[5] It is well established that catecholamine signaling through β-adrenergic receptors mediates endogenous regulation of complex central nervous system processes such as attention, arousal, learning, and memory[3,6–8] as well as important cardiac functions such as chronotropy, inotropy, and lusitropy. There is general consensus that this "cerebro-cardiac" process occurs via the β-adrenoceptor–mediated cyclic-AMP (cAMP)–dependent protein kinase pathway.[9–11]

A growing body of evidence suggests that cortisone and epinephrine may also impair memory retrieval and therefore contribute to the mechanism of peritraumatic amnesia. de Quervain and colleagues reported that stress and infusion of cortisone impair memory retrieval in rats[12] and humans.[13] Sadowski et al[10] demonstrated that infusion of epinephrine resulted in impairment of place and response learning. Furthermore, detrimental effects of cortisone on hippocampal function during memory retrieval have been shown to require concurrent norepinephrine-dependent activation of the basolateral part of the amygdala,[14,15] which may be via an inhibitory G protein–coupled suppression of cAMP signaling.[16,17] Altogether, memory formation, consolidation, and retrieval seem to be a function of β_1-adrenergic receptor function, and stress impairs memory retrieval by exerting its action on the β_2-adrenergic receptor.

Catecholamine overstimulation has been suggested as the key pathogenetic factor in takotsubo cardiomyopathy. This cardiac syndrome is now increasingly recognized by the mental health practitioner as either a disease association[18,19] or a complication of a psychiatric treatment, such as electroconvulsive therapy.[20,21] Although the exact pathogenesis has not been fully elucidated, data from animal,[22] imaging,[23] and myocardial histologic[24] studies indicate that overactive β-adrenergic signaling, in the presence of supraphysiological catecholamine concentrations, plays a significant role in mediating this phenomenon. Given the density of β-adrenergic receptors are greatest[25] in the apical segments of the myocardium, Lyon and colleagues[4] suggest these receptors are important in this disease phenomenon, which explains the apical propensity of transient myocardial stunning seen in takotsubo cardiomyopathy.

Our case report provides a collection of cardiac and cerebral clinical findings that would support the common mechanistic link described in our review. Further understanding of this complex, dynamic relationship is required to formulate a more targeted preventive and therapeutic management strategy.

References

1. Samuels MA. The brain-heart connection. *Circulation*. 2007;116(1):77–84.
2. Steptoe A, Kivimäki M. Stress and cardiovascular disease. *Nat Rev Cardiol*. 2012;9(6):360–370.
3. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci*. 2009;10(6):423–433.
4. Lyon AR, Rees PS, Prasad S, et al. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med*. 2008;5(1):22–29.
5. Jensen BC, Swigart PM, Laden ME, et al. The alpha-1D: is the predominant alpha-1-adrenergic receptor subtype in human epicardial coronary arteries. *J Am Coll Cardiol*. 2009;54(13):1137–1145.
6. Hurlemann R. Noradrenergic-glucocorticoid mechanisms in emotion-induced amnesia: from adaptation to disease. *Psychopharmacology (Berl)*. 2008;197(1):13–23.
7. Hurlemann R, Hawellek B, Matusch A, et al. Noradrenergic modulation of emotion-induced forgetting and remembering. *J Neurosci*. 2005;25(27):6343–6349.
8. Hagena H, Manahan-Vaughan D. Learning-facilitated long-term depression and long-term potentiation at mossy fiber-CA3 synapses requires activation of β-adrenergic receptors. *Front Integr Neurosci*. 2012;6:23.
9. Murchison CF, Schutsky K, Jin SH, et al. Norepinephrine and β1-adrenergic signaling facilitate activation of hippocampal CA1 pyramidal neurons during contextual memory retrieval. *Neuroscience*. 2011;181:109–116.
10. Sadowski RN, Jackson GR, Wieczorek L, et al. Effects of stress, corticosterone, and epinephrine administration on learning in place and response tasks. *Behav Brain Res*. 2009;205(1):19–25.
11. McGaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. *Curr Opin Neurobiol*. 2002;12(2):205–210.
12. de Quervain DJ, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature*. 1998;394(6695):787–790.
13. de Quervain DJ, Roozendaal B, Nitsch RM, et al. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nat Neurosci*. 2000;3(4):313–314.
14. Roozendaal B, Hahn EL, Nathan SV, et al. Glucocorticoid effects on memory retrieval require concurrent noradrenergic activity in the hippocampus and basolateral amygdala. *J Neurosci*. 2004;24(37):8161–8169.
15. Roozendaal B, Okuda S, Van der Zee EA, et al. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc Natl Acad Sci U S A*. 2006;103(17):6741–6746.
16. Schutsky K, Ouyang M, Castelino CB, et al. Stress and glucocorticoids impair memory retrieval via beta2-adrenergic, Gi/o-coupled suppression of cAMP signaling. *J Neurosci*. 2011;31(40):14172–14181.
17. Schutsky K, Ouyang M, Thomas SA. Xamoterol impairs hippocampus-dependent emotional memory retrieval via Gi/o-coupled β2-adrenergic signaling. *Learn Mem*. 2011;18(9):598–604.
18. Maldonado JR, Pajouhi P, Witteles R. Broken heart syndrome (Takotsubo cardiomyopathy) triggered by acute mania: a review and case report. *Psychosomatics*. 2013;54(1):74–79.
19. Summers MR, Lennon RJ, Prasad A. Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): potential pre-disposing factors? *J Am Coll Cardiol*. 2010;55(7):700–701.
20. Serby MJ, Lantz M, Chabus BI, et al. Takotsubo cardiomyopathy and electroconvulsive treatments: a case study and review. *Int J Psychiatry Med*. 2010;40(1):93–96.
21. Sharp RP, Welch EB. Takotsubo cardiomyopathy as a complication of electroconvulsive therapy. *Ann Pharmacother*. 2011;45(12):1559–1565.
22. Ueyama T, Kasamatsu K, Hano T, et al. Catecholamines and estrogen are involved in the pathogenesis of emotional stress-induced acute heart attack. *Ann N Y Acad Sci*. 2008;1148(1):479–485.
23. Prasad A, Madhavan M, Chareonthaitawee P. Cardiac sympathetic activity in stress-induced (Takotsubo) cardiomyopathy. *Nat Rev Cardiol*. 2009;6(6):430–434.
24. Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? *Cell Mol Neurobiol*. 2012;32(5):847–857.
25. Mori H, Ishikawa S, Kojima S, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. *Cardiovasc Res*. 1993;27(2):192–198.

Samuel L. Sidharta, MBBS, BMedSc
samuel.sidharta@adelaide.edu.au
Jithin K. Sajeev, MBBS
Adam J. Nelson, MBBS, BMedSc
Jennifer C. Cooke, MBBS
Matthew I. Worthley, MBBS, PhD

Author affiliations: Cardiovascular Research Centre, Department of Medicine, University of Adelaide, Adelaide (Drs Sidharta, Nelson, and Worthley); and Eastern Health, Department of Cardiology, Box Hill Hospital, Victoria (Drs Sajeev and Cooke), Australia.

Potential conflicts of interest: None reported.
Funding/support: None reported.
Published online: December 5, 2013.
Prim Care Companion CNS Disord 2013;15(6):doi:10.4088/PCC.13l01557

© Copyright 2013 Physicians Postgraduate Press, Inc.

© 2013 COPYRIGHT PHYSICIANS POSTGRADUATE PRESS, INC. NOT FOR DISTRIBUTION, DISPLAY, OR COMMERCIAL PURPOSES.