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EDITORIAL

Neurocardiology

From hearts too good to die[1] to brains to good to die[2] the relationship between the heart and the brain has always been of profound interest; from poets to scientists, we all find what we need in this complex interplay of the heart and the mind. Whether the heart or the brain is the seat of the soul, what cannot be debated is the tremendous impact each has on the others function. While the impact of no-flow and low-flow states is of utmost importance and the focus of intense investigation, the case presented in this issue[3] focuses our attention on the impact of the brain on the heart.

After World War II and the Korean War, interest in functional disease causing death arose.[4] At around the same time, Lown and others explored the relation of neural and psychological mechanisms to sudden cardiac death.[5] Subsequently, investigation continued along both clinical (human epidemiological studies) and basic laboratory lines (including organ, cell, and tissue receptor studies in animal and human models). A few examples of the complex interplay and areas for potential investigation will be discussed.

First, a circadian rhythm exists for many physiological processes tying the brain to distant events including the development of acute myocardial ischemia, infarction, and ventricular tachycardia.[6—8] We[9] demonstrated a circadian rhythm for the development of cardiac arrest. Not surprising, these circadian events parallel early morning increases in blood pressure, serum cortisol, platelet activation, and other manifestations of a thrombophilic state including sudden death.[10]

Our emotions also influence our health. Blood pressure increases with stress; elevated blood pressure is associated with increased risk of acute myocardial infarction, stroke, and other vascular events. Depression is associated with increased frequency of acute myocardial infarction and sudden death. Death of a spouse is associated with a 10-fold increased risk of death in their companion over the ensuing year with 1.2% of controls and 12% of bereaved widows/widowers dying in this period.[11] Lack of emotional support after a myocardial infarction was associated with an increased incidence of death with a 6-month mortality odds ratio of 2.9 compared to patients with support.[12] In patients with coronary artery disease, mental stress was associated with wall-motion abnormalities or a fall in ejection fraction in 59% and 36% of these patients, respectively. Clinically silent ischemia was noted in 83% of the group with wall motion abnormalities.[13] In addition, ventricular tachycardia has been reported due to stress-induced increased cardiac sympathetic activity, and has been treated successfully with B-adrenergic blockade.[14,15]

Animal models of emotional stress mirror these findings. Psychologically stressed pigs, when rendered ischemic, develop ventricular fibrillation spontaneously.[16] Using this model, bilateral cryoblockade of the limbic brain prevents or delays ventricular fibrillation.[17] In addition, Skinner[18] demonstrated that learned adaption to stressors and intracerebral but not intravenous injection of levo-propranolol[19,20] can prevent stress from evoking lethal cardiac arrhythmias. At least some of these effects may be mediated through the autonomic nervous system.

Sympathetic and parasympathetic innervation of the ventricles travel different routes. Sympathetic afferent and efferent nerves are distributed along the epicardial surface of the ventricles while parasympathetic nerves penetrate deeply in the atrioventricular groove and subsequently course in a subendocardial layer.[21—23] This anatomical difference in distribution is reflected in differential responses to subendocardial infarctions that predominantly effect parasympathetic nerves versus transmural MIs which can effect the sym-

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pathetic supply as well. In addition, different walls of the heart manifest either parasympathetic or sympathetic responses. For example, inferior wall myocardial infarctions are more often associated with nausea, vomiting, and bradydysrhythmias, believed to be mediated through the parasympathetic nervous system. Conversely, anterior wall infarcts more commonly present with tachycardia believed to be mediated through sympathetic efferents.[24] Selective ablation of the parasympathetic or sympathetic nerves can be either protective or increase vulnerability to ischemic-induced VF, suggesting future areas for resuscitation research. Similarly, at the cellular level, manipulation of the alpha and beta receptors through stimulation or blockade can increase or decrease the likelihood of ventricular fibrillation. For example, while beta-blockade decreases the incidence of VF and death after an acute MI, defibrillation can directly effect cardiac adrenergic nerves causing depressed myocardial function.[25,26]

Interest in heart—brain interactions extends into other disciplines such as neurosurgery and critical care. Aneurysmal hemorrhage is not uncommonly associated with neurocardiogenic shock, believed to be from an outpouring of sympathetic neural activity. Patients with no known cardiac disease may develop profound cardiogenic shock after an aneurysm ruptures. This lasts several days to weeks and usually completely normalizes as the patient recovers from the bleed. Aneurysmal rupture is also well known to cause cardiac arrest which may be sudden in onset. Usually pulseless electrical activity or asystole, VF is seen in <10%.[27]

Acute ischemic strokes may also disrupt the autonomic nervous system resulting in cardiovascular complications. Laowattana et al.[28] found the incidence of cardiac death, AMI, angina, and heart failure increased, with a relative risk of 1.75, with left insular strokes compared to right insular strokes. In patients without symptomatic cardiac disease the RR increased to 4.06, while the RR decreased to 0.36 with symptomatic coronary artery disease, believed to be due to administration of beta-blockers and/or ischemic preconditioning. Lakusic et al.[29] demonstrated decreased heart-rate variability after ischemic strokes, indicating the presence of an autonomic perturbation, which, as shown above, predisposes to dysrhythmias and sudden death.

Given that emotions, biological time clocks, aneurysmal hemorrhages, and strokes can cause or are associated with cardiac dysfunction including cardiac arrest, it is not surprising that seizures too are associated with sudden death. Seizures were reported as a possible event leading to cardiac arrest over 50 years ago when a number of otherwise healthy soldiers died suddenly. Some cases were due to intracranial hemorrhage or rupture of an intracranial aneurysm, some remained unexplained despite autopsy.[30] Seizures can result from arrhythmias or, can cause cardiac events including sudden death. For example, status epilepticus was reported to be the initial manifestation of a case of Brugada syndrome.[31] Conversely, seizures may cause or be associated with sudden death, independently, or in association with mass lesions of the brain. Bradycardia and sudden death in epilepsy is well documented.[32,33] Rossetti et al.[34] showed that left temporal seizures could cause asystole which in turn provoked generalized tonic-clonic seizures. In this issue of Resuscitation, Sikkel and Batrick report a case of episodic asystole and apnea as presenting features of a diffuse glioma involving the right amygdala, hippocampus and splenium of the corpus callosum.[3] This is a rare event with a recent review of the literature revealing only 83 cases of sudden death associated with brain tumors, with 10 due to glioblastomas while 55 were due to benign tumors.[35] Of interest, these reports demonstrate involvement of the frontal areas and septum pellucidum. Sikkel and Batrick[3] rightly point out that while various cortical and subcortical sites may cause bradycardia and asystole, the central autonomic network comprising the insular cortex, amygdala, and hypothalamus assume a pivotal role.

Beck and Safar were, of course, both right. Hearts and brains too good to die. The heart and brain are so intertwined that perhaps those interested in the science of resuscitation should focus on this relationship. Perhaps, by unraveling these pathways, we can begin to understand why so few efforts at resuscitation are successful. Neurocardiology remains a relatively undeveloped area, with potential benefit for understanding and treating all forms of cardiac arrest.

Conflict of interest

None.

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