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The central nervous system and sudden cardiac death: What should we know?

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Abstract

The role of the central nervous system in the modulation and precipitation of sudden cardiac death has been a matter of controversy for decades. Establishing a cause-effect relationship in the setting of a cerebro-vascular event has been complex, as patients with stroke usually have risk factors for coronary artery disease as well. This article will review both experimental and clinical evidence relating to the mechanisms that link the central nervous system and the cardiovascular system. Cardiovascular consequences of stroke and epilepsy will be also reviewed. (Cardiol J 2009; 16, 2: 105–112)

Key words: central nervous system, autonomic nervous system, sudden death, SUDEP

Introduction

The role of the central nervous system (CNS) in the modulation and precipitation of sudden cardiac death has been a matter of controversy for decades. Initial observations in patients with acute stroke reported by Norris [1] documented the presence of marked electrocardiogram (ECG) changes and cardiac arrhythmias in 50% of patients with an acute stroke. Establishing a cause-effect relationship in this setting has been complex as patients with stroke usually have risk factors for coronary artery disease as well. Nonetheless, some studies have documented a significant increase in ECG alterations, characterized by ST-segment and QT interval alterations, as well as a higher incidence of ventricular arrhythmias, including ventricular fibrillation in patients with acute stroke [2, 3]. This article will review both experimental and clinical evidence relating to the mechanisms that link the central nervous system and the cardiovascular system. Cardiovascular consequences of stroke and epilepsy will be reviewed as well.

The limbic system

Much experimental evidence indicates that the final common pathway for most cardiac arrhythmias induced by central neural stimulation is related to the limbic system, specifically the amygdala and insular regions [4]. Stimulation of these areas induces marked sympathetic activation that is persistent even after vagal stimulation or vagal section [4]. Acute stroke, both experimentally and clinically, has been documented to induce focal myocytolysis in a series of patients with acute stroke that died suddenly due to ventricular fibrillation [5]. Focal myocytolysis is precipitated by increased sympathetic activation, which in turn increases ventricular vulnerability [5]. Central integration of the autonomic nervous system by the limbic system and insula plays an important role in modulating cerebrogenic sudden cardiac death (Fig. 1).

The role of the insula

Sudden cardiac death often occurs in individuals with increased coronary risk factors including

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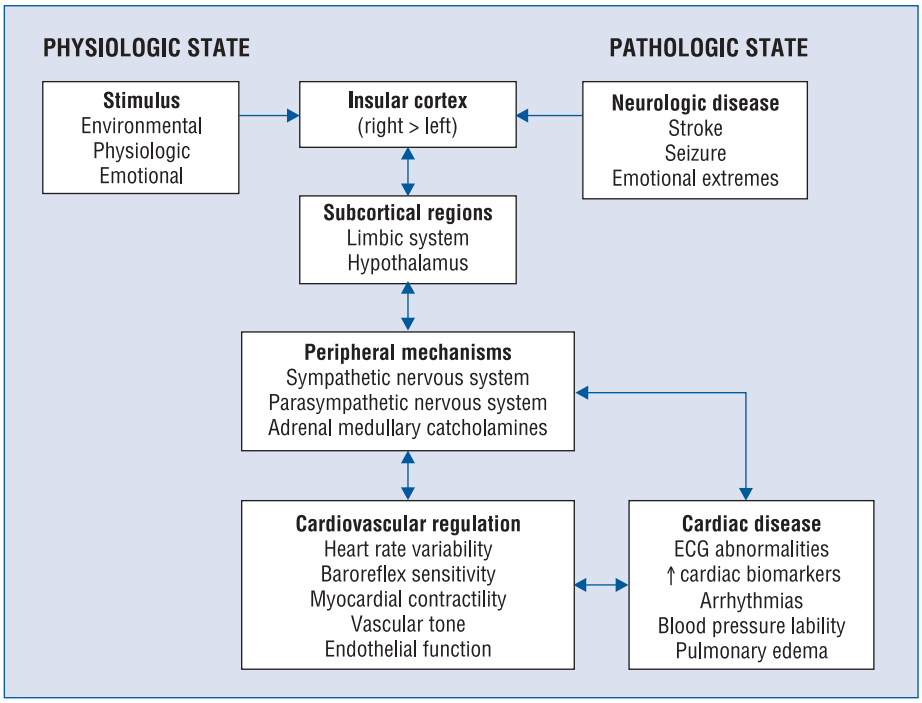

Figure 1. Brain-heart anatomical interactions. Integration of physiological responses.

hypertension, hypercholesterolemia, smoking, and stress; factors that are causally associated with coronary atherosclerosis and acute coronary syndromes. In many cases, sudden death results from a fatal arrhythmia during the acute coronary event, or is related to the resultant abnormal anatomic substrate (i.e. ischemic cardiomyopathy). However, some postmortem examinations of sudden death victims fail to identify either coronary or myocardial pathology [6]

As with coronary heart disease, there is a well-established association between sudden death and certain neurologic conditions. Moreover, both neurologic pathology and alterations of emotional states can produce autonomic imbalance resulting, at their most serious, in cerebrogenic sudden death [4, 7]. Indeed, there are a number of neurologic disorders that produce ECG alterations which may be predictive of sudden death, such as QT interval prolongation, late ventricular potentials, premature ventricular beats, non-sustained ventricular tachycardia (VT), and the R on T phenomenon. These include subarachnoid hemorrhage, intracerebral hemorrhage and ischemic stroke (Figs. 1, 2). Although less frequent, the same ECG changes can be found in patients with cerebral tumours, meningitis, multiple sclerosis, and spinal cord lesions (Table 1).

The cardio-specific isoenzyme creatine kinase increases with cerebrogenic ECG changes, but its concentration-time curve differs from that seen in acute coronary syndromes. Specifically, creatine kinase remains elevated during the four days after stroke, whereas it begins to fall within hours of an acute coronary syndrome [8].

Postmortem analyses of patients who died suddenly and without evidence of coronary artery disease frequently demonstrate myocytolysis and myofibrillar degeneration [5]. Such changes have also been observed in experimental models of hearts subjected to sympathetic overstimulation. Many have proposed a link between central nervous system pathology and the development of fatal arrhythmias involving the autonomic nervous system, specifically increases in sympathetic tone [9]. Cardiovascular conditions related to sympathetic nervous system pathology are classified as:

— central: cerebrogenic pulmonary oedema: increase in pulmonary intravascular pressure (the common final pathway is an increase in sympathetic tone due to an increase in intracranial pressure, i.e.: subarachnoid hemorrhage, focal lesions, etc);
— peripheral: increased sympathetic nervous discharge: increased secretion of adreno-medullary catecholamines, reduced parasympathetic activity. The imbalance of the autonomic nervous system over the electrical cardiac structures is the basis of the supraventricular and ventricular arrhythmias observed during cerebrogenic diseases.

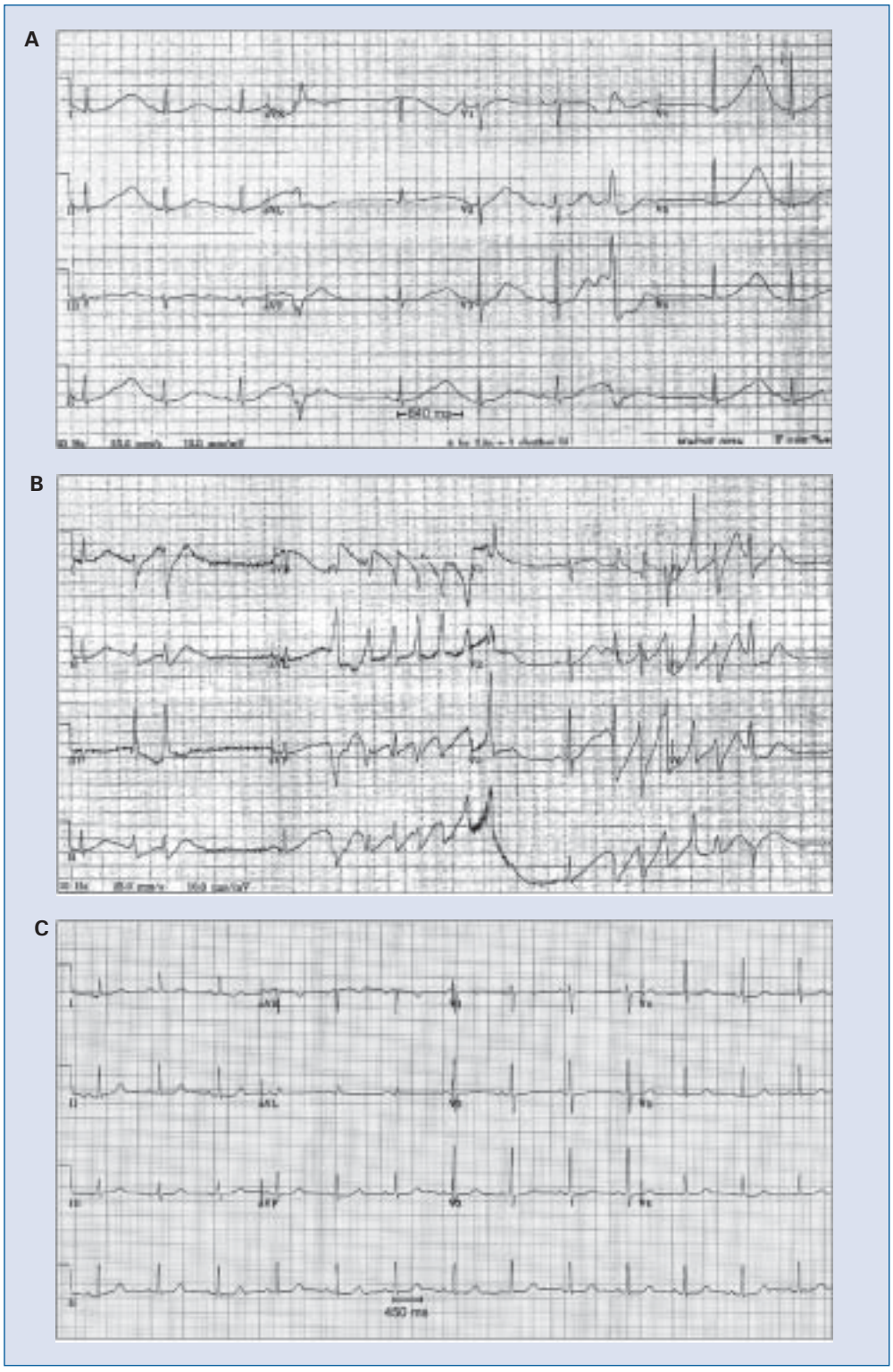

Figure 2. A. 12-lead ECG of a 64-year-old woman with no significant past medical history who collapsed in the lobby of her apartment building. The CT-scan demonstrated a right subdural hematoma with intracerebral right temporal and insular hemorrhage. The angiogram demonstrated normal epicardial coronary arteries. The 2-D echocardiogram was unremarkable. Note normal sinus rhythm with a dramatically prolonged QTc interval of 840 ms; **B.** 12-lead ECG of the same patient within 24 hours of admission. The ECG shows torsades de pointes in the setting of QTc interval prolongation; **C.** 12-lead ECG of the same patient 72 hours post-stroke. The ECG shows normal sinus rhythm with no ST changes or QTc prolongation (450 ms).

Table 1. Electrocardiographic changes during central nervous system lesions.

1. Morphology changes
   a. High peak P waves
   b. ST elevation
   c. T-wave inversion
   d. Prominent U-waves
   e. J waves (Osborne)
   f. QTc interval prolongation
   g. QTd interval prolongation
2. Bradyarrhythmias
   a. Sinus bradycardia
   b. Sinus arrest
   c. High degree AV block (suprahisian block)
3. Tachyarrhythmias
   a. Supraventricular tachyarrhythmias: AF
   b. Ventricular tachyarrhythmias: frequent premature ventricular contractions, non-sustained VT, sustained VT, ventricular fibrillation, polymorphic VT, or torsades des pointes as sociated with QTc interval prolongation

AV – atrioventricular, AF — atrial fibrillation, VT — ventricular tachycardia, QTc — corrected QT

There is a viscerotropic sensory representation in the insula. Afferent pathways arise from the taste buds, the gastrointestinal tract, the respiratory tract, and both baroreceptors and chemoreceptors in the heart. Efferent pathways include connections with the parabrachial nucleus, the contralateral insula, cortical regions, the thalamus, lateral hypothalamic areas, and the amygdala. The insula also has specific areas controlling vasopressor and vasodepressor responses [10, 11]. Experimental stimulation of the insula produces changes in arterial pressure and heart rate. Specifically, sites producing tachycardia are located in the rostral posterior insula; with bradycardia-producing sites located in the caudal posterior insula [11]. There is an important connection between the insula and the amygdala, where the central cardiovascular control within the limbic system is located. The amygdala regulates the changes over the heart during stress stimulation by liberation of neuropeptid Y and neurotensin [9, 10].

Heart rate variability (HRV) is an indirect method to assess cardiac sympathetic and parasympathetic interplay. Following acute stroke, vagal tone is reduced and the circadian variation of HRV is abolished. These changes have been implicated in the development of fatal arrhythmias and sudden death [7, 11].

Moreover, when acute stroke affects the insula, associations with higher serum epinephrine levels, higher blood pressure, and longer QT intervals can be observed [9–11].

In a retrospective analysis of 179 patients, Christensen et al. [12] analyzed 43 patients with insular lesions. Insular lesions were significantly associated with higher sinus rate ($p = 0.001$), ectopic beats ($p = 0.032$), and ST-segment elevation ($p = = 0.011$). Additionally, right-sided insular lesions were related to atrial fibrillation ($p = 0.009$) and atrio-ventricular (AV) block (0.029).

It is clear that the insula plays an important role in the interaction between the central nervous system and the autonomic nervous system. Intracranial lesions affecting the insula may trigger an autonomic imbalance that increases ventricular vulnerability and the risk of sudden death.

Lateralization of control

There is evidence to support lateralization, which is a differential effect from each cerebral hemisphere, in neurocardiac control [13]. Heart rate increases with left hemispheric inactivation and decreases with right hemispheric inactivation. Experimentally, the right cerebral hemisphere has been shown to modulate sympathetic activity [13]. Clinically, this correlates with increased arrhythmias and arrhythmic death following acute right-hemispheric stroke. Moreover, right-sided lesions not only increase sympathetic tone, but also decrease parasympathetic tone [13]. Conversely, the risk of sudden death was increased following left-sided cerebral infarcts (HR 1.40; CI 95% 1.00–2.00) over a 5 year follow-up period in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [14]. One possible explanation for these conflicting findings is that patients suffering right-sided infarcts may have died during the acute stroke. Alternatively, selection bias resulting from overrepresentation of patients with left-sided carotid disease in the trial may explain this conflict [14].

Tokgözoglu et al. [11] demonstrated a more profound decrease in HRV ($p < 0.001$) when the right middle cerebral artery and insula were affected in a cohort of 62 patients with acute ischemic stroke [11]. Correspondingly, there was a higher incidence of sudden death in patients experiencing right-sided strokes.

Inter-hemispheric connectivity between the two insulae provides an integrated patterning of cardiovascular regulation to diencephalic and brainstem autonomic centres. Zhang and Oppenheimer [15] experimentally demonstrated reciprocal insulo-insular connectivity by stimulation of the contralateral

insula using L-glutamate. This study suggests that communication between the two insulae is required for balanced interhemispheric cardiovascular control.

The level of the heart-brain link

There is evidence that precipitating triggers for sudden death are present in the central nervous system: circadian rhythms, plasmatic cortisol fluctuations, variations in sympathetic traffic, decreases in melatonin levels, increases in plasma serotonin, and cholinergic withdrawal. Furthermore, these triggers may interact on several different levels [9].

Suprachiasmatic nucleus, pineal gland, and pituitary

The circadian rhythm of sunlight and darkness are mediated through afferent pathways travelling via the retino-hypothalamic tract. Additionally, connections from the suprachiasmatic nucleus to the pineal gland stimulate the secretion of neurotransmitters following this circadian rhythm. Alteration in the daylight-darkness sequence as it relates to physical activity or inactivity may result in alterations of neurotransmitter secretion, resulting in potential triggers for cardiovascular diseases [16].

Higher centres

A number of exogenous stress triggers, including sleep deprivation and extremes of emotion, stimulate specific areas in the higher nervous centres. There is some evidence that variations in melatonin levels related to stimulation of these centres can trigger ventricular arrhythmias and affect ventricular vulnerability [16].

Sympathetic neural activity

An increase in cardiac vulnerability is observed with stimulation of the stellate ganglion. Stimulation of the left stellate ganglion predominantly affects the posterior surface of the heart, whereas stimulation of the right affects the anterior wall. Associated increases in sympathetic output following stimulation of the stellate ganglia decrease HRV by increasing sympathetic tone as well as the ventricular fibrillation threshold [17]. Similarly, during the acute phase of a myocardial infarction, abrupt increases in sympathetic tone can precipitate primary ventricular fibrillation even in the absence of structural heart disease.

Psychological factors

Psychological stress has objective validation by its repercussions throughout the autonomic nervous system. Elevations in sympathetic output increase myocardial vulnerability and, subsequently, susceptibility to ventricular arrhythmias [18]. Experimentally, stressful environments increase mean heart rate and the number of ventricular premature contractions. However, despite these well-documented effects on heart rate and rhythm, the neural pathways that integrate these circuits remain controversial.

There are several well-recognized psychological triggers of ventricular arrhythmias, including academic examinations, public speaking, and driving. Indeed, there is a strong correlation between job loss or loss of a spouse/loved one and an increase in sudden cardiac death [18]. Such triggers can be reduced by increasing vagal tone or through adrenergic blockade.

In the last few years a new clinical entity, variably called Takotsubo cardiomyopathy, transient left ventricular apical ballooning, and "broken heart" syndrome, has gained widespread recognition in the cardiovascular literature. The condition is typically characterized by transient myocardial dysfunction (ventricular mid-apical akinesis, or "ballooning") with ST-segment elevation in the anterior precordial leads followed by T-wave inversion much resembling an evolving acute anterior myocardial infarction. The epicardial arteries are usually free of significant atherosclerosis and any associated depression in left ventricular function recovers in days to weeks [19]. Both psychological and physical stressors are recognized as precipitants of this condition, and excessive catecholamine levels have been implicated as the putative mechanism. Despite a typically benign course, rare cases of associated corrected QT (QTc) interval prolongation, torsades des pointes, and conduction defects have been reported [20]. The electrocardiographic manifestations and transient wall motion abnormalities seen in Takotsubo syndrome are almost indistinguishable from those observed during intracranial lesions.

Triggering ventricular arrhythmias

Experimental evidence from microstimulation of the insula underscores the brain-heart connection as it pertains to arrhythmogenesis. Such experiments have demonstrated that stimulation of specific areas of the insula can precipitate arrhythmogenic triggers, including frequent ventricular depolarisations, high degree AV block, and the R on T phenomenon [11]. Such changes correlate with elevated norepinephrine levels and myocytolysis [5]. Furthermore, central nervous system damage

involving the insula can trigger overstimulation of the amygdala, resulting in liberation of neurochemical mediators synergistic with sympathetic stimulation [8].

The risk of sudden death in the post-stroke period

The initial stroke is the main cause of death in the first month following acute ischemic stroke. After the first year, however, non-stroke cardiovascular disease is the most common cause of death in these patients. There is no consensus about how to evaluate the post-stroke patient in order to identify a subgroup at high risk for sudden death. Frequently, these patients are limited in their ability to perform exercise tests and invasive tests should not be routinely used as screening methods.

Prolongation of the QTc interval is related to an increase in cardiovascular events [21]. Clinical observations have identified that patients with ischemic stroke, hemorrhagic stroke, or subarachnoid hemorrhage are prone to QTc interval prolongation (Figs. 2A–C). Wong et al. [21] retrospectively analyzed 404 stroke survivors with respect to QTc prolongation. Prolongation of the QTc interval in lead V6 ≥ 480 ms was found to be a strong predictor of cardiovascular death during the follow-up period (RR 2.9; 95% CI 1.6–5.3; $p < 0.001$). Such prolongation was associated with a 3-fold increase in the risk of cardiac death and 2.5-fold increase in the risk of death from any cause [21]. Kono et al. [22] demonstrated that patients who developed ST elevation during acute subarachnoid hemorrhage had reduced cardiac contractility despite identification of normal coronary arteries on angiography.

Despite these observations, it is unclear whether patients in the post-stroke period are more susceptible to sudden cardiac death related to brain-heart dysfunction, or whether sudden cardiac death is a manifestation of the overlapping risk factors for ischemic stroke and coronary artery disease. The answer may lie in the young patient with subarachnoid hemorrhage, a demographic in which preexisting coronary artery disease is extremely rare. In this population, electrocardiographic abnormalities are still present, suggesting a direct association between brain injury and cardiac outcome. In a recent review of ECG abnormalities and QT interval prolongation accompanying acute stroke, Khechinashvili et al. [23] found a high prevalence of ECG changes in the acute phase of subarachnoid hemorrhage (76%; 95% CI 73–90), intracerebral hemorrhage (96%), and ischemic stroke (91%; 95% CI 85–95). Furthermore, the frequency of such ECG changes remained significantly increased in the absence of structural heart disease.

Increased QT dispersion (QTd) is a marker of inhomogeneous cardiac repolarization. Such disordered repolarization has been proposed as a risk factor for sudden death in the setting of various cardiac diseases [24]. Afsar et al. [25] demonstrated increased QTd in the first 24 hours post-stroke in patients without evidence of previous structural heart disease. In this cohort, there were no significant differences according to the localization or type of stroke [25]. Interestingly, the size of stroke was statistically significant for QTd prolongation ($p << 0.05$), the QTd increases reverted at 72 hours, and no differences were found between patients with and without stroke [25].

Sudden unexpected death in epilepsy patients

Sudden unexpected death in epilepsy patients (SUDEP) is a common and devastating cause of death among patients with epilepsy [26]. The estimated incidence of SUDEP ranges from 0.7 to 1.3 per 1000 patients-years depending on the cohort studied, and from 3.5 to 4.1 per 1000 patients-years among patients included in anticonvulsant trials and/or surgery programs [26–28]. Overall, this amounts to a 24-fold increase in sudden death in patients with epilepsy compared with matched controls. Identified risk factors for SUDEP include generalized tonic-clonic seizures, structural cerebral lesions, sub-therapeutic plasma anticonvulsant levels, increasing number of anticonvulsants, cognitive delay/mental retardation, early onset of seizures, prone position, hyponatremia, and possibly male gender [26, 27]. More recently identified factors include early onset of epilepsy, duration of epilepsy, uncontrolled seizures, seizure frequency, and winter temperatures [27].

Although much remains to be learned about the pathophysiology of SUDEP, animal experiments have implicated postictal central apnea, prone position, and neurogenic pulmonary oedema as substrates for life-threatening ventricular arrhythmias [28, 29]. The addition of more than one anticonvulsant and/or psychotropic medications could cause excessive sedation and have a synergic effect during the postictal period. Prone position during a seizure could also result in hypoventilation during the postictal period, further predisposing to ventricular arrhythmia. Finally, autonomic nervous system alterations are well described during temporal

lobe epilepsy. Ictal discharges produce an increase in efferent sympathetic output, which in turn can be proarrhythmic and result in QTc prolongation that could lead to ventricular tachyarrhythmias [30].

Management of brain-heart dysfunction

The cornerstone of management of dysfunctional brain-heart interaction is prevention of the consequences of cardiac autonomic imbalance [31]. Both the post-stroke and post-myocardial infarction stages are characterized by increased sympathetic tone and decreased vagal tone. As described, both changes result in an increased risk of sudden death. Possible therapeutic strategies include both prevention of brain-heart dysfunction, and prevention of sudden death in the context of central nervous system damage and treatment of cardiovascular complications.

Prevention of brain-heart dysfunction

It is unclear whether lifestyle changes can contribute to prevention of brain-heart dysfunction. It makes sense to reduce stress triggers and to reorganize the circadian rhythms (day/night, total sleeping time, etc.). Christensen et al. [32] demonstrated an improvement in vagal tone in patients post myocardial infarction who were treated with n-3 fatty acids. Similarly, Singh et al. [33] demonstrated a reduction in cardiac events and beneficial modulation of the circadian rhythms after an acute myocardial infarction with fish oil consumption.

Use of drugs that modulate the renin-angiotensin-aldosterone axis, including beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists, may contribute to prevention of sudden death through an as yet unidentified interaction at the autonomic nervous system level. Further study is needed to determine whether these drugs reduce neurotransmitter plasma concentrations or brain excitation [34].

Temporal lobe epilepsy surgery demonstrated a reduction in the imbalance of the autonomic nervous system and its repercussions in the cardiovascular system [29]. Further studies are needed to confirm this observation.

Prevention of sudden death in the context of central nervous system damage and treatment of cardiovascular complications

There is no consensus on how best to identify high-risk patients for prophylactic treatment of sudden death related to brain-heart dysfunction. However, cardiovascular dysfunction in the setting of stroke or subarachnoid hemorrhage should be aggressively treated [31]. Neurogenic pulmonary oedema should be treated with diuretics, vasodilators, angiotensin converting enzyme inhibitors, and inotropes [31]. Evaluation of transient myocardial dysfunction is essential to recognize temporary stunned myocardium. The use of beta-blockers is usually beneficial in high blood pressure control and the reduction of parietal stress. Use of antiarrhythmic drugs that prolong the QTc interval (amiodarone, Class I, sotalol) should be avoided. Torsades des pointes, a dramatic complication associated with QTc prolongation during the acute phase of a stroke or intracranial hemorrhage, should be treated with temporary pacing or isoproterenol to increase heart rate and shorten the prolonged QTc interval.

The rationale for all these therapeutic options is to prevent sudden death in survivors of an acute cerebral event (ischemic stroke or cerebral bleeding). Most of these interventions are extrapolations of sudden death prevention in different clinical scenarios.

Conclusions

The links between the central nervous system and autonomic nervous system are anatomically and physiologically relevant to understand the high prevalence of cardiovascular events during the acute and post-acute period of cerebral events. Physicians involved in the prevention and treatment of sudden cardiac death should be familiar with the mechanisms of brain-heart dysfunction. Special attention should be given to patients with intracranial bleeding or ischemic stroke affecting the insula, as well as to patients with epilepsy at a high risk for SUDEP.

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