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Brain, heart, and sudden death

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Brain, heart, and sudden death

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Abstract
During the past 30 years, rate of coronary artery disease (CAD), as the main cause of sudden death (SD), has decreased more than rate of SD. Likewise, cause of SD remains elusive in not a trivial portion of its victims. One possible reason is attention to only one organ, the heart, as the cause of SD. In fact, SD literature focuses more on the heart, less on the brain, and seldom on both. A change is required. In this paper, we first review the pathological findings seen in heart autopsies of SD victims after psychological stressors such as physical assault victims without internal injuries. Then, we summarize new studies investigating brain areas, like the insula, whose malfunctions and injuries are related to SD. Next, we review prototypes of neurological diseases and psychological stressors associated with SD and look at heart failure (HF)-related SD providing evidence for the brain-heart connection. Finally, we propose a new look at SD risk factors considering both brain and heart in their association with SD, and review strategies for prevention of SD from this perspective.

Introduction

Sudden death (SD) or sudden cardiac death (SCD) is defined as an unexpected death occurring within 1 or 24 hour(s) of symptoms onset and without obvious non-cardiac causes such as end-stage obstructive lung disease, intoxication, or severe trauma.[1] It is estimated that between 180000 to 450000 SDs happen annually in the United States (US).[2] The variations in estimates reflect different SD definitions and methodologies used in the studies.[2] Using the multiple source surveillance method, studies have reported SD incidences from 40 to 100 per 100000 inhabitants in the US,[3] Germany,[4] Ireland,[5] and China.[6]

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Studies looking at trends of SD incidence showed that it has decreased in the past 30 years, but to a less extent than the decrease seen in the death rate due to coronary artery disease (CAD) which is the main cause of SD.[7,8]

SD starts from sudden cardiac arrest which results in SD when attempts for resuscitation are unsuccessful. This happens in 90% of cardiac arrests occurring in the community.[9] Survivors are recommended to undergo thorough investigations for finding the etiologies enabling physicians to protect them against recurrence.[10] Looking at the mentioned etiologies listed in such papers and guidelines,[1,10,11] we do not find a nervous system disorder as a potential cause nor do we find a recommendation for a neurological consultation after surviving cardiac arrest. In fact, studies that examined systematically sudden cardiac arrest survivors by exclusive investigation for covert heart diseases could not find the cause in up to 50% of survivors,[12] implying a possible role for brain and nervous system diseases and/or their interactions.

In this paper, we first look at human studies showing cardiac damage after brain lesions or psychological or physical stress. Second, we summarize clinical studies looking for brain areas whose injuries affect the heart's electrical and mechanical health. Third, we examine neurological brain diseases (such as stroke and epilepsy) and psychological conditions (such as stressful life events) associated with an increased risk of SD. Fourth, we look at a heart condition [heart failure (HF)] providing evidence for the brain-heart connection in SD. Finally, we mention strategies for the prevention of SD, from the perspective of the brain-heart interactions in SD.

Heart biopsies and post-mortem findings

Reliable and interesting evidence for the brain-heart connection comes from studies that have performed histopathological examinations of hearts of patients after sudden emotional stress or victims of physical assault who died without gross internal injuries. In a report of 19 patients with takotsubo cardiomyopathy (TCM) [median ejection fraction (EF): 0.2 odds ratio (OR) 20%. Interquartile range (IQR): 0.15 to 0.30]. Only one of them had angiographic evidence of a luminal narrowing of 70 percent and none of them had a significant coronary spasm.[13] Five of them underwent endomyocardial biopsy which showed extensive lymphocyte infiltrates with contraction band necrosis in one of the patients and macrophage and lymphocyte infiltrates with contraction bands but without myocyte necrosis in the other four.[13] In examining 15 victims who died as a direct result of physical assaults but without internal injuries, myofibrillar degeneration was found in the hearts of 11 victims, which is the pathology described in stressed animal experiments.[14] Such changes were not found in the age-matched controls. Of note, two of the victims with the described lesions survived the attack but suffered from arrhythmias throughout the hospital course.[14] The contraction band necrosis has also been reported in a young Japanese woman who escaped from her boyfriend's violence, ran 150 meters, and suddenly collapsed.[15]

Subarachnoid hemorrhage (SAH) is another potential cause of SD. In an autopsy report of 3 patients with SAH with electrocardiography (ECG) changes, the post-mortem examination revealed several petechial subendocardial hemorrhages (SEH).[16] In another report from 9 patients with SAH, cardiac lesions were seen in all of them that ranged from eosinophilia with preservation of cross-striations to transformation of the myocardial cytoplasm into dense eosinophilic transverse bands with intervening granularity sometimes coupled with endocardial hemorrhage.[17]

From the pathological point of view, sharp differences exist between coagulative necrosis, lesions seen in myocardial infarction (MI) after coronary occlusion, and cardiac lesions seen due to catecholamine damage with peroxidation.[18,19] The latter is called by different terms such as contraction band necrosis, myofibrillar degeneration, and coagulative myocytolysis, and is reported in victims of physical assaults without internal injury and in patients with CAD in whom helplessness and hopelessness were the basic feelings. In coagulation necrosis, cells die in a relaxed state without prominent contraction bands and the changes are not visible until several hours or days later. The area is infiltrated by polymorphonuclear cells and calcification occurs late. In contrast, in contraction band necrosis, cells die in the hypercontracted state with prominent contraction bands, mononuclear cells are the predominant cell infiltrates, calcification may happen immediately, and changes are seen within minutes of onset. Apart from necrosis, other pathological findings have also been correlated with catecholamine toxicity, including myocardial cells' disarray.

As contraction band necrosis occurs

predominantly in the subendocardial area, it can affect the cardiac conduction system and increase the risk of fatal arrhythmias, specifically when we note a propensity of catecholamines to evoke arrhythmias by themselves, even in a normal heart. In fact, this mechanism may underlie many apparently unrelated cases of SD following neurological diseases such as epileptic seizure, SAH, and ischemic stroke, or SD during grief for a loss and when frightened to death.

Brain regions associated with heart function

The field of neurocardiology started with the observations and experiments of the French physiologist Claude Bernard who was the first to describe reciprocal interactions between the heart and the nervous system.[20] The American physiologist Walter Bradford Cannon highlighted that severe emotional stress might have fatal consequences.[21] He summarized reports of voodoo death - SD due to intense emotions, often fear, in native societies - and suggested that cardiovascular shock following a hyperactivation of the sympathetic nervous system (SNS) might be the underlying pathological mechanism.

Research on the functional neuroanatomy of the autonomic nervous system and its interactions with the cardiovascular system has traditionally focused on autonomic circuits at the spinal and brainstem level and peripheral neurotransmitters such as acetylcholine[22] and norepinephrine.[23] More recently, several lines of observational and experimental evidence have suggested that a widespread brain cortical and subcortical circuitry is involved in the control of the autonomic nervous system, the central autonomic network.[24] Several converging lines of evidence have identified the core regions of the central autonomic network: the bilateral insular cortex, prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala, and hypothalamus (Figure 1).[24] The hypothalamus (Figure 1) is well-known to be involved in the autonomic nervous system control as sympathetic nerves originate from its nuclei, and will not be discussed here.

The insular cortex (Figure 1) is an area specialized in sensory, cognitive, affective, and autonomic integration[25-27] and, therefore, is regarded as a principal hub of the central autonomic network.[28] Evidence for the important role of the insula in autonomic regulation is provided by lesion studies, cortical stimulation, and functional neuroimaging. Lesions of the insular cortex, e.g., due to ischemic stroke or intracerebral hemorrhage (ICH), often result in autonomic imbalance, consecutive myocardial damage, and cardiac arrhythmias.[29,30] Intraoperative cortical stimulation of the left insular cortex causes primarily bradycardia and depressor responses, whereas stimulation of the right insular cortex is often associated with tachycardia and pressor responses.[31] Studies using functional magnetic resonance imaging (MRI) have demonstrated insular activation during different autonomic challenges, such as cognitive tasks, emotional stimulation, exercise, the Valsalva maneuver, and the cold pressor test.[32,33]

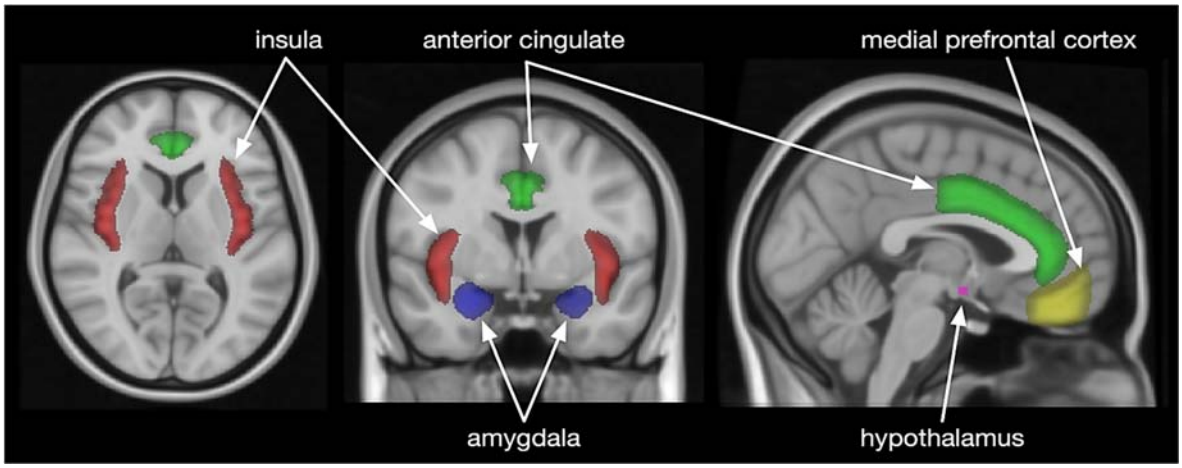

Figure 1. Core areas of the central autonomic network; it includes the insula (red), the anterior cingulate cortex (ACC) (green), the medial prefrontal cortex (PFC) (yellow), the amygdala (blue), and the hypothalamus (purple). The image shows the Montreal Neurological Institute (MNI) 152 T1 1mm template (as provided by FSL). To locate the anatomical areas, the Talairach atlas (for the hypothalamus) and the Harvard-Oxford cortical structural atlas (for all other areas) were used (as included in FSLeyes).

Clinical and neuroimaging studies have shown that the ANS is also modulated by parts of the PFC, in particular, the orbitofrontal and the medial PFC (Figure 1).[34] In a study of hand-grip exercise, more intense exercise and increased heart rate were associated with a deactivation of the ventromedial PFC (vmPFC), suggesting that parasympathetic efferents to the heart are mediated by the PFC.[35] Moreover, the vmPFC regulates the activity of the amygdala (Figure 1), which is a brain area involved in emotions, such as fear. In fact, the central nucleus of the amygdala is involved in the modulation of the ANS. In humans processing fearful faces, activity in the right amygdala was positively correlated with heart rate.[36]

Another brain region of interest is the ACC (Figure 1) which is a critical interface between the motor system, cognition, emotion, and autonomic functions.[37] During cognitive demanding tasks, evidence for modulation of the sympathetic and parasympathetic tone was found in the dorsal ACC.[38,39]

SD in brain diseases

Acute stroke: Myocardial injury, ECG abnormalities, and cardiac arrhythmias are frequent sequelae following acute stroke, even in patients without pre-existing heart disease. In a prospective study on 2123 patients with acute ischemic stroke (AIS), using a high-sensitivity troponin assay, 13.7% had elevated troponin concentrations in the acute phase.[40] Interestingly, in a subgroup of patients with acute stroke who underwent coronary angiography, half of the patients had no angiographic evidence of CAD.[40] In a meta-analysis done on 2901 patients across 15 studies, including patients with ischemic and hemorrhagic stroke, 18.1% [95% confidence interval (CI): 13.6%-22.6%] had elevated troponin concentrations.[41] Several lines of evidence suggest that an ischemic or hemorrhagic lesion, in particular involving the right insular cortex, may result in autonomic imbalance, leading to increased catecholamine secretion and finally, to diffuse myocardial injury known as myocytolysis.[42]

Irregularities of cardiac depolarization and repolarization are frequently detected on ECGs of patients with acute stroke. In a study on 279 patients with AIS, prolonged QTc interval (36%), ST depression (24.5%), and T wave inversion (17.8%) were seen at admission.[43] QT prolongation[44] and ST elevation[45] at admission were associated with ischemic lesions of the insula.

Serious arrhythmias, such as ventricular or supraventricular tachycardia, sinus node dysfunction, bradyarrhythmia, or atrioventricular (AV) block II and III were found in 25.1% of 501 patients with acute ischemic or hemorrhagic stroke during the first 72 hours after admission.[46] In another prospective study on 332 stroke patients, who were monitored for at least 48 hours, 29.5% of all patients had significant arrhythmias with tachyarrhythmias being more frequent than bradyarrhythmias (27.1% vs. 3.9%).[47] A significant association was found between the incidence of serious arrhythmias in the acute phase of stroke and a lesion involving the insula, frontal cortex, parietal cortex, amygdala, thalamus, or basal ganglia of the right hemisphere.[48] In a subgroup of stroke patients, fatal or near-fatal arrhythmias, primarily ventricular tachycardias rapidly evolving to ventricular fibrillation (VF), may occur, leading to SCD.[49] The exact mechanism of ECG alterations and serious arrhythmias after stroke is complex and multifactorial, probably including autonomic dysfunction and myocardial injury, modulated by genetic susceptibility and the cognitive and emotional situation of the patient.[50,51] Due to the potentially life-threatening cardiac complications following acute stroke, clinical guidelines recommend cardiac diagnostics including ECG and cardiac markers at admission and continuous cardiac monitoring for at least 24 hours after the event.[52] Additional studies on the interplay between ischemic stroke and heart disease are urgently needed, involving functional MRI[53] and analysis of genetic variants associated with arrhythmias.

SAH: SAH is a devastating neurological condition that usually results from an unexpected sudden rupture of a berry cerebral aneurysm. It is well known to be associated with SD; in a nationwide SAH incidence study in Finland, one fourth of victims had SD before reaching any hospital ward.[54]

Elevation of cardiac injury markers is common after SAH. ECG changes have been reported in about two thirds of SAH hospitalized patients;[55,56] the most common changes were prolonged QT interval followed by T waves inversion and ST depression or elevation,[55-57] and they predicted higher in-hospital mortality.[56] Besides, cardiac troponin was increased in 30% of patients with SAH and was associated with an increased risk of in-hospital mortality and 12-month deaths.[58] Mechanisms connecting SAH to cardiac injury and

SD are unclear, but rupture of posterior circulation aneurysms was more commonly associated with SD,[59] possibly because of vital heart-connected centers located in the brainstem and supplied by the posterior circulation.

Epilepsy: Several community-based studies have demonstrated that patients with epilepsy have an approximately threefold increased risk of SCD (with documented ECG abnormalities, such as ventricular tachyarrhythmia or VF).[60] The studies also indicate that the age of patients with sudden unexpected death due to epilepsy (SUDEP) is significantly lower than of those without epilepsy (55 ± 25 vs. 63 ± 19 years, $P < 0.001$), indicating a distinct pathology and etiology.[61] SUDEP is defined as a sudden, unexpected, nontraumatic and nondrowning, witnessed or unwitnessed death in patients with diagnosed epilepsy, with or without evidence of an acute seizure, and excluded status epilepticus (SE), with unrevealing post-mortem examination.[62] Currently, SUDEP is considered the leading cause of death in patients with epilepsy.[60,63] Several risk factors have been reported for SUDEP including young age (15-20 years), poor seizure control, use of sodium-channel blockers as antiepileptic drugs, refractory epilepsy, multiagent therapy, seizure types (tonic-clonic seizure), early-life epilepsy, and cardiovascular disease (CVD) including the presence of ischemia, previous atrial or ventricular arrhythmias, and history of cardiovascular events.[60,64]

The exact mechanism of SUDEP has not been determined; however, the main etiology of SUDEP is atrial and ventricular arrhythmias during epilepsy in the context of a previously diseased and susceptible heart.[65] The observation that patients with epilepsy have a worse cardiovascular profile[66] and a higher risk of cardiovascular events and arrhythmias compared with the normal population[67] indicates that epilepsy and CVDs might share a congenital and genetic basis affecting both the heart and brain. In brief, the epileptic discharges are associated with episodes of central autonomic imbalance with sympathetic dominance, leading to repetitive episodes of apnea, hypoxemia, and cardiac injury. Li et al. postulated that ictal discharge originating from the cortex could, primarily or secondarily, involve the insular lobe through epileptogenic signal networks, leading to cardiorespiratory dysfunction, central apnea, arrhythmias, and SUDEP.[68] Accordingly, Nayak et al. also postulated that autonomic imbalance determined by changes in heart rate variability (HRV) during epilepsy might be the main mechanism of SUDEP.[69] They demonstrated that in patients with refractory temporal lobe epilepsy (TLE), a lack of apnea-mediated HRV changes existed, leading to an alteration in baroreceptor reflex activation, predisposing them to SUDEP.[69]

Sleep apnea: One metric to define sleep apnea and its severity is the apnea-hypopnea index (AHI), derived from polysomnographic (PSG) recordings.[70] This index represents the average hourly frequency of apnea (airflow absent > 10 seconds) plus hypopnea [airflow diminution associated with a drop in arterial oxyhemoglobin saturation (SaO_2) ≥ 3% or terminated by an electroencephalographic (EEG) arousal] during sleep. AHI less than 5 per hour is normal, and severe SA is considered when AHI is > 30 per hour.[71] sleep apnea is classified into obstructive sleep apnea (OSA) and central sleep apnea (CSA) according to the presence of obstruction and/or resistance to airflow in the upper airways.

Sleep apnea was first considered as a possible diagnosis in patients complaining of excessive daytime sleepiness (EDS). Later epidemiological studies revealed an association between sleep apnea and cardiovascular events including SD.[70] Patients with OSA were more than twice susceptible to experience SD from midnight to 6:00 AM compared to the general population and patients without OSA.[72] Following more than 10000 participants for an average of 5.3 years, investigators found the lowest nocturnal oxygen (O_2) saturation, decreased in patients with OSA, as an independent SCD risk factor besides hypertension (HTN), CAD, and HF.[73] Congruent with more SD risk in patients with sleep apnea, arrhythmias such as atrial fibrillation (AF) and complex ventricular ectopy were more frequent among patients with sleep apnea. Interestingly, appropriate implantable cardioverter-defibrillator (ICD) therapy was 4 times more frequent when ICD patients had sleep-disordered breathing (SDB), defined as AHI > 10, and the difference was only seen during sleep hours from midnight to 6:00 AM.[74]

Mechanistically, excessive sympathetic and parasympathetic activity is seen in patients with sleep apnea and links sleep apnea to cardiovascular events and SD. Cessation of breathing results in an increased sympathetic outflow through different mechanisms such as stimulation of chemoreceptors by O_2 desaturation, carbon dioxide (CO_2) increase, and silencing pulmonary

stretch receptors. Such an overactive sympathetic state persists even after termination of an apnea episode which does not last beyond 90 seconds. In fact, patients with sleep apnea showed structural changes in the brain areas associated with the autonomic nervous system such as the insula and cingulate cortex and the changes were associated with O_2 desaturation.[75]

Other brain diseases: In a population-based autopsy study of consecutive SDs, neurological diseases were the most common non-cardiac causes of SD after drug overdose, and they comprised 5% of SDs.[76] Intracranial hemorrhage and SUDEP were the most common causes of the neurological SDs, followed by SAH, AIS, and Huntington's disease (HD), which is an inherited disease of abnormal movements with concomitant psychiatric and cognitive manifestations. One of the SD victims had an ICD and interrogation of the defibrillator demonstrated that the patient had been repeatedly shocked for VF, but the autopsy revealed that the cause of SD was SAH.[76] Other brain diseases (Table 1) have also been mentioned to be associated with SD including Parkinson's disease (PD), multiple sclerosis (MS), and brain tumors, such as meningioma. For instance, demyelinating lesions of MS may affect the medulla oblongata, which has cardiac innervating nuclei, and cause SD. Although many of the neurological diseases can precipitate SD through involvement of the peripheral nervous system (PNS) including the muscles, like myotonic dystrophy type 1 (DM1), they are not discussed in this review, and can be found elsewhere.[77]

Table 1. Brain diseases accounted for sudden death (SD)

More commonly accounted
ICH
Epilepsy
AIS
SAH
Sleep disorders (e.g., OSA,CSA)
Multiple system atrophy
Less commonly accounted
MS
PD
Brain tumors
HD
Friedreich ataxia
Migraine

ICH: Intracerebral hemorrhage; AIS: Acute ischemic stroke; SAH: Subarachnoid hemorrhage; OSA: Obstructive sleep apnea; CSA: Central sleep apnea; MS: Multiple sclerosis; PD: Parkinson's disease; HD: Huntington's disease

Psychological stress and SD

History of stress and SD: "There is no evidence that stress causes heart disease, nor will there ever be". This sentence was an explicit opinion addressed 30 years ago by the chair of a panel organized by an Australian national health body to review the association of mental stress and CVD.[78] However, a strong resurgence is seen among researchers and clinicians to support the idea of an association between psychological stress and heart diseases, dating back to 1628 and expressed by William Harvey by his description of angina of emotion.[79]

In 1942, Walter B Cannon published one of the earliest remarkable papers about the association between stress and SD, "voodoo death", where he recounted anecdotal experiences of death from fright.[21] Cannon found that all the recounted experiences had at least one common feature: they were induced by an absolute belief that an external power, such as a wizard, could cause their demise deliberately, and the victims did not have any power to prevent death. Newer studies have shown an increased risk of SD, not non-sudden coronary death or nonfatal CAD, in people who had reported higher levels of phobic anxiety.[80]

Earthquakes as stressors: Earthquakes are one of the acute stressors during which many papers have demonstrated increased cardiovascular risk.[81] After a major earthquake in Athens, Greece, in 1981, an excess of mortality was observed during the first few days compared with the same periods in 1980 and 1982.[82] The mortality excess was due to cardiac and external causes, while no or few increased deaths were seen due to cancer and other causes, respectively. Los Angeles, USA, was jolted by an earthquake on January 17, 1994, at 4:31 AM. From 101 recorded deaths on this day, 51 were attributed to atherosclerotic cardiovascular causes, which was more than five times the number of cardiovascular deaths in the preceding week, and relative risk (RR) of death due to atherosclerotic heart disease was 2.6 (1.8-3.7) compared with the same periods in previous years.[83] Of note was the time of death: midnight to 6 AM was the time of death in 54% of atherosclerotic deaths occurred on the day of the earthquake compared to 9% of the deaths during 7 days before the earthquake.

A study on subjects who were wearing 24-hour Holter ECG monitors during the Taiwan earthquake in 1999 showed autonomic dysregulation during the earthquake.[84] HRV study showed that sympathetic overactivity was present in 9 out of 12 patients, and was absent in three

others who were consuming beta-blockers.

Athletic games as stressors for spectators: One of the first reports in this area was about cardiovascular events among German residents during a soccer World Cup held in Germany in 2006.[85] The authors found that cardiovascular events had been increased with the highest rise in arrhythmia events. The rise was also more profound in men and during days on which the German soccer team was playing. Such an increase in cardiovascular events, including SD, has been reported in spectators of other sports such as football,[86] hockey,[87] and baseball.[88] By contrast, some studies have not found any increase in cardiovascular events during a championship series.[89] Although differences in study design can explain part of this heterogeneity, the results of other studies showed that people were not at the same risk of increased cardiovascular events while watching athletic games. Men are usually at higher risk;[85,87] age is an important factor and in some reports, younger[87] and in others, older people[88] were at higher risk. Live watching was also associated with a higher risk compared to televised watching.[90] Autonomic imbalance seems to play a major role in the increased risk of cardiovascular events as studies showed a 110% increase in heart rate[90] and increased serum levels of noradrenaline[91] during game watching.

War and terrorist attacks as stressors: In the first week of Iraqi missile attack on Israel, the incidence of MI and SD increased among Israeli civilians, but returned to its normal rate after the first week despite the continuation of missile attacks.[92] In another war report from Zagreb, Croatia, in 1991, MI and its mortality increased during the war compared to control periods. The incidence of MI increased three times in the first 48 hours following the terrorist attack of the New York World Trade Center, USA, on September 11, 2001, and returned to normal levels thereafter.[93] Moreover, studies with patients who had ICDs showed an increased incidence of ventricular tachyarrhythmias in the first 30 days following the September 11th attack.[94] Of note, tachyarrhythmias increased not only among residents of the New York area,[94] but also in patients living in Florida, USA,[95] far from the attack, highlighting the role of psychological, not physical, stress as the risk factor for the arrhythmias.

Pleasant emotions and SD: An excess of SD after natural disasters and during major sporting events has been well documented. However, pleasant events can also be associated with undesirable outcomes. It has been shown that the one day of the year in which someone is more likely to have a heart attack or a stroke is one's birthday.[96] The association of a usually pleasant event, such as a birthday, with adverse outcomes suggests that the physiological underpinnings of strong emotions are similar. Some evidence for this comes from the realization that TCM can occur not only after bad news, but also after pleasant surprises, such as winning the lottery.[97] No one can be prepared for the eventualities of life, but awareness about the risks of strong emotions may be a first step in preventing or mitigating them.

TCM: Another piece of evidence for the association between stress and heart disease comes from examining survivors of TCM. Recent studies have found injury to the insular cortex to be associated with the incidence of TCM.[98,99] In a Korean multicenter stroke registry, 23 patients with ischemic stroke had imaging characteristics of TCM from 5098 patients with ischemic stroke without any history or imaging evidence for CAD. Stroke lesions in the TCM patients involved the insular cortex more often than other brain regions.[99] In a single-center registry study of cardiology patients, 6 patients had experienced an ischemic stroke (n = 4) or epileptic seizures (n = 2) in the 2 days preceding the onset of the TCM.[98] They arrived at the hospital because of their neurological complaints and had normal ECG on admission. After a few hours, they developed ECG changes, e.g., ST-segment elevation while only 2 of them presented with chest pain, and were diagnosed to suffer from TCM. Insular lesions were seen in 4 of the 6 patients.[98] Therefore, abnormalities in the brain regions associated with the autonomic control, such as insular cortex, may have a role in predisposing victims of TCM to emotional and physical stressors. In future studies, structural and functional MRI of the brain should be performed in patients with TCM.

Another neurological condition associated with TCM is seizure. Approximately, 50 case reports have been published describing TCM after seizures.[100] Both generalized and focal seizures as well as SE have been described as types of seizures associated with TCM, and TCM has been cited as a reason for SUDEP. In a recently published study leveraging National Inpatient Sample databases, investigators found 1 in every 1000 epilepsy-related hospitalization in the US to be associated with TCM, which had increased in-hospital

morbidity and mortality of epilepsy patients.[101] Compared to TCM unrelated to seizures, seizure-related TCM is associated with much less chest pain, more cardiogenic shocks, and a much higher recurrence rate.[102] Therefore, cardiologists should be involved in the management of hospitalized epilepsy patients who may develop TCM without any cardiac symptom. In addition, more studies are needed to risk stratify epilepsy patients who will develop or re-experience TCM.

Brain-heart connection in HF-related SD

SD is a major cause of death in patients with HF, and ICDs are recommended in the HF guidelines for its prevention.[69]

Autonomic nervous system imbalance exists in HF although not every HF patient has it. It manifests as an increased sympathetic and attenuated parasympathetic nervous system activity. The autonomic nervous system imbalance leads to structural changes in cardiac muscles including myocyte dysfunction caused by excessive β-adrenergic receptor (βAR) stimulation with apoptosis and βAR desensitization, altered kinase and phosphatase activity, neurohumoral activation, increased susceptibility to arrhythmia, inflammation, and abnormal nitric oxide synthase (NOS) signaling, all of which lead to a worse clinical outcome and reduced survival in patients with HF.[103] Clinical studies showed autonomic nervous system imbalance to be a risk factor for SD in patients with HF and to be also associated with exercise intolerance, disease progression, and pump failure.[103]

Both central nervous system (CNS) and PNS dysfunctions are involved in the development of autonomic nervous system imbalance. In the brain, structural and functional changes are seen in areas related to autonomic control. A recent study demonstrated that patients with chronic HF had altered neural activation in multiple autonomic and motor control areas, including cerebellar hemispheres, vermis, left insula, left putamen, and bilateral postcentral gyrus. Structural brain changes emerged in similar autonomic, as well as cognitive and mood regulation areas.[104] These studies indicate that the functions of insular and cerebellar regions, sites that are involved in autonomic regulation, are compromised, and that autonomic nervous system imbalance has a brain structural and functional basis too. In fact, it has been demonstrated that without apparent effect on left ventricular EF (LVEF), early subclinical cardiac dysfunction and brain abnormalities are present and associated in middle-aged generally healthy individuals.[105] This demonstrates that structural and functional changes of the brain outpace the clinical HF and ventricular dysfunction could be explained by the autonomic nervous system imbalance before overt HF.[105] Thus, autonomic nervous system imbalance can be a therapeutic target for declining SD in HF, and we expect to see new horizons and perspectives soon.

Prevention of SD

CAD is the most common cause of SD followed by HF with fatal arrhythmia as the main direct reason of death in both. Identification of SD risk factors (Figure 2) can help to identify patients with increased risk and to promote the development of preventive strategies.

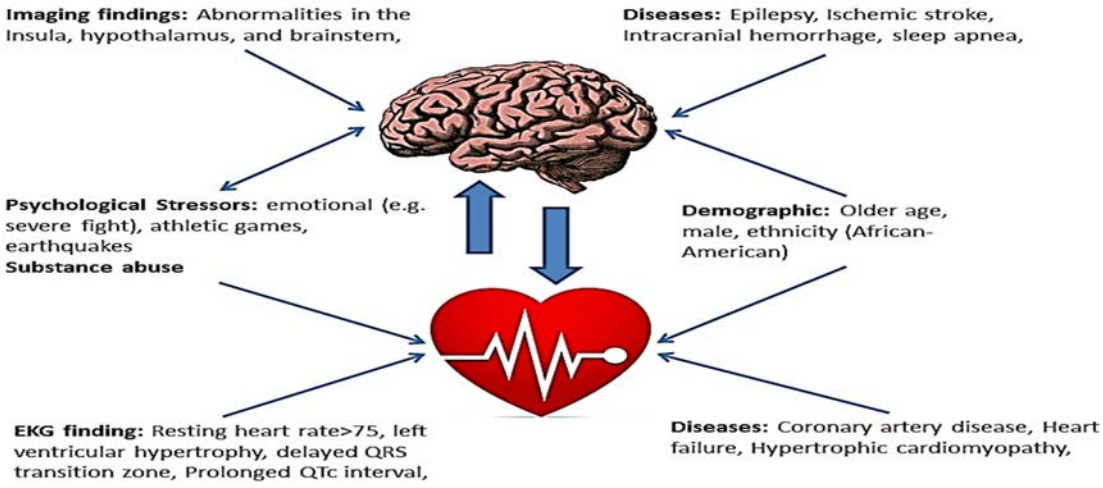

Figure 2. Selected sudden death (SD) risk factors in light of heart-brain connection; more common risk factors are summarized and classified here. Other SD risk factors can be found in the text and elsewhere.[69]

Drug addiction[106] and demographic variables[107] are among risk factors that increase SD risk by affecting the brain, heart, or both. Many cases of SUDEP or stroke are related to existing cardiac disorders;[49,108] however, SD can also occur in stroke or epilepsy patients with a structurally normal heart.

While many patients with epilepsy and their relatives want education sessions, unfortunately, fewer than 15% receive systematic education on SUDEP.[109] Whether to inform the patients about SUDEP is still argued by some physicians, and increasing awareness is recommended in most recent publications.[110] Another preventive measure is seizure control, shown to prevent SUDEP, but using seizure alert devices and anti-suffocation pillows may help too. Other preventive strategies against SUDEP are a timely referral for surgical evaluation in patients with intractable epilepsy, detecting cardiorespiratory distress through clinical observation, O_2 administration, and using respiratory and heart rate monitoring devices, particularly during sleep. Besides, use of drugs that enhance the serotonergic mechanisms of respiratory regulation [e.g., selective serotonin reuptake inhibitors (SSRIs)], decrease endogenous opioid-induced brain and brainstem depression, or inhibit adenosine receptors may be other effective preventive measures.[111] However, further high quality researches and investigating the appropriate use of pacemakers and ICDs in the patients with epilepsy are warranted.

Cardiac dysfunction following stroke is common, but its prevention needs a more detailed understanding of its complex mechanisms.[49] In most cases of SD following ischemic stroke, cardiac arrhythmia, myocardial injury in the presence or absence of CAD, and autonomic imbalance are contributing factors.[49] Defining the predictors of SD after stroke may help to develop preventive actions, but there is no systematic approach and no strong evidence to define them. However, identifying stroke locations in addition to cardiac abnormalities might be helpful in the identification of patients with high risk for SD. Some of the cardiac abnormalities are presence of HF, markers of acute myocardial injury, and cardiac conduction disorders, specifically QT prolongation. Studies in the area of genetic variants that are the underlying reasons for lethal arrhythmias related to autonomic dysfunction seem to be necessary to develop further preventive strategies.[48]

Irrespective of the EF level, arrhythmic SD is responsible for many deaths in patients with HF.[112] Among pharmacologic measures, strong evidence exists that mineralocorticoid receptor antagonists (MCRAs) are effective in SD prevention in patients with HF with low EF and New York Heart Association (NYHA) functional class II to IV. They have the same effect in all patients with systolic dysfunction following an acute MI, regardless of the existence of signs or symptoms of HF.[113] The most effective methods for SD prevention in patients with HF are ICD and cardiac resynchronization therapy defibrillators (CRT-D).[112] Although HF-related SD is decreasing, many patients with HF still develop SD and die, emphasizing new preventive targets such as ANS imbalance-related brain areas and their functions.

Conclusion

C When one of the two highly-interconnected organs such as the brain and the heart is affected, one expects that so will the other, and yet, the bulk of the SD literature focuses either on the heart or the brain, but seldom on both. This leaves a large understudied gap of interactions that might explain why half of the causes of SD remain unexplained.[12] Conceptually, it may be helpful to characterize the brain-heart relationship as a dynamic balance that can be altered by extremes of normal function such as overwhelming emotion, stress, or functional or structural damage to one of the organs, disrupting the finely-tuned equilibrium and resulting in arrhythmia generating imbalances. Many answers lie in the interphase. Circadian rhythms and the role of SA may prove important, not only in CVD but also in stroke.[70] The ANS as a therapeutic target in HF emerges as a promising area of research and intervention.[114] The spectrum of individual reactivity to stress remains largely unexplored. The tools for studying these areas continue to become more available and refined. The development of sophisticated heart and brain devices to stimulate and record, the growth of the peering power of structural and functional imaging, and the increasing availability of molecular, genetic, and epigenetic techniques to study gene-environment interaction[115] might yield a more dynamic understanding of the brain-heart relationship in health and disease. The availability of smartwatches with a US Federal Drug Administration (FDA)-approved capability to detect AF points to a future where arrhythmia monitoring and management can be personalized to minimize the risk of SD. Much has been achieved in understanding SD, but much more is needed and can be done.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

1. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden cardiac death prediction and prevention: Report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation 2010; 122(22): 2335-48.
2. Kong MH, Fonarow GC, Peterson ED, Curtis AB, Hernandez AF, Sanders GD, et al. Systematic review of the incidence of sudden cardiac death in the United States. J Am Coll Cardiol 2011; 57(7): 794-801.
3. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004; 44(6): 1268-75.
4. Martens E, Sinner MF, Siebermair J, Raufhake C, Beckmann BM, Veith S, et al. Incidence of sudden cardiac death in Germany: Results from an emergency medical service registry in Lower Saxony. Europace 2014; 16(12): 1752-8.
5. Byrne R, Constant O, Smyth Y, Callagy G, Nash P, Daly K, et al. Multiple source surveillance incidence and aetiology of out-of-hospital sudden cardiac death in a rural population in the West of Ireland. Eur Heart J 2008; 29(11): 1418-23.
6. Hua W, Zhang LF, Wu YF, Liu XQ, Guo DS, Zhou HL, et al. Incidence of sudden cardiac death in China: Analysis of 4 regional populations. J Am Coll Cardiol 2009; 54(12): 1110-8.
7. Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: The Framingham Heart Study. Circulation 2004; 110(5): 522-7.
8. Niemeijer MN, van den Berg ME, Leening MJ, Hofman A, Franco OH, Deckers JW, et al. Declining incidence of sudden cardiac death from 1990-2010 in a general middle-aged and elderly population: The Rotterdam Study. Heart Rhythm 2015; 12(1): 123-9.
9. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A report from the American Heart Association. Circulation 2018; 137(12): e67-e492.
10. Modi S, Krahn AD. Sudden cardiac arrest without overt heart disease. Circulation 2011; 123(25): 2994-3008.
11. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018; 72(14): e91-e220.
12. Krahn AD, Healey JS, Chauhan V, Birnie DH, Simpson CS, Champagne J, et al. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER). Circulation 2009; 120(4): 278-85.
13. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005; 352(6): 539-48.
14. Hunt D, Gore I. Myocardial lesions following experimental intracranial hemorrhage: prevention with propranolol. Am Heart J 1972; 83(2): 232-6.
15. Jacob WA, Van Bogaert A, De Groodt-Lasseel MH. Myocardial ultrastructure and haemodynamic reactions during experimental subarachnoid haemorrhage. J Mol Cell Cardiol 1972; 4(4): 287-98.
16. McNair JL, Clower BR, Sanford RA. The effect of reserpine pretreatment on myocardial damage associated with simulated intracranial hemorrhage in mice. Eur J Pharmacol 1970; 9(1): 1-6.
17. Samuels MA. The brain-heart connection. Circulation 2007; 116(1): 77-84.
18. Raab W, Stark E, Macmillan WH, Gigee WR. Sympathogenic origin and antiadrenergic prevention of stress-induced myocardial lesions. Am J Cardiol 1961; 8: 203-11.
19. Selye H. The chemical prevention of cardiac necroses. New York, NY: Ronald Press Co; 1958.
20. Bernard C. Study on heart physiology. Revue des Deux Mondes 1865; 56(1): 236-52. [In French].
21. Cannon WB. "Voodoo" death. Am Anthropol 1942; 44(new series): 169-81.
22. Loewi O. About humoral transferability. The cardiac nerve effect. I. Message. Pflügers Arch Ges Physiol 1921; 189: 239-42. [In German].
23. Euler V. A sympathomometic pressor substance in animal organ extracts. Nature 1945; 156(3949): 18-9.
24. Ruiz VE, Soros P, Shoemaker JK, Hachinski V. Human cerebral circuitry related to cardiac control: A neuroimaging meta-analysis. Ann Neurol 2016; 79(5): 709-16.
25. Saper CB. Convergence of autonomic and limbic connections in the insular cortex of the rat. J Comp Neurol 1982; 210(2): 163-73.
26. Simmons WK, Avery JA, Barcalow JC, Bodurka J, Drevets WC, Bellgowan P. Keeping the body in mind: Insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. Hum Brain Mapp 2013; 34(11): 2944-58.
27. Soros P, Marmurek J, Tam F, Baker N, Staines WR, Graham SJ. Functional MRI of working memory and selective attention in vibrotactile frequency discrimination. BMC Neurosci 2007; 8: 48.
28. Oppenheimer S, Cechetto D. The insular cortex and the regulation of cardiac function. Compr Physiol 2016; 6(2): 1081-133.
29. de Morree HM, Rutten GJ, Szabo BM, Sitskoorn MM, Kop WJ. Effects of insula resection on autonomic nervous system activity. J Neurosurg Anesthesiol 2016; 28(2): 153-8.
30. Krause T, Werner K, Fiebach JB, Villringer K, Piper SK, Haeusler KG, et al. Stroke in right dorsal anterior insular cortex Is related to myocardial injury. Ann Neurol 2017; 81(4): 502-11.
31. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology 1992; 42(9): 1727-32.
32. Macey PM, Wu P, Kumar R, Ogren JA, Richardson HL, Woo MA, et al. Differential responses of the insular cortex gyri to autonomic challenges. Auton Neurosci 2012; 168(1-2): 72-81.
33. Wright P, He G, Shapira NA, Goodman WK, Liu Y. Disgust and the insula: fMRI responses to pictures of mutilation and contamination. Neuroreport 2004; 15(15): 2347-51.
34. Shoemaker JK, Norton KN, Baker J, Luchyshyn T. Forebrain organization for autonomic cardiovascular control. Auton Neurosci 2015; 188: 5-9.
35. Wong SW, Masse N, Kimmerly DS, Menon RS, Shoemaker JK. Ventral medial prefrontal cortex and cardiovagal control in conscious humans. Neuroimage 2007; 35(2): 698-708.
36. Yang TT, Simmons AN, Matthews SC, Tapert SF, Bischoff-Grethe A, Frank GK, et al. Increased amygdala activation is related to heart rate during emotion processing in adolescent subjects. Neurosci Lett 2007; 428(2-3): 109-14.
37. Paus T. Primate anterior cingulate cortex: Where motor control, drive and cognition interface. Nat Rev Neurosci 2001; 2(6): 417-24.
38. Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, et al. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 2003; 126(Pt 10): 2139-52.
39. Matthews SC, Paulus MP, Simmons AN,

Nelesen RA, Dimsdale JE. Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. Neuroimage 2004; 22(3): 1151-6.
40. Mochmann HC, Scheitz JF, Petzold GC, Haeusler KG, Audebert HJ, Laufs U, et al. Coronary angiographic findings in acute ischemic stroke patients with elevated cardiac troponin: The Troponin Elevation in Acute Ischemic Stroke (TRELAS) Study. Circulation 2016; 133(13): 1264-71.
41. Kerr G, Ray G, Wu O, Stott DJ, Langhorne P. Elevated troponin after stroke: A systematic review. Cerebrovasc Dis 2009; 28(3): 220-6.
42. Norris JW, Hachinski VC, Myers MG, Callow J, Wong T, Moore RW. Serum cardiac enzymes in stroke. Stroke 1979; 10(5): 548-53.
43. Fure B, Bruun WT, Thommessen B. Electrocardiographic and troponin T changes in acute ischaemic stroke. J Intern Med 2006; 259(6): 592-7.
44. Tatschl C, Stollberger C, Matz K, Yilmaz N, Eckhardt R, Nowotny M, et al. Insular involvement is associated with QT prolongation: ECG abnormalities in patients with acute stroke. Cerebrovasc Dis 2006; 21(1-2): 47-53.
45. Christensen H, Boysen G, Christensen AF, Johannesen HH. Insular lesions, ECG abnormalities, and outcome in acute stroke. J Neurol Neurosurg Psychiatry 2005; 76(2): 269-71.
46. Kallmunzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, et al. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors--a systematic, prospective analysis. Stroke 2012; 43(11): 2892-7.
47. Fernandez-Menendez S, Garcia-Santiago R, Vega-Primo A, Gonzalez NN, Lara-Lezama LB, Redondo-Robles L, et al. Cardiac arrhythmias in stroke unit patients. Evaluation of the cardiac monitoring data. Neurologia 2016; 31(5): 289-95.
48. Seifert F, Kallmunzer B, Gutjahr I, Breuer L, Winder K, Kaschka I, et al. Neuroanatomical correlates of severe cardiac arrhythmias in acute ischemic stroke. J Neurol 2015; 262(5): 1182-90.
49. Soros P, Hachinski V. Cardiovascular and neurological causes of sudden death after ischaemic stroke. Lancet Neurol 2012; 11(2): 179-88.
50. Koppikar S, Baranchuk A, Guzman JC, Morillo CA. Stroke and ventricular arrhythmias. Int J Cardiol 2013; 168(2): 653-9.
51. Taggart P, Critchley H, van Duijvendoden S, Lambiase PD. Significance of neuro-cardiac control mechanisms governed by higher regions of the brain. Auton Neurosci 2016; 199: 54-65.
52. Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44(3): 870-947.
53. Soros P, Hachinski V. Wounded brain, ailing heart: Central autonomic network disruption in acute stroke. Ann Neurol 2017; 81(4): 495-7.
54. Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. Neurology 2016; 87(11): 1118-23.
55. Mahmoud AN, Elgendy AY, Mansoor H, Elgendy IY. Cardiovascular abnormalities and in-hospital all-cause mortality in patients with spontaneous sub-arachnoid hemorrhage: An observational study. Cardiol Ther 2017; 6(1): 33-40.
56. Zhang L, Qi S. Electrocardiographic abnormalities predict adverse clinical outcomes in patients with subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2016; 25(11): 2653-9.
57. Salvati M, Cosentino F, Artico M, Ferrari M, Franchi D, Domenicucci M, et al. Electrocardiographic changes in subarachnoid hemorrhage secondary to cerebral aneurysm. Report of 70 cases. Ital J Neurol Sci 1992; 13(5): 409-13.
58. Zhang L, Wang Z, Qi S. Cardiac troponin elevation and outcome after subarachnoid hemorrhage: A systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2015; 24(10): 2375-84.
59. Huang J, van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. Neurosurgery 2002; 51(5): 1101-5.
60. Lamberts RJ, Blom MT, Wassenaar M, Bardai A, Leijten FS, de Haan GJ, et al. Sudden cardiac arrest in people with epilepsy in the community: Circumstances and risk factors. Neurology 2015; 85(3): 212-8.
61. Stecker EC, Reinier K, Uy-Evanado A, Teodorescu C, Chugh H, Gunson K, et al. Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: A community-based study. Circ Arrhythm Electrophysiol 2013; 6(5): 912-6.
62. Nashef L. Sudden unexpected death in epilepsy: Terminology and definitions. Epilepsia 1997; 38(11 Suppl): S6-S8.
63. Winkel BG, Risgaard B, Sadjadieh G, Bundgaard H, Haunso S, Tfelt-Hansen J. Sudden cardiac death in children (1-18 years): Symptoms and causes of death in a nationwide setting. Eur Heart J 2014; 35(13): 868-75.
64. Bardai A, Blom MT, van Noord C, Verhamme KM, Sturkenboom MC, Tan HL. Sudden cardiac death is associated both with epilepsy and with use of antiepileptic medications. Heart 2015; 101(1): 17-22.
65. Scorza FA, Arida RM, Cysneiros RM, Terra VC, Sonoda EY, de AM, et al. The brain-heart connection: Implications for understanding sudden unexpected death in epilepsy. Cardiol J 2009; 16(5): 394-9.
66. Centers for Disease Control and Prevention (CDC). Comorbidity in adults with epilepsy--United States, 2010. MMWR Morb Mortal Wkly Rep 2013; 62(43): 849-53.
67. Janszky I, Hallqvist J, Tomson T, Ahlbom A, Mukamal KJ, Ahnve S. Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy--the Stockholm Heart Epidemiology Program. Brain 2009; 132(Pt 10): 2798-804.
68. Li J, Ming Q, Lin W. The insula lobe and sudden unexpected death in epilepsy: A hypothesis. Epileptic Disord 2017; 19(1): 10-4.
69. Nayak CS, Sinha S, Nagappa M, Thennarasu K, Taly AB. Lack of heart rate variability during sleep-related apnea in patients with temporal lobe epilepsy (TLE)-an indirect marker of SUDEP? Sleep Breath 2017; 21(1): 163-72.
70. Floras JS. Sleep apnea and cardiovascular disease: An enigmatic risk factor. Circ Res 2018; 122(12): 1741-64.
71. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012; 8(5): 597-619.
72. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005; 352(12): 1206-14.
73. Gami AS, Olson EJ, Shen WK, Wright RS, Ballman KV, Hodge DO, et al. Obstructive sleep apnea and the risk of sudden cardiac death: A longitudinal study of 10,701 adults. J Am Coll Cardiol 2013; 62(7): 610-6.
74. Zeidan-Shwiri T, Aronson D, Atalla K, Blich M, Suleiman M, Marai I, et al. Circadian pattern of life-threatening ventricular arrhythmia in patients with sleep-disordered breathing and implantable cardioverter-defibrillators. Heart Rhythm 2011; 8(5): 657-62.
75. Taylor KS, Millar PJ, Murai H, Haruki N, Kimmerly DS, Bradley TD, et al. Cortical autonomic network gray matter and sympathetic nerve activity in obstructive sleep apnea. Sleep 2018; 41(2).
76. Kim AS, Moffatt E, Ursell PC, Devinsky O, Olgin J, Tseng ZH. Sudden neurologic death masquerading as out-of-hospital sudden cardiac death. Neurology 2016; 87(16): 1669-73.
77. Finsterer J, Stollberger C, Maeztu C. Sudden cardiac death in neuromuscular disorders. Int J Cardiol 2016; 203: 508-15.
78. Esler M. Mental stress and human cardiovascular disease. Neurosci Biobehav Rev 2017; 74(Pt B): 269-76.
79. Harvey W. An anatomical study of the movement of heart and blood in animals. Frankfurt am-Main, Germany: Rare Book Room; 1628. [In Latin].
80. Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men.

Circulation 1994; 89(5): 1992-7.
81. Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol 2008; 51(13): 1237-46.
82. Trichopoulos D, Katsouyanni K, Zavitsanos X, Tzonou A, Dalla-Vorgia P. Psychological stress and fatal heart attack: The Athens (1981) earthquake natural experiment. Lancet 1983; 1(8322): 441-4.
83. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996; 334(7): 413-9.
84. Huang JL, Chiou CW, Ting CT, Chen YT, Chen SA. Sudden changes in heart rate variability during the 1999 Taiwan earthquake. Am J Cardiol 2001; 87(2): 245-8, A9.
85. Wilbert-Lampen U, Leistner D, Greven S, Pohl T, Sper S, Volker C, et al. Cardiovascular events during World Cup soccer. N Engl J Med 2008; 358(5): 475-83.
86. Kloner RA, McDonald S, Leeka J, Poole WK. Comparison of total and cardiovascular death rates in the same city during a losing versus winning super bowl championship. Am J Cardiol 2009; 103(12): 1647-50.
87. Gebhard CE, Gebhard C, Maafi F, Bertrand MJ, Stahli BE, Wildi K, et al. Hockey games and the incidence of ST-elevation myocardial infarction. Can J Cardiol 2018; 34(6): 744-51.
88. Onozuka D, Hagihara A. Out-of-hospital cardiac arrests during the Japanese professional baseball championship series. Am J Cardiol 2018; 121(12): 1471-6.
89. Niederseer D, Thaler CW, Egger A, Niederseer MC, Ploderl M, Niebauer J. Watching soccer is not associated with an increase in cardiac events. Int J Cardiol 2013; 170(2): 189-94.
90. Khairy LT, Barin R, Demoniere F, Villemaire C, Billo MJ, Tardif JC, et al. Heart rate response in spectators of the Montreal Canadiens hockey team. Can J Cardiol 2017; 33(12): 1633-8.
91. Piira OP, Mustonen PE, Miettinen JA, Huikuri HV, Tulppo MP. Leisure time emotional excitement increases endothelin-1 and interleukin-6 in cardiac patients. Scand Cardiovasc J 2012; 46(1): 7-15.
92. Meisel SR, Kutz I, Dayan KI, Pauzner H, Chetboun I, Arbel Y, et al. Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. Lancet 1991; 338(8768): 660-1.
93. Goldberg RJ, Spencer F, Lessard D, Yarzebski J, Lareau C, Gore JM. Occurrence of acute myocardial infarction in Worcester, Massachusetts, before, during, and after the terrorists attacks in New York City and Washington, DC, on 11 September 2001. Am J Cardiol 2005; 95(2): 258-60.
94. Steinberg JS, Arshad A, Kowalski M, Kukar A, Suma V, Vloka M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. J Am Coll Cardiol 2004; 44(6): 1261-4.
95. Shedd OL, Sears SF, Harvill JL, Arshad A, Conti JB, Steinberg JS, et al. The World Trade Center attack: Increased frequency of defibrillator shocks for ventricular arrhythmias in patients living remotely from New York City. J Am Coll Cardiol 2004; 44(6): 1265-7.
96. Saposnik G, Baibergenova A, Dang J, Hachinski V. Does a birthday predispose to vascular events? Neurology 2006; 67(2): 300-4.
97. Ghadri JR, Sarcon A, Diekmann J, Bataiosu DR, Cammann VL, Jurisic S, et al. Happy heart syndrome: Role of positive emotional stress in takotsubo syndrome. Eur Heart J 2016; 37(37): 2823-9.
98. Blanc C, Zeller M, Cottin Y, Daubail B, Vialatte AL, Giroud M, et al. Takotsubo cardiomyopathy following acute cerebral events. Eur Neurol 2015; 74(3-4): 163-8.
99. Jung JM, Kim JG, Kim JB, Cho KH, Yu S, Oh K, et al. Takotsubo-like myocardial dysfunction in ischemic stroke: a hospital-based registry and systematic literature review. Stroke 2016; 47(11): 2729-36.
100. Nandal S, Castles A, Asrar Ul HM, van Gaal W. Takotsubo cardiomyopathy triggered by status epilepticus: case report and literature review. BMJ Case Rep 2019; 12(1): e225924.
101. Desai R, Singh S, Patel U, Fong HK, Kaur VP, Varma Y, et al. Frequency of takotsubo cardiomyopathy in epilepsy-related hospitalizations among adults and its impact on in-hospital outcomes: A national standpoint. Int J Cardiol 2020; 299: 67-70.
102. Stollberger C, Wegner C, Finsterer J. Seizure-associated Takotsubo cardiomyopathy. Epilepsia 2011; 52(11): e160-e167.
103. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J 2015; 36(30): 1974-82b.
104. Song X, Roy B, Fonarow GC, Woo MA, Kumar R. Brain structural changes associated with aberrant functional responses to the Valsalva maneuver in heart failure. J Neurosci Res 2018; 96(9): 1610-22.
105. Armstrong AC, Muller M, Ambale-Venkatesh B, Halstead M, Kishi S, Bryan N, et al. Association of early left ventricular dysfunction with advanced magnetic resonance white matter and gray matter brain measures: The CARDIA study. Echocardiography 2017; 34(11): 1617-22.
106. Roohafza H, Talaei M, Sadeghi M, Haghani P, Shokouh P, Sarrafzadegan N. Opium decreases the age at myocardial infarction and sudden cardiac death: A long- and short-term outcome evaluation. Arch Iran Med 2013; 16(3): 154-60.
107. Wong CX, Brown A, Lau DH, Chugh SS, Albert CM, Kalman JM, et al. Epidemiology of sudden cardiac death: Global and regional perspectives. Heart Lung Circ 2019; 28(1): 6-14.
108. Jones LA, Thomas RH. Sudden death in epilepsy: Insights from the last 25 years. Seizure 2017; 44: 232-6.
109. Kroner BL, Wright C, Friedman D, Macher K, Preiss L, Misajon J, et al. Characteristics of epilepsy patients and caregivers who either have or have not heard of SUDEP. Epilepsia 2014; 55(10): 1486-94.
110. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 2016; 15(10): 1075-88.
111. Maguire MJ, Jackson CF, Marson AG, Nevitt SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database Syst Rev 2020; 4: CD011792.
112. Klein L, Hsia H. Sudden cardiac death in heart failure. Cardiol Clin 2014; 32(1): 135-44, ix.
113. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10): 709-17.
114. van BM, Patel HC, Bauersachs J, Bohm M, Borggrefe M, Brutsaert D, et al. The autonomic nervous system as a therapeutic target in heart failure: A scientific position statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2017; 19(11): 1361-78.
115. Alfieri O, Mayosi BM, Park SJ, Sarrafzadegan N, Virmani R. Exploring unknowns in cardiology. Nat Rev Cardiol 2014; 11(11): 664-70.