

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 acetylcholine²² 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 integration²⁵⁻²⁷ 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}

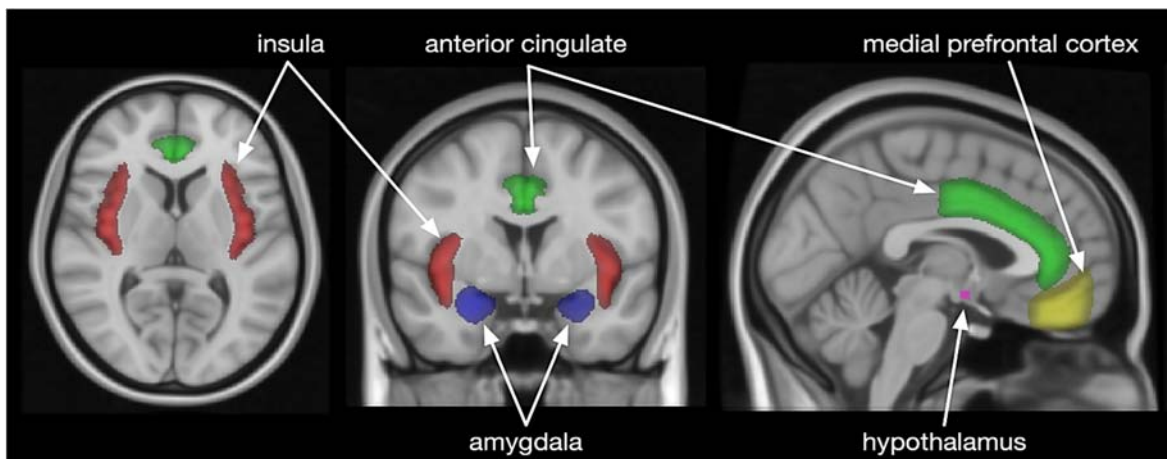


Figure 1. Core areas of the central autonomic network; it includes the insula (red), the anterior cingulate cortex (ACC) (green), the medial prefrontal cortex (PFC) (yellow), the amygdala (blue), and the hypothalamus (purple). The image shows the Montreal Neurological Institute (MNI) 152 T1 1mm template (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 prolongation⁴⁴ and ST elevation⁴⁵ 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 MRI⁵³ 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 profile⁶⁶ and a higher risk of cardiovascular events and arrhythmias compared with the normal population⁶⁷ 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) $\geq 3\%$ 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 O₂ 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, younger⁸⁷ and in others, older people⁸⁸ 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 rate⁹⁰ and increased serum levels of noradrenaline⁹¹ 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 (β AR) stimulation with apoptosis and β AR 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.

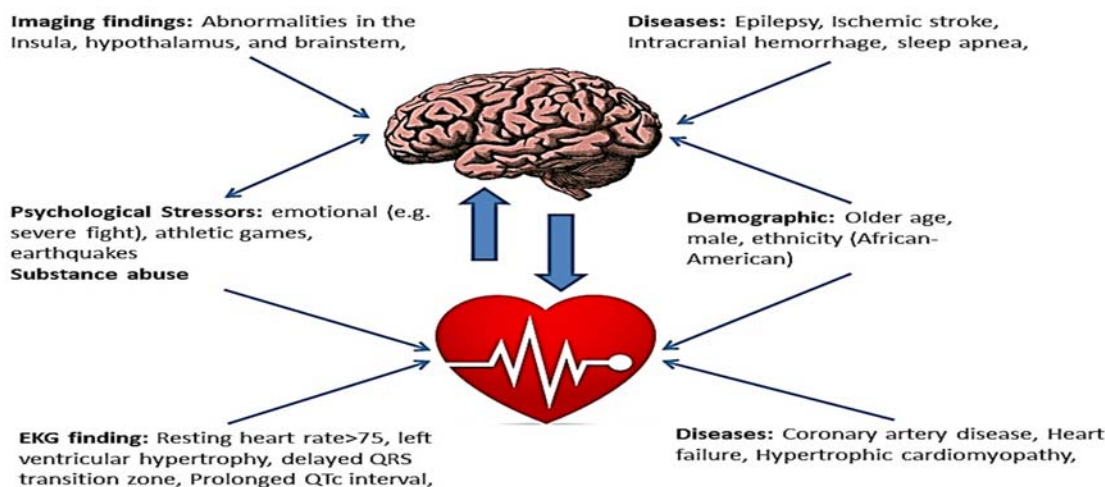


Figure 2. Selected sudden death (SD) risk factors in light of heart-brain connection; more common risk factors are summarized and classified here. Other SD risk factors can be found in the text and elsewhere.⁶⁹

Drug addiction¹⁰⁶ and demographic variables¹⁰⁷ 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, O₂ 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 interaction¹¹⁵ 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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