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Review

Sudden cardiac death in children and young adults without structural heart disease: a comprehensive review

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Sudden cardiac death (SCD) is a rare clinical encounter in pediatrics, but its social impact is immense because of its unpredicted and catastrophic nature in previously healthy individuals. Unlike in adults where the primary cause of SCD is related to ischemic heart disease, the etiology is diverse in young SCD victims. Although certain structural heart diseases may be identified during autopsy in some SCD victims, autopsy-negative SCD is more common in pediatrics, which warrants the diagnosis of sudden arrhythmic death syndrome (SADS) based upon the assumption that the usual heart rhythm is abruptly replaced by lethal ventricular arrhythmia. Despite current advances in molecular genetics, the causes of more than half of SADS cases remain unanswered even after postmortem genetic testing. Moreover, the majority of these deaths occur at rest or during sleep even in the young. Recently, sudden unexpected death in epilepsy (SUDEP) has emerged as another etiology of SCD in children and adults, suggesting critical involvement of the central nervous system (CNS) in SCD. Primary cardiac disorders may not be solely responsible for SCD; abnormal CNS function may also contribute to the unexpected lethal event. In this review article, we provide an overview of the complex pathogenesis of SADS and its diverse clinical presentation in the young and postulate that SADS is, in part, induced by unfortunate miscommunication between the heart and CNS via the autonomic nervous system.

Keywords

Sudden cardiac death (SCD); sudden arrhythmic death syndrome (SADS); ventricular fibrillation (VF); molecular autopsy; central nervous system (CNS); autonomic nervous system (ANS)

1. Unexpected occurrence of sudden cardiac death in previously healthy children and young adults

Sudden cardiac death (SCD) in previously healthy people is a rare event in pediatrics that has an immense impact on not only the victims' families but also society as a whole because of its unexpected and catastrophic nature (Wren, 2002). Unlike in adults where the primary cause of SCD is mostly related to ischemic heart disease, the etiology is diverse in young SCD victims and includes cardiomyopathies, congenital arrhythmia syndromes, myocarditis, myocardial ischemia due to coronary anomalies, advanced heart failure, and following cardiac surgery (de Noronha et al., 2009; Harmon et al., 2014a; Maron, 2003; Meyer et al., 2012; Morentin et al., 2000; Papadakis et al., 2013; Wren, 2002). The primary cause of sudden cardiac arrest (SCA) is thought to be polymorphic ventricular tachycardia or ventricular fibrillation (VF) (Berger et al., 2004; Jones and Lode, 2007; Mogayzel et al., 1995), but the underlying mechanism that initiates these catastrophic cardiac rhythm disturbances is not always clear. Sudden arrhythmic death syndrome (SADS) is defined as unexplained sudden death with no identifiable pathologic change in the heart by autopsy (Basso et al., 2010; Corrado et al., 2001; Mellor et al., 2014; Papadakis et al., 2013). A molecular genetic investigation is required to delineate the pathogenesis by molecular autopsy of the victims (Lahrouchi et al., 2017; Nunn et al., 2016). In the event where genetic testing is not feasible in the deceased, clinical screening of first-degree relatives is recommended with subsequent focused molecular analysis for any family member with features suspicious of an inherited arrhythmia or cardiomyopathy (Behr et al., 2008; Hofman et al., 2007; Wong et al., 2014).

Sudden disruption of cardiac output may result from complex biological abnormalities within the myocardium, but is also triggered by external phenomena. Rubart and Zipes postulated four possible underlying mechanisms of SCD in the myocardium, including i) aberrant intracellular calcium handling, ii) myocardial ischemia, iii) neurohormonal changes, and iv) genetic predisposition (Rubart and Zipes, 2005). Although SCD during active exercise has been highlighted in adolescents and young adults (Drezner et al., 2008; Finocchiaro et al., 2016; Harmon et al., 2014b; Marijon et al., 2011; Maron, 2003; Maron et al., 2009), it frequently occurs at rest or even during sleep (Bagnall et al., 2016; Mellor et al., 2014; Meyer et al., 2012; Tsuda et al., 2019; Winkel et al., 2011). The incidence of SCD at rest or during sleep increases with age (Bardai et al., 2011; Eckart et al., 2011). This raises the possibility of involvement of certain complex network interactions between the heart and other organs, especially the central nervous system (CNS) (Palma and Benarroch, 2014; Tahsili-Fahadan and Geocadin, 2017). The heart-CNS axis has recently gained considerable attention for the pathogenesis of SCD because of its association with certain CNS disorders, including ischemic stroke, subarachnoid hemorrhage, and epilepsy (Tahsili-Fahadan and Geo-

cadin, 2017). Lethal ventricular arrhythmias are induced primarily by baseline myocardial abnormalities, but also may be triggered by the sudden disruption of regulatory interactions between the heart and CNS.

In this review article, we provide an overview of the pathogenesis of SCD in the young without identifiable structural abnormalities in terms of 1) electrophysiology of arrhythmogenesis, 2) molecular genetics of lethal ventricular arrhythmias, and 3) disruption of the heart-CNS axis as a possible contributor to SCD.

2. Sudden cardiac death without identifiable structural heart disease

A substantial number of young SCD victims are previously healthy individuals who have no known history of underlying cardiac disease and who unexpectedly present with SCD as their first manifestation (Behr et al., 2007; Corrado et al., 2001). Sudden arrhythmic death syndrome is defined as SCD with negative toxicology results and a morphologically normal heart confirmed by autopsy (Hosseini et al., 2018; Jayaraman et al., 2018; Mellor et al., 2014). Sudden unexplained death (SUD) encompasses both autopsy of unknown significance (e.g., myocardial hypertrophy, fibrosis, mild dilatation, or mild coronary atherosclerosis) and negative autopsy (SADS), but SADS and SUD are frequently used interchangeably. Genetic testing of SADS victims may identify genetic mutations potentially responsible for SCD in fewer than 50% of cases, mostly congenital ion channelopathies, including, long QT syndrome (LQTS), Brugada syndrome, and catecholamine-induced polymorphic ventricular tachycardia (CPVT) (Basso et al., 2010; Campuzano et al., 2017; Hosseini et al., 2018; Lahrouchi et al., 2017; Nunn et al., 2016; Tester et al., 2012), and some borderline cardiomyopathies.

The epidemiology of SADS differs depending upon various factors, including the reported geographic location, patient population (ages, sex, and athletes vs. non-athletes), methods of data collection, and the extent of diagnostic investigation at autopsy (Bagnall et al., 2016; Mellor et al., 2014; Morentin et al., 2003; Winkel et al., 2011; Wisten et al., 2017). The incidence and associated events of SADS in the general population (Berdowski et al., 2013; Winkel et al., 2011) may be different from those in athletes (Cross et al., 2011; Harmon et al., 2011; Maron, 2003; Maron et al., 2009) or in military recruits (Eckart et al., 2004). Table 1 represents recent published data of SADS by multiple groups from multiple geographic locations. Allan et al. pointed out that rigorous case ascertainment strategies would provide more stringent diagnosis of SCD in uncertain cases (Allan et al., 2017). The reported incidence of SADS varies depending upon the target population and methods used (Cross et al., 2011), but predominantly occurs in previously healthy people. Glinge et al. reported that 35% of 136 young SADS victims in Denmark had preceding symptoms, including syncope/presyncope (17%), chest pain (15%), and dyspnea (13%). Seizure occurred in 22%, but no previous medical history was recorded in 45% (Glinge et al., 2015). Nonspecific symptoms, such as dizziness and palpitation, and transient loss of consciousness, including syncope and seizure-like activity, are common preceding events in potentially lethal congenital ion channelopathies (MacCormick et al., 2011). The pathophysiology of these antecedent symptoms is poorly understood but may represent aborted SCD.

Only a minority of SADS victims are reported to have positive family history (Behr et al., 2007; Lahrouchi et al., 2017). Exercise is known to trigger SCD in younger and male populations, but the majority of SCD occurs at rest or during sleep (Jayaraman et al., 2018; Wisten et al., 2017). Feasibility and reliability of preparticipation screening tests for competitive sports have been debated for a number of years (Corrado et al., 2006), but their universal value has been argued by multiple investigators (Corrado et al., 2011; Malhotra et al., 2018; Maron, 2003; Patel and Lantos, 2011; Webster et al., 2020). In a prospective study of a comprehensive cardiac screening program in 11,168 elite athletes in England over 20 years, SCD occurred in 8 individuals, 75% of whom had normal cardiac screening results including normal ECG and echocardiogram results (Malhotra et al., 2018). Thus, the value of exercise restriction in preventing SCD has been questioned unless patients are diagnosed with certain ion channelopathies or arrhythmogenic cardiomyopathies (Berdowski et al., 2013; Malhotra et al., 2018). Importantly, the reasons why more people die at rest or during sleep than induced by vigorous exercise are poorly understood.

3. Electrophysiology of SCA

3.1 Ventricular fibrillation as a primary cause of SCA

Although there are many conditions that can lead to SCA, the most frequent immediate cause of SCD in the US is VF, which seems to be a common terminal event. Historical studies of SCD in pediatric populations found that asystole and bradycardia were encountered far more commonly (82%) than VF (7%-19%) in children (Atkins et al., 2009; Mogayzel et al., 1995; Walsh and Krongrad, 1983). However, in a more recent study where non-cardiac causes were excluded, VF was reported as the presenting rhythm in 44% of pediatric SCA (Meyer et al., 2012). An initial rhythm of VF compared with asystole or bradycardia has been associated with a better outcome in adults (Adabag et al., 2010; Mayer, 1979; Valenzuela et al., 2000). A possible explanation for this includes the fact that VF is a more treatable rhythm in the field than asystole with a more likely return to a perfusing rhythm after intervention. It is also possible that VF is a pre-terminal event whereas asystole is a final terminal event (Cummins et al., 1985). This is supported by the observation that as response times have improved during the period of 1980 to 2009, the prevalence of VF as a presenting rhythm has increased from 26% to 60% (Meyer et al., 2012).

3.2 Electrophysiology of VF

Ventricular fibrillation manifests as completely chaotic electrical activity with the absence of any regularity or identifiable organized complexes. Historically, VF has been considered to be completely disorganized micro-reentrant rhythm resulting in complete or nearly complete absence of organized contractility and therefore absence of cardiac output. However, more recent data have suggested that there is perhaps more organization to VF than previously suspected. In particular, it appears that there are focal organized areas, or "rotors", that may initiate and maintain VF (Pandit and Jalife, 2013). The concept of reentry is important in understanding the mechanism of VF. Reentry refers to a circus movement of advancing wave front of depolarization through a circuit within the heart muscle which usually involves a critical barrier around which the wave front advances (Mines, 1913; Wit

Table 1. Recent Studies Regarding Sudden Arrhythmic Death Syndrome

	Authors	Years	Location	SADS Number (M/F)	SADS Ages (median)	Activities Exercise	Activities Rest	Activities Sleep	Preceding symptoms	Primary target
1	Morentin et al., 2003	1991-1998	Spain, Biscay	19 (11/8)	1-35 (19)	11%		32%	Syncope 16%	SUD, general population
2	Eckart et al., 2004	1971-2001	USA	44 (37/7)	17-35				Syncope 2% Chest pain 2% Sickle cell trait 27%	SCD, military recruits
3	Behr et al., 2007	1997-1999	UK	56 (35/21)	7-64 (24)				(FH 18%)	SADS, general population
4	Tester et al., 2012	1998-2010	USA, Mayo Clinic	173 (106/67)	1-69 (18.4*)	27%		41%	Seizure 7% Syncope 14%	SUD, general population
5	Mellor et al., 2014	1994-2010	UK	967 (590/377)	1-82 (29)	13%	55%	27%	Seizure 6 %	SADS, general population
6	Glinge et al., 2015	2000-2006	Denmark	136 (84/52)	1-35	10%	40%	46%	Seizure 18% Syncope 17% Dyspnea 13%	Autopsied SCD, general population
7	Bagnall et al., 2016	2010-2012	Australia New Zealand	198 (133/65)	1-35	13%		48%		SCD, general population
8	Campuzano et al., 2017	2012-2015	Spain, Barcelona	52 (48/4)	14-50 (37*)	100% Running 46% Gym 31%				Autopsied SADS during exercise, general population Molecular autopsy
9	Wisten et al., 2017	2000-2010	Sweden	170 (110/60)	1-35	8%	35%	37%		SCD, general population
10	Lahrouchi et al., 2017	1995-2011	New Zealand UK Demark Netherlands	302 (197/105)	17-33 (24)	11%	28%	43%	Syncope 5% Seizure 3% Palpitation 3% Chest pain 3% (FH 7%)	SADS, general population Molecular autopsy

SADS: sudden arrhythmic death syndrome; SUD: sudden unexplained death; SCD: sudden cardiac death; FH: family history.*average instead of median

and Cranefield, 1978). This barrier could be a fixed anatomic barrier such as a scar, area of ischemia, or an anatomic structure such as a valve, or it can be virtual and even be mobile (Boukens et al., 2015). In several types of arrhythmias, the circuit is large and macroscopic involving much of the heart. However, in very rapid ventricular tachycardias and VF, this circuit can be very small and appear to be focal (Pandit and Jalife, 2013).

Much attention has been focused on the concept of rotors during VF (Fig. 1) (Pandit and Jalife, 2013). Rotors are tiny spirals of depolarization that cycle extremely rapidly. These rotors do not necessarily rotate around a fixed barrier, but more often they rotate around a virtual barrier which can even move from place to place within the heart muscle. They have been demonstrated to be relatively stable. However, because of heterogeniety in the myocardium, the extremely rapid rates of activation arising from these rotors cannot be maintained in all parts of the heart. Various segments of the ventricles will display their own dominant frequency (Samie et al., 2001). A single migrating rotor will give rise to an ECG identical to torsade de pointes, a particular type of polymorphic ventricular tachycardia frequently seen in the LQTS. Multiple rotors at different frequencies will generate a surface ECG identical to VF (Asano et al., 1997; Jalife and Gray, 1996). A more accurate description of VF, however, would be that the rapidly advancing wave fronts arising from a dominant rotor will inevitably encounter pockets of tissue incapable of sustaining such rapid activation because of heterogeneity in heart muscle refractoriness (Chen et al., 2000). This will result in wavelets breaking off in different directions, a process referred to as wave break. It is likely a combination of these dominant frequency rotors and wave break resulting in multiple wavelets that results in the non-perfusing rhythm referred to as VF (Jalife et al., 2009).

3.3 Substrates and triggers that cause VF

Since VF is a common endpoint for many conditions, it is also very helpful to understand predisposing or contributory conditions that can perhaps be addressed before the onset of this fatal arrhythmia, including ischemia, channelopathies, and cardiomyopathies,

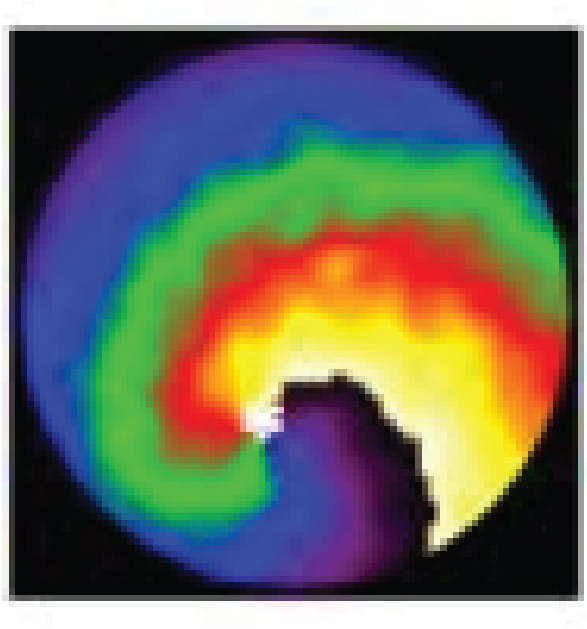

Figure 1. Rotor in Ventricular Fibrillation. This figure demonstrates a rotor during ventricular fibrillation. The various colors represent different phases of cardiac excitability and depict a spiral of advancing cardiac wavefront revolving around a central point. Note, this central point can be fixed anatomical site or a virtual site that can migrate throughout the myocardium giving rise to different ECG rhythms as noted in the text (Pandit and Jalife, 2013).

as an underlying myocardial pathology. Common external factors include medications or illicit drugs, direct physical impact on the heart, and interactions with the CNS.

Myocardial ischemia, usually secondary to myocardial infarction, is the most frequent predisposing factor related to VF among adults, but ischemia itself without infarction can alter electrical conductance of the myocardium to induce lethal arrhythmias (Di Diego and Antzelevitch, 2011; Tsuda, 2017). The pathobiology of ischemia-induced arrhythmogenesis is a complex process involving mitochondrial dysfunction (Akar and Akar, 2007), electrical instability augmented by alteration in gap junction (Kaprielian et al., 1998), and proarrhythmic sympathetic surge (Shen and Zipes, 2014). Either acquired or congenital coronary diseases may be responsible for myocardial ischemia in children (Tsuda, 2017). Maron et al. reported that coronary artery anomalies are the second most common cause of VF and SCA in young athletes (Maron et al., 2009).

Congenital ion channelopathies including LQTS, Brugada syndrome, and CPVT are common substrate to develop lethal ventricular arrhythmias or VF. Detailed ion transport mechanisms and electrophysiology of these channelopathies are discussed elsewhere (Hosseini et al., 2018; Lieve and Wilde, 2015). Molecular genetics of these diseases are discussed in the following section (4.1).

Cardiomyopathies are frequently identified as conditions associated with VF and SCD. Cardiomyopathies are associated with myopathic changes within the heart such as areas of ischemia or microinfarcts resulting in fibrosis and irritability. Areas of fibrosis can serve as boundaries for reentry and irritable tissue often exhibits abnormal automaticity which can serve as triggers (Brandenburg, 1985; Maron et al., 2013). Cardiomyopathies are the most frequently encountered identifiable cause of VF and SCD (Maron et al., 2009).

External influences can create situations predisposing the heart to VF and SCD. There are numerous medications that are known to affect ionic currents across the myocyte sarcolemma by inhibiting a current referred to as the rapid component of the delayed rectifier current (IKr) (Roden and Viswanathan, 2005). These alterations in transmembrane currents result in prolongation of the action potential similar to that seen in the LQTS and can result in the same outcome. This property is so frequently encountered that all medications approved for human use are now tested for inhibition of IKr (Food and Drug Administration, 2005). Certain illicit drugs are also known to predispose to VF and SCD. In particular, potent stimulants such as cocaine can cause intense vasoconstriction resulting in ischemia and VF (Fischbach, 2017). Notably absent from this list are the stimulant medications used for the treatment of ADHD (Cooper et al., 2011; Winterstein et al., 2007).

Commotio cordis, a very unusual but devastating cause of VF and SCD, occurs when the heart receives an abrupt impact, usually from a slow-moving projectile such as a ball, hockey puck, or other blow to the chest. If this occurs at a critical part of the action potential or cardiac cycle, it can result in VF. Interestingly, too little energy has no effect on the heart, whereas too much energy is actually defibrillatory. There is a narrow window of energy that is fibrillatory. However, when both conditions are met, VF can result. Fortunately this is an extremely rare occurrence (Link et al., 2003).

Complex interactions exist between the heart and CNS. This heart-CNS axis has recently been investigated as an important contributor to VF and SCD (Tahsili-Fahadan and Geocadin, 2017), which will be discussed in the following section.

4. Genetic analysis of SADS

4.1 Genetic ion channelopathies

Common inherited arrhythmias as a cause of SADS include LQTS, Brugada syndrome, and CPVT. Other uncommon inherited arrhythmias include short QT syndrome, early repolarization syndrome, and idiopathic VF (Bezzina et al., 2015). Characteristic ECG abnormalities at baseline or under particular stimuli may help differentiate the clinical entities among living individuals, though molecular analysis is critical in confirming a diagnosis in the event of SCD.

Long QT syndrome is characterized by QT interval prolongation with syncope and SCD caused by torsades de pointes (Schwartz et al., 1993). In the LQTS, abnormalities in various ion channels result in prolongation of the action potential, during which the heart is depolarized and contracting. Excessive prolongation results in electrical instability and spontaneous depolarizations that occur at critically vulnerable periods during the cardiac action potential The vast majority (~90%) of genotype positive patients with LQTS have a pathogenic variant in *KCNQ1* (encodes the slowly activating delayed rectifier current, I_{ks}), *KCNH2* (encodes the rapidly activating delayed rectifier current, I_{kr}), or *SCN5A* (encodes the major cardiac sodium current, I_{na}), (Acker-

man et al., 2011) though a total of 17 genes associated with LQTS have been published to date, many of which have recently been noted upon further review to have disputed or limited evidence of causation (Adler et al., 2020). The vast majority of cases of LQTS are inherited in an autosomal dominant pattern with the exception of the rare Jervell and Lange-Nielsen phenotype which historically is characterized as autosomal recessive caused by homozygous or compound homozygous mutations in *KCNQ1* or *KCNE1* (Neyroud et al., 1997; Schulze-Bahr et al., 1997).

Brugada syndrome is associated with syncope and cardiac arrest resulting from degeneration into VF of episodes of polymorphic ventricular tachycardia (Brugada and Brugada, 1992; Michowitz et al., 2019). Pathogenic changes in *SCN5A,* which encodes the α-subunit of the cardiac voltage-gated Na channel, were the first described molecular cause of Brugada syndrome and remain the only gene unequivocally associated with Brugada syndrome, although subsequently several other genes with pathogenic changes have been implicated collectively contributing to approximately 2-5% of cases (Brugada et al., 2018). Brugada syndrome was initially considered an autosomal dominant Mendelian disorder, but recent observations regarding inheritance and disease susceptibility have challenged that theory and suggested a more complex inheritance pattern in which multiple genetic variants likely contribute to disease phenotype with variable expressivity (Probst et al., 2009).

Catecholaminergic polymorphic ventricular tachycardia is characterized by bidirectional or polymorphic ventricular tachycardia during exercise, physical activity, or emotional stress (Leenhardt et al., 1995). Clinical diagnosis is often made during exercise-stress test or Holter monitor, in which bidirectional or polymorphic ventricular arrhythmia is induced by physical or emotional stress (Hayashi et al., 2009). Pathogenic changes in *RYR2,* which encodes the protein ryanodine receptor 2 and is responsible for calcium release on the cardiac muscle sarcoplasmic reticulum, are the most common cause of CPVT. Other genes implicated in CPVT include *CASQ2, CALM1,* and *TRDN* (Gyorke et al., 2004; Nyegaard et al., 2012; Roux-Buisson et al., 2012).

4.2 Clinically borderline cardiomyopathies responsible for SCD

Certain cardiomyopathies may not be diagnosed unless comprehensive histological analysis is performed at autopsy. However, autopsies with unclear significance, such as myocardial hypertrophy, fibrosis, or mild ventricular dilatation, may not support the causal relationship between the histological findings and SCD (Papadakis et al., 2013). Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by adipose and fibrous tissue replacement of the myocyte leading to right ventricular failure, arrhythmia, and SCD (Azaouagh et al., 2011; Corrado et al., 2020). Genes encoding components of the desmosome are implicated in the etiology of ARVC. Most cases of ARVC are inherited in an autosomal dominant manner (Ohno, 2016) with the exception of Carvajal syndrome and Naxos disease in which the inheritance pattern is recessive and individuals have extra cardiac features including important cutaneous lesions (Protonotarios and Tsatsopoulou, 2004). In either case, the direct cause of death is considered secondary to ventricular arrhythmias.

4.3 Importance of molecular autopsy

Autopsy-negative SCD or SUD occurs in about 30% of total SCD in young people (Tester and Ackerman, 2006). With the advent of next generation sequencing and continuous advancements in molecular diagnostics, the establishment of an accurate diagnosis of the decedent through molecular autopsy is prudent to guide appropriate screening for living relatives in attempts to prevent future deaths; several examples exist within the literature using either next generation cardiac disease gene specific panels or whole exome sequencing (Farrugia et al., 2015; Neubauer et al., 2018). In a study where exome sequencing was utilized in 34 cases of SUD, a potentially disease causing sequence change was identified in approximately 70% (Neubauer et al., 2018). Clinicians should ensure the molecular analysis includes detection of copy number changes which can be a cause of SCD and SCA in families (Tester et al., 2020). Guidelines for retaining postmortem samples for genetic testing in cases of SUD are established and provide guidance for medical examiners and coroners regarding cases in which samples should be saved, including the specific sample type, retention and storage methods, and communication with the family, medical providers, and genetic counselors in the community (Middleton et al., 2013). Genetic testing is a Class 1 recommendation for all SUD cases followed by mutation-specific targeted testing of family members once a pathogenic variant has been identified in the deceased proband (Ackerman et al., 2011).

4.4 Genetic testing in SADS

Depending on the number of genes assayed, family history, and inherited SCD in question, the likelihood of identifying a genetic cause varies: approximately 80% for LQTS, 60 - 70% for CPVT, and 20 - 30% for Brugada syndrome (Ackerman et al., 2011). In the absence of a molecular etiology in SADS, particular importance should be given to maintain routine clinical screening for first degree relatives to update clinical genetic testing in affected individuals, and periodically to keep pace with advances in genetic testing and result interpretation.

Genetic testing in SCD should be performed in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories where result interpretation is based on variant classification guidelines from a joint consensus statement of the American College of Medical Genetics and Genomics and the Association of Molecular Pathology (Richards et al., 2015). In this report, the use of standard terminology to describe a sequence change is recommended and includes five categories of variant classification: 'pathogenic', 'likely pathogenic', 'uncertain significance', 'likely benign', and, 'benign'. Additionally, in keeping with guidance from the consensus report on variant interpretation, significant effort is taken by responsible clinical laboratories to determine the above particular variant classification for each sequence change. This process takes into account evidence from population, computation, functional, and segregation data (Richards et al., 2015). The population data include frequencies of a particular variant in question in databases of control individuals as well as disease-specific databases. Computational, *in silico,* predictive programs use a variety of algorithms to predict nucleotide and amino acid level potential impact of the variant on the protein function or structure (Richards et al., 2015). Functional testing of a particular variant may include bench research partnerships utilizing animal models, enzymatic analysis,

or *in vivo* testing of patients' cells to determine the consequence of a variant. Compiling segregation data includes documenting individuals and families with a particular variant and tracking the variant and phenotype in question through many individuals and generations to determine if the disease and genetic variant in question segregate together. Responsible clinical laboratories compile data from these sources to arrive at each variant interpretation, which is then used by the clinician for patient management, as such the correct interpretation of each variant is now considered the most critical step in genetic testing (Towbin et al., 2019).

Identification of a variant of uncertain significance (VUS) should be considered non-actionable with regard to clinical management and family screening of unaffected family members until further data to re-classify the variant are available (Towbin et al., 2019); conservative management is suggested to avoid misguided screening and inappropriate risk stratification. Continued relationship with periodic follow up with the family is recommended as variant reclassification may occur over the course of years as new information becomes available. In a recent study of reinterpretation of sequence variants in genes causing inherited arrhythmogenic syndromes, reanalysis lead to reclassification of 70% of variants classified 10 years prior (Campuzano et al., 2020). Many clinical laboratories offer periodic reclassification, which often requires an ordering clinician to request the reanalysis. Hence, period re-evaluation of family members of SCD is strongly recommended. In the age of genomic medicine, involvement of a genetics professional such as a genetic counselor, trained particularly to guide families and patients through the challenges of genetic testing and uncertainty, is vitally important, not only for the families but also for the primary cardiologists (Madlensky et al., 2017).

5. Involvement of heart-CNS axis in SCD

5.1 Heart-CNS Axis in SCD

Acknowledging that hemodynamic collapse due to non-perfusing arrhythmias leads to a common final pathway for SCD, the plethora of clinical and scientific evidence has suggested that the primary pathology of the heart may not always be the sole culprit for this unexpected catastrophic process. Various CNS pathologies are known to induce abnormalities in the cardiovascular system including myocardial injury, cardiomyopathy, ventricular arrhythmias, or even SCD, indicating the potential role of the heart-CNS axis in determining survival or death (Davis and Natelson, 1993; Manea et al., 2015; Taggart et al., 2011; Tahsili-Fahadan and Geocadin, 2017; Zipes and Rubart, 2006).

Strong emotions and stressors (anger, fear, grief, and natural disasters) are known to trigger SCD in individuals with and without existing cardiovascular diseases (Engel, 1971; Rubart and Zipes, 2005), suggesting high level cortical and subcortical centers are also involved in this loop. Certain CNS disorders, ischemic stroke and subarachnoid hemorrhage, are known to induce ventricular arrhythmias or cardiac arrest (Abboud et al., 2006; Ahmadian et al., 2013). There has been increased awareness of sudden unexpected death in epilepsy (SUDEP) (Middleton et al., 2018; Tomson et al., 2008; Verducci et al., 2020). Even febrile seizure may be associated with SCD in the young, which may trigger or mimic a primary arrhythmic disorder in SADS patients (Stampe et al., 2018). Mueller et al. proposed that epilepsy can induce sudden death with concomitant brain atrophy that impairs autonomic control, suggesting the critical involvement of the autonomic nervous system (ANS) in the pathogenesis of SUDEP (Mueller et al., 2018). Recent meta-analysis by Chahal et al. suggested potential overlap between SUDEP and arrhythmogenic SCD with a common genetic ion channel abnormality that affects electrophysiology of both neurons and cardiomyocytes (cardiocerebral ion channelopathy) (Chahal et al., 2020), also supported by some case reports (Heron et al., 2010; Parisi et al., 2013). Acquired myocardial alteration secondary to refractory epilepsy may enhance vulnerability to develop lethal ventricular arrhythmias (Li et al., 2019; Verrier et al., 2020). The mechanisms underlying epilepsy-induced SCD are multifactorial and, in part, attributed to a dynamic interplay between heart and CNS (Li et al., 2019; Tolstykh and Cavazos, 2013). Hefti et al. performed detailed neuropathological investigations and reported that nearly half of children with unexplained death (n = 69) had hippocampal malformation (Hefti et al., 2016). It is plausible that SCD may be, in part, induced by a combination of variable baseline cardiac pathologies as an essential substrate and additional abnormal CNS behavior as a trigger.

5.2 Dysregulation of ANS may induce lethal ventricular arrhythmias and SCD

The heart and CNS communicate by a dense innervation of ANS, sympathetic and parasympathetic nerves, and afferent sensory nerves. These afferent and efferent fibers comprise complex feedback loop in cardiac autonomic control, disruption or misbalance of which affects cardiac electrophysiology and arrhythmias (Taggart et al., 2011). Other humoral factors, neurohormones and cytokines, are also known to participate in this crosstalk (Dal Lin et al., 2018). The ANS plays a primary role in the pathophysiology of arrhythmia leading to SCD, and neuraxial modulation is emerging as an integral target of therapeutic interventions (Franciosi et al., 2017; Fukuda et al., 2015).

The involvement of the ANS in developing life-threatening ventricular arrhythmia is variable based upon the underlying pathology of the myocardium (Franciosi et al., 2017). Patients with LQTS type 1 and type 2 develop a prolonged QT interval and lethal ventricular arrhythmia during exercise and increased sympathetic activities, whereas those with LQTS type 3, caused by abnormalities in SCN5A, have the highest risk during rest (bradycardia) when sympathetic activity is low (Moss and Kass, 2005). Autonomic susceptibility differs amongst the LQTS dependent upon the abnormality of the underlying ion channel subtype. In Brugada syndrome, with defects in SCN5A, arrhythmic events and SCD more frequently occur during sleep or at night, indicating its strong association with high parasympathetic tone and low sympathetic activity (Matsuo et al., 1999). Paul et al. demonstrated significantly reduced norepinephrine and cyclic AMP levels in myocardial biopsy inpatients with Brugada syndrome compared with those in controls, suggesting that inefficient β-adrenergic stimulation and imbalance in sympathovagal tone in these patients may lead to lethal ventricular arrhythmias (Paul et al., 2011). Patients with CPVT, caused by defects in RyR2 gene, develop polymorphic VT and potential SCD with increased sympathetic activity in young patients with structurally normal hearts when the heart rate increases beyond certain threshold (Laitinen et al., 2001; Lehnart et al., 2004). Neurological involvement is another important as-

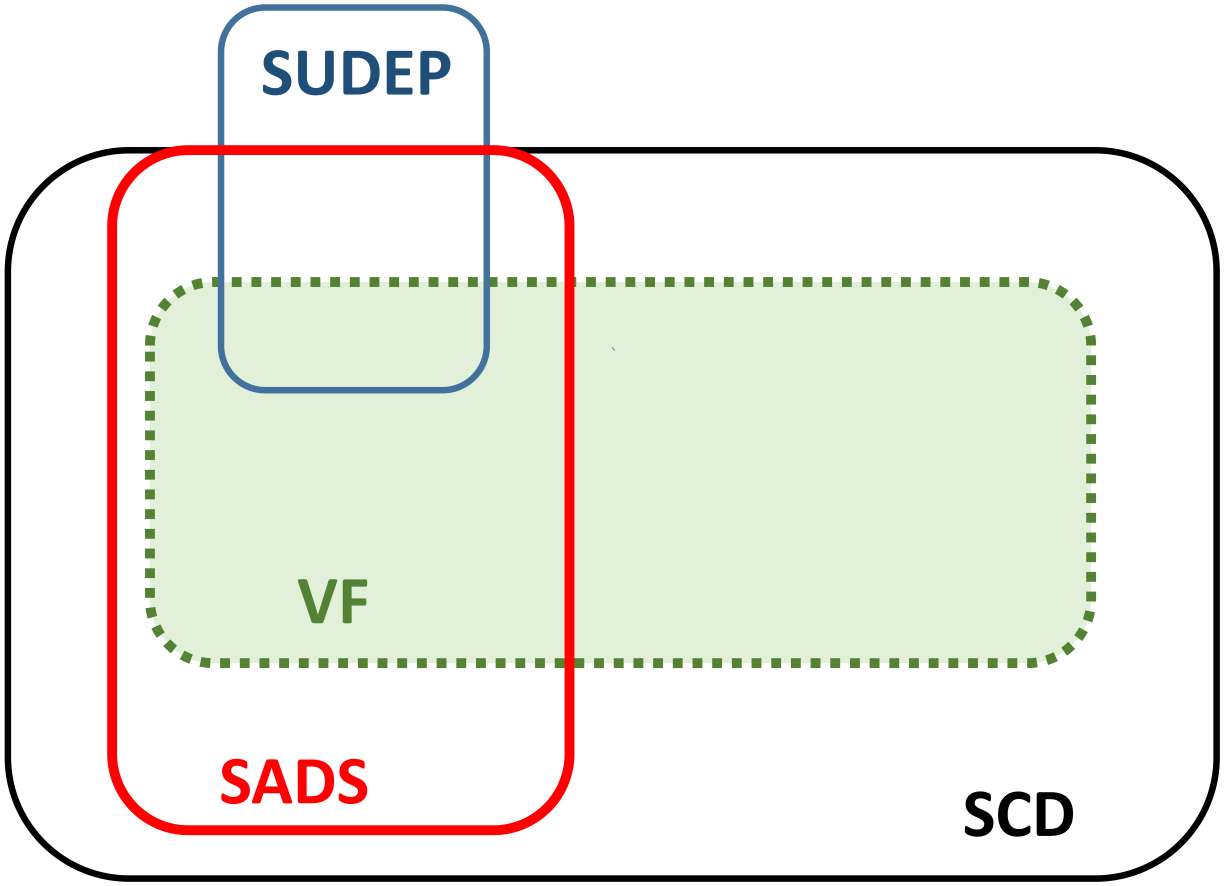

Figure 2. A diagram illustrating interrelationships between sudden cardiac death (SCD), sudden arrhythmic death syndrome (SADS), ventricular fibrillation (VF), and sudden unexpected death in epilepsy (SUDEP). Sudden cardiac death consists of SADS and SCD with structural heart disease including cardiomyopathies, coronary disease, myocarditis, and congenital heart disease. In both entities, VF can be a common terminal event responsible for cardiac arrest and death. Sudden unexpected death in epilepsy is a part of SADS, but its pathophysiology is poorly understood. Some SADS and SUDEP may not be associated with VF.

pect that contributes to the incidence of SCD.

Myocardial impairment due to inflammation or infarction may result in scar formation that alters electrical propagation. In addition, transdifferentiation of cardiac sympathetic nerves into the myocardial tissue and regional sympathetic hyperinnervation (neural sprouting) are frequently seen in hypertrophy and heart failure, which may induce heterogeneity of conduction velocity and fatal arrhythmia (Cao et al., 2000; Kimura et al., 2012).

5.3 Neural modulation, a potential therapeutic modality

The ANS plays an important role in modulating cardiac electrophysiology and arrhythmogenesis. Enhanced sympathetic drive can exacerbate pathological myocardial conditions including ischemia, hypertrophy, heart failure, and congenital ion channelopathies to initiate life-threatening ventricular arrhythmias (Fukuda et al., 2015; Shen and Zipes, 2014). Antiarrhythmic effects are expected by either eliminating excessive sympathetic activities or enhancing vagal tones. Increased evidence suggests the ANS modulation as a feasible, effective, and safe strategy in managing potentially lethal arrhythmias and preventing SCD (Franciosi et al., 2017).

Beneficial effects of β-blockers have been proven in preventing lethal ventricular tachycardia and SCD in various pathological conditions including ischemic myocardium, myocardial infarction, and ion channelopathies (Al-Khatib and Stevenson, 2018; Steinbeck et al., 1992). A more aggressive measure by directly ablating sympathetic nerves, left cardiac sympathetic denervation (LCSD), has been applied for those with potentially life-threatening ventricular tachyarrhythmias who cannot tolerate chronic β-blocker treatment or those with medically refractory ventricular arrhythmias with or without frequent shocks of internal cardioverter defibrillator (ICD) (Schwartz et al., 2004). The clinical effects of LCSD include suppressing the onset of ventricular arrhythmia after myocardial ischemia and infarction and reducing VF threshold in LQTS, in part by enhancing vagal activity (Schwartz, 2014). Therapeutic effects of LCSD have been demonstrated in medically refractory LQTS (Collura et al., 2009) and CPVT (Wilde et al., 2008).

Vagal nerve stimulation (VNS) can induce not only potential anti-arrhythmic effects by lowering heart rate and prolong-

ing action potential duration (Fukuda et al., 2015) but also cardioprotective effects in ameliorating heart failure by attenuating systemic inflammation (Zhang et al., 2009). Further investigation is warranted for applying VNS for human arrhythmic diseases.

6. Conclusion

Sudden arrhythmic death syndrome is a rare pathological condition in the young, but the underlying mechanisms are complex and poorly understood. The interrelationships between SCD, SADS, VF, and SUDEP are illustrated (Fig. 2). Despite current progress in molecular genetics, pathogenesis of SADS is not fully elucidated; the interpretation of variance of unknown significance and the feasibility of the current genetic approach in SADS victims and their families are still ongoing diagnostic challenges. Sudden cardiac arrest is not solely caused by intrinsic cardiac pathology but may be influenced or triggered by multiple external factors, including heart-CNS interactions, mainly via ANS. Sudden unexplained death in epilepsy is an important clinical entity that suggests a common background between heart and CNS (cardiocerebral ion channelopathies) as well as the dynamic interplay by the two vital organs. Neural modulation is an old and new therapeutic modality to prevent ventricular arrhythmias and SCD. Further clinical and basic investigations are warranted to better understand the pathobiology of SADS.

Authors' contrubutions

T.T. conceptualized and designed the entire structure of this article. T.T. wrote sections 1, 2, and 5, K.K.F. and J.T. wrote sections 4 and 3, respectively. T.T. critically read an entire text and organized it into a final manuscript. All authors participated in revising the manuscript in response to the reviewers. All authors approved the final version of the manuscript.

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Conflict of interest

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