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Review

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Sudden Cardiac Death in Young Individuals: A Current Review of Evaluation, Screening and Prevention

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Abstract

Sudden cardiac death (SCD) can affect all age groups, including young persons. While less common in the age < 35 population, the occurrence of SCD in the young raises concern, with multiple possible etiologies and often unanswered questions. While coronary artery disease is the leading cause in those > 35 years of age, the younger population faces a different subset of pathologies associated with SCD, including arrhythmias and cardiomyopathies. The tragic nature of SCD in the young entails that we explore and implement available screening methods for this population, and perform the necessary investigations such as electrocardiography (ECG) and echocardiography. In this review, we not only explore the vast etiology associated with SCD in those age < 35, but emphasize evaluation methods, who is at risk, and delve into screening of SCD in potential victims and their family members, in an attempt to prevent this traumatic event. Future research must work towards establishing preventative measures in order to reduce SCD, particularly unexplained SCD in the young.

Keywords: Sudden cardiac death; Young; Screening; Prevention; Evaluation; Family

Introduction

Sudden cardiac death (SCD) in children and young adults remains a tragic and sudden event that greatly affects families and communities. SCD has been defined as unexpected death due to an underlying cardiac disease, typically occurring within an hour of symptom onset, or an unwitnessed death 12 - 24 h after a person appeared well [1, 2]. A study previously conducted in New Zealand and Australia estimated the annual incidence of SCD to be 1.3 cases per 100,000 persons aged 1 to 35 years old, with 72% of those affected being males [3]. While some cases can be attributed to coronary heart disease (CHD) - especially in the 31 - 35 age range - or structural heart disease [3-5], many instances of SCD remain "unexplained", with a structurally normal heart and negative toxicology analysis [6]. These are presumed to be caused by cardiac arrhythmia syndromes associated with ion channelopathies, such as long QT syndrome (LQTS) and Brugada syndrome [2, 3, 6, 7]. Previous reviews have explored incidence, epidemiology, and post-mortem evaluation related to SCD in the young [4, 6, 8, 9], or screening of specific populations such as older adults and athletes [10, 11], with little focus on screening and evaluation in the age < 35 population. Although it poses as a challenge, identifying risk factors of SCD and developing screening methods particularly in the young population can facilitate early intervention and prevent the SCD event from occurring, along with the subsequent community distress [5, 6]. Therefore, this article aimed to review the current evidence on SCD in the young (< 35 years old) including epidemiology, etiology, and clinical presentation, with emphasis on evaluation, identifying those at risk, and screening measures for early detection and prevention of SCD in the young.

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Epidemiology

SCD remains infrequent in the young population. To ascertain the incidence, we must rely on population-based studies. Most evidence in the literature consists of retrospective studies that tend to either overestimate or underestimate incidence due to the reliance of administrative databases [9, 12].

In research published by Ackerman et al, it is shown that infants and children are at a particularly lower risk of SCD. This is affected primarily by a longer life expectancy of children as compared to the adult population. SCD in younger children can be up to one or two times less than that of the adult population, with the incidence ranging from < 1 to 10 deaths/100,000 of the population per year (while remaining exclusive of infants and people above 18 years of age, < 1 - 4 deaths/100,000 population per year) [9]. Population-based epidemiological studies with

large sample sizes are imperative in documenting the incidence of SCD among the common population.

Further, the shown prevalence has a bimodal distribution as it begins to fall in early childhood and rises again in adolescence [13], with the male counterpart being more affected by a factor of about 2:1 [9]. Similarly, a cohort study conducted in Denmark on SCD in the young found the incidence rate of SCD in young men to be twice than that of women [14].

Etiology

Regardless of age, causes of SCD can be categorized into two main subgroups - coronary causes and non-coronary causes, or cardiac and noncardiac causes [4, 15]. The former possesses diagnostic difficulties while the latter has minor or atypically pronounced morphological changes [4]. Coronary or ischemic heart causes can include CHD, myocardial infarction, dissection of arteries, arteriosclerosis, and arteritis. Non-coronary causes can be categorized into nonischemic heart disease or disease without structural changes of the heart. The former includes hypertrophic and dilated cardiomyopathy, valvular heart disease, myocarditis, congenital heart disease, and arrhythmogenic right ventricular cardiomyopathy, while the latter includes genetically acquired arrhythmias such as Brugada and LQTS, familial SCD, and any anomaly of the cardiac conduction system [4, 15]. Noncardiac causes can include neurologic disorders such as intracranial hemorrhage, as well as electrolyte, metabolic, and endocrine derangements [15]. On the basis of gender, a previous cohort study found that SCD due to potentially inherited cardiac diseases occurs half as often in women than in men, suggesting protection by female gender [14].

SCD in association with CHD

Although SCD is commonly due to CHD in the age > 35 population, the opposite is true for younger individuals. Previous autopsy studies have found that coronary artery disease (CAD) is the leading cause of SCD in individuals age > 35 years, and the second cause of SCD in individuals age < 35 years [16, 17]. For instance, an autopsy study conducted by Eckart et al concluded that SCD in those > 35 years of age is most associated with atherosclerotic coronary disease, whereas in younger individuals < 35 years of age, SCD was due to sudden unexplained death (SUD), which can be caused by primary arrhythmias [18]. For this reason, when evaluating younger patients, it is important to focus on causes associated with SUD, rather than a CHD focused evaluation. Another autopsy study conducted in Denmark compared the findings of CAD-SCD between victims age < 36 and 36 - 49 years, reporting a high frequency of cardiac symptoms prior to CAD-SCD in the young cases, and more severe occlusion of coronary arteries in the older group [17].

SUD

As mentioned above, SCD in younger individuals is often concluded as an SUD, in which the heart is structurally normal, and autopsy is negative [3, 16]. An autopsy study conducted by Bagnall et al gathered that the most common finding after autopsy in persons age 1 - 35 was unexplained SCD, accounting for 40% of cases [3]. This corroborates with data from an autopsy-based series conducted in the USA, which found that 41.3% of SCDs in persons age < 35 were SUD [18]. Both studies suggest potential causes for SUD. Eckart et al suggest ion channel mutations and arrhythmias, including Wolff-Parkinson-White, LQTS, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) [18]. Bagnall et al analyzed the genes of 113 cases of young persons with unexplained SCD, identifying a clinically relevant cardiac gene mutation in 27% of cases [3]. Similarly, Neubauer et al investigated 34 cases of unexplained SCD, identifying potentially disease-causing sequence changes in 29.4% of cases, likely associated with channelopathies [19].

Heritable and acquired cardiomyopathies

Cardiomyopathies, arrhythmogenic disorders, and primary channelopathies are predominant causes of SCD in the young [4, 16]. The prevalence of cardiomyopathies - including hypertrophic, dilated, and arrhythmogenic right ventricular - in SCD victims aged < 35 has been reported to be 15% to 30% in previous studies [16]. An autopsy study conducted in Australia and New Zealand found that among explained causes of SCD, 16% of cases were due to inherited cardiomyopathies [3]. Further, Burns et al analyzed epidemiologic data of sudden, unexpected deaths of infants and children, finding that explained cardiac causes in all ages included hypertrophic cardiomyopathy (HCM) in 12% of cases, and other cardiomyopathies in 14% of cases [20]. Many cardiomyopathies are inherited mutations, and diagnosed via cardiac imaging. Family history of SCD and history of syncope are important risk factors to keep in mind when evaluating for risk of SCD in young persons with cardiomyopathy [16].

Structural congenital heart disease

As per data in 2016, the incidence of children being born in the USA with congenital heart disease is estimated to be about 40,000 [10]. The risk of SCD is increased in this particular demographic due to an additional factor of scarring, hypertrophy and fibrosis. Individuals with congenital heart disease have an increased risk of SCD in comparison with the general population [4, 21] with SCD accounting for 15% to 25% of deaths in these patients [4, 22, 23].

The many different congenital heart disease subtypes make it challenging to calculate an overall risk estimate. However, compared to acquired cardiac illnesses such as dilated cardiomyopathy or ischemic cardiomyopathy, the overall incidence of SCD in congenital heart disease patients is lower [4].

SCD as a side effect of medications

SCD may be caused by both illegal and legal drug usage. This

can include alcohol and illegal drugs such as cocaine and amphetamines (i.e., MDMA) [22, 24, 25].

Many medications can induce sympathomimetic receptors, including stimulant medications utilized for the treatment of attention deficit and hyperactivity disorder (ADHD), and similar disorders of school function [4, 26]. However, these medications only seem to affect individuals with preexisting channel defects, such as LQTS, and is linked to an increased risk of cardiac events in males.

SCD in association with myocarditis

Myocarditis is an inflammatory disorder of the myocardium that can be caused by bacterial, fungal, or parasitic infections, with viral infections such as Coxsackie B being a predominant cause in children [4, 27]. Myocarditis remains a common cause of sudden death in infants, adolescents, and young adults [4, 16, 27]. A nationwide study conducted in Denmark found that among autopsied SCDs in persons aged 1 - 49 years, 6% were caused by myocarditis, not including non-autopsied SCDs, suggesting underdiagnosis [27]. Similarly, in a prospective study on SCD in persons 1 to 35 years of age, Bagnall et al found that 7% of cases were due to myocarditis [3]. Even more, an epidemiologic study in the USA analyzed data from SUDs of infants < 365 days and children aged 1 - 17 years, concluding that myocarditis/endocarditis was the common explained cardiac cause [20].

SCD and lifestyle

Certain lifestyle factors contribute to the incidence of SCD. A case-control study performed in Korea found that healthy lifestyle factors, specifically lesser intake of red meat or fish, higher intake of fruits or vegetables, non-smoking, regular physical exercise, and adequate sleep showed a protective effect against sudden cardiac arrest (SCA) [28]. Similarly, an umbrella review of meta-analyses concluded that current smoking is an important risk factor, whereas physical activity is an important protective factor [29]. A prospective study on smoking in women found a 2.46-fold increased risk of SCD in current smokers, with a decreased risk over time after quitting, overall concluding a strong dose-response relationship between cigarette smoking and SCD risk [30]. With regards to alcohol consumption, a study in Finland on victims of SCD due to non-ischemic heart disease found blood ethanol levels to be elevated in 42% of subjects, suggesting alcohol consumption contributing to SCD [31]. However, this study was conducted in an older population.

Presenting Symptoms of SCD

In the western world, SCD accounts for the majority of deaths as a consequence of cardiovascular conditions [32]. The possible presenting symptoms of SCD can be categorized as prodromal or antecedent symptoms. Prodromal symptoms occur hours to minutes before the onset of death, while the symptoms that evolve gradually over days to years before death are grouped as antecedent symptoms [33]. The most common symptoms that have been reported to precede SCD include pre-syncope, syncope, palpitations, chest pain, shortness of breath, generalized malaise, lethargy, infections, and gastrointestinal symptoms [34]. Studies revealed that prior to SCD, chest pain was a predominant symptom in individuals aged 30 years or above, while those less than 30 years of age had syncope/pre-syncope as the most common presenting symptom. The distribution of symptoms on the basis of gender showed a more frequent occurrence of palpitations among males as compared to females [35]. The duration of symptoms preceding SCD was found to last for more than 5 min in 90% of cases, 2 - 5 min in 7.5%, whereas only a small number of individuals experienced symptoms lasting for less than 2 min immediately before collapsing [36].

Evaluation of Survivors of SCA

In survivors of sudden cardiac arrest, it is important to investigate the underlying reversible causes such as acute or chronic ischemic heart disease, left ventricular dysfunction, or dilated cardiomyopathy. A thorough and detailed history of the survivor of SCA can be beneficial in correlating to the type of investigations needed further. The evaluation of survivors of SCA is done initially with baseline investigations including electrocardiography (ECG), coronary angiography, and echocardiography. A 12-lead ECG and coronary angiogram help in ruling out any structural heart disease or CAD. Echocardiography helps assess left ventricular function or dilated cardiomyopathy [37]. If the cardiac arrest remains unexplained, then further comprehensive evaluation must be undertaken. These investigations include high lead/signal-averaged ECG, advanced imaging (cardiac magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography (PET) scan), provocative (exercise test, epinephrine infusion), and genetic testing [38].

If the initial baseline workup fails to identify a cause, advanced imaging techniques such as contrast magnetic resonance (CMR) imaging would be of added benefit. CMR protocol includes taking images while breath is held in a supine position and with ECG gating. CMR protocols are carried out for assessing cardiac function while late gadolinium enhancement (LGE) is done to detect fibrosis in myocardial tissue. A study conducted revealed that in SCA survivors in whom the initial baseline investigations were unrevealing, an LGE detected a potential arrhythmic substrate in up to 76% of the patients [39].

During exercise stress tests (ESTs), an ECG should be done prior to, during, and within 6 min after exercise. The accurate interpretation of the EST is very important as a study conducted revealed that one-third of the patients who were the survivors of SCA and later diagnosed with CPVT had a significant delay in their diagnosis. The two reasons leading to a delayed diagnosis in these individuals were either a consequence of not performing an EST or an EST was carried out appropriately but was not interpreted correctly [40]. Epinephrine infusion tests are done

with continuous ECG monitoring. A positive epinephrine infusion for LQTS was interpreted when the QT interval was prolonged by ≥ 30 ms at 0.10 µg/kg/min. On the other hand, the epinephrine infusion test was considered positive for CPVT if it provoked three or more beats of polymorphic ventricular tachycardia or bidirectional ventricular tachycardia [41].

Moreover, genetic testing helps detect a pathognomic variant in a considerable number of survivors of unexplained SCA, even at a stage when the clinical phenotype is not yet detectable. The chances of detecting a pathognomic variant are significantly higher in individuals with either a past medical history of syncope or a positive family history of SCD. Genetic testing yields better outcomes, particularly in unexplained SCA, but must be carried out by specialist clinics with expertise in genetic interpretation [42]. A study showed that comprehensive genetic testing identified mutations in up to 50% of SCA survivors who were not previously diagnosed with any cardiac condition. Likewise, genetic testing detected the phenotypic variant in up to 67% of SCA survivors that were phenotypically positive, while in phenotypically negative cases, genetic testing detected the cause of SCA in around 17%. Furthermore, genetic testing revealed one out of six causes of phenotypically negative SCA survivors, therefore it is advised to conduct genetic testing in all SCA survivors. In addition, it would also facilitate guiding treatment plans and management decisions [43].

Who Is at Risk?

As SCD is a widely documented and fatal condition, it is imperative for us to analyze those at risk of this condition.

SCD among athletes has been found to be relatively more common as compared to the general population (< 40 years of age). The risk of athletes is found to be 0.5 to 1 per 100,000 of the population each year [44]. SCD is typically due to an underlying secondary condition. The incidence of some conditions in patients with subsequent SCDs is given below, and thus persons presenting with the symptoms for these conditions are the ones who should be primarily screened, since they are at a greater risk of SCD: 1) autopsy negative SCD (31%) [44]; 2) anomalous coronary arteries (14%) [44]; 3) HCM (8%) [44]; 4) dilated non ischemic cardiomyopathy (8%) [44]; and 5) myocarditis (8%).

Apart from certain pathologies, other factors can increase the risk of SCD in the general population as well. In a study by Ha et al, it was shown that sex, activity at the time of onset, body mass index (BMI), and residential location can affect the incidence of SCD amongst the young. It was also shown that in patients that were engaging in strenuous exercise at the time of the onset, there was a greater relation with sudden arrhythmic deaths (20%, $P = 0.02$), while in patients that were engaging in relaxing activities like sleeping at the time of the onset had a more significant relation to aortic dissection ($P < 0.001$) [45].

Screening for SCD

Screening should be done to determine the exact burden of the risk and what kind of preventative steps should be taken. Before the formation or start of a screening program, it is important to identify the population at risk and who would benefit from such screening. An early symptomatic stage or long latency of a disease of public health concern should be targeted first. After the screening, the following treatment should be practical, widely available, and affordable to the affected population [46]. Mass screening of asymptomatic young individuals could be counterproductive and has not shown any improvement of SCD in the young [47].

Initial simple modalities of screening should be used. The American Heart Association (AHA) has a 14-point screening tool questionnaire (previously 12 points before 2014) used for cardiovascular screening, particularly for young competitive athletes as a part of preparticipation cardiovascular screening. As per recommendations of certain organizations such as the AHA, a focused history and physical examination (H&P) as a part of this screening is the first step to determining any underlying cardiovascular disease that increases the risk of SCD. This questionnaire can cover the individual's personal and family history to screen for congenital or familial cardiovascular diseases. As for the physical examination, this should be conducted in a focused manner with certain pathologies in mind that have distinct physical examination findings, such as valvular disease, hypertrophic cardiomyopathy, aortic coarctation, Marfan's disease, and systemic arterial hypertension. H&P should not be the only screening modality as it yields a high false positive rate [48]. The American Academy of Pediatrics (AAP) has suggested a preparticipation physical evaluation for those between the ages of 6 and 21, regardless of their participation in sports. The use of a similar but modified AHA screening questionnaire to identify the pediatric age group's risk of SCD can be used concurrently with an expert's opinion. A positive response to any of the questions should prompt further evaluation. The AHA 14-point screening questionnaire and the modified AAP tool are compared in Table 1 [49, 50]. According to a study conducted on high school athletes by Williams et al, the 14-point questionnaire compared to the use of an ECG actually carries a lower sensitivity (18.8%), specificity (68.0%), and positive predictive value (0.3%) and its significance as the initial screening tool should be reassessed [51].

ECG has been used concurrently with focused H&P as a screening tool, although it has not been recommended explicitly by American organizations as it has been suggested to be ineffective with low incidence rates and a higher false positive rate [52]. However, the European Society of Cardiology has implemented ECG screening as a basic guideline [53]. Recent literature published in Italy in 2022 suggests the use of ECG to screen for disease and risk of SCD that may have been missed by H&P. A total of 11,949 Italian students between the ages of 13 and 19 years were enrolled over the period of 4 years in a study to determine the prevalence of ECG abnormalities among a teenage age according to their athletic nature. Results were classified by major and minor ECG abnormalities. Among this population, 16% demonstrated ECG abnormalities, with major abnormalities among 13% of them and minor in 34%, with the incidences of these abnormalities being more common in non-athletes. Amongst those with major abnormalities, 1.6% (25 pupils) were diagnosed with cardiac disease. This supports using ECG screen-

Table 1. Comparison of AHA's 14-Point Element Questionnaire for Preparticipation of Cardiovascular Screening of Athletes [50] and Modified Four Questions by the AAP Policy Statement [49]

AHA 14 points	Modified four points
Personal history	1. Have you ever fainted, passed out, or had an unexplained seizure suddenly and without warning, especially during exercise or in response to sudden loud noises, such as doorbells, alarm clocks, and ringing telephones?
1. History of chest pain/discomfort/tightness on exertion?	
2. History of unexplained syncope?	
3. History of excessive and unexplained dyspnea or palpitations associated with exertion	
	2. Have you ever experienced breathlessness or chest pain while exercise?
4. Prior history of heart murmur on examination	
	3. Has anyone in your immediate family or more distant relatives (aunts, uncles, cousins) passed away suddenly or unexpectedly before the age of 50 due to cardiac issues? This includes unexpected drownings, unexplained auto crashes in which the relative was the driver, or SIDS?
5. History of increased blood pressure	
6. Any prior restriction on sports activity	
7. Were you ever ordered heart disease investigations by a physician?	
Family history	
8. Early death of > 1 relative before the age of 50 years due to heart disease	4. Is there anyone in your family under the age of 50 who has a pacemaker or implantable defibrillator, or to anyone with hypertrophic obstructive cardiomyopathy, Marfan syndrome, LQTS, arrhythmogenic cardiomyopathy, short QT syndrome, Brugada syndrome, or CPVT?
9. Close relative of < 50 years with heart disease	
10. Family history HCM or DCM, LQTS or other channelopathies, Marfan syndrome, symptomatic arrhythmias or any other known genetic cardiac condition	
Physical examination	
11. Audible heart murmur	
12. Check for femoral pulses	
13. Marfan syndrome findings (Kyphoscoliosis, high arch palate, pectus excavatum, arachnodactyly, arm span > height, hyperlaxity, myopia, mitral valve prolapse, aortic insufficiency, systemic arterial hypertension)	
14. Brachial artery pressure	

AAP: American Academy of Pediatrics; AHA: American Heart Association; CPVT: catecholaminergic polymorphic ventricular tachycardia; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LQTS: long QT syndrome; SIDS: sudden infant death syndrome.

ing in the younger population [54]. Another study in Taipei analyzed data of 566,447 students, who were screened with surveys and ECG, and identified 685 students at risk of SCD. Amongst these students, 465 did not have any sort of past cardiac history. Without ECG screening, this could have been missed and just further highlights the importance of ECG screening [52].

In the UK, a study conducted by Dhutia et al demonstrated that using ECG with a health questionnaire was more cost-effective with the added benefit of increased disease detection. The addition of the ECG in this study showed a 36% reduction in cost per diagnosis as opposed to just a questionnaire alone [55]. However, the use of the questionnaire and ECG screening have been considered to be relatively costly compared to the number of lives saved by such screening [48]. The Western and Eastern countries have opposing views on this matter, with countries such as Italy and Japan who use ECG screening on younger school children [52]. Adding EST to the initial screening process can increase the diagnostic yield of ventricular arrhythmias. However, this leads to a concurrent increase of a false positive rate [56].

Further secondary testing should only follow abnormal results from the initial screening and typically includes imaging, such as transthoracic echocardiography, which can help diagnose common structural abnormalities [48].

Screening of Family Members

The death of an immediate family member due to SCD can cause grief and instill fear amongst others with the common question of what could have possibly been the cause of death. An autopsy following the SCD may shine some light and provide a diagnosis. Structural diseases, such as HCM, can be identified and should warrant further disease-tailored evaluation and genetic testing for family members of the deceased. Particular gene panels can be analyzed if there is an exact cardiac diagnosis on autopsy [57]. Negative autopsies can raise suspicions of inherited arrhythmias; however, other causes cannot be ruled out immediately, and therefore, a more in-depth evaluation should be done on family members [1]. With more family members being screened, the chances of diagnosing a condition increase as demonstrated by Quenin et al. In this study, screening three relatives versus one increased the diagnostic yield to 47%. The yield also increases when both parents are screened [49].

Screening family members is similar to the process of screening anyone who is at risk of SCD. The initial step is a focused history and examination, followed by a baseline ECG. A baseline echocardiogram can also be done to establish chamber size, wall thickness, and overall cardiac function [1]. Further testing can be done if no diagnosis is established by these tests. EST can be done to reveal any LQTS or exercise-induced tachycardia. A set of pharmacological tests, the sodium channel blocker challenge with either ajmaline 1 mg/kg or flecainide 2 mg/kg can be done to identify any arrhythmogenic causes that may have been missed by earlier investigations [49]. Testing with ajmaline has shown increased yield for diagnosing Brugada syndrome, a fairly common cause of SCD [58]. Epinephrine challenge has been demonstrated to reveal conditions such as prolonged QT interval in some patients and can be used in combination with genetic testing and ESTs [41]. Any suspected case of inherited arrhythmia or cardiomyopathy should warrant genetic testing to confirm the diagnosis [59].

Besides providing closure to the family, screening can help prevent SCD in surviving relatives of those victim to SCD. Early treatment can help protect family members and prevent SCD from occurring. Once a diagnosis is established, management can be started accordingly. Ion channelopathies can be treated with lifestyle modifications by avoidance of triggers such as QT-prolonging medication. Medication management can also be started (e.g., beta-blockers for LQTS) [1]. Family members at high risk of developing HCM should be screened regularly or in response to any symptoms (at least every 3 - 5 years) [60].

In a retrospective study conducted by Hansen et al, 304 families with 695 members with a relative history of SCD participated and were investigated for inherited cardiac disease. Amongst the 304 families, 47% of these families were diagnosed with an inherited cardiac disease and 73 (11%) members were identified and were offered treatment. The screening of all the members revealed a low percentage of serious cardiovascular disease [61].

Prevention

Being a leading cause of death worldwide, the prevention of SCD is a primary issue that must be tackled. It has been suggested that the prevention of SCD and SCA can be brought about by preventing or treating the underlying cardiovascular disorder. Both pharmacological and primary prevention methods can be employed in order to prevent the incidence of SCA. For example, patients with impaired left ventricular ejection fraction or CAD can be dealt with using agents like beta-blockers and statins. Antiarrhythmic agents can be used to deal with patients with ventricular arrhythmias. An implantable cardioverter-defibrillator (ICD) can be used as a superior replacement method to antiarrhythmic agents to prevent SCD [62]. ICDs are usually considered an effective tool for primary prevention. To ensure the timely treatment and prevention of the aforementioned diseases, it is important to timely diagnose potential SCD. Markwerth et al explain certain diagnostic techniques and procedures for SCD, in which they explained what the autopsy should actually investigate, according to the Association for European Cardiovascular Pathologists, which includes whether the underlying cause of death is SCD due to cardiovascular diseases or other causes of SCD, whether there was potential drug abuse, the nature of cardiac disease (if detected), whether the underlying cause of SCD was genetic, and whether third parties were involved [4].

Along with the advancement of the preventative measures of SCD, it is understood that we still have a long way to go. Garg et al have discussed the shortcomings of the current guidelines for the prevention of SCD. The study stated that the implantation of ICD in patients with less than 35% ejection fraction is not entirely a feasible option for the general public because of the expensive procedure. Strengthening of the education of bystanders in the domain of cardiopulmonary resuscitation (CPR) and the provision of home-based automatic electric defibrillators (AEDs) may be a feasible option that is easier to inculcate into the masses [63].

Conclusion

SCD in the age < 35 population remains a public health issue of concern. This can include from genetic mutations that may cause cardiac arrhythmia syndromes, which can be identified through genetic testing, especially if family history is positive for SCD. Without further research to establish effective screening and preventative measures particularly for potential "unexplained" SCD, morbidity and mortality will continue to rise. Providers should be trained to recognize risk factors and prodromal symptoms in clinics and in the emergency room. Future studies can work to frame a scored scale to evaluate for risk or likelihood of progression to SCD, whilst exploring the establishment of a standardized approach to those at risk.

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Conflict of Interest

The authors declare that they do not have a conflict of interest.

Author Contributions

All authors participated in review and contributed to the final manuscript. RA contributed to the study conception and design, literacy search, writing, final manuscript revision. AA contributed to writing and draft preparation. TKK contributed to writing and creation of table and figure. SS contributed to literacy search, writing and draft revision. KA contributed to literacy search and writing. YI contributed to literacy search and writing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

SCD: sudden cardiac death; ECG: electrocardiography; CHD: coronary heart disease; CAD: coronary artery disease; SUD: sudden unexplained death; SCA: sudden cardiac arrest; CMR: contrast magnetic resonance; LGE: late gadolinium enhancement; EST: exercise stress test; CPVT: catecholaminergic polymorphic ventricular tachycardia; AAP: American Academy of Pediatrics; AHA: American Heart Association; LQTS: long QT syndrome; ICD: implantable cardioverter-defibrillator; AEDs: automatic electric defibrillators; HCM: hypertrophic cardiomyopathy

References

1. Gray B, Ackerman MJ, Semsarian C, Behr ER. Evaluation after sudden death in the young: a global approach. Circ Arrhythm Electrophysiol. 2019;12(8):e007453.
2. London KS, Hartwell C, Cesar S, Sarquella-Brugada G, White JL. Can sudden cardiac death risk in the young be identified in the emergency department? J Emerg Nurs. 2020;46(1):105-110.
3. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, Davis AM, et al. A prospective study of sudden cardiac death among children and young adults. N Engl J Med. 2016;374(25):2441-2452.
4. Markwerth P, Bajanowski T, Tzimas I, Dettmeyer R. Sudden cardiac death-update. Int J Legal Med. 2021;135(2):483-495.
5. Perman SM. Young at Heart: Examining the Incidence and Etiology of Sudden Cardiac Death in the Young. Circ Cardiovasc Qual Outcomes. 2020;13(10):e006970.
6. Bagnall RD, Singer ES, Tfelt-Hansen J. Sudden cardiac death in the young. Heart Lung Circ. 2020;29(4):498-504.
7. Tsuda T, Fitzgerald KK, Temple J. Sudden cardiac death in children and young adults without structural heart disease: a comprehensive review. Rev Cardiovasc Med. 2020;21(2):205-216.
8. Couper K, Putt O, Field R, Poole K, Bradlow W, Clarke A, Perkins GD, et al. Incidence of sudden cardiac death in the young: a systematic review. BMJ Open. 2020;10(10):e040815.
9. Ackerman M, Atkins DL, Triedman JK. Sudden cardiac death in the young. Circulation. 2016;133(10):1006-1026.
10. Asif IM, Rao AL, Drezner JA. Sudden cardiac death in young athletes: what is the role of screening? Curr Opin Cardiol. 2013;28(1):55-62.
11. Schmehil C, Malhotra D, Patel DR. Cardiac screening to prevent sudden death in young athletes. Transl Pediatr. 2017;6(3):199-206.
12. Maron BJ, Murphy CJ, Haas TS, Ahluwalia A, Garberich RF. Strategies for assessing the prevalence of cardiovascular sudden deaths in young competitive athletes. Int J Cardiol. 2014;173(3):369-372.
13. 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):868-875.
14. Winkel BG, Risgaard B, Bjune T, Jabbari R, Lynge TH, Glinge C, Bundgaard H, et al. Gender differences in sudden cardiac death in the young-a nationwide study. BMC Cardiovasc Disord. 2017;17(1):19.
15. Kuriachan VP, Sumner GL, Mitchell LB. Sudden cardiac death. Curr Probl Cardiol. 2015;40(4):133-200.
16. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res. 2015;116(12):1887-1906.
17. Zachariasardottir S, Risgaard B, Agesen FN, Jabbari R, Glinge C, Ingemann-Hansen O, Ottesen GL, et al. Sudden cardiac death and coronary disease in the young: A nationwide cohort study in Denmark. Int J Cardiol. 2017;236:16-22.
18. Eckart RE, Shry EA, Burke AP, McNear JA, Appel DA, Castillo-Rojas LM, Avedissian L, et al. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. J Am Coll Cardiol. 2011;58(12):1254-1261.
19. Neubauer J, Lecca MR, Russo G, Bartsch C, Medeiros-Domingo A, Berger W, Haas C. Exome analysis in 34 sudden unexplained death (SUD) victims mainly identified variants in channelopathy-associated genes. Int J Legal Med. 2018;132(4):1057-1065.
20. Burns KM, Cottengim C, Dykstra H, Faulkner M, Lambert ABE, MacLeod H, Novak A, et al. Epidemiology of sudden death in a population-based study of infants and children. J Pediatr X. 2020;2:100023.
21. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Bar-

low A, Gatzoulis MA, Fernandes SM, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008;117(3):363-370.
22. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. J Am Coll Cardiol. 2007;50(13):1263-1271.
23. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, et al. Mortality in adult congenital heart disease. Eur Heart J. 2010;31(10):1220-1229.
24. Alexander CS. Electron microscopic observations in alcoholic heart disease. Br Heart J. 1967;29(2):200-206.
25. Bulloch RT, Pearce MB, Murphy ML, Jenkins BJ, Davis JL. Myocardial lesions in idiopathic and alcoholic cardiomyopathy. Study by ventricular septal biopsy. Am J Cardiol. 1972;29(1):15-25.
26. Findling RL, Short EJ, Manos MJ. Short-term cardiovascular effects of methylphenidate and adderall. J Am Acad Child Adolesc Psychiatry. 2001;40(5):525-529.
27. Lynge TH, Nielsen TS, Gregers Winkel B, Tfelt-Hansen J, Banner J. Sudden cardiac death caused by myocarditis in persons aged 1-49 years: a nationwide study of 14 294 deaths in Denmark. Forensic Sci Res. 2019;4(3):247-256.
28. Park JH, Cha KC, Ro YS, Song KJ, Shin SD, Jung WJ, Roh YI, et al. Healthy lifestyle factors, cardiovascular comorbidities, and the risk of sudden cardiac arrest: A case-control study in Korea. Resuscitation. 2022;175:142-149.
29. Tsartsalis D, Korela D, Karlsson LO, Foukarakis E, Svensson A, Anastasakis A, Venetsanos D, et al. Risk and protective factors for sudden cardiac death: an umbrella review of meta-analyses. Front Cardiovasc Med. 2022;9:848021.
30. Sandhu RK, Jimenez MC, Chiuve SE, Fitzgerald KC, Kenfield SA, Tedrow UB, Albert CM. Smoking, smoking cessation, and risk of sudden cardiac death in women. Circ Arrhythm Electrophysiol. 2012;5(6):1091-1097.
31. Kauppila JP, Pakanen L, Porvari K, Vahatalo J, Holmstrom L, Perkiomaki JS, Huikuri HV, et al. Blood alcohol levels in Finnish victims of non-ischaemic sudden cardiac death. Ann Med. 2021;53(1):413-419.
32. Kumar A, Avishay DM, Jones CR, Shaikh JD, Kaur R, Aljadah M, Kichloo A, et al. Sudden cardiac death: epidemiology, pathogenesis and management. Rev Cardiovasc Med. 2021;22(1):147-158.
33. Stormholt ER, Svane J, Lynge TH, Tfelt-Hansen J. Symptoms Preceding Sports-Related Sudden Cardiac Death in Persons Aged 1-49 Years. Curr Cardiol Rep. 2021;23(2):8.
34. Skjelbred T, Lynge TH, Nielsen J, Winkel BG, Tfelt-Hansen J. Symptoms and healthcare contact preceding sudden cardiac death in persons aged 1-49 years. Trends Cardiovasc Med. 2021;31(2):119-124.
35. Wisten A, Messner T. Symptoms preceding sudden cardiac death in the young are common but often misinterpreted. Scand Cardiovasc J. 2005;39(3):143-149.
36. Muller D, Agrawal R, Arntz HR. How sudden is sudden cardiac death? Circulation. 2006;114(11):1146-1150.
37. Subbiah R, Gula LJ, Klein GJ, Skanes AC, White J, Yee R, Krahn AD. Workup of the cardiac arrest survivor: for the symposium on sudden cardiac death for progress in cardiovascular diseases. Prog Cardiovasc Dis. 2008;51(3):195-203.
38. Cheung CC, Krahn AD. The importance of a comprehensive evaluation of survivors of cardiac arrest. Eur Heart J. 2018;39(21):1988-1991.
39. Neilan TG, Farhad H, Mayrhofer T, Shah RV, Dodson JA, Abbasi SA, Danik SB, et al. Late gadolinium enhancement among survivors of sudden cardiac arrest. JACC Cardiovasc Imaging. 2015;8(4):414-423.
40. Giudicessi JR, Ackerman MJ. Exercise testing oversights underlie missed and delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia in young sudden cardiac arrest survivors. Heart Rhythm. 2019;16(8):1232-1239.
41. Krahn AD, Healey JS, Chauhan VS, Birnie DH, Champagne J, Sanatani S, Ahmad K, et al. Epinephrine infusion in the evaluation of unexplained cardiac arrest and familial sudden death: from the cardiac arrest survivors with preserved Ejection Fraction Registry. Circ Arrhythm Electrophysiol. 2012;5(5):933-940.
42. Mellor G, Laksman ZWM, Tadros R, Roberts JD, Gerull B, Simpson CS, Klein GJ, et al. Genetic testing in the evaluation of unexplained cardiac arrest: from the CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry). Circ Cardiovasc Genet. 2017;10(3):e001686.
43. Asatryan B, Schaller A, Seiler J, Servatius H, Noti F, Baldinger SH, Tanner H, et al. Usefulness of genetic testing in sudden cardiac arrest survivors with or without previous clinical evidence of heart disease. Am J Cardiol. 2019;123(12):2031-2038.
44. Link MS. Sudden cardiac death in the young: Epidemiology and overview. Congenit Heart Dis. 2017;12(5):597-599.
45. Ha FJ, Han HC, Sanders P, Fendel K, Teh AW, Kalman JM, O'Donnell D, et al. Sudden cardiac death in the young: incidence, trends, and risk factors in a nationwide study. Circ Cardiovasc Qual Outcomes. 2020;13(10):e006470.
46. Kaltman JR, Thompson PD, Lantos J, Berul CI, Botkin J, Cohen JT, Cook NR, et al. Screening for sudden cardiac death in the young: report from a national heart, lung, and blood institute working group. Circulation. 2011;123(17):1911-1918.
47. Paratz E, Semsarian C, La Gerche A. Mind the gap: Knowledge deficits in evaluating young sudden cardiac death. Heart Rhythm. 2020;17(12):2208-2214.
48. Petek BJ, Baggish AL. Pre-participation cardiovascular screening in young competitive athletes. Curr Emerg Hosp Med Rep. 2020;8(3):77-89.
49. Quenin P, Kyndt F, Mabo P, Mansourati J, Babuty D, Thollet A, Guyomarch B, et al. Clinical yield of familial screening after sudden death in young subjects: the French experience. Circ Arrhythm Electrophysiol. 2017;10(9):e005236.
50. Maron BJ, Friedman RA, Kligfield P, Levine BD, Viskin S, Chaitman BR, Okin PM, et al. Assessment of the 12-lead ECG as a screening test for detection of cardiovascular disease in healthy general populations of young people (12-25 Years of Age): a scientific statement from the

American Heart Association and the American College of Cardiology. Circulation. 2014;130(15):1303-1334.
51. Williams EA, Pelto HF, Toresdahl BG, Prutkin JM, Owens DS, Salerno JC, Harmon KG, et al. Performance of the American Heart Association (AHA) 14-point evaluation versus electrocardiography for the cardiovascular screening of high school athletes: a prospective study. J Am Heart Assoc. 2019;8(14):e012235.
52. Liu HW, Huang LW, Chiu SN, Lue HC, Wu MH, Chen MR, Wang JK. Cardiac screening for high risk sudden cardiac death in school-aged children. Acta Cardiol Sin. 2020;36(6):641-648.
53. Webster G, Carberry T, Berger S. Screening for prevention of sudden death in the young: what is new? Curr Opin Cardiol. 2020;35(1):80-86.
54. Mancone M, Maestrini V, Fusto A, Adamo F, Scarparo P, D'Ambrosi A, Cinque A, et al. ECG evaluation in 11 949 Italian teenagers: results of screening in secondary school. J Cardiovasc Med (Hagerstown). 2022;23(2):98-105.
55. Dhutia H, Malhotra A, Finocchiaro G, Parpia S, Bhatia R, D'Silva A, Gati S, et al. Diagnostic yield and financial implications of a nationwide electrocardiographic screening programme to detect cardiac disease in the young. Europace. 2021;23(8):1295-1301.
56. Zorzi A, Vessella T, De Lazzari M, Cipriani A, Menegon V, Sarto G, Spagnol R, et al. Screening young athletes for diseases at risk of sudden cardiac death: role of stress testing for ventricular arrhythmias. Eur J Prev Cardiol. 2020;27(3):311-320.
57. Fellmann F, van El CG, Charron P, Michaud K, Howard HC, Boers SN, Clarke AJ, et al. European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death. Eur J Hum Genet. 2019;27(12):1763-1773.
58. Papadakis M, Papatheodorou E, Mellor G, Raju H, Bastiaenen R, Wijeyeratne Y, Wasim S, et al. The diagnostic yield of Brugada syndrome after sudden death with normal autopsy. J Am Coll Cardiol. 2018;71(11):1204-1214.
59. Harris SL, Lubitz SA. Clinical and genetic evaluation after sudden cardiac arrest. J Cardiovasc Electrophysiol. 2020;31(2):570-578.
60. Dunn KE, Caleshu C, Cirino AL, Ho CY, Ashley EA. A clinical approach to inherited hypertrophy: the use of family history in diagnosis, risk assessment, and management. Circ Cardiovasc Genet. 2013;6(1):118-131.
61. Hansen BL, Jacobsen EM, Kjerrumgaard A, Tfelt-Hansen J, Winkel BG, Bundgaard H, Christensen AH. Diagnostic yield in victims of sudden cardiac death and their relatives. Europace. 2020;22(6):964-971.
62. Morin DP, Homoud MK, Estes NAM, 3rd. Prediction and prevention of sudden cardiac death. Card Electrophysiol Clin. 2017;9(4):631-638.
63. Garg A. Primary prevention of sudden cardiac death - Challenge the guidelines. Indian Heart J. 2015;67(3):203-206.