Most sudden cardiac arrest (SCA) cases occur in older adults with underlying coronary heart disease (CHD) or structural heart disease. In relatively younger adults, inherited heart rhythm disorders have been identified as important risk factors for SCA. However, despite extensive evaluations, the etiology of SCA or sudden cardiac death (SCD) in those without known coronary or structural heart disease remains elusive in nearly half of cases.

The autonomic nervous system (ANS) is known to be a critical modulator of arrhythmogenesis in structurally normal and abnormal hearts. Sympathetic activation of the ANS has been shown to modulate substrates of ventricular arrhythmias in either normal or diseased myocardium as well as play a role in cardiovascular disease progression and risk of SCD. Stress—a mental, physical, or emotional tension in response to various unexpected or uncertain factors and/or circumstances—induces physiological changes by shifting tone between the sympathetic and parasympathetic systems of the ANS.

Psychosocial factors such as distress, anxiety, depression, and life dissatisfaction have been connected with increased risk for SCD and stroke. Lane et al. investigated the role of psychological stress in idiopathic ventricular fibrillation (IVF) and reported that IVF survivors experienced moderate or severe psychological stress before their cardiac event.
change units (LCUs). SCA group scores were compared with an age- and sex-matched control group.

Results: We compared 36 SCA group participants (22 USCA, 14 ESCA, age 47 ± 15 years, age at SCA 40 ± 14 years, 50% male) with 36 control participants (age 47 ± 15 years, 50% male). There was no significant difference in LCU score between the control group and the SCA group (248 ± 181 LCU vs 252 ± 227 LCU; P > .05). The ESCA subgroup had significantly lower mean LCU scores than the USCA subgroup (163 ± 183 LCU vs 308 ± 237 LCU; P = .030).

Conclusions: Stressful life events, especially those producing chronic stress, might predispose otherwise healthy individuals to lethal arrhythmias. Further investigation into the role of stress in SCA precipitation is warranted.

The Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER) is a large national, multicentre registry for cases of unexplained SCA (USCA), which promotes systematic evaluation post SCA. Within CASPER, the cause of approximately 50% of SCA cases remain elusive after rigorous examination. The role of stressful life events (SLEs) as antecedents to SCA in individuals who had no etiology after rigorous testing has not been investigated.

The purpose of this exploratory study was to investigate whether life stress contributed significantly to SCA risk in a population of USCA victims vs those with an explained SCA (ESCA). The results of this study are intended to generate hypotheses to be tested in a larger sample of cardiac arrest survivors.

Methods

Recruitment

Institutional approval for this study was obtained from the UBC Children’s and Women’s Health Centre of British Columbia Research Ethics Board, as well as from the research ethics board at each participating site. This exploratory study was conducted within the context of a larger program of research involving cardiac arrest survivors—CASPER. Participants were identified from 3 centres already part of the CASPER network.

Children and adults older than the age of 11 years who presented with SCA were recruited for this study. Thoroughe systematic evaluation of SCA in participants included but was not limited to cardiac magnetic resonance imaging, signal-averaged electrocardiogram, exercise testing, drug provocation testing, electrophysiological study, and genetic testing. SCA survivors who had no identifiable cardiac abnormalities on clinical testing and no pathogenic or likely pathogenic mutations, according to criteria by the American College of Medical Genetics and Genomics, identified on genetic evaluation were included in the USCA group. SCA survivors found to have cardiac abnormalities upon testing and/or one or more pathogenic mutations identified were included in the ESCA group. Participants who were unable to provide consent or complete the forms and questionnaires were excluded.

Recruited control group members were age- and sex-matched with those in the SCA survivors group. Control group participants were recruited through advertisement via flyers posted throughout BC Children’s Hospital, the BC Children’s Hospital Research Institute intranet mailing list, the Hearts in Rhythm Organization Web site, and Facebook. Those who were unable to provide consent, complete the questionnaires, had a history of SCA, or clinically relevant diagnoses were excluded.

Evaluation of life stress

Study consent was obtained and questionnaires were administered using REDCap (Vanderbilt University, Nashville, TN) housed at the BC Children’s Hospital Research Institute. We measured life stress in study participants who first experienced an SCA between ages 11 and 18 years, between ages 19 and 22 years, and at age 23 years or older, using the Social Readjustment Rating Scale (SRSS) for nonadults, the validated 1997 Recent Life Changes Questionnaire (RLCQ), respectively.

These questionnaires list a series of potentially SLEs each with an assigned, differentially weighted numerical value measured in life change units (LCUs). Evaluations were administered to age- and sex-matched control participants.

SCA survivors were asked to mark which SLEs occurred for them in the 12 months before their SCA. Similarly, control group participants answered for the same period as their sex- and age-matched participant in the SCA group. To
illustrate this, if an SCA group participant was recruited in 2018 but had their first SCA event in May of 2014, they were asked to complete the questionnaires for the year period from May 2013 to May 2014. The control group participant matched to that SCA group participant would also complete the questionnaires for the year period from May 2013 to May 2014. Aggregate scores > 500 LCUs in a 12 month period denote high recent life stress, and greater risk of illness.14

Statistical analysis

Elevated LCU scores reported on any of the questionnaires indicated elevated life stress and readjustment. Normalcy of our data was analyzed using a Kolmogorov-Smirnov test, and mean +/- SDs calculated from each of the groups and compared using a t test. A P value < 0.05 was interpreted as significant. All analyses were conducted using SPSS for Windows Version 23 (IBM Corp, Armonk, NY).

Results

Thirty-six survivors of SCA (50% male) and 36 control participants (50% male) were recruited into the study. At time of participation, the mean age of the SCA group participants was 47 ± 15 years and control group participants was 47 ± 15 years. The mean age at the time of the SCA event in the SCA group was 40 ± 14 years. Most patients presented with SCA within the previous 5 years (19/36; 53%; Fig. 1). The SCA participants (n = 36) were categorized into USCA (22/36; 61%) and ESCA (14/36; 39%).

Details of circumstances of SCA

Full details and circumstantial information related to the SCA events are outlined in Table 1. The SCA events were witnessed in 33/36 (92%) of cases, and most frequently occurred in the mornings (14/36; 39%). SCA events commonly occurred at home (14/36; 39%) or in public places (14/36; 39%). At the time of, or immediately before, the SCA event, individuals were commonly at rest (12/36; 33%) or engaged in exercise (7/36; 19%). Of the 14 patients who were exercising, moderately active or vigorously active, the most common activity was jogging or running (10; 71%).

Most of the SCA events that occurred were witnessed by bystanders (33/36; 92%). Of the 36 survivors, bystanders performed onsite cardiopulmonary resuscitation in 29 (81%) cases and deployed an automated external defibrillator in 9 (25%) cases. More than half of the patients (16/29; 55%) who received bystander cardiopulmonary resuscitation showed no evidence of neurological impairment. Of the SCA survivors, 6 (17%) had transient neurological impairment, 6 (17%) had mild neurological impairment, and 5 (15%) had severe neurological impairment.

Figure 1. Number of years between first SCA event and participation in current study for SCA group members. ESCA, explained sudden cardiac arrest subgroup; SCA, sudden cardiac arrest; USCA, unexplained sudden cardiac arrest subgroup.
SLEs

The most common SLEs are outlined in Table 2. For the SCA survivor group, 14 (39%) experienced changes in work responsibilities, 12 (33%) experienced changes in work hours, and 11 faced a major decision about the future (31%). The control group had many overlapping SLEs. The control group respondents listed vacation most often (20; 33%), followed by change in work responsibilities (14; 22%), and change in work hours (11; 30%) whereas some reported a relationship gain (8; 22%) as stressful.

The mean aggregate LCU score of the SCA survivor group (252 ± 227) was not significantly different from the mean aggregate LCU score of the age- and sex-matched control group (248 ± 181; P > 0.05; Fig. 2). Within the SCA group, the time that had passed since their cardiac arrest did not differ significantly between the 2 subgroups (USCA group: 4.5 ± 3.1 years; ESCA group: 10.1 ± 14.1 years; P > 0.05). When we compared responses of participants within the SCA survivors group, the ESCA group had lower LCU scores compared with the USCA group (163 ± 183 LCUs vs 308 ± 237 LCUs; P = 0.03; Fig. 3). When we compared each of the SCA subgroups with their respective age- and sex-matched control participants, LCU scores were not significantly different (USCA subgroup vs controls: 308 ± 237 LCUs vs 265 ± 205 LCUs; P > 0.05; ESCA subgroup vs controls: 163 ± 183 LCUs vs 218 ± 134 LCUs; P > 0.05). Similarly, there was no correlation between LCU scores and overall time from cardiac arrest (P > 0.05) nor between LCU score vs time from cardiac arrest for each of the 2 subgroups (USCA time from SCA vs LCU score, P > 0.05; ESCA time from SCA vs LCU score, P > 0.05).

Discussion

The main purpose of this exploratory study was to investigate the potential role of life stress in SCA events. Half of SCA and SCD among younger individuals remain unexplained despite extensive investigation. Stress has been shown previously to precede cardiac events and psychosocial factors including distress, anxiety, depression, and life dissatisfaction have been connected with increased risk for SCD and stroke. We investigated whether SCA survivors had elevated life stress in the year before SCA. There was no significant difference between SLEs measured as LCUs between the SCA group and their age- and sex-matched control participants, which was unexpected. We expected SCA survivors to have experienced more SLEs leading up to their cardiac arrest compared with age- and sex-matched control participants because previous reports indicate that stress influences cardiac health. The result was surprising and could be because of the limitations of this study as outlined in the Limitations. The critical relationship between life stress and the heart is perhaps most effectively illustrated by Takotsubo syndrome, which is classically triggered by acute emotional stressors, such as the loss of a loved one. A significant increase in myocardial infarction incidence is established around potentially stressful times of the year, especially Mondays, Christmas and New Year’s, and spring daylight savings.

\[
\text{Table 1. Demographic descriptors and circumstance of SCA group participants} \\
\begin{array}{|c|c|}
\hline
\text{Characteristic} & \text{n} & \% \\
\hline
\text{Unexplained SCA subgroup} & 22 & 61 \\
\text{Explained SCA subgroup} & 14 & 39 \\
\text{Sex} & & \\
\text{Male} & 18 & 50 \\
\text{Female} & 18 & 50 \\
\text{Age at cardiac arrest, years} & & \\
\text{11-18} & 2 & 6 \\
\text{19-22} & 2 & 6 \\
\geq 23 & 32 & 89 \\
\text{Time of day of SCA} & & \\
\text{Morning} & 14 & 39 \\
\text{Afternoon} & 8 & 22 \\
\text{Evening} & 6 & 17 \\
\text{Night} & 2 & 6 \\
\text{Unknown} & 6 & 17 \\
\text{Setting of SCA event} & & \\
\text{Home} & 14 & 39 \\
\text{Public place} & 14 & 39 \\
\text{School} & 2 & 6 \\
\text{Other} & 5 & 14 \\
\text{Unknown} & 1 & 3 \\
\text{Level of activity} & & \\
\text{Sleep} & 2 & 6 \\
\text{Rest} & 12 & 33 \\
\text{Mildly active} & 6 & 17 \\
\text{Moderately active} & 4 & 11 \\
\text{Vigorously active} & 3 & 8 \\
\text{Exercise} & 7 & 19 \\
\text{Unknown} & 2 & 6 \\
\text{Neurological damage from SCA} & & \\
\text{No damage} & 18 & 50 \\
\text{Yes, but it went away} & 6 & 17 \\
\text{Yes, and it hasn’t affected my life} & 6 & 17 \\
\text{Yes, and it has changed my life a lot} & 5 & 14 \\
\text{Unknown} & 1 & 3 \\
\text{SCA witnessed by bystanders} & & \\
\text{Yes} & 33 & 92 \\
\text{No} & 2 & 6 \\
\text{Unknown} & 1 & 3 \\
\text{CPR performed by bystander} & & \\
\text{Yes} & 29 & 81 \\
\text{No} & 3 & 8 \\
\text{Unknown} & 4 & 11 \\
\text{AED used by bystander} & & \\
\text{Yes} & 9 & 25 \\
\text{No} & 21 & 58 \\
\text{Unknown} & 6 & 17 \\
\hline
\end{array}
\]

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; SCA, sudden cardiac arrest.

\[
\text{Table 2. Commonly reported stressful life events} \\
\begin{array}{|c|c|}
\hline
\text{SCA group} & \text{n} & \% \\
\hline
\text{Change in work responsibilities} & 14 & 39 \\
\text{Change in work hours} & 12 & 33 \\
\text{Major decision about future} & 11 & 31 \\
\text{Vacation} & 11 & 31 \\
\text{Control group} & & \\
\text{Vacation} & 20 & 56 \\
\text{Change in work responsibilities} & 12 & 33 \\
\text{Change in work hours} & 11 & 31 \\
\text{Gain relationship} & 8 & 22 \\
\hline
\end{array}
\]

SCA, sudden cardiac arrest.
events, such as extreme threats to personal safety or hearing of a loved one’s death, have also been reported.22 Phobic anxiety has been linked to CHD and SCD in men and women, and additional psychosocial factors such as distress, anxiety, depression, and life dissatisfaction have been connected with increased risk for SCD and stroke.9,11,12

The lower rates of life stress in individuals from the ESCA group compared with the USCA subgroup complemented the findings from the study by Lane et al. In their study, a significantly greater number of the IVF survivors experienced moderate or severe psychological stress before their cardiac event compared with the CHD patients.13 They compared IVF survivors and CHD patients who had survived acute myocardial infarction or angina. The study by Lane et al. provided evidence for psychological stress playing a role in USCA, but reliance on participants’ perceptions of the stressful events left room for memory error and bias especially without using a proper control group.

In the current study, we observed that mornings were the most common time individuals experienced SCA. This finding aligns with the robust body of literature that identify a circadian pattern of SCA incidence. A morning peak in SCA occurrence has been reported in cohort studies and prospective studies,23-26 although the exact mechanisms for this circadian variation is still not well understood. However, some recent studies have noted a loss of morning peak, possibly because of the shifting sleep patterns.27 Alternatively, the higher LCU scores in the USCA group could be attributed to the unexplained nature of their SCA and merits further investigation.

The connection between stress and cardiac events likely lies with the ANS. Ventricular fibrillation is a common cause of SCD, and cardiac autonomic function might be an important factor in setting the arrhythmic threshold.28,29 Psychosocial factors like stress might affect arrhythmic risk by altering the sympathetic-parasympathetic balance.30 This imbalance could create an unstable cardiac state with increased risk for deadly arrhythmias, even in ostensibly healthy individuals. Although what exactly disposes individuals without an identified etiology to deadly arrhythmias is likely multifactorial; our findings suggest a role for environmental factors including chronic life stress.

**Limitations**

Reliability of participants’ responses on SLE checklists decreases as the recall period increases.31 Although the recall period between the USCA and ESCA groups did not differ, we are limited by the accuracy of individuals’ retrieval. Additionally, an individual’s current state affects how they interpret past events and can distort memories, even if the memory prompt asked is considered objective.31,32 Our study design attempted to limit this bias by using an objective list and scoring system for SLEs, but as already noted, even objective measures are susceptible to participants’ biases. It is possible that those who lack a proper explanation for their sudden cardiac event are open to alternative explanations, such as stress, might recall stressful events more easily, might report greater stress than they were actually experiencing, or believe stressful events are worth reporting. Also, our control group might not be a true representation of the general population and perhaps were more cognizant of stress in their lives and sought participation after exposure to our advertising materials. Furthermore, because of the small sample size, we were unable to determine possible associations between other confounders such as lifestyle (exposure to illicit substances, alcohol, stimulant drinks, participation in vigorous sports, etc) and onset of SCA in this cohort.
Conclusions

Although there were no significant differences in SLEs between the SCA group and age- and sex-matched control group, the unexplained nature of the SCA might give rise to an elevated life stress score or alternatively SLEs might predispose certain individuals to SCA, particularly those in whom a cardiac etiology is not identified. The ANS is a likely system that mediates the interaction between stress and SCA. Further, larger scale, prospective studies using more robust techniques are warranted to determine the association between potential confounders such as lifestyle for those whose SCA remains unexplained. The relationship between stress, the ANS, and other confounders such as lifestyle and SCA merits further investigation.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis 2008;51:213-28.
2. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. N Engl J Med 2016;374:2441-52.
3. Ringard B. Sudden cardiac death: a nationwide cohort study among the young. Dan Med J 2016;63:B5321.
4. Lahrouchi N, Raju H, Lodder EM, et al. Utility of post-mortem generic testing in cases of sudden arrhythmic death syndrome. J Am Coll Cardiol 2017;69:2134-45.
5. Krahn AD, Healey JS, Chauhan V, et al. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). Circulation 2009;120:278-85.
6. Franciosi S, Perry FKG, Roston TM, et al. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. Auton Neurosci 2017;205:1-11.
7. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res 2014;114:1004-21.
8. Gilmour RF. Life out of balance: the sympathetic nervous system and cardiac arrhythmias. Cardiovasc Res 2001;51:625-6.
27. Ni YM, Rusinaru C, Reinier K, et al. Unexpected shift in circadian and septadian variation of sudden cardiac arrest: the Oregon Sudden Unexpected Death Study. Heart Rhythm 2019;16:411-5.

28. Meredith IT, Broughton A, Jennings GL, et al. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. N Engl J Med 1991;325:618-24.

29. Barron HV, Lesh MD. Autonomic nervous system and sudden cardiac death. J Am Coll Cardiol 1996;27:1053-60.

30. Sgoifo A, De Boer SF, Buwalda B, et al. Vulnerability to arrhythmias during social stress in rats with different sympathovagal balance. Am J Physiol 1998;275:H460-6.

31. Dohrenwend BP. Inventorying stressful life events as risk factors for psychopathology: toward resolution of the problem of intracategory variability. Psychol Bull 2006;132:477-95.

32. Southwick SM, Morgan CA 3rd, Nicolaou AL, et al. Consistency of memory for combat-related traumatic events in veterans of Operation Desert Storm. Am J Psychiatry 1997;154:173-7.