Contemporary Clinical Trials Communications 37 (2024) 101252

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Sudden cardiac death and post-traumatic stress disorder: More research is needed☆

ARTICLE INFO

Keywords
Communication
Heart
Death
Sudden
Laboratory
Healthcare
Quality

ABSTRACT

Sudden cardiac death is an event which is traumatic for the individuals, who survive and their relatives. Very few research is concentrated on these survivals and the symptoms arising from post-traumatic stress disorders. In this journal, Birk et al. report on twelve eligible cardiac arrest survivors contacted, of which ten were enrolled. The authors report on heart rate variability biofeedback, which is, according to the authors, a promising non-pharmacologic approach for reducing anxiety. The intervention was comprised of daily sessions of diaphragmatic paced breathing and real-time monitoring of cardiac activity guided by a smartphone app and heart rate monitor. Ninety percent of the patients had good scores for intervention acceptability and feasibility, and 80 % reported good scores for its appropriateness and usability for reducing fear. Trait anxiety decreased significantly pre-to-post intervention. We comment on this finding highlighting other studies targeting sudden cardiac death and supporting that more research with very large randomized clinical trials is needed.

Sudden cardiac death (SCD) includes a series of events that may culminate the patients may either die or survive [1]. Patients may often receive an implantable cardioverter defibrillator (ICD) and can go psychologic therapy for emotional issues, which may culminate into a posttraumatic stress disorder (PTSD). PTSD may also affect ipsigenerational or intergenerational relatives. The ICD monitors cardiac arrhythmias. It treats such events using either anti-tachycardia cardio pacing or high-energy shock. In SCD survivors, there is often a very complex assembly of fears, which includes fear of death, fear of recurrent arrhythmias, fear of malfunctioning of the device among others [2]. Despite the level of psychological alterations have been reported in some studies, probably incompletely in the opinion of several cardiac scientists and public health experts, there is an obvious tendency of these patients to develop not only anxiety but also depression. Most probably, they can develop an iterative and cumbersome cycle of these two psychological issues (anxiety and depression), which can culminate in life-threatening events. In cardiology, it is well known that ICD patients may experience anxiety, depression, but also panic attacks. The survival after life-threatening events in ICD patients may depend on the individuals themselves, but also on the relatives and the support, the public health may provide. According to international criteria, the diagnosis of PTSD requires the response of the patient being associated with panic and aching recalling of the SCD event, the incorporation of hypervigilant behavior and/or avoidance behavior [3]. PTSD in these very problematic cardiologic patients is not trivial despite only approximately one fifth of these patients may experience symptoms that fulfilled PTSD criteria [4]. Indeed, a component needs to be fully explored and concerns with the fact that PTSD may increment the mortality rate in these individuals.

In this journal, Birk et al. report on twelve eligible cardiac arrest survivors contacted, of which ten were enrolled. The authors report on Heart Rate Variability Biofeedback (HRVB), which is, according to the authors, a promising non-pharmacologic approach for reducing anxiety. The intervention was comprised of daily sessions of diaphragmatic paced breathing coupled with real-time monitoring of cardiac activity guided by a smartphone application and continuous heart rate monitor. Ninety percent of the patients had good scores for intervention acceptability and feasibility. Four fifths of them reported good scores for its appropriateness and usability for reducing fear. There were no changes in negative affect or interoceptive fear (i.e., misappraisal of body sensations triggering emotional and physiological reactions). They suggest that a phase 2 randomized controlled trial evaluating the efficacy of HRVB on cardiac patients' psychological distress, health behaviors, and autonomic dysfunction may be warranted. This study despite the limitations of an extremely low number of patients, has tremendous potentiality to instigate further studies of PTSD or near PTSD-like disorders or symptoms in SCD survivors independently if they received an ICD monitoring or not. Of note, it does not seem that details of the ethnics of the individuals in Birk et al. study have been recorded (**REF**).

Both Hamner et al. [5] and Ansari and Arbabi [6] found that implantation of ICD is not devoid of psychological threats or fears. ICD decreases the mortality rate from serious cardiovascular diseases, but can also affect the quality of life and increments the chance of PTSD due to the previous event, which ultimately evolve to cardiogenic shock [4]. Takotsubo cardiomyopathy (broken-heart syndrome) in SCD has also been reported [7–9].

☆ Supported **by** Women and Children's Research Institute, Edmonton, Alberta, Canada.

https://doi.org/10.1016/j.conctc.2023.101252
Received 13 July 2023; Accepted 22 December 2023
Available online 8 January 2024

SADS and sudden unexplained death (SUD) are often used interchangeably [1,10–12]. Despite some authors indicate that SUD and, probably SUDI (sudden unexplained death of infancy) may contain some pathologic data of "unknown" significance, terminology may need some fine-tuning in the future. Histological patterns of SCD events include mild ventricular dilatation, myocardial hypertrophy, myocardial fibrosis, subendocardial fibrosis, and mild coronary atherosclerosis or coronary artery changes other than frank metabolic disorders, which are more common in youth [13–21]. Genetic investigations are key to identify the SCD patients and in about half of these cases congenital ion channelopathies, including, long QT syndrome (LQTS), Brugada syndrome, and catecholamine-induced polymorphic ventricular tachycardia (CPVT), have been found. SADS epidemiology is a puzzle, because various factors, including the national geographic place, ethnics, patient population (ages, sex, and athletes vs. non-athletes), data collection methodology, and the extent of post mortem investigation. In fact, SADS varies between general population, athletes, and military personnel. In 2017, Kong et al. performed a meta-analysis of published investigations on SCD. They found substantial data addressing that Asians had the highest overall mean allele frequencies of *NOS1AP* (0.36 %, 95 % CI: 0.30, 0.43; $P < 0.001$) and *SCN5A* frequencies (0.17 %, 95 % CI: 0.07, 0.27, $P = 0.001$), which are two genes associated with SCD [10]. Caucasians had the highest *KCNH2* frequency (0.21 %,95 % CI: 0.16, 0.25; $P < 0.001$), while Hispanics the highest *KCNQ1* frequency (0.16 %) suggesting that genetic differences may underground the predisposition to cardiac death in several cohorts [10]. The analysis of the Exome Aggregation Consortium also provided consistent data in agreement with the meta-analysis [10]. Allele frequencies were averaged by weight, and pooled values were calculated by inverse variance. Fixed-effects and random-effects models were used to pool effect sizes within each study and across different studies, respectively. Moreover, we used sequenced genomic data from the Exome Aggregation Consortium to compare allele frequencies between different ethnicities. Overall, Asians carried the most alleles of genes associated with sudden cardiac death. The meta-analysis reveals significant differences in allele distribution of channelopathy-associated genes among different ethnic groups. Sudden cardiac arrhythmia (SCA) may be the final event in a few conditions, although ventricular fibrillation is ascribed as the final categorical event and molecular autopsies are often not offered worldwide.

SCD survivals are more vulnerable to ventricular arrhythmias due to the recall of stressful memories and hyperstimulation of the autonomic nervous system [22]. It is appropriate to perform very large and multicentric randomized clinical trials to accurately determine the impact of any treatment on PTSD in ICD patients and SCD survivors. Cognitive behavioral interventions can improve the adherence of medical treatment on psychological symptoms efficaciously and effectively. In most of these patients, it has been observed that the Hamilton Anxiety Scale or Spielberg Anxiety Scale may not be optimal.

Armand et al. targeted 141 patients and 97 partners evaluating acute traumatic stress at three weeks and PTSD symptoms at 3 months and 1 year following cardiac resuscitation [23]. They used the Impact of Event Scale (IES) categorizing as clinical severe PTSD patients who had an IES higher than 26 at 3 months and 1 year. They found a high rate of acute traumatic stress, which was positively associated with high rate of PTSD at 3 months and 1 year in both patients and partners, and the stress was higher in women than men. Habibović et al. (2017) studied 249 patients with ICD being the majority males [24]. Laten Class analyses identified four classes of PTSD [25]. An increased vulnerability for posttraumatic stress was identified in patients with younger age, harboring increased scores of depressions at baseline, and type D personality. It seems that ICD in young adults with genetic heart disease can harbor psychological disturbances, including depression, anxiety, and posttraumatic stress, which have been related to the ICD implantation and subsequent cardiac arrests [26]. This data may suggest that a genetic workup for the most important genes associated with SCD or channelopathies needs to be implemented in randomized clinical trials.

In conclusion, we truly hope that larger randomized clinical trials will be a target in cardiology and more appropriate training programs involving cognitive-behavioral interventions will be developed for trainees and fellows in the nearest future.

Author contributions

Sergi C conceived the study, drafted the manuscript, and approved the final version of the article.Supported

Conflict-of-interest statement

The author has no conflict of interest to declare in a relationship with the topic discussed in this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] C.M. Sergi, Sudden cardiac death and ethnicity, CMAJ (Can. Med. Assoc. J.) 191 (45) (2019) E1254, https://doi.org/10.1503/cmaj.73297.
[2] G.L. Fricchione, L.C. Vlay, S.C. Vlay, Cardiac psychiatry and the management of malignant ventricular arrhythmias with the internal cardioverter-defibrillator, Am. Heart J. 128 (5) (1994) 1050–1059, https://doi.org/10.1016/0002-8703(94)90610-6.
[3] R. Yehuda, Post-traumatic stress disorder, N. Engl. J. Med. 346 (2) (2002) 108–114, https://doi.org/10.1056/NEJMra012941.
[4] K.H. Ladwig, J. Baumert, B. Marten-Mittag, C. Kolb, B. Zrenner, C. Schmitt, Post-traumatic stress symptoms and predicted mortality in patients with implantable cardioverter-defibrillators: results from the prospective living with an implanted cardioverter-defibrillator study, Arch. Gen. Psychiatr. 65 (11) (2008) 1324–1330, https://doi.org/10.1001/archpsyc.65.11.1324.
[5] M. Hamner, N. Hunt, J. Gee, R. Garrell, R. Monroe, PTSD and automatic implantable cardioverter defibrillators, Psychosomatics 40 (1) (1999) 82–85, https://doi.org/10.1016/s0033-3182(99)71277-6.
[6] S. Ansari, M. Arbabi, Cognitive behavioral therapy (CBT) in a patient with implantable cardioverter defibrillator (ICD) and posttraumatic stress disorder (PTSD), Iran. J. Psychiatry 9 (3) (2014) 181–183.
[7] H. Keller, U. Neuhold, F. Weidinger, E. Gatterer, C. Stollberger, K. Huber, J. Finsterer, Takotsubo as initial manifestation of non-myopathic cardiomyopathy due to the titin variant c.1489G, T. Medicines (Basel) 5 (3) (2018), https://doi.org/10.3390/medicines5030080.
[8] K. Kraft, M. Graf, M. Karch, R. Felberbaum, Takotsubo syndrome after cardiopulmonary resuscitation during emergency cesarean delivery, Obstet. Gynecol. 129 (3) (2017) 521–524, https://doi.org/10.1097/AOG.0000000000001850.
[9] A.A. Manolis, T.A. Manolis, H. Melita, A.S. Manolis, Takotsubo syndrome and sudden cardiac death, Angiology 74 (2) (2023) 105–128, https://doi.org/10.1177/00033197221105757.
[10] T. Kong, J. Feulefack, K. Ruether, F. Shen, W. Zheng, X.Z. Chen, C. Sergi, Ethnic differences in genetic ion channelopathies associated with sudden cardiac death: a systematic review and meta-analysis, Ann. Clin. Lab. Sci. 47 (4) (2017) 481–490. https://www.ncbi.nlm.nih.gov/pubmed/28801377.
[11] A. Perez-Serra, R. Toro, G. Sarquella-Brugada, D. de Gonzalo-Calvo, S. Cesar, E. Carro, V. Llorente-Cortes, A. Iglesias, J. Brugada, R. Brugada, O. Campuzano, Genetic basis of dilated cardiomyopathy, Int. J. Cardiol. 224 (2016) 461–472, https://doi.org/10.1016/j.ijcard.2016.09.068.
[12] H. Zhang, A. Viveiros, A. Nikhanj, Q. Nguyen, K. Wang, W. Wang, D.H. Freed, J. C. Mullen, R. MacArthur, D.H. Kim, W. Tymchak, C.M. Sergi, Z. Kassiri, S. Wang, G. Y. Oudit, The Human Explanted Heart Program: a translational bridge for cardiovascular medicine, Biochim. Biophys. Acta, Mol. Basis Dis. 1867 (1) (2021), 165995, https://doi.org/10.1016/j.bbadis.2020.165995.
[13] M. Ballantyne, B. Chiu, C.M. Sergi, Sanfilippo syndrome type A: early cardiac involvement of two patients with cardiac manifestations, Cardiovasc. Pathol. (2022), https://doi.org/10.1016/j.carpath.2022.107430.
[14] C. Sergi, EPAS 1, congenital heart disease, and high altitude: disclosures by genetics, bioinformatics, and experimental embryology, Biosci. Rep. 39 (5) (2019), https://doi.org/10.1042/BSR20182197.
[15] S.S. Sakamuri, A. Takawale, R. Basu, P.W. Fedak, D. Freed, C. Sergi, G.Y. Oudit, Z. Kassiri, Differential impact of mechanical unloading on structural and nonstructural components of the extracellular matrix in advanced human heart

failure, Transl. Res. 172 (2016) 30–44, https://doi.org/10.1016/j.trsl.2016.02.006.
[16] Y.R. Hsu, H. Yogasundaram, N. Parajuli, L. Valtuille, C. Sergi, G.Y. Oudit, MELAS syndrome and cardiomyopathy: linking mitochondrial function to heart failure pathogenesis, Heart Fail. Rev. 21 (1) (2016) 103–116, https://doi.org/10.1007/s10741-015-9524-5.
[17] N. Parajuli, L. Valtuille, R. Basu, K.S. Famulski, P.F. Halloran, C. Sergi, G.Y. Oudit, Determinants of ventricular arrhythmias in human explanted hearts with dilated cardiomyopathy, Eur. J. Clin. Invest. 45 (12) (2015) 1286–1296, https://doi.org/10.1111/eci.12549.
[18] L. Valtuille, I. Paterson, D.H. Kim, J. Mullen, C. Sergi, G.Y. Oudit, A case of lamin A/C mutation cardiomyopathy with overlap features of ARVC: a critical role of genetic testing, Int. J. Cardiol. 168 (4) (2013) 4325–4327, https://doi.org/10.1016/j.ijcard.2013.04.177.
[19] D.R.D. Cave, W. Bahitham, A. Chan, C. Sergi, I. Adatia, Mitochondrial DNA depletion syndrome-an unusual reason for interstage attrition after the modified stage 1 Norwood operation, Congenit. Heart Dis. 8 (1) (2013) E20–E23.
[20] S. Mohammed, W. Bahitham, A. Chan, B. Chiu, F. Bamforth, C. Sergi, Mitochondrial DNA related cardiomyopathies, Front. Biosci. 4 (2012) 1706–1716. https://www.ncbi.nlm.nih.gov/pubmed/22201986.
[21] B. Chiu, C. Sergi, Dilated cardiomyopathy: etio-morphologic investigation, Front. Biosci. 2 (2010) 112–116. https://www.ncbi.nlm.nih.gov/pubmed/20036933.
[22] S.F. Sears Jr., J.B. Conti, Quality of life and psychological functioning of icd patients, Heart 87 (5) (2002) 488–493, https://doi.org/10.1136/heart.87.5.488.
[23] Armand S, Wagner MK, Ozenne B, Verbunt J, Sep SJS, Berg SK, Knudsen GM, Stenbæk DS. Acute traumatic stress screening can identify patients and their partners at risk for posttraumatic stress disorder symptoms after a cardiac arrest: a multicenter prospective Cohort study. J Cardiovasc Nurs. 2022; 37(4):394-401. doi: 10.1097/JCN.0000000000000829. Epub 2021 Aug 19. PMID: 37707973.
[24] M. Habibović, J. Denollet, S.S. Pedersen, Posttraumatic stress and anxiety in patients with an implantable cardioverter defibrillator: trajectories and vulnerability factors, Pacing Clin. Electrophysiol. 40 (7) (2017) 817–823, https://doi.org/10.1111/pace.13090.
[25] S.B. Campbell, B. Trachik, S. Goldberg, T.L. Simpson, Identifying PTSD symptom typologies: a latent class analysis, Psychiatr. Res. 285 (2020), 112779, https://doi.org/10.1016/j.psychres.2020.112779.
[26] J. Ingles, T. Sarina, N. Kasparian, C. Semsarian, Psychological wellbeing and posttraumatic stress associated with implantable cardioverter defibrillator therapy in young adults with genetic heart disease, Int. J. Cardiol. 168 (4) (2013) 3779–3784, https://doi.org/10.1016/j.ijcard.2013.06.006.

Consolato M. Sergi
Anatomic Pathology Division, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada
Department of Laboratory Medicine and Pathology, Stollery Children's Hospital, Edmonton, AB, Canada
E-mail addresses: csergi@cheo.on.ca, sergi@ualberta.ca.