Send Orders for Reprints to reprints@benthamscience.ae

REVIEW ARTICLE

Electrophysiologic Considerations After Sudden Cardiac Arrest

Prakash Suryanarayana, Hyon-he K. Garza, Jacob Klewer and Mathew D. Hutchinson*

Division of Cardiovascular Medicine, Department of Medicine, University of Arizona College of Medicine, Tucson, AZ, USA

ARTICLE HISTORY

Received: February 01, 2018
Revised: March 31, 2018
Accepted: April 25, 2018

DOI: 10.2174/1573403X14666180507164443

Abstract: ***Background*:** Sudden Cardiac Death (SCD) remains a major public health concern, accounting for more than 50% of cardiac deaths. The majority of these deaths are related to ischemic heart disease, however increasingly recognized are non-ischemic causes such as cardiac channelopathies. Bradyarrhythmias and pulseless electrical activity comprise a larger proportion of out-of-hospital arrests than previously realized, particularly in patients with more advanced heart failure or noncardiac triggers such as pulmonary embolism. Patients surviving Sudden Cardiac Arrest (SCA) have a substantial risk of recurrence, particularly within 18 months post event. The timing of tachyarrhythmias complicating acute infarction has important implications regarding the likelihood of recurrence, with those occurring within 48 hours having a more favorable long-term outcome. In the absence of a clear reversible cause, implantable cardioverter defibrillators remain the mainstay in the secondary prevention of SCD. Post defibrillation electromechanical dissociation is common in patients with cardiomyopathy and can lead to SCD despite successful defibrillation of the primary tachyarrhythmia. Antiarrhythmic agents are highly effective in preventing recurrent arrhythmias in specific diseases such as the congenital long QT syndrome.

***Conclusion*:** Catheter ablation is used most commonly to prevent recurrent ICD therapies in patients with structural heart disease-related ventricular arrhythmias, however recent publications have shown substantial benefit in other entities such as idiopathic ventricular fibrillation.

Keywords: Electrophysiologic considerations, cardioverter defibrillators (ICDs), coronary artery disease, mortality, sudden cardiac arrest, survival.

1. INTRODUCTION

Sudden Cardiac Death (SCD) remains a major public health concern. With regard to years of potential life lost, SCD clearly outnumbers individual cancer-related deaths both among men and women in the US [1]. The US incidence of SCD in 2015 was estimated at 350,000 [2], accounting for up to 50% of all cardiac deaths. Bystander CPR and use of AEDs have only modestly improved the survival to hospital discharge after Sudden Cardiac Arrest (SCA), currently estimated at 6%. Although several conditions can result in SCD, coronary artery disease still remains the major cause in almost 80% of the cases [3]. Implantable Cardioverter Defibrillators (ICDs) have significantly reduced the Sudden Cardiac Death (SCD) related mortality in several clinical trials which included both ischemic and non-ischemic populations [4]. Historically, the ACC/AHA guidelines have uniformly utilized Left Ventricular Ejection Fraction (LVEF) as the major criterion for risk stratification in primary prevention populations [5]. There has been an increasing awareness that the LVEF alone may not predict the SCD risk in general population accurately [6, 7] and consequently, there are efforts to develop novel risk prediction models. LVEF is even less effective in women as a predictor of SCD compared to men [8]. Incorporation of other parameters such as imaging or the cumulative "electrical risk score" may potentially improve the predictive ability of the scoring systems [9].

In this review, we discuss electrophysiologic management in SCA survivors, including both pharmacological and invasive therapies.

2. EPIDEMIOLOGY OF POST-CARDIAC ARREST

Sudden Cardiac Arrest (SCA) generally refers to the cessation of cardiac activity with hemodynamic collapse and progression to Sudden Cardiac Death (SCD) if corrective measures are not initiated rapidly. Epidemiologic studies of SCA/SCD are difficult to interpret due to 1) inconsistencies in specific criteria defining these endpoints; 2) uncertainties regarding the underlying pathophysiology and 3) extrapolating population data to at-risk individuals. In adults over 35, the incidence of SCD is 1 in 1,000 people per year, and this risk increases steadily beyond the age of 70 in both males

*Address correspondence to this author at the Sarver Heart Center, University of Arizona, 1501 N. Campbell Avenue, 4142B, Tucson, AZ 85724, USA; Tel: (520) 626-8615; Fax: (520) 626-0964;
E-mail: MathewHutchinson@shc.arizona.edu

1573-403X/18 $58.00+.00 © 2018 Bentham Science Publishers

and females. In addition to adults over 35, the incidence of SCD also peaks in infants less than 1, occurring at a surprisingly similar rate of 0.73 per 1,000 infants per year [10]. While athletes have also been classically associated with SCD, they represent only 5% of overall SCA cases. However, the SCD rate is proportionately higher in elite athletes such as NCAA Division 1 basketball players, where the incidence is 1 in 5,200 per year [11].

As previously mentioned, coronary artery disease is by far the most common etiology of SCD, accounting for up to 75-80% of cases. In the setting of coronary artery disease, SCD can occur during an acute coronary syndrome but is more likely to occur with chronic, stable coronary artery disease without an identifiable cardiac event. The majority of the remaining cases are due to cardiomyopathy, especially alcoholic, obesity-related and fibrotic, as well as genetic channelopathies such as the Long QT Syndrome (LQTS) or Brugada Syndrome (BrS) [12, 13]. Causes of SCD can also be classified based on the patient ages they are most commonly associated with. Since the prevalence of coronary artery disease increases with advancing age, it is no surprise that coronary artery disease is the most common cause of SCD in adults over age 35, followed by non-ischemic cardiomyopathy and valvular heart disease. In contrast, common causes of SCD in infants and adults less than 35 include myocarditis, hypertrophic cardiomyopathy, long/short QT syndrome, *etc*. [14].

3. CARDIAC ARREST MECHANISMS/PATHOPHYSIOLOGY AND ELECTROPHYSIOLOGIC ABNORMALITIES

Electrical mechanisms of SCD can be categorized into either tachyarrhythmia (VF, pulseless or sustained VT) or bradyarrhythmia-asystole (PEA or asystole) events. Typically, lethal tachyarrhythmias or bradyarrhythmias are the end result of a cascade of pathophysiologic abnormalities resulting from complex interactions between coronary vascular events, myocardial injury, variations in autonomic tone, and the metabolic and electrolyte state of the myocardium [15]. Up until recently, VT or VF was thought to be the underlying rhythm in 75% of out of hospital SCA cases, while the remaining 25% were caused by bradyarrhythmias or asystole. However, more recent studies suggest that PEA (19-23%) and asystole (50%) are more frequent compared to VT or VF, citing a decline in incidence to < 30% for VT or VF as the first recorded rhythm in out of hospital SCA [16-18].

The pathophysiologic mechanism of lethal ventricular tachyarrhythmias involves the concept of a triggering event combined with an underlying susceptible myocardium that acts as a "substrate", such as scarred myocardium from previous injury or chronically hypertrophied muscle. The most common scenario, especially in the setting of coronary artery disease, is an acute ischemic event leading to changes in the metabolic and/or electrolyte state of the myocardium. These changes result in immediate mechanical, biochemical and electrical dysfunction of cardiac muscle, which creates the potential for lethal arrhythmias such as VF to occur via multiple uncoordinated re-entrant pathways [14]. Of note, the specialized conducting tissue of the heart is more resistant to the effects of acute ischemia compared to the working myocardium, which results in less intense and delayed onset electrophysiologic consequences [14].

Pulseless Electrical Activity (PEA) has primary and secondary forms and is characterized by the presence of organized cardiac electrical activity in the absence of effective mechanical function. Secondary PEA is usually caused by a mechanical obstruction such as a massive PE or cardiac tamponade that abruptly prevents cardiac venous return. The primary form of PEA is not as well understood, but it involves "failure of electromechanical coupling" in the absence of obvious secondary mechanical factors as listed above. Primary PEA most often occurs in the setting of end-stage heart disease, but can also be seen in patients with acute ischemia or after electrical resuscitation from prolonged SCA [19]. Similar to SCD from ventricular arrhythmias, the general mechanism of PEA involves a combination underlying myocardial disease with metabolic derangements and/or global ischemia. Specific mechanisms for failure of electromechanical coupling (abnormal intracellular Ca^{2+}, intracellular acidosis or ATP depletion) have been postulated, but more research must be done to prove these mechanisms [19].

4. CLINICAL PROFILE OF SURVIVORS OF SCD

As has already been noted, the most common underlying etiology for the SCD is coronary artery disease, seen in approximately 80% of out of hospital cardiac arrests in the US [3]. Analysis of the CASPER registry including 63 survivors of cardiac arrest with normal EF and no obvious heart disease failed to reveal the cause of SCD despite extensive studies in 44% of the patients [20]. Long QT syndrome was noted to be the cause in 23%, catecholaminergic polymorphic VT in 23%, RV dysplasia in 17%, early repolarization in 14%, coronary spasm in 11%, Brugada syndrome in 9%, and myocarditis in 3%.

Cardiac arrests associated with acute MI are classified as either primary or secondary. Primary cardiac arrests are due to electrical events that are not associated with the hemodynamic consequences of acute MI. These patients typically are stabilized with prompt revascularization and do not pose long-term arrhythmic risk, provided there are no recurrent ischemic events. On the contrary, secondary cardiac arrests are related to hemodynamic dysfunctions resulting from the acute coronary event and the outcome in these situations is determined by the hemodynamic status of the patients [14]. Although many patients have recurrent ventricular arrhythmias within the first 48 hours and their response to antiarrhythmic agents is variable, the risk of recurrent cardiac arrest is usually in the range of 10-20%. Unfortunately, mortality rate approaches 50% in those who have recurrent arrhythmias. There is a high incidence of new or preexisting AV or intraventricular conduction abnormalities among those with recurrent cardiac arrest and in-hospital arrhythmic deaths following out of hospital resuscitation is only 5-10% [14].

Those who survive SCD and have non-coronary etiology have a good chance of long-term survival if they have a good neurological recovery. When treated according to the existing guidelines for the underlying condition, their long-term survival probability tends to be proportionate to the extent of disease, age and gender [21-24]. A detailed workup is impor-

tant to determine the underlying cause of SCD and to plan the subsequent therapy. Prevention of recurrent events (secondary prevention) in survivors of cardiac arrest or pulseless VT and other life-threatening tachycardias is of paramount importance.

5. EARLY ELECTROPHYSIOLOGIC MANAGEMENT IN SCA SURVIVORS

Survivors of SCA fall under the highest risk group for recurrent SCD (20-40% recurrence). Although 30% of all SCD events occur in the highest risk subgroup, an absolute number of deaths is relatively low due to the group being small, thus limiting the impact of intervention [14]. Recurrence is highest during the first 6-18 months post index event [14]. Some of the predictors of recurrent cardiac arrest in the cardiac arrest survivors include presence of extensive CAD, prior MI (within the past 6 months), LV dysfunction and chronic heart failure, high B type Natriuretic Peptide (BNP) levels, ventricular electrical instability (complex ventricular ectopy) and abnormalities on Signal-averaged ECG (SAECG) [14].

Upon restoration of spontaneous circulation after cardiac arrest, patients may continue to experience dysrhythmias on arrival to the hospital. The goal of care is to maintain hemodynamic and electrical stability as well as to investigate the possible etiology of sudden cardiac death. A 12-lead Electrocardiogram (ECG) should be obtained as it will give information about possible ischemic injury or abnormalities in electrical conduction. One must exercise caution in ECG interpretation after cardiac arrest due to ischemia-mediated changes in ventricular depolarization and/or repolarization.

Patients with the suspected ischemic disease should be taken emergently to the cardiac catheterization lab. Upon further assessment, supportive care should be offered to prevent further and reverse any damage to the central nervous and cardiovascular systems. There is a growing use of targeted temperature management to preserve brain function, and arrhythmias can occur in this setting due to alteration of cardiac channel function. Bradycardia is commonly seen during therapeutic hypothermia; however adequate tissue perfusion is generally maintained *via* peripheral vasoconstriction. This leads to an active diuresis leading to fluctuations in volume and electrolytes. Disturbances in electrolyte balance, notably potassium, can lead to poor resuscitative efforts and may promote further arrhythmias. Hypokalemia, hypomagnesemia, and hypocalcemia are the most closely associated with cardiac arrest [25].

While monitoring in the intensive care unit, survivors of sudden cardiac death may continue to exhibit ventricular arrhythmias within 48 hours of initial hospitalization [26]. Antiarrhythmic agents should be considered early in the post-cardiac arrest phase to prevent recurrent arrhythmias.

6. PREVENTION OF RECURRENT SCA

6.1. Role of Noninvasive Risk Stratification

Contemporary trial data has informed the use of ICD for primary prevention of SCD in patients with ischemic or nonischemic cardiomyopathy and an LVEF of 40% or less. Unfortunately, more 80% of those who experience out of hospital SCA lack contemporary ICD criteria at the time of their arrest. Age, smoking, hypertension, hyperlipidemia, diabetes and heredity are all established risk factors that play a role in estimating the risk of SCD secondary to coronary artery disease. Other risk factors such as diabetes mellitus, specific genetic profiles, and microvolt T wave alternans have shown modest value in predicting SCD in patients with known or suspected coronary artery disease [27]. Novel risk factors such as the presence of late gadolinium enhancement on cardiac MRI are associated with increased risk of SCD or aborted SCD [28].

6.2. Role of Invasive Risk Stratification

In the absence of antiarrhythmic therapy, tachyarrhythmias can be initiated during EP studies in 70-80% of resuscitated SCD patients. Arrhythmias induced in the EP lab include sustained monomorphic VT (36-51% of patients), VF, monomorphic or polymorphic VT degenerating into VF and non-sustained VT [29]. The ability to suppress the inducibility of a previously induced sustained ventricular tachyarrhythmia following pharmacological, ablative or surgical intervention is associated with a favorable long-term outcome during follow up [30-32]. Thus, EP study in these situations may have a role in risk stratification of the cardiac arrest survivors and also in predicting the long-term outcomes following a guided therapy. Regardless of the inducibility status, the survivors of SCD without definite identifiable reversible etiology remain at a higher risk for future events as shown in a follow-up the study of patients in MADIT II [33].

Invasive programmed stimulation study may particularly be of value in cardiac arrest survivors where transient ischemia was thought to be the inciting event and the LVEF is normal to only mildly reduced. Similarly, when there is a confusion regarding the reversibility of the triggering event, EP study may have a role in risk stratification. Results of the EP study can also be used for determining the appropriate type of device and for its programming in patients who are candidates for ICD therapy. However, in the contemporary era of ICDs, the role of EP study is limited.

6.3. Role of Implantable Defibrillators

For SCA survivors, implantable cardioverter-defibrillator placement should be strongly considered prior to hospital discharge, if no reversible cause is identified for the arrest (*e.g.* related to acute coronary ischemia). Three randomized trials have evaluated ICD implantation versus antiarrhythmic therapy in secondary SCA populations: AVID, CIDS, and CASH [34-36]. These trials included patients with both VF and unstable monomorphic VT. AVID, which randomized patients with EF<40% to ICD or antiarrhythmic drugs (96% received amiodarone), showed a significant reduction in total mortality compared to antiarrhythmic therapy though the majority of benefit was due to a reduction in arrhythmic death. A subgroup analysis from AVID also showed that the benefit if the ICD was seen exclusively in patients with LV EF <35%. The CIDS and CASH trials showed a numerical reduction in total mortality in ICD treated patients although the difference did not reach statistical significance. A smaller

randomized trial of 60 patients sought to compare the strategy of first-line ICD therapy versus "conventional" therapy in SCA survivors. In the 31 patients originally assigned to conventional therapy, 15 ultimately underwent ICD implantation. A subsequent meta-analysis of the aforementioned secondary prevention trials showed a significant 25% relative reduction in total mortality in ICD treated patients (7% absolute decrease) [37]. As was evident in the individual trials, the pooled analysis suggested that the dominant mechanism of ICD benefit was a reduction in arrhythmic death. Although ICDs have a shown high efficacy in ventricular defibrillation, arrhythmic deaths are present in up to 35% of secondary prevention ICD patients most commonly due to post-defibrillation electromechanical dissociation [38].

Careful attention to ICD programming is critical to avoid inappropriate shocks for atrial arrhythmias. Given the efficacy of anti-tachycardia pacing in termination of rapid monomorphic VT, ATP should be programmed to deliver therapy for arrhythmias above 200 bpm [39]. Since many episodes of VT terminate spontaneously, extending the duration for arrhythmia detection is useful in all patients. Antiarrhythmic agents can slow the cycle length of VT, and thus care should be exercised in device programming when these agents are initiated to avoid under-detection of VT. Antiarrhythmic agents can also have unpredictable effects on defibrillation threshold. Class 1C agents and amiodarone increase DFT, while sotalol and dofetilide decrease it [40].

SCA survivors with contemporary indications for cardiac resynchronization therapy should have appropriate device therapy at the time of their implantation [41]. The REVERSE and MADIT-CRT trials support the use of CRT-D devices compared to ICD alone as it was associated with decreased heart failure hospitalization, decreased total mortality, improved clinical heart failure symptoms, and enhanced myocardial remodeling [42]. In patients with more modest heart failure symptomatology enrolled in the MADIT-CRT trial, CRT provided the greatest benefit in those with QRS durations >150msec [42].

6.4. Role of Antiarrhythmic Agents

As described above, ICD implantation significantly reduces long-term mortality in SCA survivors compared to antiarrhythmic agents. Nonetheless, these drugs can provide a substantial quality of life benefit to patients with recurrent ventricular arrhythmias due to burden reduction. These agents were added in more than 20% of patients assigned to ICD in the above secondary SCA prevention trials. Furthermore, antiarrhythmic agents may be used as primary therapy for those patients in whom ICD therapy is either contraindicated or not preferred. A number of large heart failure cohorts have shown a substantial reduction in both total mortality and arrhythmic death with the use of beta-blockers [43]. Secondary prevention data from the non-randomized AVID cohort also showed a 53% reduction in mortality in patients who were treated with beta blockers alone [44].

The OPTIC trial randomized ICD patients with spontaneous or inducible ventricular arrhythmias to beta blockers alone, sotalol, or amiodarone plus a beta blocker [45]. Recurrent ICD therapies occurred in 39% of beta blocker treated patients at 1-year; sotalol reduced arrhythmias by 39% while amiodarone plus beta blockers reduced therapies by 73%. It is important to consider potential drug interactions and patient intolerances when prescribing class III antiarrhythmics; in OPTIC the discontinuation rates of sotalol and amiodarone at 1-year were 24% and 18% respectively [45]. Treatment with sotalol has also been associated with increased mortality in patients post infarction with LV ejection fraction <40% [46].

Class IC agents (*e.g.* flecainide, propafenone) should be avoided in patients with structural heart disease or coronary ischemia due to increased mortality as shown originally in the Cardiac Arrhythmia Suppression Trial [47]. Prior to its withdrawal from the CASH trial, patients assigned to propafenone demonstrated a 61% higher mortality rate compared to the ICD recipients [36].

Antiarrhythmic agents are also a first-line therapy in many of the inherited arrhythmia syndromes. Long QT syndrome patients treated with beta-blockers have a significant reduction in both syncopal episodes and total mortality [48]. Patients with catecholaminergic polymorphic ventricular tachycardia can have unpredictable and severe arrhythmia exacerbations in response to ICD therapies, and thus nonselective beta-blockade alone or in combination with flecainide in refractory cases are a mainstay of therapy to reduce arrhythmia burden [49]. Quinidine is effective in reducing arrhythmic burden in patients with Brugada syndrome or idiopathic ventricular fibrillation due to the early repolarization syndrome [50, 51].

6.5. Role of Catheter Ablation

Catheter ablation is increasingly utilized in a range of different arrhythmia phenotypes. Despite a lack of mortality benefit, ablation can be incredibly useful in reducing arrhythmia burden.

In patients with WPW syndrome and atrial fibrillation with very rapid conduction, successful ablation of the accessory pathway can prevent further recurrences. ACC/AHA guidelines give a class I recommendation for ablation in patients resuscitated from SCD caused by atrial flutter or atrial fibrillation with a rapid ventricular response in the absence of an accessory pathway [29].

Ablative strategy in patients without structural heart disease who often have single VT morphology can be curative. However, in patients with underlying structural heart disease (especially with prior MI), multiple VT morphologies are often seen. Increased morbidity and mortality have been demonstrated in ICD patients receiving not only shocks but also anti-tachycardia pacing therapies for ventricular arrhythmias [52, 53]. As highlighted above, many patients with structural heart disease-related VT treated with antiarrhythmic drugs have arrhythmia recurrence. Catheter ablation has been shown to reduce arrhythmia burden and ICD therapies by more than 75% in drug-refractory patients with both ischemic and nonischemic cardiomyopathy [54, 55]. Epicardial ablation is often required in nonischemic cardiomyopathy patients due to the complex distribution of arrhythmia substrate.

Although VT recurrence after ablation is associated with increased mortality [56], no randomized data to date has shown a mortality benefit after VT ablation in structural heart patients. Two recent randomized trials evaluated the benefit of early VT ablation (*i.e.* contemporaneous with ICD implantation) in patients with ischemic cardiomyopathy and spontaneous or inducible ventricular arrhythmias [57, 58]. Patients were randomized to ICD with or without a substrate-based VT ablation. In both trials, catheter ablation reduced the number of appropriate ICD therapies, the frequency of recurrent VT, and the time to first arrhythmia recurrence over a mean two-year follow-up. The rate of ablation complications was fairly low at 6% with no attributable procedure mortality. Although not powered to assess mortality as an endpoint, patients undergoing ablation in SMASH VT had a 47% reduction in total mortality at 2 years (9% *vs*. 17%, p=0.29) [57].

Isolated premature ventricular foci can trigger repetitive polymorphic VT or VF in patients with or without structural heart disease [59-61]. In many cases, the Purkinje network is inked to the site of PVC origin, though other sites in the RV and LV have been described. Catheter ablation targeting the triggering PVC has been shown in a number of studies to provide both acute and long-term arrhythmia suppression.

CONCLUSION

Electrophysiologists have an important role to play in victims of SCA. Whereas bystander CPR and AEDs have improved the survival to hospital discharge, electrophysiologic interventions, both pharmacological and device-based, have decreased arrhythmia recurrence and improved long-term survival. SCD continues to be a major public health concern, and currently available methods identify only the highest risk individuals. Future studies are needed to define patients at elevated risk for SCA who are not currently captured in contemporary models. Further refinements in catheter ablation techniques and technologies may supplant antiarrhythmic agents as the first line therapy for many arrhythmia syndromes.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Stecker EC, Reinier K, Marijon E, *et al*. Public health burden of sudden cardiac death in the United States. Circ Arrhythm Electrophysiol 2014; 7(2): 212-7.

[2] Benjamin EJ, Blaha MJ, Chiuve SE, *et al*. Heart disease and stroke statistics-2017 update: A report from the American Heart Association. Circulation 2017; 135(10): e146-603.

[3] Chugh SS, Reinier K, Teodorescu C, *et al*. Epidemiology of sudden cardiac death: Clinical and research implications. Prog Cardiovasc Dis 2008; 51(3): 213-28.

[4] Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: A meta-analysis of randomized controlled trials. JAMA 2004; 292(23): 2874-9.

[5] Epstein AE, DiMarco JP, Ellenbogen KA, *et al*. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008; 51(21): e1-62.

[6] Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. Eur Heart J 2003; 24(13): 1204-9.

[7] Stecker EC, Vickers C, Waltz J, *et al*. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: Two-year findings from the Oregon Sudden Unexpected Death Study. J Am Coll Cardiol 2006; 47(6): 1161-6.

[8] Chugh SS, Uy-Evanado A, Teodorescu C, *et al*. Women have a lower prevalence of structural heart disease as a precursor to sudden cardiac arrest: The Ore-SUDS (Oregon Sudden Unexpected Death Study). J Am Coll Cardiol 2009; 54(22): 2006-11.

[9] Aro AL, Reinier K, Rusinaru C, *et al*. Electrical risk score beyond the left ventricular ejection fraction: Prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. Eur Heart J 2017; 38(40): 3017-25.

[10] Atkins DL, Everson-Stewart S, Sears GK, *et al*. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: The Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. Circulation 2009; 119(11): 1484-91.

[11] Harmon KG, Asif IM, Maleszewski JJ, *et al*. Incidence, cause, and comparative frequency of sudden cardiac death in national collegiate athletic association athletes: A decade in review. Circulation 2015; 132(1): 10-9.

[12] Risgaard B, Winkel BG, Jabbari R, *et al*. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. Circ Arrhythm Electrophysiol 2014; 7(2): 205-11.

[13] Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation 2012; 125(4): 620-37.

[14] Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's heart disease: A textbook of cardiovascular medicine. Available from: https://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C2012001143X.

[15] Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001; 345(20): 1473-82.

[16] Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA 2002; 288(23): 3008-13.

[17] Nichol G, Thomas E, Callaway CW, *et al*. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008; 300(12): 1423-31.

[18] Weisfeldt ML, Everson-Stewart S, Sitlani C, *et al*. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. N Engl J Med 2011; 364(4): 313-21.

[19] Myerburg RJ, Halperin H, Egan DA, *et al*. Pulseless electric activity: definition, causes, mechanisms, management, and research priorities for the next decade: Report from a National Heart, Lung, and Blood Institute workshop. Circulation 2013; 128(23): 2532-41.

[20] 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(4): 278-85.

[21] Laurent I, Monchi M, Chiche JD, *et al*. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002; 40(12): 2110-6.

[22] Bunch TJ, White RD, Gersh BJ, *et al*. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. N Engl J Med 2003; 348(26): 2626-33.

[23] European Heart Rhythm A, Heart Rhythm S, Zipes DP, *et al*. ACC/AHA/ESC 2006 guidelines for management of patients with

ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 2006; 48(5): e247-346.

[24] Epstein AE, DiMarco JP, Ellenbogen KA, *et al*. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2013; 127(3): e283-352.

[25] Zipes DP, Braunwald E. Braunwald's heart disease: A textbook of cardiovascular medicine. 7th ed. Philadelphia, PA.: W.B. Saunders; 2005. xxi, 2183, pp. 75.

[26] Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E. Braunwald's heart disease: A textbook of cardiovascular medicine. Tenth edition. ed. 1 online resource (xxvii, 1943, 3 pages).

[27] Chugh SS, Reinier K, Singh T, *et al*. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: The Oregon Sudden Unexpected Death Study. Circulation 2009; 119(5): 663-70.

[28] Halliday BP, Gulati A, Ali A, *et al*. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation 2017; 135(22): 2106-15.

[29] Zipes DP, DiMarco JP, Gillette PC, *et al*. Guidelines for clinical intracardiac electrophysiological and catheter ablation procedures. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures), developed in collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol 1995; 26(2): 555-73.

[30] Skale BT, Miles WM, Heger JJ, Zipes DP, Prystowsky EN. Survivors of cardiac arrest: Prevention of recurrence by drug therapy as predicted by electrophysiologic testing or electrocardiographic monitoring. Am J Cardiol 1986; 57(1): 113-9.

[31] Wilber DJ, Garan H, Finkelstein D, *et al*. Out-of-hospital cardiac arrest. Use of electrophysiologic testing in the prediction of long-term outcome. N Engl J Med 1988; 318(1): 19-24.

[32] Cox JL. Ventricular tachycardia surgery: A review of the first decade and a suggested contemporary approach. Semin Thorac Cardiovasc Surg 1989; 1(1): 97-103.

[33] Daubert JP, Zareba W, Hall WJ, *et al*. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol 2006; 47(1): 98-107.

[34] Antiarrhythmics versus Implantable Defibrillators I. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337(22): 1576-83.

[35] Connolly SJ, Gent M, Roberts RS, *et al*. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000; 101(11): 1297-302.

[36] Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). Circulation 2000; 102(7): 748-54.

[37] Lee DS, Green LD, Liu PP, *et al*. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: A meta-analysis. J Am Coll Cardiol 2003; 41(9): 1573-82.

[38] Mitchell LB, Pineda EA, Titus JL, Bartosch PM, Benditt DG. Sudden death in patients with implantable cardioverter defibrillators: The importance of post-shock electromechanical dissociation. J Am Coll Cardiol 2002; 39(8): 1323-8.

[39] Wilkoff BL, Fauchier L, Stiles MK, *et al*. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. J Arrhythm 2016; 32(1): 1-28.

[40] Hohnloser SH, Dorian P, Roberts R, *et al*. Effect of amiodarone and sotalol on ventricular defibrillation threshold: the optimal pharmacological therapy in cardioverter defibrillator patients (OPTIC) trial. Circulation 2006; 114(2): 104-9.

[41] Yancy CW, Jessup M, Bozkurt B, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62(16): e147-239.

[42] Moss AJ, Hall WJ, Cannom DS, *et al*. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009; 361(14): 1329-38.

[43] Packer M, Fowler MB, Roecker EB, *et al*. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002; 106(17): 2194-9.

[44] Exner DV, Reiffel JA, Epstein AE, *et al*. Beta-blocker use and survival in patients with ventricular fibrillation or symptomatic ventricular tachycardia: The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. J Am Coll Cardiol 1999; 34(2): 325-33.

[45] Connolly SJ, Dorian P, Roberts RS, *et al*. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: The OPTIC Study: A randomized trial. JAMA 2006; 295(2): 165-71.

[46] Waldo AL, Camm AJ, deRuyter H, *et al*. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet 1996; 348(9019): 7-12.

[47] Echt DS, Liebson PR, Mitchell LB, *et al*. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324(12): 781-8.

[48] Moss AJ, Zareba W, Hall WJ, *et al*. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000; 101(6): 616-23.

[49] Hayashi M, Denjoy I, Extramiana F, *et al*. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation 2009; 119(18): 2426-34.

[50] Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation 2004; 110(13): 1731-7.

[51] Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999; 10(10): 1301-12.

[52] Pacifico A, Ferlic LL, Cedillo-Salazar FR, Nasir N, Doyle TK, Henry PD. Shocks as predictors of survival in patients with implantable cardioverter-defibrillators. J Am Coll Cardiol 1999; 34(1): 204-10.

[53] Kleemann T, Strauss M, Kouraki K, Zahn R. Clinical course and prognostic relevance of antitachycardia pacing-terminated ventricular tachyarrhythmias in implantable cardioverter-defibrillator patients. Europace 2015; 17(7): 1068-75.

[54] Stevenson WG, Friedman PL, Kocovic D, Sager PT, Saxon LA, Pavri B. Radiofrequency catheter ablation of ventricular tachycardia after myocardial infarction. Circulation 1998; 98(4): 308-14.

[55] Piers SR, Leong DP, van Huls van Taxis CF, *et al*. Outcome of ventricular tachycardia ablation in patients with nonischemic cardiomyopathy: the impact of noninducibility. Circ Arrhythm Electrophysiol 2013; 6(3): 513-21.

[56] Tung R, Vaseghi M, Frankel DS, *et al*. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: An International VT Ablation Center Collaborative Group study. Heart Rhythm 2015; 12(9): 1997-2007.

[57] Reddy VY, Reynolds MR, Neuzil P, *et al*. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med 2007; 357(26): 2657-65.

[58] Kuck KH, Schaumann A, Eckardt L, *et al*. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in

patients with coronary heart disease (VTACH): A multicentre randomised controlled trial. Lancet 2010; 375(9708): 31-40.

[59] Haissaguerre M, Shoda M, Jais P, *et al.* Mapping and ablation of idiopathic ventricular fibrillation. Circulation 2002; 106(8): 962-7.

[60] Haissaguerre M, Shah DC, Jais P, *et al*. Role of Purkinje conducting system in triggering of idiopathic ventricular fibrillation. Lancet 2002; 359(9307): 677-8.

[61] Marrouche NF, Verma A, Wazni O, *et al*. Mode of initiation and ablation of ventricular fibrillation storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol 2004; 43(9): 1715-20.