Sudden cardiac death (SCD) is a complex disease and represents one of the largest burdens to health care worldwide. It is known to be associated with various disease conditions, including but not limited to, cardiac arrhythmias, coronary artery disease, cardiomyopathies, valvular disorders and diabetes. Although much work is left to be done in uncovering the underlying mechanisms of SCD, response of the sympathetic nervous system to a prolonged stressful stimulus and the release of excessive amounts of catecholamines and their subsequent oxidation has potential to explain the regularly observed etiologies and provide a unified mechanism for the occurrence of SCD. Current possible treatments for patients at risk for SCD range from the implantation of cardioverter defibrillators to pharmaceutical interventions including anti-arrhythmic drugs, antiplatelet agents and β-adrenoceptor blockers. However, there are some studies suggesting the merit of prophylactic treatment using antioxidants such as vitamins A, C and E in preventing arrhythmias and consequent SCD. Overstimulation of the sympathetic stress response may result in SCD, and combination therapy with antioxidants and β-adrenoceptor blockers may be suitable for its prevention.

Key Words: Antioxidants; β-adrenoceptor blockers; Cardiac arrhythmias; Catecholamines; Sudden cardiac death; Sympathetic nervous system

ETIOLOGY

According to the 2016 Heart Disease and Stroke Statistics published by the AHA, the incidence of (emergency medical services assessed) out-of-hospital sudden cardiac arrest is approximately 110.8 per 100,000 individuals (356,500 individuals per year) in the United States, and the incidence of in-hospital sudden cardiac arrest is approximately 209,000 (15). The average survival rate of patients who experience an out-of-hospital sudden cardiac arrest is 10.8% and, for those who experience an in-hospital sudden cardiac arrest is 18.4% (15). The majority of patients who experience SCD are adults, with <1% of SCDs occurring in individuals <35 years of age; the incidence of SCD is higher in men than in women (4). While channelopathies and cardiomyopathies, myocarditis and substance abuse are the major cause of SCD in young subjects, chronic degenerative diseases (CAD, valvular heart diseases and HF) predominate in the pathogenesis of the disease in older populations. Table 1 summarizes the incidence of SCD in the different cohorts indicated based on the most recent sudden cardiac arrest statistics (4,15).

Cardiac arrhythmias are the most common cause of SCD; these involve irregularity of electrical activity, the most common form associated with SCD being ventricular fibrillation (VF), which causes desynchronization of ventricular contractions (1,3). Ventricular arrhythmias are encountered in almost all SCD patients, 75% to 80%
<table>
<thead>
<tr>
<th>Disease</th>
<th>Mortalities related to disease, n</th>
<th>Incidence of SCD, % Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>538,239</td>
<td>70–75</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>46,228</td>
<td>10–15</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>50,222</td>
<td>1–5</td>
</tr>
<tr>
<td>Inherited arrhythmogenic syndromes</td>
<td>–</td>
<td>1–2</td>
</tr>
<tr>
<td>No significant cardiac abnormalities</td>
<td>Healthy population</td>
<td>–</td>
</tr>
</tbody>
</table>

Data based on the 2016 American Heart Association heart disease and stroke statistics. The total incidence of sudden cardiac death (% of total) noted is an estimate of 565,500 patients (356,500 out-of-hospital plus 209,000 in-hospital sudden cardiac arrest) with 75% to 80% of available patient ECGs displaying VF, 10% to 15% displaying bradyarrhythmias, and only 5% to 10% without indication of arrhythmia (16). This disruption in the order of the transmittance of the excitation wave (generated at the sinoatrial node) results in improper beating of the heart and, thus, incomplete pumping and circulation of blood (17). Arrhythmias in patients without structural disease/irregularities result from primary electrical abnormalities, including Wolff-Parkinson-White (WPW) syndrome, long-QT syndrome (LQTS), short-QT syndrome (SQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and bradyarrhythmias (3). These observations can form the basis for the use of defibrillators for the correction of arrhythmias and prevention of SCD. Because the incidence of SCD is dependent on the type of certain cardiac diseases, it is considered appropriate to discuss this aspect in some detail.

CAD AND CARDIOMYOPATHIES

The most common cause of SCD is CAD, which develops as a result of damage or disease (typically due to plaque formation and inflammation) affecting the coronary arteries, which supply oxygenated blood and nutrients to the heart (18). CAD is the most common cause of SCD in adults >40 years of age, with atherosclerotic CAD accounting for 75% to 80% of the cases in this cohort (19). It also needs to be emphasized that most of these CAD cases involve seemingly normal adults with no symptoms or history of CAD; therefore, some caution should be exercised for explaining the mechanisms of SCD in patients with CAD (20).

Similar to ischemic cardiomyopathy, both hypertrophic and dilated cardiomyopathies are conditions that involve abnormalities of the heart muscle, diminishing the ability of the heart to pump blood or maintain normal electrical rhythm (21). Cardiomyopathies commonly associated with SCD include hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and dilated cardiomyopathy (1). Hypertrophic cardiomyopathy is a heritable autosomal dominant disorder and is the most common cause of SCD in young athletes. It involves abnormal growth of cardiomyocytes, causing thickening of the heart’s muscular walls and cardiomyocyte misalignment (myocardial disarray), causing them to become nonfunctional (1,22).

Valvular disorders

Valvular disorders, including aortic stenosis and mitral valve prolapse, can also manifest ventricular arrhythmias, prompting SCD (1,26). Aortic stenosis is the narrowing of the aortic valve outlet, restricting blood flow to the aorta, causing shortness of breath or breathlessness, angina, palpitations, heart murmurs and syncope (27). If left untreated, a decrease in coronary blood flow and overall decreased cardiac output due to acute left ventricular failure can result in SCD (1). On the other hand, mitral valve prolapse is caused by uneven closure of the mitral valve, causing it to protrude (prolapse) into the left atrium, resulting in the backward leak of small amounts of blood (28). Even in the absence of notable hemodynamic impairment, mitral valve prolapse can produce ventricular arrhythmias and SCD (26).

Diabetes mellitus

Diabetes mellitus comprises a collection of metabolic diseases, which cause hyperglycemia rooted in faults in either insulin secretion due to pancreatic β-cell dysfunction as well as abnormalities resulting in resistance to insulin action, or both, affecting >382 million individuals worldwide (29,30). Acute symptoms of hyperglycemia include polyuria, polydipsia, weight loss and blurred vision (29). Long-term induction of hyperglycemia is linked with the impairment of growth, increased susceptibility to infections, and damage and dysfunction of various organs, mainly the eyes, kidneys, heart and blood vessels, as well as nerves (29). The risk for SCD is significantly increased in diabetes mellitus patients, with large-group studies indicating a two to four times increase in the incidence of SCD compared with the normal population (30). SCD is one of the most prominent causes of death in patients with diabetes, accounting for approximately 50% of deaths due to cardiovascular causes in this cohort (30,31).

MECHANISMS OF SCD

Several mechanisms have been proposed in an attempt to explain SCD. These include the presence of vascular anomaly and mainly cardiac structural, electrical, metabolic and electrolyte abnormalities, as well as genetic variations (Figure 1). Structural heart disease can lead to the development of SCD, giving rise to the postulation that SCD is caused solely by structural abnormalities in CAD, ischemic...
cardiomyopathies, congenital heart disease, valvular heart diseases and various cardiomyopathies (3). Electrophysiological/electrical abnormalities have also been considered as a possible mechanism for SCD, accrediting SCD to the arrhythmogenic primary electrical abnormalities including WPW, LQTS, SQTS, BrS and CPVT. The appearance of focal activity, such as enhanced automaticity and triggered activity or reentry, which can occur due to an anatomical or functional obstacle, has also been suggested to result in SCD (3,17). Life-threatening arrhythmias, which can lead to SCD, are also known to be associated with electrolyte imbalances, such as hypokalemia, but also hyperkalemia and hypomagnesemia, metabolic abnormalities, severe inflammation and endocrine disorders (hyper- and hypothyroidism) (3). More recently, several genetic variations, including those affecting ion channels, cardiac structural proteins, cardiogenesis, cardiac development, energy metabolism and genes related to neurohormonal regulation, have been implicated in development of SCD (11).

One of the proposed and, possibly unifying mechanism, is the attribution of SCD to the sympathetic stress response (1). This stress response is an adaptive mechanism that responds to aggressive stimuli to elicit behavioural (psychological) and physical (physiological) alterations through both the sympathetic-adrenal-medullary (SAM) and the hypothalamic-pituitary-adrenal (HPA) systems (32,33). The activation of these axes causes the secretion of norepinephrine and epinephrine (through SAM action), and glucocorticoids (through HPA action), to support the survival of different organs (34). Although this acute adaptability improves cardiac function for brief periods of time and is necessary for normal survival, prolonged activation of the sympathetic stress mechanism can have detrimental effects including ventricular remodelling and enhanced arrhythmogenesis (32,35).

A network of sympathetic neurons innervates cardiac tissue, including the SA node, AV node and the ventricles (36). Catecholamines are released from nerve terminals and act on α- and β-adrenergic receptors, causing an increase in heart rate (through action on SA node) and force of contraction (through action on ventricular muscle) (36). In response to acute sympathetic outflow, neuropeptide Y, a 36-amino acid polypeptide plentifully found in areas of the brain that regulate stress and emotional behaviour, is activated and inhibits the release of norepinephrine at the presynaptic level (37,38). On persistent sympathetic activation over a longer period of time, however, the activity of neuropeptide Y is significantly decreased, leading to a further increase in catecholamine release (37). Thus, it appears that a loss of modulatory action of neuropeptide Y on the sympathetic nerve terminal may play a critical role in elevating the levels of catecholamines in circulation due to prolonged stress.

An excessive amount of catecholamines has both direct and indirect consequences that may have deleterious impact on normal heart function (32,39). First, stimulation of α-adrenergic receptors by norepinephrine has been implicated to play a role in the progression of various cardiovascular diseases (40). Normal stimulation of α-adrenoceptors has a positive chronotropic effect; however, prolonged stimulation has been implicated in myocyte hypertrophy, myocardial ischemia, metabolic derangements and eventual cardiomyocyte apoptosis and the development of dilated cardiomyopathy (40-42). Despite this possible negative effect, neither the α-adrenoceptor density nor the positive inotropic effect of norepinephrine is distorted in failing human hearts, leading to the consideration that the α-adrenoceptor stimulation may be an adaptive mechanism in failing hearts (43). It should also be mentioned that stimulation of β-adrenergic receptors by catecholamines activates adenylyl cyclase, causing the conversion of ATP to cAMP, a process that depletes high-energy phosphate stores (1,44). cAMP acts as a messenger molecule to activate protein kinase A (PKA), which phosphorylates voltage gated L-type calcium channels causing a Ca 2+ influx into myocardioc cells across the sarcolemma (1,45). PKA also induces phosphorylation of phospholamban and troponin, which impedes their normal lusitropic effect (32). The excessive inflow of calcium prompts the uncontrolled release of more Ca 2+ from the sarcoplasmic reticulum (SR) via type 2 ryanodine receptors, which results in an intracellular Ca 2+ overload (46,47). This adjustment in the calcium handling process of cardiomyocytes is known to increase the probability and occurrence of arrhythmias (Figure 2) including premature ventricular contractions, nonsustained ventricular tachycardia and ventricular fibrillation, thereby relating to SCD (1,48). The severity of these arrhythmias was shown to be dose dependent; thus, as the concentration of catecholamines increases, the chance of experiencing lethal ventricular fibrillation increases (49). Prolonged stimulation of α-adrenergic receptors may also result in coronary spasms resulting in myocardial ischemia and functional hypoxia, which may cause many of the underlying etiologies of SCD (1).

Furthermore and, possibly, most of the detrimental effects of the excessive release of catecholamines is due to the oxidation of surplus circulating catecholamines into aminochromes and the formation of reactive oxygen species (ROS) (Figure 3). Catecholamines become available for oxidation in the body when mechanisms (monoamineoxidase [MAO]) and catechol-o-methyl transferase [COMT]), which

Figure 2) The mechanism by which excess catecholamines increase the occurrence of arrhythmias that may lead to sudden cardiac death. SL Sarcolemma; SR Sarcoplasmic reticulum

Figure 3) The cascade of events leading to the development of oxidative stress following a sustained stressful stimulus and the subsequent release of excess catecholamines. ROS Reactive oxygen species
degrade them are saturated or impaired due to excessive catecholamines
in the circulation or oxidative stress (50,51). This leads to the forma-
tion of aminochromes, which are known to deplete the high-energy
phosphate stores, increase the intracellular calcium concentration lead-
ing to Ca^{2+} overload, cause lipid peroxidation, coronary artery spasms,
arrhythmias, ventricular dysfunction and ultrastructural damage (46).
This was shown on the perfusion of isolated rat hearts with oxidized
isoproterenol, which generated notable morphological changes and
contractile failure unlike its unoxidized precursor (39). Furthermore,
aminochromes may induce certain defects leading to SCD in patients
with pre-existing primary electrical abnormalities (39).

The oxidation of circulating catecholamines is also known to pro-
duce oxyradicals (ie, ROS), which can easily react with a number of
 cellular structures and whose excess leads to the development of oxida-
tive stress (39,51). Amplified oxidative stress results in dysfunction of
normal electrical functioning and intracellular ion homeostasis in
cardiac myocytes, making it widespread in arrhythmogenic cardiac
conditions, including SCD (32). Along with the process of autoxida-
tion of the excess circulating catecholamines, their interaction with
MAO results in the continuation of mitochondrial damage (53). Blockade
of autophagic flux by MAO-A activity, and increased generation of ROS
through MAO-B activity, lead to the build-up of damaged mitochon-
dria and cell death (53). Detrimental effects of ROS generated in the
heart include decline in contractile force, ultrastructural changes and
arrhythmias, all of which may contribute to SCD (9). Different studies
(49,54) aimed at testing the efficacy of antioxidants in preventing the
catecholamine-induced arrhythmias support the postulation that it
may be aminochromes and ROS rather than the epinephrine and
norepinephrine themselves that play a major role in catecholamine-
induced SCD. A marked decrease in the incidence of catecholamine-
induced arrhythmias on pretreatment with antioxidants, such as
N-acetyl-L-cysteine as well as vitamins A, C, and E, has been reported
in the literature (49,54).

Activation of the HPA axis also contributes to catecholamine-
induced SCD through the action of glucocorticoids, which are
released from the adrenal cortex in response to a stressful stimulus and
amplify the effects of sympathetic stimulation (32). The main action
of glucocorticoids is the inhibition of extraneuronal uptake of cat-
echolamines. However, other effects include increased synthesis and
decreased degradation of catecholamines, directly increasing the con-
centration of circulating catecholamines (32). Furthermore, these
hormones also have been shown to increase the total population,
binding capability and affinity of β-adrenergic receptors, further
enhancing the effects of sympathetic stimulation (32).

PREVENTION AND TREATMENT
Given the high rate of sudden death in event of cardiac arrest, the
pursuit of preventive measures and effective treatment must be
unremitting (15,55). Wearable and implantable cardiac defibrillators
are one of the leading methods of prevention of SCD in HF patients
and other high-risk populations, showing notable reduction of mortal-
ity in randomized clinical trials (10,58). Holding the capability to
cadiovert, defibrillate, and pace the heart, these devices are often
used as prophylactic treatment for patients at high risk for SCD caused
by VF (1,12). More invasive treatment options include the use of per-
cutaneous angioplasty, coronary interventions such as coronary bypass
surgery for CAD patients, and the development of drug-eluting stents
to be placed in diseased coronary arteries (1). Various pharmaceutical
treatments are also available for SCD patients, the most obvious can-
didate being anti-arrhythmic drugs (10). Despite their theoretical
benefit, evidence supporting the use of these drugs is sparse due to a
lack of convincing studies to support their use for primary prevention
of SCD (10). It should be noted that various antiplatelet agents,
including sarpogrelate, a 5-HT2A antagonist, and acetylsalicylic acid
have been shown to improve cardiac function and reduce the
occurrence of ventricular arrhythmias related to SCD, indicating their
potential use as prophylactic treatment of SCD (1,48).

Because high concentrations of circulating catecholamines are
known to contribute to the development and progression of various
cardiovascular diseases, therapeutic interventions concentrate on
inhibition of sympathetic activity (56,59). This is typically achieved
through the use of β-adrenoceptor blockers, which have been shown
to decrease the risk for SCD by up to 31% in clinical trials (57). These
drugs work by weakening the effect of the activation of β-adrenergic
receptors by catecholamines, and have been shown to improve left
ventricular function, slow cardiac remodelling and reduce mortality in
HF patients (1,59,60). Although most of the beneficial effects of
β-adrenoceptor blockers have typically been attributed to the lowering
of heart rate in HF patients, β-blockers, such as metoprolol, propran-
olol and atenolol, have all been shown to depress high levels of plasma
norepinephrine and epinephrine through effects on preterminal symp-
athetic nerve endings, further highlighting these agents for treatment
of catecholamine-induced SCD (59,61). Similarly, blockade of α-adrenergic receptors by drugs, such as prazosin, has also been shown
to have a similar effect, depressing elevated plasma norepinephrine
levels (59). More invasive methods of attenuating the effects of sym-
pathetic nervous system induced cardiac pathologies include renal and
cardiac sympathetic denervation and increasing parasympathetic
activity, which opposes the effects of sympathetic stimulation through
vagal nerve stimulation. However, further studies are needed to assess
the efficacy and long-term consequences of these treatments (56,62).

As outlined previously, deleterious effects of the oxidation prod-
ucts of catecholamines and their ability to induce arrhythmias lead-
ing to SCD, different antioxidants, such as N-acetyl-L-cysteine,
vitamin A, vitamin C, and vitamin E, have been shown to attenuate
the aminochrome and ROS induced cardiac structural damage and
dysfunction (39,49,54). The beneficial effects in hypertension,
ischemic heart disease, various cardiomyopathies, and heart failure
have been reported to be due antioxidant therapy (49). N-acetyl-L-
cysteine, vitamin C, and vitamin A have been shown to exert anti-
arrhythmic effects, whereas vitamin E has been demonstrated to
reduce the incidence of premature ventricular contractions and exert
antiapoptotic action (49,54,63). Due to their ability to lower plasma
aminochrome levels and reduce the deleterious effects of oxidation
products with respect to catecholamine induced arrhythmias and
SCD, administration of antioxidants may be a promising treatment
option for patients with different types of arrhythmia. However,
because clinical evidence has not fully supported data from experi-
mental studies, further evaluation of their effects is needed before
drawing concrete conclusions (49,54).

CONCLUSIONS
SCD is one of the leading causes of death worldwide, and may be the
manifestation of a large range of different cardiovascular abnormal-
ities and diseases. Due to complications in the assessment for risk and
diagnosis for SCD, development of a distinct set of guidelines for
treatment for different causes and diseases is required, but it is only
possible with further research in this field. Due to the possibility of
many of the underlying comorbidities being caused by the sympa-
thetic stress response and the release and oxidation of excess cate-
cholamines, focus on this causation for SCD may provide insight to
the main pathophysiological mechanism of this complex disease.
Nonetheless, development of efficacious and widely applicable treat-
ment options is necessary, with a combination of β-adrenoceptor
blockers and antioxidants holding some merit in this field due to their
ability to attenuate both the direct and indirect damaging effects of
excess catecholamines.

ACKNOWLEDGMENTS: Infrastructural support for this study was
provided by the St Boniface Hospital Foundation, Winnipeg, Manitoba,
Canada. AA has been supported by a grant from APPV (15-607) and
VEGA (1/0271/16).
REFERENCES

27. American Heart Association. Problem: Aortic valve stenosis. 2016 <www.heart.org/HEARTORG/Conditions/More/HeartValveProblemsAndDisease/Problem-Aortic-Valve-Stenosis_UCM_450437_Article.jsp>V358s5MrLbP.
28. American Heart Association. Problem: Mitral valve prolapse. 2016 <www.heart.org/HEARTORG/Conditions/More/HeartValveProblemsAndDisease/Problem-Mitral-Valve-Prolapse_UCM_450441_Article.jsp>V358s5MrLY.