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Sudden cardiac death in the young: cytokines and pathways

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Abstract

Background and Purpose: *The underlying mechanisms of sudden cardiac death in terms of cytokines and pertinent signaling pathways have not been previously elaborated. The purpose of this paper is to clarify the cytokines and signaling pathways involved in the mechanisms of sudden cardiac death in the young.*

Materials and Methods: *Medical literature of sudden cardiac death in the young of recent decades were carefully collected as studying materials, and comprehensively reviewed and analyzed.*

Results: *Extrinsic and intrinsic apoptotic pathways, influenced by growth factor pathways, may render arrythmogenic cardiac disorders and ultimately lead to sudden cardiac death. Other cytokines probably involved in the mechanisms of sudden cardiac death in the young may include heme oxygenase-1 and the gaseous molecules (carbon monoxide and nitric oxide), insulin-like growth factor-1, gap junctional proteins and homeobox transcription factor NKX2-5, which may be responsible for atrioventricular conduction impairments. Active therapeutic options for the pertinent arrhythmias have significantly reduced the incidence of sudden cardiac death in the young. The apoptotic and growth factor signaling pathways are the two major ways leading to conduction system impairment and eventual sudden cardiac death.*

Conclusions: *The prophylactic antiarrhythmic agent, device therapies, or surgical operation could dramatically reduce sudden cardiac death incidence. Good understanding of the mechanisms of the cytokine-related pathways is crucial for the treatment of the causative cardiac disorders responsible for sudden cardiac death in the young. New agents including apoptotic blockers, heme metabolite homologues, and c-Src, PIK3 and NKX2-5 inhibitors,* etc.*, are anticipated for the prevention of sudden cardiac death in the near future.*

INTRODUCTION

Sudden cardiac death (SCD) is an unexpected death from cardiac events, and occurs within one hour of onset of cardiac symptoms. In 25% of the cases, SCD occurred within 6 hours of physical activity *(1)*. Preceding symptoms were reported in 35% of the cases prior to SCD. The symptoms can be circulatory (syncope, chest pain, dyspnea and palpitations), neurological (headache and visual disturbances), digestive, or institutional (*e.g.*, recent febrile disease, usually a few days prior to SCD). It has been recognized that causes of SCD vary depending on age, gender, ethnicity and genetics *(2)*. The incidence of SCD relies on population, of whom those in exercise are more likely vulnerable to SCD

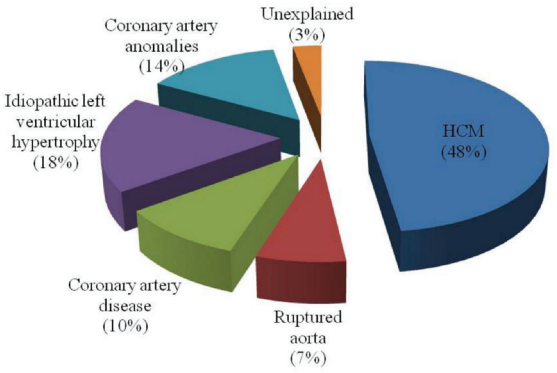

Figure 1. *Distributions of causes of sudden cardiac death in the young athletes (11). HCM: hypertrophic cardiomyopathy.*

(Table 1) *(3-8)*. The incidence also varies on patients' gender, age and season: 2.3-fold higher in male than in female, increased with age, and highest in October and lowest in August *(3)*. In a recent authoritative review, Ackerman *et al*. *(9)* made a summative assessment on the population-based estimates of SCD incidence in the young based on large medical centers from the world. The incidence differed depending on patient's age, hospitals and regions, but showed an overall range of 0.7-10.1 per 100,000 patient-years. However, the underlying mechanisms of SCDs in terms of cytokines and pertinent signaling pathways have not been previously elaborated. The purpose of this paper is to given a comprehensive review discussing the possible cytokine-related signaling pathways of SCDs in the young.

Table 1. *Incidence of sudden cardiac death*

Population	Incidence (per 100,000 person-year)	Reference
General population	0.0092	(3)
Young individuals	2.28	(4)
0–2 years of age	2.1	(4)
3–13 years of age	0.61	(4)
14–24 years of age	1.44	(4)
25–35 years of age	4.40	(4)
Healthy men of exercise	5.56	(5)
Joggers	13.12	(6)
Basketball players	32.26	(7)
Young athletes (9-40 years)	0.11–33.33	(8)

ETIOLOGIES

Berger *(10)* classified the etiological disorders for SCDs into structural or functional abnormalities, primary electrical abnormalities, acquired conditions and postopera-

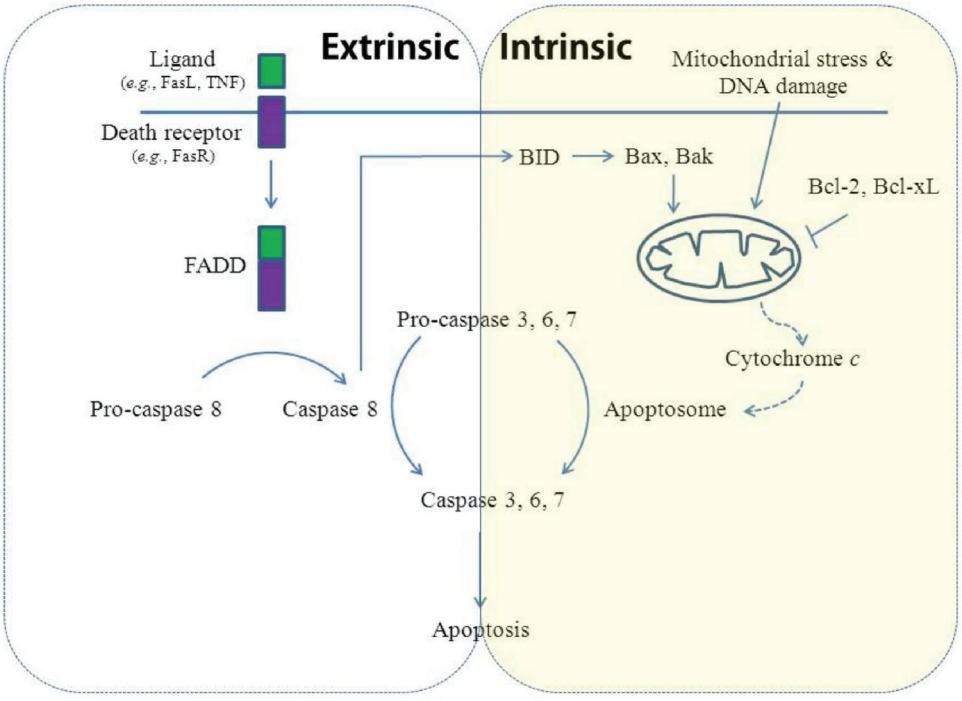

Figure 2. *Apoptotic signaling pathways (17). The extrinsic pathway is triggered by a binding of a ligand and a death receptor and the intrinsic pathway is activated by mitochondrial stress leading to cytochrome c release. By activating the initiator caspases and further the execution caspases, the apoptosis is initiated. Bak: Bcl-2 homologous antagonist/killer; Bax: BCL-2-associated X protein; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; BID: Bcl-2 interacting protein; FADD: Fas-associated death domain; FasL: Fas ligand; TNF: tumor necrosis factor.*

Table 2. *A summary of potential cytokines and pathways involved in the mechanisms of sudden cardiac death in the young*

Type of cytokines	Participating factors	Signaling pathways	Function
Apoptotic regulator	Tumor necrosis factor, anti-apoptotic proteins (Fas-L & Bcl-2) & pro-apoptotic proteins (Bak, Bax & Bad)	Apoptosis signaling pathways	Triggering cardiac apoptosis
Heme oxygenase	Heme oxygenase-1	p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K)/Akt pathway, Jak-STAT pathway, toll-like receptor (TLR)-4 pathway	Inhibition of proinflammatory cytokines & chemokines
Insulin-like growth factor (IGF)-1	IGF-1	IGF-1 signaling pathway	Promotion of the cell proliferation & differentiation & apoptosis inhibition
Cardiac gap junctions	Connexins 40, 43 & 45	PI3K/Akt-mediated pathway	Electrical impulse propagation & coordinated contraction of the heart, maintenance & modulation of vascular tone
Vascular endothelial growth factor	Vascular endothelial growth factor	Vascular endothelial growth factor signaling	Promotion of mitosis of the vascular endothelial cells & angiogenesis
NKX2-5	NKX2-5	Wnt signaling	Cardiomyogenesis
HF-1b zinc finger protein	HF-1b	Ras pathway	A component of the endogenous HF-1b/myocyte enhancer factor (MEF) 2 binding activity in cardiac muscle cells
Heat shock proteins	Heat shock proteins	IGF-1 receptor signaling	Suppression of apoptosis of cardiomyocytes, suppression of ubiquitination of IGF-1 receptor, augmentation of IGF-1 receptor signaling
Heat shock factor 1	Heat shock factor 1	Heat shock factor 1 signaling, IGF-1, transforming growth factor-β & cyclic guanosine monophosphate (cGMP) signaling	Protection against endotoxic shock
Calcineurin	Calcineurin	Calcineurin signaling	Activation of the local production of nitric oxide by inducible nitric oxide synthase in myocardiocytes

tive congenital heart disease. A representative review respectively proposed that hypertrophic cardiomyopathy is the most common cause of SCD in young athletes (Fig. 1) *(11)*. Post-mortem analysis of cardiovascular pathology in SCD victims showed structurally normal heart in 27%, coronary artery disease in 21% and hypertrophic cardiomyopathy in 15% *(12)*. Consensus revealed hypertrophic cardiomyopathy the most common, congenital coronary artery anomalies, myocarditis, dilated cardiomyopathy, Marfan's syndrome and arrhythmogenic right ventricular dysplasia (ARVD) the more common, and cardiac tumor, mitral valve prolapse, aortic valve stenosis, atherosclerotic coronary artery disease and long QT syndrome the lest common causes of SCDs in the young *(13)*.

In infancy, the most common cause of death is congenital cardiac malformations. SCD may occur postoperatively in children with hypoplastic left heart syndrome between Norwood stage I and bidirectional Glenn procedures *(14)*. The cause of SCD can be surgical technical problems, ventricular dysrhythmias, aspiration and altered baroreceptor reflexes, and electrical instability resulting from postoperative anatomical modifications. Majority of SCDs after repair of tetralogy of Fallot were due to ventricular arrhythmia, which could be screened by routine electrocardiogram (ECG) in whom SCDs occur later, and successful antiarrhythmic treatment could effectively prevent from SCDs *(15)*.

Stenosis of the sinus node artery, which is frequent in patients younger than 40 years old as an important cause of SCD, is often associated with interstitial proliferation of the sinoatrial node. The etiologies of stenosis of the coronary orifice, an alternative common cause of SCD, include atheromatous plaque obstruction, syphilitic aortitis and congenital anomalies, with the latter one being less common than the previous two. Ion channelopathies represented by long QT, Brugada and Lev-Lenegre's syndromes with mutations of genes encoding sodium channels, as well as ventricular electrical storm characterized

by critically malignant dysrhythmias due to extremely unstable electrical activities of the ventricle are also important causes of SCDs. In such patients, SCD has been evidenced histologically in the young victims by investigating the pathology of conduction system. A congenital abnormality of the His bundle, such as loop formation and fragmentation or displacement found in the pathological inspections was considered to be the cause of arrhythmogenic sudden death *(16)*.

CYTOKINES AND PATHWAYS

Several potential cytokines and pathways that implicate in the pathogenesis of SCD in the young have been proposed. They are summarized in Table 2. Their potential roles for further targeting are described below.

Apoptotic regulators

Apoptosis is a complex process of a programmed cell death that involves collapse of cell, protein degradation and deoxyribonucleic acid fragmentation. Unlike necrosis where the cells swell and soon disintegrate, thereby evoking an inflammatory response, apoptotic cells do not swell but actually shrink with extensive intracellular degeneration. Apoptosis may inevitably lead to electric instability of the myocardium and cause SCD. A close correlation between apoptotic rate and left ventricular remodeling has been noted. Tumor necrosis factor (TNF) mediates cardiac apoptosis by way of both the extrinsic and intrinsic pathways (Fig. 2) *(17)*. The Fas-mediated apoptotic pathway is a major extrinsic pathway triggering cardiac apoptosis as a result of interactions between the cell surface death receptors (TNF receptor and Fas receptor) and extracellular ligands (TNF and Fas-L). The mitochondria-dependent apoptotic pathway releases apoptosis-regulating proteins from the intermembrane, exemplified by the B-cell lymphoma 2 (Bcl-2) family, such as Bcl-2 homologous antagonist/killer (Bak), Bcl-2, Bcl-2-associated X protein (Bax) and Bcl-2-associated death promoter (Bad). Immunohistochemical studies on SCD victim heart revealed a direct proportion between Fas-L, caspase 9 and Bax expression, indicating the role of apoptotic signal transduction mediated by Fas/Fas-L pathway in SCD *(18)*. Experimental studies in transgenic mice ischemia-reperfusion model showed cardiac apoptosis could be inhibited by modification of apoptosis regulators and blockade of apoptosis executors. Moreover, extracellular signal-regulated kinases (ERK1/ERK2) and p38 mitogen-activated protein kinase (MAPK) pathways can be interacted with apoptosis pathways *(19)*. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway was found to be closely related to inflammatory and apoptotic process. As a new downstream molecular target, it might regulate apoptosis and cell proliferation induced by deoxynivalenol (DON) and T-2 toxin. In turn, JAK/STAT pathway might be the activated by the phosphorylation of MAPK, the release of proinflammatory cytokines from the cells through binding to the cytokine receptor and activating the kinase JAK. In addition, the JAK/STAT pathway might also be involved in the cardiotrophin-1, a member of the interleukin-6 family, and pressure overload-induced cardiomyopathy *(20)*.

Heme oxygenase (HO)

HO, isoformed by HO-1, HO-2 and HO-3, is responsible for the physiological breakdown of heme into equimolar amounts of biliverdin, carbon monoxide (CO) and iron. HO-1 is ubiquitous and its messenger ribonucleic acid (mRNA) can be overexpressed by several folds in the presence of heme, other metalloporphyrins, transition metals and stress. HO-2 is present chiefly in the brain and testes and is virtually uninducible. HO-3 has very low enzyme activity. In isolated rat heart ischemia-reperfusion model, a significant reduction of HO-related CO production was noted to be associated with reperfused ventricular fibrillation (VF), indicating the important arrhythmogenic role of the endogenous CO *(21)*. Experimentally, zinc protoporphyrin IX (Zn-PPIX) (5 mM) treatment caused downregulation of HO-1 mRNA and a reduction of HO activity in VF hearts *(22)*.

HO-1 overexpression inhibits proinflammatory cytokines and chemokines under hypoxia, alleviates cardiomyocyte apoptosis and regulating pathological left ventricular remodeling *(23)*. The anti-inflammatory properties of HO-1 may rely on its ability to degrade heme and generate bilirubin, free iron and CO, and to reverse IL-18-mediated p38α MAPK and nuclear factor-κB activation, phosphatase and tensin homolog (PTEN) induction, Akt suppression and endothelial cell death *(24)*. HO-1 mRNA upregulation prevents from reperfused VF by promoting endogenous CO formation *(21)*. Genetic missense mutation in cardiac potassium- and calcium-channel proteins might be responsible for SCD from ventricular arrhythmias.

The nuclear factor-erythroid (NF-E) 2-related factor 2 (Nrf2) is a positive regulator of HO-1 gene induction *(25)*. It is involved in protection against oxidant stress in cardiovascular diseases, such as atherosclerosis, hypertension, heart failure and ischemia-reperfusion injury as well as aging. Alam *et al*. *(25)* have provided substantial evidence that overexpression of Nrf2M, a mutant of Nrf2, inhibits HO-1 mRNA accumulation in response to heme, zinc, cadmium and arsenic. Under conditions of Nrf2M overexpression, HO-1 mRNA accumulation in response to heme, cadmium, zinc, arsenite and tert-butylhydroquinone was inhibited.

Insulin-like growth factor-1 (IGF-1)

IGF-1 displays multiple biological functions including promotion of the cell proliferation and differentiation and apoptosis inhibition by regulating gene expressions of the

myocytes. IGF-1 upregulates the phosphorylation levels of the Akt protein of the heart. LY294002, a specific inhibitor of the phosphatidylinositol 3-kinase (PI3K), not only reduces the level of Akt phosphorylation induced by IGF-1 itself, but also reverses IGF-1, promotes the functional recovery of the cryopreserved heart, thereby playing an important anti-apoptotic role *(26)*. Cardioprotective effects of IGF-1 against apoptosis are present through inhibition of apoptotic inducers, by upregulation of the renin-angiotensin system, or by downregulation of Kruppel-like factor 9, which further downregulates cytochrome P450, a member of the cytochrome *c* family *(27)*. IGF-1 partly recovers mitochondrial function of the myocytes through downregulation of cytochrome *c* gene expression induced by hydrogen peroxide through downregulation of *rKLF9* gene expressions. IGF-1 may exert dual effects, either protective or harmful, on cardiomyoytes and on the vascular wall depending on whether the vascular endothelium is intact or impaired. Chisalita *et al*. *(28)* reported that the IGF-1 level was significantly higher in patients with heart failure or ischemic heart disease with angiotensin converting enzyme-inhibitor than those without (103.4 ± 39.7 μg/L *vs*. 84.4 ± 30.0 μg/L, $p = 0.02$). By contrast, Boquist *et al*. *(29)* offered a divergent concept that fasting serum free IGF-1 correlated inversely with atherosclerosis-associated events based on a study on 96 healthy subjects.

Gap junctional proteins

The gap junctional channels are formed from connexins (Cx'es), responsible for electrical impulse propagation and coordinated contraction of the heart. Altered gap junction distribution and function may lead to disturbed cardiac rhythmicity, including reentry. The human cardiomyocytes express three different types of gap junction subunits: Cx43, Cx40 and Cx45 *(30)*. Gap junction α-1 protein, also known as Cx43, is a major gap junction protein maintaining normal electrical conduction in the heart. In Cx43-deficient mice, a 30-44% reduction of ventricular conduction velocity and prolongation of the QRS waves were observed *(31)*. *Cx* gene deletion adversely affected the conduction system to a moderate degree as proved by the experiments in the heterozygous Cx40 and Cx43 knock-out mice. Cx43 conditional knockout mice with induced deletion of Cx43 in the heart exhibited reduced conduction velocity, increased dispersion of conduction, and enhanced electrical vulnerability on the ventricular level *(32)*. Experimental studies revealed that Cx45 could be a substitute of Cx40 when the latter was deficient in the atrioventricular node, at least partly identifying the compensating properties of various Cx proteins *(33)*. In 156 probands with progressive familial heart block type I, a novel germ line heterozygous missense mutation in exon 2 of the Cx40 gene GJA5 was identified, whereas mutations were not found in connexin genes *GJA1 (Cx43)* or *GJC1 (Cx45)*. Increased Cx43 mRNA and protein may lead to enhanced dye permeability and propagation of calcium *(34)*.

Gap junction protein expression or functional alteration may implicate an arrhythmogenic substrate in hypertrophic, ischemic, or dilated cardiomyopathies. Downregulation of Cx43 was observed in the ventricle of patients with hypertrophic, dilated and ischemic cardiomyopathies. Increased heterogeneity of Cx43 was found in both patients with congestive heart failure and documented ventricular tachycardias and the heart failure mouse model that showed inducible polymorphic ventricular tachycardia in the setting of heterogeneous Cx43 loss. Cx43 is a plausible candidate gene for premature sudden death and a *Cx43* mutation is a pathogenic substrate for sudden infant death syndrome. Right ventricular endomyocardial biopsy in ARVD patients showed a significant reduced Cx40 mRNA and Cx45 mRNA expressions. Therefore, loss of gap junctions and shifted composition of gap junction channels of the conduction system might contribute to the development of ventricular arrhythmias in patients with ARVD *(35)*.

Vascular endothelial growth factor (VEGF)

VEGF is a strong and specific cytokine that promotes mitosis of the vascular endothelial cells and angiogenesis. When subjected to hypoxia or ischemia, especially in the myocytes adjacent to the myocardial infarct area, the VEGF expressions are upregulated in the local tissues, probably due to the angiogenesis in that area *(36)*. The patchy immunohistochemical positivity of hypoxia-inducible factor-1α, erythropoietin and VEGF in cardiomyocytes in the acute myocardial infarction and sporadic positivity in cardiomyocytes of SCD case without infarction indicate a proportion between the expressions and the structure damage of cardiomyocytes *(37)*.

NKX2-5 and HF-1b

NKX2-5 and HF-1b implicate in conduction system development and disease. Several candidate molecules, including homeobox transcription factor NKX2-5, are related to SCD due to the resultant impaired conduction system, for example, in the context of gene mutations. HF-1b is a transcriptional factor preferentially expressed in the cardiac conduction system and ventricular myocytes. HF-1b-deficient mice in associated with Cx40 redistribution predisposes to conduction system impairment, subsequent malignant lethal arrhythmia and sudden death *(38)*.

Heat shock proteins (HSPs) and calcineurin

HSPs confer protection against cardiovascular disease. Heat shock transcription factor (HSF)1 is one of the transcription factors that regulate the expression of HSPs.

HSF1 is repressed by GSK-3β (Ser303), ERK (Ser307) and JNK (Ser363) under normal conditions; whereas, it is activated by hyperphosphorylation (Ser-230) upon exposure to different stressors. HSFs including HO-1 provide significant protection against a variety of chemical and physical tissue damages associated with excessive production of reactive oxygen species. In the heart of transgenic mice with HSF1 or inducible HSP70 overexpressions, more resistance to ischemia-reperfusion injury was shown in compared with wildtype mice. In addition, HSPs may also protect against myocardial infarction and doxorubicin-induced cardiomyopathy *(39)*. HSP90 was remarkably decreased in the tissues of hypertrophic cardiomyopathy pigs of sudden death, but not in the tissues of non-hypertrophic cardiomyopathy or normal pigs. Calcineurin, a protein phosphatase also known as protein phosphatase 3, and calcium-dependent serine-threonine phosphatase, activates the local production of NO by inducible NO synthase in cardiac myocytes. Overexpression of calcineurin significantly contributes to sudden death, heart block, left ventricular dilation and impaired systolic performance of the ventricle *(40)*.

MANAGEMENT

Screening investigations

In order to predict any potential SCDs, US Preventive Services Task Force proposed an analytic framework for screening including descriptive epidemiology and etiology, screening methodology and optimal management. Of importance, ECG may reveal the causative cardiovascular diseases responsible for SCD, such as cardiomyopathies, channelopathies and cardiac conduction system diseases. Resting ECG serves as an adjunctive for disclosing heart block of any degree or early repolarization syndrome; while stress ECG, for induced symptoms including chest pain, ischemic ECG changes, conduction abnormalities and early repolarization during the exercise test; and echocardiogram, for cardiac structural or functional abnormalities. Family evaluation and genetic testing are also helpful in the early warning of SCDs *(41)*.

Conservative treatment

Timely diagnosis of the underlying cardiovascular diseases, prohibition of high intensity exercise, pharmacotherapy and other treatments help to prevent SCDs in the affected athletes. In the event of ventricular electrical storm, electric defibrillation and cardioversion should be performed as soon as possible for hemodynamic stabilization. Current views support that β-blockers (metoprolol is preferred) is the drug of first choice, which is followed by amiodarone or sotalol, and a combination of both if necessary. As mitochondrial damage and Bcl-2-to-Bax balance play a central role in ischemia-dependent apoptosis while angiotensin II and β_1-adrenergic-stimulation may be the major causes of receptor-mediated apoptosis, treatment with angiotensin-converting enzyme inhibitors and β-blockers could reduce myocardial apoptosis *(42)*. Quinidine and isoproterenol are effective for the electrical storm of Brugada syndrome. In other genetic arrhythmias, such as idiopathic long QT syndrome or short QT syndrome, β-blockers, quinidine and isoproterenol, *etc*., still have their places. c-Src inhibitor, such as 1-(1,1-dimethylethyl)-1-(4-methylphenyl)-1H-pyrazolo(3,4-d) pyrimidin-4-amine (PP1), reduces c-Src and raises Cx43 levels. Cx43 upregulation occurs primarily at the intercalated disks and correlates with gap junction functional improvement, and associated with a reduced risk of ventricular tachycardia inducibility and SCD. The activation of renin-angiotensin system is associated with c-Src upregulation, Cx43 loss, reduced myocyte coupling and arrhythmic sudden death *(43)*.

Interventional therapy

Transcutaneous cardiac pacing may be considered in the patients with bradycardia and asystole. Radiofrequency ablation is indicated for abnormal electrical pathway arrhythmias including bundle-branch block and ventricular tachycardia. However, implantable cardioverter defibrillator (ICD) is indicated in those with SCD and there are growing evidences showing the additional benefit of radiofrequency ablation in treating ventricular arrhythmia and electrical storm. Prophylactic cardioverter defibrillator therapy in patients at high risk of SCD has been attempted, and the annual SCD rate has been reduced dramatically *(44)*.

Catheter ablation is a possible alternative to decrease the incidence of ICD therapy and is useful especially during electrical storm after ICD implantation. Successful catheter ablation of focal VF and VF storm targeting Purkinje-like potentials in patients with non-ischemic dilated cardiomyopathy has been performed *(45)*.

Cardiac surgery

Cardiac surgery can be a primary treatment for SCD. SCD in patients with anomalous origin of coronary artery is associated with the anatomical features including abnormal coursing, acute angle take-off and ostial abnormalities. Surgical treatment is a definitive therapy. However, simple coronary artery bypass grafting is not recommended due to the potential hazards of coronary steal phenomenon and poor patency of the mammary arterial grafts. Nevertheless, modified maneuvers, such as coronary ostial reimplantation, impinged coronary segment unroofing and coronary stent deployment, are advocated instead *(46)*. Surgical treatment of ventricular arrhythmias includes excision of ventricular tachycardia foci and excision of left ventricular aneurysms. Aortic valve replacement and mitral valve repair or replacement, associated with improved outcome of patients with hemo-

dynamically significant valvular stenosis and well-preserved ventricular function. Orthotopic heart transplantation is indicated in patients with pending SCD and refractory heart failure with expected survival improvement. Patients with long QT syndrome who do not respond to β-blockers are candidates for ICD implantation or high thoracic left sympathectomy *(44)*.

DISCUSSION

Ventricular arrhythmogenesis has been regarded as the main pathophysiological provocateur of SCD. The heterogeneous structural and functional conduction system impairments that disrupt the normal propagation of action potentials through the ventricles initiated by certain cytokine-related pathways predisposes to the impulses around an anatomic barrier in ischemic or scarred myocardium, or around a reentry in non-ischemic or structurally normal myocardium. Three general mechanisms of arrhythmia in genetic conditions predisposing to SCD have been known as abnormal repolarization (long QT syndrome, short QT syndrome and Brugada syndrome), slow ventricular conduction (Brugada syndrome) and aberrant intracellular calcium homeostasis (catecholaminergic polymorphic ventricular tachycardia). Molecular and genetic mechanisms interfering the $NADH/NAD^+$ imbalance, protein kinase C activation and phosphorylation of a specific serine residue (Ser1503) on NaV1.5 and mutations of the ion channel genes have been illustrated. More broad research in this regard is warranted.

The autonomic nervous system serves as to modulate cardiac electrophysiology and arrhythmogenesis. In inherited arrhythmia disorders, sympathetic stimulation implicates in ventricular tachyarrhythmias and SCDs. In the animals susceptible to sudden death, modulation of the autonomic tone may increase cardiac vagal activity and reduce the risk for VF and SCDs *(47)*.

Inflammatory arrhythmogenic mechanisms of proinflammatory cytokines have been received much attention. Inflammation links to various pathological processes, such as oxidative stress, apoptosis, fibrosis and arrhythmic substrate formation in the presence of endothelial dysfunction, platelet activation and coagulation cascade activation. Increased TNF-α, interleukin-6 and interleukin-4 levels was associated with more ventricular arrhythmias. Myocarditis, the actual inflammation of myocardium, represents a frequent cause of life-threatening ventricular arrhythmias and sudden death possibly through a modulation of ion channel function, mainly potassium and calcium channels in both viral and autoimmune myocarditis *(48)*. Gap junctions are critical for maintaining synchronized impulse propagation and repolarization. Heterogeneous expression of the principal ventricular gap junction protein Cx43 is associated with action potential duration dispersion across the anterior ventricular wall *(49)*. The Cx-containing channels are completely inactivated under inflammatory conditions, and the subsequent transmural electrophysiological heterogeneity of the left ventricle contributes to the underlying arrhythmia susceptibility *(49)*. Treatment with probucol by its antioxidant and/or antiinflammatory effects effectively attenuated left ventricular dysfunction and remodeling in tachycardia-induced heart failure model *(50)*.

CONCLUSIONS

The mechanisms of SCD are complex, and all might ultimately be attributed to their arrthmogenic property. Apoptotic and growth factor signaling pathways are the two major ways that the cytokines follow, in a common sense, with the gaseous molecules CO and NO involved, leading to conduction system impairment and eventually SCDs. The prophylactic antiarrhythmic agent or device therapy could reduce SCD incidence dramatically. Good understanding of the mechanisms of these cytokine-related pathways is crucial for the prevention and treatment of the causative cardiac disorders. New agents including apoptotic blockers, heme metabolite homologues, and c-Src, PIK3 and NKX2-5 inhibitors, *etc*., are highly anticipated in the prevention of SCDs in the near future.

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