Chapter 4

Ventricular Arrhythmia Risk in Noncardiac Diseases

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1. Introduction

Electrocardiographic changes were mentioned in several noncardiac diseases, due to multiple mechanisms: changes of the position of the heart, autonomic imbalance, hormonal abnormalities, interposition of fluid or tissue between the heart and the electrodes, increased blood pressure, cardiomyopathy of systemic diseases, electrolyte imbalances, or due to therapy [1, 2].

A prolonged ECG *QT interval* and an increased *QT dispersion* (QTd, the difference between the longest and shortest QT interval duration in all 12 standard ECG leads), are markers of ventricular arrythmia risk. Sudden cardiac death, a major public health problem, is caused, mainly, by ventricular fibrillation [3].

Besides a prolonged QT interval, longer than 450 ms in male and 460 ms in female [4], *late ventricular potentials* (LVPs), which are low amplitude and high frequency waveforms, appearing in the terminal part of the QRS complex, and are markers of an electrophysiological substrate for reentry ventricular arrythmias in a diseased myocardium, were also detected in several extracardiac diseases using signal averaged ECG [5].

Standard 12-lead ECG provides a bedside snapshot of the electrial activity of the heart, but *Holter electrocardiogarphy* enables detection of episodes of arrhythmia and evaluate therapeutic interventions [6].

2. Objective

The aim of the present chapter was to provide a concise overview of available data regarding epidemiology and pathophysiology of ventricular arrhythmias in several noncardiac

diseases, to mention the main methods used to assess arrhythmia risk, as well as to elucidate their relation to long-term outcome. Dyslipidemia, obesity, diabetes mellitus, liver, hematologic, neurologic and psychiatric disorders, are discussed.

3. Dyslipidaemia and ventricular arrhythmia risk

Elevated LDL cholesterol was associated with all manifestations of coronary artery disease including sudden cardiac death [7]. *Hypercholesterolemia* is not only atherogenic, but is also associated with autonomic imbalance, alteration of the contractile properties of the myocardium, increased oxidative stress and ventricular electrophysiological remodeling [8, 9]. Myocardial electrical remodeling due to hypercholesterolemia caused prolonged action potential durations, longer QTc (heart rate corrected QT interval durations), conduction slowing and increased repolarization dispersion [9, 10].

Several clinical and autopsy studies demonstrated an association between elevated cholesterol levels and sudden cardiac death [11, 12]. Gualdiero et al. reported a positive correlation between cholesterol level, QT dispersion and premature ventricular contractions in patients with isolated hypercholesterolemia, and normalization of serum cholesterol and QT dispersion and improvement of ventricular ectopic activity, with simvastatin [13]. Szabo et al. found significant correlations of QT interval duration and QT dispersion with total and LDL cholesterol, triglycerides and apoplipoprotein B, respectively, in patients with *type IIb hyperlipoproteinemia*, without myocardial ischemia, suggesting a direct effect of hyperlipidemia on ventricular repolarization [14]. LDL increases the cholesterol to phospholipid ratio in the cell membrane, enhancing membrane rigidity and impairing functionality of the ion channels and ventricular repolarization [14, 15]. Ventricular repolarization is reflected by the QT interval on the ECG, which is regulated mainly by potassium channels. On the other hand, type II hyperlipoproteinemia is characterized by accelerated atherosclerosis, related to small dense LDL synthesis.

It was also hypothesized that hypercholesterolemia causes repolarization abnormalities, probably, by beta or IK channel phosphorylation mediated mechanisms [9]. Hypercholesterolemia causes also endothelial dysfunction, with impaired microvascular vasodilatation, facilitating vasoconstriction, and electrical heterogeneity and extrasystolic activity [13]. The increase in the QT interval duration in cholesterol fed rabbits was lesser if L-Arginine was supplemented, suggesting a beneficial role of L-Arginine (a nitric acid precusror) in hypercholesterolemia induced repolarization characteristics [9]. L-Arginine increases endogenous nitric oxide, which may activate ATP dependent K channels, shortening the action potential [9].

Late ventricular potentials were detected in patients with high and moderately elevated serum cholesterol [5, 16].

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Statins have antiarrhythmic properties, exhibiting a protective effect against the occurrence of ventricular arrhythmias and atrial fibrillation, in addition to their lipid-lowering and anti-atherogenic effects [5, 12, 13, 17, 18]. The main mechanisms explaining, probably, the antiarrhythmic properties of statins are as follows: prevention of ischemia-induced electrophysiological effects that predispose to ventricular arrhythmias and ischemia-induced oxidative stress, decrease in ischemia-induced myocyte hypertrophy, reverse of neural remodeling induced by hypercholesterolemia, increase of heart rate variability, decrease of QT interval duration and variability, reversion of electrophysiological remodeling induced by hypercholesterolemia, increase in parasympathetic tone, changes in transmembrane ion channel properties, decrease of the incidence of late ventricular potentials [10, 12].

4. Ventricular arrhythmias in obesity and eating disorders

Morbid *obesity* was associated with high rates of sudden cardiac death [19, 20]. Lalani et al. reported a high prevalence of abnormal signal averaged ECGs in obese without known cardiovascular disease [20]. An increased QT dispersion was found in obese women, associated with left ventricular hypertrophy [21] and prolonged QT intervals were measured in obese patients [22-24]. Several mechanisms explain the high sudden cardiac death risk in obese, including: parasympathetic withdrawal, conduction abnormalities, cardiomyopathy of obesity with cardiomegaly and myocyte hypertrohy, lipotoxicity of the myocardium induced by free fatty acids, released from hypertrophied adipocytes in obese persons with myocardial steatosis, structural heterogeneity due to fatty infiltration of the heart, focal myocardial disarray, fibrosis and mononuclear cell infiltration [5, 19, 20, 25, 26]. Premature ventricular contractions (PVCs) are very prevalent in obese [27] and sudden cardiac death risk is increased in obese compared to normal weighted survivors of a myocardial infarction [28].

Weight loss causes a shortening of the QT interval, correlated with diastolic blood pressure decrease, and changes in time and frequency domain parameters of heart rate variability, with recovery of the physiological autonomic control (increase in parasympathetic and reduction in sympathetic indices [29].

QT prolongation, signal averaged ECG abnormalities and late ventricular potentials were reported in *eating disorders*, including both anorexia and bulimia nervosa [30]. Bulimia nervosa, an eating disorder characterized by binge eating and purging, was associated with QT interval prolongation, related to electrolyte imbalances, especially hypokalemia [31]. Anorexia nervosa carries the highest mortality of any psychiatric disorder, very often attributable to sudden cardiac death. Delayed cardiac repolarization and QT prolongation, not correlated with disease severity, were reported [32]. Any patient with an eating disorder should undergo standard 12-lead ECG.

Disease	Mechanisms	Methods and arrhythmia
Obesity	parasympathetic withdrawal, conduction abnormalities, cardiomyopathy of obesity, lipotoxicity of the myocardium induced by free fatty acids, structural heterogeneity due to fatty infiltration of the heart, focal myocardial disarray, fibrosis, mononuclear cell infiltration	SAECG QTd QT PVCs
Hypercholesterolemia	autonomic imbalance, endothelial dysfunction, oxidative stress, impaired functionality of ion channels	QTc QTd LVPs PVCs
Anorexia nervosa, Bulimia nervosa	electrolyte imbalances (hypokalemia)	QT, LVPs
Diabetes mellitus	autonomic imbalance, oxidative stress, increased cytosolic calcium, increased Na current, hyperinsulinemia, insulinresitance, hypokalemia	QT, QTd LVPs
Liver cirrhosis	cirrhotic cardiomyopathy, cardiac ion channel remodeling, electrolyte imbalances, impaired autonomic function	QT
Stroke, Subarachnoid hemorrhage	cardiac autonomic imbalance, neural interventions, norepinephrine, calcium influx, myocytolysis, hypokalemia, concomitant myocardial ischemia and heart failure, risk factors for coronary heart disease, aging, inflammation, Takotsubo cardiomyopathy	QT QTd VT, R/T, VF, Vf Holter monitoring
Intracranial hemorrhage	intraventricular blood, hydrocephalus	QTc PVCs, TdP
Neuromuscular disorders	cardiomyopathy, diffuse cardiac fibrosis and fatty acid infiltration, myocyte degeneration	QTcd, JTcd QTc, LVPs
Parkinson's disease	autonomic disturbance (intrinsic or iatrogenic), cardiovascular comorbidities, electrolyte imbalances, degeneration of cardioselective neurons	QT
Epilepsy	sympathovagal imbalance, impaired cardiac repolarization, dysfunction of cortical networks, ictal hypoxemia and hypercapnia, stress hormones, cardiorespiratory interactions, fibrosis (perivascular, interstitial)	QT QTd LVPs PVCs
Anemia	left ventricular hypertrophy, sympathetic nervous system activation, oxidative stress, chronic inflammation, decreased myocardial oxygen supply	QT QTd LVPs

Table 1. Mechanisms of ventricular arrhythmias and methods used to assess sudden cardiac risk in some extracardiac diseases

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5. Glucose metabolism disorders and ventricular arrhythmia risk

Several studies associate diabetes mellitus and hyperglycemia with sudden cardiac death, related to QT interval prolongation, appearance of late ventricular potentials, impaired depolarization and repolarization, enhanced sympathetic activity, oxidative stress, increased cytosolic calcium content, defective phosphoinositide 3-kinase signaling with increased persistent sodium current, premature and accelerated atherosclerosis, transient hypoglycemic episodes due to drug therapy, duration of diabetes, and renal failure, as target-organ damage, causing electrolyte imbalances [5, 33-36]. QT interval prolongation and increase of QT dispersion are predictive for sudden cardiac death in patients with *type 1 and 2 diabetes mellitus* [37]. QT interval duration was independently associated with glycated hemoglobin in patients with type 1 diabetes mellitus [38], and hyperinsulinemia and insulinresistance can contribute to QTc prolongation [39]. Li et al found a high prevalence of prolonged QTc intervals, and low height, high waist circumference, increased diastolic blood pressure levels, high postprandial glucose levels, high fasting insulin and presence of microalbuminuria, as risk factors for QTc prolongation among Chinese patients with type 2 diabetes mellitus [40].

Stress hyperglycemia on admission was found to be a predictor of mortality and arrhythmias in patients with acute myocardial infarction and could be used in the stratification of risk in these patients [5, 41, 42]. An independent association between hyperglycemia and prolonged QTc and increased QT dispersion was found in healthy, nondiabetic subjects [39].

Severe *hypoglycemia* is also associated with ventricular repolarization abnormalities, prolongation of the QT interval, and ventricular arrhythmias [35]. QTc interval prolongation was observed during the episodes of sever hypoglycemia compared to the recovered stage, in patients with type 2 diabetes mellitus, associated with increase in serum catecholamines, altered neural regulation and hypokalemia [43, 44]. The likelihood of ventricular arrhythmias is increased, particularly when hypoglycemia occurs in a patient with autonomic neuropathy [35]. Sudden nocturnal death in young people with type 1 diabetes could be due to cardiac arrhythmias induced by hypoglycemia [45]. Hypokalemia, caused by hyperinsulinemia and intracellular shift of potassium, could explain the altered cardiac repolarization during the episodes of hypoglycemia [43].

6. Liver diseases and ventricular arrhythmia risk

Several cardiac problems have been reported in patienst with *liver cirrhosis*, including chronotrope incompetence, cardiomyopathy and prolonged QT intervals, proportional to the Child-Pugh class [46]. A prolonged QT interval represents the most common electrocardiographic (ECG) finding in patients with liver cirrhosis and is the electrophysiological hallmark of "cirrhotic cardiomyopathy" [47, 48, 49]. Cirrhotic cardiomyopathy can appear in all forms of cirrhosis and includes systolic and diastolic dysfunction and electrophysiological abnormalities, in the absence of any known cardiac disease [48]. Cardiac ion channels remodeling has been noticed in patients with liver cirrhosis, with impaired K and Ca channels, due to

endotoxins and increased biliary acids, which alter beta-adrenoreceptor, G protein and ionic channels in patients with cholestasis [46].

QT prolongation in liver pathology was first described in alcoholic liver diseases [50]. Alcohol effects on life-threatening arrhythmias correlate directly with the amount and duration of alcohol intake; even small quantities are significant in susceptible individuals [35]. Further studies reported prolonged QT intervals in patients with *primary biliary cirrhosis* and other *chronic non-alcoholic liver diseases*, related to the severity of the autonomic neuropathy, and could detect patients with increased cardiovascular risk [51]. QT interval prolongation was related to the pathophysiology of cirrhosis itself and not to a specific cause of cirrhosis [52]. Prolonged QTc intervals were related to the presence of portal hypertension, including mild portal hypertension, and liver dysfunction [53]. Genovesi et al. reported significant correlations between QTc and each of the following: plasma calcium level, portal hypertension, and the hepatic venous pressure gradient [47]. Liver disease severity, alcoholic etiology, and serum uric acid were associated with prolonged QT interval in patients with liver cirrhosis, according to another study [48]. *Liver transplantation* may revert cardiac dysfunction [54] and prolonged QTc returns to normal values, in most of the patients, after liver transplantation, suggesting that liver disease may not be the only factor in the pathogenesis of prolonged QTc [52, 55]. Acute gastrointestinal bleeding was found to further prolong QTc in patients with liver cirrhosis, and QTc prolongation predicted bleeding induced mortality [56].

Concluding, the mechanisms by which liver cirrhosis affects ventricular repolarization are as follows: electrolyte imbalances, impaired autonomic function, subclinical cardiomyopathy, reduced β-adrenoreceptor function, postreceptor pathway defects, altered physical properties of myocyte plasma membrane, elevated levels of cardiotoxins, ion channel remodeling, portosystemic shunting and systemic circulatory disturbances [46-48, 53, 54, 57].

The clinical significance of QT prolongation in liver cirrhosis is unclear, considering that sudden cardiac death and torsades de pointes are rare [58].

QTc interval was also measured in patients with *chronic hepatitis C*, showing non-significant increases six months after starting combination therapy with pegylated interferon and ribavirin, in order to achieve sustained virological response [59].

7. Cerebrogenic arrhythmias and ventricular arrhythmia risk in neurologic diseases

Cardiac diseases are a well-known *stroke* risk factors and complicate stroke outcome [60]. Cardiac arrhythmias and electrocardiographic abnormalities are frequently observed after acute cerebrovascular events, even in the absence of structural heart disease [61]. With improved survival after major cardiovascular events and aging of the population, stroke followed by myocardial infarction and arrhythmias will be an increasing clinical entity in the coming decades [60]. The neurologic event is the main cause of death only in the first week after stroke [62]. After the first year, cardiovascular diseases are the main cause of death in

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stroke patients [63]. Atrial fibrillation, the most common arrhythmia in clinical practice, is a major risk factor for embolic stroke [60, 64]. Stroke and *subarachnoid hemorrhage* cause other cerebrogenic ECG findings as well, prolong the QT interval, increase QT dispersion and ventricular arrhythmia risk, mainly due to an autonomic nervous system dysregulation [1, 61, 65, 66]. Large, inverted T waves following a prolonged QTc interval, common after subarachnoid hemorrhage, are often termed as "cerebral" or "neurogenic" [67]. Brady- and tachyarrhythmia, including polymorphic ventricular tachycardia (PVT), have been also described in the setting of neurologic injury [68]. The greatest risk of arrhythmias is, probably, within the first 24 h after stroke, with a marked decline in time [69]. Activation of both sympathetic and parasympathetic systems has cumulative effect in the development of arrhythmias and myocardial damage after cerebral incidents, and the damage of the hypothalamic, insular, and brainstem region is crucial for the genesis of cardiac arrhythmias, due to neural connections with other cortical sites and the autonomic nervous system [61]. Sander et al, found increased norepinephrine levels in patients with insular infarction, significantly related to adverse outcome and QTc [70]. The sympathetic system has a major role in the pathogenesis of hypokalemia and may indirectly result in QTc prolongation after subarachnoid hemorrhage [61]. Probably constant catecholamine stimulation of beta-adrenoreceptors linked to membrane Na^+/K^+-ATPases causes a potassium influx, resulting in hypokalemia, and thus precipitating ventricular arrhythmias [62]. Both reduced heart-rate variability (HRV) and impaired baroreceptor reflex sensitivity (BRS) suggest impaired physiological central and cardiac autonomic reflex function [62]. Ventricular arrhythmogenesis following stroke, related to the cardiac autonomic imbalance is explained by two hypotheses [62]. The first involves damage to central nervous structures controlling the autonomic nervous system, resulting in sympathetic amplification or parasympathetic inhibition, with subsequent ECG changes, without permanent myocardium damage, and the second hypothesis proposes an augmented sympathetic discharge, resulting in increased secretion of catecholamine, causing myocytolysis [62]. The insula plays an important role in autonomic nervous function imbalance after stroke [62, 71]. Involvement of the right insula decreases basal sympathetic tone and may result in parasympathetic hyperactivity, and left insular lesions decrease parasympathetic activity and augment cardiac sympathetic tone [71]. Sympathetic hyperactivity prolongs repolarization duration and increases arrhythmogenesis [62].

A concomitant myocardial ischemia or necrosis, elevated blood pressure and heart failure may be also considered [1]. Autopsy of stroke patients, who developed repolarization abnormalities, revealed no obvious coronary artery atherosclerosis in most of them, and the only findings were petechial subendocardial hemorrhages and focal myofibrillar degeneration, reproducible with intravenous administration of catecholamines or electrical stimulation of the vagus nerve in laboratory animals [61]. Sudden calcium influx, mediated by catecholamines, impairs myocardial relaxation, leads to myocytolysis, myofibrillar degeneration, coronary vasoconstriction, myocardial ischemia and ECG changes, and is proarrhythmic [61, 62]. Elevated serum uric acid, direct neural interventions, inflammation, reactive oxygen species, electrolyte imbalances, the structural and electrophysiological changes of a senescent heart and comorbities can increase sudden cardiac death risk in stroke [61, 66]. Stroke survivors with a prolonged QT in V6, were identified to have an increased sud-

den cardiac death risk [72]. Prolonged QT intervals were associated with decreased survival rates and worse neurological outcomes at hospital discharge [73]. The prevalence of cardiac arrhythmias after acute stroke may reach 28%, higher after subarachnoid hemorrhage (37.5%) and in right sided lesions [61]. The most prevalent ECG findings were, besides atrial fibrillation, sinus tachycardia, atrio-ventricular block, repolarization changes, premature ventricular contractions, R on T phenomenon (R/T), non-sustained, sustained and polymorphic ventricular tachycardia (VT), ventricular fibrillation (VF) and flutter (Vf) [61, 62]. Independent risk factors for the development of ventricular arrhythmias in patients with aneurysmal subarachnoid hemorrhage were prolonged QTc and decreased heart rate, and therapy with angiotensin converting enzyme inhibitors and angiotensin receptor blockers was protective [74]. Literature data are insufficient to support the hypothesis that subarachnoid hemorrhage and stroke cause ventricular arrhythmias, considering that in most patients additional QT prolonging causes were mentioned, including hypokalemia, hypomagnesaemia, and congenital long QT syndrome, and patients with stroke usually have risk factors for coronary artery disease, such as hypertension, diabetes mellitus, and smoking, or advanced age, or left ventricular hypertrophy [61, 62, 75]. Several studies did not control pre-existing arrhythmias, were of short duration and did not explore the long-term consequences of ventricular arrhythmogenesis [62]. Another important limitation of most of the studies is the use of single surface ECG, because it may underestimate arrhythmia incidence in the acute phase of a stroke [62]. Holter monitoring revealed a higher incidence of ventricular arrhythmias after transient ischemic attacks, cerebral infarction and intracerebral hemorrhage compared to patients who were not continuously monitored (56% vs. 8%) [76].

It is also possible that in some cases, prolonged QTc actually existed before the development of stroke and it could be used as a *predictor of future stroke* in the general population [75]. The association of QTc with cardiovascular risk factors does not fully explain the prognostic significance of QTc as a stroke predictor, but it is possible, that prolonged QTc interval is a marker of silent undetected atherosclerotic vascular disease [75]. QTc was previously associated with markers of subclinical atherosclerosis, including carotid intima media thickness, arterial stiffness and endothelial dysfunction [77-80]. Probably, QTc prolongation may be a surrogate indicator of subclinical atherosclerosis and subsequently can be predictive of future atherosclerotic vascular events such as stroke, but it is not clear if it represents a marker, a limited adaptive or pathological process [75].

The ECG abnormalities observed in *intracranial hemorrhage* may also influence clinical outcome. QTc prolongation correlated with insular cortex involvement, presence of intraventricular blood, and hydrocephalus on admission CT scans in patients with intracranial hemorrhage [81]. A case of a 58-year-old woman, with several episodes of self-terminating torsade de pointes (TdP) following nonspecific ST-T changes, and prolonged QT after brainstem hemorrhage, has been reported in the literature [82]. Maramattom et al. found premature ventricular contractions and QTc prolongation at 24 hours from admission, not related with the location, volume and side of the hemorrhage, nor with the presence of hydrocephalus, extraparenchymal extension or troponin T elevation [83].

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It is uncertain whether ECG abnormalities are caused by the cerebrovascular event itself, considering that in the majority of studies patients' previous ECG data were unavailable [61]. Current management after stroke focuses mostly on the neurological function [62]. The QT interval and electrolyte levels should be monitored, and QT prolonging drugs should be avoided in patients with acute cerebrovascular events, especially for female patients with insular cortex lesions [61]. Multiple studies recommend continuous ECG monitoring, however, others believe that only severely QTc interval prolongation predicts cardiac complications [62]. Follow up studies with large sample sizes, considering previous arrhythmias and coronary heart disease, are needed, to establish the incidence of ventricular arrhythmias after stroke, and clear guidelines for clinicians approaching stroke patients with increased ventricular arrhythmia risk [62].

Goldberger et al. reported an unusual case of idiopathic acute *encephalopathy*, with persistent fever, refractory seizure, marked ventricular repolarization with bursts of torsade de pointes, diffuse ST elevations and Brugada-like pattern, treated with propofol [68].

Two mechanisms connecting cardiomyopathies and neurological diseases have been described: cardiomyopathies may either secondarily cause neurological disease or may represent the cardiac manifestation of a neurological disease, especially neuromuscular disorders [2]. Sudden cardiac death and ventricular arrhythmias occur mainly in neurological diseases causing hypertrophic cardiomyopathy (in adolescents and young adults), or dilated cardiomyopathy (among which syncope is a common clinical manifestation), or arrhythmogenic right ventricular dysplasia [2]. Takotsubo cardiomyopathy ("the broken heart" syndrome) was reported after stroke, subarachnoid bleeding, spontaneous intracerebral bleeding, *spinal injury and head trauma*, and the patients are prone to arrhythmias, heart failure or thrombus formation within the left ventricle during the acute phase [2]. *Inherited neuromuscular disorders* may predispose to premature ventricular contractions, monomorphic and polymorphic ventricular tachycardia and sudden cardiac death, due to degenerative changes in the myocardium [35]. Electrical abnormalities, including QTc and JTc dispersion (the difference between the longest and shortest JT interval duration), may be the earliest manifestation of cardiomyopathy in patients with *Emery-Dreifuss muscular dystrophy*, a hereditary muscle disorder characterized by slowly progressive muscle wasting and weakness, with humero-peroneal distribution [84]. QTc and JTc dispersions (QTcd, JTcd) reflect ventricular repolarization heterogeneities, due to diffuse fibrosis and fatty acid infiltration in Emery-Dreifuss muscular dystrophy, and if elevated, increase the risk of development of malignant ventricular arrhythmias via early afterdepolarization and reentry (polymorphic ventricular tachyarrhythmia), facilitated by intramural functional conduction blocks [84]. The mechanisms underlying sudden cardiac death in *myotonic dystrophy type 1* are: bradyarrhythmias due to cardiac conduction abnormalities, and the increased values of the QT variability index, demonstrating an important heart involvement, extended beyond the conduction system [85]. *Duchenne muscular dystrophy*, related to a mutation in the dystrophin gene, the most common neuromuscular disease, causes progressive proximal muscle weakness of the legs and pelvis and a loss of muscle mass. It affects also the heart (myocyte degeneration, fibrosis and fatty infiltration), impairing ventricular repolarization, causing autonomic dysfunction, QTc prolongation and increase of QT

dispersion, as an independent risk factor for ventricular arrhythmias of Lown grade III or higher [86-88]. Late ventricular potentials were reported in patients with Duchenne muscular dystrophy (31%), indicating the presence of a substrate for reentry ventricular arrhythmias, associated with local myocardial fibrosis, and identifying patients at high risk for sudden cardiac death [89]. Cardiac involvement was also mentioned in other dystrophinopathies, due to the replacement of myocardium by connective tissue or fat, but it remains subclinical in Duchenne and *Becker muscular dystrophy* [86]. Patients with primary and secondary neuromuscular disorders need to be obligatorily screened for cardiac disease and ventricular arrhythmia risk, as soon as the neurological diagnosis is established, and cardiac investigations should be regularly repeated, especially in the case of severe cardiac involvement [2]. Once cardiac involvement occurs, the clinician should consider invasive electrophysiological studies and ICD implantation [35].

In *Parkinson's disease* factors affecting cardiac conduction may include intrinsic or iatrogenic autonomic disturbances, cardiovascular comorbidities (cardiac ischemia, ventricular hypertrophy), and electrolyte imbalances due to diuretics [90]. The most common prescribed drugs with QT prolonging effect were: Dromperidone, with antiemetic effect and also used to treat symptomatic postural hypotension, Citalopram, an antidepressant, and some antimicrobial agents (macrolides, azoles and fluoroquinolones) in a study conducted by Malek et al. [90]. Combining such drugs with some antipsychotics, tricyclic antidepressants, antihistamines and anti-retrovirals has additive influence on QT interval prolongation [90]. Large epidemiological studies emphasized the difficulties in detecting transient drug-induced ventricular arrhythmia in outpatient clinics, due to too few events, despite frequent syncope [91]. Oka et al considered that QTc intervals are closely related to autonomic nervous system dysfunction in patients with Parkinson's disease, related to the progression of the disease [92, 93]. Deguchi et al. found prolonged QTc intervals in patients with Parkinson's disease, reflecting the degeneration of cardioselective sympathetic and parasympathetic neurons [94]. Artifacts related to muscle tremor may affect ECGs in patients with Parkinson's disease, but methods were found to reduce noise and variance of QTc [95]. Drugs known to prolong the QT interval are often prescribed in patients with Parkinson's disease, and therapy should consider additional risk factors, especially comorbidities, autonomic dysfunction and degeneration of cardioselective neurons [90, 94].

Sudden unexpected death in *epilepsy* is probably caused by periictal cardiorespiratory alterations, such as central apnea, bradyarrhythmia, and neurogenic pulmonary edema, and ventricular arrhythmias [96, 97]. Sudden cardiac death in patients with seizure disorders is facilitated by associated cardiovascular diseases, pathologic cardiac repolarization, sympathovagal imbalance and therapy used to treat the disease [35, 96, 97]. A pathologic cardiac repolarization has been described in epileptic patients, with prolonged intercritical and periictal QT intervals, increased QT dispersion and shortened QTc after generalized tonic-clonic seizures, but fatal seizure-related ventricular arrhythmias are very rare [96]. On the other hand, no LVPs and significant standard ECG abnormalities were recorded in patients with newly diagnosed epilepsy, without clinical evidence of heart disease, three to nine months after therapy start, demonstrating lack of antiepileptic drugs induced electrocardiographic

abnormalities [98]. Rejdak et al. reported abnormal SAECGs and late ventricular potentials in epilepsy patients, associated with disease duration, higher monthly seizure frequency, refractory epilepsy and tendency for higher number of generalized tonic-clonic seizures, polytherapy [99]. Data about intercritical QT intervals in epileptic patients are contradictory; it was found within normal limits, shorter or longer, and antiepileptic drugs and the ketogenic diet are potential confounders [96]. Transient dysfunction of cortical networks, as interictal epileptiform electroencephalographic discharges, can impair cardiac repolarization causing transient QTc prolongation [100]. Potential mechanisms of periictal QTc prolongation include cerebral dysregulation, ictal hypoxemia and hypercapnia, cardiorespiratory interactions, sympathetic stimulation, release of stress hormones and cardiac dysfunction [96, 101]. Generalized tonic-clonic seizures are a risk factor for sudden cardiac death, and cause QTc shortening due probably to seizure-related release of catecholamines, hyperkalemia, and acidosis [96]. The increased QT dispersion is explained by autonomic dysfunction with increased sympathetic tone, and subtle perivascular and interstitial fibrosis, which have been described in epilepsy [102, 103].

In order to reduce the risk of, or prevent, sudden cardiac death, 12-lead ECG should be performed in every patient with epilepsy, in order to identify those at high risk, and, therapy may include antiarrhythmic medication and implantation of cardiac combined pacemaker–defibrillator devices [96]. Cardiogenic syncope is often a difficult differential diagnosis for seizures, and long QT with recurrent syncope has been mistaken for epilepsy, and, epileptic seizures, probably due to cerebral hypoperfusion, have been described in patients with congenital long QT [96, 104]. Mutations of ionic channels could affect both heart and brain function, thereby leading to a susceptibility to epilepsy and cardiac arrhythmias [96].

8. Hematologic diseases and ventricular arrhythmia risk

Anemia and red blood cells transfusions have been associated with arrhythmias. Several electrocardiographic changes were previously mentioned in patients with *anemia*, including prolonged QT intervals, ST segment depression, inverted T waves, increased R amplitude after stress test [105]. Anemia was associated with prolonged QT intervals in hypertensive [106] and end stage renal disease patients [107], as well. Associations between the QT interval and serum ferritin level [108] and anisocytosis [106], respectively, were mentioned. Scheller et al. [109] reported a gradual prolongation of the QT and QTc interval in normovolemic anemia. Anemia may increase cardiac output and heart rate, may lead to eccentric left ventricular hypertrophy, activation of the sympathetic nervous system, stimulation of the renin angiotensin aldosterone system, and is closely associated with chronic inflammation and increased oxidative stress [106, 110]. Tissue hypoxia and changes in blood flow patterns due to low hemoglobin may play an atherogenic role [110]. The pathophysiological link between anemia and prolonged QT intervals and ventricular arrhythmia risk is, probably, hypoxia and decreased myocardial oxygen supply [106].

Jaja et al [111] reported a blunted autonomic cardiovascular response to changes in posture in patients with *sickle cell anemia*. Left ventricular systolic and diastolic dysfunction, increased

QTc intervals and QT dispersions and late ventricular potentials were found in patients with *beta-thalassemia*, a genetic cause of anemia, due to reduced synthesis of beta-globin chains [112, 113]. Several mechanisms explain increased sudden cardiac death in patients with thalassemia, including iron overload thalassemic cardiomyopathy, with patchy cardiac iron depostition (due to intensive blood transfusions), changes in calcium homeostasis, elevated prostaglandin E2 to prostacyclin ratio, increased interleukin 1 level and lipid peroxidation [106, 113, 114].

Athar et al. reported that packed red blood cells (PRBC) *transfusions* were independently associated with an increased risk of new onset cardiac arrhythmias and conduction abnormalities in patients with acute myocardial infarction [64]. Multiple factors contributed to the development of atrial fibrillation in the setting of acute myocardial infarction, including pericarditis, atrial ischemia, infarction, changes in autonomic tone, metabolic abnormalities, increased atrial pressures and inflammation [64]. The inflammatory process, exacerbated by PRBC transfusion, tissue hypoxia, exacerbations of cardiac ischemia and reinfarctions resulting from deficiencies in the ability of stored packed red blood cells to deliver oxygen to tissue, may explain the appearance of ventricular arrhythmias [64].

A significant correlation was found between QT dispersion and *platelet count* in healthy centenarians, hypothesizing that a reduced number of platelets and the maintenance of normal QT dispersion may contribute to the extreme longevity and protects centenarians from cardiovascular events [115].

Anthracyclines, used in therapy of patients with *hematological malignancies*, may have cardiotoxic effects, and the typical cardiac manifestations include cardiomyopathy, QT prolongation, ventricular ectopy and torsade de pointes [35, 116]. High intermittent doses and excessive cumulative doses increase the risk of cardiomyopathy and fatal arrhythmias, risk factors including age, female gender, hypertension, preexisting cardiac diseases, electrolyte imbalances, associated therapy with other QT prolonging drugs [35, 117]. Long term cardiac monitoring of patients is needed, in order to prevent sudden cardiac death and cardiac decompensation.

9. Conclusions

Sudden cardiac death, due to fatal ventricular arrhythmias, continues to be an important public health problem in developed countries. A high ventricular arrhythmia risk has been reported in several noncardiac diseases, including metabolic, liver, blood, neurological and psychiatric disorders. The most common mechanisms were: autonomic and electrolyte imbalances, ion channel remodeling, cardiomyopathies, increased oxidative stress and QT prolonging drugs. Most of the mentioned studies used standard 12-lead ECG and surrogate markers of ventricular arrhythmia risk (QT interval duration, QT dispersion and signal averaged ECG), but several papers reported ventricular arrhythmias, as well.

Considering that there are no guidelines for the prevention and therapy of arrhythmias appearing in most of extracardiac disorders, the present review highlighted important epidemiological and pathophysiological issues related to this topic.

Selected patients could benefit from electrocardiographic monitoring, specific therapy and avoidance of QT prolonging drugs, decreasing the burden of sudden cardiac death. Large follow up studies are needed, controlling for previous QT interval durations, arrhythmias, coronary heart disease and cardiovascular risk factors, in order to assess the prevalence of ventricular arrhythmias in noncardiac diseases, to identify further mechanisms and risk factors for arrhythmogenesis, and to elaborate clear guidelines for clinicians approaching the mentioned pathology.

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