

REVIEW



Mechanisms of toxic cardiomyopathy

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ABSTRACT

Background: Dilated cardiomyopathy is a frequent disease responsible for 40–50% of cases of heart failure. Idiopathic cardiomyopathy is a primary disorder often related to familial/genetic predisposition. Before the diagnosis of idiopathic cardiomyopathy is made, clinicians must not only rule out viral and immune causes, but also toxic causes such as drugs, environmental agents, illicit substances and natural toxins.

Objective: The objective of this review is to present recent data on the mechanisms underlying toxic cardiomyopathy.

Methods: The US National Library of Medicine Pubmed database was searched from 1980 to December 2017 utilizing the combinations of the search terms “toxic cardiomyopathy”, “drugs”, “anticancer drugs”, “azidothymidine”, “rosiglitazone”, “carbon monoxide”, “alcohol”, “illicit drugs”, “cocaine”, “metamfetamine”, “metals”, “venom”. A total of 339 articles were screened and papers that dealt with the pathophysiology of toxic cardiomyopathy, either in animal models or in clinical practice were selected, with preference being given to more recently published papers, which left 92 articles.

Anticancer drugs: The mechanisms of anthracycline-induced cardiotoxicity are primarily related to their mechanisms of action as anticancer drugs, mainly the inhibition of topoisomerase II β and DNA cleavage. Additional metabolic or oxidative stress factors may play a part, together with interference with iron metabolism. The more recent drugs, trastuzumab and imatinib, also influence stress pathways.

Antiretroviral agents: Azidothymidine is cardiotoxic as a result of mitochondrial toxicity. In addition to energy depletion, azidothymidine also increases the production of mitochondrial reactive oxygen species (ROS).

Antidiabetic drugs: The cardiotoxicity of thiazolidinedione antidiabetic drugs is still under investigation, though interference with mitochondrial respiration or oxidative stress is suspected.

Cocaine: Among the multiple mechanisms involved in cocaine-related cardiotoxicity, excessive sympathetic stimulation with increased myocardial oxygen consumption is well documented in the acute form of left ventricular dysfunction. As for cocaine-related cardiomyopathy, the role of apoptosis and ROS is under investigation.

Ethanol: The aetiology of ethanol-related cardiotoxicity is multifactorial, with individual susceptibility being important. It involves apoptosis, alterations of the excitation–contraction coupling in cardiac myocytes, structural and functional alterations of the mitochondria and sarcoplasmic reticulum, changes in cytosolic calcium flows, changes in calcium sensitivity of myofilaments, alterations of mitochondrial oxidation, deregulation of protein synthesis, decrease of contractile proteins and disproportion between the different types of myofibrils, changes in the regulation of myosin ATPase, up-regulation of the L-type calcium channels, increase of oxidative stress, and induction of ANP and p21 mRNA expression in ventricular myocardium.

Metamfetamines: Catecholamine-mediated toxicity is the probable cause, with a possible role for genetic susceptibility.

Carbon monoxide: In addition to hypoxic injury, carbon monoxide is also directly toxic to the mitochondria, with impairment of mitochondrial respiratory chain at the cytochrome c oxidase level, decrease of glutathione concentrations and of ATP production. There is no evidence for a delayed dilated cardiomyopathy in survivors of an acute exposure.

Metals: Cobalt-related cardiomyopathy probably results from interference with energy production and contractile mechanisms, but additional factors (nutrition, hypothyroidism) are often required. Antimony may cause lethal oxidative stress and cell death mediated by elevation in intra-cellular calcium. Proposed mechanisms for mercury toxicity include glutathione depletion, production of ROS, and interruption in selenium-dependent endogenous enzymatic reactions. The existence of a lithium-induced cardiomyopathy is still debated.

Scorpion venom: Catecholamine release is the probable cause of acute cardiomyopathy following scorpion envenomation.

Conclusions: The mechanisms behind toxic cardiomyopathy are complex and multifactorial but include interference with myocardial cell bioenergetics and intracellular calcium handling, the generation of ROS, neurohormonal stress, and induction of apoptosis.

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Introduction

Cardiomyopathy is usually defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality [1]. The modern classification of cardiomyopathies relies on specific morphological and functional phenotypes and on further sub-classification into familial (with genetic determinants) and non-familial forms. Briefly, hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy are distinguished.

The term takotsubo cardiomyopathy refers to a transient, reversible ventricular dysfunction with normal coronary arteries. Acute physical or emotional distress may play a significant role in the development of this catecholamine-mediated cardiomyopathy. Drug overdose or substance abuse may also be triggering factors [2]. The clinical presentation and pathophysiology of takotsubo cardiomyopathy clearly differs from other cardiomyopathies and should probably be included more appropriately within the spectrum of ischemic heart disease [3].

Dilated cardiomyopathy is defined by the presence of left ventricular (LV) systolic dysfunction in the absence of abnormal loading conditions (arterial hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment [1]. A family history of dilated cardiomyopathy is present in over 50% of patients. Before clinicians conclude that cardiomyopathy is of the idiopathic type, toxic as well as viral and immune causes must also be considered.

The true prevalence of toxins related-dilated cardiomyopathy in the general population is not known. For some drugs (anticancer drugs), a clear signal is arising from epidemiological studies [4], while the relationship remains more doubtful for numerous other substances.

Objective

The objective of this review is to present recent data (where available) on the possible mechanisms of the chronic forms of cardiomyopathy, particularly dilated cardiomyopathy, and the most commonly implicated drugs, environmental agents, substances of abuse or natural toxins. Acute toxicity will also be considered when the pathophysiology is helpful to clarify the mechanisms leading to subacute or chronic injury, or when a reversible form of cardiomyopathy is dominant at the acute phase of exposure. The pathophysiology of takotsubo cardiomyopathy will not be discussed. Specific cardiovascular drugs (e.g., calcium-channel blockers, beta-blockers) will be excluded from this review as they are mostly associated in overdose with acute heart failure.

Methods

We performed a target search of available English literature on pubmed.gov and scholar.google.com from 1980 to

December 2017. A first search using “toxic cardiomyopathy” as key word identified 1089 papers; only 166 papers were found by the combination (drugs AND toxic cardiomyopathy). Based on review papers, the search was refined by including the following terms: (anticancer drugs OR azidothymidine OR rosiglitazone OR carbon monoxide OR alcohol OR cocaine OR metamfetamines OR metals OR venom) AND toxic cardiomyopathy. A total of 339 articles were screened. Papers that pertained to the diagnosis or treatment of toxic cardiomyopathy were excluded and full-length articles dealing with the pathophysiology of toxic cardiomyopathy, either in animal models or in clinical practice, were selected. Papers published after 2010 were preferentially considered in order to cover the more recent developments in the understanding of the causative mechanisms, which left 92 articles.

Anticancer drugs

There is an abundant literature on anticancer drug-related cardiotoxicity and a detailed approach is beyond the scope of this review. Only recent mechanisms of toxicity or predisposing factors of the chronic (and less reversible) form will be discussed.

Established risk factors for antineoplastic drug-induced cardiotoxicity include a greater cumulative dose (as mainly shown for anthracyclines), concomitant cardiac irradiation, higher individual doses, shorter infusion time, association with another cardiotoxic drug, age older than 65 years, female sex and cardiovascular comorbidity [5]. The reversibility of the dose-dependent anthracyclines-related cardiotoxicity is poor or absent.

Anthracyclines

The dose-dependent nature of doxorubicin-induced heart failure was confirmed in a recent retrospective analysis [6]. In this study, the estimated incidence of cardiac toxicity was much higher than previously reported (5% at a cumulative dose of 400 mg/m², 26% at 550 mg/m² and 48% at 700 mg/m²) [6]. Associated therapies (mediastinal irradiation, trastuzumab) are increasing the risk of anthracycline-related cardiotoxicity. Acute toxicity is uncommon (\approx 1%) and generally reversible, whereas early-onset chronic progressive toxicity (1.6–2.1%) developing during treatment and late-onset chronic progressive types (1.6–5%) are more likely to be irreversible. The chronic form may develop after a delay of 10–15 years after the initial chemotherapy.

The mechanisms of anthracycline-induced cardiotoxicity are mostly in relationship with their mechanisms of action as anticancer drugs. The main mechanism of cytotoxicity, including to the myocardium, is the cleavage of DNA by the inhibition of topoisomerase II β . Anthracyclines may also disrupt neuregulin-Erb (NRG) receptor signalling, a mechanism that is involved in cardiomyocytes growth and survival [7]. In addition, there is experimental evidence for lipid peroxidation and oxidative stress, cardiomyocyte apoptosis, impaired synthesis of DNA, RNA and transcription factors, changes in mitochondrial bioenergetics and in calcium

homeostasis [7–11]. The implication of iron metabolism is still debated, as among iron chelators, only desrazoxane seemed to offer some cardioprotection through its action on topoisomerase II [12].

The contribution of genetic factors to the variability of the anthracycline-induced cardiotoxicity is supported by a limited number of observations in adults. The role of NAD(P)H oxidase and oxidase stress seems important for anthracycline induced-cardiotoxicity. Wojnowski et al. [13] have looked in a case-control study at single nucleotide polymorphisms in genes involved in reactive oxygen species (ROS) generation or in drug efflux transporters. They found a relationship between some variants of a NAD(P)H subunit and of a multidrug efflux transporter, and a higher risk for developing cardiotoxicity. However, the results in the pediatric population appear discordant and a clear genotype-response correlation has not so far been demonstrated.

Trastuzumab

Trastuzumab is a monoclonal antibody that inhibits the activation of a tyrosine-protein kinase receptor. Trastuzumab has been shown to aggravate anthracycline-induced cardiac damage, with a higher incidence of heart failure in patients receiving this combined therapy [14]. In patients treated with trastuzumab alone, a decreased LV ejection fraction while undergoing therapy occurs frequently (up to 28%) and is usually reversible [15]. This questions the need to stop trastuzumab in patients who remain asymptomatic. Trastuzumab triggers cellular oxidative stress and alters the expression of myocardial genes essential for DNA repair and cardiac and mitochondrial function [16].

Imatinib

Imatinib is also a tyrosine kinase inhibitor. Mitochondrial impairment, with alterations in the endoplasmic reticulum stress pathways is the main hypothetical mechanism; cell death is aggravated further by the presence of oxidative stress [17,18].

Sunitinib

Sunitinib is a potent antiangiogenic drug. Sunitinib is undoubtedly cardiotoxic, probably by inhibiting ribosomal S6 kinase and AMP-activated protein kinase [19,20].

Antiretroviral agents

Azidothymidine

Long-term treatment with azidothymidine has been associated with the development of cardiomyopathy as a result of mitochondrial toxicity. In addition to energy depletion, it seems also that azidothymidine increases ROS production in mitochondria [21]. This is supported by the fact that azidothymidine-induced cardiomyopathy is prevented in mitochondrial superoxide dismutase transgenic mice [22].

Antidiabetic drugs

Rosiglitazone

A suspicion of drug-related cardiotoxicity is arising for rosiglitazone. The exact mechanism of cardiotoxicity is not known, though interference with mitochondrial respiration or oxidative stress is under investigation [23,24].

Antidepressants and antipsychotics

The possibility that some antidepressants and antipsychotic drugs (imipramine, fluvoxamine, venlafaxine, olanzapine, clozapine or venlafaxine) can cause cardiomyopathy has been suggested [4]. This complication should be clearly differentiated from the acute effects on cardiac conduction illustrated by the widening of QRS complexes on the electrocardiogram (EKG) induced by fast sodium channel inhibition. An acute but reversible form of diffusely depressed myocardial contractility has been observed occasionally with large venlafaxine overdoses; there is a probable overlap with more typical forms of takotsubo cardiomyopathy. One of the most likely explanations is that this is due to catecholamine-induced myocardial damage in conjunction with the inhibition of nor-epinephrine (and dopamine) reuptake. A possible role for CYP2D6 polymorphism has also been proposed. [25,26].

Cocaine

The exact incidence of cocaine-induced cardiomyopathy is unknown and likely underreported. The amount and duration of cocaine use necessary to develop cocaine cardiomyopathy is currently unclear. Among 430 consecutive patients with dilated cardiomyopathy, 10 (2.3%) were ascribed to congestive cardiomyopathy on the basis of a history of chronic cocaine exposure (12.8 ± 6 years), detectable concentrations of cocaine metabolites, and on the histological and ultrastructural modifications [27].

Cocaine exerts numerous cardiotoxic effects both acutely and as a result of chronic use. Acute cardiovascular manifestations include arterial hypertension, aortic dissection, arrhythmias, and myocardial ischemia. The mechanisms behind these effects are mainly related to excessive sympathetic stimulation, with consequent increased chronotropic and inotropic effects, and increased peripheral vasoconstriction [28]. Myocardial ischemia results also from the imbalance between oxygen delivery and consumption and from a prothrombotic state.

The acute form of heart failure with LV dysfunction may be explained by animal and humans experiments showing that the intracoronary administration of cocaine caused an acute elevation in LV pressures, LV dilation and reduction in contractility [29,30]. The negative inotropic and lusitropic response may be mediated by the local anesthetic property of cocaine, with consequent alterations of intracellular calcium handling [31]. There is a dose-effect relationship as low to moderate concentrations of cocaine have positive inotropic and lusitropic effects, due to sympathetic stimulation, while the negative effects of higher concentrations are due

to the direct local anesthetic effects of cocaine on excitation–contraction coupling [31].

The repeated description of takotsubo cardiomyopathy among cocaine abusers suggests that catecholamine surge is involved in acute reversible LV dysfunction [32].

The prevalent hypothesis for the more chronic form of cocaine-related dilated cardiomyopathy was that repeated ischemic injury led to myocardial scarring. However, recent research proposes a role for apoptosis and ROS production [33,34]. ROS can be produced by auto-oxidation of catecholamines which have accumulated in the myocardium, due to the interference of cocaine with monoamine reuptake systems. Catecholamines may also contribute to ROS formation through adrenergic stimulation and through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADPH oxidase-generated ROS may play an important role in modulating ROS production by other enzymatic sources such as endothelial NOS or xanthine oxidoreductase.

The hypothesis of ROS involvement in the acute form of LV dysfunction was studied in a rat experimental model [35]. It was shown that the echocardiographic changes of acute LV dysfunction could be prevented by the administration of apocynin, an inhibitor of NADPH oxidase, and allopurinol, an inhibitor of xanthine oxidoreductase. Concurrently, there was a reduction in the production of superoxide anions.

In humans, the hypothesis of myocardial oxidative damage was also investigated from endomyocardial biopsies obtained from patients with chronic cocaine-related cardiomyopathy that were compared to biopsies obtained from patients with postoperative LV dysfunction [27]. The results confirmed the absence of any significant inflammatory reaction in the myocardium, with as main features contraction bands and lysis of the myofibrils, myocyte swelling and blebbing of the sarcolemma. Myocyte necrosis and apoptosis were higher in comparison with patients with dilated cardiomyopathy from other origin.

Finally, a more classical pattern of myocarditis, with cellular infiltrates (lymphocytes or eosinophils) has been reported rarely [36].

Ethanol

Studies examining the acute effect of alcohol intoxication on myocardial function parameters are inconsistent, depending upon age, gender, quantity of alcohol consumed, and the imaging methods used to detect cardiovascular changes. Recent echocardiographic investigations in human volunteers have shown that acute excessive alcohol ingestion was able to cause a transient toxic effect on myocardial deformation [37]. The mechanism of this impairment is unclear and it is too early to affirm that the chronic alteration of myocardial function is the result of repeated acute effects.

The existence of a direct causal link between excessive alcohol intake and the development of dilated cardiomyopathy is still controversial, but alcoholic cardiomyopathy is now considered as a distinct entity [38,39]. Basic research is still ongoing to identify the mechanisms of alcohol-induced damage to the cardiomyocyte. It is now well accepted that

the mechanisms are multifactorial and would include at least the following: apoptosis, alterations of the excitation–contraction coupling in cardiac myocytes, structural and functional alterations of the mitochondria and sarcoplasmic reticulum, changes in cytosolic calcium flows, changes in calcium sensitivity of myofilaments, alterations of mitochondrial oxidation, deregulation of protein synthesis, decrease of contractile proteins and disproportion between the different types of myofibrils, changes in the regulation of myosin ATPase, up-regulation of the L-type calcium channels, increase of oxidative stress, induction of ANP and p21 mRNA expression in ventricular myocardium, and activation of the renin–angiotensin system and of the sympathetic nervous system [38–43].

The central role of individual susceptibility has been outlined. In order to explain this susceptibility, metabolic and genetic factors were investigated [44]. The main enzymatic pathways involved in ethanol metabolism are alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), cytochrome P450 (CYP2E1) and catalase [40]. The prevalent hypothesis is that acetaldehyde, the first oxidized metabolite of ethanol, is far more reactive and toxic than ethanol and may contribute to the cardiac damage following chronic alcohol abuse [45].

Hypothetically, the mechanisms of ethanol toxicity and cardiac injury may involve different pathways: more rapid acetaldehyde conversion and accumulation by the activity of fast alcohol dehydrogenase (ADH1B), delayed metabolism of toxic acetaldehyde due to reduced enzyme activity due to the variant aldehyde dehydrogenase 2 (ALDH2) and ROS generation by higher CYP2E1 activity due to genetic polymorphisms [46]. Among the enzymes involved in ethanol detoxification, the mitochondrial ALDH2 demonstrated cardioprotective effects against ethanol toxicity in a transgenic mouse model with ALDH2-overexpressing hearts [47].

A recent study in an Asian population demonstrates the possible influence of genetic variants (ADH1B, ALDH2, CYP2E1) on alcohol myocardial susceptibility [40]. By contrast, polymorphisms in genes coding for components of the renin–angiotensin–aldosterone system were not associated with an increased risk to develop the pattern of alcoholic cardiomyopathy [48].

Metamfetamines

Metamfetamines are sympathomimetic amines that have numerous cardiovascular adverse effects [49]. Co-ingestion of other substances (cocaine) or prior chronic use of cardiotoxic drugs causing cardiomyopathy may further potentiate cardiac impact of metamfetamines. The cardiac complications of metamfetamines are hypothesized to arise from a variety of mechanisms. Animal data support the hypothesis of a catecholamine-mediated toxicity, with pathognomonic histological features of cellular death, fibrosis and contraction band necrosis [50]. A similar pattern was observed in some human myocardial postmortem specimens [51].

However, different patterns of metamfetamine-associated cardiomyopathy have been described and the presumed

mechanisms of toxicity may be somewhat different. The hypertrophic form and the takotsubo pattern may be related to the stimulation of peripheral or myocardial adrenoceptors [51], while the dilated form may be due to the direct toxicity of metamfetamine to cardiac myocytes [52].

In addition, some abusers will also develop true ischemic cardiomyopathy. Vulnerability to the development of metamfetamine-associated cardiomyopathy appears to be genetically influenced with an elevated risk in the subpopulation of cytochrome P450 CYP2D6 extensive metabolizers [53]. Finally, some reversibility appears possible after abstinence from metamfetamines.

Carbon monoxide

The incidence of carbon monoxide (CO)-related cardiomyopathy following acute CO exposure is extremely variable. Different patterns exist, from apical ballooning (takotsubo cardiomyopathy) to global hypokinesia. After acute CO exposure, the incidence of CO-induced cardiomyopathy on transthoracic echocardiography may vary from 3% when all patients are considered to as high as 74.4% when myocardial injury has been previously documented by troponin elevation [54,55]. The recovery time appears shorter in patients with global dysfunction (usually within 72 h) in comparison with the takotsubo pattern. The patients developing transient myocardial dysfunction have an incidence of additional cardiovascular risk factors (hypertension, smoking) comparable to that observed in the general population [55]. In a rabbit experimental model, exposure to 180 ppm of carbon monoxide for 2 weeks led to ultrastructural myocardial changes [56].

There is no evidence for a delayed dilated cardiomyopathy in patients who survive acute CO exposure. There are limited data regarding the relationship between CO poisoning and cardiac structural deterioration. Usually, the regional LV dysfunction does not match with the territory of coronary arteries [57]. While the direct role of hypoxia cannot be discarded, no direct correlation between the carboxyhemoglobin concentration and severity of LV dysfunction has been demonstrated to date.

The classical hypothesis is that the binding of CO to intracellular myoglobin in the myocardium impairs oxygen delivery to the mitochondria, and that subsequent energy disorders lead to cardiac contractile decrease [58–62]. Carbon monoxide is also directly toxic for mitochondria, with impairment of mitochondrial respiratory chain at the cytochrome c oxidase level, decrease of glutathione concentrations and of ATP generation [63–65]. Finally, a catecholamine surge is also likely involved, mainly for the takotsubo pattern [55].

As CO is also an environmental pollutant, prolonged CO exposure is also responsible for oxidative and inflammatory stresses in the heart. In particular, in an experimental model of low CO exposure in rats it was shown that CO induced the expression of the inducible isoform of nitric oxide synthase, with a possible impact on excitation/contraction coupling and on myocardial ischemia/reperfusion injuries [66].

The complexity of the mechanisms of action of CO is illustrated by the fact endogenous CO provides protective effects on the cardiovascular system. The endogenous production of CO occurs through the activity of constitutive (haem oxygenase 2) and inducible (haem oxygenase 1) haem oxygenases. Despite the apparent paradox that CO gas is perceived as an inhibitor of mitochondrial respiration and of cytochrome c oxidase, it appears that endogenous CO may play a beneficial role in mitochondrial bioenergetics and this important signaling pathway is currently being investigated [67].

Metals

Antimony

Antimony is still the mainstay for the treatment of Leishmaniasis. Significant modifications of the electrocardiogram, and even “torsades de pointe” and sudden death have been reported in patients undergoing therapy with antimonials; these effects are related to the dose and duration of the treatment. While modifications of T wave or ST segment and arrhythmias have been documented in experimental models, contradictory results have appeared regarding the effects of antimony on contractility. The cardiac effects could be related to oxidative stress producing lipid peroxidation, glutathione (GSH) decrease, inhibition of glutathione peroxidase, significant alterations in cellular thiol homeostasis and lactate dehydrogenase (LDH) release [68–69]. It seems also that antimony is able to interfere with intracellular calcium handling [68].

Cobalt

Cobalt-related subacute cardiomyopathy was first described in patients exposed to environmental cobalt or in heavy beer drinkers when cobalt was added in the 1960s to the beer to restore and stabilize the foam [70]. Since that time, the incidence of cobalt-related cardiomyopathy has significantly decreased. It appeared also that there was no strict correlation between cobalt blood concentrations or cobalt accumulation in the heart and the development of cardiac dysfunction [69]. Other factors seemed to be required to develop cardiomyopathy, including hypothyroidism and low vitamin diet.

The diagnosis of cobalt cardiomyopathy requires (1) demonstration of biventricular dilatation and systolic dysfunction at a time when blood/tissue concentrations of cobalt are increased; and (2) normalization of cardiac structure and function when exposures ceases and blood/tissue concentrations of cobalt decline into range close to that expected in nonexposed individuals [71]. Despite the increasing interest in cobalt toxicity in patients with malfunctioning hip prostheses, the incidence of demonstrated cobalt-related cardiomyopathy remains low [72,73].

People who developed cardiac complications attributed to cobalt poisoning following metal-containing replacements or failed ceramic prostheses had considerably high serum or blood cobalt concentrations. In patients with well-functioning

prostheses, chronic exposure to low circulating concentrations of cobalt has been associated with subtle changes in myocardial function, but a dose–effect relationship has not been established. Histological findings in cobalt-related cardiomyopathy are poorly specific with the exception of the presence of dense osmophilic intramitochondrial particles [70].

Several mechanisms have been proposed to explain cobalt cardiotoxicity but none of the experimental studies are recent [71]. Cobalt may interfere with the binding of calcium to sarcolemma, the transport of calcium into the myocyte, and the inotropic effects of calcium [74,75]. Cobalt may reduce the generation of ATP production by aerobic cellular respiration through the interruption of citric acid cycle and also by interference with the mitochondrial respiratory chain enzymes [76,77]. The cobalt (II) ion is able to react with hydrogen peroxide under physiological conditions to form ROS [77,78].

Acute cobalt exposure in a rat model reduced the activity of manganese-superoxide dismutase (Mn-SOD) in rat myocardium, with a direct correlation with the cobalt myocardial content [79]. Chronic exposure confirmed the reduction of Mn-SOD activity, with also a moderate decrease in mitochondrial ATP production rate and a general reduction in capacity of the respiratory chain. The link between the reduction of Mn-SOD activity and ATP production is not demonstrated.

Lithium

Experimentally, lithium alters the electrolyte pumps and channels, modifying the action potentials with subsequent abnormalities in contractile activity [80,81]. Lithium enters into cardiac myocyte similarly to Na^+ , but is not removed as efficiently as sodium ions [80]. Lithium also contributes to depletion of intracellular potassium and displacement of intracellular calcium.

Serious cardiac toxicity due to lithium is uncommon and generally occurs in individuals with an underlying heart disease [82]. Following acute lithium overdose, there is some description of reversible global or segmental LF dysfunction, with a possible overlap with takotsubo cardiomyopathy [83–85]. Drug safety databases are suggesting an association between lithium treatment and the development of dilated cardiomyopathy, but these data must be interpreted with caution due to numerous biases including the presence of a preexisting cardiac disease. Exceptionally, histological features could be consistent with a true pattern of myocarditis (myofibrillar degeneration, myocardial lymphocyte cell infiltrates, fibrosis) [86]. There are isolated reports of cardiac improvement after lithium discontinuation [87].

Mercury

Proposed mechanisms for mercury toxicity include glutathione depletion, production of ROS, and interruption in selenium-dependent endogenous enzymatic reactions [88,89]. Mercury may also act as a Ca^{++} antagonist at the

actin–myosin junction. However, there is no clinical evidence linking mercury exposure to the development of cardiomyopathy.

Scorpion venom

The clinical manifestations of scorpion envenomation may vary in type and severity according to scorpion species [90]. Severe cardiovascular events were observed with species found in North Africa (*Andronoctus* and *Buthus*), the Middle East (*Leiurus quinquestriatus*), India (*Mesobuthus tamulus*) and Brazil (*Tityus*) [91]. The exact physiopathology of cardiovascular effects of scorpion envenomation is still debated; in summary, they could be related either to direct effects of the venom on the target organs (including the heart and vasculature) or mediated by neurohormonal release [91].

The hypothesis of a “catecholamine storm” is supported by experimental studies conducted on canine model. Soon after the experimental injection of the venom, there was a marked increase of plasma concentrations of norepinephrine and epinephrine, but also of other vasoconstrictive peptides, including neuropeptide Y and endothelin [92]. In parallel, there was an increase in mean arterial pressure and systemic vascular resistance. Interestingly, in an additional canine study, a rechallenge with the same amount of circulating toxins 30 min after the first challenge was not able to produce the same hemodynamic changes, suggesting that catecholamines stocks were exhausted after the first toxic challenge and reinforcing the primary role of catecholamine release [93].

The trigger for neurohormonal release could be a direct action of neurotoxins on sodium, potassium, calcium and chloride channels [94,95]. The Na^+ and K^+ channel toxins synergize to cause intense and prolonged depolarization, leading to neuronal excitation. This in turn stimulates postganglionic nerve endings of the sympathetic and parasympathetic nervous system and of the adrenal medulla. Human observations do well correlate with the experimental data. In the first phase of scorpion envenomation (“vascular phase”), catecholamine-mediated vasoconstriction is dominant and leads to increased LV afterload, impaired LV emptying, increased LV pressure, increased capillary pressure and increased RV afterload [91]. Cardiac output could be transiently maintained after an increase of LV work and oxygen consumption, but a second phase (“myocardial phase”) rapidly follows with decreased cardiac output, hypotension and even shock.

There is converging evidence that scorpion-related cardiomyopathy is a form of takotsubo cardiomyopathy [96–98]. The following features are in favor of this hypothesis: a profound but potentially reversible biventricular depression, a context of catecholamine release, ischemic changes at EKG, with minimal CPK and troponin release, abnormalities in myocardial perfusion without evidence of coronary vessels abnormalities. Typical or atypical forms of takotsubo cardiomyopathy have been recently documented either by echocardiography or magnetic resonance imaging [98–100].

Table 1. Main mechanisms of toxic cardiomyopathy. ■■■

Proposed mechanisms of toxicity	Substances
DNA cleavage, inhibition of topoisomerase II β	Anthracyclines
Impaired DNA synthesis	Anthracyclines, trastuzumab
Disruption NRG receptor signalling	Anthracyclines
Inhibition ribosomal S6 kinase	Sunitinib
Inhibition of AMP-activated protein kinase	Sunitinib
Lipid peroxidation, oxidative stress	Anthracyclines, trastuzumab, imatinib, azidothymidine, rosiglitazone, cocaine, ethanol, antimony, cobalt, mercury
Induction of apoptosis	Anthracyclines, cocaine, ethanol
Impairment of mitochondrial bioenergetics	Anthracyclines, azidothymidine, rosiglitazone, ethanol, carbon monoxide, cobalt
Interference with intracellular calcium homeostasis or calcium-mediated contractile mechanisms	Anthracyclines, cocaine, ethanol, antimony, cobalt, lithium, mercury
Interference with iron metabolism	Anthracyclines
Influence of genetic factors	Anthracyclines, ethanol, metamfetamines
Excessive adrenergic stimulation	Antidepressants, cocaine, metamfetamines, carbon monoxide, lithium, scorpion venom
Impaired myocardial O ₂ delivery or increased myocardial O ₂ consumption	Cocaine, carbon monoxide
Interference with ion channels	Scorpion venom

Conclusions

The true incidence of toxic cardiomyopathy is difficult to establish due to a large variability in toxic exposure and to the frequent prevalence of an underlying cardiac pathology. The mechanisms behind the development of toxic cardiomyopathy appear multifactorial and complex (Table 1), though a key mechanism is interference with cardiomyocyte bioenergetics. Some substances are also able to produce direct toxicity to cardiomyocytes. Indirect toxicity can be mediated by a neurohormonal response involving excessive catecholamine release. Further possible mechanisms include apoptosis and ROS production. While an increased generation of ROS is present in several experimental models of toxic cardiomyopathy, it remains difficult to affirm if mitochondrial oxidative stress is a cause or a consequence. Few specific therapies exist for toxic cardiomyopathy; however, some reversibility is possible after discontinuation from toxic exposure.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

- [1] Elliott P, Andersson B, Arbustini E. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. *Eur Heart J*. 2007;29:270–276.
- [2] Ghadri J-R, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J*. 2018; 39:2032–2046.
- [3] Pelliccia F, Sinagra G, Elliott P, et al. Takotsubo is not a cardiomyopathy. *Int J Cardiol*. 2018;254:250–253.
- [4] Montastruc G, Favreliere S, Sommet A, et al. Drugs and dilated cardiomyopathies: a case/noncase study in the French Pharmacovigilance Database. *Br J Clin Pharmacol*. 2010;69: 287–294.
- [5] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003; 97:2869–2879.
- [6] Deidda M, Madonna R, Mango R, et al. Novel insights in pathophysiology of antineoplastic drugs-induced cardiotoxicity and cardioprotection. *J Cardiovasc Med*. 2016;17:e76–e83.
- [7] McGowan JV, Chung R, Maulik A, et al. Anthracycline Chemotherapy and Cardiotoxicity. *Cardiovasc Drugs Ther*. 2017;31:63–75.
- [8] Mercurio V, Pirozzi F, Lazzarini E, et al. Models of heart failure based on the cardiotoxicity of anticancer drugs. *J Card Fail*. 2016;22:449–458.
- [9] Varga ZV, Ferdinandy P, Liaudet P, et al. Drug-induced mitochondrial dysfunction and cardiotoxicity. *Am J Physiol Heart Circ Physiol*. 2015;309:H1453–H1467.
- [10] Kankeu C, Clarke K, Passante E, et al. Doxorubicin-induced chronic dilated cardiomyopathy—the apoptosis hypothesis revisited. *J Mol Med*. 2017;95:239–248.
- [11] Bloom MW, Hamo CE, Cardinale D, et al. Cancer therapy-related cardiac dysfunction and heart failure part 1: definitions, pathophysiology, risk factors, and imaging. *Circ Heart Fail*. 2016; 9:e002661.
- [12] Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. *Heart*. 2018;104:971–977. pii: heartjnl-2017-312103.
- [13] Wojnowski L, Kulle B, Schirmer M, et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. *Circulation*. 2005;112:3754–3762.
- [14] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344: 783–792.
- [15] Baron KB, Brown JR, Heiss BL, et al. Trastuzumab-induced cardiomyopathy: incidence and associated risk factors in an inner-city population. *J Card Fail*. 2014;20:555–559.
- [16] ElZarrad MK, Mukhopadhyay P, Mohan N, et al. Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. *PLoS One*. 2013;8:e79543.
- [17] Rainbolt TK, Saunders JM, Wiseman RL. Stress-responsive regulation of mitochondria through the ER unfolded protein response. *Trends Endocrinol Metab*. 2014;25:528–537.
- [18] Maharsy W, Aries A, Mansour O, et al. Ageing is a risk factor in imatinib mesylate cardiotoxicity. *Eur J Heart Fail*. 2014;16:367–376.
- [19] Hasinoff BB, Patel D, O'Hara KA. Mechanisms of myocyte cytotoxicity induced by the multiple receptor tyrosine kinase inhibitor sunitinib. *Mol Pharmacol*. 2008;74:1722–1728.
- [20] Kerkela R, Woulfe KC, Durand J-B, et al. Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase. *Clin Transl Sci*. 2009;2:15–25.

- [21] Gao RY, Mukhopadhyay P, Mohanraj R, et al. Resveratrol attenuates azidothymidine-induced cardiomyopathy by decreasing mitochondrial reactive oxygen species generation in human cardiomyocytes. *Mol Med Rep.* 2011;4:151–155.
- [22] Kohler JJ, Cucoranu I, Fields E, et al. Transgenic mitochondrial superoxide dismutase and mitochondrially targeted catalase prevent antiretroviral-induced oxidative stress and cardiomyopathy. *Lab Invest.* 2009;89:782–790.
- [23] Lee YH, Goh WW, Ng CK, et al. Integrative toxiproteomics implicates impaired mitochondrial glutathione import as an off-target of troglitazone. *J Proteome Res.* 2013;12:2933–2945.
- [24] Nadanaciva S, Dykens JA, Bernal A, et al. Mitochondrial impairment by PPAR agonists and statins identified via immunocaptured OXPHOS complex activities and respiration. *Toxicol Appl Pharmacol.* 2007;223:277–287.
- [25] Vinetti M, Haufroid V, Capron A, et al. Severe acute cardiomyopathy associated with venlafaxine overdose and possible role of CYP2D6 and CYP2C19 polymorphisms. *Clin Toxicol.* 2011;49:865–869.
- [26] Haufroid V, Hantson P. CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants. *Clin Toxicol.* 2015;53:501–510.
- [27] Frustaci A, Russo MA, Morgante E, et al. Oxidative myocardial damage in human cocaine-related cardiomyopathy. *Eur J Heart Fail.* 2015;17:283–290.
- [28] Havakuk O, Rezkalla SH, Kloner RA. The cardiovascular effects of cocaine. *J Am Coll Cardiol.* 2017;70:101–113.
- [29] Hale SL, Alker KJ, Rezkalla S, et al. Adverse effects of cocaine on cardiovascular dynamics, myocardial blood flow, and coronary artery diameter in an experimental model. *Am Heart J.* 1989;118:927–933.
- [30] Pitts WR, Vongpatanasin W, Cigarroa JE, et al. Effects of the intracoronary infusion of cocaine on left ventricular systolic and diastolic function in humans. *Circulation.* 1998;97:1270–1273.
- [31] Perreault CL, Hague NL, Ransil BJ, et al. The effects of cocaine on intracellular Ca²⁺ handling and myofilament Ca²⁺ responsiveness of ferret ventricular myocardium. *Br J Pharmacol.* 1990;101:679–685.
- [32] Arora S, Alfayoumi F, Srinivasan V. Transient left ventricular apical ballooning after cocaine use: is catecholamine cardiotoxicity the pathologic link? *Mayo Clin Proc.* 2006;81:829–832.
- [33] Li G, Xiao Y, Zhang L. Cocaine induces apoptosis in fetal rat myocardial cells through the p38 mitogen-activated protein kinase and mitochondrial/cytochrome c pathways. *J Pharmacol Exp Ther.* 2005;312:112–119.
- [34] Kovacic P. Role of oxidative metabolites of cocaine in toxicity and addiction: oxidative stress and electron transfer. *Med Hypotheses.* 2005;64:350–356.
- [35] Isabelle M, Vergeade A, Moritz F, et al. NADPH oxidase inhibition prevents cocaine-induced up-regulation of xanthine oxidoreductase and cardiac dysfunction. *J Mol Cell Cardiol.* 2007;42:326–332.
- [36] Virmani R, Robinowitz M, Smialek JE, et al. Cardiovascular effects of cocaine: an autopsy study of 40 patients. *Am Heart J.* 1988;115:1068–1076.
- [37] Paratz ED, Cunningham NJ, Mac Isaac AI. The cardiac complications of methamphetamines. *Heart Lung Circ.* 2016;25:325–332.
- [38] Islam MN, Kuroki H, Hongcheng B, et al. Cardiac lesions and their reversibility after long term administration of methamphetamine. *Forensic Sci Int.* 1995;75:29–43.
- [39] Nishida N, Ikeda N, Kudo K, et al. Sudden unexpected death of a methamphetamine abuser with cardiopulmonary abnormalities: a case report. *Med Sci Law.* 2003;43:267–271.
- [40] Ito H, Yeo KK, Wijetunga M, et al. A comparison of echocardiographic findings in young adults with cardiomyopathy: with and without a history of methamphetamine abuse. *Clin Cardiol.* 2009;32:E18–E22.
- [41] Sutter ME, Gaedigk A, Albertson TE, et al. Polymorphisms in CYP2D6 may predict methamphetamine related heart failure. *Clin Toxicol.* 2013;51:540–544.
- [42] Steiner JL, Lang CH. Etiology of alcoholic cardiomyopathy: mitochondria, oxidative stress and apoptosis. *Int J Biochem Cell Biol.* 2017;89:125–135.
- [43] Laurent D, Edwards JG. Alcoholic cardiomyopathy: multigenic changes underlie cardiovascular dysfunction. *J Cardiol Clin Res.* 2014;2:1022.
- [44] Leibing E, Meyer T. Enzymes and signal pathways in the pathogenesis of alcoholic cardiomyopathy. *Herz.* 2016;41:478–483.
- [45] Li SY, Gilbert SA, Li Q, et al. Aldehyde dehydrogenase-2 (ALDH2) ameliorates chronic alcohol ingestion-induced myocardial insulin resistance and endoplasmic reticulum stress. *J Mol Cell Cardiol.* 2009;47:247–255.
- [46] Hung CL, Chang SC, Chang SH, et al. Genetic polymorphisms of alcohol metabolizing enzymes and alcohol consumption are associated with asymptomatic cardiac remodeling and subclinical systolic dysfunction in large community-dwelling Asians. *Alcohol Alcohol.* 2017;52:638–646.
- [47] Ma H, Yu L, Byra EA, et al. Aldehyde dehydrogenase 2 knockout accentuates ethanol-induced cardiac depression: role of protein phosphatases. *J Mol Cell Cardiol.* 2010;49:322–329.
- [48] Husemoen LL, Fenger M, Friedrich N, et al. The association of ADH and ALDH gene variants with alcohol drinking habits and cardiovascular disease risk factors. *Alcohol Clin Exp Res.* 2008;32:1984–1091.
- [49] Schröder J, Hamada S, Altiok E, et al. Detection of acute changes in left ventricular function by myocardial deformation analysis after excessive alcohol ingestion. *J Am Soc Echocardiogr.* 2017;30:235–243.
- [50] Guzzo-Merello G, Cobo-Marcos M, Gallego-Delgado M, et al. Alcoholic cardiomyopathy. *World J Cardiol.* 2014;6:771–781.
- [51] Mirijello A, Tarli C, Vassallo GA, et al. Alcoholic cardiomyopathy: what is known and what is not known. *Eur J Intern Med.* 2017;43:1–5.
- [52] Ren J, Wold LE. Mechanisms of alcoholic heart disease. *Ther Adv Cardiovasc Dis.* 2008;2:497–506.
- [53] Piano MR, Phillips SA. Alcoholic cardiomyopathy: pathophysiological insights. *Cardiovasc Toxicol.* 2014;14:291–308.
- [54] Jung YS, Lee JS, Min YG, et al. Carbon monoxide-induced cardiomyopathy. *Circ J.* 2014;78:1437–1444.
- [55] Cha YS, Kim H, Hwang SO, et al. Incidence and patterns of cardiomyopathy in carbon monoxide-poisoned patients with myocardial injury. *Clin Toxicol.* 2016;54:481–487.
- [56] Kjeldsen K, Thomsen HK, Astrup P. Effects of carbon monoxide on myocardium. Ultrastructural changes in rabbits after moderate, chronic exposure. *Circ Res.* 1974;34:339–348.
- [57] Cha YS, Kim H, Lee Y, et al. Evaluation of relationship between coronary artery status evaluated by coronary computed tomography angiography and development of cardiomyopathy in carbon monoxide poisoned patients with myocardial injury: a prospective observational study. *Clin Toxicol.* 2018;56:30–36.
- [58] Prockop LD, Chichkova RI. Carbon monoxide intoxication: an updated review. *J Neurol Sci.* 2007;262:122–130.
- [59] Thom SR. Carbon monoxide-mediated brain lipid peroxidation in the rat. *J Appl Physiol.* 1990;68:997–1003.
- [60] Fitzgerald RS, Dehghani GA, Kiihl S. Autonomic control of the cardiovascular system in the cat during hypoxemia. *Auton Neurosci.* 2013;174:21–30.
- [61] Takahashi K. Cardiac disturbances due to CO poisoning in experimental animals. II. Changes of the heart excitability due to acute CO poisoning. *Tohoku J Exp Med.* 1961;74:224–233.
- [62] Cooper CE, Brown GC. The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. *J Bioenerg Biomembr.* 2008;40:533–539.
- [63] Lippi G, Rastelli G, Meschi T, et al. Pathophysiology, clinics, diagnosis and treatment of heart involvement in carbon monoxide poisoning. *Clin Biochem.* 2012;45:1278–1285.
- [64] Chen KC, McGrath JJ. Response of the isolated heart to carbon monoxide and nitrogen anoxia. *Toxicol Appl Pharmacol.* 1985;81:363–370.

- [65] Suner S, Jay G. Carbon monoxide has direct toxicity on the myocardium distinct from effects of hypoxia in an ex vivo rat heart model. *Acad Emerg Med*. 2008;15:59–65.
- [66] Meyer G, André L, Kleindienst A, et al. Carbon monoxide increases inducible NOS expression that mediates CO-induced myocardial damage during ischemia-reperfusion. *Am J Physiol Heart Circ Physiol*. 2015;308:H759–H767.
- [67] Motterlini R, Foresti R. Biological signaling by carbon monoxide and carbon monoxide-releasing molecules. *Am J Physiol, Cell Physiol*. 2017;312:C302–C313.
- [68] Alvarez M, Malécot CO, Gannier F, et al. Antimony-induced cardiomyopathy in guinea-pig and protection by L-carnitine. *Br J Pharmacol*. 2005;144:17–27.
- [69] Tirmenstein MA, Plews PI, Walker CV, et al. Antimony-induced oxidative stress and toxicity in cultured cardiac myocytes. *Toxicol Appl Pharmacol*. 1995;130:41–47.
- [70] Grice HC, Munro IC, Wiberg GS, et al. The pathology of experimentally induced cobalt cardiomyopathies. A comparison with beer drinkers' cardiomyopathy. *Clin Toxicol*. 1969;2:273–287.
- [71] Packer M. Cobalt cardiomyopathy: a critical reappraisal in light of a recent resurgence. *Circ Heart Fail*. 2016;9:e003604. pii: e003604.
- [72] Bradberry SM, Wilkinson JM, Ferner RE. Systemic toxicity related to metal hip prostheses. *Clin Toxicol*. 2014;52:837–847.
- [73] Prentice JR, Clark MJ, Hoggard N, et al. Metal-on-metal hip prostheses and systemic health: a cross-sectional association study 8 years after implantation. *PLoS One*. 2013;8:e66186.
- [74] Harrow JA, Das PK, Dhalla NS. Influence of some divalent cations on heart sarcolemmal bound enzymes and calcium binding. *Biochem Pharmacol*. 1978;27:2605–2609.
- [75] Kleinfeld M, Stein E. Action of divalent cations on membrane potentials and contractility in rat atrium. *Am J Physiol*. 1968;215:593–599.
- [76] Hervouet E, Pecina P, Demont J, et al. Inhibition of cytochrome c oxidase subunit 4 precursor processing by the hypoxia mimic cobalt chloride. *Biochem Biophys Res Commun*. 2006;344:1086–1093.
- [77] Clyne N, Hofman-Bang C, Haga Y, et al. Chronic cobalt exposure affects antioxidants and ATP production in rat myocardium. *Scand J Clin Lab Invest*. 2001;61:609–614.
- [78] Lewis CP, Demedts M, Nemery B. Indices of oxidative stress in hamster lung following exposure to cobalt(II) ions: in vivo and in vitro studies. *Am J Respir Cell Mol Biol*. 1991;5:163–169.
- [79] Hatori N, Pehrsson SK, Clyne N, et al. Acute cobalt exposure and oxygen radical scavengers in the rat myocardium. *Biochim Biophys Acta*. 1993;1181:257–260.
- [80] Singer I, Rotenberg D. Mechanisms of lithium action. *N Engl J Med*. 1973;289:254–260.
- [81] Abdel-Zaher AO, Abdel-Rahman MM. Lithium chloride-induced cardiovascular changes in rabbits are mediated by adenosine triphosphate-sensitive potassium channels. *Pharmacol Res*. 1999;39:275–282.
- [82] Serinken M, Karcioglu O, Korkmaz A. Rarely seen cardiotoxicity of lithium overdose: complete heart block. *Int J Cardiol*. 2009;132:276–278.
- [83] Asim K, Selman Y, Suleyman Y, et al. Heart attack in the course of lithium overdose. *Iran Red Crescent Med J*. 2016;18:e21731.
- [84] Anantha Narayanan M, Mahfood Haddad T, Bansal O, et al. Acute cardiomyopathy precipitated by lithium: is there a direct toxic effect on cardiac myocytes?. *Am J Emerg Med*. 2015;33:1330.e1–1335.
- [85] Kitami M, Oizumi H, Kish SJ, et al. Takotsubo cardiomyopathy associated with lithium intoxication in bipolar disorder: a case report. *J Clin Psychopharmacol*. 2014;34:410–411.
- [86] Aichhorn W, Huber R, Stuppaek C, et al. Cardiomyopathy after long-term treatment with lithium - more than a coincidence? *J Psychopharmacol*. 2006;20:589–591.
- [87] Rosero Enríquez ÁS, Ballesteros Prados A, Petcu AS. Cardiomyopathy secondary to long-term treatment with lithium: a case report and literature review. *J Clin Psychopharmacol*. 2018;38:157–159.
- [88] Perez AL, Tang WH. Contribution of environmental toxins in the pathogenesis of idiopathic cardiomyopathies. *Curr Treat Options Cardiovasc Med*. 2015;17:381.
- [89] Frustaci A, Magnavita N, Chimenti C, et al. Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction. *J Am Coll Cardiol*. 1999;33:1578–1583.
- [90] Cupo P. Clinical update on scorpion envenoming. *Rev Soc Bras Med Trop*. 2015;48:642–649.
- [91] Abroug F, Souheil E, Ouane I, et al. Scorpion-related cardiomyopathy: Clinical characteristics, pathophysiology, and treatment. *Clin Toxicol*. 2015;53:511–518.
- [92] Nouira S, Elatrous S, Besbes L, et al. Neurohormonal activation in severe scorpion envenomation: correlation with hemodynamics and circulating toxin. *Toxicol Appl Pharmacol*. 2005;208:111–116.
- [93] Ouane-Besbes L, El Atrous S, Nouira S, et al. Direct vs. mediated effects of scorpion venom: an experimental study of the effects of a second challenge with scorpion venom. *Intensive Care Med*. 2005;31:441–446.
- [94] Padilla A, Govezensky T, Possani LD, et al. Experimental envenoming of mice with venom from the scorpion *Centruroides limpidus limpidus*: differences in mortality and symptoms with and without antibody therapy relating to differences in age, sex and strain of mouse. *Toxicon*. 2003;41:959–965.
- [95] Quintero-Hernández V, Jiménez-Vargas JM, Gurrola GB, et al. Scorpion venom components that affect ion-channels function. *Toxicon*. 2013;76:328–342.
- [96] Abroug F, Ouane I, Maatouk M, et al. Inverted takotsubo syndrome in *Androctonus australis* scorpion envenomation. *Clin Toxicol*. 2018;56:381–383.
- [97] Madias JE. Scorpion envenomation cardiomyopathy: a promising model for takotsubo syndrome. *Clin Toxicol*. 2015;53:787.
- [98] Madias JE. Voltage attenuation of the electrocardiogram QRS complexes in a patient with "scorpion envenomation"-induced takotsubo syndrome. *Am J Emerg Med*. 2015;33:838.
- [99] Miranda CH, Braggion-Santos MF, Schmidt A, et al. Evolution of the electrocardiogram QRS complexes voltage in scorpion envenomation-induced takotsubo syndrome. *Am J Emerg Med*. 2015;33:837–838.
- [100] Miranda CH, Braggion-Santos MF, Schmidt A, et al. The first description of cardiac magnetic resonance findings in a severe scorpion envenomation: Is it a stress-induced (takotsubo) cardiomyopathy like? *Am J Emerg Med*. 2015;33:862.e5–867.