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Drug-Induced Cardiomyopathies

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1. Introduction

Heart failure represents one of most important causes of death in Western countries. Its high mortality originates in part from severe complications like cardiac contractile dysfunction and/or sudden cardiac death caused by ventricular arrhythmias (Shin et al. 2007). Unfortunately, significant portion of heart failure stems from use (and misuse) of several drugs and medications. Indeed, the cardiac muscle is widely known as a target of injury for many drugs and many other chemical compounds. Following their cardiotoxic action, these could be divided into two relevant categories: i) drugs and cardiotoxic substances leading to heart failure in terms of abrupt contractile performance, and ii) drugs affecting ion channels or pumps and, in most cases, leading to prolongation of cardiac repolarisation (and QT interval) and to increased risk of severe cardiac arrhythmias (such as *Torsades de Pointes*) and premature death. In some cases, it is very difficult to divide them in those categories as they have both of actions. Additionally, drug-induced cardiomyopathies not only belong to the serious adverse events of drug actions but they are widely used as experimental models for studying several cardiac conditions and diseases, offering the advantage of precise control of the onset time and can often be studied in a longitudinal fashion. This chapter covers in detail certain drug groups, as for example anthracyclines or some drugs of abuse, which are clearly associated with the development of cardiomyopathy followed by heart failure. Similarly, note is made regarding experimental models of primary or secondary drug-induced cardiomyopathies, QT prolonging agents and rhythm disturbances-triggering drugs. It must be noted that some of the mentioned substances are of clinical importance, the others have their use largely limited, but some of them lost their therapeutic use because of their cardiotoxicity.

2. Drugs inducing heart failure

Some substances cause acute cardiac depression as they lower heart rate, contractility and conduction and in certain causes even cardiac arrest. These substances include barbiturates (thiopental) or halogenated hydrocarbons (halothane, metoxyflurane and enflurane), even at concentrations used in surgery. However, many of drugs are administered chronically and are cardiotoxic and may trigger the development of cardiac injury even when used appropriately. As mentioned in ESC guidelines, there are some specific drug groups and substances which are strongly related to development of heart failure. Literally, beta-

blockers, calcium antagonists, antiarrhythmics, cytotoxic agents, alcohol, cocaine and some trace elements are mentioned (Dickstein et al. 2008). Several pathophysiologic mechanisms of action have been proposed how and why drugs affect the cardiac tissue. They vary depending on the inciting agent, including direct toxic effects, neurohormonal activation, altered calcium homeostasis, and oxidative stress (Figueredo 2011). Conclusively, numerous chemicals and drugs are implicated in cardiomyopathy and even many of them remain unrecognised.

Amphetamine	Ethanol
Anabolic-androgenic steroids	Idarubicin
Anthraquinone	Imatinib
Antipsychotic phenothiazine derivates	Isoproterenol
Arnica herb	Ephedrine
Arsenic	Melarsoprol
Azidothymidine	Methamphetamine
Anagrelide	Methylphenidate
Catecholamines	Minoxidil
Cytarabine	Mitomycin
Clozapine	Mitoxantrone
Cobalt	Paclitaxel
Cocaine	Pentamidine
Chloroquine	Stibogluconate
Cyclophosphamide	Sunitinib
Daunorubicin	Trastuzumab
Diazoxide	Tricyclic antidepressants
Doxorubicin	Zidovudine

Table 1. Drugs and substances implicated in cardiomyopathy (Figueredo 2011).

2.1 Anthracyclines

In the first line, anti-cancer drugs are long recognised as strong cardiotoxic substances. Predominantly, anthracyclines are the best known and the most discussed drugs which hardly affect cardiac muscle. They were discovered in the 1960s and remain one of the mainstays of modern cancer therapy. The first two members of this group – daunorubicin (also known as daunomycin and rubidomycin) and doxorubicin (also known as adriamycin), were isolated from *Streptomyces peucetius*, a species of actinobacteria (Tan et al. 1967; Arcamone et al. 1969) and are well established as highly efficacious antineoplastic agents for various hemopoietic and solid tumors (such as breast cancer, sarcoma, ovarian and bronchogenic carcinoma as well as lymphoma, and certain forms of leukemia). Newer derivates are epirubicin and idarubicin. Despite their extensive use (and despite of the fact that they are extensively studied), their precise anticancerous mechanism is not completely understood. Most probably, it is a combination of several different actions, what accounts for the high efficiency of this class of anti-cancer drugs (Gewirtz, 1999; Minotti et al. 2004). It might include inhibition of DNA replication by intercalating between the base pairs which prevents replication of rapidly growing cancer cells (Sinha et al. 1984). However, contradictory to that, some studies have shown that at clinically relevant anthracycline

concentrations, intercalation is unlikely to play a major role and stressed the topoisomerase II as the key target for anthracyclines (Binaschi et al. 2001). According to this, they act by stabilizing a reaction intermediate in which DNA strands are cut and covalently linked to tyrosine residues of topoisomerase II, which blocks subsequent DNA resealing. Failure to relax the supercoiled DNA blocks DNA replication and transcription. Other important mechanisms participating in the anticancer effects should be the apoptosis of cancer cells via the p-53 dependent pathway (Ruiz-Ruiz et al. 2003) as well as modifications of cellular proteins and organelles by formation of reactive oxygen species and lipid peroxidation (Muindi et al. 1984).

The cardiotoxicity of anthracyclines, which has been recognized shortly after their introduction in clinical practice, continues to limit their therapeutic potential and to threaten the cardiac function of many patients with cancer. Its manifestation can be diverse and may range from QT interval prolongation to acutely induced cardiac arrhythmias, changes in coronary vasomotion with consecutive myocardial ischemia, myocarditis, pericarditis, severe contractile dysfunction, and potentially fatal cardiac insufficiency (Zuppinger et al. 2007). Three distinct types of anthracycline-induced cardiotoxicity have been described (Shan et al. 1996). First, acute or subacute injury can occur immediately after treatment. This rare form of cardiotoxicity may cause transient arrhythmias, infrequently a pericarditis-myocarditis syndrome, or acute failure of the left ventricle. These manifestations usually respond promptly to the cessation of anthracycline infusion and rarely preclude further continuation of anthracycline treatment. Second, anthracyclines can induce chronic cardiotoxicity resulting in cardiomyopathy. This is a more common form of damage and is clinically the most important. Finally, late-onset anthracycline cardiotoxicity causing late-onset ventricular dysfunction and arrhythmias, which manifest years to decades after anthracycline treatment has been completed, is increasingly recognized. Both, chronic or late-onset forms most frequently lead to cardiomyopathy with a bad prognosis for the affected patients. Indeed, survival of patients with anthracycline-associated heart failure is worse than that of patients with ischemic or dilated cardiomyopathy (Felker et al. 2000). Echocardiography is currently the gold standard method for diagnosis and monitoring of anthracycline-induced cardiac impairment. Abnormalities in diastolic dysfunction detected by Doppler echocardiography likely represent early cardiotoxicity that precedes the onset of apparent systolic dysfunction (Wu 2008; Carver et al. 2008). However, some data suggest that the risk of anthracycline-associated heart failure is higher than usually estimated (Swain et al. 2003).

There are several known risk factors for anthracycline-associated cardiotoxicity. The total cumulative dose has been earlier identified as to be the major risk factor (Von Hoff et al. 1979). When focused on doxorubicine in a clinical study, the estimated cumulative percentage of patients who developed congestive heart failure at a cumulative dose of 400 mg/m^2 was 3%, increasing to 7% at 550 mg/m^2 and to 18% at 700 mg/m^2. It also was shown that doxorubicin-related congestive heart failure is schedule dependent. Consequently, modern adjuvant anthracycline regimens typically contain less than the cumulative dose associated with increased risk of cardiomyopathy (Wu 2008; Carver et al. 2008). Moreover, the incidence is lower with a once-weekly schedule when compared to a once-3-weekly schedule of doxorubicin administration (Von Hoff et al. 1979). Except of dosing schedule, the age may play a critical role – childhood as well as old age seem to be of risk. Young females who were treated with high cumulative doses of anthracyclines or with regimens of

high individual doses, as well as patients of both sexes who were relatively young at the time of treatment or have had long periods of follow-up since doxorubicin therapy, appear to be at the highest risk for late cardiotoxic effects (Lipshultz et al. 1995). Patients who are younger at the time of diagnosis have the greatest reductions in left ventricular mass and the most profound increases in afterload. It was suggested that this difference could be due to the inhibition of myocardial growth by anthracycline, which would be accentuated in younger children, whose left ventricular mass is smaller (Lipshultz et al. 1991). Moreover, it was evidenced that limiting the cumulative dose of doxorubicin may not suffice to prevent late cardiotoxic effects in patients treated for cancer during childhood. Similarly, patients of advanced age (over 65 years old) may be at greater risk for congestive heart failure and may benefit from the early administration of a cardioprotectant (Swain et al. 2003). Interestingly enough, female gender is associated with a higher risk of cardiotoxicity as compared to males. Other risk factors include combination cancer therapy, prior or concomitant mediastinal radiotherapy, previous cardiac disease, and hypertension (Singal and Iliskovic 1998).

2.1.1 Mechanisms of cardiotoxicity of anthracyclines

In general, the pathophysiological mechanisms leading to chemotherapy-induced cardiomyopathy are mainly associated with myocardial cell loss, either due to apoptosis or necrosis what consequently leads to mild, moderate or even severe contractile dysfunction. The same is true for anthracyclines as well, but precise identification of exact mechanisms is frequently difficult since the majority of cancer patients is not only treated with a multitude of cancer drugs but might also be exposed to potentially cardiotoxic radiation therapy.

Similarly to antineoplastic action, the main cardiotoxic mechanism of anthracyclines is extensively under debate (Wu and Hasinoff 2005; Simůnek et al. 2009). As anthracyclines and their related compounds are well characterised as substances that lead to myocardial cell loss (Bristow et al. 1978; Mackay et al. 1994), it is likely that some of their anti-cancer mechanisms are involved in cardiotoxicity as well. In other words, cardiotoxicity may be viewed as an effect of the entire class of anthracyclines, which may indicate that it is inseparable from their antitumor effect. Early works on the pathogenesis of anthracycline cardiomyopathy had focused on DNA and protein synthesis (Pigram et al. 1972; Rosenoff et al. 1975; Levey et al. 1979). Currently, at least four hypotheses explaining the cardiotoxicity of anthracyclines have been proposed (Outomuro et al. 2007). First, in the 'iron and free-radical theory' an increased oxidative stress and antioxidant deficit have been suggested to play a major role. Although the molecular basis is not still clear enough, mitochondria is accepted as the locus where progressive molecular disorder is triggered. Second, the 'metabolic hypothesis' implicates C-13 alcohol metabolites of anthracyclines as mediators. Anthracycline alcohol metabolites can affect myocardial energy metabolism, ionic gradients, and calcium movements. Third, in the 'unifying hypothesis', chronic cardiotoxicity induced by C-13 alcohol metabolite might be primed by oxidative stress generated by anthracycline redox cycling. The two main possible mechanisms of cardiac damage that have been proposed, *i.e.* an increase calcium concentration in the interior of myocardial fibers, and damage to cell and organelle membranes by doxorubicin-generated oxygen radicals that produce an increase in the rate of endogenous lipid peroxidation, can obviously be sequentially ordered: first, doxorubicin radicals are generated and secondly they would lead, through lipid peroxidation and membrane damage, to a loss of membrane-selective

permeability and towards increased calcium levels in the myocardial fibers. Fourth, the 'apoptosis hypothesis' is based on findings of myocyte cell loss through apoptosis in doxorubicin cardiomyopathy. The up-regulation of proapoptic proteins (Bax, caspases and cytochrome C), with or without the down-regulation of antiapoptotic proteins (Bcl2, Akt), has been documented and mitogen-activated protein kinases have been shown to be involved in both apoptosis and cell survival. Likewise, apoptosis is related with oxidative mechanisms as increased oxidative stress has been shown to promote apoptosis and antioxidants have been shown to inhibit this process.

Notably, the currently still prevailing hypotheses based on free radical production appeared in the centre of interest, as to be a major mechanism of anthracycline-associated cardiac dysfunction, in 1970's. And, during a time, the iron-mediated formation of reactive oxygen species and promotion of myocardial oxidative stress remains by far the most frequently proposed mechanism (Simůnek et al. 2009). It was demonstrated that anti-cancer agents whose structure contained quinone moieties could function as free radicals in NADPH-dependent microsomal oxidative reaction (Handa et al. 1975). Because superoxide dismutase inhibited this enhancement, it was suggested that the reaction precedes by formation of a free radical semiquinone which presumably then acts as both a chain initiator and in the transfer of electrons from molecular oxygen to superoxide anion. It was described that anthracyclines augments electron flow from NADPH to molecular oxygen in cardiac sarcosomes (Bachur et al. 1977) and others supported this (Myers et al. 1976; Myers et al. 1977) starting a focus on oxidative stress in explanation of cardiotoxicity of these drugs. In other words, the myocyte damage has been almost exclusively attributed to a concentration-dependent increase of intracellular oxidative stress with a consecutive increase in cytosolic calcium, mitochondrial dysfunction (Tokarska-Schlattner et al. 2006), and induction of myocyte apoptosis or necrosis (Hasinoff 1998; Gille and Nohl 1997; Doroshow 1983). Moreover, it is believed that reactive oxygen species not only lead to cell death, but also directly affect excitation-contraction coupling and calcium signaling in cardiomyocytes (Zuppinger et al. 2007). In addition to reactive oxygen species, reactive nitrogen species are also referred as to be implicated in anthracycline cardiotoxicity. The influence of anthracyclines on the NO signaling pathway has been studied in several experimental models and has been extensively reviewed (Fogli et al. 2004). It is known that anthracyclines may increase the expression of the inducible NO-synthase and so massively increase the NO production. Regarding chronic cardiotoxicity, prolonged anthracycline exposure may induce a large synthesis of byproducts of the NO-synthase mediated anthracycline redox-cycling, including $ONOO^-$, which can rapidly react with manganese-superoxide dismutase, leading to an inactivation of the enzyme (Radi et al. 2002). This results to initiation a deleterious faulty mechanism that will favour further formation of $ONOO^-$ and other NO-derived reactive nitrogen species, therefore promoting cardiomyocyte damage (Fogli et al. 2004). In addition, the generation of free radical species could lead to lipid peroxidation (primarily of the cell membrane); however, such lipid peroxidation would not indicate whether free radicals were being generated intracellularly or extracellularly (Gewirtz 1999).

The question – why is the heart so much more susceptible to the oxidative stress produced by anthracyclines than other tissues – has been widely studied. As proposed, cardiac tissue has weak antioxidant activity, since it lacks catalase (Doroshow 1983) and so cardiomyocytes could be exposed to high levels of hydrogen peroxide. In addition,

cardiomyocytes are rich in mitochondria, which represent up to 50% of cardiomyocyte mass and which serve as both source and target of reactive oxygen species (Simůnek et al. 2009). Moreover, an important role has been attributed to exogenous NADH dehydrogenase. Unlike cardiac mitochondria, liver mitochondria lack the NADH-related pathway of reducing equivalents from the cytosol to the respiratory chain. As a result, liver mitochondria do not generate significant amounts of anthracycline semiquinones (Nohl et al. 2003).

One of the long reported hypotheses of cardiotoxicity of anthracyclines is based on the calcium overload (Olson et al. 1974), as they disrupt cellular and mitochondrial calcium homeostasis (Solem et al. 1994). Fleckenstein's calcium theory of myocardial cell necrosis from 1970' is widely quoted in literature as a general mechanism of myocardial cell damage (Fleckenstein et al. 1974). It must be noted that intracellular calcium dysregulation is present in all types of advanced cardiomyopathy and apparently is a late stage event that represents a final common pathway for myocardial cell damage and death. Similarly to that, anthracyclines dose-dependently increase diastolic intracellular calcium in single cardiomyocytes (Mijares and López 2001). There is a variety of modes how calcium regulating mechanism can strongly disrupt the calcium handling in cardiac cells. As anthracyclines may cross the cell surface and membranes of organelles and they, and their metabolites (doxorubicinol and daunorubicinol), may alter sarcoplasmic reticulum's calcium regulation, the recent focus is shifted to this organelle (Charlier et al. 2005; Kim et al. 2005; Park et al. 2005; Ondrias et al. 1990; Dodd et al. 1993; Arai et al. 1998). Indeed, there is now increasing evidence that depression of contractility in heart failure is linked to a malfunction of sarcoplasmic reticulum calcium release (Kirchhefer et al. 2007; Kirchhof et al. 2007). Calcium release is maintained by a macromolecular protein complex that is activated by L-type calcium current. It consists of the cardiac specific ryanodine receptor 2 (calcium release channel of sarcoplasmic reticulum), calsequestrin (calcium storage protein of sarcoplasmic reticulum), FK506-binding protein FKBP12.6, triadin, and junctin (Zhang et al. 1997; Bers 2002). Aside from cytosolic calcium, ryanodine receptor activity is also regulated by luminal calcium. Its storage and release are under the control of calsequstrin (Györke et al. 2002), whereas triadin and junctin may serve as linker proteins between calsequestrin and the ryanodine receptor. The interaction between these proteins appears to be critical for the regulation of calcium release. Importantly, anthracyclines may directly affect the calcium release complex because there is a direct anthracycline binding site on cardiac specific ryanodine receptor and on cardiac calsequestrin (Saeki et al. 2002; Park et al. 2005; Charlier et al. 2005). Indeed, it was shown that anthracyclines have biphasic effect on cardiac ryanodine receptor – initially, activate the channel, whereas after a few minutes, the channel becomes irreversibly inhibited (Ondrias et al. 1990). The ability of anthracyclines to inhibit calcium release may be more important pharmacologically than their ability to stimulate calcium release, since only nanomolar to low micromolar concentrations are required to produce inhibition, whereas release requires concentrations in the micromolar range (Olson et al. 2000). In addition to calcium regulation by sarcoplasmic reticulum, anthracyclines can affect L-type calcium channels, probably via formation of reactive oxygen species (Campbell et al. 1996), as well as Na^+/Ca^{2+} exchanger activity (Goldhaber 1996).

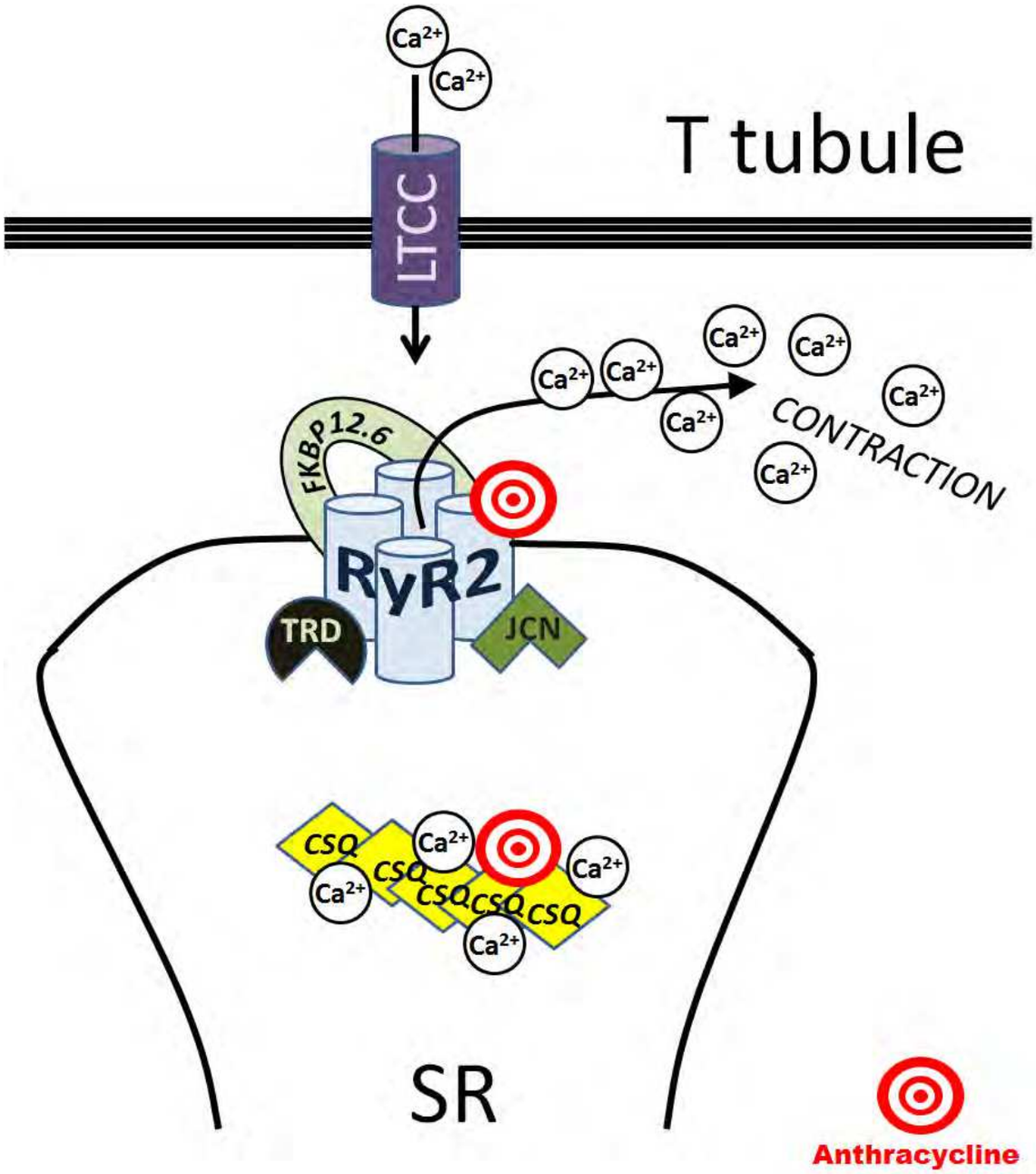


Fig. 1. Potential mechanism of anthracycline induced cardiotoxicity is based on direct binding of anthracycline on cardiac ryanodine receptor (RyR2) and/or calsequestrin (CSQ). The drug may directly modulate the calcium-induced calcium release from sarcoplasmic reticulum (SR). (Other abbreviations: LTCC - L-type Ca^{2+} channel, FKBP12.6 - FK506-binding protein 12.6, TRD - triadin, and JCN – junctin.)

Other suggested cardiotoxicity mechanisms of anthracyclines include impaired expression of various important cardiac proteins and depletion of transcription factors (Boucek et al. 1999; Aries et al. 2004), metabolism of anthracyclines into more hydrophilic and cardiotoxic substances, which subsequently accumulate in cardiomyocytes (Minotti et al. 1996), induction of mitochondrial DNA lessions (Lebrecht et al. 2005), disruption of mitochondrial bioenergetics (Tan et al. 1967), degradation of myofilamental and cytoskeletal proteins (Lim et al. 2004; Chen et al. 2006), interference with various pro-survival kinases (Peng et al. 2005) and some data suggest that the erbB2/neuregulin system might modulate anthracycline-associated cardiac toxicity, as it has been demonstrated that signaling via the erbB2 receptor can modulate doxorubicin-induced oxidative stress and myofibrillar structural damage *in vitro* (Lim t al. 2004; Sawyer et al. 2002; Pentassuglia et al. 2007). Importantly enough, all these proposed cardiotoxic pathways may contribute to cardiac cell damage, ultimately resulting in myocyte death, either by the pathway of necrosis or the pathway of apoptosis (Sawyer et al. 1999).

2.1.2 Therapy and cardioprotection against anthracycline-induced cardiotoxicity

As it is accepted that drug-induced cardiac remodelling is, similarly to other types of cardiac injury, mediated by the activation of the renin-angiotensin-aldosteron system and adrenergic system, treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and beta blockers are consequently used to slow the progression of disease (Mann 1999). Thus, standard treatment for systolic heart failure is indicated for treatment for both asymptomatic and symptomatic cases, with angiotensin-converting enzyme inhibitors in first line, as some trials have suggested that these drugs may reduce the incidence of left ventricular dysfunction in high risk patients after chemotherapy (Wu 2008). However, the management of such patients remains complicated.

Clinicians confront a clinical dilemma as they have to balance the efficacy of longer duration of therapy against the cardiotoxicity associated with higher cumulative doses of anthracyclines. In an effort to prevent or reduce this cardiotoxicity, numerous less cardiotoxic anthracycline analogs have been developed (epirubicin, idarubicin) such as including liposomal anthracyclines (Batist et al. 2001; Muggia and Green 1991; Muggia et al. 1997), and the cumulative and peak doses of anthracycline therapy have been diminished (Legha et al. 1982; Von Hoff et al. 1979). Another cardiotoxicity reducing strategy is based on the use of cardioprotective agents, mainly on those which might reduce oxidative stress and/or may have chelating properties. From those, dexrazoxane (also known as cardioxane) is the most investigated agent (Swain et al. 1997; Wexler et al. 1996). Moreover, it is the only approved cardioprotective agent in anthacycline chemotherapy. Interestingly, dexrazoxane prevents heart damage but there is no evidence for a difference in response rate or survival (van Dalen et al. 2011). Other agents like L-carnitine, probucol, coenzyme Q10, N-acetylcysteine, vitamin E, digoxin, enalapril, phenethylamines, deferoxamine, ethylenediaminetetraacetic acid, superoxide dismutase and monohydroxyethylrutoside are less investigated; however cardioprotective effects have been reported in numerous studies (De Leonardis et al. 1985; Elihu et al. 1998; Guthrie and Gibson 1977; Iarussi et al. 1994; Kawasaki et al. 1992; Silber et al. 2004; Singal et al. 1995; Unverferth et al. 1983; Van Acker et al. 2000). Unfortunately, none of them achieved any clinical relevance as cardioprotective agent.

2.2 Other anti-cancer agents

Several non-anthracycline based anti-cancer drugs have also been associated with significant cardiac side effects. An alkylating agent – cyclophosphamide is mainly cardiotoxic at high doses, such as those used before bone marrow or stem cell transplantation (Meinardi et al. 2000). The reported cardiotoxicity ranges from transient electrocardiographic changes and asymptomatic increases of serum levels of cardiac enzymes to more severe cardiotoxicity such as exudative pericardial effusion, ventricular hypertrophy and fatal myopericarditis and (haemorrhagic) myocardial necrosis. The onset of the latter types of cardiotoxicity is acute, with fatal consequences within 15 days. The cardiotoxic effects of cyclophosphamide probably result from direct influence on the myocardial capillaries and can probably be partly explained by damage to the endothelium with resultant increase in permeability and extravasation of plasma, red blood cells and toxic metabolites (Gottdiener et al. 1981; Fraiser et al. 1991). From the group of antimetabolites (capecitabine, cytarabine, 5-fluorouracil), the cardiotoxicity of 5-fluorouracil is the best described one. It appears to have direct toxic effects on the myocardium, although toxic effects on the coronary arteries are probably the main pathogenetic factor (Meinardi et al. 2000). Necropsy findings in humans who died from fatal myocardial infarction or cardiogenic shock after 5-fluorouracil therapy showed patchy myocardial necrosis and mononuclear inflammation unrelated to the distribution of the coronary arteries (Sasson et al. 1994). A direct interference of 5-fluorouracil with the myocardial cell metabolism leading to cellular hypoxia has been suggested from a study with an isolated perfused rat heart model (Millart et al. 1992). In addition, cases of dilated cardiomyopathy and congestive heart failure have been reported after 5-fluorouracil treatment, also suggesting a direct toxic effect on the myocardium (Schöber et al. 1993; Weidmann et al. 1995). Capecitabine may cause ischaemia and cytarabine may cause pericarditis (Wu 2008). Some risk of cardiovascular toxicity has been attributed to antimicrotubules (paclitaxel, vinca alkaloids) as well. Paclitaxel may cause hypotension or arrhythmias, both supraventricular or ventricular and atrioventricular block, and vinca alkaloids may cause ischaemia (Wu 2008).

Recently, new biological therapy opens new possibilities in the treatment of cancer. New drugs were developed with the goal to specifically inhibit selected targets and to stop cancer cell proliferation and metastasis. These targeted therapies were thought to be more effective than traditional chemotherapeutic treatments and less harmful to non-cancerous cells. However, some of the targets inhibited by these new anti-cancer drugs appear to be important also for the maintenance of cellular homeostasis of normal tissue, in particular during exposure to cytotoxic chemotherapy (Zuppinger et al. 2007). Some of the new biological anti-cancer drugs associated with myocardial contractile dysfunction are trastuzumab, imatinib, and possibly bevacizumab (Slamon et al. 2001; Tan-Chiu et al. 2005; Drímal et al. 2006; Kerkelä et al. 2006). Importantly, most of these new biological therapeutics are not cytotoxic *per se* and, therefore, need to be combined with traditional chemotherapeutics and radiation therapy. Tyrosine kinase inhibitors (sunitinib, imatinib) are small molecule agents that inhibit cellular signalling involved in tumour cell angiogenesis and proliferation. Although this targeted approach results in improved anti-tumour activity and fewer side effects, tyrosine kinases regulating non-cancer functions are also affected, leading to undesired toxic side effects, including heart failure and hypertension (Chu et al. 2007). Trastuzumab is a recombinant IgG monoclonal antibody that binds to the human epidermal growth factor receptor 2 protein and is used for treatment of

breast cancer that overexpresses this growth factor. It should be noted that agents like this are still relatively new, and full understanding of long term toxicities is still evolving (Jones et al. 2007). But as expected, the combination of trastuzumab with cytotoxic agents, in particular anthracyclines, bares a significant risk of cardiotoxicity (Slamon et al. 2001; Strasser et al. 2001). Multivariate analysis for the development of cardiac dysfunction in the pivotal trastuzumab trials identified prior or concomitant anthracycline exposure, over 50 years of age, and prior cardiac disease as independent risk factors. Many of these risk factors are similar to those for doxorubicin-induced cardiac dysfunction. However, in contrast to anthracycline-induced cardiomyopathy, trastuzumab-associated cardiac dysfunction appears to be mostly reversible and non-progressive (Ewer and Lippman 2005; Ewer et al. 2005).

2.3 Stimulants

Psychomotor stimulants have a marked influence on mental function and behaviour, producing excitement and euphoria, reduced sensation of fatigue, and an increase in motor activity. Clinically, abuse of stimulants such as cocaine, ephedrine, amphetamines or methamphetamines is associated with cardiovascular action such as tachycardia, supraventricular arrhythmias, ventricular arrhythmias, impaired conduction, hypertensive crises, acute coronary syndromes, shock and cardiac arrest. A number of cellular, animal and autopsy studies, individual case reports and case series suggested that exposures of such drugs are potentially associated with structural and functional changes of myocytes, as well as clinical manifestations of cardiomyopathy and congestive heart failure (Wijetunga et al. 2003; Yeo et al. 2007). The pathogenesis is probably similar to that of catecholamine-induced cardiomyopathy, *i.e.* sympathomimetic action, as for example pathologic similarities between cocaine cardiomyopathy and those seen in pheochromocytomas suggest that chronic adrenergic stimulation may play a role in the development of cardiomyopathy. It is possible that adrenergically driven recurrent hypertensive crises ultimately result in failure of the ventricle in exactly the same way as essential hypertension, in particular when combined with inappropriate life style (Crean and Pohl 2004). Apart from that, *in vitro* experiments showed that continuous exposure to a low concentration of methamphetamine may directly facilitate the development of cellular hypertrophy (Maeno et al. 2000).

2.3.1 Amphetamines and metamphetamines

Clinically, these drugs cause central nervous system stimulation that may induce euphoria, increase alertness, intensify emotions, increase aggression, alter self-esteem, and allegedly increase sexuality. Both oral and intravenous misuses are well documented. Deaths related to intoxications from these drugs have been associated with assaults, suicides, homicides, accidents, driving impairment, and maternal-fetal and infant exposures (Albertson et al. 1999). Pharmacologically, these drugs are substrates for the neuronal uptake transporters for norepinephrine, serotonin and dopamine, and cause release of these mediators from nerve terminals in the brain. Indirectly, the hyperstimulated neurons can stimulate various other pathways. Changes in mood, excitation level, motor movement, and appetite appear to be more directly mediated by central dopaminergic alterations. Serotonin alterations may also contribute to the amphetamine-related mood changes, psychotic behavior, and aggressiveness. Cardiovascular symptoms, including chest pain, palpitations, and dyspnea,

are common. The exact frequency of such events is unknown but a clinical study showed that acute coronary syndrome is common (25%) in patients hospitalized for chest pain after methamphetamine use and the frequency of other potentially life-threatening cardiac complications is not negligible. These events occur in patients with and without underlying coronary disease and may involve multiple pathophysiologic mechanisms (Turnipseed et al. 2003). When considering cardiomyopathy, the incidence of 18% has been described in subjects abusing methamphetamine (Wijetunga et al. 2003). In other clinical study, methamphetamine use was documented in 40% of young patients with cardiomyopathy and was more severe compared to other non-ischemic cardiomyopathies. This findings support the hypothesis that methamphetamine use may be a possible cause of unexplained cardiomyopathy in young patients because its widespread use (Yeo et al. 2007).

Acute and chronic cardiomyopathy from abuse is thought to be secondary to both direct cardiac toxicity and indirect amphetamine-induced hypertension, necrosis, and ischemia (Albertson et al. 1999). The 3,4-methylenedioxymethamphetamine, commonly known as ecstasy, can cause myocardial infarction, arrhythmias, and cardiomyopathy (Mizia-Stec et al. 2008; Figueredo 2011). Animal studies showed that repeated methamphetamine administration may directly induce cellular hypertrophy of cardiomyocytes, myocarditis with inflammatory infiltrates and areas of necrosis, and consequently, may cause eccentric left ventricular dilation and diastolic dysfunction, as well as contractile dysfunction in myocytes (Shenouda et al. 2009). High dose administration may lead to cardiac function disorder with disruption of microtubules and actin (Maeno et al. 2000). It was suggested that metabolites are responsible for cardiotoxicity (Shenouda et al. 2008) as 3,4-methylenedioxymethamphetamine is metabolized to catechols that can undergo redox cycling, producing reactive oxygen and nitrogen species (Bolton et al. 2000). This suggests that potential mechanisms of 3,4-methylenedioxymethamphetamine–induced cardiomyopathy are related to oxidative stress, as well as catecholaminergic stimulation. Additionally, the recreational use of 3,4-methylenedioxymethamphetamine is often characterized by a repeated pattern of frequent drug applications (binge) followed by a period of abstinence what significantly alter cardiovascular and cardiovascular reflex function and produce cardiac toxicity (Badon et al. 2002). On the other hand, experimental as well as clinical data suggest that cardiac lessions are reversible after withdrawal of methamphetamine (Islam et al. 1995; Lopez et al. 2009).

2.3.2 Cocaine

Cocaine (benzoylmethylecgonine) is an alkaloid extracted from the leaves of the *Erythroxylon coca*, a plant native to South America. It was first used as a local anesthetics in 1884 and, interestingly, was used as an ingredient in a popular cola beverage in the early 20th century (Maraj et al. 2010). Cocaine inhibits catecholamine uptake by the norepinephrine and dopamine transporters at the presynaptic adrenergic terminals, causing an accumulation of catecholamines at the postsynaptic receptor, thereby enhancing peripheral effects of sympathetic nerve activity and producing a marked psychomotor stimulant effect. Its effects resemble those of amphetamines, although it has less tendency to produce stereotyped behaviour, delusions, hallucinations and paranoia (Johanson and Fischman 1989). It also causes the release of norepinephrine and epinephrine from the adrenal medulla and thus acting as a powerful sympathomimetic agent that can cause significant central and peripheral vasoconstriction. Cocaine has multiple cardiovascular and

hematologic effects that likely contribute to the development of myocardial ischemia and/or myocardial infarction. Cocaine causes increased heart rate and blood pressure in a dose-dependent fashion, as well as increased cardiac index and dP/dt. The chronotropic effects of cocaine use are intensified in the setting of alcohol use, as well as smoking. By increasing heart rate, blood pressure, and contractility, cocaine leads to increased myocardial demand. Importantly, cocaine causes coronary vasoconstriction and thrombosis and so decreases oxygen supply and induces myocardial ischemia through a variety of mechanisms (McCord et al. 2008). Acute cellular effects include changes in calcium flux that are similar to other cardiac toxins, including digoxin. Increased intracellular concentrations of calcium have been suggested as a cause of depolarisation of the cardiac membrane and, therefore, a trigger of arrhythmias.

When misused chronically, cocaine administration can reduce left ventricular function, increase end-systolic wall stress and can cause a rare form of cardiomyopathy. The exact incidence of cocaine-induced cardiomyopathy is unknown and likely underreported. The medical literature to date consists mostly of case reports describing young men with a history of cocaine abuse and reversible cardiomyopathy (Awtry and Philippides 2010). In a review of 1278 cases of dilated cardiomyopathy patients, 10 cases were related to cocaine use (Felker et al. 1999). In a study of asymptomatic apparently healthy cocaine users, left ventricular systolic dysfunction was diagnosed in 7% by radionuclide angiography performed two weeks after cocaine use (Bertolet et al. 1990). The exact mechanism by which cocaine abuse causes cardiomyopathy is not fully understood. Furthermore, the amount and duration of cocaine use necessary to develop cocaine cardiomyopathy is currently unclear. Several pharmacologic effects of cocaine appear to be directly and indirectly related to its toxic myocardial action. Importantly, cocaine has been estimated to cause the development of cardiac hypertrophy without associated increases in arterial blood pressure, heart rate, renin, aldosterone, or cortisol, indicating a direct action on cardiac tissue remodelling and leading to heart failure. Nevertheless, whether it is a consequence of cocaine cardiomyopathy or ischemic cardiomyopathy due to cocaine vascular effects remains unclear. Finally, as direct putative pathophysiologic mechanisms of cocaine-induced cardiomyopathy and myocarditis, the following has been introduced: hyperadrenergic state produces contraction band necrosis in myocardium, direct toxic effect of cocaine on myofibrils and interstitial fibrosis, and hypersensitivity reaction of myocardium to cocaine. Other mechanisms include myocardial ischemia and infarction as a consequence of increased sympathomimetic activity with increased myocardial oxygen demand, altered calcium flux across myocyte cell membrane, altered vascular endothelium integrity (reduced prostacyclin production), increased platelet thromboxane production and increased plasminogen activator inhibitor production (Maraj et al. 2010; Awtry and Philippides 2010).

Four mechanisms have been described in more detail (Awtry and Philippides 2010). All of them alters cardiac function acutely but may lead to cardiac injury in a long-term fashion. First, promotion of intracoronary thrombus formation is widely recognised. Cocaine ingestion stimulates platelet hyperaggregability and increased thromboxane production, often in the setting of coronary vasospasm. These physiologic effects promote acute intracoronary thrombus formation and myocardial ischemic events and account, in part, for the increased incidence of myocardial infarction noted in cocaine users. Acute coronary ischemia and extensive or recurrent myocardial infarction also contribute to the left ventricular dysfunction and

cardiomyopathy associated with cocaine abuse. However, many cocaine abusers with severe regional or global left ventricular dysfunction do not have a clear history of obstructive coronary disease or myocardial infarction. Thus, myocardial dysfunction can result from transient ischemic insults, perhaps in the setting of vasospasm or spontaneous coronary thrombosis. Alternatively, it is likely that nonischemic mechanisms of myocyte injury may also contribute. Second, sympathomimetic effects have to be taking into account as cocaine acts as a powerful sympathomimetic agent. Stimulation of the beta-adrenergic receptors in myocardial tissue results in increased contractility and heart rate, whereas stimulation of the alpha-adrenergic receptors in coronary and peripheral arteries results in increased coronary resistance, decreased coronary blood flow, elevated blood pressure, and increased myocardial wall stress (Kloner et al. 1992). Animal studies suggest that the increased wall stress seen in acute cocaine intoxication plays an important role in the acute depression of left ventricular function. Following cocaine infusion, ejection-phase indices of left ventricular function are reduced but the effects are attributable to increased wall stress not to reduced contractility (Mehta et al. 1995). Pathologic studies showed similarities between cocaine cardiomyopathy and chronic catecholamine stimulation (Tazelaar et al. 1987). Third, increased calcium flux into myocardial cells, and fourth, enhanced oxidative stress have been suggested as co-factors (Isabelle et al. 2007). Importantly, cocaine may alter cardiac electrophysiology what results in electrocardiological abnormalities, as evidenced in numerous experimental studies. The drug prolongs the PR, QRS, QT, and QTc durations, prolongs atrioventricular nodal conduction time and maximum sinoatrial conduction time, and may trigger frequent atrial extrasystoles and atrial fibrillation and tachycardia as well as transient ventricular tachycardia (Kloner et al. 1992).

2.3.3 Ephedra (Ma Huang)

The dietary supplement ephedra, also known as *Ma Huang* and obtained from the *Ephedra sinica* plant, contains 2 alkaloids – ephedrine and its enantiomer, pseudoephedrine. In traditional Chinese medicine this plant has been used for millennia to treat disorders such as asthma, upper respiratory illnesses and seasonal allergies. In recent years ephedra has gained tremendous popularity as a diet drug because of its biochemical activity as a stimulant and a pro-thermogenic agent. The stimulant activity of ephedra suppresses appetite while the pro-thermogenic property increases the body's metabolism, all leading to improved weight loss. However, over the past decade a number of well-documented reports of ischemic stroke and adverse cardiac events such as myocardial infarction, sudden death, and cardiomyopathy linked to ephedra have lead to a FDA ban of the drug in April 2004 as a dietary supplement (Lillegard and Porterfield 2010). Pharmacologically, ephedra increases catecholamines at synaptic areas in the brain and heart and directly stimulates alpha- and beta-adrenergic receptors. Thus, it can increase heart rate, blood pressure, cardiac output, and peripheral resistance. Coronary artery spasm and pro-arrhythmic effects can account for acute events and death. Prolonged catecholamine excess with long-term ephedra use is one likely underlying mechanism for cardiomyopathy (Figueredo 2011). Importantly, ephedra is often co-abused with anabolic-androgenic steroids (Clark and Schofield 2005; Achar et al. 2010).

2.4 Anabolic-androgenic steroids

The adrenals and the testes produce various compounds that stimulate androgen receptors. Dihydrotestosterone and testosterone are the most potent, but precursors such as dehydroepiandrosterone and androstenedione also have androgenic effects. 17-carbon

androgenic precursors from either the adrenals or the gonads can be converted to testosterone by 17-hydroxysteroid dehydrogenase in the testis or ovary. In target tissues where intracellular enzymes are present, the action of testosterone is mediated by metabolism. The enzyme 5alpha-reductase produces the potent androgen dihydrotestosterone in the prostate, skin, sebaceous glands and brain. Due to this tissue-specific expression of 5alpha-reductase, androgenic effects on prostate growth and male pattern baldness are largely mediated by dihydrotestosterone. Conclusively, testosterone is irreversibly converted by the enzyme 5alpha-reductase to 5alpha-dihydrotestosterone, which binds with greater affinity to the androgen receptor, or by aromatase to oestradiol, which binds to the oestrogen receptor (Kicman 2008). All steroids that are anabolic are derivatives of testosterone (Hartgens and Kuipers 2004) and are androgenic as well as anabolic, as they stimulate growth and function of male reproductive tract. Individual drugs vary in their balance of anabolic:androgen activity but none of the currently available drugs are purely anabolic. Derivatives or structural modifications of testosterone differ by its pharmacokinetics, bioavailability, or, as mentioned above, balance of androgenic to anabolic activity. The large group of anabolic-androgenic steroids include testosterone itself, all of the derivatives that are used clinically, as well as numerous plant products that at least claim to possess anabolic actions (Kuhn 2002). Importantly, the group include many agents with chemical structures derived from cholesterol that are synthesized in the liver and then metabolized to anabolic-androgenic steroids. Their structure resembles that of corticosteroids, explaining some similarities in actions in terms of renal sodium retention and hypertension (Achar et al. 2010).

2.4.1 Therapeutic use and abuse of anabolic-androgenic steroids

Predominantly, anabolic-androgenic steroids are used in the treatment of disorders of puberty, prostatic disease and hirsutism. Testosterone replacement therapy is for hypogonal men who demonstrate clinical (reduced shaving frequency, exercise endurance, libido and testicular size) and laboratory findings (reduced free or free plus albumin-bound testosterone). Testosterone replacement therapy improves physical performance, sexual function, mood and lipid profiles within four weeks in most cases. The orally active androgens methyltestosterone and fluoxymesterone are not commonly used for androgen replacement, but are commonly abused by body builders. Other orally active androgenic steroids (testolactone, oxandrolone, stanozolol, oxymetholone) and intramuscular preparations (nandrolone) have androgenic effects and are used clinically for their anabolic actions in cancer and refractory anaemia. Newly, testosterone may have therapeutic benefit and be cardioprotective in heart failure for a number of reasons. Anabolic/catabolic imbalance, which favours catabolism, is a key pathological feature of patients with severe chronic heart failure and anabolic deficiency is an important component of the imbalance (Jankowska et al. 2006). In addition, it has been shown that pharmacological augmentation of anabolic drive can result in favourable changes in the body composition, sexual function and psychological status of aging men. Moreover, testosterone is viewed as a potential natural tonic for the failing heart (Pugh et al. 2000) and testosterone therapy has been proposed as a useful add-on treatment for men with congestive heart failure as its administration increases cardiac output acutely (Pugh et al. 2003; Pugh et al. 2004; Rauchhaus et al. 2006). Indeed, there is a clinical evidence that testosterone replacement therapy regimen in men with congestive heart failure was followed by improvement in NYHA class and functional capacity (Allan and McLachlan 2004; Malkin et al. 2006).

People have been taking testosterone to restore 'vitality' since the efficacy of some hormonal component of the testes was first described by Brown-Sequard in 1889. He reported the reversal of his own aging by self-injection of a testicular extract, thereby stimulated a flurry of experimentation into the putative anti-aging effects of testicular hormones long before the identity of testosterone was confirmed. The first use to improve athletic performance occurred shortly thereafter, in 1896. A contemporary of Brown-Sequard self-administered testicular extract, then measured his finger strength (Kuhn 2002). In modern age, anabolic-androgenic steroids, which include more than 30 natural and synthetic derivatives of testosterone, were designed in 1939 to treat conditions such as eunuchoid syndromes, impotence, depression, starvation, and cryptorchidism. The first suggestion that these drugs might enhance physical performance occurred later that same year. Mass trials conducted by Nazi Germany on their own soldiers during World War II, combined with concurrent animal studies, provided compelling data to support these theories. During the 1954 Vienna world weight lifting championships, the Russian national team introduced the use of anabolic-androgenic steroids as ergogenic aids. By the 1964 Olympics, athletes from around the world were consuming the drugs. In a survey of weight lifters at the 1968 United States Olympic Training camp, 100% had taken some form of the substance. During the 1972 Olympics held in Munich, 68% of those competing in middle or short distance and field events admitted to having taken anabolic-androgenic steroids as part of their preparation for the games. Proliferation of anabolic-androgenic steroids use throughout international competition had reached such epidemic proportions that by the 1976 Olympic games they were declared banned substances (Sullivan et al. 1998). After that, anabolic-androgenic steroids continued to be used clandestinely by Olympic athletes, and its use spread quickly to high school, intercollegiate, and professional sports. According to clinical data, self-reported rates of abuse in bodybuilders and powerlifters to enhance performance range from 29% to 67% (Curry and Wagman 1999; Achar et al. 2010). Also, there is now widespread use among non-competitive bodybuilders, recreational athletes, and those who simply desire an improved physique (Dhar et al. 2005). Thus, the risk of incidence of adverse effects in general population is relatively high. In general, anabolic-androgenic steroids are abused by athletes primarily to increase lean muscle mass, enhance appearance, and improve performance. Increased cellular protein synthesis results in build-up of tissue (anabolism), especially in muscles. A variety of anabolic-androgenic steroids are often taken simultaneously (so called 'stacking'), and in doses which result in 10–100 fold increases in androgen concentrations. Administration regimens usually involve a 6–12 week cycle and are often administered in a 'pyramidal' fashion, with doses tapering from low to high to low (Payne et al. 2004). Abused substances include testosterone, its 17-beta esters, and those based on modified steroid rings (including 17-alpha derivatives).

2.4.2 Cardiac injury

Several adverse effects of steroids have been described, predominantly when taking inappropriately. In healthy men, high-dose testosterone or synthetic androgens produce small increases in muscle mass and exercise performance, while posing the risks of aggressive mood disorder, priapism, erythrocytosis, oligospermia and worsened lipid profile. Adverse hepatic effects such as blood-filled hepatic cysts (*peliosis hepatis*), hepatic adenomas and cholestatic hepatic injury have been reported primarily with oral synthetic androgens. In elderly men, androgen supplementation increases serum concentrations of prostate-specific antigen and may worsen prostate hypertrophy.

Testosterone is a potent ligand of the human androgen receptor in muscles but also directly modulates transcription, translation, and enzymatic function in numerous other tissues (Sullivan et al. 1998). Consequently, the adverse effects from use of anabolic-androgenic steroids are widespread and affect multiple organ systems, including the heart and vessels. Several actions on cardiovascular system, and predominantly on heart, have been reported. Anabolic-androgenic steroids share with endogenous steroids influences on left ventricular hypertrophic response through direct actions on the androgen receptor (Marsh et al. 1998) what is a DNA-linked ligand-activated transcription factor with homology to mineralocorticoid and progesterone steroid receptors. Androgen receptors are ubiquitously expressed, found not only in skeletal muscle cells but also in cardiac myocytes. Anabolic-androgenic steroids can cause hypertension, dyslipidemia, and impaired fasting glucose, as well as alterations in heart structure, including left ventricular hypertrophy and dilation, and impaired contraction and relaxation. Potential sequelae include hypertension, acute myocardial infarction, sudden cardiac death, abnormal cardiac repolarisation with QT interval prolongation, ventricular fibrillation triggered by exercise, atrial fibrillation, cardiac tamponade, development of dilative cardiomyopathy, and heart failure at a dose-dependent manner (Hausmann et al. 1998; Stolt et al. 1999; Du Toit et al. 2005; Karila et al. 2003; Figueredo 2011). Several case reports have linked adverse cardiac events and anabolic-androgenic steroids abuse in healthy young athletes (Stergiopoulos et al. 2008; Ahlgrim and Guglin 2009). Recently, 49 reports describing a total of 1,467 athletes has been extensively reviewed (Achar et al. 2010). In aggregate, studies evaluated lipoprotein concentrations in 643 subjects, blood pressure in 348, left ventricular dimensions in 561, and sudden death in 102. As concluded, otherwise healthy young athletes abusing anabolic-androgenic steroids may show elevated levels of low-density lipoprotein and low levels of high-density lipoprotein. Although data are conflicting, anabolic-androgenic steroids have also been linked with elevated systolic and diastolic blood pressure and with left ventricular hypertrophy that may persist after anabolic-androgenic steroid cessation. Nevertheless, mortality appears to be significantly higher in anabolic-androgenic steroids abusers than in non-abusing athletes.

The potential pathophysiological mechanisms responsible for adverse cardiac effects are incompletely understood. Four mechanisms of anabolic-androgenic steroids-induced cardiovascular toxicity have been proposed: atherogenic, thrombotic, vasospastic, and direct myocardial injury (Melchert and Welder 1995). As already mentioned, anabolic-androgenic steroids bind to androgen receptors in the heart but in arteries as well, and physiologic levels (*e.g.*, of testosterone) may have a beneficial effect on coronary arteries via endothelial release of nitric oxide and inhibition of vascular smooth muscle tone. Conversely, animal studies show that administration of high doses of anabolic-androgenic steroids may reverse this vasodilator response and lead to growth-promoting effects on cardiac tissue, as seen in hypertrophic cardiomyopathy, followed by apoptotic cell death. These effects are likely associated with increased intracellular calcium influx and calcium release from the sarcoplasmic reticulum. This increase of intracellular calcium may be directly responsible for the development of cardiac hypertrophy as well as for the activation of apoptosis (Lieberherr and Grosse 1994; Zaugg et al. 2001). Postmortem histopathological findings of young anabolic-androgenic steroid abusers include cardiac hypertrophy, what seems to be dose-dependent and reversible (Ahlgrim and Guglin 2009). In addition, several other complications have been described, such as myocardial and endocardial fibrosis, cardiac steatosis, myocardial coagulation necrosis, decreased inotropic capacity of the myocardium,

and irreversibly reduced compliance of the left ventricle, and coronary atheroma (Figueredo 2011). In other studies, endomyocardial biopsy specimens have revealed increased fibrous tissue and fat droplets in the myocardium of anabolic-androgenic steroid abusers (Nieminen et al. 1996). Direct cell injury occurs by disruption of myocardial mitochondria and induction of intrafibrillar collagen dysplasia. Cell injury ensues, and scar tissue replaces dead cells, leading to fibrosis and the potential for ventricular arrhythmias. Development of hypertension also occurs, followed by left ventricular hypertrophy and structural changes to the ventricular wall. Increased ventricular septal thickness develops rapidly and is disproportionate to the expected degree of compensatory hypertrophy from resistance training. Other studies reveal increased incidence of diastolic dysfunction, greater left ventricular posterior wall thickness, and greater left ventricular end-diastolic dimensions. In this setting, sudden death may have been caused by vasospasm potentiated by diastolic dysfunction–mediated ischemia (Dhar et al. 2005). Cardiomyopathy, cardiomegaly, and biventricular dilatation induced by anabolic-androgenic steroids can occur as a result of remodelling after myocyte injury and have been noted to be reversible after discontinuation of anabolic-androgenic steroids administration (Hausmann et al. 1998). However, it is still unclear whether such detrimental effects are directly associated with the action of anabolic-androgenic steroids or they are a consequence of co-presence of developing hypertension, hyperdynamics in cardiovascular system and dysbalance in blood lipids. Moreover, athletes abusing anabolic-androgenic steroids often exhibit left ventricular hypertrophy and because the hypertrophy may relate to increased afterload from isometric exercise, the interpretation of cardiac hypertrophy in elite athletes who admit to anabolic-androgenic steroids abuse is complex. Possible associations between anabolic-androgenic steroids and left ventricular hypertrophy may be explained as secondary to hypertension or as a direct effect on the myocardium. Notably, studies in isolated human myocytes have shown that anabolic-androgenic steroids bind to androgen receptors and may directly cause hypertrophy. It was clearly demonstrated that mammalian cardiac myocytes from hearts of different species and both sexes express the androgen receptor gene (Marsh et al. 1998). Androgens are capable of mediating a hypertrophic response of cultured adult myocytes of a magnitude nearly that of the most efficacious hypertrophic stimuli identified for heart. Consequently, androgens must be considered among the neuroeffectors, paracrine factors, and hormones that act directly on the cardiac myocyte and regulate the cardiac hypertrophic response. Indeed, a clinical study suggests a distinct form of left ventricular hypertrophy, as the abuse of anabolic-androgenic steroids in weight-lifters determines some alterations of the myocardial textural parameters when analyzed by videodensitometry (Di Bello et al. 1999). In contrast to these definite findings, studies comparing echocardiographic variables between anabolic-androgenic steroids using and nonusing strength athletes have not yielded unequivocal results (Ahlgrim and Guglin 2009). Some studies have not demonstrated any structural difference with abuse (Thompson et al. 1992) or showed that the myocardial remodeling is independent from anabolic-androgenic steroid use in power athletes (Dickerman et al. 1998). Considering the high prevalence of anabolic-androgenic steroids abuse in population, the number of cases featuring associated cardiac illness reported in current literature appears rather small. Thus the type or the intensity of training might play an important role (Ahlgrim and Guglin 2009). It remains open, whether the use of anabolic-androgenic steroids is causally related to these events or is just coincidental. Some animal studies suggest that these adverse effects cardiac muscle are causal and not coincidental. In adult rat

cardiomyocytes *in vitro*, anabolic-androgenic steroids induce apoptotic cell death increasing the expression of the pro-apoptotic oncogene Bax-alpha in a dose-dependent manner (Zaugg et al. 2001). When studying the cardiac cell ultrastructure, mitochondria and myofibrils show changes similar to those observed in early heart failure, *i.e.* swollen and elongated mitochondria with sparse matrix and decreased number of cristae, and myofibrils show either disintegration and widened and twisted Z-bands or a complete dissolution of the sarcomeric units (Behrendt and Boffin 1977). Long-term testosterone administration results in myocarditis characterized by interstitial oedema, round cell infiltration, and fibrosis (Imai et al. 1978). Interestingly enough, cardiac tissue was protected from testosterone cardiotoxicity by chelating agent dexrazoxan indicating that oxidative stress might be involved (Belhani et al. 2009). Additionally, it was showed that ischemia/reperfusion injury is increased when cardiac hypertrophy develops after chronically administered nandrolone (Penna et al. 2011).

Additionally, in coronary artery disease, there is a contradiction between a documented risk and the evidence that tends to suggest just the opposite. Some short-term interventional studies show that testosterone produces a modest but consistent improvement in cardiac ischemia over placebo, comparable to the effects of existing antianginal drugs as intracoronary artery infusion of testosterone causes coronary artery dilatation and not constriction as previously thought (Liu et al. 2003). Notably, reduced testosterone levels were associated with coronary artery narrowing premature atherosclerosis, increased visceral adipose tissue, hyperinsulinemia, insulin resistance, increased body mass index, reduced high density lipoprotein levels and other risk factors for myocardial infarction (Bain 2007). Similarly in experiments, administration of testosterone significantly improves recovery from global ischemia what might be associated with an attenuation of reperfusion induced intracellular calcium overload (Callies et al. 2003). In contrast to that, testosterone overdose led to increase of apoptosis of cardiac cells after ischemia/reperfusion experiments and it was suggested that testosterone has inhibitory effects on cardioprotective Heat-Shock Protein 72 expression by modulating transcription, through testosterone receptor-mediated genomic mechanisms (Kohno et al. 2007). Similarly, testosterone decreases myocardial function after ischemia/reperfusion injury what is attributed to its proinflammatory and/or proapoptotic properties (Wang et al. 2005). It was shown that testosterone decreases the activation of cardioprotective pathway of the Signal Transducer and Activator of Transduction-3 following ischemia/reperfusion injuries (Wang et al. 2009).

3. Other cardiotoxic substances

3.1 Alcohol

Similarly to stimulants, the abuse of alcohol, as a substance affecting the central nervous system, has long recognised direct toxic effects on the heart (Bing 1978). Ethanol may induce 1) direct dose-dependent myocardial damage manifested as acute effects on rhythm and left-ventricular function, and/or 2) chronic progressive left ventricular dysfunction that may remain subclinical for a long time and is known as alcoholic cardiomyopathy.

Acute harmful drinking may induce 1) changes in cardiac contractility with systolic and diastolic dysfunction, and 2) rhythm disturbances, including sudden death (Urbano-Márquez and Fernández-Solà, 2004). The acute cardiodepressive action of ethanol is well established as it reduces the force of contraction of human heart when plasma levels exceed 75 mg per 100 ml. Such an acute intoxication causes reversible myocardial dysfunction, *i.e.* it

has a direct negative inotropic action with a reversible dose-dependent decrease in myocardial contractility. Most studies of isolated myocardium have sought to explain these acute and reversible changes in the force of contraction by using pharmacologic concentrations of ethanol in the 1% (by volume) range (Knochel 1983; Guarnieri and Lakatta 1990). These studies have demonstrated that ethanol has multiple effects on the myocardium, and as such could depress the force of contraction at several points in the process of electromechanical coupling, probably at the level of the myofilaments. The effect was found to be reversible by increasing the amount of calcium presented to the myofilaments or by washing out the ethanol (Guarnieri and Lakatta 1990). This cardiodepresive action of ethanol is evidenced in experimental models designed with autonomic blockade, heart denervation, or isolated cells. On the other hand, negative inotropic action of ethanol is often masked by indirect actions resulting from an enhanced release of catecholamines *in vivo*. Remarkably, the acute cardio-depressant effect of alcohol usually has fewer clinical consequences in non-alcoholic patients with normal cardiac function, but may be more relevant in patients with previous cardiac disease or in patients with alcoholic cardiomyopathy. In these patients, episodes of heart failure may be induced by acute alcohol poisoning. When considering chronotropy, the acute negative chronotropic effect with combination of augmented release of catecholamines may induce a variety of arrhythmias, known as the 'Holiday Heart' arrhythmias, with paroxysmal atrial fibrillations and ventricular premature depolarisations (Ettinger 1984). The prolongation of conduction times and a heterogeneous increase in the refractory period may be directly associated with propensity of arrhythmias. Chronic alcoholism, acute abstinence from ethanol and coexistence of electrolyte deficiencies are strong co-factors increasing the pro-arrhythmogenicity of ethanol abuse. Moreover the presence of chronic cardiomyopathy increases the risk of arrhythmias such as ventricular fibrillation or even sudden cardiac death.

Long-standing ethanol consumption may induce more important deleterious effects on the myocardium what is usually described as alcoholic cardiomyopathy manifesting as cardiac hypertrophy, disrupting contractile function and myofibrillary architecture. When comparing alcoholics with healthy controls, the alcoholics show a lower ejection fraction, a lower mean shortening fraction, a greater mean end-diastolic diameter and left ventricular enlargement. One third of the alcoholics have an ejection fraction of 55 percent or less, and when analysed using endomyocardial biopsy specimens those patients show histologically defined changes of cardiomyopathy (Urbano-Márquez et al. 1989). The chronic ventricular dysfunction develops independently of other factors such as malnutrition or vitamin deficiencies, with both systolic and diastolic dysfunction, manifested as a decrease in left-ventricular ejection fraction and disturbances in left-ventricular relaxation, respectively. These effects may first be subclinical and, later, overt clinical alcoholic dilated cardiomyopathy with left ventricular or congestive heart failure may appear. In general, one-third to one-half of alcohol consumers, in doses higher than 100 g/day for a minimum of 10 years, is affected by progressive diastolic and systolic dysfunction.

A disproportionately large majority of reported cases of alcoholic cardiomyopathy are men. In line with this, the female gender is believed to be protected from cardiovascular morbidity because of hormones (so called 'oestrogen umbrella' effect). However, this seems to be false in the case of chronic ethanol consumption. As shown in a clinical study, a third of the alcoholic women had evidence of cardiomyopathy what is comparable to men.

Despite the fact that the mean lifetime dose of alcohol in female alcoholics is only 60% that in male alcoholics, cardiomyopathy is as common in female alcoholics as in male alcoholics. Ejection fractions in women inversely correlate with the total lifetime dose of ethanol, whereas the left ventricular mass shows a direct correlation. Similarly to women, ejection fractions also correlate inversely with the total lifetime dose of ethanol in men. However, the threshold dose for the development of cardiomyopathy is considerably less in women than in men, and the decline in the ejection fraction with increasing alcohol dose is steeper. This indicates that women are more sensitive than men to the toxic effects of alcohol on cardiac muscle (Urbano-Márquez et al. 1995).

Importantly, diastolic dysfunction is the earliest sign of subclinical alcoholic cardiomyopathy. Symptoms of alcoholic cardiomyopathy are similar to other causes of low-output dilated cardiomyopathies, with shortness of breath and early fatigue during exercise, progressing to attacks of breathlessness, orthopnea, and paroxysmal nocturnal dyspnea. Negative dromotropism and lowering of the threshold level for ventricular fibrillation have been observed in chronic drinkers, leading to ventricular fibrillation and sudden death. Alcoholism also decrease the myocardial capacity at increased cardiac activity, resulting in shortness of breath due to congestion in the pulmonary vessels. Interestingly, although the development of alcoholic cardiomyopathy is independent of liver function parameters, alcoholics with cardiomyopathy have a higher incidence of liver cirrhosis. As showed in clinical study, alcoholics with diagnosed cardiomyopathy have a higher prevalence of cirrhosis than unselected alcoholics without heart disease. Similarly, actively drinking alcoholics with cirrhosis show impaired cardiac performance, whereas abstaining alcoholics with liver disease tend to manifest normal cardiac function (Estruch et al. 1995).

As already mentioned, the long-term heavy alcohol consumption (of any beverage type) is the leading cause of a nonischemic, dilated cardiomyopathy (Piano 2002). However, there appears to be a biphasic cardiovascular effect based on the chronic dose of alcohol ingested. At low to moderate doses, studies suggest that alcohol has a favourable impact on cardiovascular outcomes, *i.e.* lower incidence of myocardial infarctions and an improved survival. At chronic high-dose intake of alcohol, there is a direct relationship to elevated blood pressure. Also, prolonged exposure to alcohol increases the likelihood of developing congestive heart failure. The exact duration and intensity of alcohol consumption preceding preclinical and symptomatic heart failure is not definitively known. It is estimated that a minimum of 10 years of exposure to excessive alcohol intake leads to the onset of heart failure. However, this link to duration and amount of alcohol consumption is weak. Some heavy users of alcohol never develop a cardiomyopathy, while others who ingest only a modest amount can be at risk for developing a cardiomyopathy. Men may be more susceptible to this risk. Concurrent smoking, hypertension, and malnutrition appear highly associated with the increased risk for developing an alcoholic cardiomyopathy. The incidence of alcohol as a major contributor to cardiomyopathy has been reported to be in the range of 20%–30%, emphasizing the clinical need to recognize the risk and contribution of alcohol in heart failure patients (Lee and Regan 2002). Some studies have observed asymptomatic cardiac dysfunction in patients reporting consumption more than 90 g/day of alcohol (8–21 standard drinks) with an average duration of drinking of 15 years. The disease is characterised by ventricular dilation and systolic dysfunction, in the absence of other causative factors such as coronary disease. In preclinical stages of alcoholic cardiomyopathy, ventricular enlargement and diastolic dysfunction can be observed on echocardiography

(Piano 2002; Wu 2008). Although alcoholic cardiomyopathy may be reversible after abstention, severe cases may still progress into congestive heart failure despite a cessation of alcohol use.

The pathophysiological mechanisms underlying alcoholic cardiomyopathy are poorly understood and diverse pathogenic theories have been postulated about the mechanisms of alcohol-induced cardiac muscle damage. Except the effects of ethanol on blood lipids and systemic blood pressure, they likely involve direct myocyte injury and several direct cellular, subcellular, and molecular derangements of cardiac tissue. In past (Bing 1978), several mechanisms have been proposed such as mitochondrial effects (decreased respiratory function, loss of mitochondrial enzymes, deterioration of ultrastructure), decreased calcium uptake by sarcoplasmic reticulum, altered myocardial lipid metabolism (triglyceride accumulation, decreased fatty acid oxidation), effects by formation of acetate and acetaldehyde, non-thrombotic myocardial infarctions and nutritional defects (thiamine deficiency, protein deficiency). It was previously supposed that malnutrition (electrolyte or vitamin deficiencies) is the main pathogenic factors. However, experimental and clinical studies have clearly demonstrated that ethanol itself is a direct noxious agent to heart in a progressive, cumulative, and dose-dependent manner, and its effects are independent of nutritional, vitamin, or mineral factors. According to current knowledge, the main relevant pathogenic mechanisms of alcohol-induced damage are due to interference in carbohydrate metabolism, protein synthesis, changes in oxidative status and mitochondrial function, disruption of transduction signals, and induction of apoptosis (Urbano-Márquez and Fernández-Solà, 2004). Alcohol alters the permeability of the sarcoplasmic reticulum to calcium ions and thus reduces the efficiency by which calcium activates muscle contraction, and it reduces the synthesis of cardiac proteins in both the contractile actin-myosin complex and in mitochondria, predominantly in alcoholics with high blood pressure. Similarly, a metabolite acetaldehyde and free radicals may contribute to decreased protein synthesis as well. In addition, there is enough evidence that alcohol can induce cardiac muscle damage by increasing the expression of a certain genes, which can promote programmed cell death, resulting in muscle cell loss (Zakhari 1997). In cell cultures, the acute alcohol exposure triggers the process of apoptosis inducing the expression of the pro-apoptotic protein Bax and increased caspase-3 enzyme activity (Chen et al. 2000). However, it is also possible that other cell types or systems are activated, such as the sympathetic nervous system, renin-angiotensin system, cytokines, and natriuretic peptides which may contribute to the overall injury. Interestingly enough, the excessive use of alcohol is not the exclusive cause of development of alcoholic cardiomyopathy *per se* as not all excessive alcohol consumers develop significant myocardial damage. When taking account the high prevalence of alcohol consumption the incidence of alcoholic cardiomyopathy is relatively low in the general population (Urbano-Márquez et al., 1995). Conclusively, in addition to the toxic effect of ethanol causing apoptosis, necrosis and cell loss, other mechanisms may influence the development of cardiac functional and structural damage.

3.2 Heavy metals

Some heavy metals, as cadmium, lead and cobalt, are known to be involved in selective cardiotoxicity. They are negatively inotropic and dromotropic and may cause structural changes. As for example, cobalt has been discovered to be the cause of an endemic cardiomyopathy in heavy beer drinkers in Canada in 1966 where it was used as an

additive to stabilize the froth (Alexander 1972). The cardiac muscle of autopsied patients contained a high concentration of cobalt (Sullivan et al. 1968) but to produce the cardiac disease required a combination of: 1) protein deficient diet and 2) cobalt administration (Rona and Chappel 1973). Although the amount of ingested cobalt was lower than in certain therapies, the poor general nutritional state that is typical of chronic drinkers resulted in higher susceptibility to the cardiotoxicity of cobalt. The exact mechanism for developing of cardiomyopathy is unclear but it is known that cobalt may decrease myocardial contractility by a competitive antagonism with calcium (Hashimoto et al. 1989). Amino and sulfhydryl groups of amino acids can provide protection against cobalt effects by combining with cobalt and preventing the chelation of cobalt with sulfhydryl gropus of the myocardial tissue. One lesson to be learnt from this endemic cardiomyopathy, widely known as cobalt-beer cardiomyopathy, is that effects of any given noxious agent can be compounded and exaggerated by other coexisting metabolic defects, such as protein deficiency (Rona and Chappel 1973), thiamine and zinc depletion and prior ethanolic damage to the myocardium (Alexander 1972).

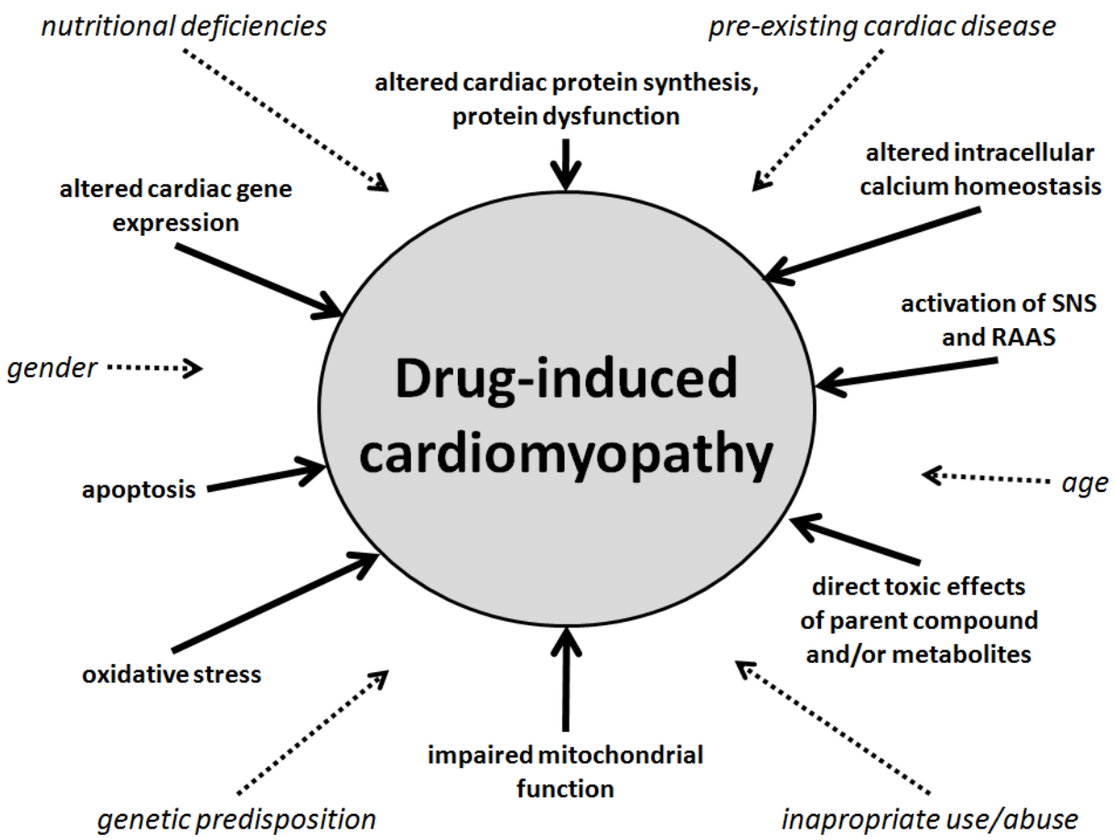


Fig. 2. Potential mechanisms (bold) and risk factors (italic) involved in drug-induced cardiomyopathies. (Abbreviations: SNS – sympathetic nervous system, RAAS – renin-angiotensin-aldosterone system.)

3.3 Experimental models of primary or secondary drug-induced cardiomyopathies

3.3.1 Catecholamines

The harmful effects of excess doses of experimentally administered catecholamines on the myocardium have been established for a long time when infarct-like lesions were produced by administration of large doses of isoproterenol (Rona et al. 1959). One of the best described models of experimental cardiomyopathies is the model of isoproterenol-induced myocardial infarction followed by cardiac hypertrophy, fibrosis and failure (Szabó et al. 1975). Similarly in clinical practice, the cardiotoxicity of catecholamines in treatment of severe asthma has been well established (Maguire et al. 1991). Moreover, catechoalmines are involved in the development of the rare 'Broken Heart Syndrome', also known as Takotsubo cardiomyopathy (Wittstein 2008). The probable mechanisms for such harmful effects of catecholamines on myocardium are not only direct effects, but also, in the case of epinephrine and isoproterenol, severe systemic hypotension with the combination producing a massive myocardial infarction. Although norepinephrine has a predominant vasopressor action, it also produces myocardial damage, which is generally of a patchy necrotic type limited to subendocardial zone occurred in patients with fatal pheochromocytoma or tetanus (Rose 1974). In past, some important mechanisms of catecholamine cardiotoxicity have been proposed: excess of calcium ions with excess excitation-contraction coupling and loss of high-energy phosphate compounds (Fleckenstein et al. 1974), increased cell membrane permeability (Rona 1985), intracellular accumulation of cyclic AMP (Lubbe et al. 1978), and increased ischemic damage (Opie et al. 1979). An important action of catecholamines is their ability to induce myocardial hypertrophy. Importantly, activation of beta-receptors induces the expression of proto-oncogenes c-fos and c-myc (Zimmer 1997). Moreover, some catecholamines induce the development of sub-endocardial fibrosis activating the proliferation of cardiac fibroblasts (Turner et al. 2003). Additionally, the role of oxidative stress (Zhang et al. 2005; Dhalla et al. 2010) and nitric oxide signalling cascade should not be neglected (Krenek et al. 2006; Krenek et al. 2009).

3.3.2 Hyperglycaemia inducing agents

Application of several drugs may lead to alterations which result in cardiac injury secondarily. One of such alteration is the long term hyperglycaemia and the development of diabetes mellitus. In experimental cardiology, two models of diabetic cardiomyopathy are widely established – streptozotocin- and alloxan-induced hyperglycaemia, diabetes and followed diabetic cardiomyopathy. Streptozotocin is a nitrosurea derivative isolated from *Streptomyces achromogenes* with broad-spectrum antibiotic and antineoplastic activity. It is a powerful alkylating agent that has been shown to interfere with glucose transport, glucokinase function and induce multiple DNA strand breaks. A single large dose of streptozotocin can produce diabetes in rodents, probably as a result of direct toxic effects characterized by a specific destruction of the pancreatic beta cells (Rees and Alcolado 2005). Streptozotocin injected rats develop severe diabetes characterized by both fasting and postprandial hyperglycemia with lack of growth in body weight and heart mass. The diabetes induced by streptozotocin can be considered as a model of both type 1 and 2 diabetes, as pancreatic islet beta cell death occurs in both types of diabetes, leading to absolute or relative insulin deficiency. Nevertheless, the model has its limits for each type. On the one hand, a single injection of streptozotocin usually does not lead to an autoimmune reaction as observed in type 1 diabetes, and on the other hand, the animals lack

a significant resistance to insulin action as seen in type 2 diabetes. Nevertheless, metabolic changes typically observed in patients with diabetes, characterized by hyperglycemia and increased circulating free fatty acids, are induced. Thus, eventually the heart is exposed to the major compounds of a diabetic milieu (Dyntar et al. 2006). The developing cardiomyopathy is characterized by a decreased left ventricular performance and bradycardia under basal conditions as well as under beta-adrenergic stimulation, presence of elevated cardiac oxidative stress and changes in electrocardiograms such as the prolongation of QRS and QT interval (Howarth et al. 2005; Jankyova et al. 2009; Klimas et al. 2010). Similarly to streptozotocin, injections of alloxan induce the same blood glucose and plasma insulin responses and cause diabetes syndrome. Alloxan has two distinct pathological effects: it selectively inhibits glucose-induced insulin secretion through specific inhibition of glucokinase, the glucose sensor of the pancreatic beta cell, and it causes a state of insulin-dependent diabetes through its ability to induce reactive oxygen species formation, resulting in the selective necrosis of beta cells (Lenzen 2008). Consequently to persistent hyperglycaemia, degenerative myocardial changes are detectable in experimental settings (Mir and Darzi 2009).

3.3.3 Monocrotaline

In general, right ventricular failure is far rarer than the left ventricular failure. Experimental cardiology uses monocrotaline to induce pulmonary hypertension resulting in right ventricular hypertrophy and *cor pulmonale*. Monocrotaline is a pyrrolizidine alkaloid present in the seeds and foliage of the leguminous plant *Crotalaria spectabilis*. The administration of this alkaloid to rats produces pulmonary hypertension, hypertensive pulmonary vascular disease what results in right ventricular failure (Kay et al. 1982). The precise mechanism remains elusive but is known that to produce pulmonary insult, monocrotaline must first be activated by the liver to the putative electrophile monocrotaline pyrrole. Its stabilization by red blood cells facilitates subsequent transport to the lung where it harms the pulmonary endothelium (Lamé et al. 2000) as has been showed *in vitro* and *in vivo* as well (Boor et al. 1995).

4. Drugs inducing cardiac arrhythmias and cardiac arrest

Except of drugs inducing cellular injury or impairment resulting in depressed cardiac contractility and subsequent contractile failure, there is a number of drugs which affect ion channels and pumps and so destabilize ion homeostasis and trigger conduction defects, arrhythmias or even cardiac arrest. Importantly, these drugs do not acutely affect molecular targets but their chronic administration may affect gene expression and so change the cardiac tissue properties.

4.1 Digoxin

For more than 200 years, digoxin, a cardiotonic steroid, and its congeners have been used to treat congestive heart failure. Cardiac glycosides come from foxgloves (*Digitalis* spp.) and related plants. Nowadays, there is evidence in mammals of an endogenous digitalis-like factor closely similar to another cardiac glycoside, ouabain, and this is of potential physiological and pathological significance (Schoner 2002). Cardiotonic steroids are specific inhibitors of the the Na^+/K^+-ATP-ase of plasma membranes and this leads to an increase in the concentration of

intracellular calcium via Na^+/Ca^{2+} exchanger as a secondary event. Moreover, this modulates the calcium content of the sarcoplasmic reticulum and Ca^{2+} signalling, and contributes finally to the positive inotropic effect of cardiac glycosides and an altered gene expression of proteins (Blaustein et al. 1998; Scheiner-Bobis and Schoner 2001). Because Na^+/K^+ exchange is electrogenic, inhibition of the pump by glycosides causes depolarisation, predisposing to disturbances in cardiac rhythm. Furthermore, the increased intracellular calcium causes increased after-depolarisation, leading first to bigeminy, followed eventually by ventricular tachycardia and, in certain cases, by ventricular fibrillation.

4.2 QT prolonging and Torsades de Pointes triggering drugs

The duration of QT interval measured by 12-lead electrocardiography, as a characterization of ventricular repolarisation, is one of the stable cardiac parameters widely used to describe cardiac abnormalities and safety of drugs (Klimas et al. 2008; Kmecova and Klimas 2010). The prolongation of QT interval on the surface electrocardiogram because of abnormally prolonged ventricular repolarisation is mostly referred as long QT syndrome. From a clinical perspective, it may translate into a propensity to develop syncope and sudden cardiac death. In most documented cases, death was caused by the malignant polymorphic ventricular arrhythmia called *Torsades de Pointes*. This arrhythmia is defined as a polymorphic ventricular tachycardia characterized by a 'twisting of the points' around the isoelectric line on the electrocardiogram (also formerly known as 'ballet rhythm'), and is preceded by a long QT interval (Ponte et al. 2010). Common manifestations of *Torsades de Pointes* are palpitation, symptoms of impaired cerebral circulation such as dizziness, syncope or seizures. Importantly, *Torsades de Pointes* is potentially fatal. In 20% of cases it can subsequently degenerate into ventricular fibrillation with mortality of around 10%. Predicting the development of a life-threatening arrhythmia is a hard task but, in the case of *Torsades de Pointes*, there are some useful markers. Among them, the prolongation of the QT interval is the most remarkable (Giorgi et al. 2010).

In the past few years, much attention has been focused on drugs that prolong the QT interval, potentially leading to malignant cardiac rhythm disturbances and fatal *Torsades de Pointes*. Several drugs were withdrawn from the market because they either directly caused electrocardiographic abnormality or resulted in drug-drug interactions that led to unacceptable rates of cardiotoxicity. In 1964, it was first described what would subsequently be termed drug-induced long QT syndrome with the observation that quinidine could provoke QT prolongation and arrhythmias in otherwise healthy patients (Selzer and Wray 1964). Indeed, drug administration is the most common cause of *Torsades de Pointes*. The most frequent triggers are QT-prolonging antiarrhythmics, such as quinidine, procainamide, disopyramide (class Ia) and sotalol, amiodarone, dofetilide or ibutilide (class III). With these agents, 1–8% of patients develop marked QT prolongation and *Torsades de Pointes*. On the other hand, there is a wide range of drugs developed for non-cardiovascular indications prolonging QT and inducing *Torsades de Pointes*, as well. These include high-profile drug withdrawal cases, such as terfenadine, astemizole and cisapride, as well as a variety of drugs that are in common clinical use, such as methadone, clarithromycin, erythromycin and other antibiotics, and thioridazine and other antipsychotics. An up-to-date list is maintained at the www.torsades.org website. Nevertheless, the incidence of *Torsades de Pointes* with these 'non-cardiovascular' agents is lower than with QT-prolonging antiarrhythmics (Roden 2008).

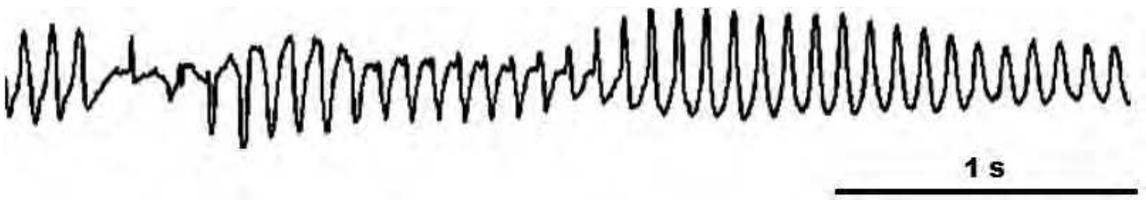


Fig. 3. The risk of *Torsades de Pointes* rises when risk factors are combined. As shown in electrocardiogram, the repeated co-administration of clarithromycin and furosemide may induce adrenergically-triggered *Torsades de Pointes* in rat (Klimas et al. 2010a).

The electrophysiological basis of QT length is the action potential of ventricular cardiomyocytes. First principles in cardiac electrophysiology dictate that an increase in QT interval must reflect an increase in action potential duration in at least some regions of the ventricle. Such increased action potential duration, in turn, must reflect an increase in inward current or a decrease in outward current (Roden 2008). Most drugs that cause *Torsades de Pointes* prolong the action potential of cardiac myocytes by blocking potassium channels (Roden 2004). Notably, the most important ionic current related to drug-induced potential of action prolongation is the delayed rectifier potassium current I_{Kr} during phase 3 of action potential. Most drugs block the I_{Kr} (Kv11.1) channel by binding to the alpha-subunits. The channel is encoded in the *human ether-a-go-go related gene* (HERG) gene. The relationship between QT prolongation and *Torsades de Pointes* has been initially supported by the fact that subjects with some forms of long QT syndrome (which have a mutation in the HERG) frequently developed *Torsades de Pointes*. Thus, extending that concept, drugs that inhibit the HERG encoded I_{Kr} channel may increase the duration of the action potential, QT interval and it might lead to *Torsades de Pointes*. In spite of this scientific evidence, the inhibition of HERG channel does not always provoke action potential and QT prolongation, mainly when the drug also blocks other ionic channels, as it happens with L-type calcium channels blockers. Moreover, some non-antiarrhythmic drugs that clearly prolong QT (as it was observed for sodium pentobarbital and ranolazine) have not been associated to *Torsades de Pointes* (Giorgi et al. 2010). However, some drugs like arsenic trioxide and pentamidine prolong the QT interval by reduced number of I_{Kr} (Kv11.1) channels on the myocardial cell membrane by causing abnormal trafficking of proteins which form the I_{Kr} (Kv11.1) channel. Importantly, only a few individuals receiving drugs that block the I_{Kr} (Kv11.1) channel develop significant QT prolongation and potentially fatal *Torsades de Pointes*. Predisposing factors include interactions with concomitantly used drugs resulting in supra-therapeutic drug levels, female gender, advanced age, bradycardia, hypokalaemia, hypomagnesaemia, ventricular hypertrophy, renal failure, central nervous system lesions, low-salt diet, congestive heart failure and nutritional disorders like prolonged starvation and anorexia nervosa. It is believed that some patients experiencing *Torsades de Pointes* may have genetic polymorphisms of genes coding for cardiac ion channels (Salvi et al. 2010).

Amiodarone	Ibutilide
Arsenic trioxide	Levomethadyl
Astemizole	Mesoridazine
Bepridil	Methadone
Chloroquine	Moxifloxacin
Chlorpromazine	Pentamidine
Cisapride	Probucol
Clarithromycin	Procainamide
Disopyramide	Quinidine
Dofetilide	Sotalol
Domperidone	Sparfloxacin
Droperidol	Terfenadine
Erythromycin	Thioridazine
Halofantrine	Vandetanib
Haloperidol	

Table 2. Drugs with a documented risk of Torsades de Pointes (Salvi et al. 2010).

5. Conclusion

The fact that drug-induced heart disease, and in particular drug-induced cardiomyopathy, does not occur more often, as would be expected from the diversity of various mechanisms, is perhaps surprising. In spite of this, cardiotoxicity remains a major problem of hundreds of pharmaceutical agents, industrial chemicals and naturally occurring products and is often a limiting factor in treatment of certain diseases. Hence, it must be taken in account in the process of clinical decision making and treatment as well as in the process of drug research and development.

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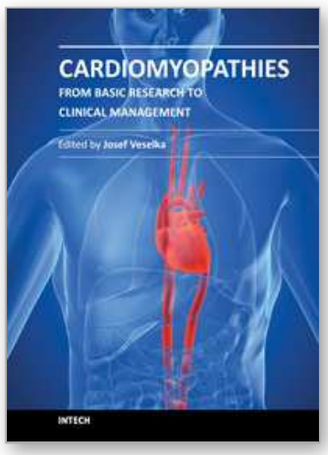
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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