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Cardiac toxicity

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A growing number of studies now demonstrate that alterations in the function of cell membrane transporters, as a result of drug interactions or genetic polymorphisms, may explain a significant portion of efficacy or toxicity in the response to treatment with certain drugs. One prominent example is the variability observed in effects of treatment with digoxin, as discussed in this issue of *Heart and Metabolism* in the article by Lelièvre and Lechat. Fifteen years ago, digoxin, a substrate of the ATP-binding cassette (ABC) transporter known as ABCB1, was shown to be transported by this adenosine triphosphate (ATP)-dependent export pump termed 'P-glycoprotein'. The finding that ABCB1 is expressed in cardiac capillaries and arterioles raised the possibility that the cardiac ABCB1 export pump might prevent accumulation of digoxin in the heart. The article by Couture, Nash and Turgeon provides a concise overview of the role of ABC transporters in distribution of drugs to the heart and protection of the heart from toxic compounds.

Members of the ABC protein superfamily are integral membrane proteins involved in energy-dependent transport of a wide variety of substrates across biological membranes. The most up-to-date information concerning nomenclature of ABC transporters shows that this superfamily is divided into seven different subfamilies (see <http://www.nutrigene.4t.com/humanabc.htm>; last updated March 2005). Currently, there are approximately 50 functional ABC transporters identified in the human genome, most of which are highly conserved across species.

Many human ABC transporters, such as ABCB1 (P-glycoprotein) or ABCC9 (also known as sulfonylurea transporter SUR2), are expressed in the heart. It

is of note that mutations in ABCC9, a constituent of cardiac K_{ATP} channels, have been identified in individuals with heart failure and rhythm disturbances. Interestingly, it was reported that the expression of ABC transporters in the heart could be modulated by pathological cardiac conditions. In this respect, a number of recent findings support the idea that expression of ABC transporters in human heart may alter the intracardiac concentrations, and hence the effects, of therapeutic agents and cardiotoxic drugs. Importantly, cardiotoxic effects have been reported that are linked to increased heart drug concentrations after co-administration of antineoplastic agents and agents that reverse multidrug resistance. Thus, in-vitro and in-vivo studies have shown that co-administration of the anthracycline, doxorubicin, a substrate of ABCB1, and of inhibitors of ABCB1, results in an increase in cardiotoxicity.

Cardiotoxicity is, indeed, a well recognized side effect of anthracycline therapy that limits the amount of drug administered and can cause heart failure in some patients. The review by Vergely, Delemasure, Cottin and Rochette points out that the induction of an oxidative stress within myocardial tissue is an important component of anthracycline cardiotoxicity. It also highlights promising strategies aimed at reducing the associated production of reactive oxygen species and consequent cell damage. Furthermore, the Basic Article by Vander Heide provides recent data at the molecular level showing how early anthracycline-induced myocyte DNA damage may be different from the damage induced by a pure oxidative stress, and may represent a novel therapeutic target that may lead to a reduction in cardiac toxicity.

Molecular basis of anthracycline-induced cardiotoxicity

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Abstract

Anthracyclines are highly effective chemotherapeutic agents used to treat a wide variety of malignancies. Cardiotoxicity is a well recognized side effect of anthracycline therapy that limits the total amount of drug administered and can cause heart failure in some patients. Most experimental data support oxidative stress as the etiology of anthracycline-induced cardiotoxicity. This review will discuss the effect of anthracycline cardiotoxicity on human hearts and present insight into the cellular and subcellular mechanisms believed to be responsible for the lethal myocyte injury associated with anthracycline cardiotoxicity.

■ *Heart Metab.* 2007;35:5–8.

Keywords: Anthracycline, cardiotoxicity, cardiac muscle, oxidative stress, apoptosis, mechanism

Introduction

Anthracyclines are highly effective chemotherapeutic agents used to treat a wide variety of common malignancies, including breast cancer, Hodgkin's lymphoma, non-Hodgkin lymphoma, and acute leukemia. The advent of anthracycline in chemotherapy regimens has resulted in dramatic increases in cancer survival, especially in childhood malignancies, with increases in survival of up to 80% being reported since the introduction of the drug. However, cardiotoxicity is a well recognized side effect of anthracycline treatment that limits the total amount of drug administered and can cause heart failure in some patients. Early retrospective studies from the 1970s demonstrated that anthracycline toxicity and heart failure were dose-related, with the incidence of complications increasing sharply when the cumulative dose exceeded 550 mg/m² of body surface area. The incidence of heart failure was approximately 4% when the cumulative dose was between 500 and

550 mg/m², but increased to 18% when the dose was increased to 551–600 mg/m² and to as much as 36% when the total dose was at least 601 mg/m² [1,2]. The prognosis of the cardiomyopathy, once developed, is grave, and it is difficult to predict which individuals will develop heart failure on a case-by-case basis. Children treated with anthracycline can develop cardiotoxicity even when exposed to cumulative doses well below that believed to be safe in adults [3]. The problem of anthracycline-induced cardiotoxicity is considerable and will continue to grow, because more than 50% of long-term survivors of childhood cancer have received at least one treatment with anthracycline during their chemotherapy.

Mechanism of cardiotoxicity

A possible pathway for anthracycline-induced cardiac dysfunction, described here, is summarized in *Figure 1*.

Basic article

Richard S. Vander Heide and Thomas J. L'Ecuyer

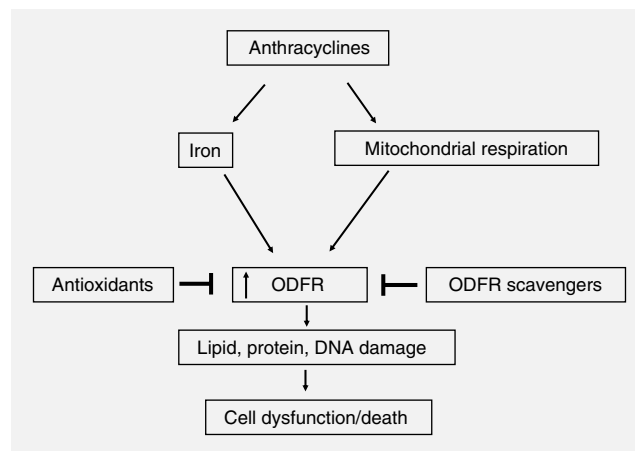


Figure 1. Proposed pathway of anthracycline-induced cardiac dysfunction/death. ODFR, oxygen-derived free radicals.

Most experimental studies have pointed to oxidative stress as the primary cause of anthracycline-induced cardiotoxicity. Evidence to support this hypothesis is derived from studies showing that the administration of anthracycline causes oxidative stress in the heart and that protection from cell death is afforded by administration of antioxidants [4]. The oxidative stress is believed to be secondary to the generation of oxygen-derived free radicals*.

Coupled with the increase in free-radical generation, adult myocytes are terminally differentiated cells with highly oxidative metabolism and limited oxidative defenses [5]. Many experimental studies have shown success in limiting anthracycline-induced injury through manipulations designed to increase antioxidant defenses. For example, in cultured cardiac myocytes, administration of amifostine, trolox, 5-aminosalicylic acid, or α -phenyl-tert-butyl nitron (all antioxidants) before administration of anthracycline reduced indices of oxidative stress and myocyte injury [6,7]. In small-animal models, the degree of anthracycline-induced injury was also reduced by pretreatment with the antioxidants thymoquinone, butylated hydroxyanisole, and probucol [8]. The major antioxidant enzymes that protect myocytes from oxidative injury include superoxide dismutase (SOD)*, glutathione S-transferase (GST)*, catalase*, and glutathione peroxidase*. Transgenic overexpression of both SOD and catalase has been shown to be cardioprotective [9,10], as has overexpression of thioredoxin, a redox-sensitive protein [11]. We have shown in cardiac myoblasts that regulated increased expression of GST protects against anthracycline-induced cell death [4]. In that study, controlled overexpression of the α 4-isoform of GST reduced oxidative stress, as measured by DFDA fluorescence, and both oncotic and apoptotic cell death. These results also support the concept that anthracycline-induced cell death is closely correlated with increased oxidative stress.

Anthracyclines induce the generation of oxygen-derived free radicals through two main pathways: a non-enzymatic pathway that utilizes iron [12,13], and an enzymatic mechanism using the mitochondrial respiratory chain. Iron is an important cofactor in the generation of many toxic free-radical species, catalyzing the Haber–Weiss reaction*. Iron chelation reduces the generation of free radicals and therefore has been studied in many experimental systems, and in some human clinical trials, for its ability to reduce anthracycline-induced cardiotoxicity. Small clinical trials have shown that iron chelation allowed for the administration of greater doses of anthracycline and reduced the number of patients developing heart failure [14,15]. Meta-analysis of a number of clinical trials examining one of the more promising chelating agents, dexrazoxane, has shown a reduction in the incidence of heart failure in some patients with advanced cancer [16]. However, dexrazoxane has serious myelosuppressive side effects and may reduce the efficacy of antitumor drugs, which may limit its wider therapeutic use [16–19].

The enzymatic pathway of free-radical generation involves mitochondria. Anthracyclines have a high affinity for cardiolipin*, a phospholipid that is enriched in the inner mitochondrial membrane; this affinity may allow for anthracyclines to concentrate inside myocytes [20]. The specific mechanism(s) by which this occurs is not entirely known, but includes the possibilities, first, that anthracycline-induced mitochondrial damage may cause respiratory chain defects which would allow for continued production of free radicals and, secondly, that mitochondrial damage may result in the release of cytochrome *c*, which is integral to the pathway for the induction of apoptosis. Other investigators have hypothesized that targeting the myocardial energetic network is part of anthracycline-induced cardiotoxicity [21]. This hypothesis is based on data showing that anthracycline causes significant reductions in high-energy

Basic article

Anthracycline-induced cardiotoxicity

phosphate concentrations in heart and myocytes. Anthracycline is also believed to reduce the activity of respiratory complexes and to compromise the function of the adenine nucleotide translocator or the voltage-dependent anion channel*, or both; these are proteins important in the generation and transport of ATP from the mitochondria to the cytosol, where it is utilized for many cellular functions. It is also possible that anthracycline-induced alterations in gene expression may preferentially affect metabolic enzymes, including enzymes from both oxidative metabolism and glycolysis [21].

Free radicals cause direct damage to several different types of macromolecules, including proteins [22], lipids [23], and DNA, through the generation of free-radical chain reactions, direct intercalation into DNA, or both. A large part of the antitumor effects of anthracyclines may occur by irreversible damage to the tumor-cell DNA. If this is the case, it is not surprising that anthracyclines may also cause cardiotoxicity through a similar mechanism. It has been reported that oxidative stress can cause base modifications in myocyte nuclear DNA under conditions of ischemia-reperfusion [24] or depletion of antioxidant defenses [25]. Anthracyclines bind avidly to DNA in the nucleus of tumor cells, forming adducts that interfere with protein binding and therefore replication and transcription [26]. DNA damage is well known to activate the p53 pathway*. Activation of p53 results in translocation of the protein to the nucleus, where it induces transcriptional changes in proteins that prevent cell division (ie, p21) and cause apoptosis [27]. Alternatively, once a cell sustains DNA damage, DNA repair pathways are activated. Such repair enzymes excise oxidized bases before replication [28], remove oxidized bases from the nucleotide pool [28], or remove oxidized bases from DNA after replication [29]. Because myocytes are terminally differentiated cells, repair pathways may play an important part in the outcome of administration of anthracycline to the heart.

Recent data from our laboratory suggest that DNA damage may have an important role in anthracycline-induced cardiotoxicity [30]. Doxorubicin (a well-known anthracycline) induces oxidative DNA damage, with specific lesions including oxidized pyrimidines and 8-hydroxyguanine. DNA oxidation was followed by activation of p53 and loss of mitochondrial membrane potential in cultured myocytes. Chemical inhibition of p53 prevented activation of p53, the loss of mitochondrial membrane potential, and doxorubicin-induced cell death, but did not prevent DNA damage. In addition, in contrast to the purely oxidative injury produced by hydrogen peroxide, the DNA damage resulting from anthracycline administration is *not* repairable. These results suggest that DNA damage plays an important early part in

anthracycline-induced cardiotoxicity through a pathway that involves p53 and the mitochondria.

Summary

Anthracyclines are highly effective chemotherapeutic agents that have substantially increased survival for cancer patients, but use of which is limited by dose-related cardiotoxicity. Anthracycline-induced cardiotoxicity is believed to be secondary to oxidative stress. Recent data indicate that early anthracycline-induced DNA damage is different from the DNA damage induced by a pure oxidative stress, and may represent a novel therapeutic target that may reduce cardiotoxicity or lead to better therapeutic regimens for patients with cancer. ■

* See glossary for definition of these terms.

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Mechanisms, manifestations, and management of digoxin toxicity

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Abstract

Well known functional structures are implicated in the development of digoxin toxicity in the heart: (Na⁺/K⁺-) Mg²⁺-ATPase, the Na⁺-Ca²⁺ exchanger, and sarcoplasmic reticulum; there is both direct and indirect involvement of sodium, potassium, and calcium ions. The therapeutic effect of digoxin in doses between 1 and 2 ng/ml involves the alpha 2 isoform of Na⁺/K⁺-ATPase. Toxic effects occur at doses of digoxin exceeding 3 ng/ml, when the main three Na⁺/K⁺-ATPase isoforms become – at least partially – inhibited. As a result, calcium overload and an imbalance of K⁺ concentration induce arrhythmias and atrial systolic tachycardia with atrioventricular blockade. These types of arrhythmia can be treated effectively by pharmacological approaches involving antidigoxin Fab fragments.

■ *Heart Metab.* 2007;35:9–11.

Keywords: Arrhythmias, digoxin, cardiotoxicity, human Na⁺/K⁺-ATPase isoforms, ventricular tachycardia

Introduction

The mechanisms of action of digitalis (digoxin) in the human heart have been studied extensively, including the clinical and molecular basis of both its therapeutic and its toxic effects.

Molecular mechanisms of action of digoxin

Digoxin is a cardiac glycoside that binds to and inhibits sarcolemma-bound (Na⁺/K⁺-) Mg²⁺-ATPase*. This ATPase catalyses both an active influx of 2 K⁺ ions and an efflux of 3 Na⁺ ions against their respective concentration gradients, the energy being provided by the hydrolysis of ATP. The inhibition induced by digoxin leads to an efflux of potassium from the cell and, in proportion to the extent of inhibition of the ATPase, an increase in internal sodium ion concentration ([Na⁺]) at the inner face of the cardiac membranes. This local accumulation of

sodium causes an increase in free calcium concentrations via the Na⁺-Ca²⁺ exchanger. This free cellular calcium concentration ([Ca²⁺]) is responsible for the inotropic action of digoxin, secondary to the release of Ca²⁺ from the sarcoplasmic reticulum *Figure 1* [1].

Toxic effects of digoxin (ie, arrhythmias) occur when the cytoplasmic Ca²⁺ increases to concentrations exceeding the storage capacity of the sarcoplasmic reticulum [2,3]. As a consequence of this internal Ca²⁺ overload, several cycles of Ca²⁺ release–reuptake are required to restore the Ca²⁺ equilibrium between sarcoplasmic reticulum and cytoplasm. In addition, high internal concentrations of Ca²⁺ activate a depolarizing (inward) current corresponding to the forward mode of the electrogenic Na⁺-Ca²⁺ exchanger (3Na/2Ca)*. This current generates delayed after-depolarizations that give rise to extra-systoles and sustained ventricular arrhythmias in vivo [4]. The increase in internal Na⁺ induces two effects on calcium concentrations: the

Main clinical article

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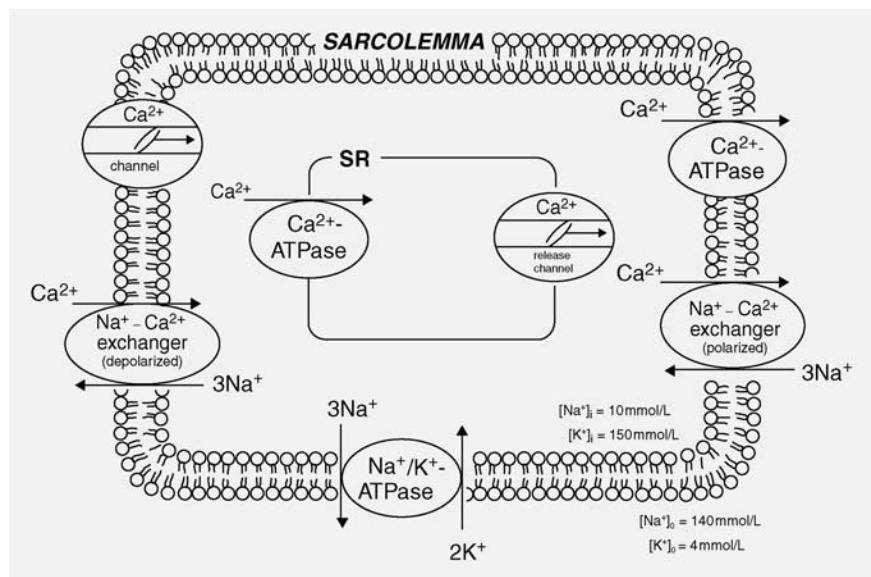


Figure 1. Effect of Na^+ pump inhibition on cellular Ca^{2+} homeostasis. (From Smith et al [1], with permission.)

Ca^{2+} efflux that normally occurs via the electrogenic $\text{Na}^+-\text{Ca}^{2+}$ exchanger is diminished, and Ca^{2+} influx is promoted via the $\text{Na}^+-\text{Ca}^{2+}$ exchanger in the reverse mode as a result of high internal concentrations of Na^+ .

The toxicity of digoxin could also be amplified in human heart failure, because the $\text{Na}^+-\text{Ca}^{2+}$ exchanger is upregulated [5].

The pharmacological properties of the three main human cardiac Na^+/K^+ -ATPase isoforms explain the role of hypokalemia in the toxic effects of digoxin. The functional Na^+/K^+ -ATPase is a heterodimer of alpha and beta subunits. The alpha subunit bears the catalytic site and binds digoxin, ATP, Na^+ , and K^+ . The three isoforms have the same apparent affinity for digoxin, in the nanomolar range [6]; however, their apparent affinities vary according to the concentration of potassium. In the presence of physiological concentrations, the alpha 1 and alpha 3 isoforms exhibit 3–5-fold lower sensitivities to digoxin; potassium exerts a protective effect. In contrast, the alpha 2 isoform remains highly sensitive to cardiac glycosides. Furthermore, the alpha 2 isoform very rapidly binds and releases digoxin (within a few minutes), whereas the half-times for the dissociation of digoxin from alpha 1 and alpha 3 are 80 and 30 min, respectively. Thus, under physiological conditions, the alpha 2 isoform could be effectively inhibited at low concentrations of digoxin. It has been assumed that, in the presence of high concentrations of digoxin, alpha 1 [7] and alpha 2 isoforms are inhibited and induce toxic effects. Indeed, according to James et al [8], a 50% genetically reduced concentration of the functional alpha 2 isoform in the heart leads to an inotropic effect that mimics that of digitalis. In the case of the alpha 3 isoform, the same genetic approach leads

to cardiac hypocontractility, which mimics the toxic effects of digoxin (reviewed in [9]).

Manifestations of digoxin toxicity

Therapeutic effects of cardiac glycosides are observed in the presence of plasma concentrations between 1 and 2 ng/ml (about 2 nmol/L). Toxicity occurs at doses exceeding 3.1 ng/ml; its origin can be either a therapeutic overdose (5% of reported cases) or ingestion of a large quantity.

There are extracardiac and cardiac manifestations of digoxin toxicity. In 80% of the toxic episodes observed, anorexia is an early symptom of toxicity that can be hidden by vomiting that is directly related to the plasma concentration of digoxin. High concentrations of digoxin also affect color vision, and between 25 and 67% of patients have neurological problems, mainly headache and dizziness (vertigo).

Several other symptoms of digoxin toxicity have been described: significant arterial vasoconstriction, muscular and cutaneous pathologies (caused by hypersensitivity to cardiac glycosides), severe thrombocytopenia that disappears over a period of 7 days after withdrawal of digoxin, and interference with estrogen as a result of structural similarities that it shared with digoxin metabolites.

The cardiac manifestations of toxicity caused by digoxin are characterized by 'abnormal' rhythms and alterations in conduction. Atrial systolic tachycardia with atrioventricular blockade immediately evoke the typical digitalis-induced arrhythmias. Ectopic rhythms as a result of re-entry and increases in automatism lead to atrial flutter, atrial fibrillation, ventricular premature beats and ventricular tachycardia. These

Main clinical article

Digoxin toxicity – clinical and molecular aspects

phenomena are the results of increased excitability of fibers and diminished conduction velocity at the level of the Tawara node.

Non paroxysmal junctional tachycardias are frequently observed. Redundant 3- or 4-multiform ventricular extra-systoles also represent a frequent manifestation, but this is a less specific criterion in the presence of previous cardiac impairment. Digoxin toxicity is clearly characterized when ventricular extra-systoles and atrioventricular block are associated symptoms. It is worthy of note that these manifestations are enhanced by pre-existing factors such as age, cardiomyopathies, plasma concentration of digitalis, and hyperkalemia (>6.5 mmol/L)

Management of digoxin toxicity

When the toxic effects of digoxin are associated with hypokalemia, the hydroelectrolytic imbalance can be corrected by intravenous perfusion of potassium chloride 40 mmol/L per hour, with electrocardiographic monitoring. Hyperkalemia can be corrected only by using digoxin-specific immunoglobulin fragments (Fab)* that remove the drug from the Na⁺/K⁺ pumps and restore the potassium fluxes into the cells. Such antidigoxin Fab fragments represent a rapid and efficient treatment of this drug-induced toxicity. Prescribed in humans since 1976, this approach is used even in the presence of plasma concentrations of digoxin as high as 100 ng/ml (200 nmol/L). Typically, potassium concentrations are normalized in 1 h, by which time normal behavior is also partially restored; complete neutralization of toxicity occurs in 4 h.

For the treatment of arrhythmias, classical anti-arrhythmic compounds – β -blockers, converting enzyme inhibitors, and vagolytic agents such as atropine – can be used (reviewed in [10]). Intracavitary ventricular stimulation can also be prescribed. ■

* See glossary for definition of these terms.

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Myocardial perfusion imaging and cardiac events in asymptomatic patients with diabetes

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Abstract

Myocardial perfusion single-photon emission computed tomography (MP-SPECT) has become essential for screening diabetic patients at high risk of silent myocardial ischemia. The combined use of pharmacological and exercise stress, together with the generalization of gated studies has increased both the sensitivity and the specificity of MP-SPECT, leading to a better identification of balanced coronary artery disease, of coronary artery disease with normal coronary angiography, and artifacts. In addition, the incremental prognostic value of gated MP-SPECT over myocardial perfusion and clinical data has been demonstrated. However, the selection of those asymptomatic diabetic patients who will benefit from screening remains an open question. A more refined estimation of cardiovascular risk factors is required.

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Keywords: Diabetes mellitus, occult coronary artery disease, myocardial perfusion imaging, scintigraphy, screening

Introduction

Projections indicate that the worldwide prevalence of diabetes is likely to increase from about 200 million today to more than 300 million in 2025 [1]. This dramatic increase, and the association between diabetes and coronary artery disease (CAD), constitute a major public health problem in developed countries.

Patients with diabetes are at a 2 to 4-fold greater risk of cardiovascular mortality and are both more likely to have silent ischemia and less likely to survive a myocardial infarction than non diabetic individuals. In the population of patients with diabetes, most experience in the clinical setting for the assessment of ischemia has been obtained with myocardial perfusion single-photon emission computed tomography (MP-SPECT). Gated stress–rest MP-SPECT not only provides information about the physiological significance of flow-limiting CAD, but also assesses several

independent risk factors for subsequent cardiac events (extent of scarring, global left ventricular ejection fraction, end-systolic volume, ventricular remodeling, transient ischemic dilatation). The risk of cardiac death, myocardial infarction, or need for revascularization after non fatal myocardial infarction is more than 7-fold greater in diabetic patients with myocardial perfusion defects than in diabetic patients for whom scintigraphic data are normal [2,3]. However, although occult CAD is a common finding in asymptomatic patients with diabetes, the prevalence of occult coronary disease differs widely among the various published results, ranging from 20% to 60% [4]. This discrepancy most probably reflects differences in the diabetic populations included in the studies, thus indicating the need for a more refined selection of those patients who would benefit from screening for occult CAD.

This article will focus on three points. First, it will consider the improvement in accuracy of myocardial

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perfusion scintigraphy that has resulted from the development of pharmacological stress procedures and gated studies. Secondly, the overall accuracy of MP-SPECT will be discussed, in comparison with coronary angiography, for the specific case of asymptomatic diabetic patients. Hypotheses to explain the so-called 'false positive' findings of MP-SPECT will be considered. Thirdly, the limits of the guidelines for CAD screening in patients with diabetes will be reviewed and discussed.

Recent improvements in MP-SPECT

Although myocardial perfusion imaging has been available in routine clinical settings since the 1970s, the development of gated SPECT over the past two decades has made possible a combined assessment of myocardial perfusion and left ventricular function (Figure 1). This additional information on ventricular function has proven to be useful for both the diagnosis and prognosis of CAD. Using gated studies, the quantification of post-stress wall motion abnormalities or ejection fraction increases the sensitivity of stress–rest

MP-SPECT, especially in patients with three-vessel CAD, in whom a diffuse decrease in subendocardial blood flow may cause an impairment of ventricular function without focal perfusion defects [5,6]. Moreover, quantification of wall motion is a powerful tool with which to differentiate actual scars from attenuation artifacts, thus leading to better specificity of gated MP-SPECT compared with non gated studies [7]. Finally, post-stress left ventricular ejection fractions and end-systolic volumes measured by gated MP-SPECT are independent predictors of cardiovascular events and have incremental prognostic values over myocardial perfusion and clinical data in predicting cardiac death [8].

These recent advances in MP-SPECT have been enhanced by improvements in the stress procedure used, especially for patients with diabetes, who are less likely to achieve peak stress using conventional procedures than are non diabetic patients. It has been shown that the combined use of a vasodilator-induced pharmacological stress (intravenous dipyridamole or adenosine) and submaximal exercise on a treadmill or bicycle reduces the non cardiac side effects of vasodilatation and arrhythmias while producing

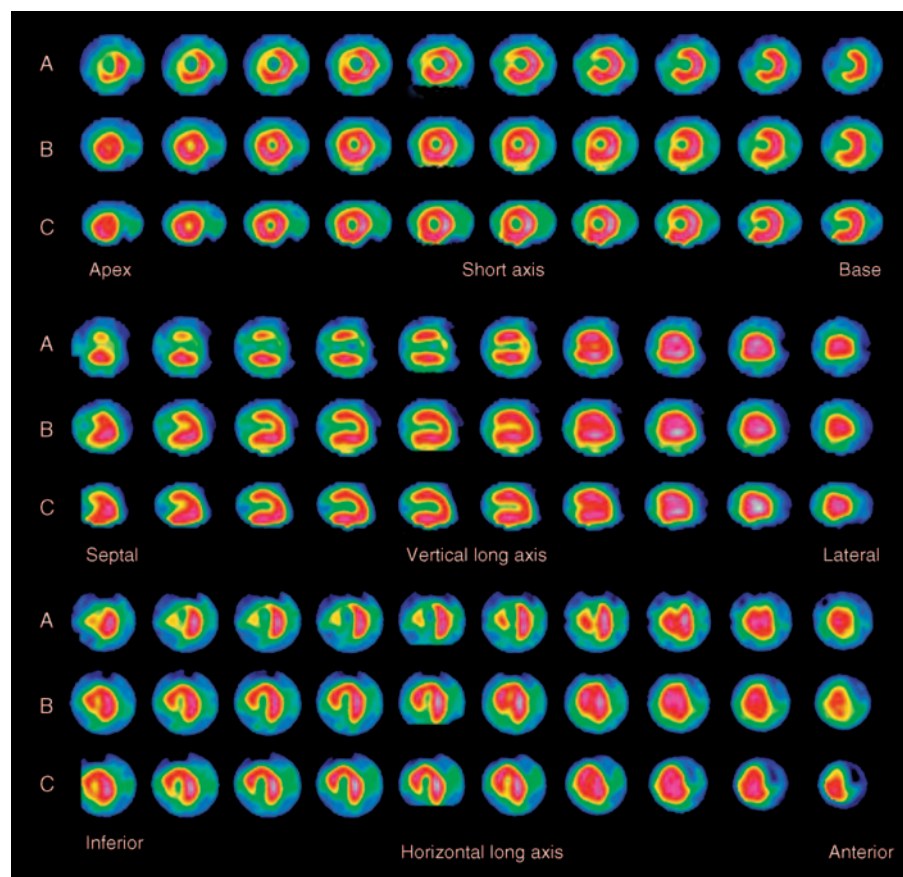


Figure 1. Stress- (lines A) and rest- (lines B) gated myocardial perfusion single-photon emission computed tomography (MP-SPECT) performed during a screening test for silent myocardial ischemia in a 45-year-old woman with type 2 diabetes with two cardiovascular risk factors. The scintigraphic data were consistent with reversible septal and apical ischemia. Six months after percutaneous coronary intervention, stress MP-SPECT was performed again to eliminate a thrombosis of the stent (lines C). The scintigraphic data confirmed a normal stress perfusion.

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images that are similar to that produced when maximal exercise is achieved [9]. In the case of obstructive airways disease, dobutamine can be used as an alternative to vasodilator agents, so that an optimal stress–rest MP-SPECT is usually possible, even with patients who cannot perform maximal exercise.

Accuracy of MP-SPECT

A meta-analysis published in 2004 [10] confirmed the high sensitivity of MP-SPECT for the detection of a critical stenosis in patients with known or suspected CAD (the range of sensitivity was 85–90%). In diabetic patients, objective data are lacking; only one study has reported a similar accuracy of MP-SPECT in diabetic and non diabetic patients [11]. However, there is growing evidence that MP-SPECT may be more sensitive than coronary angiography to detect ischemia in patients with diabetes. Given that patients with diabetes and no evidence of CAD have a risk of myocardial infarction similar to that of patients with a history of myocardial infarction [12], the finding of a reversible myocardial perfusion defect in a diabetic patient without obstructive CAD may reflect anomalies in the coronary vasodilator function induced by diabetes [13]. The development of positron emission tomography (PET) myocardial imaging has provided insight into the specificities of endothelial function in patients with diabetes. Using [¹³N]ammonia to measure the coronary blood flow, it was shown that non insulin-dependent diabetic patients without evidence of epicardial CAD had an impaired increase in coronary blood flow after infusion of dipyridamole. This dysfunction was reversed by infusion of an angiotensin-converting enzyme inhibitor [14]. Another PET tracer, [¹¹C]meta-hydroxyephedrine, was used to associate a sympathetic dysfunction in patients with type 1 diabetes with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation [15,16]. This latter finding is consistent with those reported in the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects study, in which the strongest predictor of an abnormal MP-SPECT scan was the Valsalva heart rate ratio, a marker of autonomic dysfunction [17]. These results need to be confirmed by larger clinical trials, but they are consistent with the interest in the use of MP-SPECT in the assessment of cardiovascular risk in diabetic patients with normal coronary angiography.

Which diabetic patients should be screened for silent myocardial ischemia?

Diabetic patients have a high incidence of occult CAD, ranging from 20% to nearly 60%, depending

on the patient populations included in the various studies [5,18]. Moreover, a meta-analysis involving patients with normal MP-SPECT [19] demonstrated that the median annual rate of cardiac death or non fatal myocardial infarction is much smaller in non diabetic patients (0.6%) than in diabetic populations, in whom published rates have ranged from 1.6 to 3.3% [2,3]. This highly variable prevalence, together with the fact that a normal MP-SPECT is associated with a greater cardiovascular risk in diabetic patients, points to the need for additional clinical or imaging data to select the patients who will actually benefit from a screening procedure for occult CAD.

The European and American guidelines recommend screening asymptomatic diabetic patients with evidence of peripheral or carotid occlusive arterial disease, microvascular disease (proliferative retinopathy, nephropathy), or at least two cardiovascular risk factors (diabetic dyslipidemia, hypertension, smoking, family history of premature CAD) [20–22]. Although the emerging evidence supports the appropriateness of testing patients with vascular disease [18], recent studies have reported a similar frequency of abnormal MP-SPECT studies in asymptomatic diabetic patients with and without two or more cardiovascular risk factors [17,23]. These results indicate the need for a more refined estimation of cardiovascular risk factors, especially in countries where the prevalence of CAD is relatively low [24]. This may necessitate further clinical studies to assess the individual cardiovascular risk factor of an asymptomatic diabetic patient as a continuous variable, accounting for both the presence and severity of cardiovascular risk factors, which probably should include age and sex, in addition to markers of atherosclerosis [25] and autonomic dysfunction [17].

Summary

The risk of cardiac death, myocardial infarction, or revascularization is more than 7-fold greater in diabetic patients with myocardial perfusion defects than in diabetic patients with normal scintigraphic data. Although complementary studies are needed to test whether the treatment of silent ischemia will influence outcome, MP-SPECT has become an essential diagnostic tool in the management of patients with diabetes. However, the prevalence of occult CAD depends largely on the severity of the diabetes, and diabetic patients with a normal MP-SPECT still present a greater cardiovascular risk than non diabetic patients. This indicates the need for a more refined selection of those patients with diabetes who are likely to benefit from scintigraphic screening for occult CAD. There is consistent evidence that diabetic patients with peripheral or carotid occlusive

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arterial disease or microvascular disease must be screened. Further clinical studies are needed to assess more accurately the individual cardiovascular risk factor of an asymptomatic diabetic patient as a continuous variable accounting for both the presence and severity of risk factors, including age and sex, in addition to markers of autonomic dysfunction and atherosclerosis. ■

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Role of ATP-binding cassette transporters in drug distribution to the heart and protection from toxic compounds

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Abstract

ATP-binding cassette (ABC) transporters consist of a family of proteins that translocate substrates against a concentration gradient from the intracellular toward the extracellular milieu. Among the members of the ABC transporter superfamily, P-glycoprotein has been studied most extensively and has been found to be expressed in tissues such as liver, kidneys, and intestines. This suggests a physiological function for this transporter in the protection and detoxification of the organism. P-glycoprotein and other ABC transporters were also found to be expressed in the myocardium. Current literature suggests that ABC transporters have a role in controlling distribution of xenobiotics to the heart, thus protecting this organ.

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Keywords: ABC transporters, cardiac drug distribution, cardiotoxicity, drug efflux, heart protection

Introduction

Accumulation of xenobiotics* into tissues depends not only on their ability to enter cells, but also on their ability to leave them. The ATP-binding cassette (ABC) proteins represent a large family of transmembrane transporters of around 50 ABC members that translocate substrates against a concentration gradient from the intracellular toward the extracellular regions after hydrolysis of ATP. The member of the ABC transporter superfamily that has been studied most extensively is P-glycoprotein. It was first found to be overexpressed in tumor cells, in which it conferred resistance to

several anticancer drugs [1]. Although it was at first believed to be confined to tumor cells, it was subsequently recognized to be expressed in normal tissues such as at the apical surface of liver hepatocytes, in proximal tubular cells of kidneys, and in enterocytes of the intestines. This suggested a physiological function for P-glycoprotein in the detoxification of the organism by excreting its substrates into bile, urine, and the intestinal contents [2–4]. Given the importance of these tissues in the absorption, metabolism, and excretion of drugs, the idea was rapidly conceived that P-glycoprotein had an important influence on drug disposition. ABC

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transporters were also found to be expressed in other tissues such as the heart, suggesting a role in detoxification and protection of the heart from the accumulation of xenobiotics [5]. The aim of this paper is to shed light on the involvement of ABC transporters in the distribution of xenobiotics to the heart, and to discuss their role in the protection of this organ from toxic compounds.

Expression of ABC transporters in the heart

The superfamily of ABC transporters is divided into seven different subfamilies [6], presented in *Table 1*. Encoded proteins are classified on the basis of the sequence and organization of their nucleotide-binding domain(s) and similarity in gene structure. To date, eight of those recognized to have a role in the transport of xenobiotics in tissues have been found to be expressed in the heart (they are highlighted in *Table 1*). These proteins are ABCB1 (P-glycoprotein or MDR1), ABCC1 (MRP1), ABCC3 (MRP3), ABCC4 (MRP4), ABCC5 (MRP5), ABCC10 (MRP7), ABCG2 (BCRP), and ABCA8. Molecular biology techniques used in human and rodents revealed these transporters to be expressed in either myocytes or vascular endothelial cells of the heart in these species [5]. Because P-glycoprotein was expressed in endothelial cells of human cardiac vasculature, it was proposed that P-glycoprotein serves as a functional barrier between blood and cardiac myocytes in a manner similar to the blood–brain barrier [7,8].

ABC transporters and evidence of their role in the protection of the heart

ABC transporter drug substrates, and cardiotoxicity associated with deficiency in ABC transporter genes

Mice genetically deficient in genes coding for ABC transporters such as P-glycoprotein or *mrp1* have been useful models to demonstrate the role of transporters in preventing the accumulation of xenobiotics in the heart. Indeed, in mice genetically deficient in genes coding for P-glycoprotein, significantly greater concentrations of drugs such as vinblastine, loperamide, and enaminone anticonvulsants were observed in the heart compared with those observed in wild-type mice [9–11]. In addition, greater concentrations of drugs such as etoposide, grepafloxacin, and vincristine were observed in the heart of mice genetically deficient for the gene coding for *mrp1* [12–14] in comparison with wild-type mice. These findings suggest that these ABC transporters contribute to the protection of the heart from xenobiotics.

A team of investigators generated transgenic mice that overexpressed *MDR1*, the human gene coding for P-glycoprotein, specifically in the cardiac muscle. The administration of single or repeated intravenous doses of doxorubicin led to degenerative changes in the heart of control mice that were absent in transgenic animals [15]. These findings confirmed the role of P-glycoprotein in detoxification processes in the heart.

Table 1. Classification of human ATP-binding cassette (ABC) transporters into subfamilies. (Adapted from [5].)

ABC1 (Subfamily A)	MDR/TAP (Subfamily B)	MRP/CFTR (Subfamily C)	ALD (Subfamily D)	OABP (Subfamily E)	GCN20 (Subfamily F)	White (Subfamily G)
ABCA1	ABCB1 (MDR1 or P-GP)	ABCC1 (MRP1)	ABCD1 (ALDP)	ABCE1 (OABP)	ABCF1	ABCG1
ABCA2	ABCB2 (TAP1)	ABCC2 (MRP2 or cMOAT)	ABCD2 (ALDR)		ABCF2	ABCG2 (BCRP)
ABCA3	ABCB3 (TAP2)	ABCC3 (MRP3)	ABCD3		ABCF3	ABCG4
ABCA4	ABCB4 (MDR3)	ABCC4 (MRP4)	ABCD4			ABCG5
ABCA5	ABCB5	ABCC5 (MRP5)				ABCG8
ABCA6	ABCB6	ABCC6 (MRP6)				
ABCA7	ABCB7	ABCC7 (CFTR)				
ABCA8	ABCB8	ABCC8 (SUR1)				
ABCA9	ABCB9	ABCC9 (SUR2)				
ABCA10	ABCB10	ABCC10 (MRP7)				
ABCA12	ABCB11 (BSEP or SPGP)	ABCC11 (MRP8)				
ABCA13		ABCC12 (MRP9)				
		ABCC13				

Shaded cells represent ABC transporters expressed in the heart and having recognized activities in the transport of drugs.

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Table II. Examples of commonly used drugs that are substrates of ATP-binding cassette (ABC) transporters and may be related to cardiotoxicity related to drug–drug interactions.

Transporter	Cardiac drugs			Antibiotic drugs		
	Sodium channel blockers	Calcium channel blockers	Cardiac glycosides	Fluoroquinolones	Macrolides	Clarithromycin
ABC B1 (MDR1 or P-gp) ABC C1 (MRP1) ABC A8	Quinidine	Verapamil	Digoxin	Grepafloxacin	Erythromycin	[29]
	[20,21]	[22,23]	[24,25] [30]	[26,27] [26]	[21,28]	
ABC B1 (MDR1 or P-gp) ABC C1 (MRP1) ABC C3 (MRP3) ABC C5 (MRP5) ABC C10 (MRP7) ABC G2 (BCRP) ABC A8	Anthracyclines			Vinca alkaloids		
	Doxorubicin			Etoposide (VP-16)		
	[31]	[1,32]	[1,32]	[32]		[33]
	[34]	[34,35]	[34]	[34,35]		[34]
	[36]	[36]	[35]	[36]		[35]
	[38]	[37]	[37]	[37]		[36]
[40]	[39]	[39]	[38]		[39]	
[40]	[40]	[40]	[39]		[40,41]	
[30]	[30]	[30]	[40,41]		[40,41]	
HIV drugs	Immunosuppressive drugs					
Protease inhibitor						
ABC B1 (MDR1 or P-gp) ABC C1 (MRP1)	Indinavir	Nelfinavir	Ritonavir	Saquinavir	Cyclosporin A	Tacrolimus (FK506)
	[42]	[42,43]	[43]	[42,43]	[10,44]	[44]
[45]	[45]	[43]	[43]			
ABC C3 (MRP3) ABC C4 (MRP4)	[45]	[45]	[45]	[45]		
ABC C5 (MRP5) ABC G2 (BCRP)	[45]	[45]	[45]	[45]		
[41,45]	[41]	[45]	[45]	[45]		

Clear cells represent evidence that the drug is a substrate (or inhibitor) of the ABC transporter.
Shaded cells represent evidence that the drug is not a substrate (or inhibitor) of the ABC transporter.

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In humans treated with anthracyclines for non-Hodgkin lymphoma, the propensity for anthracycline-induced cardiotoxicity was increased in patients carrying single nucleotide polymorphisms in MRP1 and MRP2. The acute anthracycline-induced cardiotoxicity was associated with the Gly671Val variant of MRP1 and with the Val1188Glu-Cys1515Tyr haplotype* of MRP2. The association of polymorphisms in the gene coding for MRP1 and MRP2 and the observed anthracycline-induced cardiotoxicity provide further proof of the importance of ABC transporters in the protection of the heart [16].

Cardiotoxicity and interactions of ABC transporter drug substrates

Many cases of cardiotoxicity have been linked to an increase in drug concentrations in the heart after co-administration of antineoplastic drugs and multidrug-resistance-reversing agents (drugs identified as P-glycoprotein inhibitors and having the capability of restoring the drug sensitivity of antineoplastic-resistant tumor cells). For instance, it was found that the co-administration of doxorubicin and the multidrug-resistance-reversing drug, verapamil, increased the peak concentration of doxorubicin in the heart of mice by 40%. The co-administration augmented the incidence and severity of degenerative changes in cardiac tissue, and decreased the survival rate compared with doxorubicin alone [17]. Other studies in rodents demonstrated that two other multidrug-resistance-reversing agents, cyclosporine A or its analog, PSC 833, could also increase doxorubicin concentrations [18,19]. This latter finding correlated with a greater incidence and severity of myocardial damage [19]. The mechanism involved is probably related to an accumulation of drugs in the heart as a result of inhibition of the normal protective function of P-glycoprotein, or other ABC transporters, by multidrug-resistance-reversing agents. These findings suggest that caution is advisable when prescribing a combination of ABC transporter substrates to patients. *Table II* lists some drugs commonly used for the treatment of cardiac diseases, cancer, infections, and human immunodeficiency virus, and immunosuppressive drugs that are substrates of ABC transporters and may be associated with cardiotoxicities related to drug-drug interactions [20–45].

ABC transporters and cellular mechanisms of cardiotoxicity such as drug-induced long QT syndrome

ABC transporter activities control intracellular access of drugs to their binding sites and can modulate the efficacy or toxicity of the drugs. Drug-induced

prolongation of cardiac repolarization (drug-induced long QT syndrome) is currently a major concern for patient safety and the pharmaceutical industry. The block of a specific cardiac potassium current, the rapid component of the delayed rectifier channel (I_{Kr})*, encoded by the human ether-a-go-go-related gene* (*HERG*), is the underlying mechanism of prolonged repolarization observed in patients undergoing treatment with most QT-prolonging drugs. Excessive prolongation of cardiac repolarization (QT interval) increases the risk of early after-depolarization, which, in the context of increased dispersed repolarization, could trigger a polymorphic ventricular tachycardia termed *torsades de pointes*. The I_{Kr} -binding site for currently used drugs is believed to be on the intracellular site of the channel embedded in the plasma membrane [46,47]. Consequently, factors such as ABC transporters that regulate intracellular concentrations of I_{Kr} -binding drugs could modulate the risk of the drug-induced long QT syndrome. Recently, the risk of QT prolongation after concomitant administration of two P-glycoprotein substrates, domperidone and ketoconazole, has been recognized [48]: cardiac QT interval prolongation was observed when domperidone and ketoconazole were administered concomitantly, but not when domperidone was administered alone.

Conclusion

It is now widely accepted that transporters, along with CYP450 enzymes, contribute significantly to the bioavailability and drug disposition of xenobiotics. Cases of increased concentrations of drugs in the heart, cardiotoxicity occurring after the administration of concomitant ABC transporter substrates, and the use of knockout mice demonstrate the important role of these proteins in the efflux of drugs from the heart. We are still at an early stage in the discovery of ABC transporters in the myocardium and their involvement in the cardiac disposition of drugs. Nevertheless, there is increasing evidence that already indicates a major role of these transporters in the protection of the heart from toxic compounds. ■

* See glossary for definition of these terms.

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New therapeutic approaches

ABC transporters and drug distribution to the heart

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The importance of a metabolic approach to anti-ischemic protection

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Abstract

Trimetazidine acting as a metabolic agent reduces symptomatic and silent ischemia – the total ischemic burden. Its cellular action in improving myocardial metabolism is cardioprotective and may explain the improvement in left ventricular function seen in the failing heart as a result of its use. The metabolic approach to myocardial ischemia is becoming increasingly important, with symptomatic and potentially prognostic benefits.

■ *Heart Metab.* 2007;35:22–24.

Keywords: Ischemia, ischemic burden, metabolic agents, trimetazidine

Introduction

The management of the patient with ischemic heart disease can be viewed in terms of providing symptomatic benefit or improving prognosis – preferably, both [1]. This philosophy extends to all groups of patients, but the emphasis may change on an individual basis – we treat people as individuals and not as statistics. For example, for the same symptom limitation, an elderly person may be more focused on quality of life and accept some restriction in preference to an invasive strategy with its initial risks, whereas a younger individual with lower initial risks may elect to undergo intervention if the evidence base for a prognostic benefit is good enough. Although we consider the patient as an individual, we also need to recognize each patient's circumstances within their family, and the importance of involving relatives and friends in the management decisions. This is particularly important with respect to the elderly, who may live alone and, to some extent, be dependent on others to maintain their quality of life.

Targeting ischemia

Under normal aerobic conditions, free fatty acids (FFA) account for 60–90% of the energy generated in the adult heart, whereas carbohydrates contribute 10–40%. During ischemia, there is a shift towards glucose metabolism, which is advantageous because, to generate the same amount of ATP, fatty acids require 10–15% more oxygen than is required by glucose.

As ischemia increases, the myocardium increases its utilization of glucose, even though FFA oxidation remains the major energy substrate. In addition to requiring more oxygen to generate energy, an increase in the rate of FFA oxidation leads to suppression of glucose oxidation as a result of inhibition of pyruvate dehydrogenase. This leads to the accumulation of lactate and protons in the ischemic cells, acidosis, and a reduction in contractile function, in addition to decreasing the threshold to ventricular arrhythmias [2]. Reversing this process would be expected to benefit the ischemic heart clinically,

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Metabolic approach to anti-ischemic protection

and perhaps prognostically. Suppressing FFA oxidation leads to an increase in myocardial glucose utilization, and, because pyruvate dehydrogenase is not suppressed to the same degree, there is a decrease in lactate production.

Achieving the objective of decreasing oxygen demand can be indirect, using hemodynamic agents, or direct, using the metabolic agent, trimetazidine [3].

Hemodynamic approach

The traditional hemodynamic approach to reducing oxygen demand by the use of β -blockers, calcium antagonists, and nitrates is a well established anti-ischemic strategy. The principal mechanism of achieving a reduction in oxygen demand is by decreasing blood pressure, contractility, and heart rate, with a debatable effect on improving oxygen supply secondary to coronary vasodilatation. Unfortunately, when titrated to effect, these agents reach a plateau of hemodynamic suppression, so that adding further dose increments or agents with a similar mechanism of action confers no benefit symptomatically, whereas adverse effects increase, especially in the elderly [4]. There is no evidence base for the use of several hemodynamic drugs with similar actions, yet it is widely practiced. Many patients are therefore receiving excessive medication and suffer side effects that limit their quality of life. Hemodynamic agents are undoubtedly beneficial; however,

an alternative but complementary metabolic mechanism for reducing ischemia has been extensively investigated [5].

Metabolic therapy

In contrast to the hemodynamic approach, metabolic agents do not reduce oxygen demand or increase blood supply [5]. Trimetazidine is the most widely studied agent, and there is a strong evidence base for its effectiveness as an anti-anginal treatment, whether used as monotherapy or in combination with hemodynamic agents [4–6]. Trimetazidine inhibits 3-ketoacyl coenzyme A thiolase, which leads to a reduction in fatty acid oxidation and stimulation of glucose oxidation (Figure 1). By modifying the energy substrates, trimetazidine reduces ischemia and brings about an improvement in symptoms. Importantly, a significant literature now exists supporting a direct anti-ischemic effect of trimetazidine on myocardial cells that is recognized to be a cardioprotective action [6].

Recently, improvement in symptoms, left ventricular function and, possibly, prognosis have been identified in patients with heart failure who were treated with trimetazidine, taking the concept of cardioprotection into a clinical arena traditionally associated with a reduced quality of life and poor prognosis even when all conventional evidence-based approaches to treatments are utilized [7].

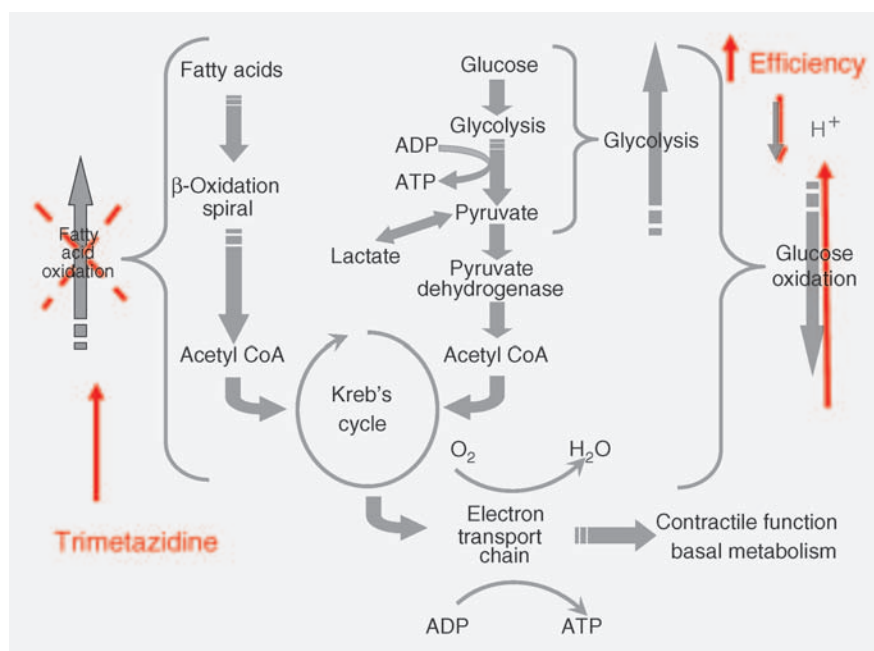


Figure 1. Glucose and fatty acid metabolism in the heart. Trimetazidine inhibits 3-ketoacyl coenzyme A thiolase, which leads to a reduction in fatty acid oxidation and stimulation of glucose oxidation. By shifting metabolism from fatty acid oxidation to glucose oxidation, trimetazidine improves cardiac efficiency. CoA, coenzyme A.

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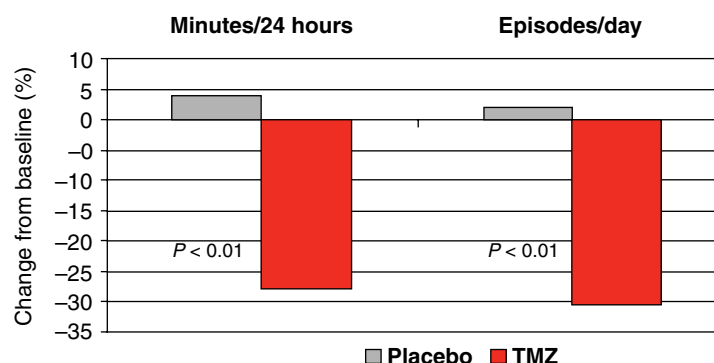


Figure 2. Comparison of the effect of placebo or trimetazidine added to standard anti-anginal therapy on episodes of silent myocardial ischemia and total ischemic burden. TMZ, trimetazidine. (From Marazzi et al [9], with permission.).

Patients with diabetes are well known to be at increased cardiovascular risk. A diabetic individual with no evidence of cardiovascular disease has a vascular risk similar to that of a non diabetic individual with coronary disease, and a diabetic person with coronary disease has a cardiac death rate twice that of a person who is not diabetic. The use of metabolic agents in diabetic patients represents a logical approach to their treatment, given the mechanism of action of these agents, because patients with diabetes exhibit reduced glucose uptake and utilization, and an increased uptake and utilization of FFAs [8] – in short, patients with diabetes are metabolically vulnerable to ischemia. The use of trimetazidine in diabetes has been shown to reduce the incidence of symptomatic and silent ischemia – the total ischemic burden (Figure 2) [9]. These benefits, combined with the evidence that trimetazidine can improve the failing heart in addition to decreasing the symptoms of angina, places metabolic therapy at the centre of the management of ischemia, not the periphery. The metabolic approach to anti-ischemic protection is gathering both momentum and importance. ■

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Trimetazidine and left ventricular dysfunction: patients must play their part also

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Abstract

A case of ischemic left ventricular dysfunction worsened by excessive alcohol consumption is reported. In addition to improving symptoms of breathlessness, the addition of trimetazidine to conventional evidence-based medicine may improve this patient's prognosis, secondary to its cardioprotective actions. Lifestyle advice complements any medical therapeutic strategy and should be routinely incorporated into the management of a patient.

■ *Heart Metab.* 2007;35:25–26.

Keywords: Alcohol excess, pre-diabetes, left ventricular dysfunction, lifestyle, trimetazidine

Case report

A 60-year-old man with pre-diabetes (glucose 6.4 mmol/L) had been a regular attendee at the cardiac clinic. In the past he had undergone coronary artery bypass surgery after a large inferior infarct (*Figure 1*). He had been treated for ventricular tachycardia with an implantable defibrillator and amiodarone and, because of his reduced ejection fraction (30%), a resynchronization pacing system. He again presented at the clinic, on this occasion complaining of breathlessness on effort; he did not experience chest pain. In addition to amiodarone he was taking bisoprolol 2.5 mg, frusemide 40 mg, perindopril 8 mg, spironolactone 25 mg daily, atorvastatin 20 mg, and aspirin 75 mg daily.

Unfortunately, the patient's lifestyle was not helping his management. He denied drinking an excess of alcohol, but accepted that he drank daily; however, his γ -glutamyl transpeptidase enzyme concentration was 1352 units (normal value <72 units), indicating a considerable ingestion of alcohol. He was overweight and smoked an average of 10 cigarettes a day.

The patient's belief that he could be cured by further cardiac surgery had not been supported by a recent coronary angiogram, which had identified a good left internal mammary artery graft to a stenosed left anterior descending artery, no significant circumflex disease, and an occluded right coronary artery subtending the inferior infarct. Discussions with the cardiac surgical team and interventional cardiologists resulted in a decision to continue medical treatment because no target lesions were available for intervention. In addition, a perfusion scan confirmed the major problem to be irreversible left ventricular dysfunction, with no areas of reversible ischemia.

The patient's treatment was reviewed and seen to be evidence-based. His blood pressure was 115/72 mmHg and examination revealed no evidence of volume overload, but bronchospasm caused by smoking was noted (it was not felt necessary to stop the β -blocker). The only therapeutic option other than radically altering his lifestyle was to introduce trimetazidine 20 mg three times daily.

After 2 months of treatment, the patient showed signs of symptomatic improvement, with less breathlessness.

Case report

Graham Jackson

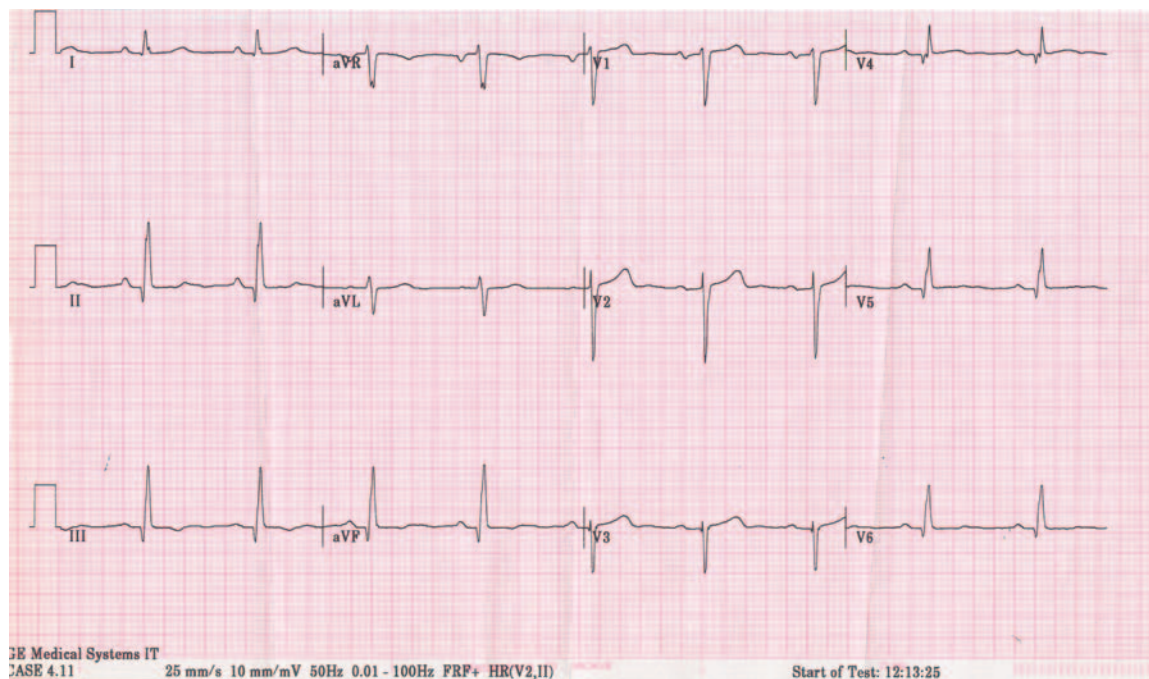


Figure 1. 12-Lead electrocardiogram demonstrating sinus rhythm and evidence of old inferior infarction.

An echocardiogram gave unchanged findings with regard to ejection fraction, but there may be improvement over time. He had not modified his lifestyle, in spite of a concerted effort from his family doctor and the suggestion that he might join a cardiac rehabilitation program, which he declined to do.

Comment

Some patients are their own worst enemies. This man's left ventricular dysfunction was secondary to his documented coronary disease, with excess alcohol consumption further compromising his cardiac output. In spite of his lifestyle, he now remains a regular attender seeking help and is compliant with his medication. He has been offered help from several medical agencies, but continues to fail to change his ways. The difficulty in managing cases of this nature is both frustrating and time-consuming. However, all individuals merit the same medical opportunities, whether they are 'good' or 'bad' patients.

The encouraging evidence for improvement in left ventricular function with trimetazidine [1,2] was explained in detail to the patient and he agreed to

pursue this medical approach. Of relevance to him is the evidence of improvement in ejection fraction in the presence of coronary artery disease, suggesting a benefit at the cellular level. In addition to improving glucose metabolism, trimetazidine may diminish mitochondrial uncoupling, enhance the efficiency of production of ATP, and reduce apoptosis [1]. The patient reported here could benefit symptomatically and, in theory, prognostically from the addition of trimetazidine to his treatment [2,3]. It will also be interesting to see if his vulnerability to ventricular arrhythmias decreases as the adverse effects of free fatty acids on the myocardium are reduced. ■

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Preventing the cardiotoxic effects of anthracyclines: from basic concepts to clinical data

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Abstract

Anthracyclines are among the most active and broad-spectrum antineoplastic agents used in the treatment of several cancers. Unfortunately, the cardiac toxicity of this group of drugs, resulting in a cardiomyopathy with irreversible congestive heart failure and high mortality, is one of the main factors that limit their use. The molecular mechanisms explaining the cardiotoxicity of anthracyclines are complex, but it appears that the induction of an oxidative stress within myocardial tissue constitutes a common denominator. Some promising new strategies to reduce the production of reactive oxygen species and protect the function of the heart are now available for the treatment of patients in order to lessen the myocardial injury associated with anthracyclines.

■ *Heart Metab.* 2007;35:27–33.

Keywords: Anthracyclines, cardiotoxicity, congestive heart failure, reactive oxygen species, ACE inhibitors

Introduction

Anthracyclines are among the most active and broad-spectrum antineoplastic agents used in the treatment of several cancers, such as solid tumors, leukemias, and lymphomas. Unfortunately, the conventional and cardiac toxicities of anthracyclines are among the main factors that limit their use. Clinically, the cardiotoxicity results in a cardiomyopathy with irreversible congestive heart failure and a high mortality.

Basic concepts

The molecular basis of the cardiotoxicity of anthracyclines remains a matter of debate. The cardiotoxi-

city of the drug appears to be distinct from its therapeutic mechanism, and has been attributed to a large number of effects, including apoptosis (*Figure 1*), alterations in iron homeostasis, deregulation of calcium homeostasis both in the sarcoplasmic reticulum and in the mitochondria, and mitochondrial dysfunction. However, the common trigger of these events appears to be linked to an oxidative stress caused by the production of reactive oxygen species (ROS).

Generation of ROS by anthracyclines

The chemical structure of anthracyclines consists of a tetracycline moiety containing a quinone and a

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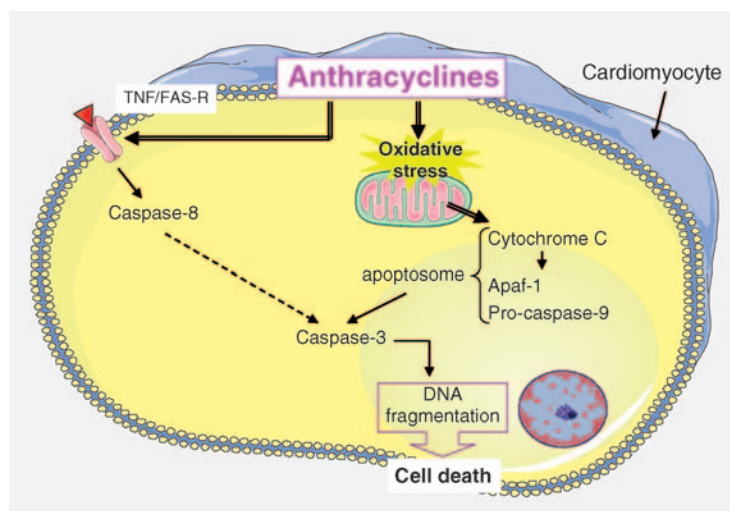


Figure 1. Apoptosis hypothesis for the cardiotoxicity of anthracyclines. Apaf-1, Apoptotic protease activating factor-1; TNF/FAS-R, tumor necrosis factor/Fas receptor.

conjugated amino sugar residue (Figure 2). In the cellular environment, anthracyclines might undergo redox activation* through their interaction with several flavoprotein oxidoreductases (Figure 3). This semiquinone can rapidly auto-oxidize using molecular oxygen (O_2) as an electron acceptor, returning to the parent compound which is then available for a new redox cycle. This reaction leads to the formation of superoxide anion ($O_2^{\bullet-}$), which, in aerobic

conditions, can be produced in substantial amounts. Driven by superoxide dismutases (SOD), or spontaneously in acidic pH, superoxide anion is converted into hydrogen peroxide (H_2O_2) which, in the presence of traces of transition metals such as iron or copper, will be converted to the very reactive oxidizing species, hydroxyl radical (HO^\bullet).

These mechanisms are compounded by the fact that anthracyclines can directly form complexes

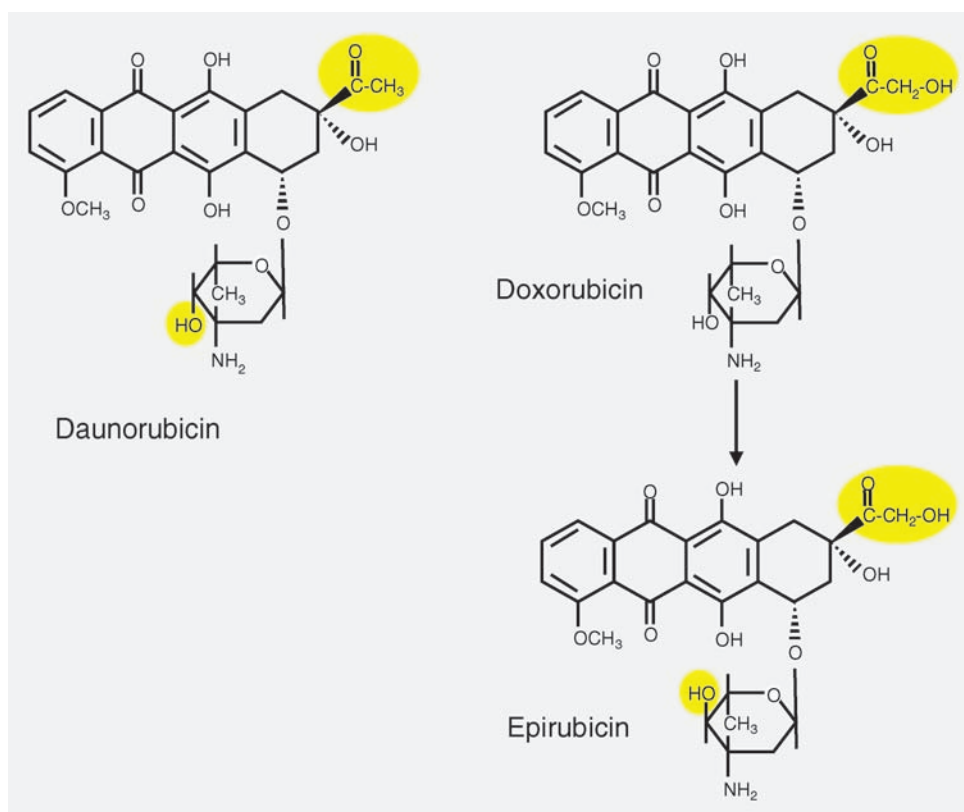


Figure 2. Molecular structures of anthracyclines.

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Cardiotoxicity of anthracyclines

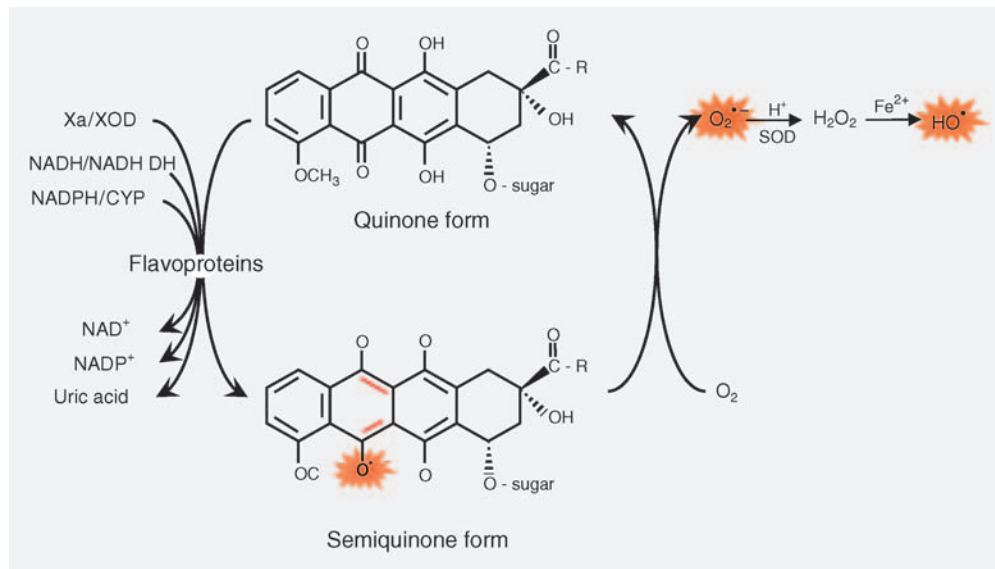


Figure 3. Formation of reactive oxygen species via the redox quinone cycle of anthracyclines. NADPH/CYP, NADPH-dependent cytochrome P450 reductase; NADH DH, NADH dehydrogenase (complex I); Xa, xanthine; XOD, xanthine oxidase; SOD, superoxide dismutase.

with ferrous iron displaced from its sites of storage within the cell. These complexes are apt to generate ROS in the presence or the absence of reducing components.

If insufficient antioxidant compounds are available [1], ROS would be expected to affect cellular com-

ponents such as proteins, lipids, and nucleic acids, leading to modifications that are more likely to have an effect on the nucleus, the sarcoplasmic reticulum, or the mitochondria [2] – cellular organelles that are in close proximity to the site of generation of ROS (Figure 4).

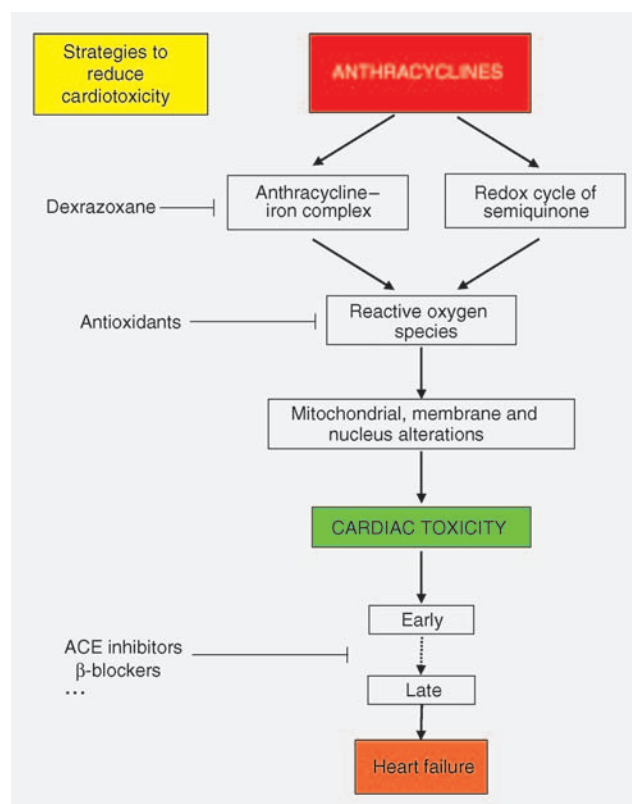


Figure 4. General scheme explaining the cardiac toxicity of anthracyclines that is driven by reactive oxygen species, and strategies to reduce the cardiotoxicity. ACE, angiotensin-converting enzyme.

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Protection against the cardiotoxicity of anthracyclines in experimental models

Despite some conflicting evidence, possibly attributable to variability in the delivery of antioxidants to the site of generation of ROS, support for ROS-driven oxidative damage to cardiac cells comes from studies using antioxidant treatment that has conferred protection from cardiotoxicity. For instance, vitamin E [3,4], lycopene [5], sulfur-containing antioxidants (glutathione [6,7], mercaptopropionyl glycine [8], *N*-acetyl cysteine [4]), and also antioxidant enzymes such as SOD [9,10] or catalase [9] have been shown to protect against the cardiotoxicity of anthracyclines in several experimental models (Table I). Moreover, evidence for this theory concerning ROS as the primary initiator of anthracycline cardiotoxicity has been obtained in several studies on transgenic animals overexpressing antioxidant enzymes [11–14], which are largely protected from myocardial damage during treatment with anthracycline (Table II).

As the interaction of anthracyclines with iron is considered to be of importance in exerting their deleterious effects on the heart, some transition metal chelators have been tested, with success [15]. For instance, dexrazoxane (ICRF-187), a prodrug from an ethylenediamine tetra-acetic acid analog that acts via displacing irons from anthracycline–iron complexes and removing free irons from the vicinity of biomolecules, has been proposed for clinical use as a cardioprotector and found to be successful [16].

Several other strategies have also been developed [17] in order to reduce the cardiotoxic effects associated with anthracyclines.

Clinical data

Clinical features of anthracycline cardiotoxicity

The damage to the heart that occurs after anthracycline therapy can be categorized as:

- Early cardiotoxicity: happening during anthracycline treatment or in the first year after its completion, which manifests as non specific ST-segment and T-wave abnormalities.
- Late cardiotoxicity: happening at least 1 year after the completion of anthracycline treatment, which is cumulative, dose-related and can result in congestive heart failure and left ventricular dysfunction.

It has been reported that more than 50% of patients exposed to anthracyclines show cardiac abnormalities 10–20 years after the initial oncological diagnosis: arrhythmias were found to occur in 40% of patients, whereas 5% developed congestive heart failure [18].

There is a wide variation in the frequency of both clinical and subclinical cardiotoxicity after anthracycline therapy. In children, studies have shown that the prevalence of subclinical cardiac damage was more than 57% at a median of 6.4 years after treatment, and that the incidence of clinical heart failure was 16% 0.9–4.8 years after the treatment. In adults, the prevalence of subclinical cardiac damage has been reported to be 36% during anthracycline therapy, and the incidence of clinical heart failure 30% at a median of 37 months after the treatment [19].

The cardiac side effects of anthracyclines also depend on the schedule of its administration: continuous infusion over 24–92 h rather than rapid intravenous injection could reduce the cardiotoxicity of these agents [18].

Early detection and treatment of cardiotoxicity can significantly reduce the development of clinical manifestations. While the evolution of diastolic function assessed with echocardiography is an early sign of anthracycline-induced cardiac dysfunction, several studies have confirmed the usefulness of measuring B-type natriuretic peptide, which is increased before the development of left ventricular dysfunction, in the diagnosis of congestive heart failure.

Strategies to reduce the cardiotoxicity of anthracyclines

Figure 4 summarized the factors involved in the toxicity of anthracyclines and some strategies that are available to reduce the toxicity. We [20] and others [21] have reported on these aspects in greater depth elsewhere.

From a clinical point of view, the prevention of anthracycline cardiotoxicity relies on three approaches: rigorous cardiac monitoring, the use of anthracycline analogs with lower cardiotoxicity, and modifications of the program of administration. The use of cardioprotective agents during chemotherapy would be of great interest in achieving optimal use of anthracyclines, but the major concern is whether a cardioprotective agent could provide a selective decrease in the incidence and intensity of heart damage without reducing the antitumor efficacy of the chemotherapy and without negative side effects.

Anthracycline toxicity can be minimized by:

- Changing the process of administration to one of continuous infusion.
- Reducing the total cumulative dose to <400 mg/m².
- Using liposome-encapsulated anthracyclines.
- Reducing the amount of free iron by the use of dexrazoxane (however, this compound is not recommended at the beginning of treatment, because of the possibility that it could diminish the effect of anticancer agents [16,22]).

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Cardiotoxicity of anthracyclines

Table 1. Experimental studies showing the use of antioxidants in the prevention of the cardiotoxic effects of doxorubicin (Dox) or epirubicin (Epi).

Antioxidant	Model	Dose	Results	Ref.
Vitamin E	Rat	High doses	Abolition of ST-segment elevation induced by the administration of a single dose of Dox, reduction of cardiac enzymes (CPK-MB, LDH).	[3]
Vitamin E, N-acetyl cysteine	Rat	100 mg/kg per day for 10 days	Protection towards lipid tissue cardiac and hepatic peroxidation induced by the administration of a single dose of Dox (20 mg/kg; i.p.). Protection of action potentials and cardiac electric activity.	[4]
N-(2-mercapto-propionyl) glycine	Rat	2.5 mg/kg per os	Reduction of lipid tissue cardiac peroxidation (TBARS) and of cardiac enzymes release (CPK-MB, LDH), induced by the administration of a single dose of Dox (15 mg/kg; i.p.).	[8]
Lycopene	Rat	4 mg/kg per day for 10 days	Protection towards tissue cardiac and renal oxidation induced by the administration of a single dose of Dox (10 mg/kg).	[5]
Glutathione	Rat	5 mg/kg	Reduction of cardiac and renal histological alterations. Reduction of cardiac tissue lipid peroxidation (MDA) and of cardiac enzymes release (CPK-MB, LDH), induced by the administration of a single dose of Dox (20 mg/kg).	[6]
SOD	Rat	250–500 mg/kg iv	Reduction of QT elongation and of cardiac contractility alterations, induced by the administration of repeated doses of Dox (3 mg/kg/week, 4 weeks, i.v.). Reduction of cardiac histological alterations.	[7]
Mn TBAP (SOD mimic)	Rat Adult cardio-myocytes	10 IU/ml	Prevention of Dox (10 µM) or Epi (10 µM)–induced reduction of cardio-myocytes' contractility.	[9]
	Rat Adult cardio-myocytes		Prevention of Dox (1–40 µM)–induced release of LDH and formation of antioxidants. Protection of aconitase activity.	[10]

CPK-MB, creatine phosphokinase-MB; LDH, lactate dehydrogenase; MDA, Malonedialdehyde; Mn TBAP, manganese III tetrakis (4-benzoic acid) porphyrin; SOD, superoxide dismutase; TBARS, Thiobarbituric acid reactive species.

Refresher corner

Catherine Vergely, Stéphanie Delemasure, Yves Cottin, Luc Rochette

Table II. Studies in transgenic animals that overexpress antioxidant enzymes and are protected from anthracycline-induced myocardial damage.

Enzyme over-expressed	Model	Results	Ref.
GPx1	Mice B6C3	Better resistance to the acute effects of in-vitro administration of 5 µmol/L Dox (contractility, EDLVP, heart rate). Preservation of mitochondrial function	[13]
Mn SOD	Mice B6C3 ± KO iNOS	Protection against mitochondrial damage induced by Dox (20 mg/kg)	[11]
Human Mn SOD	Mice B6C3	Protection against Dox-induced ultrastructural alterations and mitochondrial lesions Reduction in serum concentrations of creatine kinase and LDH	[14]
Catalase Cardiac promoter	Mice	Protection against cardiac damage (lipid peroxidation), increase in serum creatine phosphokinase, and isolated atrial functional alterations induced by Dox (20 mg/kg)	[12]

Dox, doxorubicin; EDLVP, end-diastolic left ventricular pressure; GPx1, Glutathion peroxidase-1; KO iNOS, knockout inducible nitric oxide synthase; LDH, lactate dehydrogenase; Mn SOD, manganese superoxide dismutase.

- Lessening the production of ROS with *N*-acetyl cysteine, coenzyme Q10, or a combination of antioxidant vitamins. Other cardioprotective agents such as L-carnitine, probucol, and deferoxamine are being investigated [23].

Finally, an appropriate treatment of early and late cardiac events is necessary, to slow down the evolution of anthracycline-induced cardiotoxicity. Early dysfunction such as arrhythmias and pericarditis is treated with antiarrhythmic agents [24] and aspirin. For late dysfunction, angiotensin-converting enzyme inhibitors [25] and β-blockers form the basis of treatment. Angiotensin-converting enzyme inhibitors have been shown to slow the progression of left ventricular dysfunction in several clinical settings and, in patients undergoing high-dose chemotherapy, early treatment with enalapril seemed to prevent the development of late cardiotoxicity and the occurrence of adverse clinical events [25].

Conclusion

The molecular mechanisms explaining the cardiac toxicity of anthracyclines are complex, but it appears that the induction of an oxidative stress within myocardial tissue constitutes a common denominator. Some promising new strategies to reduce the production of ROS and protect heart function are now available to patients and can lessen the myocardial injury that is associated with the use of anthracyclines. ■

* See glossary for definition of these terms.

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Reduction of hyperacute rejection and protection of metabolism and function in hearts of human decay accelerating factor (h-DAF)-expressing pigs

Smolenski RT, Forni M, Maccherini M, et al. *Cardiovasc Res.* 2007;73:143–152.

Heart failure is currently one of the major causes of mortality and factors affecting the quality of life in humans. Despite advances in pharmacological treatment and recent developments in mechanical circulatory support devices, cardiac transplantation remains the most effective treatment of endstage heart failure. However, the availability of human donor hearts is limited, and only a small percentage of those who would benefit from this treatment could actually receive a transplant. It is expected that the disparity between organ availability and demand will increase even further in the future. One possible solution of the donor organ shortage is the use of animal organs. To date, pigs seem to be the best source of organs for xenotransplantation because of their physiological compatibility and ethical acceptability. However, after transplantation into primates, pig hearts undergo a rapid and vigorous reaction termed hyperacute rejection, causing total dysfunction within minutes. An important challenge is therefore the development of effective and inexpensive procedures for the generation of transgenic animals. Sperm-mediated gene transfer (SMGT), developed by Lavitrano and colleagues several years ago [1], appears to be an efficient and cost-effective procedure for that purpose. Lavitrano et al successfully established a pig strain expressing human decay-accelerating factor (hDAF) [2]. They evaluated in the present paper whether hearts of hDAF transgenic pigs generated using SMGT were protected from structural damage, metabolic changes, and mechanical dysfunction during perfusion with human blood.

Commentary

Hearts from control or transgenic pigs were perfused ex vivo for 4 h with fresh human blood using an ex-vivo working model system allowing monitoring of function, metabolism, and structure.

Cardiac output remained constant in transgenic animals throughout the experiment, whereas it decreased in control pigs after 30 min of perfusion ($P < 0.01$ compared with transgenic animals). The maximum increase in coronary perfusion pressure was reduced to $154 \pm 16\%$ in transgenic animals, and to $237 \pm 10\%$ in control pigs ($P < 0.001$). After 4 h, myocardial ATP was 21.1 ± 1.1 nmol/mg dry weight (similar to the baseline value) in transgenic pigs, whereas it decreased to 17.2 ± 1.4 nmol/mg dry weight in control animals ($P < 0.05$).

Deposition of complement factors C3 and C5b9 was present in control but not transgenic animals after perfusion. Attenuation of hyperacute rejection was further confirmed by microscopic analysis of cardiac specimens: there was no structural damage in transgenic hearts.

There are several limitations to the system used in this study. First, it allows for only several hours of perfusion, essentially limiting its application to the study of hyperacute rejection. Secondly, not all mechanisms of rejection could be reproduced; for example, platelet-mediated rejection that was blunted by high-dose heparin. The ex-vivo system also neglects the effect of other organs on blood homeostasis. However, this study has shown that hearts from transgenic pigs produced by SMGT were protected from hyperacute rejection after exposure to human blood, and that those hearts, in a human blood environment, were relatively metabolically stable and maintained mechanical function above the threshold for life support. Further application of this method for the generation of multigene transgenic pigs, and in

particular its combination with knockout techniques, could be a significant step towards clinical xenotransplantation.

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Danielle Feuvray

Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure

Tuunanen H, Engblom E, Naum A, et al. *Circulation*. 2006;114:2130–2137

Metabolic modulators that enhance myocardial glucose metabolism by inhibiting free fatty acid (FFA) metabolism may improve cardiac function in patients with heart failure. The effect of acute FFA withdrawal on cardiac function was studied in 18 fasting non-diabetic patients with heart failure caused by idiopathic dilated cardiomyopathy (IDCM) (14 men, four women, ages 58.8 ± 8.0 years, ejection fraction $33 \pm 8.8\%$) and eight matched healthy controls. They underwent examination of myocardial perfusion and oxidative and FFA metabolism before and after acute reduction of serum FFA concentrations by acipimox, an inhibitor of lipolysis. Metabolism was monitored by positron emission tomography (PET) and [^{15}O]H $_2\text{O}$, [^{11}C]acetate, and [^{11}C]palmitate. Left ventricular function and myocardial work were measured by echocardiography and the efficiency of forward work was calculated. Acipimox decreased myocardial FFA uptake by $>80\%$ in both groups. The rate–pressure product and myocardial perfusion remained unchanged, but stroke volume decreased similarly in both groups. In the healthy controls, reduced cardiac work was accompanied by a decrease in oxidative metabolism (from 0.071 ± 0.019 l/min to 0.055 ± 0.016 l/min; $P < 0.01$). In patients with IDCM, cardiac work decreased, whereas oxidative metabolism remained unchanged and efficiency decreased (from 35.4 ± 12.6 mm Hg/ μL per μg to 31.6 ± 13.3 mm Hg/ μL per μg ; $P < 0.05$). It was concluded that acutely decreased serum FFA depresses cardiac work. In healthy hearts, this was accompanied

by a parallel decrease in oxidative metabolism, and myocardial efficiency was preserved. In failing hearts, FFA depletion did not downregulate oxidative metabolism, and myocardial efficiency deteriorated. Thus failing hearts are, unexpectedly, more dependent than healthy hearts on the availability of FFA. It is proposed that both glucose and fatty acid oxidation are required for optimal function of the failing heart.

Commentary

In this interesting study, both patients with IDCM and healthy volunteers underwent [^{11}C]acetate PET imaging for measurement of oxidative metabolism, [^{11}C]palmitate PET imaging for measurement of the free fatty acid uptake and the rate of β -oxidation, [^{15}O]H $_2\text{O}$ PET imaging for myocardial perfusion, and echocardiography to determine left ventricular stroke volume and left ventricular mass. The same measurements were repeated after administration of acipimox, a drug that decreases free fatty acid concentrations in blood.

The most significant part of the study concerned the measurement of cardiac efficiency in patients and volunteers. This parameter is determined by combining the echocardiographic data with the [^{11}C]acetate data:

$$\text{efficiency} = (\text{LV work power}/\text{LV mass})/\text{LV } K_{\text{mono}}$$

where LV (left ventricular) work power is ‘systolic blood pressure \times stroke volume \times heart rate’ and K_{mono} is a value derived from [^{11}C]acetate in which the decline in tracer activity of the heart is fitted with a monoexponential curve. (For an overview of cardiac efficiency, see [1].)

As expected, acipimox decreased fatty acid concentrations in both patients and volunteers. Also expected was that left ventricular work power was decreased in patients with IDCM compared with that in healthy volunteers, both before and after the administration of acipimox. In both groups, administration of acipimox led to a small but non significant reduction of left ventricular work power. Oxidative metabolism (K_{mono} value) was similar between patients and healthy volunteers at baseline but, after the administration of acipimox, K_{mono} values decreased significantly in the healthy volunteers alone. By combining these work power data and K_{mono} values in the calculation of efficiency, the authors showed that decreasing the concentration of fatty acids by the use of acipimox resulted in a small but significant decrease (of 11%) in cardiac efficiency in patients with IDCM and an increase (of 18%) in the healthy volunteers.

These findings are quite surprising, and in contrast with what was to be expected. A wealth of experimental and clinical data have shown that a metabolic

intervention that increases glucose metabolism and inhibits fatty acid metabolism in heart failure (eg, trimetazidine or glucose–insulin–potassium) improves cardiac function.

In the editorial accompanying the paper by Tuunanen and colleagues, Taegtmeyer and Ballal [2] offered some explanations for the observed phenomena. First, recent data in lipase-deficient mice have shown that fatty acids are needed for normal cardiac contraction. This is in line with the findings discussed here. Secondly, acipimox itself may have direct hemodynamic effects. This was not measured in the study, and may have altered left ventricular work power. Thirdly, acipimox itself may decrease insulin secretion. As the patients were insulin-resistant, the intervention to decrease fatty acids, combined with the insulin resistance, may have depleted the heart of the required energy nutrients.

Another point worthy of consideration is that, in this study by Tuunanen et al, K_{mono} values before the acipimox intervention were similar between IDCM patients and volunteers. Other studies [3] have shown that K_{mono} values were lower in patients with cardiomyopathy, suggesting a patient bias in the present study. Finally, earlier experimental studies have clearly shown that the clearance of radioactivity from the heart is biexponential: the fast part of the time–activity curve is related to turnover of [^{11}C]acetate in the Krebs' cycle, and the slower part is related to clearance of the radioactivity from Krebs' cycle intermediates such as glutamate [4]. As is usual in human studies, in the present study oxidative metabolism was measured by fitting the time–activity curve solely with a monoexponential curve. It is therefore unknown to what extent the second, slow, component of the tracer influenced the values of the first. This may be different in healthy volunteers and in patients.

Despite some points of criticism, the findings of Tuunanen and colleagues show that the relationship between cardiac function and metabolism is complex, and that there remain many details that need to be studied. In conclusion, I will quote a statement by Taegtmeyer and Ballal: 'When it comes to energy substrate metabolism of the heart, extremes are never good'.

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Frans Visser

Effect of ramipril on the incidence of diabetes

Bosch J, Yusuf S, Gerstein HC, et al; the DREAM Trial Investigators. *N Engl J Med*. 2006;355:1551–1562.

Previous studies have suggested that blockade of the renin–angiotensin system may prevent diabetes in people with cardiovascular disease or hypertension. In a double-blind, randomized clinical trial with a 2-by-2 factorial design, we studied 5269 participants without cardiovascular disease but with impaired fasting glucose concentrations (after an 8 h fast) or with impaired glucose tolerance. They were randomly assigned to receive ramipril (up to 15 mg per day) or placebo (and rosiglitazone or placebo) and followed for a median of 3 years. We studied the effects of ramipril on the development of diabetes or death, whichever came first (the primary outcome), and on secondary outcomes, including regression to normoglycemia. The incidence of the primary outcome did not differ significantly between the ramipril group (18.1%) and the placebo group (19.5%; hazard ratio for the ramipril group 0.91, 95% confidence interval [CI] 0.81 to 1.03; $P=0.15$). Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (hazard ratio 1.16, 95% CI 1.07 to 1.27; $P=0.001$). At the end of the study, the median fasting plasma glucose concentration was not significantly lower in the ramipril group (102.7 mg/dL [5.70 mmol/L]) than in the placebo group (103.4 mg/dL [5.74 mmol/L]; $P=0.07$), although plasma glucose concentrations 2 h after an oral glucose load were significantly lower in the ramipril group (135.1 mg/dL [7.50 mmol/L] compared with 140.5 mg/dL [7.80 mmol/L]; $P=0.01$). Among persons with impaired fasting glucose concentrations or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death, but does significantly increase regression to normoglycemia. (ClinicalTrials.gov number, NCT00095654 [ClinicalTrials.gov].)

Commentary

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin type I receptor blockers (ARBs) have been

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shown to reduce the incidence of diabetes in a number of trials. In the main, these trials were designed to examine other aspects of ACEI/ARB efficacy and the observed effect on diabetes was either an incidental finding or at best a prespecified, although self-reported, secondary endpoint. The lack of rigid determination of diabetes in all individuals before study initiation and at study end could have introduced systematic biases that resulted in the antidiabetic effect being spurious. For example, in most of these trials, ACEIs/ARBs reduced events, and those with events would have been under greater medical scrutiny than those without events. This may have increased the recognition, but not the true incidence, of diabetes. Further, in some studies it may not have been the effect of the ACEI or ARB being protective, but rather the increased likelihood of the use of diabetogenic antihypertensive drugs in the non ACEI/ARB group(s). For these, and other reasons, a prospective randomized trial was required.

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) trial investigators enrolled individuals with 'pre-diabetes', based on plasma glucose concentrations. The inclusion criteria necessitated a plasma glucose of either at least 110 mg/dL (6.1 mmol/L) but not more than 126 mg/dL (7.0 mmol/L) after an overnight fast, or at least 140 mg/dL (7.8 mmol/L) but not more than 200 mg/dL (11.1 mmol/L) 2 h after a 75 g oral glucose load. At the 2 year and final visits, the glucose tolerance tests were repeated in those who had not already developed overt diabetes. The primary outcome was newly diagnosed diabetes or death. Over the average of 3 years of follow-up, death occurred in only 1.2% of individuals and there was no difference by group. The predominant outcome driving the primary endpoint was therefore new diabetes. As can be seen from the abstract, this did not differ significantly between groups. However, a number of secondary endpoints such as reversion to normoglycemia and plasma glucose concentrations after oral glucose loading were modestly, but significantly, improved. When these are considered together with the 95% confidence interval of the primary endpoint (0.81 to 1.03), one is left with the distinct impression that ramipril probably does have an antidiabetic effect. However, the magnitude of this effect is modest and not as robust as that suggested in previous trials, such as Heart Outcomes Prevention Evaluation.

As the DREAM trial failed to reach its primary endpoint, and the results as a whole suggest the antidiabetic effect of ramipril at doses as high as 15 mg is modest, what should we do? First, the basic 'reverse translational' studies to find the molecular mechanism by which ACEI reduces diabetes are now less urgent. Secondly, there is no compelling reason to prescribe ACEI in those with pre-diabetes unless there

is an alternative accepted indication such as hypertension. Obviously, once diabetes develops, an ACEI or ARB is indicated. Unfortunately, apart from oral hypoglycemic agents, the only interventions known to reduce the progression to overt diabetes are weight loss and exercise. Once again, healthy lifestyle wins through!

M. Marber

Acute impairment of regional myocardial glucose uptake in the apical ballooning (takotsubo) syndrome

Bybee KA, Murphy J, Prasad A, et al. *J Nucl Cardiol.* 2006;13:244–250.

Apical ballooning syndrome is a poorly understood clinical entity characterized by acute, transient systolic dysfunction of the left ventricular apex in the absence of epicardial coronary artery disease, and commonly associated with acute emotional stress. We report abnormal regional myocardial perfusion and glucose uptake in four consecutive patients with apical ballooning syndrome who were studied using positron emission tomography with [¹³N]ammonia and [¹⁸F]fluorodeoxyglucose within 72 h of presentation with the syndrome. All patients were postmenopausal women, three of whom had a major recent life stress event. Coronary angiography revealed no or minimal obstructive epicardial coronary artery disease. All patients exhibited reduced glucose uptake in the mid left ventricular and apical myocardial segments, which was out of proportion to perfusion abnormalities in 50% of the cases. In all four patients, affected regions recovered regional left ventricular systolic function within 6 weeks.

Commentary

Takotsubo syndrome is a relatively new syndrome that was described for the first time in 1991 by Dote et al [1]. It is characterized by a transient systolic left ventricular dysfunction, typically localized in the distal and apical parts of the myocardium, by abnormalities on the electrocardiogram mimicking acute myocardial infarction, and by an increase in cardiac enzymes, in the absence of significant coronary artery disease. Its prognosis is relatively benign (see review [2]). The etiology is unknown but, because the onset of this syndrome is often preceded by emotional or physical stress and it is also observed in subarachnoid hemorrhage. Catecholamine-mediated multivessel

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epicardial spasm, microvascular coronary spasm, or possible direct catecholamine-mediated myocyte injury have been proposed as possible pathophysiological mechanisms.

Metabolic and perfusion studies in these patients reveal an interesting pattern. Studies have shown that perfusion is decreased in the affected regions. Kurisu et al [3] described a decrease in fatty acid uptake during the acute phase of the disease, which gradually improved over time. The observation of decreased perfusion and decreased fatty acid uptake can be explained by the presence of myocardial stunning, as has been described earlier in patients with reperfused myocardial infarction. In the present study by Bybee et al, a decrease in glucose uptake was also found. This is in contrast to the classical concept of myocardial stunning, because, in stunning, an increase in glucose uptake is observed. Thus a possibly new metabolic profile in Takotsubo cardiomyopathy may emerge: decreased perfusion in combination with decreased uptake of both fatty acid and glucose. Of course, the data are from two different studies, with different patients, and a combination of fatty acid and glucose imaging has not been done, thus the observations need further confirmation.

Bybee et al suggest two possible mechanisms for the decreased glucose uptake: direct effect of catecholamines on insulin resistance or a direct toxic effect of catecholamines on glucose metabolism. The latter may also involve fatty acid metabolism. An additional explanation may be that flow and metabolism are adapted to the decreased function of the myocardial areas involved. Why and how function is primarily depressed is unknown, but it may also be related to the toxic effects of catecholamines. As usual, further studies are needed!

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F.C. Visser

Glossary

Gary Lopaschuk

Adenine nucleotide translocator and/or the voltage dependent anion channel

The adenine nucleotide translocator (ANT) is a mitochondrial membrane protein that carries ATP from the matrix into the inter-membrane space and transports ADP back. ANT is also a component of a mitochondrial voltage dependent anion channel. The ANT/voltage dependent anion channel can contribute to apoptosis via its capacity to become a lethal pore.

Cardiolipin

Cardiolipin is a glycerol lipid containing two phospholipids, and is an important and abundant lipid component of the inner mitochondrial membrane. Cardiolipin has an important function as a stabilizer of mitochondrial protein complexes important to the electron transport chain. Mutations in the biosynthesis of cardiolipin can result in Barth syndrome, a rare genetic disorder in which mitochondria are abnormal, and affected individuals cannot sustain adequate production of ATP. Cardiomyopathy and general weakness is common to these patients.

Catalase

Catalase is a common enzyme that functions to catalyze the decomposition of hydrogen peroxide to water and oxygen. Catalase is an important anti-oxidant enzyme that protects the cell from free radical injury.

Delayed rectifier channel (I_{Kr})

The human ether-a-go-go-related gene (hERG) encodes a channel that conducts the rapidly activating delayed rectifier K(+) current (I_{Kr}) which is important for cardiac repolarization. Mutations in hERG reduce I_{Kr} and cause congenital long QT syndrome (LQTS).

Electrogenic NCX (3Na⁺/2Ca²⁺)

The Na⁺/Ca²⁺ exchanger is a membrane ion transporter that exchanges Na⁺ for Ca²⁺.

Because the exchange involves 3 Na⁺ for 2 Ca²⁺, the current exchange is not equal, and therefore the exchange is considered electrogenic.

Fab

Antibodies are immune system-related proteins that consists of four polypeptides– two heavy chains and two light chains joined to form a “Y” shaped molecule. The amino acid sequence in the tips of the “Y” give the antibody its specificity for binding antigen. Treating the antibody with a protease cleaves this region, producing Fab or fragment antigen binding.

Glutathione S-transferase (GST)

Glutathione S-transferase (GST) is a cytosolic, mitochondrial, and microsomal protein that catalyses the conjugation of reduced glutathione via the sulfhydryl group, to electrophilic centres on a wide variety of substrates. GST can detoxify peroxidised lipids, and therefore acts as an anti-oxidant.

Glutathione peroxidase

Glutathione peroxidase is a peroxidase found in cells that helps to prevent lipid peroxidation of the cell membrane. The function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water.

Gly671Val variant of MRP1 and with the Val1188Glu-Cys1515Tyr haplotype

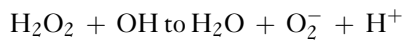
Anthracycline-induced cardiotoxicity (ACT) is a condition mainly presenting as arrhythmias or congestive heart failure. This cardiotoxicity can be associated with a mutation in multi drug resistance proteins (MRP1 or MRP2) responsible for doxorubicin transport. This can involve mutation in the MRP1 gene consisting of a Gly671Val variant and a mutation in the MRP2 gene involving a Val1188Glu-Cys1515Tyr haplotype. These genetic variants in doxorubicin transport increase an individual risk of developing ACT.

Glossary

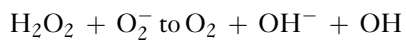
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Haber-Weiss reaction

The Haber-Weiss reaction is a chemical reaction that can produce highly toxic hydroxyl (OH⁻) radicals. The reaction consists of the following two reactions:



and



This reaction is often catalyzed by iron, creating a source of oxidative stress in tissues. The second part of this reaction is a source of very toxic hydroxyl radicals.

Human ether-a-go-go related gene

A gene was discovered in *Drosophila* called the ether-a-go-go gene, since mutations in the gene caused the legs of the ether anesthetized *Drosophila* to shake. A human related ether-ago-go gene encodes a voltage-gated potassium channel. Abnormalities in this channel may lead to either Long QT syndrome (with loss of function mutations) or Short QT syndrome (with gain of function mutations). Both long and short QT syndromes can cause potentially fatal cardiac arrhythmia, due to repolarisation disturbances of the cardiac action potential.

(Na⁺/K⁺) Mg-ATPase (NKA)

Na/K-ATPase is an ion pump that is involved in the transport of ions across membranes. This ATPase pumps Na⁺ and K⁺ against their concentration gradient, and therefore energy is required, which is provided by the hydrolysis of ATP, the main energy currency in cells (hence the name ATPase). Na/K-ATPase pumps Na⁺ out of cells, while simultaneously pumping K⁺ into cells. In the heart this helps to re-establish ionic changes that occur during the action potential, in which Na⁺ flows into the heart cell, and K⁺ flows out of the heart cell.

Oxygen-derived free radicals

Oxygen-derived free radicals are usually either oxygen or hydroxyl groups that have an unpaired electron. These free radicals are unstable and react

with lipids, proteins, or DNA and RNA. This can result in tissue damage.

p53 pathway

P53 is a tumour suppressor protein that has the important function of inhibiting abnormal growth of cells. P53 helps to ensure genomic integrity and has important functions, such as DNA repair, promoting apoptosis, and inhibition of angiogenesis. p53 is a nuclear transcription factor that binds to defined consensus sites within DNA as a tetramer and affects the transcription of its target genes. Activation of p53 results in translocation of the protein to the nucleus where it induces transcriptional changes in proteins that prevent cell division and cause apoptosis.

Redox activation

A chemical reactions in which atoms have their oxidation number (oxidation state) changed is considered a redox reaction (shorthand for oxidation/reduction reaction). Oxidation describes the loss of electrons by a molecule, while reduction describes the gain of electrons by a molecule. This can involve simple molecules such as carbon or complex molecules. If a molecule is undergoing reduction/oxidation the process is often called redox activation.

Superoxide dismutase (SOD)

Superoxide is a free radical, that is an oxygen molecule that has an unpaired electron. This molecule can react with lipids, proteins, DNA, and RNA, causing tissue damage. Superoxide dismutase is an enzyme that "detoxifies" superoxide by converting superoxide radicals to hydrogen peroxide.

Xenobiotics

A xenobiotic is a chemical which is found in an organism but which is not normally produced or expected to be present in it. An example of a xenobiotic are antibiotics drugs because the human body does not produce them. The term xenobiotic can also refer to organs transplanted from one species to another.