Reversible heart failure: toxins, tachycardiomyopathy and mitochondrial abnormalities

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ABSTRACT
Heart failure is usually a relentless condition associated with a poor prognosis. Triggered by a physiological insult, maladaptive neurohumoral processes result in an ever-spiralling deterioration of cardiovascular function. However, there are certain underlying conditions which are associated with a temporary reduction in contractile function leading to reversible heart failure. These conditions affect a relatively small number of patients when compared with heart failure secondary to inherited cardiomyopathies and ischaemic heart disease. There are two broad mechanisms responsible for reversible myocyte dysfunction: acute inflammatory activation in which cytokines depress myocyte function, and toxic effects in which there is impairment of intra-cellular energetics. In this review, we discuss reversible heart failure caused by toxic effects. These effects can be caused by drugs (prescribed and illicit) and by tachycardiomyopathy (tachycardiomyopathy), and are caused by abnormalities of mitochondrial function and myocyte calcium processing. The underlying pathological mechanisms, clinical features and management options are discussed, illustrated by clinical case studies.

INTRODUCTION
Heart failure is usually a relentlessly progressive condition characterised by dyspnoea, oedema and cachexia. The prognosis for patients with heart failure remains poor with a 5-year survival rate from first presentation, of only 45–59%. This is despite advances in pharmacological therapy with β-blockers, ACE inhibitors, spironolactone and device-based, resynchronisation therapy. However, there are some more uncommon causes of heart failure in which the clinical course is variable, and from which patients may recover in terms of both clinical status and left ventricular function. This is in contrast with heart failure caused by inherited cardiomyopathy, or ischaemic heart disease, which rarely demonstrate significant reversibility, and which are more common.

We have previously discussed the role of inflammation in the aetiology of reversible heart failure. Transient heart failure may be seen in conditions associated with acute pro-inflammatory cytokine activation, such as severe infections, auto-immune inflammatory conditions (eg, rheumatoid arthritis), in some women during the peripartum period and in multi-system disease states requiring intensive care management. Box 1 outlines a summary of this article. In this review, we discuss another mechanism for reversible heart failure seen in patients with incessant tachycardia and after ingestion of myocardial toxins, which may include prescribed and illicit drugs. The underlying mechanisms responsible for the transient myocardial suppression observed in these circumstances are centred around abnormalities of mitochondrial function. Mitochondrial DNA is more susceptible than nuclear DNA to stress-induced oxidative damage. Toxins and incessant tachycardic states negatively influence the enzymes involved in the tricarboxylic acid cycle, disturb the balance of oxidative and antioxidant enzymes, and impair the uptake and binding of calcium within the mitochondria. These mitochondrial abnormalities impair the synthesis of adenosine-5'-triphosphate (ATP) in the myocyte, and result in impaired contractility. A greater understanding of these underlying mechanisms may lead to novel drug therapies for heart failure. In this review, we use clinical case examples to consider the effects of mitochondrial toxins and incessant tachycardia on mitochondrial metabolism, in the context of reversible cardiomyopathy.

ALCOHOL
Chronic alcohol abuse is a well recognised cause of impaired cardiac contractility which may reverse with abstinence. It is associated with significant biventricular systolic dysfunction and dilatation. Left ventricular hypertrophy may also be observed, but is likely to be mediated by hypertension which accompanies chronic alcohol abuse. A combination of increased left ventricular end diastolic diameter (left ventricular dilatation) and hypertrophy accounts for the increase in left ventricular mass, observed even in asymptomatic individuals.

The main problem, however, is loss of myocardial contractility. Alcohol damages mitochondria and is a myocardial suppressant. As cardiac myocytes do not contain the enzyme alcohol dehydrogenase, the toxic effects of alcohol may result directly from the toxicity of ethanol. Peripherally synthesised acetaldehyde is also toxic to the myocyte. Ethanol inhibits mitochondrial respiration by impairing the function of enzymes in the tricarboxylic acid cycle. It also impairs the uptake and binding of calcium in the mitochondria. Acetaldehyde reduces myocardial protein synthesis and inhibits calcium-activated myofibrillar ATPase. The combination of these effects results in diminution in contractility and function.

ILLUSTRATIVE CASE
A 39-year-old man was admitted with a history of dry cough, worsening breathlessness, weight gain and abdominal swelling. He was a smoker of 20 cigarettes daily and admitted to drinking over 70 units of alcohol per week. Examination revealed signs of severe congestive cardiac failure with...
resting tachycardia of 126 bpm, blood pressure (BP) 131/90 and raised central venous pressure to 10 cm. There was a summation gallop and bilateral pitting oedema. Chest radiograph demonstrated cardiomegaly and pulmonary congestion with fluid in the horizontal fissure. The mean cell volume and gamma-GT were raised, and there was ECG and echocardiographic evidence of left ventricular hypertrophy and severe global left and right ventricular systolic dysfunction with a left ventricular end-diastolic dimension (LVEDD) of 57 mm. He was treated with ACE inhibitors and low-dose β blockade. After 3 months of abstinence, he reported normal exercise capacity with no overt clinical signs of cardiac dysfunction. At 12 months, echocardiography revealed normal left and right ventricular dimensions (LVEDD 47 mm) and ejection fraction. He has remained abstinent and well since, and an echocardiogram over 18 months later showed a further reduction in LVEDD to 40 mm.

**COMMENT**

Although treated with ACE inhibitors and β blockade, the key intervention here was abstinence from alcohol. Current evidence suggests that a mild to moderate intake of alcohol is beneficial to the heart. The Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) trial studied over 50,000 men and women over a 10-year period and found that in men, the frequency of coronary events was inversely proportional to the amount of alcohol consumed, with coronary events being more than 30% less likely in drinkers than non-drinkers. However, there was no additional benefit in men drinking ‘high’ and ‘very high’ amounts of alcohol.6 There was no significant relationship in women which might be explained by a lower event rate in the female cohort. At higher levels of consumption, the cardiac response to alcohol is highly variable. Some hearts tolerate higher levels of consumption than others. Although environmental factors, such as the effects of prescribed and illicit drugs have an additive effect, there is evidence of a genetic predisposition to alcohol-induced cardiomyopathy. One study of alcoholic men demonstrated a specific polymorphism of the ACE genotype in 57% of alcoholic persons with a left ventricular ejection fraction (LVEF) of <50% but only in 7% of alcoholics with normal cardiac function.7 Even with complete abstinence, the degree of reversibility of cardiac function is variable, although, ensuring patients are truly abstinent is not always easy.

**Box 1 Reversible heart failure: the role of inflammatory activation: summary**

- Acute inflammatory activation can cause transient suppression of myocardial cell function.
- The underlying mechanism appears to be mediated via the activation of inflammatory cytokines and autoantibodies.
- These effects can be abrogated, at least partially, by immune modulating therapies such as intravenous immunoglobulin therapy.
- Supportive treatment while the underlying disease process is corrected results in cardiac recovery.
- Inflammatory activation as part of maladaptive physiology in patients with chronic heart failure is associated with a worse prognosis.

**Sympathomimetic drugs (cocaine and amphetamines)**

Recreational sympathomimetic drugs include cocaine, amphetamines and ecstasy. They have broadly similar stimulant effects, inducing euphoria, and a heightened psychological and physical state. Illegal use of sympathomimetic agents is highly prevalent in the UK with use steadily rising year on year. After cannabis, sympathomimetic compounds are the most confiscated class of drugs in the UK. An estimated 16.5% of people between 15 and 54 years of age admit to some level of use.8

Cocaine is a crystalline tropane alkaloid that is obtained from the leaves of the coca plant. Its anaesthetic, stimulatory, medicinal and aphrodisiac properties have been recognised for centuries. However, cocaine and its free base ‘crack-cocaine’ are highly addictive, and are potent sympathomimetic agents with potentially lethal cardiovascular effects.9 Cocaine may cause an acute or chronic fall in left ventricular performance. Acute left ventricular systolic and diastolic dysfunction is caused, at least in part, by its sodium and potassium channel-blocking effects which impair myocardial calcium transport.10 Focal myocarditis, myocyte necrosis and myocardial loss have been demonstrated in myocardial biopsy specimens in the context of acute cocaine toxicity.11 Cocaine blocks presynaptic uptake of catecholamines and dopamine, leading to postsynaptic over-activation of sympathetic and dopaminergic receptors.12 It also has a small central effect, causing noradrenaline (NA) release from the adrenal medulla.13 In actively intoxicated users, the level of circulating NA can be as much as five times higher than normal.10 Cocaine causes alterations in endothelial cytokine production and in circulating leucocytes. These changes activate the transcription of genes responsible for changing the composition of myocardial collagen and myosin, and inducing myocyte apoptosis. Chronic left ventricular systolic dysfunction is seen in 7% of asymptomatic long-term cocaine users.14 Cocaine has a short serum half-life of 30–50 min but can be detected in the urine for up to 2 weeks after administration, providing ample opportunity for clinicians to detect its use.

Amphetamines are synthetic compounds named from their full chemical name, α-methyl-phenethylamine. They represent a range of psychoactive drugs, produgs and derivatives, including metamphetamine and ecstasy. In contrast with cocaine, amphetamines freely cross the blood-brain barrier and act mainly via the central nervous system to release NA, dopamine, leading to postsynaptic over-activation of sympathetic and dopaminergic receptors. It also has a small central effect, causing noradrenaline (NA) release from the adrenal medulla.13 In actively intoxicated users, the level of circulating NA can be as much as five times higher than normal.10 Cocaine causes alterations in endothelial cytokine production and in circulating leucocytes. These changes activate the transcription of genes responsible for changing the composition of myocardial collagen and myosin, and inducing myocyte apoptosis. Chronic left ventricular systolic dysfunction is seen in 7% of asymptomatic long-term cocaine users.14 Cocaine has a short serum half-life of 30–50 min but can be detected in the urine for up to 2 weeks after administration, providing ample opportunity for clinicians to detect its use.
Cardiotoxicity occurs during treatment with many cytotoxic drugs. This may be the dose-limiting factor in cancer treatment
and may, therefore, affect tumour response. Cardiotoxicity can also be responsible for long-term effects and may cause severe morbidity in surviving cancer patients. Different mechanisms of chemotherapy-induced cardiotoxicity have been proposed, ranging from cellular damage from oxygen free radicals, induced immunogenic reactions with antigen-presenting cells in the myocardium, to the effects of chemotherapeutic agents on cardioliopin which affects ATP synthesis in mitochondria.

**ANTHRACYCLINES**

The association between anthracycline treatment and increased risk of heart failure has been known since the 1970s. The risk of heart failure depends on the cumulative dose received. The anti-cancer effects of anthracyclines are primarily mediated through inhibition of DNA synthesis, transcription and replication. Anthracyclines generate oxygen-derived free radicals using iron as a co-factor, and this impairs the mitochondrial respiratory chain. Free radicals damage proteins, lipids and DNA directly. Evidence suggests that increased myocyte apoptosis is related to the consequent increase in oxidative stress. This hypothesis is mainly based on in vitro experiments with only scant in vivo studies. The specific susceptibility of cardiac cells to oxidative stress may be due to relatively low levels of antioxidant enzymes in the heart. Oxidative stress results in the formation of oxidative free radicals which induce apoptosis. Another mechanism involves the influence of anthracyclines on calcium homeostasis. Oxidative stress can induce alterations in mitochondrial permeability which influences mitochondrial calcium transport. Changes in calcium transport can lead to impaired contractility, tissue injury and cell death. In vitro experiments have shown that doxorubicin treatment causes an irreversible decrease in mitochondrial calcium-loading capacity.

**ILLUSTRATIVE CASE**

A 15-year-old boy was admitted with evidence of decompenated heart failure. At the age of four years, he had been treated for a rhabdomyosarcoma with a combination of carboplatin, ifosfamide, etoposide, vincristine, actinomycin and epirubicin (anthracycline). The cumulative dose of epirubicin was 600 mg/m². Echocardiography revealed a dilated left ventricle with severely reduced contractile function and an ejection fraction of <20%. He was referred for a cardiac transplant assessment, but improved on medical therapy in the interim period (furosemide, ACE inhibition, nitrate and digoxin). Twelve months later, he was reviewed in clinic, still on medical therapy. At this point, he was asymptomatic, and a repeat echocardiogram revealed normal pulmonary artery pressure, but improved on medical therapy in the plant assessment, but improved on medical therapy in the plant assessment. However, chronic effects can persist after discontinuation of therapy, with all the features of cardiomyopathy. One of the commonest presentations of anthracycline-induced cardiomyopathy is in women treated for metastatic breast cancer. Direct toxic damage to the myocardium usually affects the inter-ventricular septum first. A range of damage is seen in patients exposed to this drug, but the majority do not develop clinically significant failure. There are a number of risk factors which increase the likelihood of developing heart failure after anthracycline therapy. In a retrospective study of 1097 patients with metastatic breast cancer treated with epirubicin, Ryberg et al found that 11.4% developed congestive cardiac failure with a 40% increase in risk for every 100 mg/m² administered. Other factors which increased the risk of heart failure during treatment were: increasing age (28.5% for every 10 years in age), a predisposition to cardiac disease, a prior (not adjuvant) history of mediastinal irradiation (20%) or prior use of anti-hormonal treatments for breast cancer (87%). By the age of 70 years, the risk of developing heart failure with the lowest dose of epirubicin given was 5%, but this increased to nearly 20% for those given higher doses. The same authors also studied the time course for the development of heart failure after epirubicin therapy, showing that the median time to heart failure onset was 57 days (range 0–853 days). Previous irradiation directed over the left hemithorax increased the risk of death due to cardiac failure and reduced the median survival time. A French study of low-dose epirubicin reported lower frequencies of heart failure, but risk increased in women over 65 years of age, and in those with a body mass index >27 kg/m².

Aside from cumulative dose reduction, attempts have been made to develop chemoprotectants to prevent anthracycline-induced cardiotoxicity. Antioxidants used as free radical scavengers have not shown any cardioprotective effect. Iron chelators have been developed to reduce cardiotoxicity by binding intracellular iron and removing the iron from the anthracycline-iron complex, thus preventing free radical formation. Dexrazoxane was found to be the most promising agent reducing cardiac side effects from 31% to 15% (p=0.001) in one study, and from 24% to 4% in another (p=0.02). However, there is a concern that the antioxidant effects of Dexrazoxane may reduce the anti-tumour efficacy of anthracyclines. Attempts have also been made to change the formulation of the anthracyclines, for example, to liposomal doxorubicin which may reduce toxicity.

**TRASTUZUMAB (HERCEPTIN)**

Trastuzumab is a humanised anti-HER2 monoclonal antibody used in the treatment of breast cancer in patients with over-expression of human epidermal growth factor receptor type 2 (HER2). Trastuzumab alone is associated with cardiac toxicity and increases the risk of congestive heart failure when used in patients with early or with metastatic disease. When used in combination with or after an anthracycline drug, the risk of CHF is even higher. Studies of mutant mouse models have shown a pivotal role of the erbB2 gene in the postnatal heart. ErbB2-mediated pathways are lost in trastuzumab cardiotoxicity. These pathways normally blunt the effects of stress-signalling pathways activated by anthracyclines. ErbB2 protein-deficient mice are, therefore, particularly susceptible to the effects of haemodynamic overload and anthracyclines by developing left ventricular dysfunction. ErbB2 is also fundamental in triggering myocyte-survival pathways that are required during the activation of acute stress signals. After trastuzumab treatment, the loss of these survival cues can result in irreversible loss of cardiac myocytes resulting in clinical signs of heart failure.
in overt cardiac dysfunction. However, the precise mechanism of the trastuzumab and anthracycline interaction remains unknown.

ILLUSTRATIVE CASE
A 50-year-old woman with metastatic breast carcinoma was referred with echocardiographic evidence of deteriorating left ventricular function. She had initially been treated with eight courses of palliative chemotherapy, including an anthracycline. At presentation, she was taking capetibamine and herceptin. Pretreatment LVEF was >60% but had fallen to only 30–58% with an increase in LVESD to 56 mm and associated functional moderate mitral regurgitation. It was felt that herceptin treatment may have unmasked occult damage induced by prior anthracycline therapy. Herceptin therapy was withheld and she was commenced on ACE inhibition and low-dose β-blocker therapy. After 4 weeks, there was echocardiographic improvement with an increase in ejection fraction to ~40%, and less mitral incompetence. Within 2 months, another echocardiogram demonstrated continued improvement with a LVEF of 50% and only mild mitral regurgitation. At this point, spironolactone was added. She was recommenced on herceptin after a 5-month break with frequent echocardiographic monitoring. Twelve months after her original clinical cardiac deterioration, echocardiogram demonstrated a non-dilated left ventricle, trivial mitral regurgitation and an ejection fraction of 60% with no evidence of diastolic dysfunction.

COMMENT
Although this case demonstrates reversal of the presenting cardiomyopathy, she remains at high risk of recurrent cardiac damage from herceptin and will require ongoing monitoring of left ventricular function. Current guidelines suggest that patients receiving herceptin should have LVEF monitored by echocardiography, or by the radionucleotide MUGA scan every 12 weeks. The frequency of surveillance needs to be increased if there is evidence of deterioration. The risk of cardiotoxicity following trastuzumab administration is associated with older age, lower LVEF at onset of treatment, concomitant use of antihypertensive medications and in patients who had also received anthracyclines. The cardiac toxicity is much more common when trastuzumab and anthracyclines are given together or within a recent time span, therefore, concomitant administration of these two drugs should be avoided as recommended by recently proposed guidelines. Identification of patients at high risk, especially in the setting of trastuzumab in combination with an anthracycline, and optimisation of their cardiac risk factors is required to reduce the risk of cardiac toxicity with these drugs.

MITOCHONDRIAL ABNORMALITIES IN HEART FAILURE
The illustrative cases in this review demonstrate the role of toxins in the aetiology of cardiac failure. Most notably, it is the toxic effect upon the mitochondria within the cardiac myocyte that causes a reduction in cellular energetics resulting in decreased contractile function. There is then a tendency for the development of further abnormalities in mitochondrial metabolism especially relating to oxygen consumption and oxidative phosphorylation. Myocyte, and consequent cardiac work, requires a high rate of ATP hydrolysis, matched by ATP production through mitochondrial oxidative phosphorylation. Lower concentrations of ATP are found in patients with chronic heart failure. In addition to the drop in ATP content, the failing heart has abnormalities in the mitochondrial metabolism of carbon substrates for the generation of reducing equivalents (eg, the reduced forms of the electron transporters, Nicotinamide Adenine Dinucleotide and Flavin Adenine Dinucleotide: NADH and FADH2). Fatty acid oxidation provides significant energy for oxidative phosphorylation. Impaired oxidation of glucose and lactate may contribute to cardiac contractile dysfunction. Furthermore, electron microscopy has found mitochondria to be disrupted and damaged in failing hearts. Evidence supporting a causal link between impaired mitochondrial metabolic function and cardiac failure has been found in several cases of inherited cardiomyopathy. Cardiac mitochondria exist as two different populations, interfibrillar and subsarcolemmal, and these have been shown to respond differently to insults, for example, ageing, ischaemia and inherited cardiomyopathy.

DRUG TOXICITY AND MITOCHONDRIA
Mitochondrial dysfunction has been increasingly implicated in drug-induced toxicity. Medications can damage mitochondria, both, directly and indirectly. For example, medications can directly inhibit mitochondrial DNA transcription of electron transport chain complexes, or inhibit enzymes required for glycolysis, or indirectly damage mitochondria by formation of free radicals, as with the anthracyclines. Damage to mitochondria was first demonstrated in vitro with barbiturates inhibiting mitochondrial respiration. Damage to mitochondria is primarily caused by reactive oxygen species created by mitochondria themselves. Inflammatory mediators such as tumour necrosis factor α (TNF-α) have been associated in vitro with mitochondrial dysfunction and increased radical oxygen species generation.

MITOCHONDRIA-DIRECTED THERAPY IN HEART FAILURE PATIENTS
Approximately two-thirds of the energy required for oxidative phosphorylation is derived from the oxidation of fatty acids.

Main messages
- Not all forms of heart failure are relentlessly progressive
- Heart failure caused by toxins and tachycardia can show reversibility
- The underlying mechanisms involve abnormalities in mitochondrial respiration and calcium processing
- These mechanisms may provide useful targets for the development of novel drug therapies for heart failure.

Current research questions
- Can partial fatty acid oxidation inhibitors, like trimetazidine and ranolazine, be trialled for use in heart failure?
- How important is the genetic predisposition to alcohol-induced cardiac toxicity, and is there a genetic crossover with ‘idiopathic’-dilated cardiomyopathy?
- Can key anthracycline modifications be developed and utilised clinically to reduce cardiac toxicity?
Patients with heart failure may have impaired metabolism of lactate and glucose, and enhanced fatty acid oxidation that contributes to cardiac dysfunction. Drugs aimed at increasing the myocardial oxidation of derivatives of lactate and lactate could be beneficial in heart failure patients. Pharmacological activation of pyruvate dehydrogenase has been demonstrated to increase left ventricular function without an ecological activation of pyruvate dehydrogenase has been demonstrated to reduce fatty acid oxidation and increase mitochondrial respiration. In heart failure remains to be fully tested. Existing heart failure therapies exert some of their therapeutic effects by their actions on mitochondria. For example, long-term treatment with the β-receptor antagonist, Metoprolol, has been demonstrated to reduce fatty acid oxidation and increase carbohydrate oxidation with an associated improvement in LVEF. Studies in rats have demonstrated that ACE inhibitors, slow down heart failure progression following myocardial infarction in association with a fall in the rate of cardiac mitochondrial respiration.

CONCLUSION
Mitochondrial dysfunction appears to play a pivotal role in patients with toxin- and tachycardia-induced heart failure. In these circumstances, heart failure may demonstrate marked reversibility. Existing heart failure therapies already exert beneficial effects on mitochondrial function. Prompt identification of such cases, cessation of the causative toxic agent or restoration of normal heart rate and standard heart failure therapy remain the current treatment modalities. Trials of new agents specifically aimed at improving mitochondrial function in heart failure are ongoing.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)
1. Regarding alcohol and the heart
A. Myocytes contain high levels of the enzyme alcohol dehydrogenase.
B. Any level of alcohol consumption is detrimental to cardiovascular morbidity and mortality.
C. Ethanol and acetaldehyde are directly toxic to actin and myosin protein filaments.
D. Toxicity to alcohol in the heart is influenced by predisposing genetic factors.

2. Regarding sympathomimetic drugs and the heart
A. Sympathomimetic drugs affect cardiac function acutely but not chronically.
B. Cocaine blocks the presynaptic uptake of catecholamines and dopamine.
C. Cocaine has more centrally acting effects than amphetamines.
D. Sympathomimetic drugs may induce coronary spasm which may result in myocardial infarction.

3. Regarding tachycardia-mediated cardiomyopathy
A. Tachycardia is a common cause of cardiomyopathy.
B. It is mediated by mitochondrial oxidative damage.
C. Treatment of tachycardic arrhythmia in cardiomyopathy frequently reverses the cardiomyopathy.
D. The combination of cardiomyopathy and arrhythmia should alert the physician to consider anticoagulation, if appropriate.

4. Regarding chemotherapy and the heart
A. Anthracyclines inhibit DNA synthesis.
B. Anthracycline use is associated with the generation of oxygen free radicals.
C. Cardiac myocytes contain relatively high amounts of antioxidant enzymes.
D. The ErbB2 protein appears to have a protective role in patients treated with trastuzumab.

5. Regarding myocardial toxins and cardiomyopathy
A. Cardiac myocytes contain relatively low numbers of mitochondria.
B. In the failing heart, mitochondrial function is activated and made more efficient.
C. Mitochondrial damage is primarily caused by reactive oxygen species created by mitochondria themselves.
D. Drugs aimed at improving the oxidation of derivatives of glucose and lactate may prove to be beneficial in heart failure patients in the future.

REFERENCES
Review


ANSWERS

1. A (F); B (F); C (F); D (T)
2. A (F); B (T); C (F); D (T)
3. A (F); B (T); C (T); D (F)
4. A (F); B (F); C (F); D (T)
5. A (F); B (F); C (T); D (T)