Reversible dilated cardiomyopathy: into the thaumaturgy of the heart - Part 2

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Abstract

Dilated cardiomyopathy (DCM) is a genetic or acquired heart muscle disorder characterized by dilation and impaired contraction of one or both ventricles. In the acquired forms of the disease, if the pathogenic agent is persistent, undiagnosed or untreated, permanent ultrastructural and morphological changes may lead to irreversible dysfunction. Conversely, when DCM is promptly recognized and treated, the heart may show an extraordinary ability to recover from left ventricular (LV) systolic dysfunction. While much research in heart failure has focused on morbidity and mortality associated with persistent LV systolic dysfunction, relatively little attention has been devoted to this remarkable potential for recovery. In this two-part review we will focus on the most common types of reversible DCM. The second part will deal with chemotherapy-induced cardiomyopathy, alcohol-related cardiomyopathy, myocarditis and peripartum cardiomyopathy. Although diverse in etiopathogenesis, genetic background, therapeutic options and outcome, the forms of DCM characterized by reversible LV dysfunction share similar challenges in diagnosis and clinical management. The identification of pathways to recovery may show the way for novel therapeutic targets ultimately benefitting all cardiac patients.

Chemotherapy-induced cardiomyopathy

Chemotherapy is a well-known cause of cardiomyopathy (Table 1) and the cardiac toxic effects of anthracyclines, prototypal in oncology, have been investigated for more than 30 years.1 Although acute cardiotoxicity is possible, chronic cardiotoxicity is more common; its occurrence and severity are proportional to the cumulative dose (for example doxorubicin >400-500 mg/m² is associated with significant risk) and may become evident several years after exposure. Occasionally, the gap may be sufficiently long as to render the association between chemotherapy and cardiomyopathy counterintuitive. Serial echocardiographic assessment of left ventricular (LV) systolic function is commonly used to evaluate chemotherapy-induced cardiomyopathy, while cardiovascular magnetic resonance (CMR) is indicated as a second-line investigation when evident disease or borderline abnormalities are identified.2 Historically, cardiotoxicity is defined by a ≥5% decline in LV ejection fraction (LVEF) resulting in an LVEF <55% with symptoms of heart failure, or a 10% decline to result in an LVEF <55% without symptoms of heart failure, or ≥20% or >15% LVEF decline from baseline, but remaining ≥50%, or any LVEF decline to <50%.3 Clinical manifestations vary from mild, subclinical systolic impairment to severe dilated cardiomyopathy and refractory heart failure. Today, about half of the patients surviving cancer die of cardiovascular complications of treatment. There are 2 major types of cardiotoxicity-type 1 and 2. Type 1 (typical caused by anthracyclines) is associated with ultrastructural changes, poor prognosis and lower recovery rates. Type 2 cardiotoxicity (for example caused by trastuzumab), is not associated with histological changes and have better prognosis.4 Chemotherapy-induced cardiomyopathy represents 2.5% of all heart transplant recipients.5

Biomarkers such as troponin, natriuretic peptides, C-reactive proteins and others have been proposed as early markers of cardiotoxicity and are useful in predicting risk. Treatment is still empirical and mainly based on standard heart failure medications. Recovery of LV systolic function has been reported up to 55% of patients in 2 years.6 Prevention of chemotherapy-induced cardiomyopathy involves careful evaluation of the type and dose of oncologic regimens and the use of dexrazoxane, an ethylenediaminetetraacetic acid-like chelator that reduces oxidative damage. In addition, preventive therapy with β-blockers (carvedilol), angiotensin-converting enzyme (ACE)- inhibitors and statins may be effective, although the evidence supporting their protective role is limited. A recent meta-analysis of a small number of trials showed a relative risk reduction in risk of heart failure or LVEF decline following chemotherapy of approximately 70% for β-blockers and 90% for ACE-inhibitors.6 These data support the concept that optimization of hemodynamics and neurohormonal milieu prior to anthracycline therapy may help to prevent myocyte injury. Another promising strategy for the management of LV dysfunction due to anticancer treatment relies on the use of novel, more sensitive diagnostic techniques allowing earlier recognition of myocardial damage. Most relevantly, strain echocardiography and cardiac MRI, along with biomarkers such as cardiac troponins and NT-proBNP have shown the best results in terms of risk assessment for the timing of early interventions.7,8

To date, the pathogenesis of cardiotoxicity associated with anthracycline therapy is still poorly understood. The most commonly accepted hypothesis for anthracycline-induced car-
Alcohol-related cardiomyopathy

Daily consumption of low to moderate amounts of alcohol has been shown to have potent beneficial effects on the cardiovascular system. In contrast, it is known since late 19th century that chronic exposure to high levels of alcohol for a long period could lead to progressive cardiac dysfunction and heart failure. Excessive alcohol intake is currently recognized as a common cause of dilated cardiomyopathy (DCM), and DCM due to alcohol abuse is known as alcohol-related cardiomyopathy (ACM) (Table 1, Figure 1). The evidence supporting excessive alcohol exposure as a cause of DCM includes several experimental studies, epidemiological studies showing higher prevalence of excessive alcohol consumption in DCM patients than in the general population, and echocardiographic studies in asymptomatic alcohol abusers.

Based on experimental studies the pathophysiology of ACM includes several processes with a crucial role of apoptosis and oxidative stress. In addition, genetic predisposition is likely to play a major role. Individual susceptibility to ACM is supported by the fact that only a small subset of alcohol abusers develop the disease. Prevalence of ACM in DCM series range from 23 to 47% making ACM the leading cause of DCM in western countries. The diagnosis of ACM is usually one of exclusion in a patient with DCM with no identified cause and a long history of heavy alcohol abuse.

Data on the amount of alcohol consumption required to cause ACM are limited and controversial in that a proportional relationship between myocardial damage and alcohol intake has not been proven. In most studies on the natural history and the long-term prognosis of ACM, an amount of 80 g a day (equivalent to 10 U or 5 glasses of 12% wine or 3-4 pints of beer) during at least 5 years was deemed sufficient to produce the disease. However, average alcohol consumption shown by the patients included in these series was much higher and consumption periods were much longer. Furthermore, the accepted definition of ACM does not take into account important factors such as body mass index (BMI) or sex. For example, women and individuals with lower BMI are significantly more susceptible to the negative effects of alcohol.

A recent study examined the contemporary natural history of ACM. In this study involving 94 patients evaluated at a single referral center during the period 1994-2011, approximately one third died or needed a heart transplant while another third showed persistent LV dysfunction despite lack of adverse events. The final third progressively normalized their cardiac function. In this study predictors of poor outcome (death and heart transplant) were absence of β-blocker treatment, atrial fibrillation and QRS>120 ms.

Recommended treatment in ACM does not differ from other forms of DCM and should include guideline-based anti-failure medications. Special attention should be paid to β-blocker treatment given its protective effect in the above mentioned study. Although there are no specific randomized studies examining the efficacy of implantable cardioverter defibrillators (ICDs) on ACM, a device should always be considered in patients with ACM and severely impaired systolic function, who seem to be at higher risk of malignant ventricular arrhythmias compared to other DCM patients. On the other hand, the ultimate decision regarding an ICD is challenging, because LVEF can greatly improve in the first year after diagnosis. Only one study has specifically investigated the incidence of ventricular arrhythmias in ACM. Investigators reported that no malignant ventricular arrhythmias were found among ACM patients if LVEF had improved to or remained ≥40%.

Complete withdrawal is recommended to all patients with ACM and may lead to complete recovery of cardiac function, and three long-term studies have shown better outcomes of ACM in abstainers than in patients who maintained alcohol consumption. Nevertheless, there is controversy regarding the need for complete alcohol withdrawal in ACM. The controversy emerges from the observation that...
studies evaluating the effect of alcohol abstinence included patients who reduced alcohol intake to low/moderate levels alongside with those who stopped consuming alcohol completely. Furthermore, the only contemporary study found that prognosis and degree of LVEF recovery in ACM patients who decreased alcohol intake to moderate levels was comparably favorable to that of abstainers. Ultimately, complete alcohol cessation appears desirable for ACM patients giving the fact that these patients have suffered an important addiction and may find it extremely difficult to maintain low-moderate intakes over time.

Basic research studies have described several mechanisms that could be involved in determining the functional and structural alterations found in ACM, linked both to ethanol and its main metabolite, acetaldehyde. Most studies highlight abnormalities of intracellular organelles causing alterations in the energetic metabolism and calcium homeostasis, which are especially relevant for the development of contractile anomalies. The mechanisms described to date include: apoptosis, up-regulation of the L-type calcium channels, alterations of the excitation-contraction coupling in cardiac myocytes, structural and functional alterations of the mitochondria and sarcoplasmic reticulum, changes in calcium sensitivity of myofilaments, alterations of mitochondrial oxidation, deregulation of protein synthesis, decrease of contractile proteins and activation of the renin-angiotensin system and of the sympathetic nervous system. To date, however, the sequence of events that occur in alcohol-induced myocardial damage are unresolved.

### Myocarditis

Myocarditis (Table 1) is an inflammatory disease of the heart muscle and is defined immunohistochemically by the presence on endomyocardial biopsy of ≥14 leucocytes/mm², including up to 4 monocytes/mm², with the presence of CD3 positive T-lymphocytes ≥7 cells/mm². Myocarditis can be suspected clinically in symptomatic subjects [chest pain, pseudosymmetric electrocardiographic (ECG) pattern, dyspnea, unexplained arrhythmias, cardiogenic shock] in the presence of one or more of the following criteria:

### Table 2. Reversible dilated cardiomyopathies.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnosis</th>
<th>Clinical manifestations</th>
<th>Prognosis</th>
<th>Specific therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy-induced CMP</td>
<td>A ≥5% decline LVEF resulting in an LVEF &lt;55% with symptoms of heart failure, or a ≥10% decline to result in an LVEF &lt;55% without symptoms of heart failure</td>
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|                                    | - ROS generation                                                         | Prevalence: Up to 10% of all heart, and statins (debated)                               | - Poor for type I cardiotoxicity: 60% mortality at 2-3 years for doxorubicin,
|                                    | - Formation of DNA adducts                                               | Up 55% in 2 years                                                                     | up to 40% for cyclophosphamide                                |
|                                    | - Top2B inhibition                                                       | At 4 years from diagnosis                                                              | Low mortality for type II cardiotoxicity: 5%                           |
|                                    | - Dysfunction of resident myocardial cells                               | At 11 years follow ±50% mortality at 2-3 years                                         | 2.5% of all heart transplant                                      |
|                                    | - Ischemia (cispatin, 5-fluorouracil and rituximab)                      | - Complete alcohol withdrawal                                                          | - Reduce dose/discontinuation of the chemotherapeutic agent             |
|                                    | - Activation of the renin-angiotensin system and of the sympathetic nervous system (antineutrophil granulocyte antibodies) | - Standard anti-failure medications, with special priority to β-blockers               | - Earlier detection of myocardial damage (strain echocardiography, CMR, proBNP, etc.) |
| Alcohol-related CMP                | Dilatation and impaired contraction of the left ventricle or both ventricles related to excessive alcohol intake | 80 g a day of alcohol intake (equivalent To 10 U or 5 glasses of 12% wine or 3-4 pints of beer) for at least 5 years | Up to 40% of DCM pts in western countries6 | - Antiviral agents                                      |
|                                    | - Viral infections (PVB19, HHV6, enterovirus, adenovirus, influenza A virus, EBV, CMV, HCV, HIV)       | At 4 years from diagnosis                                                             | 37% at 4 years from diagnosis                                        |
|                                    | - Other infectious agents (bacterial, fungal, protozoal)                  | - Complete alcohol withdrawal                                                          | - Poor for type I cardiotoxicity: 60% mortality at 2-3 years for doxorubicin, up to 40% for cyclophosphamide |
|                                    | - Immuno-mediated toxicity agents                                        | - Reduced dose/discontinuation of the chemotherapeutic agent                          |
| Myocarditis                        | Inflammatory disease of the heart muscle on EMB. ≥14 leucocytes/mm², including up to 4 monocytes/mm², with the presence of CD3 positive T-lymphocytes ≥7 cells/mm² 6 | - Viral myocarditis                                                                  | - 50% non-fulminant acute myocarditis6  | - Autotol agents (interferon), immunosuppression (azathioprine, cortisone), immunomodulation (intravenous immunoglobulin) (debated and controversial) |
|                                    | - Other infectious agents (bacterial, fungal, protozoal)                  | - Up to 90% of fulminant myocarditis56                                               | - At 11 years follow ±50% mortality at 2-3 years for doxorubicin, up to 40% for cyclophosphamide |
|                                    | - Hemorrhagic stress and apoptosis                                       | - 1:4000 to 1:1000 live births in the Western World81                                   | - If dilution and systolic dysfunction persist, the prognosis is poor |
|                                    | - Malnutrition                                                           | Up to 65% of patients within 6 months of delivery87                                    | - If there is full recovery within 6 months from delivery, the prognosis is excellent |
|                                    | - Prolactin                                                              | - Avoid all teratogenic drugs if pregnancy/lactation is ongoing, including             | - Avoid all teratogenic drugs if pregnancy/lactation is ongoing, including |
|                                    | - Hemodynamic stress and Genetic milieu (Titin gene)                     | ACE-inhibitors and ARBs                                                                | ACE-inhibitors and ARBs                                             |
|                                    |                                                                          | Bromocriptine (debated)                                                               | - Bromocriptine (debated)                                           |
|                                    |                                                                          | Pentoxifylline (debated)                                                              | - Pentoxifylline (debated)                                         |

CMP: cardiomyopathy; LVEF: left ventricular ejection fraction; ROS: reactive oxygen species; CMR: cardiovascular magnetic resonance; ACE-inhibitors: angiotensin-converting enzyme inhibitors; DCM: dilated cardiomyopathy; EMB: endomyocardial biopsy; PVB19, parvovirus B19; HHV6, human herpesvirus 6; EBV, Epstein-Barr virus; CM: citomegalovirus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; FS: fractional shortening; ARBs, angiotensin II receptor blockers.

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Viral infections [parvovirus B19 (PVB19), human herpesvirus 6, enterovirus, adenovirus, influenza A virus, Epstein-Barr virus, citomegalovirus, hepatitis C virus, human immunodeficiency virus] are the most common cause of myocarditis, followed by other infectious agents (bacterial, fungal, protozoal, etc.), immuno-mediated causes and toxic agents. Using polymerase chain reaction technology, viral RNA or DNA is commonly identified within the myocardium of affected patients. Extensive studies performed in biopsy and autopsy myocardial specimens have linked specific viral infections with up to 69% of cases of clinical myocarditis. Moreover, elevated serum levels of antibodies against specific viruses have been detected in patients with idiopathic dilated cardiomyopathy.

Little is known about the early stages of acute viral myocarditis in patients. Enteroviruses (e.g., Coxsackie-B viruses) are responsible for one quarter of cases and their mechanism of damage to the myocardium has been well characterized in animal models. Enteroviruses gain access to the host via the gastrointestinal or respiratory tracts, the heart being a secondary target. Myocardial infection occurs in 3 subsequent phases: i) viral entry into cardiomyocytes and activation of innate immunity; ii) viral replication and activation of acquired immune responses; iii) resolution with recovery or development of chronic dilated cardiomyopathy. Initial viral entry is mediated by a specific cell-surface receptor. Enteroviruses and adenoviruses recognize a common transmembrane receptor on cardiomyocytes, the coxsackievirus and adenovirus receptor. This is essential for the initiation of the infection and subsequent viral replication leading to myocyte necrosis. Natural killer cells, macrophages, and T lymphocytes migrate towards the infection site, causing additional myocardial injury. The latter starts the second phase, where autoimmune reactions activate T cells that target host myocardium. High levels of cytokines are liberated during which can further potentiate cardiomyocyte damage and reduce contractile function. Phase 2 (the subacute phase) can last weeks to months; in most patients, ventricular contractile function improve as the amount of replicating viruses diminishes. However, the cardiomyopathy may enter a chronic phase, which becomes irreversible.

Other viruses cause myocarditis by different mechanisms. PVB19 can hibernate after a primary infection in childhood and later infect the cardiac endothelium. PVB19 genomes have been found in cardiac endothelial cells in patients with fulminating myocarditis. Though not directly infecting cardiomyocytes, the virus exerts its pathogenic effects by local activation of cytokines [tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6)] and induction of endothelial apoptosis. Endothelial damage may in turn compromise tissue perfusion, causing myocardial ischemia. Moreover, accumulation of lymphocytes in the coronary microcirculation leads to a sustained rise in coronary resistance, contributing to myocyte necrosis.

Although myocarditis is an acquired disease, genetic polymorphisms may facilitate viral infection and direct cellular damage and may play a role in subsequent immuno-mediated injury. In addition, genetically determined DCM may represent a preferential substrate for myocarditis. Clinical presentation may be: i) fulminant (lymphocytic, giant cell myocarditis), which can rapidly evolve towards cardiogenic shock and death, but may resolve completely in survivors; ii) acute, which often resolves completely; and iii) chronic active myocarditis, characterized by ongoing inflammation and damage leading to DCM.

Complete recovery of LV function occurs in about 50% of patients with non-fulminant acute myocarditis and up to 90% of patients with fulminant myocarditis. In one study, at 11 years follow up 93% of fulminant myocarditis patients were alive compared to 45% of patients with acute myocarditis. Supportive and standard anti-failure medications are still the cornerstone of treatment. The evidence favoring specific therapy with antiviral agents (for example interferon), immunosuppression (azathioprine, cortisone), immunomodulation (intravenous immunoglobulin) is still based on small studies and controversial. It is unclear why some patients have full recovery and others have persistent LV dysfunction. In addition, it is not clear how long heart failure treatment is needed after normalization of LV function. Finally, it is still controversial whether family screening should be considered, as evidence of myocarditis does not exclude genetically determined DCM or - in patients presenting with sudden cardiac death - a channelopathy.

Figure 1. Echo still frame images (diastole top panels, systole bottom panels) from a 52-year old male admitted for acute heart failure and past medical history including hypertension, atrial fibrillation and consumption of 100 g of alcohol per day for more than 20 years and normal coronary arteries. An echocardiogram (left panels) showed a very dilated left ventricle (LV), with LV ejection fraction <25% and right ventricular (RV) mild to moderate systolic dysfunction. An echocardiogram performed 6 years after first evaluation (right panels), after standard heart failure medication and complete alcohol intake withdrawal, shows normal LV and RV size and function.
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**Peripartum cardiomyopathy**

Peripartum cardiomyopathy (PPCMP) (Table 1) is an increasingly recognized entity characterized by LV dysfunction (defined as LV ejection fraction <45% or fractional shortening <30% or both) presenting with signs of cardiac failure during the last month of pregnancy or within 5 months of delivery, where no other cause of heart failure is found. LV function tends to recover in the majority of cases within 6-12 months. Duration of standard anti-failure medication after normalization of LV function is unknown. The risk of PPCMP with subsequent pregnancies, although still uncertain, depends on recovery of LV function, and has been described in up to 50% of patients with persistent dysfunction compared to 20% in patients with LVEF normalization.20 The mechanism of relapse remains unclear and it is unknown whether preventive measure can be implemented in patients with prior history of PPCMP undergoing a new pregnancy.

The prevalence of PPCMP has been estimated to be 1:4000 to 1:1000 live births in the Western world.21-23 Advanced maternal age, race (African), twin gestation, multiparity, gestational hypertension, chronic hypertension, preclampsia, prolonged use of tocolytics are known risk factors for PPCMP.24 The etiology remains largely unknown. Viral myocarditis, auto-immunity, inflammation, increased oxidative stress and apoptosis, genetic predisposition, malnutrition, prolactin and hemodynamic stress have all been proposed as pathogenic or contributing mechanisms. Familial occurrence of PPCMP has been described and genetic association has been shown in mice and humans.24-26 Recently, a large study on 172 PPCMP patients, showed a prevalence of truncating variants (especially in the Titin gene) similar to DCM patients, suggesting that these variants may predispose to the condition.27-29

Myocarditis appears to be the main pathophysiological mechanism in PPCMP. A 76% incidence of myocarditis at myocardial biopsy was reported in a study on a large number of patients with PPCMP.30 Inflammatory cytokines have also been named as possible leading causative factors for PPCMP. In patients with PPCMP; some studies found elevated plasma levels of cytokines, such as TNF-α and IL-6, as well as Fas/APO-1 (a apoptosis-signaling surface receptor).31 Cytokines may lead to PPCMP through initiation of an inflammatory cascade when they come in contact with fetal cells that have reached the maternal circulation during delivery. These cells may have initially escaped the maternal immune system because of the immunosuppressive state of pregnancy. These cells are therefore able to settle in various organs, including cardiac tissue, leading to an autoimmune trigger when the maternal immune system effectiveness is restored shortly after delivery.32 The hemodynamic stress associated with pregnancy (increased preload and decreased afterload) has been shown to cause LV remodeling and hypertrophy.33 The physiological reduction in LV systolic function brought on by the reverse-remodeling process after delivery may be more exaggerated in subjects with peripartum cardiomyopathy. Animal studies supported the role of prolactin in peripartum cardiomyopathy. Decreased levels of myocardial signal transduction lead via catabolism of prolactin to an antiangiogenic and proapoptotic isoform of the hormone in the heart, which may cause PPCMP.34 Of note, these results have been confirmed in patients, supporting a specific anti-prolactin therapeutic strategy.

Recovery of LV systolic function has been reported in up to 65% of patients within 6 months of delivery.35 Management of PPCMP includes standard heart failure regimen, but careful consideration must be made to avoid all teratogenic drugs if the pregnancy is ongoing, including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Hydralazine and nitrates may be safely used as alternative therapies. β-adrenergic receptor blockers may also be used during pregnancy. Immunosuppressive agents and immunoglobulins may be considered in patients with biopsy-proven myocarditis that have not improved after two weeks of standard heart failure therapy.36-38 Bromocriptine, which inhibits prolactin secretion, has been shown to promote recovery of LV function in a small PPCMP cohort,39 but safety issues have limited its use in clinical practice.40 The anti-inflammatory agent pentoxifylline has been investigated in a small trial41 and shown to be effective, but further evidence is required.

**Clinical perspective**

The diverse forms of dilated cardiomyopathy associated with a potential for recovery of LV dysfunction share a number of features. The etiology may be uncertain and a specific diagnosis may be often difficult. An history of stressful events may lack in Tako-Tsubo cardiomyopathy, the role of concomitant tachyarrhythmias may be unclear in tachycardia-induced cardiomyopathy (TIC), patients may have had chemotherapy in the past with dubious impact on later occurrence of LV dysfunction, the amount of alcohol consumption may be difficult to ascertain and DCM found during pregnancy may be pre-existing. Sometimes, more than a possible cause is found, and all these conditions may represent acquired disease sponsored by genetic predisposition or unmask true genetic DCM, which should prompt family screening. The molecular mechanisms underlying these conditions are often unclear and it is still unknown how long heart failure treatment needs to be continued once LV function has recovered and whether primary or secondary prevention is possible, for example before starting a potential cardiac toxic chemotherapy or planning a new pregnancy. Specific treatments are emerging for some conditions (e.g., peripartum cardiomyopathy or autoimmune myocarditis), but still based on small studies. In all these forms, early recognition appears a cornerstone for clinical management, before permanent ultrastructural and structural damage occur, in order to improve likelihood of recovery. For example, recognizing TIC is fundamental as LV dysfunction may be completely reversible once tachycardia has been controlled, even though it may have been so severe as to be considered for transplantation.42 It is also important to note that a significant minority of cases of dilated cardiomyopathy recover even in absence of reversible factors. Finally, these conditions represent paradigms of cardiac recovery suggesting a number of molecular mechanisms, which might be exploited in other cardiac conditions that are at present progressive and unresponsive to therapy. The identification of pathways to recovery also shows the way for novel therapeutic targets ultimately benefiting all cardiac patients. However, the road ahead towards definite evidence and practical application remains long and winding.

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