Reversible dilated cardiomyopathy: into the thaumaturgy of the heart - Part 1

Giovanni Quarta,¹ Raffaele Coppini,²
Pier Lambiase,³ Pablo Garcia-Pavia,⁴
Alice Calabrese,¹ Anna Maria Iorio,¹
Niccolò Maurizi,⁵ Maria Iascone,⁶
Antonello Gavazzi,⁷ Iacopo Olivotto,⁵
Michele Senni¹

¹Cardiovascular Department, Papa Giovanni XXIII Hospital, Bergamo, Italy;

²Department of Preclinical and Clinical Pharmacology and Center of Molecular Medicine, University of Florence, Florence, Italy; ³Institute of Cardiovascular Science, University College and Bart's Heart Centre, Bart's Health NHS Trust, London, UK; ⁴Heart Failure and Inherited Cardiac Diseases Unit, Department of Cardiology, Puerta de Hierro University-Hospital, Madrid, Spain; ⁵Referral Center for Cardiomyopathies, Careggi University-Hospital, Florence, Italy; ⁶Medical Genetics Lab, Papa Giovanni XXIII Hospital, Bergamo, Italy; ⁷Research Foundation (FROM), Papa Giovanni XXIII Hospital, Bergamo, Italy

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 first part will deal with Tako-Tsubo cardiomyopathy, tachycardia-induced cardiomyopathy, metabolic DCM and recovery after Left ventricular assist device implantation. 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.

Introduction

Dilated cardiomyopathy (DCM) is a genetic or acquired heart muscle disorder characterized by dilation and impaired contraction of one or both ventricles.¹ 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, deriving from intrinsic reparative processes, natural history of the underlying conditions and medical or device-based invasive therapy (such as resynchronization therapy). 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. In this two-part review we will focus on the most common types of reversible DCM, with special emphasis on etiology and etiopathogenesis.

Tako-Tsubo cardiomyopathy

Tako-Tsubo cardiomyopathy (TTC) is an emblematic example of reversible DCM (Table 1). TTC, also known as apical ballooning syndrome or stress-induced cardiomyopathy (as well as more than 70 additional names²) is characterized by transient LV systolic dysfunction, usually affecting the apical or mid-apical segments, mimicking an acute coronary syndrome but without evidence of coronary artery disease, producing a balloon-like appearance of the distal ventricle in systole. Reverse or inverted Tako-Tsubo,³ right ventricular Tako-Tsubo,⁴ mid-ventricular Tako-Tsubo,⁵ focal mid-ventricular apical ballooning⁶ and global hypokinesis⁷ have also been described as atypical forms. TTC was first described in Japan in 1990 arousing clinical and research interest with over 300 publications in the past 20 years.⁸

Most patients are post-menopausal women. TTC is present in all ethnicities, with preva-

Correspondence: Giovanni Quarta, Cardiovascular Department, Papa Giovanni XXIII Hospital, piazza OMS 1, 24127 Bergamo, Italy.
Tel.: +39.035.267.4346 - Fax: +39.035.267.4965.
E-mail: gquarta@asst-pg23.it

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lence in Caucasians and few cases in African Americans and Hispanics. Recent estimates indicate that approximately 1-3% of all admissions classified as acute coronary syndrome are TTC.⁹ Symptoms can usually be managed with β -blockers, and angiotensin receptor blockers if needed. Historically, prognosis has been considered benign,¹⁰ albeit with an up to 11% risk of recurrence over 4 years.¹¹ Overall long-term mortality rate ranges from 0 to 17%, cardiovascular mortality from 0 to 7%.¹² TTC is a truly reversible disease, as LV ejection fraction returns to normal within 4-6 weeks from the onset in the majority of patients (reported as high as 96%¹¹). At a cellular level, functional and structural changes are also almost completely reversible in time-frame leading to normalization of LV ejection fraction.¹³ However, a large study involving 249 patients followed for 4.7 years, has shown that TTC is not as benign as previously believed, with 19% experiencing early complicated clinical course (including a 3% in-hospital mortality) and a standardized mortality ratio of 1.4 ($P=0.005$) compared to the general US population.¹⁴ Thrombotic milieu has been observed in 5% of patients, with multiple LV thrombus formation due to blood stasis from left ventricular dysfunction

and adrenaline vasoconstrictive, platelet activating and pro-thrombotic effects.¹⁵ Sporadic left ventricular rupture has been described.¹⁶

Emotional and physical stressful events are typical triggers of TTC, although in one third of patients no trigger is found. In this situation diagnosis may be more difficult. Several studies suggest a role of genetics¹⁷ and familial cases have been reported.^{18,19} Polymorphisms in β_1 , β_2 or α_2 adrenergic receptors, as well as in the G-protein coupled receptor kinase 5, have been associated with the disease in some studies,^{20,21} but this association has been disputed by other studies.^{22,23} Ultimately, the pathogenesis of TTC is likely multifactorial: direct toxic effect of catecholamines on the myocardium, epicardial coronary artery spasm, microvascular impairment, oxidative stress and estrogen deficiency all may be involved and superimposed on a genetically susceptible milieu. Catecholamine activation of α - and β -adrenoceptors has been proposed as the primary trigger of TTC; indeed epinephrine and norepinephrine levels have been found to be high during the acute phase of TTC, up to 2-3 times higher than those of patients with acute myocardial infarction.²⁴ Catecholamine-mediated stunning of myocardium may occur *via* a number of mechanisms, including mid-ventricular obstruction, coronary spasm, microvascular dysfunction and direct toxic effects on cardiomyocytes. Specifically, there is now evidence suggesting that LV dysfunction may be related to oxidative stress in response to catecholamine overload.²⁵

Excessive β -2-adrenoceptor activity (*i.e.*, due to exceptionally high circulating epinephrine levels) has been postulated as the main determinant of TTC, leading to cardiomyocyte injury through calcium leakage due to hyperphosphorylation of the ryanodine receptor.²⁶ Predominant apical involvement has been explained by a denser concentration of adrenoceptors (and in particular β -2-receptors) in the apex as compared with the basal segments of the LV, as ascertained by experiments in canine heart.²⁷ In a rat model, the injection of high-dose epinephrine, but not norepinephrine, produced the reversible apical depression of myocardial contraction, coupled with basal hypercontractility, typical of Tako-Tsubo cardiomyopathy.²⁸ Interestingly, this effect was prevented *via* inhibitor G-protein (G(i)) inactivation by pertussis toxin pretreatment. High-dose epinephrine was in fact able to induce direct cardiomyocyte cardiodepression *via* the alternative signaling pathway associated with β (2)AR receptors, *i.e.*, the G(i)-dependent pathway. At very high concentrations, epinephrine selectively favors the activation of the G(i) pathway of the beta-2 receptor, while it preferably activates the β (2)AR-G(s) excitatory pathway at lower concentrations. Such epinephrine-specific β (2)AR-G(i) signaling may

have evolved as a cardioprotective strategy to limit catecholamine-induced myocardial toxicity during acute stress.

Transient coronary artery spasm leading to transient myocardial stunning was proposed as the main mechanism of TTC 20 years ago.²⁹ Prolonged spasm in multiple coronary arteries induced by both hyperventilation and provocative tests was reported in TTC.^{30,31} However, in one study this mechanism was present in less of one-third of patients,³² ruling out its role as the main mechanism of myocardial depression in Tako-Tsubo. Finally, TTC is largely a disease of postmenopausal women but the reason for such predominance is mostly unknown. Estrogen hormones appear to be clearly protective in animal models, while the cardiodepressive effects of catecholamine-excess are exacerbated in ovariectomized animals.³³ Myocytes express alpha and beta estrogen receptors. Estrogens increase production of cardioprotective factors such as AN, heat shock proteins, and protect the heart from toxic effects of catecholamine, calcium overload and oxidative stress.³⁴ This suggests that postmenopausal women may lose the protective effect of estrogens, becoming more susceptible to circulating catecholamines.

There is no universally accepted diagnostic definition of TTC. The most commonly used criteria are the Mayo Clinic proposed criteria, reviewed in 2008:³⁵ i) transient hypokinesia, akinesia, or dyskinesia of the mid left ventricle with or without apical involvement that extends beyond the distribution of a single vascular territory; ii) absence of obstructive coronary artery disease; iii) new electrocardiographic abnormalities (either ST-segment elevations or t wave inversions) or modest elevation in cardiac troponin; iv) absence of pheochromocytoma or myocarditis. The most difficult differential diagnosis involves ACS and myocarditis. Cardiovascular magnetic resonance (CMR) may help in differential diagnosis. Eitel *et al.*³⁶ reported CMR-based criteria for the diagnosis: i) severe LV dysfunction in a noncoronary regional distribution pattern; ii) myocardial edema co-located with the regional wall motion abnormality; iii) absence of high-signal areas in late gadolinium enhancement images; and iv) increased early myocardial gadolinium uptake. The confirmative criterion (with >4-week follow-up) for all diagnostic criteria is complete or near-complete resolution.

TTC has no specific treatments, as no randomized double blind study has been performed. Management of TTC is based only on experts' opinion. If cardiogenic shock is present, standard heart failure care is needed. Intra aortic balloon pump should be used with caution as it reduces afterload and may increase left ventricular outflow tract obstruction (LVOTO). For the same reason, diuretics should be used with caution. Levosimendan could be

used for its inotropic and vasodilator effects. Nitrates should be avoided. In case of suspected vasospasm, verapamil or diltiazem can be added. Angiotensin-converting-enzyme (ACE) inhibitors are safe. Sympathomimetic drugs should be avoided. Given the findings in the animal model, treatment with a combined alpha and beta-blocker seems rational. In case of LVOTO, β -blockers and α -agonist (phenylephrine) and volume expansion are suggested. There is no consensus on estrogen therapy. Since apical ballooning increases the risk of cardiac rupture, it is still controversial whether treatment with aspirin or heparin is indicated. The fact that epinephrine promotes platelet activation by stimulating platelet α_2 adrenoceptors provides additional rationale for treatment with a combined α and β -blocker. There is no consensus regarding long-term management with ACE inhibitors or β -blockers or other therapies to prevent recurrence of TTC.^{37,38}

Tachycardia-induced cardiomyopathy

Tachycardia-induced cardiomyopathy (TIC) is an insidious, under-recognized and treatable cause of cardiomyopathy, which may affect structurally normal hearts or exacerbate a pre-existing cardiomyopathy (Table 1, Figure 1). Poorly controlled atrial tachy-arrhythmias - most frequently atrial fibrillation, frequent ventricular ectopic beats and persistent rapid ventricular pacing - are the commonest causes of TIC. In addition, thyrotoxicosis can induce cardiomyopathy mediated by sustained tachycardia, but additional mechanisms are also involved.³⁹ TIC can also occur in patients with automatic atrial tachycardia, atrioventricular nodal re-entry tachycardia, permanent reciprocating junctional tachycardia (PJRT), and accessory pathway tachycardia. TIC is classically defined as the reversible impairment of ventricular function induced by persistent arrhythmias. However, it is becoming increasingly evident that deterioration in LV function may also be caused by frequent atrial and ventricular ectopy promoting dyssynchrony.^{40,41} Thus, a more current definition of TIC is the following: *Atrial and/or ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction, partially or completely reversed after treatment of the causative arrhythmia.*⁴² An important element in the definition of true TIC is the exclusion of underlying structural heart disease, since LV dysfunction is totally reversible in TIC as opposed to structural heart disease. To date, the rate of persistent SVT likely to cause LV impairment remains unclear. A threshold of sustained tachycardia >130 bpm seems to be consistently associated with TIC although direct compar-

isons of heart rates in arrhythmic patients with and without TIC show considerable overlap. Thus, besides heart rate, the duration and persistence of tachycardia seems to be an important determinant.⁴³ TIC can occur at any age. It has been documented in fetuses (24 to 33 weeks in gestation) with persistent supraventricular tachycardia,⁴⁴ with resolution occurring following intrauterine cardioversion. It also occurs in infants and children, adolescents and adults. The incidence of tachycardia-induced cardiomyopathy is unknown; most reports have been small retrospective series or case studies involving mostly patients with atrial fibrillation. In children, 18% of PJRT cases had TIC.⁴⁵ In patients with atrial fibrillation, approximately 25% to 50% of those with left ventricular dysfunction in selected studies have some degree of tachycardia-induced cardiomyopathy. Presumed risk factors include the type, rate, and duration of tachyarrhythmia, and underlying heart disease. The mechanisms of TIC are not fully defined but include subclinical ischemia, abnormalities in energy metabolism, redox stress and calcium overload.^{46,47} In animal models of high-rate atrial or ventricular pacing, ventricular impairment is also associated with changes in myocardial electrophysiology including prolongation of the action potential

Figure 1 and online Videos 1-2. Cardiovascular magnetic resonance steady-state free precession cine still frames (diastole top panels, systole bottom panels), showing poor left ventricular (LV) function in a 35-year old patient with new onset atrial fibrillation (AF) and congestive cardiac failure (left panels, Video 1) and recovery of LV function 3 months post AF ablation with maintenance of sinus rhythm (right panels, Video 2) (Courtesy by Professor Richard Schilling, Bart's Heart Centre, London, UK).

Table 1. Reversible dilated cardiomyopathies.

Disease	Diagnosis	Etiology	Incidence	Recovery	Prognosis	Specific therapy
Tako-Tsubo CMP	<ul style="list-style-type: none"> - Transient hypokinesis, akinesis, or dyskinesis of the mid left ventricle with or without apical involvement that extends beyond the distribution of a single vascular territory - Absence of obstructive coronary artery disease - New electrocardiographic abnormalities (either ST-segment elevations or t wave inversions) or modest elevation in cardiac troponin - Absence of pheochromocytoma or myocarditis³⁵ 	<ul style="list-style-type: none"> - Direct toxic effect of catecholamines - Epicardial coronary artery spasm - Microvascular impairment - Oxidative stress - Estrogen deficiency - Genetically susceptible milieu 	Around 1-3% of acute coronary syndrome ⁹	Up to 96% ¹¹	<ul style="list-style-type: none"> - Long-term mortality from 0 to 17%¹² - CV mortality 0-7%¹² - 11% recurrence over 4 years¹¹ 	<ul style="list-style-type: none"> - β-blockers and angiotensin receptor blockers are cornerstone - Diuretics should be managed with cautions - Nitrates and sympathomimetic drugs should be avoided
Tachycardia induced CMP	<ul style="list-style-type: none"> - Atrial and/or ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction, partially or completely reversed after treatment of the causative arrhythmia⁴² 	<ul style="list-style-type: none"> - Persistent atrial tachycardia or accessory pathway mediated supraventricular tachycardias - Atrial fibrillation with poor HR control - Frequent PVCs - Persistent rapid atrial/ventricular pacing - PJRT - Ventricular tachycardia - Inappropriate sinus tachycardia (rare) 	Largely unknown 10% in pts with focal atrial tachycardia ⁴⁷ 18% in children with PJRT ⁴⁵	Largely unknown 97% 3 months after atrial tachycardia ablation ⁴⁷	<ul style="list-style-type: none"> - Depending on the rate and duration of the precipitating arrhythmia - Sudden cardiac death cases have been described³⁹ 	<ul style="list-style-type: none"> - Aggressive HR control - Catheter ablation when possible

CMP, cardiomyopathy; CV, cardiovascular; HR, heart rate; PVCs, premature ventricular ectopics; PJRT, permanent junctional reciprocating tachycardia.

and spontaneous ventricular arrhythmias. Furthermore, persistent left bundle branch block leads to lateralization of gap junctions promoting functional anisotropy and apoptosis.⁴⁸ This can be reversed by left ventricular pacing in heart failure models. Studies performed in animal models shed some light on the pathophysiology of TIC. In response to rapid pacing in animals, LV remodeling and heart failure occur in a time-dependent predictable manner. During the early phase (3 to 7 days), LV dilation occurs and ejection fraction declines.³⁹ This early remodeling phase is adaptive and is not paralleled by reduction in cardiac output or systemic perfusion. By the second week, however, both an increase in central venous and pulmonary capillary wedge pressures and systemic vasoconstriction occur,³⁹ followed by symptoms of heart failure. A number of cellular and molecular events in response to the high ventricular rates occurs during a period of approximately 3 to 4 weeks and involve both extracellular matrix and myocyte remodeling. The normal architecture of the extracellular matrix is gradually lost, paralleled by alterations in cellular growth and viability, defects in Ca²⁺ handling, and neurohormonal activation, ultimately causing LV dilation and contractile dysfunction.

Of note, another hallmark of TIC is the activation of sympathetic pathways, resulting in norepinephrine excess and hyper-activation of the renin-angiotensin-aldosterone system.⁴⁹ Clinical and animal studies have documented the resolution of signs and symptoms of heart failure and the progressive recovery of LV dysfunction following termination of the causal arrhythmia. In several large animal models of pacing-induced cardiomyopathy, the end of rapid pacing leads to significant improvement of LV function and normalization of neurohormonal activation.⁵⁰ In 75 patients with cardiomyopathy caused by frequent premature ventricular ectopics, LV ejection fraction normalized in 5±6 months following successful transcatheter ablation.⁵¹ However, in patients with long-standing tachycardia-induced cardiomyopathy, echocardiographic evaluations following resolution of the causal arrhythmia showed persistence of elevated stroke volumes and LV end-systolic and end-diastolic volumes, as well as diffuse fibrosis at contrast magnetic resonance imaging, suggesting persistent maladaptive remodeling.^{52,53}

A common cause of TIC is persistent atrial tachycardia or accessory pathway mediated supraventricular tachycardias. These are eminently amenable to ablation and there are a number of pediatric and adult case series highlighting the benefits of treatment.⁵⁴⁻⁵⁶ In one study examining atrial tachycardia induced cardiomyopathy, the incidence of TIC was 10%. After successful ablation, LV function was restored in 97% of patients at a mean of 3

months.⁵⁷ TIC may manifest months to years after the onset of the responsible tachycardia, but because TIC is a rate dependent cardiomyopathy, those patients with higher tachycardia rates develop TIC earlier.⁴⁶ Time to onset of ventricular dysfunction is also dependent on the presence of an underlying structural heart disease. Other factors include the type and duration of tachyarrhythmia, the patient's age, drugs, and coexisting medical conditions.⁴¹ Conversely, the role of AF remains debated. Although it is undoubtable that rapidly conducted AF may promote heart failure,⁵⁸ dissecting whether this is due to underlying structural heart disease or the lack of atrial transport and rapid ventricular rates in their own right is difficult. Randomized studies of AF ablation in structurally normal hearts do demonstrate positive effects on left ventricular remodeling once sinus rhythm is re-established over and above pure rate control using atrioventricular node ablation and cardiac resynchronization therapy.^{59,60} The use of the latter approach confounds the dissection of pacing effects from atrial transport but points to the fact that restoration of sinus rhythm is an important determinant of LV recovery is maintained long-term. Patients most likely to achieve *rhythm control* by ablation are those without evidence structural heart disease. Patients with a short history of symptoms coinciding with the onset of AF appear to have the highest chance of success using this approach, although large randomized controlled trials are required to address this issue formally.

Another area of much investigation and debate is the role of ventricular ectopy in promoting LV dysfunction. This issue has been addressed by several studies examining the relationship of ventricular ectopic (VE) burden and LV impairment.^{61,62} A recent study identified a 13% VE burden per 24 h, which equates to approximately 30,000 ectopic beats, as critical in determining TIC. Interestingly, transcatheter ablation in patients with >13% baseline VE burden predicted improvement in LV ejection fraction with 100% sensitivity and 85% specificity, regardless the evidence of structural heart disease.⁶² A recent trial examining the outcome of VE ablation identified patients with a 22% VE threshold as most likely to improve their LV function following a successful procedure.⁶³ The question of whether to ablate asymptomatic monomorphic VEs when the burden is in this range should be discussed carefully with the patient as the procedure, particularly in the right ventricular outflow tract, does carry a small but important risk of tamponade (<1%) and even death. Since VE ablation restores normal LV function in structurally normal hearts anyway, a pragmatic approach is simply to monitor the patient for signs of LV impairment and only intervene should LV function deteriorate. Conversely,

isolated VEs have an excellent prognosis in normal hearts with preserved function and may be managed conservatively. Recently, Bhushan and Asirvatham have proposed diagnostic criteria for VE-induced cardiomyopathy. They suggest that otherwise young healthy individuals, without abnormal cardiovascular substrate having over 20,000 VEs per day, with no more than two morphologies, originating from outflow tracts or from the fascicles and with preserved myocardial wall thickness are the best candidates for presumption of VE-induced cardiomyopathy.⁴⁷

Metabolic dilated cardiomyopathy

Nutritional deficiency, electrolyte and endocrinological disturbances can be causes or contributors to dilated cardiomyopathy.¹ Examples are: thiamine deficiency (Beri-Beri), zinc and copper deficiency (as possible contributors to DCM), selenium deficiency, carnitine deficiency (especially in pediatric population); hypo- and hyper-thyroidism, Cushing or Addison disease, phaeocromocytoma, acromegaly, diabetes mellitus, iron overload (secondary to transfusions or hemochromatosis). It is therefore of paramount importance to recognize these unbalances with specific tests as correcting them in timely fashion may completely reverse LV systolic dysfunction.

Left ventricular assist device recovery

An interesting model of LV systolic dysfunction is recovery described in some patients after left ventricular assist device (LVAD) implantation. It has been proposed by the group of Yacoub that prolonged unloading of the myocardium with LVAD can lead to myocardial recovery.⁶⁴ They studied 15 patients with severe heart failure due to nonischemic cardiomyopathy and with no histologic evidence of active myocarditis. Among those patients, 11 (73%) had sustained LV function recovery after a combination of LVAD and full pharmacologic support including β₂-adrenergic-receptor agonist clenbuterol (at a mean follow-up of 59±5 months, the mean left ventricular ejection fraction (LVEF) was 64±12%, compared to 12±6% before LVAD implantation). They suggested that LVAD could facilitate reverse remodeling through LV mechanical unloading, and subsequent reduction in neuroendocrine activation and myocyte hypertrophy. In order to explore the possible molecular pathways involved in LV recovery, the same group used

microarray analysis on six paired human heart samples harvested at the time of LVAD implant and at the time of LVAD explant. They found a significant association of integrin pathway signaling with recovery and the identification of several novel targets, in particular in the cAMP pathway.⁶⁵ This initial evidence was confirmed by a larger study involving 80 consecutive LVAD patients, although lower recovery rate was reported (after 6 months 19% of the study population had LVEF ≥ 40).⁶⁶

Reverse remodeling seen in patients with LVAD is associated with favorable morphological changes in myocytes, interstitium and microvessels.⁶⁷ Several animal and clinical studies have investigated myocyte changes following LV unloading from LVAD and have documented regression of cardiac hypertrophy,⁶⁸ some suggesting to a point of myocardial atrophy.⁶⁹ Diakos *et al.*⁷⁰ have prospectively assessed morphological myocardial changes in 44 LVAD patients. They found regression of cardiomyocyte size, but not beyond that of normal donor hearts. In addition, electron microscopy ultrastructural evaluation and echocardiographic assessment of LV mass did not show evidence of myocardial atrophy. In LVAD patients, there is improvement in dystrophin expression, which is impaired in severely dysfunctional LV, and it is important for myocyte sarcolemma integrity.⁷¹ Unloaded ventricles show decrease in polyploid and myocyte DNA content and increase in binucleated myocyte,⁷² suggesting a possible proliferation of stem cells or cardiomyocyte duplication and regeneration. There is conflicting evidence on the effects of LVAD on extracellular matrix, with some studies showing decreased,⁷³ others increased⁷⁴ fibrosis. Using digital histopathology and advanced image analysis techniques, Drakos *et al.*⁷⁵ showed that collagen content is increased in LVAD patients, reflecting a complex changes in neurohormonal milieu.⁷⁶ In addition LVAD unloading results in changes in gene expression involved in the regulation of vascular organization and migration, endothelial activation and increased small vessels density. More recently, miRNAs differential expression thorough next generation sequencing has been studied in LVAD patients,⁷⁷ showing involvement of specific miRNAs in focal adhesion/integrin pathway and in actin cytoskeleton regulation.

In summary, LVAD recovery represents a formidable model for studying the mechanism of LV function recovery, from a clinical, histopathological and molecular point of view, and may be useful to understand also other diseases' pathological processes, becoming potential targets for therapeutic interventions.

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