Update in cardiomyopathies and congestive heart failure
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What is the role of cardiovascular magnetic resonance in the differential diagnosis of cardiomyopathies?

The approach to the cardiomyopathy work-up is systematised. Diagnosis is based on history, clinical examination, electrocardiography, chest radiograph, and blood tests (including B type natriuretic peptides and genetic testing). Imaging in cardiomyopathy is challenging and requires a multimodality approach. Echocardiography is the first-line investigation for assessment of cardiac anatomy, function, and dynamics. However, it is limited by inconsistent image quality in some patients and gives very little information about tissue characteristics. Cardiovascular magnetic resonance (CMR) provides additional incremental data in patients with cardiomyopathies helping to determine aetiology, detecting phenocopies, aiding prognosis and predicting response to and selecting therapy. In the last 10 years, CMR has emerged as a gold standard test for myocardial anatomy and function. There are also the key advantages of perfusion and tissue characterisation (Figure 1). Tissue characterisation may detect either intrinsic myocardial abnormalities such as fatty infiltration, inflammation (myocarditis or oedema in acute infarct area at risk) or iron infiltration. The addition of a contrast agent permits, in the first pass, myocardial perfusion assessment, with early imaging (1 to 3 min) of regions of reduced vascularity (including microvascular obstruction – the tissue equivalent of no-reflow, and thrombus). Late imaging (5 min onwards) after gadolinium administration allows detection of late gadolinium enhancement (LGE) areas, that is areas of focal infiltration, scar/amyloid or fibrosis interstitial expansion. Different patterns of enhancement have been reported according to the underlying aetiology and LGE CMR has become a first-line non-invasive exam for the etiologic assessment of new onset myocardial dysfunction. Evaluation of heart muscle disease (including myocarditis) is currently the leading referral reason for CMR internationally, although stress perfusion is rapidly overtaking. At current referral levels, CMR impacts on management in two thirds of patients and in 16% a new cardiac diagnosis may be made.

What is the role of scar imaging (late gadolinium enhancement) in determining the prognosis of cardiomyopathies?

Scar imaging (LGE) has pushed our ability to accurately and precisely analyze myocardial tissue composition, especially fibrosis. Fibrosis has an increased volume of distribution for contrast and a prolonged washout related to the decreased capillary density within the myocardial fibrotic tissue so focal areas of scar appear bright. LGE may be considered either as presence/absence, or the extent can be quantified – the better technique, even though consensus is not fully achieved about the optimal LGE quantification technique. Across the spectrum of heart muscle disease, the presence of LGE is associated with adverse outcomes and the lack of LGE the potential for recovery of function. In dilated cardiomyopathy, the presence of myocardial LGE is associated with a 3-fold increase of hospitalization for heart failure or cardiac death and a 5-fold increase of sudden cardiac death or ventricular arrhythmias. In hypertrophic cardiomyopathy LGE is associated with the presence of risk factors for sudden death and with the presence of known arrhythmia. In prospective studies, LGE strongly predicts heart failure, and in one

![Figure 1. Cardiovascular magnetic resonance is a multiparametric imaging modality, providing information on 3D structure and function, presence of ischemia and tissue characterisation (as presence of oedema or fibrosis).](image-url)
study, was a univariate predictor of serious arrhythmia, but in multivariate analysis, the presence of non-sustained ventricular tachycardia was the stronger risk factor (Figure 2). It remains unclear how LGE as a risk factor fits into conventional risk factors. LGE predicts adverse outcome in a range of other conditions such as cardiac amyloidosis (where the LGE represents amyloid fibrils rather than fibrosis), hypertensive\(^4\) and diabetic\(^5\) patients free of any cardiac symptoms and with preserved ejection fraction. Finally, LGE may predict response to therapy or offer insight into therapeutic targeting. For example, using LGE to define a dilated cardiomyopathy phenotype, excluding mimicking ischaemic heart disease improves gene:phenotype correlation;\(^6\) and using scar may predict response to resynchronisation or anti-heart failure therapy.\(^7\)

What is the role of cardiovascular magnetic resonance in the assessment of coronary artery disease (scar, perfusion, differential diagnosis with myocarditis)?

The use of CMR in ischaemic cardiomyopathy helps to confirm the underlying aetiology, risk stratification and guide targeted invasive therapy such as revascularisation or resynchronisation.

Left ventricular dysfunction secondary to coronary artery disease typically is either reversible as in states of ischaemia/hibernation, or irreversible, as in transmural myocardial infarction.

Myocardial infarction causes a characteristic LGE pattern due to the wavefront of myocardial necrosis, beginning in the subendocardium and spreading through the wall depending on the severity of the infarct. LGE transmurality predicts potential functional recovery but with a grey-zone of 50% transmural infarction recovery with revascularisation it is more difficult to predict.\(^8\) The identification of viable (dark on late gadolinium imaging) myocardium in a patient with regional or global left ventricular systolic dysfunction in the setting of ischaemic heart disease can represent hibernation, stunning, dilated cardiomyopathy, or dyssynchrony.\(^9\) Such myocardium may recover functionally with time (stunning), revascularisation (hibernation), resynchronisation, or with medical therapy (such as beta-blockers).\(^10\)

Ischaemia testing can be performed with adenosine perfusion CMR (ischaemia will appear as a stress perfusion defect compared with rest) or dobutamine-CMR (ischaemia will result in a changed regional function).

Evaluation of ischemia should then be combined with the viability assessment and revascularization strategies could be guided by presence of ischemia in viable territories.

In patients presenting with chest pain and electrocardiogram/biomarkers suggesting myocardial infarction, but a non-explanatory coronary angiogram, myocarditis is the most important differential diagnosis; whilst other patients may have flush side-branch occlusion. One recent study found that 60% of patients presenting in this manner had myocarditis.\(^11\) In patients with myocarditis specific CMR sequences will show areas of acute inflamma-

![Figure 2](image1.png)

**Figure 2.** A 31-year-old asymptomatic male with hypertrophic cardiomyopathy (HCM) but with a family history of sudden cardiac death and one single episode of 3 beats of non-sustained ventricular tachycardia 6 years previously. The echo (panel A) showed features of HCM. The cardiovascular magnetic resonance confirmed the hypertrophy (panel B, cine images) and showed extensive late gadolinium enhancement (LGE) (panel C) in a non-ischemic distribution. The presence of LGE strongly predicts heart failure and in this case precipitated re-discussion/re-evaluation and ultimately implantable cardioverter defibrillator implantation.

![Figure 3](image2.png)

**Figure 3.** The scar pattern [late gadolinium enhancement (LGE)] differentiates myocardial infarction (left panels), where the LGE is subendocardial and spreads through the wall, from myocarditis where the LGE distribution is in the mid or subepicardial layers (right panels).
tion and LGE will identify areas of necrosis or severe oedema. The myocarditis LGE distribution in the mid or subepicardial layers is different to myocardial infarction, where the LGE pattern, due to the wavefront of myocardial necrosis, begins in the subendocardium and spreads through the wall12 (Figure 3), and is commonly found even without regional wall motion abnormalities so tissue characterisation using CMR is the only noninvasive method for making the diagnosis.

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Cardiac resynchronization therapy: questions and answers

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When to implant an automated implantable cardioverter-defibrillator in arrhythmogenic right ventricular cardiomyopathy?

The indications for automated implantable cardioverter-defibrillator (AICD) implantation in arrhythmogenic right ventricular cardiomyopathy (ARVC) are primarily informed by 2 large studies of outcomes in patients undergoing implantable cardioverter-defibrillator (ICD) implantation lead by Corrado and his collaborators. The studies were designed to evaluate whether ICD implantation actually reduces mortality and hence evaluated ICD therapies for ventricular fibrillation (VF) as a surrogate of sudden death as opposed to ventricular tachycardia (VT) therapy alone. A number of risk factors were examined including inducibility of VT at electrophysiologic (EP) study. In a cohort of patients which included patients with prior cardiac arrest or VT, it was evident that VT inducibility did not predict sudden death (i.e., VF events) with a positive predictive value of 49%, negative predictive value of 54%. Independent predictors of sudden death were prior cardiac arrest, VT with haemodynamic compromise, left ventricular involvement and presentation at a young age. In a separate cohort without prior sustained VT or VF, VT inducibility at EP study was still not predictive of life-saving AICD therapy, neither was family history of sudden death, only a prior history of syncope was predictive.2

Therefore, the risk of sudden death in ARVC patients can be stratified on 3 levels as low, intermediate and high. The lowest risk group have event rates of <1% per year and includes asymptomatic individuals who satisfy task force criteria for ARVC with no history of syncope or left ventricular impairment and hence an AICD is not indicated. The high-risk groups have event rates of 8-10% per year and include those with prior VF arrest, haemodynamically compromising VT and syncope and would clearly benefit from AICD prophylaxis. The intermediate group present the major dilemma and at this stage given the limited data available the implantation of an AICD should be individualised-patients with non-sustained VT on Holter or asymptomatic sustained VT have a sudden death rate of 1-2% per annum whilst in those who are asymptomatic with early onset structural disease age <35 years or severe right/left ventricular involvement, the event rates are unknown. The risk:benefit ratio of an AICD needs to be carefully weighed in such individuals as there are issues related to long term lead complications, perforation, inappropriate shock therapy plus the additional risks of sepsis with multiple generator changes. The emergence of subcutaneous ICD systems may mitigate the long term intravascular lead issues in the future, but at this stage such patients in the intermediate group need to be monitored carefully for symptoms of syncope and disease progression and the risk: benefits of AICD carefully explained to tailor therapy.

What is the role of cardiac resynchronization therapy in non-ischemic cardiomyopathies?

Cardiac resynchronization therapy (CRT) is primarily of benefit in non-ischemic cardiomyopathy patients with typical left bundle branch block and ejection fraction <35%. This has been borne out by a number of randomised controlled trials illustrating reductions in heart failure hospitalisations, mortality and left ventricular remodelling including CARE-HF, Companion, MADIT-CRT.3-5 A significant reverse remodelling effect in non-ischemic cardiomyopathy patients with class II symptoms of heart failure and QRS duration of >150 ms was clearly demonstrated in the MADIT-CRT and REVERSE trial of patients with mild heart failure symptoms.4 Therefore, there is an emerging role to consider CRT in the prevention of left ventricular dilatation before heart failure symptoms progress. This has been acknowledged in the recent European Society of Cardiology guidelines recommending CRT in patients, left bundle branch block, QRS >150 ms in sinus rhythm and ejection fraction <35% on optimal medical therapy. The reverse remodelling effect was strongly concordant with the development of death or a heart failure event and suggests a compelling cardiac structural and functional mechanism by which CRT therapy improves outcomes. These latter data applied to dilated cardiomyopathy patients. In the hypertrophic cardiomyopathy population recent small studies have examined the effect of CRT on exercise tolerance and outflow tract obstruction.6 These demonstrated reductions in left ventricular outflow tract gradients and some evidence of regression of hypertrophy although this needs to be examined in a formal randomised controlled clinical trial.

Can we improve response rate in patients undergoing cardiac resynchronization therapy?

The main limitations in improving CRT response rates are related to the ability to deliver a pacing lead to the site of latest contraction in viable myocardium and ensure that the activation wave front induced by pacing engages the left ventricular wall and optimally synchronises the ventricles. This will also depend upon the recruitability of the myocardium and its contractile reserve. Simple ways to improve CRT responses include optimising antiventricular delays to maximise diastolic left ventricular (LV) filling and altering interventricular timing may be beneficial in certain cases. However, a major barrier remains lead delivery via the coronary venous circulation. This has improved recently with lower calibre leads to enter smaller venous branches and the development of multi-polar leads to electrically re-position the lead in cases of phrenic capture.

There are further emerging strategies to potentially improve CRT responses. Small series indicate that endocardial pacing can produce greater haemodynamic benefits than epicardial pacing. This strategy offers the advantage of being able to position the LV lead anywhere within the ventricle and by recruiting the Purkinje network offering more physiological rapid myocardial recruitment. The current disadvantages of this approach are the concerns related to risk of left sided valvular endocarditis with potentially more devastating consequences than right sided sepsis, the technicalities of simple lead placement (transseptal puncture and lead steering systems) and the requirement for long term anticoagulation post implant. There is also emerging data that dual site LV epicardial pacing offers advantages over single site LV CRT offering
the opportunity to recruit more regions of the LV simultaneously as opposed to relying on myocardial conduction from one pacing site to activate a remote region, which may be prevented by a line of functional or structural block. The development of multipolar leads may mean that 2 or more LV multipolar leads could be implanted in a single patient—significantly increasing the range of pacing options available to improve haemodynamics.

Finally, there is new technology utilising leadless pacing electrodes that could be implanted endocardially and employed to pace a site of choice in the LV endocardium without the attendant issues of lead interference with valvular apparatus or difficult lead placement. Improved cardiovascular magnetic resonance (CMR) imaging of the LV to define tissue viability and contractility will enable optimal sites to pace to be identified employing computational modelling of predicted responses. Significant technical developments are still emerging in the CRT field such that one day in the near future a pre-operative work-up involving CMR/echocardiographic 3D imaging would identify the optimal site(s) to pace and a leadless pacing electrode delivered to produce the maximal haemodynamic response tailored to the individual patient.

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Genetics, management and risk: questions and answers

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**Question 1: Do genetics have a role in the diagnosis of cardiomyopathy?**

Cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertensive, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality. Thus, in the clinical setting, the initial diagnosis of cardiomyopathy relies not on genetic information, but instead an assessment of cardiac morphology and function. However, the fact that similar or identical phenotypes can be caused by a spectrum of genetic and non-genetic diseases means that genetic testing does have an important role in determining the underlying cause of cardiomyopathies and, by inference, their management.

Whenever offering genetic testing it is important to define the purpose of the test; i.e. diagnosis, management of proband or screening/management of family members. It is also important to consider the consequences of a positive (or negative) test for the patient and their family.

For all cardiomyopathies, genetic testing should always be performed by expert teams after detailed clinical and family assessment. Current European Society of Cardiology recommendations for genetic testing include the following clinical scenarios: i) for the diagnosis of a rare or particular cardiomyopathy, especially in the presence of atypical phenotypic features; ii) for predictive diagnosis in asymptomatic relatives of a patient with a cardiomyopathy when the disease-causing mutation has been previously characterised in the family; iii) in the proband of a family (the first or most clearly affected patient with a cardiomyopathy), as a first condition for the proposal of predictive diagnosis within the family; iv) predictive diagnosis in children can be considered at the age at which cardiac examination is useful (10-12 years of age for most cardiomyopathies).

Genetic testing is not routinely indicated for the diagnosis of a borderline or doubtful cardiomyopathy.

Ideally, the genetic testing strategy should be based on an analysis of the family pedigree (pattern of inheritance) and careful phenotyping with particular consideration of the age at presentation, the presence of particular cardiac manifestations (e.g. conduction disease) and a search for extracardiac features suggestive of skeletal myopathy, syndromic disorders or metabolic phenotypes.

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**Question 2: When do we use genetics to guide treatment?**

Genetic testing has the potential to impact on many different aspects of disease management. First and foremost is the prevention of complications by medical intervention and lifestyle adjustments. The long-term ambition (for it remains so at present) is to prevent the development of phenotypes in asymptomatic carriers and to tailor specific therapies in those with manifest disease.

One of the major impediments to the translation of genetic information into therapeutic strategies is the relatively poor understanding of genotype-phenotype relations. In the cardiomyopathy field, further challenges include a high rate of novel sequence variants (30%), uncertain pathogenicity, missed mutations in other genes and technical limitations of current sequencing technologies. Never-theless, even with the current knowledge base, genetic testing can be important in the treatment of specific diseases (for example, some metabolic disorders) and has general utility in advice to families about lifestyle/reproductive choices.

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**Question 3: What are the pitfalls of clinical genetics in cardiomyopathy?**

**Variable disease expression**

In all cardiomyopathies, the expression of genetic mutations can be remarkably heterogeneous, even within the same family. This has many implications for the counseling of families and the genetic testing strategies employed in everyday clinical practice.

**Polygenic disease**

While all cardiomyopathies are inherited in accordance with Mendelian principles, the growing practice of extensive phenotyping in families coupled with the use of high throughput genetic testing strategies, is revealing the coincidence of multiple disease causing mutations in the same class of genes, and sometimes in completely unsuspected genes. This phenomenon may be more common in some phenotypes than others (for example, in arrhythmogenic right ventricular cardiomyopathy). Clinicians need to be alert to this possibility and to exert caution and flexibility when evaluating patients and families.
New frontiers in genetics of cardiomyopathies

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The inherited cardiomyopathies are defined clinically by diagnostic phenotypes e.g. hypertrophic cardiomyopathy (HCM) – left ventricular (LV) hypertrophy, dilated cardiomyopathy (DCM) – LV dilatation and impaired function, arrhythmogenic cardiomyopathy (AC) – arrhythmia with or without ventricular dysfunction. HCM is predominantly caused by mutations in sarcomeric genes, DCM by mutations in myocyte cytoskeletal genes, and AC by desmosomal genes. The discovery of disease causing genes has informed our understanding of these conditions, though specific molecular therapeutic targets remain elusive.

In HCM, a disease of the sarcomere, the myocyte disarray (the pathological hallmark) and LVH (the diagnostic feature) develop as a consequence of heterogeneous force and calcium sensitivity of individual myofibrils with variable concentrations of mutant and wild-type protein. Preliminary genotype-phenotype studies do not suggest clinically useful associations. Disease caused by non-sarcomeric genes accounts for up to 40% of HCM. Fabry-Anderson disease and Noonan syndrome are the commonest phenocopies. The presence of an associated phenotype, e.g. an accessory pathway, conduction disease, retinal or hearing abnormalities or features of a skeletal myopathy, is suggestive of non-sarcomeric disease.

DCM, a disease of the myocyte cytoskeleton, is characterised by a low-grade chronic inflammatory response with myocyte death and fibrous replacement. The presence of organ specific autoantibodies targeted at heart specific alphamyosin is consistent with an autoimmune component of pathogenesis. Within DCM families the presence of the alphamyosin antibody is a weak predictive marker of subsequent disease development. Recognised triggers of the inflammatory process include viral infection, alcohol, fluid overload and pregnancy. In DCM, the clinical presentation is usually with features of heart failure. An arrhythmic presentation with conduction disease, ventricular arrhythmia or a family history of unexpected premature sudden death is usually associated with disease caused by mutations in lamin A/C, SCN5A, or desmosomal genes; in such patients ventricular function is usually normal or near normal or may deteriorate later in the disease course.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is the most recognised form of AC. Recently, predominantly LV forms of ARVC, also caused by desmosomal mutations, have been reported. The finding of a high prevalence of desmosomal variants (up to 15%) in control populations complicates the use of mutation analysis and cascade screening within families, but also indicates the potential for desmosomal gene abnormalities to contribute to arrhythmic phenocopies characterised by electrocardiogram abnormalities and ventricular arrhythmia in the absence of significant LV or right ventricular dysfunction; such patients fall within the designation of arrhythmogenic cardiomyopathy.

To date, the logistics of mutation analysis has limited its clinical application. Genetic testing requires cost effective sequencing platforms, the expertise and informatics infrastructure to interpret sequence variants, and an expert team to deliver the results to families. Rapid changes in sequencing platforms (e.g. next generation sequencing) are demanding the necessary informatics to interpret results, and these improvements in technology should lead rapidly to clinical gene testing becoming a routine component of clinical diagnosis and management of inherited forms of cardiovascular disease.
A COMMON POLYMORPHISM IN SCN5A (CARDIAC SODIUM CHANNEL) GENE IS ASSOCIATED WITH DILATED CARDIOMYOPATHY

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Background: Dilated cardiomyopathy (DCM) is characterized by ventricular dilation and impaired systolic function, which may proceed into congestive heart failure. Up to 50% of DCM cases are reported to be idiopathic (without any obvious aetiological trigger) and approximately 20% of DCM cases display familial prevalence. More than 20 genes are associated with DCM in humans, encoding structural proteins of cardiomyocytes and ion channels. We hypothesized that the p.H558R polymorphism in SCN5A gene could be a genetic risk factor in DCM, as the R minor allele of this polymorphism has been shown to alter SCN5A function, by reducing depolarizing sodium current and modulating the biological effects of concomitant SCN5A mutations.

Methods and Results: We recruited 134 DCM patients (50 with familial DCM - FDCM; 58 with idiopathic DCM and 26 patients affected by post-ischemic DCM) and 168 age, ethnicity, and gender matched controls. The mean age at diagnosis was 45±12 years, with a mean follow-up of 8.2±5.5 years. SCN5A was subject to comprehensive mutation scanning in all cases and to targeted genotyping of a common loss-of-function p.H558R polymorphism in controls. The Hardy-Weinberg law was observed across the three genotypes and categorical variables were compared with 51% of controls. The minor R allele frequency was 42% in controls. The mean age at diagnosis was 45±12 years, with a mean follow-up of 8.2±5.5 years.

Conclusions: Our data demonstrate that mutations in coding regions of SCN5A are not a common cause for DCM; the SCN5A p.558RR genotype is associated with dilated cardiomyopathy in patients with familial DCM. This result may help to early identify candidates to develop DCM among asymptomatic relatives of FDCM patients in families without an identified mutation.

RIGHT HEART MORPHOLOGY AND FUNCTION IN HEART TRANSPLANTATION RECIPIENTS

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Background: The right heart is a major determinant of prognosis in cardiac transplant recipient patients (CT).

Methods: The aim of the study was to investigate right ventricular (RV) morphology and function in CT using standard transthoracic echocardiography and a new three-dimensional (3D) echocardiographic software adapted for RV analysis. 115 stable CT (71 males; 58.3±5.8 years; 7.8±4.5 years after transplantation) and 80 healthy age- and sex-comparable controls underwent standard echocardiography, Tissue Doppler Imaging (TDI) and 3D echocardiography, focused on the RV analysis. Along with left heart parameters, RV measurements included: end-diastolic diameters at basal and mid-cavity level; base-to-apex length, tricuspid annulus plane systolic excursion (TAPSE), RV systolic peak velocity (Sm), and 3D ejection fraction. Using the peak systolic tricuspid regurgitation velocity and the end-diastolic pulmonary regurgitation velocity, the modified Bernoulli equation was used to calculate the pulmonary artery systolic (PASP) and diastolic pressures. Pulmonary artery vascular compliance (PAVC) was finally estimated by LV stroke volume/4 x (TRV2 – pulmonary regurgitation velocity²).

Results: LV diameters and ejection fraction did not significantly differ among the 2 groups, while mass index was increased in CT (P<0.01). RV diameters were significantly increased (P<0.001), while TAPSE and RV Sm were significantly lower in CT. Conversely, 3D RVEF was not significantly impaired in CT (P<0.001). In a subgroup of 20 CT undergoing cardiac magnetic resonance, a close correlation was observed between 3D and magnetic resonance assessment of RVEF (r=0.89; P<0.0001). On the other hand, both PASP and PAVC were impaired in CT. By multivariable analysis, age (P<0.01) and PASP (P=0.001) were the only independent determinants of RV ejection fraction in CT.

Conclusions: Despite the reduction of RV performance along the long axis suggested by TAPSE and RV Sm, the increased RV diameters along with absence of a decrease in 3D RVEF support the hypothesis of geometrical rather than functional changes of RV in CT. Furthermore, altered PASP and PAVC may reflect early pathologic changes in the pulmonary circulation.

LONG-TERM GROWTH HORMONE REPLACEMENT THERAPY IN CHRONIC HEART FAILURE: PRELIMINARY DATA

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Background: A reduced activity of the GH/IGF-1 axis (GHD) in chronic heart failure (CHF) has been described by several independent groups, and short-term evaluation of its correction has recently proven to be beneficial. No data are currently available regarding the long-term safety and efficacy of GH replacement therapy in patients with GHD and CHF.

Methods: The aim of the current study was to report data obtained from 17 CHF+GHD patients treated with GH replacement therapy and 17 controls followed over a two-year period. All patients included had GHD diagnosed by means of a standard GH stimulation test and were treated...
with GH replacement therapy on top of standard medical therapy.

**Results:** The main results are summarized in the table below. Patients treated with GH displayed a significant improvement of cardiopulmonary performance, vascular reactivity, and ejection fraction while left ventricular end-systolic stress decreased significantly compared with control CHF patients. Safety was good, considering that only one patient complained of transient arthralgia. Compared with 6-months data (not shown), there was not only a sustained GH effect to improve clinical status and cardiovascular performance, but some parameters such as peak oxygen consumption and flow mediated vasodilation exhibited additional increments at two years.

**Conclusions:** Long-term GH replacement therapy appears safe and effective.

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**SKELETAL MUSCLE INVOLVEMENT IN EARLY CARDIOMYOPATHIES**

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**Background:** Cardiomyopathies are a heterogeneous group of diseases associated with mechanical and/or electrical dysfunction of the myocardium that may lead to ventricular hypertrophy or dilatation. The American Heart Association differs primary cardiomyopathies, which are solely, or predominantly confined to the heart muscle, from the secondary in which myocardial involvement is part of a widespread systemic disorder. Some cardiomyopathies, such as Left Ventricular Non Compaction, have been frequently described, indeed, associated with genetically determined neuromuscular disorders. This study aims to evaluate the prevalence and clinical impact of neuromuscular disorders in patients with early primary cardiomyopathy.

**Methods:** Sixty-two patients (age ranging 4-60 years) were enrolled in this study complaining with weakness and/or fatigability and/or cramps. They were part of 395 consecutive patients with primary cardiomyopathy observed at the Department of Cardio-Thoracic and Respiratory Sciences of the Second University of Naples from 2004 to June 2011. All patients, after direct and instrumental cardiac assessment (12-lead ECG, 2D color Doppler-echocardiography, cardiopulmonary exercise test and ECG Holter monitoring within 24 h), were evaluated by a protocol for neuromuscular disorders including history, neurological examination, muscle function rating scales (MRC, MFS), serum muscle enzymes and electromyography. Muscle biopsy (histology, histochemistry, immuno-histology, western blot) as well as genomic and/or mitochondrial DNA examination were performed after informed consent when appropriated.

**Results:** Thirty-two out of 62 patients had familiarity for cardiomyopathy and/or myopathy. Muscle strength reduction mainly involving the limbs (MRC score 131-143; normal 150) was evident in 16 out of 62 patients (25%) and 7 of them also disclose increased serum CK (203-1625U/L; normal 174U/L) that was altered in further 7 patients who complained early neuromuscular symptoms yet at the time of the diagnosis were mitochondrial- (N 5), vacuolar- (N 2), metabolic- (N 1), and lamina A/C- (N 1) myopathy. Five of the patients who complained early neuromuscular symptoms yet at the time of the diagnosis of cardiomyopathy, had worse cardiovascular outcomes (sudden death pacemaker and automatic cardio-verter defibrillator implantation, EF <35%), during 78 months follow-up.

**Conclusions:** A careful evaluation of and a comprehensive and multidisciplinary approach to the patients with early cardiomyopathy are warrantable to identify neuromuscular disorders possibly associated with the cardiomyopathy, especially when the cardiac phenotype is mild. The association myopathy-cardiomyopathy may affect the outcome in terms of sudden death and restricting the advisability of heart transplantation.

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**B1 AND B2-ADRENERGIC RECEPTORS POLYMORPHISM IN PATIENTS WITH TAKO-TSUBO CARDIOMYOPATHY**

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**IN PATIENTS WITH TAKO-TSUBO CARDIOMYOPATHY**

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**Background:** The Tako-Tsubo cardiomyopathy (TTC) is a novel cardiomyopathy characterized by normal coronary arteries and often caused by a precipitating stressor. The underlying pathophysiologic mechanism remains unknown but catecholamine excess along with an exaggerated stimulation of the sympathetic nervous system appears to play a major role. Our aim was to analyze the frequency of β1 and/or β2 adrenergic receptor in TTC subjects.

**Methods:** β1 and/or β2 adrenergic receptor polymorphisms in 56 patients with TTC compared with 103 normal subjects.

**Results:** The β1 adrenoreceptor (amino acid position 389) genotype frequencies were significantly different from the control group (homozygous Arg/Arg in 42%, heterozygous Arg/Gly in 49% and homozygous Gly/Gly in 9% of TTC patients; O.R. 2.81, 95% CI 1.74-4.55; P<0.0001). The β2 adrenoreceptor (amino acid position 16) genotype frequencies was not different from the controls (homozygous Gly/Gly 27%, heterozygous Gly/Arg 63% and homozygous Arg/Arg in 11%) while β2 adrenoreceptor (amino acid position 27) genotype frequencies were statistically different from the control group (homozygous Gly/Gly 11%, heterozygous, Gly/Glu 55% and homozygous Glu/Glu in 34%; O.R. 0.61, 95% CI 0.38-0.98; P=0.029).

**Conclusions:** TTC phenotype seems to be associated with 1AR amino acid position 389 and β2AR amino acid position 27 polymorphisms.

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**EARLY IDENTIFICATION OF LEFT VENTRICULAR DYSFUNCTION WITH SPECKLE TRACKING ECHOCARDIOGRAPHY IN ANTINEOPLASTIC THERAPY-INDUCED CARDIOTOXICITY**

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**Background:** New anti-ErbB2 therapies have improved the prognosis of patients with breast cancer, but are associated with an increased risk of left ventricular (LV) dysfunction. Trastuzumab (T) can increase by 3-18% the frequency of asymptomatic decrease in LV ejection fraction (LVEF), and by 2-4% the risk of heart failure (HF). Opposite to the well-known anthracyclin-induced cardiotoxicity, these conditions are reversible, in absence of apparent ultrastructural changes. Indexes of cardiac function, such as fractional shortening (FS) and EF, are not very sensitive in detecting early myocardial damage. Aim of this study is to evaluate whether myocardial strain by speckle tracking (ST) is able to identify early LV dysfunction in mice treated with doxorubicin (D) and T, alone or in combination (D+T).

**Methods:** We measured radial myocardial strain (%) with ST, and FS...
by M-mode echocardiography in sedated C57BL/6 mice (8-10-week old) at day 0, and after 2 and 6 days of daily administration of D (2.17 μg/g/day), T (2.25 μg/g/day), D + T (2.17 μg/g/day + 2.25 μg/g/day respectively), and in a control group.

Results: FS was able to identify early (2 days) LV dysfunction only in group D and D+T: 52±0.2% and 49±2%, respectively, both P<0.001 vs. 60±0.4% (sham), while in group T it decreased only at 6 days (49±1.5% vs. 60±0.5%, P=0.002). In contrast, after 2 days, myocardial strain was already reduced not only in D and D+T, but also in T alone: 43±3%, 49±1%, and 44±7%, respectively, all P<0.05 vs. sham (66±0.6%).

Conclusions: In mice treated with D or T, myocardial strain identifies LV systolic dysfunction earlier than conventional echocardiography. We plan to apply this technique to clinical studies, to evaluate the impact of early identification of T-related cardiotoxicity in the treatment of women affected by breast cancer, and to better elucidate the mechanisms of T myocardial effects.

**SPECKLE TRACKING ECHOCARDIOGRAPHY IDENTIFIES CARDIAC DYSFUNCTION INDUCED BY THE ANTICANCER ERBB2-BLOCKER LAPATINIB**

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**Background:** Anti-ErbB2 therapies have improved the prognosis of patients with breast cancer. Still, they are associated with an increased risk of left ventricular (LV) dysfunction. Trastuzumab (Herceptin) increases the frequency of asymptomatic decrease in LV ejection fraction (LVEF) by 3-18%, and the risk of heart failure (HF) by 2-4%. The newer agent Lapatinib (L) is associated with a lower risk of LV dysfunction. Traditional indexes of cardiac function in vivo (fractional shortening and ejection fraction) may underestimate subtle changes that occur with L. Here, we test whether early sensitive indices of LV dysfunction can reveal L-induced cardiotoxicity.

**Methods:** In vivo cardiac function was measured with LV fractional shortening (FS) by M-mode echocardiography, and with radial myocardial strain (%) with speckle tracking (ST) in sedated C57BL/6 mice (8-10 wk. old) after 7 and 14 days of daily administration of 25 or 100 mg of L, and in control mice. After the echo studies, the hearts were excised and interstitial fibrosis was evaluated with picrosirius red staining.

**Results:** After 7 and 14 days of treatment, L 25 mg did not affect FS nor strain, while with 100 mg of L, FS decrease was almost significant at 7 and 14 days (53±5% and 52±5% vs. 60±1%; P=0.08 and 0.07 vs. sham, respectively). Most of all, with 100 mg of L there was a clear reduction in myocardial strain at both 7 and 14 days: 48±2% and 24±4%, respectively, vs. 61±0.3%, both P<0.02 vs. sham. This early LV dysfunction detected with ST was paralleled by an increase in collagen content: 5±0.4% at 14 days vs. ±0.3% (sham; P=0.005).

**Conclusions:** Myocardial strain identifies LV systolic dysfunction earlier than conventional echocardiography, and parallels histological changes earlier than FS. Still, the clear mechanisms of anti ErbB2-induced cardiotoxicity are to be elucidated. We plan to study such mechanisms, and to apply ST technique in clinical practice, in order to evaluate the impact of early identification of L-related cardiotoxicity in the treatment of women affected by breast cancer.

**FREQUENCY OF FAMILIAL DILATED CARDIOMYOPATHY: A META-ANALYSIS OF 23 TRIALS**

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**Background:** First studies carried to define the prevalence of familial transmission in patients with dilated cardiomyopathy (DCM) showed a very low frequency. Subsequent prospective studies showed familial clustering in more patients. However, also the results of these latter studies are different in account of population enrolled and study methods. To our knowledge no systematic review and meta-analysis of the frequency of the familial form of DCM is actually available.

**Methods:** In this study we aim to estimate the prevalence of familial form in patients with DCM and to assess the extent of the heterogeneity in reported prevalence estimate. Therefore, using PubMed, MEDLINE, Cochrane and the ISI Web of Science databases, articles published until December 2010 were identified. Of the initial 2320 studies identified, 1750 were excluded based on title, 502 on abstract, and 45 on text. Thus, a total of 23 studies evaluating the prevalence of familial DCM were selected according to aforementioned criteria. For each study, demographic characteristics and the echocardiographic criteria utilized to define the presence of DCM were analyzed. These data were not available in all studies; in particular age and gender in some studies are reported for the DCM probands, while in some studies for all study population. Also the criteria utilized to define the presence of familial form of DCM were different. For the summation of the prevalence finding, we computed the prevalence point estimates and 95% confidence intervals using the logit transformation formula.

**Results:** We found an aggregate estimate of clinical confirmed familial DCM of 24% (CI: 0.18-0.31). However, the prevalence rates reported across these studies varied widely ranging from 2% to 65% and the analysis showed a very high heterogeneity (Q=299, P<0.0001; I²=93%). Meta-regression analysis between logit event rate and year of publication showed that this regression explained 18% of between-study variance (P<0.05).

**Conclusions:** Cumulative meta-analysis confirmed the influence of year of publication on the reported prevalence of familial DCM among the different studies. However, most of heterogeneity observed may be explained considering that the various studies utilized different preselcted criteria for the diagnosis of familial DCM. Therefore, data obtained from trials performed utilizing standardized criteria are needed to better define the true prevalence of familial DCM.

**PROGNOSTIC SIGNIFICANCE LEFT VENTRICULAR REVERSE REMODELLING IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY RECEIVING OPTIMAL MEDICAL TREATMENT**

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**Background:** Tailored medical therapy can lead to LVRR in IDC. The prevalence and prognostic impact of LVRR remain unclear.
Methods: The aim of this study was to identify prevalence and prognostic role of left ventricular reverse remodeling (LVRR) in Idiopathic Dilated Cardiomyopathy (IDCM). We consecutively enrolled 361 IDCM patients. LVRR was defined as LV ejection fraction (LVEF) increase ≥10 units or LVEF ≥50% and reduction of indexed LV end-diastolic diameter (LVEDDI) ≥10% or LVEDDI ≥33 mm/m2 at 24 (range 9-36) months. Follow-up echocardiographic data were available in 242 cases (67%), 34 (9%) died/unwarranted heart transplant (HTx) before re-evaluation, and 85 (24%) did not have a complete re-evaluation. After re-evaluation the surviving patients were followed for 110±53 months, and there were 55 (23%) deaths and 32 (13%) HTxs.

Results: LVRR was found in 89/242 (37%) patients. Baseline predictors of LVRR were higher systolic blood pressure (P=0.047), and absence of left bundle branch block (P=0.009). When added to prognostic baseline model-male gender, heart failure duration, NYHA III-IV, LVEF, significant mitral regurgitation and beta-blockers- LVRR, NYHA III-IV and significant mitral regurgitation after 24 months emerged as independent predictors of death/HTx and heart failure death/HTx. The model including follow-up variables showed additional prognostic power with respect to baseline model (for death/HTx: area under the curve 0.80 vs. 0.70 respectively, P=0.004). Furthermore, only LVRR was significantly associated to SD/MVA in the long-term.

Conclusions: LVRR characterized approximately one third of IDCM patients surviving 2 years under optimal medical therapy, and allowed a more accurate long-term prognostic stratification of the disease.

CARDIOVASCULAR ABNORMALITIES IN THE LOW IGF-1 SYNDROME: INSIGHTS FROM THE TOSCA PROJECT
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Background: Extensive evidence supports the concept that multiple hormonal and anabolic deficiencies are common in Chronic Heart Failure (CHF) and identify subgroups of patients with higher mortality. Chief among these is the reduced activity of the GH/IGF-1 axis.

Methods: Ninety-nine patients with CHF, selected from a larger cohort participating in a multicenter trial, were divided according to their IGF-1 levels. Low IGF-1 syndrome was defined in CHF patients with IGF-1 levels below the 25th percentile of an age and sex-matched population.

Results: Results are shown in the table below. Patients with low IGF-1 levels displayed higher depression and anxiety scores, reduced indices of quality of life as well as of cardiopulmonary performance compared with CHF patients with normal IGF-1 levels. Moreover, LV volumes tended to be higher in low IGF-1 patients with significantly higher wall stress and larger mitral regurgitation jets.

Conclusions: Low IGF-1 syndrome defines a subgroup of CHF patients characterized by worse clinical status, cardiopulmonary performance, and LV dynamics.
mutations in HCM patients with end-stage disease. Therefore, aim of the present study was to assess the genotype of a large cohort of patients with end-stage HCM undergoing comprehensive mutational screening (10 genes) in Italian referral centers.

Methods: One hundred and fifty-six HCM patients, since 1980, consecutively found to have a left ventricular ejection fraction <50% (end-stage) underwent complete sequencing of 8 sarcomere protein genes (MYH7, MYBPC3, TNNI3, TNN2, TPM1, MYL2, MYL3, and ACTC) and 2 metabolic genes (PRKAG2 and LAMPP) implicated in idiopathic cardiac hypertrophy.

Results: One hundred and twenty-nine mutations (47 novel - 36%) were identified in 104 patients (67%); mutations occurred predominantly (>75%) in MYH7 and MYBPC3. Eighty-three patients (53%) had single mutations (39 MYBPC3, 24 MYH7, 12 TNNI3, 3 TPM1, 2 TNN2, 2 MYL2, and 1 MYL3). Twenty-one patients (13%) had complex genotypes characterized by double-gene mutation heterozygosity (N=7; 4%), compound heterozygosity (N=9; 6%), and triple mutations (N=5; 3%). A novel LAMP gene mutation was identified in 1 patient who also had a sarcomeric mutation in TNN2 previously described. Patients with positive genotype were younger at HCM diagnosis (29±17 vs. 36±18, P=0.04) and at first evaluation (40±16 vs. 46±19, P=0.04) compared to patients with negative genotype; additionally they had a higher prevalence of family history of HCM (68% vs. 50%, P=0.04). Dividing the patients according to the structural characteristics of sarcomeric mutated proteins, patients with MYBPC3 mutations were older at HCM diagnosis and at first evaluation compared to patients with thick and thin filament mutations and to patients with multiple mutations. No significant differences in terms of prognosis (sudden death or HCM-related death) were found in patients with or without identified mutations or according to the structural characteristics of sarcomeric mutated proteins.

Conclusions: Sarcomeric mutations were highly prevalent in patients with end-stage HCM, although not qualitatively dissimilar from those found in unselected HCM populations. Complex genotypes characterized by double or triple mutations were frequent in this cohort, suggesting that, genetic screening may play a role in the identification of HCM patients at risk of disease progression.

EFFECTS OF MYOCARDIAL FIBROSIS ASSESSED BY MAGNETIC RESONANCE IMAGING ON DYNAMIC LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

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Background: While functional implications of myocardial fibrosis on left ventricular (LV) function at rest have been studied in hypertrophic cardiomyopathy (HCM), the pathophysiological consequences on dynamic LV outflow tract (LVOT) gradient have so far not been investigated in detail. We evaluated the role of myocardial fibrosis, detected by magnetic resonance imaging (MRI) as late gadolinium enhancement (LGE), on LV outflow obstruction in a cohort of HCM patients with normal ejection fraction (EF) at rest.

Methods and Results: Seventy-six HCM patients underwent cardiac MRI and performed bicycle exercise echocardiogram within the same month. LGE was present in 54 patients (71%), ranging from 0.2% to 32.4% of LV mass. There was a weak correlation between the amount of fibrosis and variation in LV gradient during exercise in the overall population (r = -0.243, P = 0.034) and a stronger correlation in patients with obstructive HCM at rest (r = -0.524, P = 0.021). Patients with an increase in LVOT gradient ≥50 mmHg during exercise had a significantly lesser extent of fibrosis than those with an increase <50 mmHg (0.7% (IQR 0.2-4.4) vs. 3.2% (IQR 0.2-7.4), P = 0.006). The extent of fibrosis was significantly lower among the highest quartiles of LVOT gradient increase (P = 0.009).

Conclusions: In patients with HCM and normal EF at rest, myocardial fibrosis is associated with a lower increase in LVOT gradient during exercise, probably due to a lesser degree of myocardial contractility recruitment. This negative association is more evident in patients with an obstructive form at rest.

ECHOCARDIOGRAPHIC PREDICTORS OF VENTRICULAR ARRHYTHMIAS IN FAMILIAL LEFT VENTRICULAR NON-COMPACTION CARDIOMYOPATHY

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Background: Left Ventricular Non Compaction (LVNC) is an unclassified cardiomyopathy characterized by left ventricular hypertrofication and deep intertrabecular recesses in communication with the ventricular cavity. LVNC is often associated with other cardiomyopathies or with genetic disorders, and is familial at least in 25% of cases. The diagnosis is based on echocardiographic criteria. Risk stratification is needed to optimally target preventive therapies in patients with LVNC. The aim of this study was to assess the value of echocardiographic parameters in predicting the occurrence of arrhythmic events in patients with familial LVNC (none had concomitant hypertension, diabetes mellitus or other significant cardiovascular disorder).

Methods: We studied 26 subjects (aged 39.9±16.2 years), 11 males and 15 females, at a single institution, representing 7 families with isolated LVNC. Patients were evaluated at 3-month interval either clinically or with 12-Lead ECG, echocardiography and 24-hour Holter monitoring. The average duration of follow up was 24±6 months. Echocardiographic parameters, ejection fraction (EF) and end-diastolic diameter (EDD) were matched with ventricular arrhythmias (VA) to assess their predictive value. The Kaplan-Meier method was used to calculate the probability of ventricular events.

Results: Left Ventricular (LV) systolic function was depressed in 10 patients (38.5%), with a mean EF of 44±3.2% at the first visit. Nine of 26 patients (34.6%) had LV dilatation (EDD ≥60 mm): among them only 5 patients (55.5%) had EF <45%. Six of 26 patients (23.1%) underwent episodes of ventricular tachycardia (VT) during follow up. All 6 patients (100%) had LV dilatation, among them only 3 patients (50%) had depressed EF. By Chi square test and Kaplan Meier analysis, the only echocardiographic predictor of VA was LV dilatation (P=0.001).

Conclusions: In families with isolated LVNC, LV dilatation was the only echocardiographic predictor associated with subsequent development of ventricular arrhythmias. This finding might be helpful to optimally target preventive therapies in patients with familial isolated LVNC.
DNA SEQUENCE CAPTURE AND HIGH THROUGHPUT SEQUENCING TECHNOLOGIES ENABLE THE IDENTIFICATION OF NEW DISEASE-CAUSING GENES: THE CASE OF HYPERTROPHIC CARDIOMYOPATHY

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Background: Next generation sequencing technologies enable the simultaneous study of large numbers of genes and the detection of a wide variety of mutation types. We have set-up and validated an analytic procedure able to sequence simultaneously 202 genes associated with hypertrophic cardiomyopathy (HCM) in groups of patients within a shorter time and at less expense than current procedures. Hypertrophic cardiomyopathy is the most frequent genetic cardiovascular disease worldwide. To date, about 50 disease-causing genes have been identified and the number is increasing. We tested the efficacy of a novel procedure designed to identify causative mutations in a large number of HCM-related and candidate genes.

Methods: Three HCM patients previously analysed by DHPLC/Sanger sequencing for causative mutations in 8 sarcomeric genes were enrolled in this study. A total of 202 genes were selected and a custom sequence capture array was designed to enrich all their coding regions and 500 bp of the flanking regions. Our target measured 3,908,196 bp. Each DNA sample was sequenced in two independent runs by the GS FLX System (454 and Roche Life Science).

Results: We obtained an average of 164 Mb/sample, which is equivalent to 503,775 different sequencing reads/sample with an average read length of 325.6 bp. Sequence and data analysis were performed using the Roche/454 gsMapper software. High confidence variants were blasted against the SNP database to distinguish between known and unknown variants. We found 7864 different variants, of which 6725 were intrinsic, 424 intergenic and 715 exonic. About 31% of the latter were novel, and 56 of them occurred in 35 HCM-related genes. We confirmed the mutations and polymorphisms previously identified with DHPLC/Sanger sequencing in the 3 patients.

Conclusions: The simultaneous analysis of a vocabulary of genes may provide additional information in patients in whom traditional screening was not conclusive. The procedure may also reveal mutations responsible for clinical variability thereby helping to shed light on the pathogenesis of HCM. Moreover, by reducing time and costs and increasing the sensitivity of molecular testing, HCM molecular diagnosis may provide additional information in patients in whom traditional screening was not conclusive. The procedure may also reveal mutations

REGIONAL LEFT VENTRICULAR WALL MOTION ANALYSIS IN ACUTE PATIENTS WITH TAKO-TSUBO CARDIOMYOPATHY COMPARED WITH ANTERIOR MYOCARDIAL INFARCTION

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Background: The aim of the study was to assess the echocardiographic distribution of regional wall motion abnormalities (RWMA) in patients with Tako-Tubo cardiomyopathy (TTC) compared with acute anterior ST-elevation myocardial infarction (ant-STEMI).

Methods: Thirty-seven TTC and 37 ant-STEMI patients underwent standard echocardiographic examination at the time of hospital admission. RWMA and the involvement of the left ventricular territories supplied by each coronary artery according to the American Society of Echocardiography classification were reported.

Results: TTC patients showed a lower left ventricular ejection fraction (37.6±5.1 vs. 40.9±3.7%; P=0.002) and a higher wall motion score index (WMSI; 1.98±0.2 vs. 1.51±0.14; P<0.001) compared with ant-STEMI patients. No significant differences were observed between groups with regard to detection of RWMA in the territory supplied by the left anterior descending coronary artery (LAD) (37 vs. 37; P=1). Conversely, in TTC patients, the territories supplied by the LAD/left circumflex coronary artery (LCX) (37 vs. 31; P=0.011), LAD/right coronary artery (RCA) (34 vs. 13; P<0.001), RCA (33 vs. 5; P<0.001) and RCA/LCX (31 vs. 2; P<0.001) were more frequently involved. A cut-off value of WMSI ≥ 1.75 (area under the curve 0.956) and for the number of territories with RWMA ≥ 4 (AUC=0.928) predicted TTC with a sensitivity of 83% and 84% and a specificity of 100% and 97%, respectively.

Conclusions: Echocardiography revealed a distinctive pattern of contractility in TTC patients, characterized by symmetrical RWMA extending equally into the territory of distribution of all coronary arteries.
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