Cardiomyopathies: definition, diagnosis, causes, and genetics

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Under the term cardiomyopathies, numerous alterations in myocardial function are subsumed. The most common forms are dilated and ischemic cardiomyopathies. While the latter has a well-defined aetiology, i.e. ischaemia and infarction with subsequent loss of contractility and remodelling, the definition of dilated cardiomyopathies is less clear, although progress in their genetic classification has been made. In a position statement entitled ‘Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice’, the ESC Working Group on Myocardial and Pericardial Diseases proposes a revised definition of dilated cardiomyopathy in an attempt to bridge the gap between our recent understanding of the disease spectrum and its clinical presentation in relatives, which is key for early diagnosis and the institution of potential preventative measures.

Ischaemic heart disease remains the most important cause of mortality due to sudden cardiac death and pump failure. Despite improvements in medical and device-based therapy, heart failure (see the new ESC 2016 Guidelines) and its sequelae remain an important complication of ischaemic cardiomyopathy worldwide. While most current interventions are palliative in nature, patients with ischaemic heart disease would benefit from therapies accelerating natural processes of post-natal collateral vessel formation and/or muscle regeneration. In another position paper, this time by the ESC Working Group on Cellular Biology of the Heart, entitled ‘Cell-based therapies for myocardial repair and regeneration in ischaemic heart disease and heart failure’, the authors discuss the use of cells in the context of cardiac repair, and the most relevant results and current limitations from clinical trials using cell-based therapies to treat ischaemic heart disease and heart failure. They further identify and discuss promising potential new therapeutic strategies that include ex vivo cell-mediated gene therapy, the use of biomaterials, and cell-free therapies aimed at increasing the success rates. Their overall aim is to provide recommendations on how to improve the therapeutic application of cell-based therapies for cardiac regeneration and repair.

Besides alterations of large epicardial coronary arteries that are the main cause of ischemic cardiomyopathies, dysfunction of the coronary microcirculation is an often overlooked cause of cardiac disease. In a Clinical Review, ‘Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases’, Paolo G. Camici and colleagues from the Vita-Salute University and Scientific Institute San Raffaele in Milan Italy remind us that chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis are important risk factors for the development of ischemic heart disease and are a source of high morbidity and mortality, with a wide spectrum of clinical manifestations. Of note, inflammatory mechanisms can affect coronary microvascular function and contribute to the development of myocardial ischaemia and cardiovascular events even in the absence of obstructive epicardial coronary artery disease. Understanding the molecular aspects that underscore the development of coronary microvascular dysfunction in chronic inflammatory conditions is of fundamental importance to identifying specific therapeutic targets. The authors review the pathogenic mechanisms leading to coronary microvascular dysfunction in chronic inflammatory conditions, report the controversial results with different therapeutic strategies, and propose a diagnostic algorithm for the identification of coronary microvascular dysfunction in patients with chronic inflammatory conditions.

Left ventricular remodelling impacts on the end-diastolic pressure–volume relationship, which is different in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. In their paper entitled ‘Risk factors for heart failure are associated with alterations of the left ventricular end-diastolic pressure–volume relationship in non-heart failure individuals: data from a large-scale, population-based cohort’, Michael Schwarzl and colleagues from the University Heart Center Hamburg Eppendorf in Germany investigated in a large-scale, population-based cohort, the Gutenberg Health Study, alterations of the end-diastolic pressure–volume relationship in heart failure patients and their association with risk factors and all-cause mortality in non-heart failure individuals. Based on clinical and echocardiographic data, 14,511 participants were classified as without heart failure, 215 as having heart failure with reduced ejection fraction, and 79 as having heart failure with preserved ejection fraction. The end-diastolic pressure–volume relationship was shifted rightward in heart failure with reduced ejection fraction, but leftward in heart failure with preserved ejection fraction, compared with subjects without heart failure, while the stiffness coefficient β was increased in both forms of heart failure. In individuals without heart failure, a higher stiffness coefficient β was associated
with age, female gender, hypertension, diabetes, and obesity. Age and female gender were associated with a leftward shift of the end-diastolic pressure–volume relationship, whereas dyslipidaemia, obesity, smoking, and impaired renal function were associated with a rightward shift thereof. Importantly, both changes of the end-diastolic pressure–volume relationship were associated with increased all-cause mortality. In the population at large, distinct alterations of the end-diastolic pressure–volume relationship in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction occur in certain individuals over time. Even in non-heart failure individuals, the presence of risk factors for heart failure is linked to alterations of the end-diastolic pressure–volume relationship, which are associated with increased mortality.

An important cardiomyopathy with preserved left ventricular function is hypertrophic cardiomyopathy. Numerous genetic mutations have been found in affected patients. However, phenotypic heterogeneity and incomplete penetrance are common in these patients. In their paper entitled ‘Hypertrophic remodelling in cardiac regulatory myosin light chain (MYL2) founder mutation carriers’, Godelieve Claes and colleagues from the Maastricht Universitair Medisch Centrum in Maastricht in The Netherlands investigated the genotype–phenotype relationship in hypertrophic cardiomyopathy and particularly the contribution of a myosin light chain founder mutation and risk factors to left ventricular hypertrophic remodelling. To that end, they analysed 14 hypertrophic cardiomyopathy families of whom 38 family members shared the myosin light chain c.64G>A or p.(Glu22Lys) mutation and a common founder haplotype. Interestingly, the mutation alone showed benign disease manifestation with low penetrance. However, the presence of additional risk factors for hypertrophy such as hypertension, obesity, or other sarcomeric gene mutations increased disease penetrance substantially, leading to the phenotypic hypertrophic cardiomyopathy in 89% of myosin light chain mutation carriers. The most prominent risk factor was hypertension, in 71% of carriers. The authors conclude that the myosin light chain mutation c.64G>A on its own does not lead to phenotypic hypertrophic cardiomyopathy, but additional risk factors, particularly hypertension, do so. Early diagnosis of risk factors is therefore important for early treatment of myosin light chain mutation carriers. The paper is accompanied by a thought-provoking Editorial by Sharlene M. Day from the University of Michigan Medical School in Ann Arbor, Michigan, USA.

While increased left ventricular wall thickness is a common finding in cardiac patients, such findings may not always reflect myocardial hypertrophy, but rather may be due to storage diseases of different kinds. In the paper ‘Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness’, the authors Thibaud Damy and colleagues from Creteil, France remind us that it is not known how often hereditary transthyretin-related familial amyloid cardiomyopathy is responsible for left ventricular wall thickness. As several therapeutic modalities for transthyretin-related familial amyloid cardiomyopathy are currently in clinical trials, it appears important to establish its prevalence and clinical characteristics. In a prospective multicentre cross-sectional study, the transthyretin gene was sequenced in 298 consecutive patients diagnosed with increased left ventricular wall thickness. Their median age was 62 years, 74% were men, 23% were of African origin, and 36% presented in NYHA class III–IV. Median left ventricular wall thickness was 18 mm, with a range of 16–21 mm. One in 20 or 5.7% of the patients had transthyretin-related familial amyloid cardiomyopathy, the vast majority with the familial form. The most frequent mutations were V142I, V50 M, and I127V. All patients with hereditary transthyretin-related familial amyloid cardiomyopathy were older than 63 years, with a median age of 74 years, and about half of them were of either African or European descent. In an adjusted multivariate model, African origin, neuropathy, carpal tunnel syndrome, ECG low-voltage, and late gadolinium enhancement at cardiac magnetic resonance imaging (MRI) were all independently associated with hereditary transthyretin-related familial amyloid cardiomyopathy. The authors conclude that ~5% of patients diagnosed with hypertrophic cardiomyopathy in fact have hereditary transthyretin-related familial amyloid cardiomyopathy. Thus, genetic screening will soon be warranted in elderly subjects with increased left ventricular wall thickness, particularly those of African descent with neuropathy.

![Figure 1](https://example.com/fig1.jpg) **Figure 1** Characteristics of an arrhythmogenic cardiomyopathy patient (H1) who underwent heart transplant. (A) Twelve-lead electrocardiogram of a patient with an advanced form of arrhythmogenic cardiomyopathy, recorded 2 years before heart transplant, characterized by sinus rhythm, complete right bundle branch block, ST-T wave abnormalities in leads II, III, aVF, V1–V4 where an e wave can also be identified. Frequent monomorphic premature ventricular beats originating from the inferior right ventricular wall are recorded. (B) Explanted heart of a late-stage arrhythmogenic cardiomyopathy patient, with biventricular involvement. Severe fibro-fatty infiltration is visible in the right ventricle, which is dilated with thin walls. A high-voltage implantable cardioverter defibrillator lead is visible in the right ventricular chamber. (C) Histological preparation of right ventricle tissue sample of the explanted heart (haematoxylin and eosin staining). The scale bar indicates 100 μm (from E. Sommariva, S. Brambilla, C. Carabucchio, E. Gambini, V. Meraviglia, A. Dello Russo, F.M. Farina, M. Casella, V. Catto, G. Pontone, M. Chiesa, I. Stadiotti, E. Cogliati, A. Paolin, N. Ouali Alami, C. Preziuso, G. d’Amati, G.I. Colombo, A. Rossini, M.C. Capogrossi, C. Tondo, and G. Pompilio. Cardiac mesenchymal stromal cells are a source of adipocytes in arrhythmogenic cardiomyopathy. See Pages 1835–1846).
carpal tunnel syndrome, ECG low-voltage, or late gadolinium enhancement at cardiac MRI.

Arrhythmogenic cardiomyopathy is another genetic cardiomyopathy mainly caused by mutations of desmosomal genes, and facilitated in its expression by competitive sports, characterized by progressive fibro-adipose replacement of the myocardium, arrhythmias, and sudden death. It is still unclear which molecular mechanisms and which cell type are responsible for this process. Cardiac mesenchymal stromal cells are the most abundant cells in the heart, with the ability to differentiate into several cell types, including adipocytes. As their role in arrhythmogenic cardiomyopathy is unknown, Elena Sommariva from the Centro Cardiologico Monzino in Milan, Italy investigated in their paper entitled ‘Cardiac mesenchymal stromal cells are a source of adipocytes in arrhythmogenic cardiomyopathy’ whether or not cardiac mesenchymal stromal cells contribute to excess adipocytes in patients with arrhythmogenic cardiomyopathy. They found that in expanded heart sections of such patients, cells actively differentiating into adipocytes are of mesenchymal origin. Therefore they isolated cardiac mesenchymal stromal cells from endomyocardial biopsies of patients with or without arrhythmogenic cardiomyopathy and found that cardiac mesenchymal stromal cells from both patient groups express desmosomal genes, with cardiac mesenchymal stromal cells from those with arrhythmogenic cardiomyopathy showing lower expression of plakophilin protein than those from controls. Further, arrhythmogenic cardiomyopathy cardiac mesenchymal stromal cells cultured in adipogenic medium accumulated more lipid droplets than controls. Accordingly, the expression of adipogenic genes was higher in the former than in the latter, while expression of cell cycle and antiadipogenic genes was lower. Both lipid accumulation and transcription reprogramming were dependent on plakophilin deficiency. Thus, cardiac mesenchymal stromal cells contribute to the adipogenic substitution occurring in arrhythmogenic cardiomyopathy. Moreover, cardiac mesenchymal stromal cells from arrhythmogenic cardiomyopathy patients recapitulate the features of adipogenesis, representing a novel, scalable, patient-specific in vitro tool for future mechanistic studies. The paper is accompanied by an educational Editorial by Daniel Jacoby from the Yale School of Medicine in New Haven, Connecticut, USA. The editors hope that this issue of the European Heart Journal will be of interest of its readers.

References


