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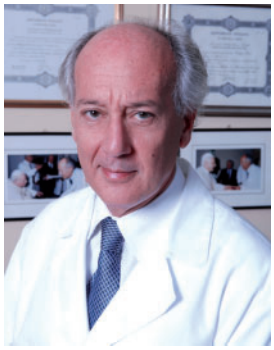
The multiple causes and treatments of heart failure: focus on genetic and molecular mechanisms and non-pharmacological interventions



Filippo Crea [1,2]

[1]Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy: and [2]Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, Rome, Italy

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Dilated cardiomyopathy (DCM) is currently defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions, or coronary artery disease sufficient to cause global systolic impairment. Research over recent decades has shed new light on the aetiology and natural history of DCM. In particular, it is recognized that many patients have a long pre-clinical phase characterized by few if any symptoms and minor cardiac abnormalities that fall outside current disease definitions. It is also clear that distinct subtypes in fact share a common DCM phenotype.[1,2]

This Focus Issue on heart failure (HF) opens with two contributions on DCM. The first contribution is a Current Opinion entitled **'Dilated cardiomyopathy: so many cardiomyopathies!'** by Gianfranco Sinagra from the University of Trieste in Italy, and colleagues.[3] The authors note that despite gaps in knowledge, precision medicine in cardiology is no longer a theoretical vision, but a realistic opportunity for the future treatment of patients with DCM. They also point out that the movement from symptomatic to treatments targeting specific disease mechanisms represents a conceptual shift from slowing disease progression to a paradigm of disease reversal or prevention as the main objective. The authors propose that a novel approach to DCM patients, including a comprehensive evaluation, from the identification of possible environmental triggers to the identification of likely pathogenic genetic variants, should be promoted in order to apply individualized therapeutic strategies.

The second contribution is a clinical research manuscript entitled **'Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry'**. Karen Sliwa from the University of Cape Town in South Africa and colleagues sought to describe the clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy (PPCM) globally.[4] In 2011, >100 national and affiliated member cardiac societies of the European Society of Cardiology (ESC) were contacted to contribute to a global registry on PPCM, under the auspices of the ESC EORP Programme. These societies were tasked with identifying centres who could participate in this registry. A total of 739 women were enrolled in 49 countries in Europe (33%), Africa (29%), Asia-Pacific (15%), and the Middle East (22%). Mean age was 31 ± 6 years, mean left ventricular ejection fraction (LVEF) was 31 ± 10%, and 10% had a previous pregnancy complicated by PPCM. Symptom onset occurred most often within 1 month of delivery (44%). At diagnosis, 67% of patients had severe (NYHA III/IV) symptoms, 67% had an LVEF ≤35%, and 15% received bromocriptine, with significant regional variation. The 6-month mortality was 6% overall, lowest in Europe (4%), and highest in the Middle East (10%) (*Figure 1*). Myocardial recovery (LVEF >50%) occurred only in 46%, most commonly in Asia-Pacific (62%) and least commonly in the Middle East (25%). Neonatal death occurred in 5%, with marked regional variation (Europe 2%, the Middle East 9%).

The authors conclude that PPCM is a global disease, but clinical presentation and outcomes vary by region. Just under half of women experience myocardial recovery. The manuscript is accompanied by an **Editorial** by Uri Elkayam and Hezzy Shmueli from the University of Southern California in Los Angeles, USA.[5] The authors conclude that more research is required to determine the socioeconomic and genetic reasons for different geographical and racial characteristics of PPCM and to develop effective population-specific diagnostic and therapeutic approaches.

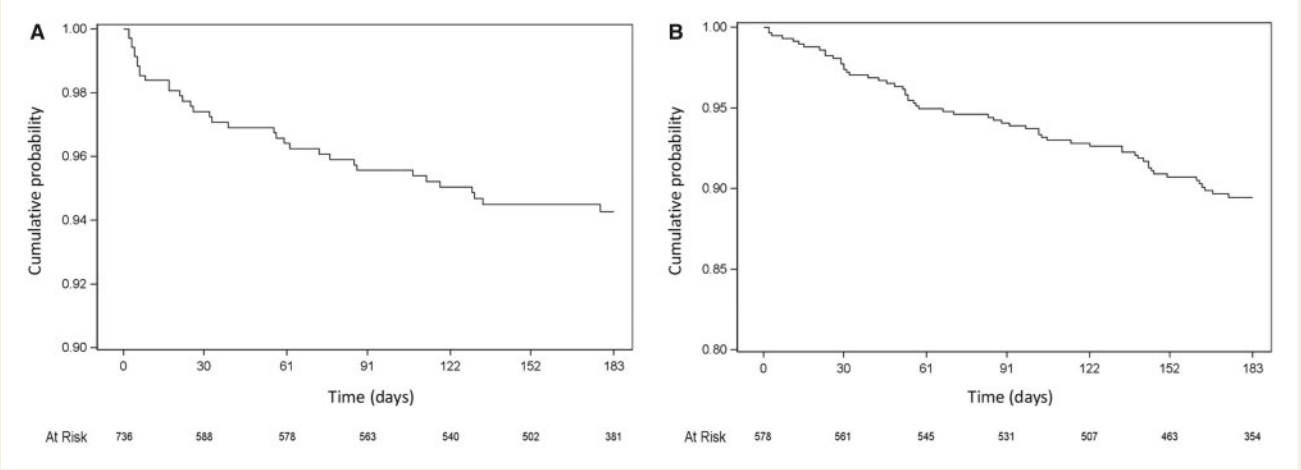

Figure 1 Kaplan-Meier survival curves for 6-month outcomes in women with peripartum cardiomyopathy: (*A*) Death from any cause and (*B*) Re-hospitalization for any cause (from Sliwa K, Petrie MC, van der Meer P, Mebazaa A, Hilfiker-Kleiner D, Jackson AM, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, Roos-Hesselink JW, Seferovic P, Spaendonck-Zwarts Kv, Mbakwem A, Böhm M, Mouquet F, Pieske B, Johnson MR, Hamdan R, Ponikowski P, Van Veldhuisen DJ, McMurray JJV, Bauersachs J, on behalf of the EurObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry. See pages 3787–3797).

Patients with end-stage HF have a poor quality of life, a very high mortality rate, and are potential candidates for implantation of a left ventricular assist device (LVAD). Although cardiac transplantation is associated with high 1- and 10-year survival rates, organ supply is limited. The technical improvements and proven success of implantable LVADs have made it a reasonable treatment option in these patients, either as a bridge to cardiac transplantation or as destination therapy.[6] The ELEVATE Registry was designed to study long-term outcomes with the Heartmate 3 (HM3), a fully magnetically levitated centrifugal ventricular assist device, in a real-world population following CE-mark approval. In a clinical research article entitled '**Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: results from the ELEVATE Registry**', Daniel Zimpfer from the Medical University Vienna of Austria and colleagues assessed 463 patients receiving the HM3 as primary implant in Europe and in Middle East enrolled in the ELEVATE Registry.[7] Data collection included demographics, survival, adverse events, quality of life assessment, and 6-min walk distance . Mean age was 55.6 ± 11.7 years (89% male, 48% ischaemic cardiomyopathy). Seventy percent of patients were in INTERMACS Profile 1–3 and 12.7% were on temporary mechanical circulatory support. The survival rate was 83% after 2 years while stroke was observed in 10.2%, gastrointestinal bleedings in 9.7%, pump thrombosis in 1.5%, and outflow graft twists in 3.5%. HM3 implantation resulted in a significant and sustained improvement of functional capacity and quality of life.

Zimpfer and colleagues conclude that in a real-world population cohort implanted with the HM3 LVAD, the long-term survival is good with sustained improvement of functional capacity and low rates of adverse events. This manuscript is accompanied by an **Editorial** by Stephen James Pettit from the Royal Papworth Hospital NHS Foundation Trust in Cambridge, UK, and colleagues.[8] They note that the ELEVATE Registry provides reassuring data about survival with the HM3 LVAD, demonstrates that low adverse event rates with the HM3 are achievable in the real world, but also highlights that adverse events remain problematic. Thus, we do not yet have a perfect implantable LVAD for the long-term treatment of patients with advanced heart failure.

Cardiac resynchronization plays a key role in the management of chronic heart failure,[9] but the identification of responders remains challenging.[10] In a clinical research article entitled '**Imaging predictors of response to cardiac resynchronization therapy: left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance**', John Aalen from the Oslo University Hospital and University of Oslo in Norway, and colleagues investigated if septal and left lateral wall function measured as myocardial work, alone and combined with assessment of septal viability, identified responders to cardiac resynchronization therapy (CRT).[11] In a prospective multicentre study of 200 CRT recipients, myocardial work was measured by pressure–strain analysis and viability by cardiac magnetic resonance imaging (CMR). Before CRT, septal work was markedly lower than left lateral wall work, and the difference was largest in CRT responders. Work difference between the septum and lateral wall predicted CRT response, with an area under the curve (AUC) of 0.77 (*Figure 2*). In patients undergoing CMR, combining work difference and septal viability significantly increased the AUC to 0.88. This was superior to the predictive power of QRS morphology, QRS duration, and the echocardiographic parameters septal flash, apical rocking, and systolic stretch index.

The authors conclude that assessment of myocardial work and septal viability identifies CRT responders with high accuracy. The manuscript is accompanied by an **Editorial** by Frits W. Prinzen and Joost Lumens from the Cardiovascular Research Institute Maastricht in the Netherlands[12] who note that this study provides a strong

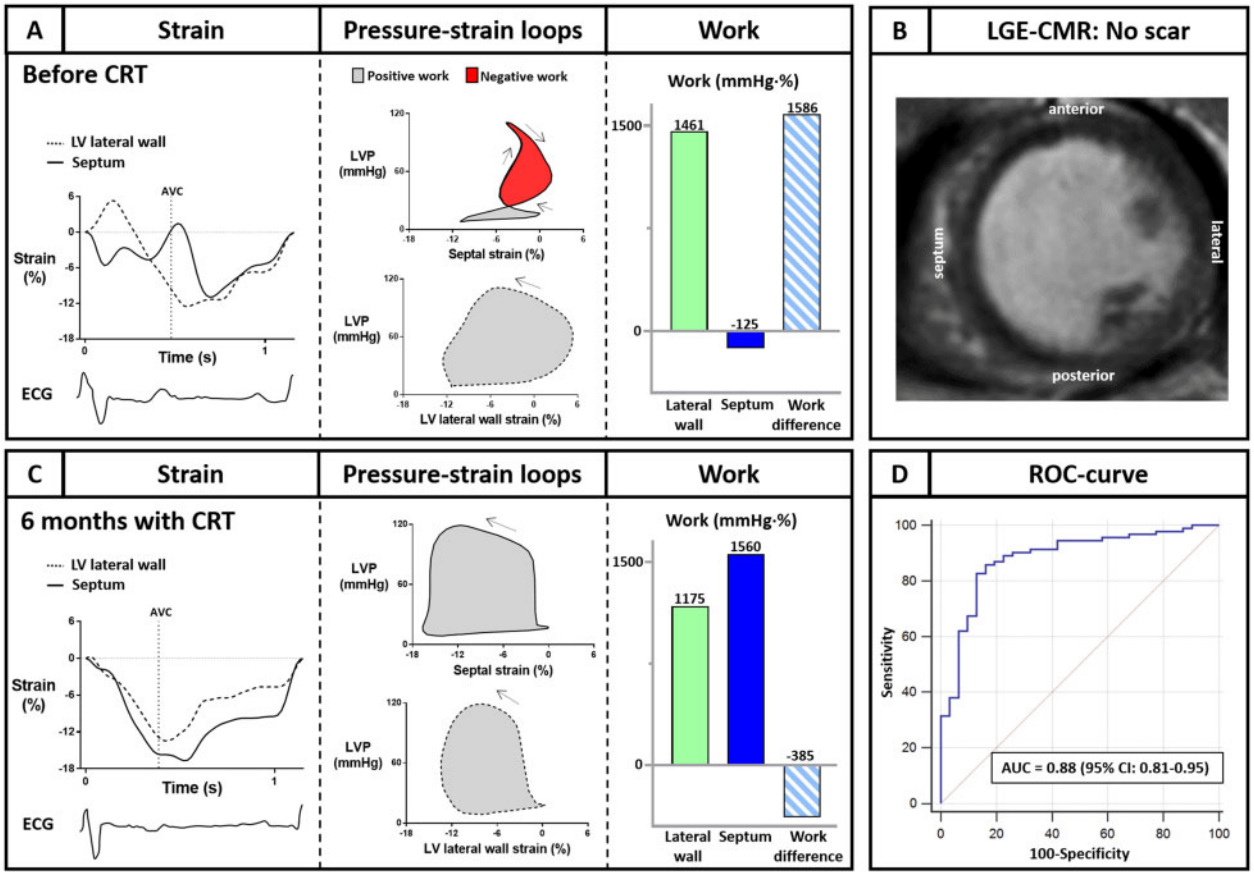

Figure 2 Left ventricular work asymmetry combined with septal viability identifies cardiac resynchronization therapy responders. (*A–C*) The panels are from the same patient and illustrate how the lateral-to-septal work difference is used in combination with viability by LGE-CMR to identify cardiac resynchronization therapy responders. Before cardiac resynchronization therapy (*A*) there is dominantly negative septal work, as indicated by the red-coloured pressure-strain loop area, but compensatory increase in left ventricular lateral wall work, which gives a large lateral-toseptal work difference. Viable septum (*B*) indicates potential for recovery of septal function. After 6 months with cardiac resynchronization therapy (*C*), there is fine recovery of septal function. The highly inefficient septal contractions before cardiac resynchronization therapy are converted to positive work throughout systole. The improvement in septal function was accompanied by reduced workload on the lateral wall. (*D*) ROC curve displaying combined assessment of work difference and septal viability for cardiac resynchronization therapy response prediction (n = 123). AUC, area under curve; AVC, aortic valve closure; CI, confidence interval; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LVP, left ventricular pressure; ROC, receiver operating characteristic (from Aalen JM, Donal E, Larsen CK, Duchenne J, Lederlin M, Cvijic M, Hubert A, Voros G, Leclercq C, Bogaert J, Hopp E, Fjeld JG, Penicka M, Linde C, Aalen OO, Kongsgård E, Galli E, Voigt J-U, Smiseth OA. Imaging predictors of response to cardiac resynchronization therapy: left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance. See pages 3813–3823).

extension of our understanding of CRT response and that it would not be a waste of work to perform a larger prospective study to prove the clinical feasibility and benefit of a meaningful measure of LV mechanical discoordination as an important additional selection criterion for CRT in the real-world setting.

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been associated with cardiovascular features of myocardial involvement including elevated serum troponin levels, acute heart failure with reduced ejection fraction, and myocarditis.[13–15] In a clinical research article '**Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study**' Cristina Basso from the University of Padua in Italy and colleagues note that the cardiac pathological changes in these patients with COVID-19 have yet to be well described.[16] In an international multicentre study, cardiac tissue from the autopsies of 21 consecutive COVID-19 patients was assessed by cardiovascular pathologists. Myocarditis, as defined by the presence of multiple foci of inflammation with associated myocyte injury, was determined, and the inflammatory cell composition analysed by immunohistochemistry. Other forms of acute myocyte injury and inflammation were also described, as well as coronary artery, endocardium, and pericardium involvement. Lymphocytic myocarditis was present in 3 (14%) of the cases. A mild pericarditis was present in four cases. Acute myocyte injury in

the right ventricle most probably due to strain/overload was present in four cases. A non-significant trend toward higher serum troponin levels was observed in the patients with myocarditis compared with those without. The authors conclude that in SARS-CoV-2 there are increased interstitial macrophages in a majority of the cases and multifocal lymphocytic myocarditis in a small fraction of the cases. Other forms of myocardial injury are also present in these patients. The macrophage infiltration may reflect underlying diseases rather than COVID-19. The manuscript is accompanied by an **Editorial** by Nikolaos Frangogiannis from the Albert Einstein College of Medicine in the Bronx, New York, USA and colleagues.[17] He notes that the findings of the current study are consistent with the notion that direct COVID-19-mediated cardiac pathology is uncommon.

The incidence of cardiogenic shock (CS) has increased remarkably over the past decade and remains a challenging condition, with mortality rates of ~50%. CS encompasses cardiac contractile dysfunction; however, it is also a multiorgan dysfunction syndrome, often complicated by a systemic inflammatory response with severe cellular and metabolic dysregulations. In a clinical review article entitled '**Molecular signature of cardiogenic shock**', Antoni Bayes-Genis from the Hospital Universitari Germans Trias i Pujol in Badalona, Spain, and colleagues sought to review the evidence on the biochemical manifestations of CS, elaborating on current gold standard biomarkers and novel candidates from molecular signatures of CS.[18] Novel genomic, transcriptomic, and proteomic data are discussed, and a recently reported molecular score derived from unbiased proteomic discovery, the CS4P, which includes liver fatty acid-binding protein (L-FABP), beta-2-microglobulin (B2MG), fructose-bisphosphate aldolase B (ALDOB), and SerpinG1 (IC1), is comprehensively described.

In another clinical review article entitled '**When genetic burden reaches threshold**', Roddy Walsh from the University of Amsterdam in the Netherlands, and colleagues note that rare cardiac genetic diseases have generally been considered to be broadly Mendelian in nature, with clinical genetic testing for these conditions predicated on the detection of a primary causative rare pathogenic variant that will enable cascade genetic screening in families.[19] Substantial variability in penetrance and disease severity among carriers of pathogenic variants, as well as the inability to detect rare Mendelian variants in considerable proportions of patients, indicates that more complex aetiologies are likely to underlie these diseases. Recent findings have suggested that genetic variants across a range of population frequencies and effect sizes may combine, along with non-genetic factors, to determine whether the threshold for expression of disease is reached and the severity of the phenotype. The availability of increasingly large genetically characterized cohorts of patients with rare cardiac diseases is enabling the discovery of common genetic variation that may underlie both variable penetrance in Mendelian diseases and the genetic aetiology of apparently non-Mendelian rare cardiac conditions. It is likely that the genetic architecture of rare cardiac diseases will vary considerably between different conditions as well as between patients with similar phenotypes, ranging from near-Mendelian disease to models more akin to common, complex disease. Uncovering the broad range of genetic factors that predispose patients to rare cardiac diseases offers the promise of improved risk prediction and more focused clinical management in patients and their families.

The two primary molecular regulators of lifespan are sirtuin-1 (SIRT1) and mammalian target of rapamycin complex 1 (mTORC1). In a Special Article entitled '**Longevity genes, cardiac ageing, and the pathogenesis of cardiomyopathy: implications for understanding the effects of current and future treatments for heart failure**', Milton Packer from the Baylor University Medical Center at Dallas in Texas, USA notes that each plays a central role in two highly interconnected pathways that modulate the balance between cellular growth and survival.[20] The activation of SIRT1 [along with peroxisome proliferator-activated receptor-gamma coactivator (PGC-1a) and adenosine monophosphate-activated protein kinase (AMPK)] and the suppression of mTORC1 (along with its upstream regulator, Akt) act to prolong organismal longevity and retard cardiac ageing. Both activation of SIRT1/PGC-1a and inhibition of mTORC1 shifts the balance of cellular priorities so as to promote cardiomyocyte survival over growth, leading to cardioprotective effects in experimental models. These benefits may be related to direct actions to modulate oxidative stress, organellar function, proinflammatory pathways, and maladaptive hypertrophy. Additionally, a primary shared benefit of both SIRT1/PGC-1a/AMPK activation and Akt/mTORC1 inhibition is the enhancement of autophagy, a lysosome-dependent degradative pathway, which clears the cytosol of dysfunctional organelles and misfolded proteins that drive the ageing process by increasing oxidative and endoplasmic reticulum stress. Interestingly, most treatments that have been shown to be clinically effective in the treatment of chronic heart failure with a reduced ejection fraction have been reported experimentally to activate SIRT1/PGC-1a/AMPK and/or suppress Akt/mTORC1, and, thereby, to promote autophagic flux. Therefore, the impairment of autophagy resulting from derangements in longevity gene signalling is likely to represent a seminal event in the evolution and progression of cardiomyopathy.

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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