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Heart failure subgroups: HFrEF, HFmrEF, and HFpEF with or without mitral regurgitation

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Heart failure has recently undergone major changes: while heart failure with reduced ejection fraction or HFrEF is declining due to effective revascularization of patients with acute coronary syndromes,[1–3] the prevalence and incidence of heart failure with preserved ejection fraction or HFpEF, mainly characterized by diastolic dysfunction,[4,5] is increasing due to ageing Western societies.[6] In between there is a gap, and this has recently been filled in the most recent ESC Guidelines on Acute and Chronic Heart Failure[7] with the introduction of a novel category, i.e. HFmrEF or heart failure with mid-range ejection fraction. The future will tell if this category can survive the test of time. Of note, the reproducibility and precision of echocardiography, the most frequently used imaging modality in these patients, is not good enough to categorize such patients reliably. Furthermore, a subanalysis of the TOPCAT trial suggests that HFmrEF and HFrEF might be comparable at least in their responsiveness to heart failure drugs such as spironolactone.[8] In a Fast Track paper entitled '**Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials**', Dipak Kotecha and colleagues from the University of Birmingham College of Medical and Dental Sciences in Birmingham, UK address this issue with an additional heart failure drug in 11 double-blind, randomized, placebo-controlled trials employing an intention-to-treat analysis.[9] In patients in sinus rhythm, beta-blockers reduced all-cause and cardiovascular mortality compared with placebo, an effect that was consistent across left ventricular ejection fraction strata, except for those in the small subgroup with left ventricular ejection fraction ≥50% (*Figure 1*). Left ventricular ejection fraction increased with beta-blockers in all groups in sinus rhythm except in those with a value of ≥ 50%. In patients with atrial fibrillation, beta-blockers increased left ventricular ejection fraction when <50% at baseline, but did not improve prognosis. Thus, beta-blockers improve left ventricular ejection fraction and prognosis for patients with heart failure in sinus rhythm with a reduced left ventricular ejection fraction. The data are most robust in HFrEF, but similar benefit was observed in HFmrHF. These relevant findings suggesting that HFrEF and HFmrEF are just the same disease with different severities, are put into context in an **Editorial** by Douglas Mann from the Washington University School of Medicine in Saint Louis, Missouri, USA.[10]

Significant efforts are currently being undertaken to better quantify[11,12] and eventually reduce functional mitral regurgitation in patients with chronic heart failure in the hope of improving prognosis.[13–15] In their manuscript entitled '**Refining the prognostic impact of functional mitral regurgitation in chronic heart failure**', Georg Goliasch and colleagues from the Medical University of Vienna in Austria assessed the impact of functional mitral regurgitation in HFrEF under optimal medical therapy.[16] They prospectively included 576 HFrEF patients in their observational study with a median follow-up of 62 months. Severe functional mitral regurgitation was a significant predictor of mortality with an adjusted hazard ratio of 1.38 independent of clinical and echocardiogrphic confounders. Severe functional mitral regurgitation was associated with poor outcome in an intermediate-failure phenotype of heart failure with reduced ejection fraction, i.e. those with NYHA class II, moderately reduced left ventricular function, and within the second quartile of NT-proBNP. Thus, in a patient cohort under optimal medical therapy, the adverse prognostic impact of functional mitral regurgitation is predominant in those with intermediate heart failure.

Maladaptions of the peripheral circulation are importantly involved in the pathophysiology of ageing,[17] hypertension,[18] atherosclerosis, and heart failure.[19] Retinal vessel analysis represents a non-invasive and reliable method to study the microcirculation and endothelial function in the eye.[20] In a further article entitled '**Retinal microvascular dysfunction in heart failure**', Andreas Flammer and colleagues from the University Hospital Zurich in Switzerland assessed the extent of retinal microvascular dysfunction in patients with chronic heart failure.[21] In 74 patients with compensated chronic heart failure with HFrEF, flicker-induced dilatation of retinal arterioles was assessed. Flicker-induced dilatation was significantly reduced in patients with HFrEF compared with those with risk factors of healthy

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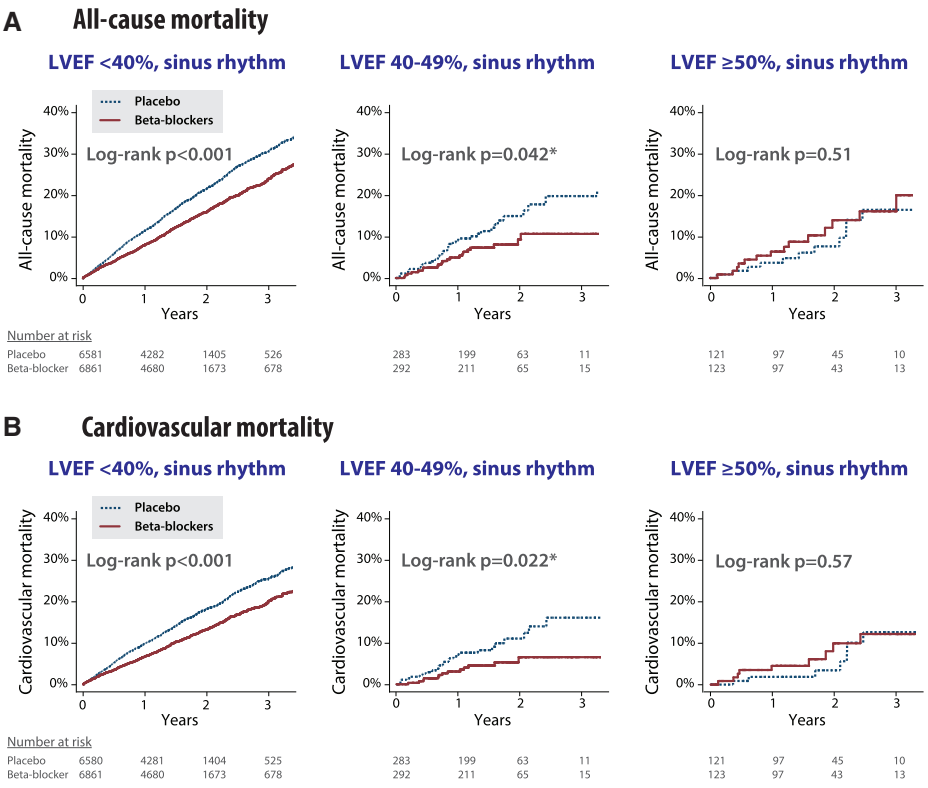

Figure 1 Beta-blockers vs. placebo in sinus rhythm according to heart failure phenotype. Kaplan–Meier plots for unadjusted (*A*) all-cause mortality and (*B*) cardiovascular mortality according to baseline left ventricular ejection fraction (LVEF). * Similar results in *post-hoc* analysis when excluding patients with an LVEF reported as exactly 40% from the 40–49% group: (*A*) log-rank $P = 0.030$ and (*B*) log-rank $P = 0.039$; $n = 147$ placebo, and $n = 143$ beta-blockers (from Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson é,Wikstrand J, Kotecha D; on behalf of the Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. See pages 26–35).

controls. Similar differences were seen for venular flicker-induced dilatation. Of interest, flicker-induced dilatation was less impaired in patients with dilated compared with ischaemic cardiomyopathy. Impaired flicker-induced dilatation was associated with echocardiographically estimated systolic pulmonary artery pressure and left atrial volume index. Thus, flicker-induced dilatation of retinal microvascular vessels is impaired in chronic heart failure, which may provide a new method to monitor microvascular abnormalities in heart failure. These findings are commented on in a timely **Editorial** by Giuseppe Mancia from the Milano-Bicocca University in Italy.[22]

Rapid overactivation of the sympathetic nervous system[23] and the β-adrenergic receptor in particular upon stress leads to cardiac inflammation, a prevailing factor that underlies cardiac injury in infarction, heart failure, and peripartum cardiomyopathy.[24] However, mechanisms by which acute β-adrenergic receptor stimulation induce cardiac inflammation remain unknown. In a Basic Science article entitled '**Interleukin-18 cleavage triggers cardiac inflammation and fibrosis upon β-adrenergic insult**', Youyi Zhang and colleagues from the Peking University Third Hospital in Beijing, China investigated the role of the inflammasome and of interleukin-18 in cardiac inflammatory cascades upon β-adrenergic receptor insult in C57BL/6 mice injected with a single dose of isoproterenol or saline.[25] Isopretorenol up-regulated inflammasome-dependent activation of interleukin-18, but not that of interleukin-1β, and promoted early macrophage infiltration. In patients with chest pain, a positive correlation was observed between the serum levels of norepinephrine and interleukin-18. Genetic deletion of interleukin-18 or the upstream inflammasome NLRP3 significantly attenuated isoproteronol-induced chemokine expression and macrophage infiltration, as did interleukin-18-neutralizing antibodies. Moreover, blocking interleukin-18 early treatment markedly attenuated cardiac inflammation and fibrosis in response to isoproteronol. The authors therefore conclude that β-adrenergic receptor activation activates inflammasome-dependent and interleukin-18, triggering a cytokine cascade, macrophage infiltration, and pathological cardiac remodelling, while specific blockade of this pathway successfully prevents inflammatory responses and cardiac injuries (*Figure 2*). The translational value of these experimental findings is further discussed in a comprehensive **Editorial** authored by Tanja Zeller from the University Heart Center Hamburg in Germany.[26]

Patients with acute heart failure often require intensive care including ventilation due to respiratory failure. Non-invasive ventilation, i.e. the application of positive intrathoracic pressure through an interface, might be a novel, less invasive approach in the management of

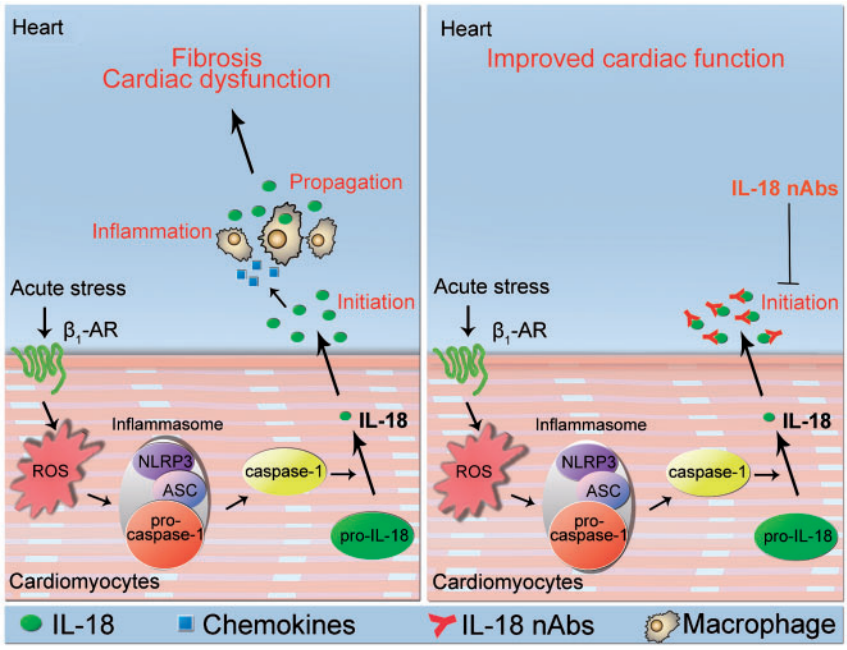

Figure 2 Working model for the β-adrenergic activation-induced cardiac inflammatory cascade which finally results in cardiac remodelling (left) and therapeutic strategy (right) (from Xiao H, Li H, Wang J-J, Zhang J-S, Shen J, An X-B, Zhang C-C, Wu J-M, Song Y, Wang X-Y, Yu H-Y, Deng X-N, Li Z-J, Xu M, Lu Z-Z, Du J, Gao W, Zhang A-H, Feng Y, Zhang Y-Y. IL-18 cleavage triggers cardiac inflammation and fibrosis upon β-adrenergic insult. See pages 60–69).

such patients, an issue that is addressed in a Review entitled '**Indications and practical approach to non-invasive ventilation in acute heart failure**' **by** Josep Masip and colleagues from the Hospital de Sant Joan Despi Moises Broggi in Barcelona, Spain. Non-invasive ventilation has been shown to be useful in the treatment of moderate to severe respiratory failure in several scenarios.[27] There are two modalities of non-invasive ventilation: continuous positive airway pressure and pressure support ventilation with positive end expiratory pressure. Appropriate equipment and experience are needed for pressure support ventilation, whereas continuous positive airway pressure may be administered without a ventilator, not requiring special training. Both modalities have been shown to be effective in acute cardiogenic pulmonary oedema, by a reduction of respiratory distress and the endotracheal intubation rate compared with conventional oxygen therapy, but the impact on mortality is less conclusive. There are no differences in the outcomes in the studies comparing both techniques, but continuous positive airway pressure is a simpler technique that may be preferred in low-equipped areas such as the pre-hospital setting, while pressure support ventilation may be preferable in patients with significant hypercapnia. The new modality 'high flow nasal cannula' seems promising in cases of acute heart failure with less severe respiratory failure. The selection of patients and interfaces, early application of the technique, the achievement of a good synchrony between patients and the ventilator avoiding excessive leakage, close monitoring, pro-active management, and, in some cases mild sedation may be warranted for a successful application of the technique.

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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