The ventricles of the heart are the engine of our body and their dysfunction is associated with a grim outcome, in spite of huge progress in their management over the last decades and recent developments in particular. The cardiac chambers may become stiff due to hypertrophy and/or infiltration of myocardial tissue, leading to diastolic dysfunction and/or weakening with reduced pump function, conditions that are referred to as heart failure with preserved ejection fraction (HFrEF) and heart failure with reduced ejection fraction (HFrEF), respectively.

Systolic and diastolic myocardial dysfunction is associated with activation of the circulating and local renin-angiotensin-aldosterone system and with a subsequent inappropriately increased production of reactive oxygen species (ROS). While low concentrations of ROS modulate physiological functions through changes in cellular signalling and gene expression, overproduction of the radicals may adversely affect cardiac mechanics. In addition, vascular endothelial dysfunction due to uncoupling of nitric oxide synthase, activation of vascular and phagocytic membrane oxidases or mitochondrial oxidative stress may lead to increased vascular dysfunction and stiffness, thereby further compromising cardiac performance.

Accordingly, this issue contains a timely Clinical Review entitled ‘Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications’, by Müazel et al., in which the authors address the potential role of ROS in myocardial and vascular dysfunction and their therapeutic targeting. Specifically, possible mechanisms underlying the failure of antioxidant vitamins in improving patients’ prognosis, the impact of angiotensin-converting enzyme (ACE) inhibitors or AT1 receptor blockers on oxidative stress and the mechanism of the benefit of combination hydralazine and isosorbide dinitrate. Further, the authors provide evidence supporting the existence of differences in the pathophysiology of HFpEF vs. HFrEF and that targeting mitochondrial ROS might be a particularly interesting therapeutic option for patients with preserved ejection fraction.

Patients with HFpEF, especially those with pulmonary hypertension, are an increasingly large medical problem. Phosphodiesterase type 5 (PDE5) inhibition may be of value in this population, but data are scarce and inconclusive. In the first FAST TRACK, entitled ‘Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial’, Hoendermis et al. report on the results of a single-centre, randomized, double-blind, placebo-controlled trial involving 52 patients with heart failure and an ejection fraction ≥45% and a mean pulmonary artery pressure >25 mmHg. Patients were randomized to the PDE5 inhibitor sildenafil, titrated to 60 mg three times daily, or placebo for 12 weeks. The primary endpoint was the change in mean pulmonary pressure after 12 weeks. The mean age of the patients was 75 years, with 71% being female and a median N-terminal pro-bra natriuretic peptide level of 1087 ng/L. After 12 weeks, mean pulmonary pressure decreased by 2.4 mmHg in patients receiving sildenafil and 4.7 mmHg with placebo. Sildenafil did not have a favourable effect on pulmonary capillary wedge pressure, cardiac output or peak volume of oxygen (VO2).

The authors conclude that in patients with HFpEF and pulmonary hypertension, sildenafil did not reduce pulmonary pressure nor did it improve other invasive haemodynamic or clinical parameters. Therefore this study does not support the use of sildenafil in those patients. This article is accompanied by an editorial by Barry A. Borlaug, from the Mayo Clinic in Rochester, NY, USA.

In HFrEF, the novel combined angiotensin receptor and nephrilisin antagonist LCZ696 markedly improves outcome on top of current guideline-based therapy. However, the effectiveness of LCZ696 in different age groups remains uncertain. Of note, the age at which heart failure develops varies widely between countries, and drug tolerance and outcomes also vary by age. Accordingly, in the second clinical research paper, ‘Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF’, McMurray et al. examined the efficacy and safety of LCZ696 in different age groups of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial. In PARADIGM-HF, 8399 patients ages 18–96 years and in New York Heart Association functional classes II–IV with a ejection fraction of ≤40% were randomized to either enalapril or LCZ696.

The authors concluded that the rate (per 100 patient-years) of the primary outcome of cardiovascular death or heart failure hospitalization increases from 13.4 to 14.8 across the age categories. The LCZ696enalapril hazard ratio was <1.0 in all age categories. Specifically, heart failure hospitalizations were similar, as was cardiovascular and all-cause mortality, and the age-category by treatment interactions were not significant. The pre-specified safety outcomes of hypotension, renal impairment and hyperkalaemia increased in both treatment groups with age, although the differences between treatments were consistent across age categories. Of note, there was more hypotension but less renal impairment and hyperkalaemia...
with LCZ696. As a result, in PARADIGM-HF, LCZ696 was more beneficial than enalapril across the entire age spectrum, with a favourable benefit-risk profile in all age groups.

HFpEF is a heterogeneous clinical syndrome with multiple underlying causes, including hypertension, hypertrophic cardiomyopathy and amyloid heart disease, among others. Wild-type transthyretin amyloidosis is an underdiagnosed cause of HFpEF that might benefit from new specific treatments currently under development. Transthyretin amyloidosis can be diagnosed non-invasively by technetium-99m-Diphosphono-1,2-Propanodioxime (99mTc-DPD) scintigraphy. In the third clinical research paper, entitled ‘Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction’, Garcia-Pavia et al.20 sought to determine the prevalence of transthyretin amyloidosis among elderly patients admitted due to HFpEF. The authors prospectively screened consecutive patients ≥60 years of age with HFpEF and left ventricular hypertrophy of ≥12 mm. A total of 120 such patients underwent 99mTc-DPD scintigraphy, of which 16 (13%) showed moderate to severe uptake of the tracer. All patients with a positive scan underwent genetic testing for the transthyretin gene, but no mutations were found. An endomyocardial biopsy was performed in four patients, confirming transthyretin amyloidosis in all cases. There were no differences in age, gender, hypertension, diabetes, coronary artery disease or atrial fibrillation between patients with transthyretin amyloidosis and patients with other causes of HFpEF. Although patients with transthyretin amyloidosis exhibited higher levels of NT-proBNP (6467 vs. 3173 pg/L), troponin I (0.135 vs. 0.025 μg/L), mean left ventricular maximal wall thickness (17 vs. 14 mm), a higher rate of pericardial effusion (44% vs. 19%) and a higher rate of pacemakers (44% vs. 12%), clinical overlap between transthyretin amyloidosis and other HFpEF forms was high.

The authors conclude that transthyretin amyloidosis is an under-diagnosed condition in patients with HFpEF, a fact that will become clinically relevant with the advent of emerging transthyretin-modifying drugs. This article is accompanied by an editorial by Mathew Maurer from Columbia University, New York, NY, USA. A much more common cause of HFpEF is hypertension.22 In the fourth research paper, ‘Dietary counselling has no effect on cardiovascular risk factors among Chinese grade 1 hypertensive patients in primary care. A parallel-group, randomized controlled trial was conducted among Chinese grade 1 hypertensive patients in primary care. A parallel-group, randomized controlled trial was conducted among patients newly diagnosed with grade 1 hypertension in primary care. Subjects were randomized to usual care or usual care plus DASH-based dietary counselling. The study endpoints included blood pressure, lipid profile and body mass index at 6 and 12 months. Blood pressure levels declined in both groups. Disappointingly, the intervention group did not show a greater reduction in either systolic or diastolic blood pressure as compared with the control group. In contrast, improvements in lipid profile and body mass index were observed among all subjects, yet no significant differences were detected between intervention and control groups.

The authors conclude that the DASH diet in primary care does not appear to confer long-term benefits on top of physician’s usual recommendations.

Finally, the issue contains a Special Article entitled ‘Report of an ESC-EAPCI Task Force on the Evaluation of Coronary Stents in Europe: executive summary’, by Byrne et al.24 In 2013, the European Society of Cardiology (ESC) was asked by the European Commission to provide recommendations for a revision of their medical device advisory document on the evaluation of coronary stents. The ESC delegated the task to the European Association of Percutaneous Cardiovascular Interventions (EAPCI), with the request to establish an expert advisory group in the field of percutaneous coronary intervention with specific expertise in the evaluation of coronary artery stents. As a basis for this expert advisory document, the ESC-EAPCI Task Force established a comprehensive list of all drug-eluting coronary stents that have received a CE (Conformité Européenne) mark to date, which was provided for review to representatives of the European Notified Bodies. In addition, the task force performed a systematic review of the literature of all published randomized clinical trials evaluating coronary artery stents between 2002 and 2013. In this document, the ESC-EAPCI Task Force proposes guidance on the process to evaluate stent technologies by means of preclinical and clinical studies prior to approval for clinical use.

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

References


