Novel aspects of heart failure: from combined neurohormonal blockade to embryonic stem cells

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Neurohormones are crucial regulators of the cardiovascular system, in particular the renin--angiotensin--aldosterone system and the natriuretic peptides. Their plasma levels are regulated by physiological stimuli, as well as activating and inactivating enzymes. Neprilysin is a neutral endopeptidase and its inhibition increases bioavailability of natriuretic peptides, bradykinin, and substance P, resulting in natriuretic, vasodilatatory, and antiproliferative effects.1

In concert, they lower blood pressure and unload the heart. LCZ696 or valsartan/sacubitril is a first-in-class combined angiotensin II receptor and neprilysin inhibitor with likely indications in heart failure and hypertension.

In this issue, Franz Messerli from the St. Luke’s-Roosevelt Hospital Center and Columbia University in New York provides a very timely Review on the ‘Role of neprilysin inhibitor combinations in hypertension: insights from hypertension and heart failure trials’.2 Messerli discusses the mechanisms of action, pharmacokinetics, and pharmacodynamics of this novel drug as well as its efficacy, safety, and tolerability in hypertension based on available trial information. Furthermore, he tries to identify areas of research in hypertension in which future trials with LCZ696 would be useful. Whether or not inhibition of neprilysin is truly associated with unwanted effects on β-amyloid in brain tissue remains to be determined.3

Besides neurohormones, the sympathetic nervous system4 is another essential modulator of cardiovascular function. Cardiovascular autonomic imbalance as it occurs in heart failure has adverse effects on symptoms as well as cardiac, renal, and immune function, exercise capacity, life expectancy, and mode of death. A second Clinical Review entitled ‘The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction’ by John S. Floras and colleagues from the Toronto General and Mount Sinai Hospitals in Canada summarizes current knowledge on the dysbalance of parasympathetic and sympathetic circulatory control in heart failure with reduced ejection fraction, and its clinical and prognostic implications.

Further, the authors demonstrate the patient-specific nature of abnormalities underlying this common phenotype and illustrate how such variation provides opportunities to improve or restore normal sympathetic/parasympathetic balance through personalized drug or device therapy.5

Acute heart failure is associated with a high mortality in spite of modern management in which emergency physicians, cardiologists, intensivists, nurses, and other healthcare providers co-operate for optimal outcome. However, many treatment decisions are opinion based rather than evidence based. In a comprehensive Current Opinion paper entitled ‘Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine, and the Society of Academic Emergency Medicine—short version’ Alexandre Mebazaa from the Hôpital Lariboisière in Paris, France and colleagues provide guidance to practising physicians and nurses on how to manage acute heart failure in the pre-hospital and hospital setting.6 Criteria of hospitalization and discharge and gaps in knowledge and management are discussed in the hope of further homogenizing practice in the future.

Cardiac resynchronization therapy (CRT) has revolutionized the treatment of patients with chronic heart failure with reduced ejection fraction7 and has become a cornerstone in the management of severe heart failure with a wide QRS complex.8 In EchoCRT, a randomized trial evaluating the effect of CRT in patients with a shorter QRS duration (i.e. <130 ms) and echocardiographic evidence of left ventricular dyssynchrony, the primary outcome of death or first hospitalization for heart failure occurred more frequently in the CRT than in the control group.9 Thus, according to current heart failure guidelines, CRT is recommended in patients with a QRS duration ≥120 ms. There, is however, some ambiguity from clinical trial data regarding the benefit of patients with an intermediate QRS duration of 120–130 ms.

The results of this pre-specified subgroup analysis are reported in the first FAST TRACK paper entitled ‘The effect of QRS duration on cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial’ by Jan Steffel from the University Hospital Zurich in Switzerland.10 To that end, the authors compared data for CRT-ON vs. CRT-OFF in patients with QRS <120 and QRS 120–130 ms. At baseline, the latter patients were older, more often men, had larger left ventricles, and the disease was more likely to be of ischaemic origin. No significant interaction was observed between the two groups for primary or...
secondary endpoints. However, on multivariable analysis, a higher risk for the primary endpoint occurred in those with a QRS of 120–130 ms on CRT-ON than CRT-OFF, with a hazard ratio of 2.18. However, no significant interaction compared with patients with QRS < 120 ms randomized to CRT-ON vs. CRT-OFF was noted. The authors conclude that CRT provides no benefit in patients with a QRS duration of 120–130 ms. Together with the consistent data from other trials, these results have important implications for selecting patients who will potentially benefit from CRT. These findings are further discussed in an Editorial by John Cleland from the University of Hull in the UK.

The second research paper, entitled ‘Effect of the angiotensin receptor–nephrisin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients’ by Scott Solomon and colleagues from the Brigham and Women’s Hospital in Boston expands our knowledge on the effects of LCZ696 in patients with chronic heart failure. The authors provide additional data from a subanalysis of the Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF) study that randomized 8399 patients with chronic heart failure with NYHA class II–IV symptoms and an ejection fraction of ≤ 40% to receiving either guideline-recommended medical therapy or LCZ696. The mode of death was adjudicated by a blinded clinical endpoints committee and was cardiovascular in 81%. LCZ696 reduced the risk of cardiovascular death by 20%. Among the modes of deaths, both sudden cardiac death and death due to worsening heart failure were reduced by LCZ696 by 20% and 21%, respectively, compared with enalapril. Deaths attributed to other cardiovascular causes, including myocardial infarction and stroke, were infrequent and distributed evenly between groups, as were non-cardiovascular deaths. The authors conclude that LCZ696 was superior to enalapril in reducing both sudden cardiac deaths and deaths from worsening heart failure, which accounted for the majority of cardiovascular deaths. The findings are further discussed in an Editorial by John Parker from the University of Toronto in Canada.

Although exercise and sport is considered protective and hence is recommended by current guidelines, in rare cases it is associated with sudden death and, particularly in extreme forms, with inflammation, troponin release, ventricular dysfunction, and even sudden death. Intense exercise does put disproportionate strain particularly on the right ventricle, which may cause proarrhythmic remodelling under certain conditions. Andrew La Gerche and colleagues from the Baker IDI Heart and Diabetes Institute in Melbourne expanded our knowledge on the effects of exercise on the right ventricle amongst athletes. Right ventricular stress testing reveals right ventricular contractile dysfunction amongst athletes with right ventricular arrhythmias. Right ventricular stress testing shows promise as a non-invasive means of risk-stratifying athletes. This issue is also discussed in a comprehensive Editorial by Sanjay Sharma from St. George’s University of London, UK.

Regenerative medicine is a big hope also for cardiovascular patients, particularly those after acute myocardial infarction and heart failure. Although experimental results are exciting, the results of clinical trials unfortunately were largely disappointing, possibly due to stem cell dysfunction in cardiovascular patients. Thus, embryonic stem cells (ESCs) committed to a cardiac lineage might be more effective in improving cardiac function than those featuring an extracardiac phenotype.

In the EHJ Brief Communication paper ‘Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report’, Philippe Menasche and colleagues from the Hôpital Européen Georges Pompidou in Paris, France for the first time report their clinical use in a cardiac patient. The authors have developed a population of human ESC-derived cardiac progenitor cells. Undifferentiated human ESCs (I6 line) were amplified and cardiac committed by exposure to bone morphogenetic protein and a fibroblast growth factor receptor inhibitor. Cells responding to these cardio-instructive cues express the cardiac transcription factor Isl-1 and the stage-specific embryonic antigen SSEA-1, which were then used to purify them by immunomagnetic sorting. The Isl-1- SSEA-1+ cells were then embedded into a fibrin scaffold which was surgically delivered onto the infarct area in a 68-year-old patient suffering from severe heart failure with a left ventricular ejection fraction of 26%. The implanted cells featured a high degree of purity, had lost the expression of Sox-2 and Nanog, known markers of pluripotency, but strongly expressed Isl-1. The intra-operative delivery of the patch was expeditious and the post-operative course was uncomplicated. After 3 months, the patient has improved in symptoms and his ejection fraction rose to 36%. Of note, a new-onset contractility was echocardiographically evident in the previously akinetic area treated with the cell patch.

No complications such as arrhythmias, tumour formation, or immunosuppression-related adverse events were noted. The authors conclude that this first observation demonstrates the feasibility of generating a clinical-grade population of human embryonic stem cell-derived cardiac progenitors and their delivery.
within a tissue-engineered construct. Although premature, the patient’s functional outcome is encouraging. Thus there is a reasonable hope that stem cells may help to repair the chronically damaged myocardium in the future.

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

References


