Novel prognostic markers and treatment options in heart failure: from palliative to regenerative medicine

Thomas F. Lüscher, MD, FESC

In spite of impressive progress in the last decades, the management of heart failure remains essentially palliative in nature.\(^1\)\(^-\)\(^2\) Rates of rehospitalizations and death remain high even in patients on optimal therapy, according to current guidelines.\(^3\)\(^-\)\(^4\) Thus, ongoing research at the basic and clinical levels is urgently needed to address this unmet clinical need. This issue of the European Heart Journal is devoted to novel insights into the mechanisms, outcomes, and treatment options in chronic and acute heart failure at the basic and clinical level.

Although interfering with neurohumoral activation was most successful so far therapeutically,\(^5\)\(^-\)\(^6\) it is obvious that the primary problem, particularly in dilated cardiomyopathy, is due to altered cardiac muscular function. The first paper, entitled ‘Ultrastructural features of cardiomyocytes in dilated cardiomyopathy with initially decompensated heart failure as a predictor of prognosis’\(^7\) by Tsunenori Saito from the Department of Cardiovascular Medicine of the Nippon Medical School in Tokyo, Japan, which is accompanied by an excellent Editorial by Carsten Tschope from the Charité University in Berlin, Germany,\(^8\) attempted to characterize myocardial ultrastructural changes by electron microscopy in endomyocardial biopsy specimens of the left ventricle obtained from 250 patients with dilated cardiomyopathy presenting with decompensated heart failure. During a follow-up period of 5 years, 10% died and 27% were readmitted with heart failure. Myofilament changes, classified as either focal derangement of myofilaments (sarcomere damage) or diffuse myofilament lysis (disappearance of most sarcomeres in cardiomyocytes), were found in 66% of the patients. Multivariate analysis identified that a family history of dilated cardiomyopathy, atrial fibrillation, haemoglobin level, and diffuse myofilament lysis were independent predictors of mortality. A family history, haemoglobin, focal derangement of myofilaments, and diffuse myofilament lysis were also predictors of readmission for heart failure. This study shows for the first time that in patients with dilated cardiomyopathy and a first episode of decompensated heart failure, myofilament changes are strongly associated with mortality and recurrence. As a next step, it appears mandatory to understand the molecular mechanisms of such structural changes to define novel therapeutic targets.

Although left ventricular and right ventricular function are well recognized determinants of outcome in patients with heart failure,\(^9\) atrial function has not been studied in detail. In the second paper, entitled ‘Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value’,\(^10\) Pierpaolo Pellicori et al. from Hull and East Yorkshire Medical Research and Teaching Centre in Kingston upon Hull, UK carefully studied left atrial emptying function using cardiac magnetic resonance imaging (MRI) in 664 outpatients referred with heart failure with reduced left ventricular function and elevated N-terminal pro brain natriuretic peptide (NT-proBNP). The paper is accompanied by an Editorial by Carolyn S.P. Lam from the Mayo Clinic and National University Health System, Singapore.\(^11\) Left atrial emptying function was 42% and 55% in patients with and without heart failure, respectively. Patients with heart failure in the lowest quartile of left atrial emptying function had a lower left and right ventricular ejection fraction, and greater ventricular mass and higher plasma NT-proBNP than those in the highest quartile. Log left atrial emptying function and log NT-proBNP were inversely correlated. During a median follow-up of >2 years, 59% of patients died or were admitted with heart failure and 15% developed atrial fibrillation. In a multivariable Cox model, increasing left atrial emptying function, but not left ventricular ejection fraction, was associated with survival. On the other hand, increasing age and decreasing left atrial emptying function predicted atrial fibrillation. Thus, in heart failure, left atrial emptying function predicts adverse outcome independently of other measures of cardiac dysfunction. Left atrial function should, therefore, be considered routinely in the assessment and risk stratification of patients with heart failure.

The third paper, by Philippe Menasché from the Hôpital Européen Georges Pompidou in Paris, France, focuses on a truly experimental approach. Although stem cell therapy has received a lot of attention in recent years, its effectiveness in patients after infarction,\(^12\)\(^-\)\(^14\) as well as in those with heart failure remains controversial.\(^15\) There is, however, evidence that precursor cells committed to a cardiac lineage might effectively improve the function of infarcted hearts.\(^16\) This has been established by the author’s preclinical studies entailing transplantation of human embryonic stem cell-derived cardiac progenitors in rat and non-human primate models of myocardial infarction. In this third paper, ‘Towards a clinical use of human embryonic stem cell-derived cardiac progenitors: a translational experience’,\(^17\) Menasché et al. present their translational experience.
programme aimed at a phase I clinical trial. The main steps of this programme have included: (i) the expansion of a clone of pluripotent human embryonic stem cell-derived cardiac progenitors to generate a master cell bank under Good Manufacturing Practice (GMP) conditions; (ii) a growth factor-induced cardiac specification; (iii) the purification of committed cells by immunomagnetic sorting to yield an SSEA-1-positive cell population strongly expressing the early cardiac transcription factor IsI1; (iv) the incorporation of these cells into a fibrin scaffold; (v) a safety assessment focused on the loss of teratoma-forming cells by in vitro (transcriptomics) and in vivo (cell injections in immunodeficient mouse) measurements; (vi) an extensive cyto genetic and viral testing; and (vii) the characterisation of the final cell product and its release criteria. These data have led to the approval by the French regulatory authorities for a first-in-man clinical trial of transplantation of such SSEA-1-positive progenitors in patients with severely impaired cardiac function. Although we are aware of the fact that the road to evidence is a bumpy one, and several aspects of this manufacturing process still need to be improved, this approach may prove a useful platform for the production of human embryonic stem cell-derived cardiac progenitors under safe and cost-effective GMP conditions, and certainly is a first step towards the development of a regenerative therapy of heart failure.

The fourth paper, by Eduardo Marban from the Cedars-Sinai Medical Center in Los Angeles, USA entitled ‘Therapeutic efficacy of cardiosphere-derived cells in a transgenic mouse model of non-ischaemic dilated cardiomyopathy,’ pursues a similar strategy by testing the effects of transplantation of cardiosphere-derived cells in mice with cardiac-specific Gqα overexpression, which predictably develop cardiac dilation, heart failure, and accelerated mortality. Indeed, it has been shown that cardiosphere-derived cells exhibit regenerative effects in the post-infarct setting, while it remains unknown whether such cells are beneficial in dilated cardiomyopathy. Wild-type mouse cardiosphere-derived cells or vehicle were injected intramyocardially in 6-, 8-, and 11-week-old Gqα mice. Over 3 months, cardiac function deteriorated in vehicle-treated mice accompanied by oxidative stress, inflammation, and ventricular remodelling. In contrast, cardiosphere-derived cells preserved cardiac function and volumes, improved survival, and promoted cardiomyogenesis, while blunting Gqα-induced oxidative stress and inflammation in the heart. The mechanism of benefit is indirect, as long-term engraftment of transplanted cells is vanishingly low. The authors conclude that cardiosphere-derived cells reverse fundamental abnormalities in cell signalling, prevent adverse remodelling, and improve survival in a mouse model of dilated cardiomyopathy. The ability to impact favourably on disease progression in non-ischaemic heart failure heralds new potential therapeutic applications of cardiosphere-derived cells.

This issue ends with a review on a potentially novel treatment of acute heart failure. The short- and long-term morbidity and mortality of acute heart failure is still unacceptably high. The use of vasodilator drugs in acute heart failure has received a lot of attention after the potentially life-saving effects of seralaxin in this patient population became public. In the review article by Stefan D. Anker from the University of Göttingen in Germany, the current evidence supporting the future use of the novel vasodilator and natriuretic peptide ‘Ularitide for the treatment of acute decompensated heart failure: from pre-clinical to clinical studies’ is discussed. Ularitide, a synthetic form of the human natriuretic peptide urodilatin produced in distal renal tubule cells involved in sodium homeostasis, is currently in clinical testing in a phase III trial. Ularitide exerts its pharmacological actions, i.e. vasodilation, diuresis, and natriuresis, through the natriuretic peptide receptor and activation of particulate guanylate cyclase, and in turn a reduction in intracellular calcium. In animal models as well as Phase I and II clinical studies in patients with heart failure, ularitide exerted beneficial effects such as symptom relief and vasodilation, while preserving renal function. The pivotal acute decompensated heart failure Phase III study, the TRUE-AHF trial, is currently under way and has recruited >2000 patients. This trial will confirm or refute whether in patients presenting with acute heart failure an infusion of ularitide will improve the clinical status and mortality.

The editors sincerely hope that this issue of the European Heart Journal will be received with interest by its readers.

References


