

## Heart Failure: An Exploration of Recent Advances in Research and Treatment

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## Supplement Aims and Scope

The supplement aims to provide readers with an exploration of recent advances in research on and treatment of heart failure. This includes but is not limited to the following topics:

- Pathophysiology
- Evaluation
- Management
- Diagnosis
- Prognosis
- Treatment
- Screening
- Prevention
- Epidemiology
- Risk factor modification

- Systematic reviews
- Observational studies
- Commentary on clinical trials
- Risk and safety of medical interventions
- Epidemiology and statistical methods
- Evidence-based medicine
- Evaluation of guidelines
- Translational medicine

Article types include original clinical and basic research articles, case reports, commentaries, meeting reports, methodology, perspective, research proposal, reviews, software/database reviews, and technical advance.

There is not a single approach to study heart failure (HF) due to the complexity of processes that are influenced by the interaction of several factors like the metabolism of the myocardium, cellular mechanism of muscle contraction, contractility linking ventricular suction and filling to cardiac ejection, preload and afterload, relaxation at end-diastole and relaxation at end-systole. Consequently this supplement presents a few studies on HF performed by researchers looking at HF from different perspectives that reflect the diversity of views on a complex problem. A look at current cardiac research reveals an exciting, and at the same time somewhat turbulent field. With the advent of non-invasive but complex surrogate measures, in addition to a wide variety of more or less specific biomarkers, it may become increasingly challenging to reach the heart of the matter. The vast number of data available may imply the risk of blurring a clear view on the fundamentals. Also, old concepts carry a tradition

likely to be cherished, while novel findings may overenthusiastically be embraced as attractive. Finding a new balance certainly requires a thorough overview, with delicate attention to both true insights and practical feasibility. Besides, real progress may also be derived from careful interpretation and critical reinterpretation.

The article by Kawada et al is an experimental study conducted on rats in order to study the effect of the arterial baroreflex regulation on the arterial pressure in cases of chronic heart failure as compared with a normal control group. The arterial pressure response to intravenous bolus injections of phenylephrine or norepinephrine in rats with chronic heart disease is shown to be reduced with respect to the group of normal rats.

As an alternative to the classical Starling curve, Kerkhof introduced the volume regulation graph (VRG), allowing the description of heart failure (HF) phenotypes in the volume domain. The major shortcoming in the Starling representation



resides in the use of the differential termed stroke volume, which is liable to spurious correlations when analysed as a function of end-diastolic volume (EDV). In contrast, the relationship of end-systolic volume (ESV) to EDV emerges as an insightful framework, incorporating both systolic and diastolic properties. The VRG immediately discloses information on ejection fraction (EF), a common descriptor of left ventricular (LV) function. The paper presents a survey of various approaches used thus far to describe clinical determinants of heart failure, including the Forrester model and the (dis)cordance concept. Applications of the newly introduced VRG paradigm are illustrated in two accompanying papers, which each venture a unique approach by applying Support Vector Machines (SVM), and a mathematical model for a monoventricular circulation, respectively. Alonso-Betanzos et al. address clinically relevant issues regarding guidelines to distinguish HF phenotypes by employing machine learning tools such as SVM. These authors found that EF may not represent the preferred criterion to separate HF patient groups, and they rather advocate the potential impact of ESV. Additionally, they were able to formulate guidelines for HF patients not covered by current rules, namely those with near normal EF combined with a slightly enlarged LV volume (ie, EDV above 97 mL/m<sup>2</sup>). Future research related to HF guidelines should focus on sex-specific determinants of the VRG, and the ensuing consequences for a more dynamic interpretation of EF. The study by Faes and Kerkhof concentrates on a succinct mathematical model for LV function, with results again presented in terms of the VRG framework. This contribution emphasizes the clear distinction between the popular ratio EF and the more fundamental ESV-EDV framework, in favour of the latter. Obviously, the current limited prototype model will be expanded to comply with a more realistic biventricular system, and should in the future also include features of nervous regulation, guided by clinical data presented in the VRG format. From the present basic design we can learn, again, that the use of differentials (such as SV) or, even worse, a ratio which includes a differential (cf. EF) should strongly be discouraged when quantifying LV function. Rather, alternative routes with focus on the pivotal parameter ESV deserve further exploration, especially in the field of HF diagnosis and patient management.

The article of Liu et al is a comprehensive review of the pathophysiologic, clinical and laboratory manifestations of Takotsubo cardiomyopathy. Particular emphasis is made on differentiating acute anterior wall myocardial infarction from Takotsubo cardiomyopathy by non-invasive measures. Differentiation of these two entities will help limit potentially harmful therapies in patients without underlying coronary artery disease. As with anterior wall myocardial infarction, Takotsubo cardiomyopathy often presents with congestive heart failure. The authors describe possible pathophysiologic mechanisms for the heart failure including acute mitral regurgitation and left ventricular outflow obstruction from a hyperdynamic basal myocardium. Understanding these mechanisms should

help guide treatment of heart failure caused by this entity. The echocardiographic finding of right ventricular (RV) apical akinesis with otherwise hyperdynamic RV function, or reverse McConnell sign, is described which is virtually pathognomonic of Takotsubo cardiomyopathy.

In cases of symptoms of heart failure, survival may be critically dependent on the timing of mechanical circulatory support. The article by Lawson and Koo provides a review of the effectiveness, ease of insertion and reduction in complications of ventricular assist devices, as well as indications on the future trend to use of percutaneous ventricular assist devices.

Diastolic heart failure or heart failure with preserved ejection fraction (HFpEF) constitutes about 50% of all heart failure admissions and it is the topic discussed by Kovacs. The article is an approach to help the reader in understanding what diastolic function really is. It provides the reader with an insight on suction and how the heart works when it fills, the difference between volume pumping and pressure pumping, conventional measures of diastolic function, application of Doppler tissue imaging for the assessment of the diastolic function of the heart left ventricle.

Li et al.'s paper emphasizes how the coupling and interaction of the LV and its arterial system (AS) can significantly modify underlying heart failure with preserved (HFpEF) or reduced (HFrEF) ejection fraction conditions. Parameters governing the interplay of preload, afterload and intrinsic contractility were analyzed. These include the clinically relevant  $E_{max}$ ,  $LV (dP/dt)_{max}$ ,  $(dQ/dt)_{max}$  and maximum velocity of shortening of the contractile element in systole and filling pressure and end-diastolic pressure-volume relation in diastole, as well as arterial compliance and peripheral resistance of the AS and the LV-AS coupling coefficient. It seems that in HFpEF, the LV is decoupled from the AS, such that EFs are relatively independent to changes in peripheral resistance or compliance. Overall, the indices that are related to structural changes of LV and AS are more able to accurately describe the underlying differences between HFpEF and HFrEF.

The study by Dhakal et al is focused on the problem of renal dysfunction in patients with heart failure. This complex interaction reflects a pathophysiological disequilibrium between the heart and the kidney, in which cardiac malfunction promotes renal impairment, which in turn feeds back, resulting in further deterioration of cardiovascular function. This vicious circle results in serious clinical outcomes. The study is based on experimental results from renal denervation in animals with heart failure and suggests that its application in humans with heart failure is safe and can be tolerated.

The work of Singh et al underlines the importance of coronary artery disease in the study of ischemic left LV dysfunction and heart failure. The study distinguishes between LV dysfunction caused by infarction and scar tissue formation and LV dysfunction of a viable myocardium which is due to ischaemia that has the potential to recover its function, either by itself over time or after revascularisation. The study also discusses the



best choice between coronary artery bypass grafting (CABG), Percutaneous Coronary Intervention (PCI, formerly known as angioplasty with stent) and medical therapy.

In the study by Shoucri it is shown that the EF is just one index that can be used to assess the ventricular function, several new indexes can be derived from the parameters describing the end-systolic pressure-volume (ESPVR). Relations between percentage of HF and EF has been extended by deriving new relations between percentage of heart failure and the parameters describing the ESPVR, it has important implications for the study of the problem of HFpEF. Bivariate (or multivariate) analysis of data is superior to univariate analysis (by using one index like EF) for the purpose of segregating between different clinical groups, a similar observation is reported in the study by Kerkhof et al where the use of two volume indexes is preferred to the use of one index EF in order to assess the ventricular function. Another important feature in the study by Shoucri is the introduction of the peak active pressure generated by the myocardium  $P_{\text{isom}}$  (also called peak isovolumic pressure by physiologists) in the formalism describing the ESPVR,  $P_{\text{isom}}$  is affected by the initial stretch of the cardiac muscle (Frank-Starling mechanism) and consequently reflects the diastolic state of the myocardium. The difference between the active pressure and the cavity pressure determines the resultant pulse on the endocardium that ejects the blood out of the ventricle. It is also shown that the introduction of the peak active pressure of the myocardium in the formalism describing the ESPVR determines areas under the ESPVR (having units of energy) that can be used to distinguish between normal state of the left ventricle, mildly depressed state of the left ventricle and severely depressed state of the left ventricle.

The study by Iyngkaran and M. Thomas stresses the importance of the clinician-scientist collaboration and the transfer

of bedside-to-bench and bench-to-bedside information in the treatment of heart failure. The study explores key diagnostic and therapeutic aspects related to topics such as heart failure and diabetes, heart failure and renal impairment, heart failure and indigenous population. It stresses better interaction between those generating and those translating evidence.

The study of Miyamoto et al is a system identification approach for the determination of the dynamic and static properties of the controller and the plant of the respiratory chemoreflex feedback system. Ventilatory abnormalities are cardinal symptoms in patients with chronic heart failure. The study is conducted on healthy patients and tends to simulate the dynamic function of the respiratory chemoreflex system in a way to explain the mechanism of periodic breathing in patients with chronic HF. When abnormality occurs in a part of the system, instability of the control system is amplified and results in the manifestation of respiratory abnormalities.

The preceding review is not exhaustive but provides an insight into some aspects of current research with direct impact on the study of HF, a complex process influenced by several interacting factors. Clinical observation is evidently important in our study of HF. Our understanding of physiology and biology today is enriched by the growing contribution of basic sciences like chemistry, physics, mathematics, informatics, genetics and sophisticated instrumentation, which will have on the progress of our knowledge of life sciences an enormous impact. We are entering a challenging era in which the complexity of knowledge requires a growing collaboration between clinicians and scientists, and contributions coming fresh from the benches of our universities. This complexity of knowledge explains in a sense the difficulty to progress, and at the same time it offers the hope for a better understanding of HF.

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