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EDITORIAL

Do we understand why the heart fails?

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This editorial refers to 'Left ventricular mass predicts heart failure not related to previous myocardial infarction: the Cardiovascular Health Study'† by G. de Simone *et al.* on page 741

In Western countries, heart failure has become one of the most prominent health care problems. Increased prevalence of coronary artery disease (CAD), improvements in CAD and hypertension treatment, and ageing of the population are major factors contributing to the fact that 1–2% of the Western populations suffer from heart failure, with a prevalence of 10% or more in the very elderly. Despite advances in heart failure therapy, morbidity and mortality remain high and quality of life is severely impaired.[1] Heart failure is a leading cause of hospital admissions, and hospitalizations for heart failure are often of long duration, resulting in enormous health care costs. It is estimated that they account for ~2% of the total health care budget in these countries.

Despite the importance of heart failure, both to the affected patients and to the health care providers, and much effort in basic as well as clinical research, many aspects in heart failure are still incompletely understood. For a long time, the focus was almost exclusively on systolic dysfunction. Heart failure was considered as the final common pathway of different cardiac disorders and, as a consequence, difficult to reverse. Once left ventricular systolic function is significantly depressed, uniform therapeutic response and results from human and animal studies suggested that the underlying cause is of lesser relevance. Therapy focuses primarily on delay of disease progression and complications of heart failure, whereas treatment of underlying diseases or risk factors is the main focus in prevention of heart failure only.[2] In the 1990s, it was recognized that many patients with the clinical symptom of heart failure do not have left ventricular systolic dysfunction, particularly in the elderly population, where at least half of the heart failure patients have preserved left ventricular systolic function.[3] Various population-based studies such as the Cardiovascular Health Study have contributed significantly to this understanding.

In heart failure with preserved left ventricular systolic function, diastolic dysfunction is considered to be the main cause, but the pathophysiology behind it is still incompletely understood. Different factors are believed to contribute to this.[4] Traditional cardiovascular risk factors were found to be related to the development of heart failure with preserved left ventricular systolic function. Various other factors, some associated with the traditional risk factors, are recognized to be of importance. Among those, left ventricular hypertrophy may be of particular significance, as it is considered not only to be the result of risk factors, particularly arterial hypertension, but also to be an independent risk factor of both systolic and diastolic left ventricular dysfunction. As a consequence, left ventricular hypertrophy is now considered a pre-clinical disease.[5]

However, to differentiate between left ventricular hypertrophy being the cause or the result of heart failure may be difficult as all these factors interact significantly. Thus, little is known about whether left ventricular hypertrophy is related to incident heart failure independent of coronary vascular events. de Simone *et al.* have provided strong evidence that this is indeed the case.[6]

They analysed a subgroup of >2000 patients of the Cardiovascular Health Study cohort, who did not have evidence of previous myocardial infarction. They show that not only load-dependent, but, possibly more importantly, also load-independent concentric left ventricular hypertrophy is a strong risk factor for the development of heart failure during the upcoming years, independently of other risk factors. This increased risk was independent of incident myocardial infarction, suggesting that mechanisms other than myocardial ischaemia and haemodynamic load may play an important role in the development of heart failure in patients with left ventricular hypertrophy. In addition, this study supports the shifting paradigm that left ventricular hypertrophy may be detrimental already in its early stage, and prevention of the hypertrophic response is actually associated with preserved ventricular function.[7]

Why is this finding important? The pathophysiological understanding of incident heart failure may be enhanced, although data from a cohort study do not allow direct conclusions. de Simone *et al.* discuss potential mechanisms,[6] amongst which myocardial fibrosis may be the central one, also potentially having therapeutic implications. However, there are numerous other potential mechanisms, and a huge variety of pathways were found to be involved

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in animal studies (for a review, see Meijs *et al.*[7]). Another important aspect of the study by de Simone *et al.* is that their data support the concept of diastolic and systolic heart failure being a continuum rather than two different entities, since small changes in systolic function were observed with increasing hypertrophy despite overall left ventricular systolic function being in the normal range. Additionally, left ventricular hypertrophy was associated with left atrial dilation, which was an independent predictor of incident heart failure and was found to be an indicator for heart failure in patients with preserved left ventricular systolic function in another study.[8] Unfortunately, de Simone *et al.* do not provide information on further structural and functional changes during follow-up. This would help to see if left ventricular hypertrophy *per se* may directly cause systolic dysfunction, independently of vascular damage. The clinical course of severe aortic stenosis with progressive deterioration of systolic function in late stages may be seen as an indicator for this, but hypertrophy in aortic stenosis is not load independent. Still, increased left ventricular mass in aortic stenosis predicts the presence of heart failure and may be maladaptive rather than beneficial.[9] Animal studies also support the concept of hypertrophy being independently associated with heart failure, but many of these studies did not use physiologically relevant models, most were in rodents and of very limited duration.[7] Further, in the analysis of de Simone *et al.*, a substantial number of patients were excluded from their analysis as no sufficient echocardiographic images were available. This may be relevant since it is known that subjects with insufficient echocardiographic quality differ significantly from those with adequate image quality.[10]

The question of left ventricular systolic and diastolic dysfunction being a continuum may be important for new therapeutic targets. While treatment in systolic dysfunction is well established and effective,[11] treatment of heart failure with preserved left ventricular systolic function remains challenging. There are only a very limited number of studies in such patients and most of them were rather small. Importantly, the only large trial so far, the CHARM preserved trial,[12] failed to show an improvement in outcome above what would have been expected from the achieved blood pressure-lowering effect. The reason for lack of significant outcome improvement is not clear, but diagnosing diastolic dysfunction is difficult and not well defined. In CHARM preserved, it was mainly a clinical diagnosis,[12] and some of the patients included, therefore, may not have had heart failure. This assumption is supported by the recently published CHARM echocardiographic substudy in preserved left ventricular systolic function, where only two-thirds of patients had objective evidence of diastolic dysfunction and only in less than half of them was it truly relevant.[13] In addition, underlying causes and pathophysiological mechanisms of heart failure with preserved left ventricular systolic function may not be uniform and may be more relevant in the treatment of these patients compared with systolic dysfunction.

The question remains whether therapy-induced regression of left ventricular hypertrophy is associated with a direct effect on prognosis and prevention of heart failure. It is well established that antihypertensive therapy leads to both regression of left ventricular hypertrophy and improvement in prognosis.[14] Again, it is very difficult to differentiate between a direct therapeutic effect on hypertrophy and associated prognostic improvement and an indirect effect by reduction of vascular events. Interestingly, indirect evidence from the HOPE trial suggests that regression of left ventricular hypertrophy may result in a larger reduction in heart failure events than in myocardial infarctions.[15] Animal studies suggest that inhibition of neurohumoral stimulation such as the sympathetic nervous system and the renin–angiotensin–aldosterone system may provide a beneficial effect on left ventricular hypertrophy, remodelling, and diastolic function independently of blood pressure lowering.[16] Still further studies, particularly in humans, are required to address this question more specifically. Complete follow-up including detailed information on medication at different time points in large cohort studies may also add to the understanding.

The task of understanding the mechanisms of heart failure, particularly at the very early stage and in patients with preserved left ventricular systolic function, is complex. Many contributing factors are known, but, as all interact significantly, their importance is not well known. Studies such as the one by de Simone *et al.*[6] may help to shed further light on this as it aims to differentiate contributing factors. However, there is still much to be done.

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