Gender differences in heart failure: paving the way towards personalized medicine?

Stephan H. Schirmer, Mathias Hohl, and Michael Böhm*

This editorial refers to ‘The gene expression profile of patients with new-onset heart failure reveals important gender-specific differences’, by B. Heidecker et al., on page 1188.

Patients respond with individual variations to therapeutic approaches. When studying drug effects in preclinical research models we are spoiled by a uniform response in the treatment group, often raising hopes about the translation of novel treatment strategies to clinical application. Subsequent clinical studies frequently show, however, that only certain subgroups of patients benefit from our therapy. Knowledge of individual differences in the molecular pathophysiology of a disease might help to optimize treatment strategies in patient groups or even individual patients. Gender, creating the largest two patient subgroups, can influence study results considerably. Naturally, this is of particular interest in disease entities where aetiology varies. Idiopathic dilated cardiomyopathy (IDCM) is a disease entity which is diagnosed based on clinical parameters and after exclusion of other causes such as ischaemic coronary disease. After initial diagnosis of heart failure due to IDCM, the individual's prognosis varies greatly. Large clinical trials have tried to shed light on differences in the optimal treatment strategy in demographic subgroups. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) has demonstrated ethnic variations in the ideal antihypertensive strategy. Next to ethnic diversity, gender differences, which have gained considerable interest in the past years, are often considered to implicate potential imbalances in treatment response. Clinical data are already available on gender-related disparities in outcome after myocardial infarction, the progression of myocardial hypertrophy, the clinical course after valve replacement, or ventricular arrhythmias. Also in heart failure, differences in aetiology and left ventricular (LV) function between men and women have been described.

In parallel to these clinical issues, advances in experimental research have made high-throughput studies of molecular processes possible. Gene transcription arrays, analysing mRNA expression levels at a whole genome level, provide a comprehensive study of the genetic programme of a small tissue sample, thus allowing a functional characterization of pathophysiological processes. This technique offers the possibility to detect dissimilarities between groups in an unbiased approach, serving on the one hand as a hypothesis-generating tool providing novel targets of interest that were previously unthought of, and on the other hand, looking at pathway and context analyses, as a means to characterize a cell or tissue functionally. mRNA expression arrays (transcriptome analyses) must be distinguished from DNA arrays investigating chromosomal aberrations or SNPs (single nucleotide polymorphisms). The latter serve, for example, to detect hereditary predisposition to a disease. Gene expression arrays, in contrast, can reveal characteristics of a pathophysiological process at the time of investigation. Recognizing previously unexpected functional differences in disease pathology may thus provide the basis for personalized medicine. Predominantly in oncology, gene expression signatures have been employed for the diagnosis and treatment of disease. Before single patients are differentiated, an approach distinguishing (demographic) patient groups can be made. This is of particular interest in the attempt to optimize gender-specific therapies. While manifestations and outcomes of cardiovascular disease have long been known to differ between men and women, molecular and cellular evidence of gender differences has only recently started to become the focus of research (Figure 1).

Heidecker and colleagues have now presented differential gene expression profiles of men and women with new-onset heart failure. For the first time, comprehensive clinical molecular data thus become available at the beginning of heart failure, where it potentially offers information that can be applied in the differential treatment of the two genders. In a recent study, the same authors for the first time described a transcriptome data set which they have used to find biomarkers that predicted prognosis in heart failure patients. The group has longstanding experience in gene expression investigations in cardiovascular disease. In 2004, transcriptome analyses of endomyocardial biopsies from 48 heart failure patients from two institutions were shown to predict...
cardiomyopathy aetiology accurately (ischaemic vs. non-ischaemic). Gene expression differences between genders were first described in another study which looked for a heart failure-related expression signature. In that study, the majority of heart failure genes were found to be sex and age dependent. In the investigation by Heidecker et al., the authors found a panel of genes differentially expressed between men and women. A large proportion of the genes are sex chromosome related. A minority of autosomal genes warrant special attention. Among them, CD24 was found to be overexpressed in men. CD24 is a surface marker associated with prognosis in various cancers, and has now for the first time also been described to have prognostic value in heart failure. Through its expression on leucocytes it may have an important function in immunological processes. Interestingly, up-regulation of chemokine receptor and early growth response (EGR) genes in circulating mononuclear leucocytes had earlier been related to heart failure. The transcriptome of circulating immune cells such as monocytes can also reflect progression of other cardiovascular problems. Further up-regulated genes, a potassium channel (KCNK1) in men and a phosphodiesterase (PDE6B), a glucose transporter (SLC2A12), and a potential regulator of adrenergic and angiotensin signalling (GATAD1) in women, are suggested to provide potential targets for personalized pharmacological heart failure therapy. Indeed, genes found to be differentially expressed can potentially be targeted by antiarrhythmic drugs (KCNK1), phosphodiesterase inhibitors or adrenoreceptor inhibitors (GATAD1) (Figure 1).

Heidecker et al. are to be complimented on another study from a well set-up clinical database. In contrast to investigations from end-stage heart failure biopsies, data from new-onset heart failure can potentially influence clinical decision making. In this context, it is important to note that the differences detected for a large part disappeared during later stages of the disease, where autosomal genes in particular no longer showed differential expression between males and females. Also, data from an earlier study of differences in gene expression in relation to gender in transplanted hearts, i.e. during end-stage heart failure, could not be fully confirmed in the present investigation.

However, the study of Heidecker et al. has some limitations. One is the lack of matched LV function and dimensions between men and women. Women had smaller ventricles and a higher ejection fraction. Although the authors claim that this was also the case in other heart failure populations, it limits the conclusion that the detected differences in gene expression arise solely from gender differences. When the groups were adapted to achieve matched conditions, autosomal genes in particular were no longer found to be differentially expressed. The differences found, therefore, are at least partly due to discrepancies in LV function between the genders. Heidecker et al. claim that better myocardial function in women reflects results found in other trials and the clinical situation, and that the detected transcriptome differences constitute a possible molecular explanation for the functional differences. However, other circumstances might explain the observed differences. Adherence to heart failure medication differs between men and women.

**Figure 1** Gender differences in heart failure are based on distinct characteristics in diagnosis, management, and prognosis in men and women. Molecular details of cardiac pathophysiology may influence the clinical phenotype. Genes differentially expressed (top) and phenotypic characteristics (bottom) are depicted relative to the other gender, where the left column represents genes and characteristics more prevalent in women, and the right column those more prevalent in men.
genders. As drug compliance is critical in non-invasive therapies, non-adherence to drug treatment in a patient group might be one of the causes of functional differences between the sexes. Another recent report described that heart failure medication was not prescribed to target dose as recommended in the guidelines. Here, physician gender also played a role, with female patients treated by male physicians being least likely to receive the full dosage, and female doctors being more likely to prescribe target doses of heart failure medication to female patients. At the cellular level, an inevitable limitation arises from biopsy techniques, where myocardial as well as endocardial tissue is obtained. In contrast to histological studies, gene expression analyses from biopsies cannot exclude a potential influence of the tissue type sampled. In a relatively small patient population, the proportion of endocardial and myocardial tissue, respectively, may vary between the two groups. Finally, while single genes were found to be differentially transcribed in men and women, the authors fail to show differentially regulated clusters of genes which could indicate distinct regulation of functional pathways.

Currently, there is not a clinical application based on gender-specific gene expression differences. First, the results of the current study need to be validated in an independent, large patient population and will have to be tested in experimental models. A follow-up study, where whole genome expression analyses are carried out both at the onset and during therapy of heart failure, would be of particular interest as potential differences in the treatment response might be revealed. The study of Heidecker et al. brings us further towards treatment approaches that are adjusted to demographic groups. However, true personalized medicine, where pharmaceutical therapies are tuned to individual patient needs, is yet to come.

**Acknowledgements**

The authors are supported by a research grant by the Deutsche Forschungsgemeinschaft (KFO 196) and by the Wissenschaftsgemeinschaft (KFO 196) and by the Wissenschaftsgemeinschaft (KFO 196) and by the Wissenschaftsgemeinschaft (KFO 196) and by the Wissenschaftsgemeinschaft (KFO 196). Conflict of interest: none declared.

**References**