Biomarkers and personalized medicine in heart failure
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CHAPTER 8

Summary and Future Perspectives

Jasper Tromp
This thesis investigated the role of biomarkers in personalized and precision medicine approaches in heart failure. A personalized medicine approach targets the correct individual, while a precise treatment targets the correct pathophysiological mechanism. We used two novel approaches using biomarkers to (1) identify pathophysiological mechanisms relevant to patients with heart failure with a reduced (HFrEF), mid-range (HFmrEF) and preserved (HFpEF) ejection fraction and (2) establish novel subtypes in heart failure using an unbiased cluster analysis approach.

PATHOPHYSIOLOGICAL DIFFERENCES BETWEEN HFRREF AND HFPEF

Current medical treatment possibilities for heart failure include angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and mineralocorticoid receptor analogists (1). Overall, these therapies have proven effective in patients with HFrEF and have significantly improved outcomes for these patients. This, however, is not the case for patients with HFpEF (1–4), which suggests that HFrEF and HFpEF are two distinct disease entities. There are clear differences in phenotype between patients with HFrEF and HFpEF. Patients with HFrEF are more frequently men with an ischemic etiology of heart failure. In contrast, patients with HFpEF are more often women and have a plethora of comorbidities such as atrial fibrillation, hypertension and obesity (5–7). These differences between patients with HFrEF and HFpEF are also apparent when studying circulating biomarkers, which can help in characterizing the pathophysiology of HFrEF and HFpEF. For example, a previous study showed that biomarker levels related to collagen deposition are higher in HFpEF compared to HFrEF (8). Yet, these studies often investigated individual or a limited number of biomarkers. Improved techniques in biomarker measurement have allow us to measure larger numbers of biomarkers in individual patients. This provides more comprehensive data that characterizes pathophysiological differences. Therefore, it is timely to develop more advanced data-analysis techniques to characterize pathophysiological differences between HFrEF and HFpEF and identify single biomarkers of interest.

In Chapter 2, we investigated fibrosis and inflammation marker syndecan-1 in patients with HFrEF and HFpEF. In this chapter, we showed that syndecan-1 is significantly associated with worse survival rates in patients with HFpEF, but not in patients with HFrEF, despite similar levels of syndecan-1 between patients with HFrEF and HFpEF. In addition, levels of syndecan-1 were associated with inflammation biomarkers, but not with markers of fibrosis. Both fibrosis and inflammation are key in the pathophysiology of HFpEF (10–13). Syndecan-1 was associated with a higher risk of developing worsening renal function during hospitalization during hospitalization, in a separate study (14). This suggests that syndecan-1 might be associated with a risk of developing worsening renal function in HFpEF. The development of worsening renal function is associated with more adverse outcomes in HFpEF than in HFrEF (15, 16). Furthermore, renal dysfunction is associated with the pathophysiology of HFpEF(11). Renal dysfunction can be a potential cause of HFpEF...
due to a negative spiral of reduced kidney perfusion, leading to increased inflammation, which in turn leads to additional stiffening of the heart muscle, which then further reduces kidney perfusion. While a plethora of studies have investigated single biomarkers in HFrEF and HFpEF (8, 17–19), the number of studies investigating differences in biomarker profiles between HFrEF and HFpEF is limited (20, 21). In Chapter 3 we studied differences in levels, predictive association and correlations between biomarkers using network analysis in HFrEF and HFpEF (22). Results of this study showed that levels of NT-proBNP were considerably lower in patients with HFpEF than in HFrEF, which is in line with earlier reports (23). Lower levels of NT-proBNP in HFpEF are potentially caused by less cardiac stretch in patients with HFpEF. Patients with HFpEF had higher levels of hs-CRP compared to patients with HFrEF, which is an important marker of inflammation. Fibrosis marker osteopontin and endothelial damage marker angiogenin were both associated with more adverse outcomes in HFpEF than in HFrEF. These findings add to existing evidence that the pathophysiology in HFpEF is associated with adverse cardiac fibrosis as well as endothelial damage (10, 24). To study correlations between biomarkers we used a network analysis approach. These analyses identify biomarkers that have a strong association with several other biomarkers in the network. When these so-called “central hubs” are “removed” from the network, the network of biomarkers falls apart. This suggests that these hubs reflect active pathophysiological processes in these patients. In Chapter 3 we found that inflammatory biomarkers were important hubs in HFpEF, while NT-proBNP was an important hub in HFrEF. In addition, we found that exclusive correlations between biomarkers in HFrEF were associated with NT-proBNP. In contrast, exclusive correlations between biomarkers in HFpEF were associated with markers of inflammation and endothelial damage.

In Chapter 4 we studied biomarker profiles in patients with acute heart failure. We were particularly interested in differences between patients with HFrEF, HFmrEF and HFpEF. The main results of this study were that biomarker profiles of patients with HFmrEF are between those of patients with HFrEF and HFpEF. Levels of BNP were considerably higher in patients with HFrEF compared to patients with HFmrEF and HFpEF. Furthermore, we found that fibrosis markers syndecan-1 and galectin-3 were associated with adverse outcomes in HFpEF, but not in HFrEF, confirming earlier findings (9, 25). In addition, biomarkers pentraxin-3, receptor for advanced glycation end-products (RAGE), and tumor-necrosis factor receptor 1-alpha (TNF-R1a) were associated with higher rates of mortality and/or hospitalization at 60 days after admission in HFpEF, but not in HFrEF. Levels of pentraxin-3 are increased in patients with HFpEF and associated with more severe diastolic dysfunction (26). Lastly, a network analysis of biomarkers within HFrEF, HFmrEF and HFpEF showed that BNP was an important hub in patients with HFrEF. In contrast, inflammatory markers were important hubs in patients with HFpEF. Patients with HFmrEF, showed an intermediate profile, with both BNP as well as inflammatory biomarkers as important hubs in the network of patients with HFmrEF. Results of our study in Chapter 4 suggest that patients with HFmrEF are similar to both patients with HFrEF and those with HFpEF in terms of clinical characteristics and
biomarker profiles. Future studies can potentially identify patients with HFmrEF who have a similar biomarker profile to patients with HFrEF and can thus benefit from guideline-directed treatment.

In Chapter 5 we identified biological mechanisms that are either unique for patients with HFrEF or unique for patients with HFpEF. Results of this study showed that a large part of correlations between biomarkers were overlapping between HFrEF, HFmrEF and HFpEF. We observed that interleukin-1 receptor type 1 (IL1RT1), growth-differentiation factor 15 (GDF15), activating transcription factor 2 (ATF2) and NT-proBNP were important hubs in HFrEF. In networks in HFpEF, we identified ITGB2 and catenin-beta as important hubs. Lastly, we found that biomarker networks in HFrEF were associated with sequence-specific DNA binding, phosphorylation of peptidyl-serine, proliferation of smooth muscle cells, protein kinase B signaling and MAPK cascade. Both protein kinase B signaling and MAPK are related to cell proliferation and an increase in metabolism. In contrast, biomarker networks in HFpEF were associated with inflammation, integrin signaling and extracellular matrix organization. These data suggest future studies should focus on protein-protein interactions within certain existing pathways such as integrin mediated signaling and extracellular matrix organization (10, 24).

The aim of Chapter 6 was to identify novel subtypes within heart failure based on biomarker profiles. Results from previous chapters showed that the pathophysiology of HF shows substantial interindividual heterogeneity. Nevertheless, patients with particularly HFrEF are all treated according to guidelines with ACE-inhibitors (ACEi) and beta-blockers. We identified 8 subtypes with considerable differences in treatment response to uptitration of ACE-inhibitors and beta-blockers. One particular subtype was characterized by very low levels of chitinase 1 (CHIT1). CHIT1 is a hydrolyzing enzyme involved in many physiological and pathophysiological processes (27). Interestingly, about 10-20% of individuals in the European population are unable to produce CHIT1 (28). In our study, about 5% of patients were in the subgroup deficient for CHIT1. Patients from this subtype seemed to derive no benefit from uptitration of ACE-inhibitors and beta-blockers to guideline directed dosages. Future studies should investigate what the effect of CHIT1 is on the effectiveness of ACE-inhibitors and beta-blockers.

Chapter 7 is an editorial about the role of risk and disease heterogeneity in predicting heart failure. This editorial discusses a paper by Delles et al., which identified predictive biomarkers for incident heart failure using metabolomics. The authors found phenylalanine as a potential novel target, yet this new marker did not improve risk prediction models beyond a C-index of 0.7. In Chapter 7, therefore, we discussed how prediction of incident heart failure can possibly be improved by making use of risk and disease heterogeneity. We argue that to improve risk prediction of incident heart failure, individuals in the community need to be stratified into risk groups (risk heterogeneity). A previous study showed that the predictive value of biomarkers for incident heart failure can be improved by a-priori clinical risk stratification of individuals (29).

Four main conclusions can be drawn from the research in this thesis:
(1) Particularly markers of inflammation, fibrosis and angiogenesis are the main drivers of outcome in HFpEF, but not in HFrEF.

(2) Correlations between biomarkers in HFpEF are associated with inflammation and endothelial dysfunction, while correlations between biomarkers in HFrEF are associated with cardiac stretch and pressure overload, as revealed by network analyses.

(3) Biomarker profiles in patients with HFmrEF are in between patients with HFrEF and HFpEF.

(4) Selection of patients who respond to guideline directed treatment with ACE-inhibitors and beta-blockers might be improved by reclassifying patients into subgroups based on their biomarker profiles.

The methods in this thesis were used for the first time in biomarker research in heart failure. The actual value of these methods in identifying novel treatment targets has to be further established. Future studies could evaluate possible targets found in this thesis on further clinical and mechanistic relevance. Further, it should be noted that the biomarkers investigated in this thesis were measured in the peripheral circulation. Therefore, although heart failure is primarily a cardiac problem, future studies on possible treatment targets could build on the findings in this thesis in the examination of systemic effects of heart failure.

**FUTURE PERSPECTIVES**

To effectively target disease mechanisms in heart failure using more precise approaches (*precision medicine*), we first need to identify mutually exclusive patient groups with heart failure who represent a relatively homogenous pathophysiological subgroup (*personalized medicine*). Results of this thesis provided a first step in a novel classification of heart failure. We used biomarker profiles, as surrogates for pathophysiological processes, to identify clinically meaningful subgroups within heart failure. Nevertheless, this study was also limited by the choice of biomarkers and the availability of other determinants of pathophysiology. To optimize clustering analyses in order to correctly reclassify patients with heart failure into mutually exclusive homogenous subgroups, several crucial steps are needed. First of all, we need more comprehensive and unbiased approaches in establishing the input for cluster analysis. A combined approach utilizing proteomic, RNA-sequencing and genetic data is preferred over using biomarkers alone. This data can then be combined with important phenotypic data such as echocardiographic information. An early study from 2002 by Petricoin et al. used proteomic data to identify patients with ovarian cancer from healthy individuals using a proteomic signature (31). The authors only selected the relevant proteins by extracting proteins which were either up- or downregulated in patients with ovarian cancer versus healthy controls. A similar approach can be employed in patients with heart failure, by only using proteins, genes and RNA fragments relevant to heart failure by comparing these -omics profiles to healthy controls. These more meaningful -omics profiles can then be used to define clinically meaningful subgroups.
Following a more comprehensive identification of homogenous and clinically relevant subgroups of heart failure patients, we can study specific disease mechanisms within subgroups using precision medicine tools. Instead of using a selected set of biomarkers, a combined -omics approach is preferred to give a more comprehensive and unbiased insight into possible pathophysiological mechanisms. System biology approaches can integrate data ranging from the gene- to protein and even phenotype, to explore possible relevant disease mechanisms in homogenous subgroups of heart failure patients.
REFERENCES


