Distinguishing heart failure with reduced ejection fraction from heart failure with preserved ejection fraction: A phenomics approach

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Pathophysiological differences between patients with heart failure with preserved (HFrEF) and reduced (HFrEF) ejection fraction (EF) remain unclear. Therefore we used a phenomics approach, integrating selected proteomics data with patient characteristics and cardiac structural and functional parameters, to get insight into differential pathophysiological mechanisms and identify potential treatment targets.

We report data from a representative subcohort of the prospective Singapore Heart Failure Outcomes and Phenotypes (SHOP), including patients with HFrEF (EF <40%, n = 217), HFrEF (EF ≥50%, n = 213), and age- and sex-matched controls without HF (n = 216). We measured 92 biomarkers using a proximity extension assay and assessed cardiac structure and function in all participants using echocardiography. We used multi-block projection to latent structure analysis to integrate clinical, echocardiographic, and biomarker variables. Candidate biomarker targets were cross-referenced with small-molecule and drug databases. The total cohort had a median age of 65 years (interquartile range 60–71), and 50% were women. Protein profiles strongly discriminated patients with HFrEF (area under the curve [AUC] = 0.89) and HFrEF (AUC = 0.94) from controls. Phenomics analyses identified unique druggable inflammatory markers in HFrEF from the tumour necrosis factor receptor superfamily (TNFRSF), which were positively associated with hypertension, diabetes, and increased posterior and relative wall thickness. In HFrEF, interleukin (IL)-8 and IL-6 were possible targets related to lower EF and worsening renal function.

We identified pathophysiological mechanisms related to increased cardiac wall thickness parameters and potentially druggable inflammatory markers from the TNFRSF in HFrEF.
CA125, carbohydrate antigen 125; CTSL, cathepsin L; DKK1, Dickkopf-related protein 1; HBEGF, heparin-binding EGF-like growth factor; HFP EF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IL6, interleukin-6; IL6R, interleukin-6 receptor; IL8, interleukin-8; LV, left ventricular; NGF, neurotrophic growth factor; PlGF, placental growth factor; TNFRSF, tumour necrosis factor receptor superfamily. Study design and main study results.

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Methods

Study population

We report data from a representative subcohort of the Singapore Heart Failure Outcomes and Phenotypes (SHOP) study. The design and primary outcomes of the SHOP study were published previously. SHOP was a Singapore-based prospective, observational cohort study with the primary aim of determining the characteristics and outcomes of patients with HFrEF compared to patients with HFrEF. A total of 1098 patients were recruited from six Singaporean centres, serving >80% of Singapore’s population. All participants presented to the hospital or the clinic with a primary diagnosis of heart failure (HF), which occurred within 6 months before recruitment. HF episodes were determined by cardiologists blinded to biomarker values and following the 2012 European Society of Cardiology criteria defining HF. Patients with HF secondary to specific aetiologies (e.g. infiltrative or congenital heart disease, severe valve disease), with end-stage renal failure (defined as estimated glomerular filtration rate [eGFR] <15 ml/min/1.73 m²), a left ventricular ejection fraction (LVEF) between 41% and 49%, and those with life-limiting comorbidities resulting in <1 year life expectancy were excluded.

The non-HF controls were free-living adults participating in the Singapore Longitudinal Aging Study (SLAS). The SLAS study randomly sampled all residents aged ≥55 years in contiguous precincts within five districts in the Southeastern region of Singapore who were identified from a door-to-door census and invited to participate. SLAS excluded participants who could not participate because of severe physical or mental disabilities.

This study included a subset of 217 participants with HFrEF, 213 participants with HFrEF, and 216 participants without HF. All HFrEF and HFrEF patients with sufficient stored plasma were considered for inclusion, and samples with a wide range of N-terminal brain natriuretic peptide (NT-proBNP) plasma levels were selected to include both patients with mild and severe HF. Next, all HF samples were matched 1:1:1 with control subjects based on age, sex, and ethnicity. All participants signed informed consent and this study received ethical approval. Ethics and legal requirements restrict sharing of the dataset outside Singapore.

Clinical and biomarker measurement

All participants had demographic and medical history collected and their signs and symptoms of HF at the baseline assessment. Blood plasma was drawn and stored at −80°C in EDTA tubes to measure NT-proBNP and other biomarkers. Additionally, blood samples were taken, and participants underwent comprehensive transesophageal Doppler echocardiography using standardized equipment (Vivid ultrasound systems, General Electric, Milwaukee, WI, USA) in compliance with the American Society of Echocardiography recommendations from 2009. The LVEF was measured using the biplane method of disks. Based on this measurement, patients were classified into two groups: those with HFrEF for LVEF <40% and those with HFrEF for LVEF ≥50%. The E/e’ ratio, an index of left ventricular filling pressure, was also recorded. Comorbidities were defined based on medical history. Obesity was defined as a body mass index ≥30 kg/m².

Concentrations of NT-proBNP were measured on Cobas e411 immuno-analysers (Roche Diagnostics GmbH, Mannheim, Germany) by electrochemiluminescence immunoassay using the Elecsys proBNP II assay kit. The measurement range of NT-proBNP is 5–35000 pg/ml. Laboratory average concentration and inter-assay coefficient of variation of low (148 pg/ml, 4.85%) and high (4691 pg/ml, 5.61%) quality control samples of the NT-proBNP assay were established over 63 independent assays. The Proseek Multiplex16x96 CVD I kit (Olink Bioscience, cat no. 94200) was used to measure 92 cardiovascular-related proteins. This kit uses a proximity extension assay (PEA) to measure proteins in 1 µl plasma samples. PEA is a homogeneous assay that uses pairs of antibodies with DNA reporter molecules. When the antibodies bind to their targets, they produce DNA amplicons that barcode the respective antigen. Preamplification was performed on the BioRad T-100 thermal cycler and the amplicons were quantified using the 96.96 Gene Expression Dynamic Chip (Fluidigm Corporation) on the BioMark™/Biomark HD real-time polymerase chain reaction platforms. The assay includes four internal controls added to each sample to be tested, and two external controls (interplate and negative controls) in triplicates. Raw data were exported and preprocessed using the Olink Wizard in GenEx software (MultiD Analyses). Quality control checks and data normalization were performed by TATAA Biocentre AB (Goteborg, Sweden) and returned as normalized protein expression values that indicate a relative concentration of each analyte. The laboratory operators were blinded to the study population's information.

Statistical analysis

Baseline characteristics were presented as the median and interquartile range (IQR) for continuous data and count and percentage for discrete data types. Differences between groups were tested using the Kruskal–Wallis test for continuous variables and the Chi-square test for proportions. Eleven samples had missing protein data and were excluded from the analysis, resulting in a total sample size of 646. All proteins were annotated with HGNC symbols (HUGO nomenclature symbols).

First, the integrated phenomics analysis was performed using the Diablo Package in R. Block sparse partial least squares discriminant analysis (SPLS-DA) was used, which takes blocks of explanatory data (clinical data [n = 9], echo parameters [n = 18], and proteins [n = 92]) and the outcome variable (type of HF) to identify the most relevant features (either clinical, echocardiography or protein data) from each group. The relevancy of the features is determined by how well certain features help to distinguish between the types of HF. First, the number of latent components is chosen to best distinguish the phenotypes of interest. The number of components was chosen based on the classification error rate compared to the number of components, a visual representation of the error rate by the number of components can be found in online supplementary Figure S1. Second, the optimal number of parameters (either clinical, echocardiographic or biomarker variables) was chosen, this was done with five-times cross-validation and 100 number of repeats.

In the next step, features that were more specific for either HFrEF or HFrEF were identified. This was done by making three comparisons: HFrEF versus controls, HFrEF versus controls, and HFrEF versus HFrEF. To determine features that were more specific for HFrEF or for HFrEF, the comparisons between HFrEF and controls and HFrEF and controls were assessed first. When a feature was present in one of those comparisons but not in the other, the feature was classified as being more specific to that phenotype. When features differed in HFrEF from controls and HFrEF from controls but not in the comparison between HFrEF versus HFrEF, they were classified as common HF features. When features were different in both HFrEF
versus controls and HFrEF versus controls but also differentiated HFpEF from HFrEF; they were classified as more specific to that HF phenotype. Some features were higher in HFpEF than controls but lower in HFrEF than controls or vice versa; those features were classified as specific for HFpEF and HFrEF.

In the final step, networks for HFpEF and HFrEF were constructed correlating clinical, echocardiographic and protein data. The colour of the edges represents the direction of the association. Red edges indicate a positive correlation, and blue edges a negative correlation. Features that were more specific for HFpEF and HFrEF were highlighted by colour. The nodes of features that were specific for HFrEF are red and features specific of HFpEF are green.

External databases of the druggable genome were queried to identify potentially druggable proteins. In Finan et al., Tier 1 druggable targets are proteins for which licensed and clinically available drugs or drugs in clinical development are available. According to Finan et al., proteins that were Tier 1 druggable (targets of approved drugs and drugs in clinical development) were highlighted in bold font in the networks.

Table 1 shows the baseline characteristics of the community-based controls (n = 216), patients with HFpEF (n = 213) and patients with HFrEF (n = 217). The median age was 65 years in the control group and 69 years and 64 years in the HFpEF and HFrEF groups, respectively. Most participants were of Chinese origin. Obesity (26% vs. 17%), hypertension (87% vs. 70%) and anaemia (62% vs. 49%) were more prevalent in patients with HFpEF than HFrEF. NT-proBNP concentrations were lowest in participants without HF (median 76 pg/ml, 95% confidence interval [CI] 46–131 pg/ml), higher in patients with

Two-sided p-values of <0.05 were considered statistically significant. All analyses were performed in R version 4.0.5.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the community-based controls (n = 216), patients with HFpEF (n = 213) and patients with HFrEF (n = 217). The median age was 65 years in the control group and 69 years and 64 years in the HFpEF and HFrEF groups, respectively. Most participants were of Chinese origin. Obesity (26% vs. 17%), hypertension (87% vs. 70%) and anaemia (62% vs. 49%) were more prevalent in patients with HFpEF than HFrEF, whereas coronary artery disease (CAD) was more prevalent in HFrEF (57% vs. 34%) than HFpEF. NT-proBNP concentrations were lowest in participants without HF (median 76 pg/ml, 95% confidence interval [CI] 46–131 pg/ml), higher in patients with
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Table 2

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<th>Table 2 Echocardiographic parameters in controls, heart failure with preserved and reduced ejection fraction</th>
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<td><strong>Controls</strong></td>
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HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter.

Figure 1

Receiver-operating characteristic (ROC) curve for biomarkers on all three components for (A) heart failure with preserved ejection fraction (HFpEF) and (B) heart failure with reduced ejection fraction (HFrEF). AUC, area under the curve.

HFrEF (median 970 pg/ml, 95% CI 371–2239 pg/ml) and highest in HFpEF (median 2880 pg/ml, 95% CI 1299–7005 pg/ml, p < 0.001).

Echocardiographic parameters

Table 2 shows the echocardiographic parameters for the study groups. The median LVEF was 64% (95% CI 62–67%) in controls, 60% (95% CI 55–63%) in HFpEF and 30% (95% CI 23–38%) in HFrEF. Left ventricular mass index, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left atrial volume index were lowest in participants without HF, higher in HFpEF and highest in HFrEF. Diastolic function was worse in patients with HFrEF (e′ lateral 5 cm/s, [95% CI 4–7 cm/s] and e′ medial 4 cm/s [95% CI 3–5 cm/s]) than in HFpEF (7 cm/s [95% CI 5–9 cm/s] and 5 cm/s [95% CI 4–6 cm/s]) and controls (8 m/s [95% CI 7–9 cm/s] and 7 cm/s [95% CI 5–8 cm/s]).

Integration of clinical variables, echocardiographic parameters and biomarkers

First, we used multi-block projection to latent structure analysis on biomarker, clinical and echocardiographic data to discriminate HFpEF or HFrEF from controls without HF and patients with HFrEF from HFpEF. The analyses selected 93 unique features as most optimal to discriminate HFpEF from controls, 117 to discriminate HFrEF from controls, and 48 to discriminate HFpEF from HFrEF. Online supplementary Figures S2–S4 show the selected features and loading weights. Biomarkers discriminated HFpEF (area under the curve [AUC] 0.95) and HFrEF (AUC 0.89) from controls with good accuracy (Figure 1). Online supplementary Figure S5 shows that clinical characteristics and echocardiographic parameters separated HFpEF (AUC 0.94 and 0.65, respectively) and HFrEF (AUC 0.90).
Figure 2 Venn diagram of features most pronounced in heart failure (HF) with reduced (HFrEF) or preserved ejection fraction (HFpEF).

In the next step, we identified features specific to HFpEF and HFrEF. Figure 2 shows the Venn diagram with specific and common features of HFrEF and HFpEF. Twenty-five features, such as older age, hypertension, higher relative wall thickness and increased inflammatory protein concentrations, were specific to HFpEF. The 51 specific features of HFpEF included male sex, a history of CAD and markers related to cardiac metabolism. Notably, biomarkers cathepsin L (CSTL), proheparin-binding EGF-like growth factor (HBEGF), galectin-3, thrombomodulin were higher in HFpEF versus controls, but lower in HFrEF versus controls.

In the final step, we performed integrated network analysis to provide a mechanistic and phenotypic context to markers found in the previous step. The HFpEF network in Figure 3 shows that wall thickness parameters (diastolic interventricular septal thickness, relative wall thickness and left ventricular mass) were hubs (central nodes). These parameters were positively correlated with diabetes mellitus, hypertension, and most biomarkers, including inflammatory markers TNFRSF1A, TNFRSF1B and TNFRSF10B. Cross-referencing the specific HFpEF markers in the network against druggable genes suggests that tumour necrosis factor receptor superfamily (TNFRSF) 1A, TNFRSF10B, HBEGF, and placental growth factor are potentially druggable (proteins in bold in Figure 3 and online supplementary Table S1).

Figure 4 shows the HFrEF network. Age, posterior wall thickness, e’ lateral and e’ medial were central hubs next to LVEF, CAD and brain natriuretic peptide. Older age was connected to a reduced LVEF through higher concentrations of inflammatory markers, such as increased concentrations of HBEGF, interleukin-6 receptor (IL6R), Dickkopf-related protein 1 (DKK1), CTS, and neurotrophic growth factor. Notably, carbohydrate antigen 125 (CA125) was associated with CAD and a reduction in LVEF and was part of the druggable genome.

Discussion

In this study, we applied an integrative phenomics approach to investigate pathophysiological differences between patients with HFrEF and HFpEF. Our study has three main findings. First, HFrEF and HFpEF had unique biomarker profiles. In HFrEF, biomarker profiles correlated both with comorbidities and echocardiographic parameters. Second, we identified potentially druggable HFrEF-specific proteins that correlated with increased wall thickness parameters and showed a strong association with hypertension and diabetes. Third, we identified HFpEF-specific markers associated with older age and CAD. Our study shows that an integrated phenomics approach might provide new insights into the complex pathophysiology of HFrEF.
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Figure 3 Correlation network of biomarkers, clinical variables and echo data in patients with heart failure with preserved ejection (HFpEF). Highlighting features that were specific for HFpEF. Bold features are Tier 1 druggable targets.

Figure 4 Correlation network of biomarkers, clinical variables and echo data in patients with heart failure with reduced ejection fraction (HFrEF). Highlighting features that were specific for HFrEF. Bold features are Tier 1 druggable targets.
and HFrEF by providing phenotypical and mechanistic context to possible druggable treatment targets, summarized in the Graphical Abstract.

The protein variation in HfPEF strongly correlated with comorbidities but not echocardiographic parameters. In HFrEF, protein variation was strongly associated with comorbidities and echocardiographic parameters. Paulus and Tschöpe suggested that comorbidities play a more critical role in the pathophysiology of HfPEF than HFrEF by causing a pro-inflammatory state leading to cardiac stiffening and increased filling pressures. Several studies showed comorbidities were more prevalent in HfPEF than in HFrEF. In studies investigating incident HF, non-cardiac comorbidities, such as renal dysfunction, obesity or hypertension, were associated with a higher risk of HfPEF than HFrEF. Previous biomarker studies showed that protein–protein interaction networks in HfPEF were more complex than protein–protein interaction networks in HFrEF. Our findings extend previous studies by suggesting that biomarker concentrations in HfPEF are more often a reflection of comorbidities than cardiac dysfunction, emphasizing the pathophysiological complexity of the HfPEF syndrome.

Our study identified unique biomarker networks in HfPEF with a central role in inflammatory markers of the tumour necrosis factor-alpha (TNF-α) family. These markers were strongly related to diabetes and increased wall thickness. Notably, Asian patients with HfPEF more often have a lean-diabetic phenotype. These patients have potentially higher levels of inflammation due to increased visceral fat and worse outcomes than other HfPEF phenotypes. Therefore, the networks with increased inflammation markers might express the higher prevalence of the lean-diabetic phenotype in the Singapore population. TNFRSF1A is a TNF-α receptor. TNF is a key pro-inflammatory cytokine that promotes left ventricular remodelling. Trials with anti-TNF-α therapies (etanercept, infliximab and phosphodiesterase inhibitors) in patients with HFrEF did not improve outcomes and worsened patient conditions. However, studies with these or other anti-inflammatory therapies have not been performed in HfPEF and such trials may be warranted. TNFRSF10B (also known as death receptor 5 [DR5]) is the main receptor bound by apoptosis-inducing ligand (TRAIL) and is highly expressed in human cardiomyocytes. Due to its ability to selectively activate apoptosis in cancer cells, it has been studied as cancer therapeutic and multiple DR5 agonists have been studied in phase I or II trials. Elevated plasma levels of DR5 are associated with adverse outcomes. In cardiomyocytes, however, DR5 signalling seems beneficial, enhancing physiological hypertrophy and limiting fibrosis. As multiple DR5 agonists are readily available, DR5 presents an attractive therapeutic target in HfPEF.

In HFrEF, we identified IL6 and CA125 as potentially druggable proteins. It has been shown that IL6 correlates with lower LVEF, atrial fibrillation and worse clinical outcomes in patients with predominantly HFrEF. Several IL6 blockers are available, and a study investigating the monoclonal antibody ziltivekimab showed that it markedly reduced biomarkers of inflammation and thrombosis in patients with high atherosclerotic risk. In HfPEF, ziltivekimab will be tested in patients with HfPEF (NCT05636176); however, anti-IL6 therapies are not currently under investigation in HFrEF. In our study, CA125 was found to be associated with CAD. Previous phase III clinical trials targeting CA125 with the antibody abagovomab for ovarian cancer showed no safety concerns. CA125 has been studied in HF as a congestion and inflammatory marker, where it has been shown to cluster with IL6. In HF, CA125 has not been studied as a treatment target.

To enhance the practical implications of this study, we cross-referenced HfPEF and HFrEF-specific proteins with the druggable genome. This approach was previously used in a study by Henry et al., in which they aligned proteins causally related to incident HF to the druggable genome. Interestingly, they also identified galectin-3 and CTL-1 as potentially druggable targets. Our study extends this previous effort by differentiating between HF subtypes.

Limitations

Several limitations should be addressed. First, our study was cross-sectional and cannot demonstrate causality. The results of this study should be considered hypothesis-generating and future studies should provide evidence for causality. Second, protein abundance was assessed in peripheral blood; other mechanistic studies are needed to confirm the role of potential targets in the human heart. Thirdly, our study is limited by using a small pre-selected panel of proteins. Fourth, the study may have been underpowered to detect differences in some biomarkers. Fifth, the study used PEA technology to measure biomarkers and did not validate druggable targets through immunoassays. Lastly, our study was performed in an Asian population. Whether our findings are generalizable to other non-Asian populations is still being determined.

Conclusion

Unique pathophysiological networks in HfPEF were associated with inflammatory markers of the TNF-α family, with comorbidities such as hypertension and diabetes — and with increased cardiac mass and wall thickness. In HFrEF, unique pathophysiological networks were associated with unique markers, such as CA125 and inflammatory proteins IL6 and IL8. These markers were associated with older age and CAD. Our study shows that an integrative phenomics approach can provide mechanistic and phenotypical context to potentially novel druggable targets in HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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