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Discussion

The present analysis showed that (i) ICAM-1 plays an important role in inflammatory response in symptomatic patients with preserved ejection fraction prior to diastolic dysfunction. Moreover we showed that (ii) immunohistological markers interact significantly among each other (macrophages and ICAM-1) and correlated significantly with highly normal (reference < 14) E/e' values.

Studies in human myocardium or patients prior to HFpEF development are limited [25]. The endothelium involves the endothelial cells of the coronary microvasculature and of the intramyocardial capillaries. Cardiovascular comorbidities such as obesity, metabolic syndrome or hypertension related to HFpEF leading to systemic and cardiac microvascular inflammation and subsequently to endothelial activation [5,11,26]. Pro-inflammatory properties dominate this condition affecting primarily the coronary microvascular endothelium [27-29].

Systemic and cardiac inflammation influence endothelial cell activity significantly in a way that CAMs are upregulated and overexpressed during these processes. Consistent with our findings, the role of CAMs like E-selectin, ICAM-1, perforin or VCAM-1 in the development of HF and especially HFpEF has been previously described [11,22, 30-34].

Recent studies showed increased ICAM-1 levels as significant driver in the development of HFpEF. Franssen et al. found, that ICAM-1 was upregulated in myocardial samples of HFpEF patients, but not in those with HFrEF [8]. Another very interesting finding is that from Salvador et al., where HFpEF murine models with a deficient ICAM-1 expression had less pro-inflammatory monocyte infiltration leading to less fibrotic changes [35]. In our study, patients with higher ICAM-1 levels had significantly increased NT-proBNP and E/e' values. The higher prevalence of ICAM-1 revealed the endothelial activation and microvascular inflammation in these patients and the comorbidity-induced pro-inflammatory status [36]. Patel et al. showed that CAMs were associated with worse diastolic dysfunction but the effect was weakened by adjustment for covariates [37]. This finding strengthened the assumption that the relation of CAMs with diastolic dysfunction is explainable by the comorbidity burden [37]. Interestingly, we found that patients with higher ICAM-1 levels had significantly more comorbidities than those with lower ICAM-1 levels.

The expression of adhesion molecules favors myocardial infiltration of inflammatory cells. There is an increased promotion and activation of pro-fibrotic macrophages in HFpEF patients [36]. Furthermore, Hulsmans and colleagues highlighted the role of cardiac macrophages in the development of diastolic dysfunction [16]. Our findings regarding the macrophages were consistent with previous studies due to the increased macrophage level in the EMBs of our patients. There was a strong association of macrophages with ICAM-1 and higher E/e' values. Our findings strengthened the assumption that these immunohistological markers can often be found in the early phase of inflammatory processes in HF development.

Macrophage activation can occur either in the M1 phenotype with pro-inflammatory properties or in the M2 phenotype with anti-inflammatory properties. Glezeva et al. demonstrated a M2 macrophage activation in the HFpEF pathogenesis [36]. We focused in our study on the macrophage number and did not consider the macrophage phenotype. Additionally, the endothelial activation triggers the endothelial-to-mesenchymal transition (EndMT), whereby endothelial cells are converted to mesenchymal-cells resulting in fibroblasts to develop cardiac fibrosis [38]. Moreo and colleagues proved in 252 patients that severe myocardial fibrosis correlated significantly with the degree of diastolic dysfunction [39]. Hypertrophy and fibrosis leading to cardiac function impairment are significantly more common in HFpEF patients compared to those without [25]. In our analysis, more than half of our patients had already fibrotic changes and not that much less hypertrophy. We found a significant correlation of LAVI with fibrosis in our study. Experimental models of diabetes induced an increased endothelial expression of endothelin-1 and therefore EndMT and fibrosis [40].

In our correlation and linear regression analysis, age was significantly associated with higher E/e' values (OR: 1.410). HFpEF is often considered a disease of the elderly and its prevalence increases significantly with age, as reported in a sub-analysis of the EPICA study (8%-10% in women and 4%-6% in men > 80 years) [41,42].

There are considerable sex-differences in the area of HFpEF, particularly concerning sex-specific inflammatory mechanisms contributing to disease development and progression [41,43]. Results from the Framingham Heart Study showed the odds of HFpEF were 2.8-fold higher in women compared to men [44]. We found a trend in form of a significant correlation between female sex and higher E/e' values, however results remained statistically non-significant in further analysis. This may be explainable due to the absence of diastolic dysfunction and clear evidence of HFpEF in our patients. Although no universally accepted consensus exists on sex-specific inflammatory mechanisms in HFpEF [41]. General hypotheses include greater endothelial dysfunction and systemic microvascular inflammation that occur earlier in women [41,45]. Beyond traditional risk factors of HFpEF that have been extensively discussed, female-specific risk factors involving sex hormones, pregnancy-related disorders and reproductive aspects may provoke a more severe inflammatory response [41]. Evidence suggests that sex hormones are of particular importance in the regulation

of inflammatory response. While higher levels of estrogen downregulate inflammatory mechanisms such as nitric-oxide signaling and production of reactive oxygen species, the decline at menopause is linked to systemic inflammation and contribute to the pathogenesis of HFpEF [46]. Additionally, patients with pregnancy-related disorders like preeclampsia are at greater risk to develop HFpEF [47].

CAMs have been strongly correlated with HFpEF prevalence [8], but the chronological order from endothelial activation to subclinical alterations in cardiac function and the definitive manifestation of HFpEF remains to be clarified [37]. Interestingly, in the Coronary Artery Risk Development in Young Adults (CARDIA) trial was shown that ICAM-1and E-selectin levels in young adulthood preceded subclinical HFpEF in midlife, in the form of impaired systolic function measured by LV-global longitudinal strain (GLS) [37]. Both, diastolic and systolic dysfunction are driver in HFpEF development and have a decisive prognostic impact, as reported in larger clinical trials [48,49]. In our analysis, no significant associations between inflammatory markers and LVEF as a marker of cardiac systolic function were seen. Thus, LV-GLS add some valuable prognostic information beyond conventional LVEF to quantify LV contractile performance and to identify subclinical HFpEF [48-50].

Limitation of the study

There are limitations of a retrospective analysis which have to be considered when interpreting the obtained results and possible effects of selection bias cannot be denied. The number of patients is low that limits the power of our analysis. We investigated patients across different cardiovascular disease etiologies. This limits the accuracy of our results to describe a common inflammatory pathway in the development of HFpEF.

Conclusion

In summary, our data provide further evidence for the importance of ICAM-1 in the early stage of inflammatory response and endothelial dysfunction in symptomatic patients with preserved ejection fraction prior to diastolic dysfunction development.

Because the current success of treatments in terms of symptomatic improvement and prognosis for HFpEF patients has been limited, a personalized therapy option with suppression of microvascular inflammation and endothelial protective strategies may have potential benefit in preventing development of diastolic dysfunction. This hypothesis needs to be proven in large randomized trials.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Informed Consent / Ethics Statement

Informed consent was obtained from all subjects involved in the study and approved by Ethics Committee of Charité – University Medicine Berlin (EA4/236/20).

Supplementary Material: None

Data Availability Statement

All relevant data is contained within the article:

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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