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Enhanced Adhesion Molecules are Early Inflammatory Driver in Symptomatic Patients with Preserved Ejection Fraction Prior to Diastolic Dysfunction

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Abstract

Background: Patients with diastolic dysfunction exhibit signs of chronic myocardial inflammation. However, which inflammatory markers are crucial in the early inflammatory process in symptomatic patients with preserved ejection fraction leading to the development of diastolic dysfunction remain elusive.

Methods: We retrospectively analyzed n=72 (49 male/23 female) consecutive patients with heart failure symptoms according to the New York Heart Association (NYHA) classification stages II-IV. Only patients with preserved left ventricular ejection fraction (LVEF) > 50% and without echocardiographic findings of diastolic dysfunction including E/e' < 14 or left atrial volume index (LAVI) < 34 ml/m^2 were enrolled. All patients underwent endomyocardial biopsies (EMBs).

Results: The mean LVEF was 58±2%. According to EMBs, immunohistological signs of inflammatory processes were shown in n=29 (40%) patients. In univariable regression analysis, age (OR: 1.410, 95% CI: 1.040-1.751, p <0.001) and adhesion molecules ICAM-1 (OR: 1.395, 95% CI: 1.029-1.780, p <0.05) were significantly associated with E/e' in patients with microvascular inflammatory processes, respectively. The association of age and ICAM-1 with E/e' remained virtually unchanged after adjustment for both variables. In contrast, in patients without inflammatory processes, we observed in univariable regression analysis, age (OR: 1.619, 95% CI: 1.430-1.951, p <0.001), female sex (OR: 1.449, 95% CI: 1.164-1.733, p <0.05) and low-grade CD11$^+$cells (OR: 1.548, 95% CI: 1.273-1.823, p <0.05) were significantly associated with E/e'. After multivariable regression analysis, age (OR: 1.597, 95% CI: 1.337-1.856, p <0.001) remained significant.

Conclusion: ICAM-1 is a key marker in the early inflammatory processes of symptomatic patients with preserved ejection fraction that are prior to diastolic dysfunction.

Keywords: Inflammatory Markers; ICAM-1; Diastolic Dysfunction; Heart Failure with Preserved Ejection Fraction; Endomyocardial Biopsies

Introduction

The aging population and steadily rising prevalence of risk factors associated with cardiovascular diseases develop more and more to a global health burden [1].

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Cardiovascular risk factors and comorbidities, such as obesity, metabolic syndrome, lipid disorders and hypertension trigger a low-grade proinflammatory state leading to an abnormal vascular endothelial function [2-4]. Cellular adhesion molecules (CAMs) such as vascular cell adhesion molecule-1 (VCAM-1), endothelial (E)-selectin, intracellular adhesion molecule-1 (ICAM-1) or perforin are biomarkers of endothelial activation and of particular importance in the initiation of an inflammatory response [2,5]. In this context, CAMs are expressed on the surface of endothelial cells and upregulated [5-8]. Higher circulating levels of CAMs initiate a cascade leading to a monocyte release that turn into macrophages and produce transforming growth factor-ß (TGF-ß), followed by an increased collagen and thereby scar tissue production. Detrimental effects on myocardial tissue include disturbances in diastolic myocardial relaxation due to left ventricular (LV) stiffness and subsequently diastolic dysfunction [9-14].

It has been demonstrated that endothelial cell activation and coronary microvascular dysfunction represent central mechanisms in the pathogenesis of heart failure with preserved ejection fraction (HFpEF) [2,7,8]. Several human studies and animal models addressed the major negative impact of upregulated CAMs on myocardial structural and functional alterations [15-18].

However, the pathophysiological understanding of the exact inflammatory processes linked to endothelial activation in patients at greater risk for HFpEF remains poor. Furthermore, relatively little is known about potential markers that play a key role in HFpEF development over time [2,19,20].

The aim of this analysis was to improve the immunohistological understanding based on endomyocardial biopsies (EMBs) regarding inflammatory processes in symptomatic patients with preserved ejection fraction prior to the development of diastolic dysfunction.

Materials and Methods

Study population

Seventy-two consecutive patients with heart failure symptoms, but without prior LV dysfunction, undergoing EMBs at Charité-University hospital, Berlin, Germany within the period of 5 years, were retrospectively analyzed. Patients were classified according to the New York Heart Association (NYHA) stages II-IV. Patients with coronary artery disease and other possible causes of the clinical complaints (e.g. valvular heart disease, storage disorders) or active myocarditis had been excluded. All patients underwent an echocardiographic examination within four days regards to EMB sampling. Only patients with preserved left ventricular ejection fraction (LVEF) > 50%, but without clear evidence of diastolic dysfunction that was defined as elevated values of E/e' > 14 or left atrial volume index (LAVI) > 34 ml/m^2 were enrolled. Medical history, comorbidities and clinical status were recorded. Routine parameters from venous blood sampling were collected. Written informed consent was obtained from all study participants. The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee at the Charité-Universitätsmedizin Berlin.

Investigation methods

Echocardiography

Echocardiographic examination was performed. Cardiac chambers were quantified using standard four- and two-chamber views and LVEF was assessed based on the biplane Simson's method. Tissue doppler was performed from the apical four-chamber view. Early diastolic mitral annulus peak velocity was measured and the ratio of the transmitral diastolic peak velocity to the mitral annular diastolic peak velocity (E/e') was calculated. LAVI was calculated in the apical four-chamber view. Diastolic dysfunction was defined as elevated values of E/e' > 14 or LAVI > 34 ml/m^2, respectively.

Histological and Immunohistological Staining for Assessment of Inflammation

The EMB specimens were analyzed in the Institute for Cardiac Diagnostic and Therapy (IKDT) Berlin, Germany, including histology, immunohistochemistry and molecular virology. Histology was used to confirm appearance of active myocarditis as established by the Dallas Criteria. Immunohistochemistry was used for the characterization of inflammatory infiltrates. Antibodies used: CD3$^+$ lymphocytes (Dako, Glostrup, Denmark), CD11a$^+$/LFA-1$^+$ lymphocytes (Immuno Tools, Friesoythe, Germany), CD45R0$^+$ (Dako, Glostrup, Denmark), perforin$^+$- cytotoxic infiltrates (BD Bioscience, San Jose, California, USA), CD11b$^+$/Mac-1$^+$ macrophages (ImmunoTools, Friesoythe, Germany), ICAM-1/CD54 (ImmunoTools, Friesoythe, Germany), and VCAM-1/CD106 (ImmunoTools, Friesoythe, Germany). As secondary antibody we used enhancing EnVisionTM peroxidase-conjugated anti-mouse antibody (Dako, Glostrup, Denmark). Immunohistological staining was visualized using 3-amino-9-ethylcarbazole (Merck, Darmstadt, Germany) as chromogenic substrate. Finally, slides were counterstained in hematoxylin and mounted with Kaiser's gelatinR (Merck, Darmstadt, Germany). The staining and peroxidase reactions in all samples were carried out identically and in parallel for all samples. Immunoreactivity was quantified by digital image analysis as described previously [21,22].

Detection of viral genomes by nested PCR (nPCR) and reverse transcription-PCR (RT-PCR)

EMBs were subjected to molecular biological investigation of cardiotropic viral genomes according to the published techniques [23]. In brief, a PCR was performed on RNA extracted from EMBs for enterovirus, adenovirus, and on DNA for Epstein-Barr virus, Erythrovirus genomes and human Herpesvirus 6.

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Statistical analysis

Baseline descriptive data included demographic, clinical, echocardiographic, immunohistological and laboratory characteristics. Continuous data were presented as mean and standard deviation (SD). Categorical data were presented as counts and percentages. All data were investigated for a normal distribution using the Shapiro-Wilk-test.

The analysis was performed in the entire patient cohort and separately according to immunohistological signs of inflammatory processes (patients with inflammatory processes versus those without). Differences between the groups were compared using Student t-test, Mann-Whitney U test, X^2 test and Fisher exact test (when appropriate).

Pearson correlation test for normally distributed continuous variables and Spearman correlation test for non-normally distributed continuous variables were conducted to detect significant associations between patient's characteristics and echocardiographic diastolic parameters encompassing E/e' and LAVI. Furthermore, we tested significant associations between inflammatory markers and LVEF as a measure of cardiac systolic function using correlation analysis. Only variables that were significant in correlation analysis (p <.05) were subsequently included in univariable and multivariable regression analysis.

Univariable and multivariable linear and logistic regression were used to evaluate the independent associations between patient's characteristics (independent variables) and echocardiographic indices of diastolic function including E/e' and LAVI (dependent variables). Due to different scale ranges, levels of data were standardized (per SD) for the regression models. Models were adjusted for age and sex and significant covariates obtained from correlation analysis were included. Univariable and multivariable effects were reported with calculation of the regression coefficient, odds ratio (OR) and 95% confidence interval (CI) for each observation.

Two-tailed p values <.05 were considering statistically significant. The statistical analysis was performed using R version 4.3.2 "Eye Holes" from October 2023 (R Foundation for Statistical Computing, Vienna, Austria) [24].

Results

Baseline characteristics

The demographic, clinical and echocardiographic data of the 72 patients, classified into two groups according to inflammatory or non-inflammatory processes, are demonstrated in Table 1. Mean age was 42.9 years and 68% were male. Mean LVEF was 58%, E/e' was 8 and LAVI was 23ml/m^2. The mean NT-proBNP was 494 ng/L and most of the patients presented in NYHA stage II (78%). Hypertension was the leading comorbidity in these patients (24%). Sixty-six patients (92%) received a left ventricular biopsy and six patients (8%) underwent a right ventricular biopsy. The most histomorphological changes were fibrosis (50%), followed by myocyte hypertrophy (35%) and atrophy (22%). The immunohistological and laboratory data of the 72 patients, classified into two groups according to inflammatory or non-inflammatory processes, are shown in Table 2.

Table 1: Clinical and echocardiographic parameters presented as mean±SD or counts and percentages (%).

Variables	Inflammatory processes	Non-inflammatory processes	*p* value
Number of patients, No. (%)	29 (40)	43(60)	
Men, No. (%)	21 (72)	28 (65)	0.55
Women, No. (%)	8 (28)	15 (35)	0.38
Age, mean±SD, (years)	45.8±14.2	40.9±16.0	0.18
Laboratory parameters, mean±SD			
NT-proBNP, ng/L	708±1390	349±832	**<0.05**
Echocardiography, mean±SD			
LVEF, %	56±2.0	58.9±5.1	0.05
Average E/e'	8.3±2.2	7.1±2.0	**<0.05**
LAVI, ml/m^2	23.5±5.7	22.2±5.7	0.37
NYHA-classification, No. (%)			
NYHA-II	23 (80)	33 (77)	0.18
NYHA-III	4 (14)	9 (21)	0.17
NYHA-IV	2 (6)	1 (2)	0.56
Medical history, No. (%)			
Hypertension	9 (31)	8 (19)	0.09
Obesity	8 (28)	7 (16)	0.07
Diabetes	1 (3)	1 (2)	0.65
Dyslipidemia	6 (21)	6 (14)	0.24

No., number; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; NYHA, New York Heart Association; *p* value, significance level.

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Table 2: Immunohistological and laboratory parameters presented as mean±SD or counts and percentages (%).

Variables	Inflammatory processes	Non-inflammatory processes	*p* value
Immunohistology, mean±SD			
CD11⁺cells/mm²	35.3±51.0	9.7±6.3	**<0.001**
Macrophages⁺cells/mm²	59.5±63.1	20.7±14.1	**<0.001**
CD3⁺T-cells	9.5±2.6	2.4±2.0	**<0.001**
Perforin⁺cells/mm²	2.9±1.3	1.9±0.8	**<0.001**
ICAM-1/AF	1.1±2.4	0.4±1.1	0.08
VCAM-1/AF	0.03±0.02	0.06±0.15	0.66
Histomorphometry, No. (%)			
Hypertrophy	10 (34)	15 (35)	0.90
Fibrosis	12 (41)	24 (56)	0.13
Atrophy	5 (17)	11 (26)	0.17
Myocyte diameter, µm	19.8±2.3	19.9±2.5	0.80
Laboratory parameters, mean±SD			
C-reactive protein, mg/l	23.7±50.0	10.4±20.1	0.34
Leucocytes, /nl	8.1±3.1	7.4±2.6	0.33

No., number; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; AF, area fraction; *p* value, significance level.

Correlation analysis of immunohistological markers

There was a moderate positive and significant correlation between ICAM-1 and macrophages (r=0.42, p <0.05) (Figure 1).

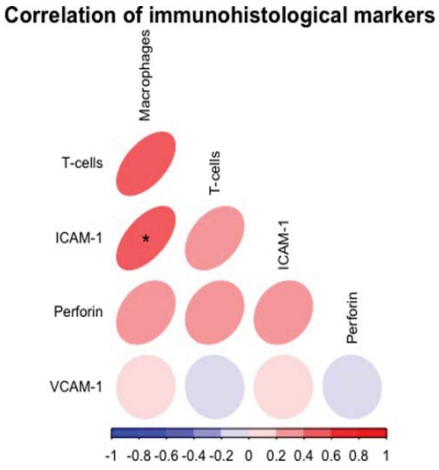

Figure 1: Correlation of immunohistological markers.

Correlation and regression analysis in patients with inflammatory processes

In the correlation analysis was a significant correlation between E/e' and the following parameters: age (r=0.47, p <0.001), female sex (r=0.24, p <0.05), CD11⁺cells (r=0.37, p <0.001), CD3⁺T-cells (r=0.38, p <0.001), perforin⁺cells (r=0.34, p <0.05) and ICAM-1 (r=0.27, p <0.05) (Figures 2 and 3). In univariable linear and logistic regression analysis of the significant parameters obtained from correlation analysis, age (OR: 1.410, 95% CI: 1.040-1.751, p <0.05) and ICAM-1 (OR: 1.395, 95% CI: 1.029-1.780, p <0.05) remained significantly associated with E/e' (Table 3).

There was a significant correlation between LAVI and the following parameters: age (r=0.15, p <0.05) and fibrosis (r=0.23, p <0.05). In univariable logistic regression analysis, LAVI was significantly associated with fibrosis (OR: 1.507, 95% CI: 1.163-1.851, p <0.05).

Correlation and regression analysis in patients without inflammatory processes

In the correlation analysis was a significant correlation between E/e' and the following parameters: age (r=0.53, p <0.001), female sex (r=0.24, p <0.05) and CD11⁺cells (r=0.44, p <0.01) (Figure 4).

In univariable linear and logistic regression analysis of the significant parameters obtained from correlation analysis, age (OR: 1.619, 95% CI: 1.430-1.951, p <0.001), female sex (OR: 1.449, 95% CI: 1.164-1.733, p <0.05) and CD11⁺cells (OR: 1.548, 95% CI: 1.273-1.823, p <0.05) remained significantly associated with E/e' (Table 4). After multivariable-adjusted logistic regression analysis, age (OR: 1.597, 95% CI: 1.337-1.856, p <0.001) remained significantly associated with E/e' (Table 5, Figure 5). There was a significant correlation between LAVI and age (r=0.23, p <0.05), that remained significant in univariable analysis (OR: 1.332, 95% CI: 1.040-1.626, p <0.05).

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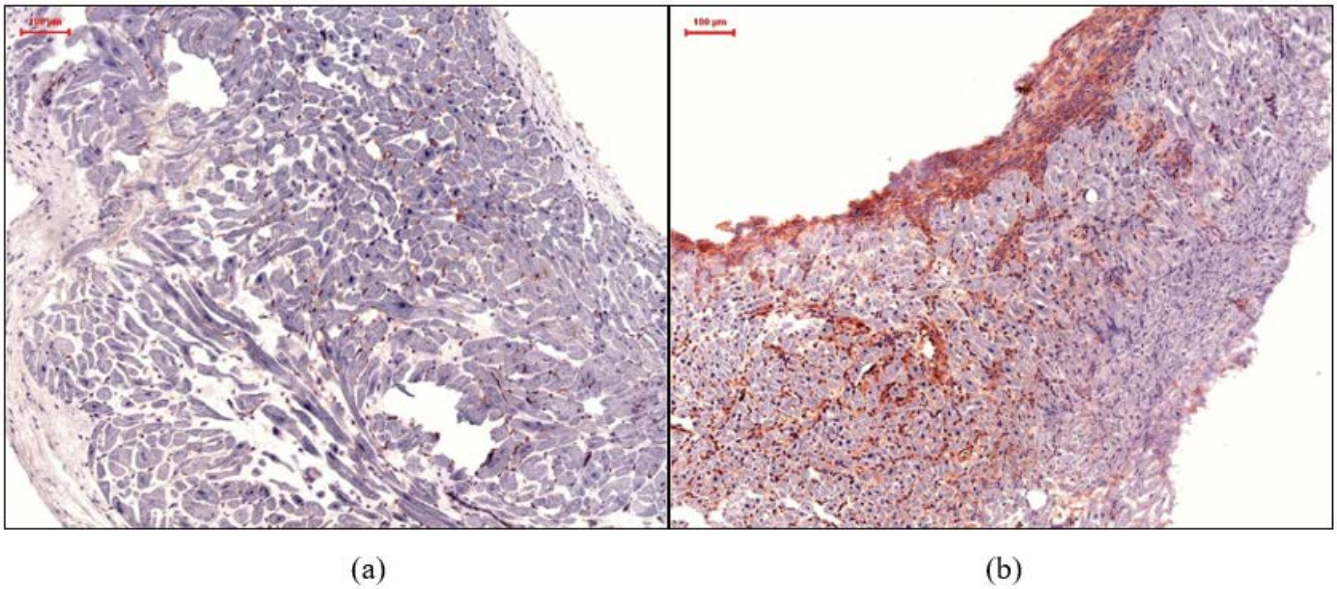
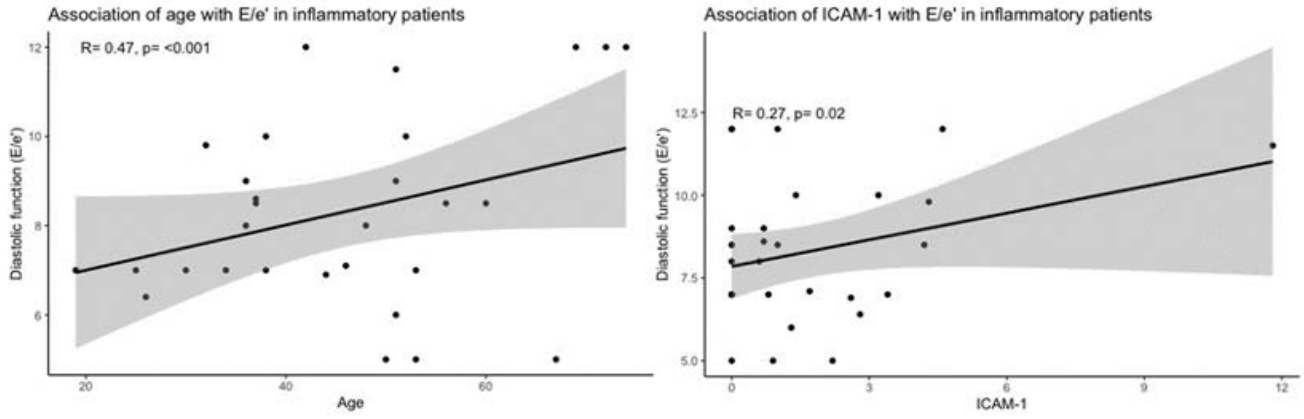


(a) (b)

Figure 2: Representative Images from EMBs. Immunohistological staining of normal expression of ICAM-1 (a). Immunohistological staining of increased expression of ICAM-1 (b). Scale bars: 100um.



(a) (b)

Figure 3: Relationship between E/e' and age (a) and ICAM-1 (b). Scatterplots showing the actual values (scatter points) for each observation, line of best fit and 95% confidence interval (CI) values as ribbon of patients with inflammatory processes.

Table 3: Univariable regression analysis in patients with inflammatory processes; LAVI, left atrial volume index; *p* value, significance level.

Variables	Coefficient	Adjusted OR (95% CI)	*p* value
E/e'			
Age	3.335	1.410 (1.040, 1.751)	**<0.001**
Sex (female)	1.561	0.985 (0.607, 1.362)	0.94
CD11⁺*cells*	9.425	1.190 (0.724, 1.475)	0.63
T-cells	2.004	1.223 (0.852, 1.591)	0.30
Perforin⁺*cells*	1.091	1.115 (0.740, 1.490)	0.57
ICAM-1	3.331	1.395 (1.029, 1.780)	**<0.05**
LAVI			
Age	1.045	1.110 (1.735, 1.485)	0.59
Fibrosis	4.102	1.507 (1.163, 1.851)	**<0.05**

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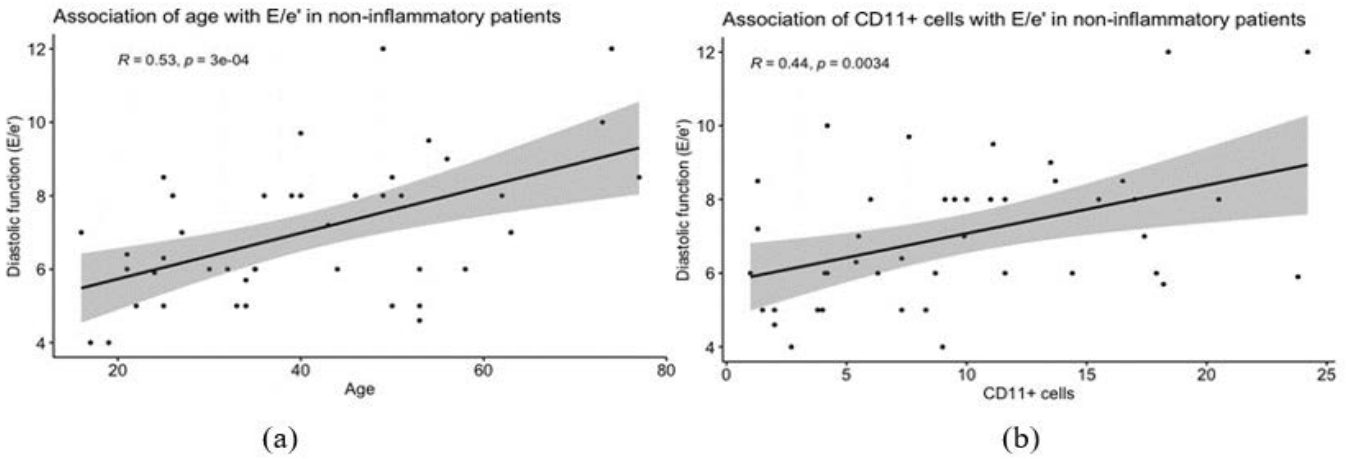

Figure 4: Relationship between E/e' and age (a) and CD11^{+}cells (b). Scatterplots showing the actual values (scatter points) for each observation, line of best fit and 95% confidence interval (CI) values as ribbon of patients without inflammatory processes.

Table 4: Univariable regression analysis in patients without inflammatory processes; LAVI, left atrial volume index; *p* value, significance level.

Variables	Coefficient	Adjusted OR (95% CI)	*p* value
E/e'			
Age	5.324	1.619 (1.430, 1.951)	**<0.001**
Sex (female)	3.493	1.449 (1.164, 1.733)	**<0.05**
CD11^{+}*cells*	4.496	1.548 (1.273, 1.823)	**<0.05**
LAVI			
Age	2.874	1.332 (1.040, 1.626)	**<0.05**

Table 5: Multivariable regression analysis in patients without inflammatory processes; variables were standardized (per SD) before inclusion; *p* value, significance level.

Variables	Coefficient	Adjusted OR (95% CI)	*p* value
E/e'			
Age	4.679	1.597 (1.337, 1.856)	**<0.001**
Sex (female)	1.584	1.172 (0.883, 1.461)	0.29
CD11^{+}*cells*	1.997	1.221 (0.941, 1.501)	0.17

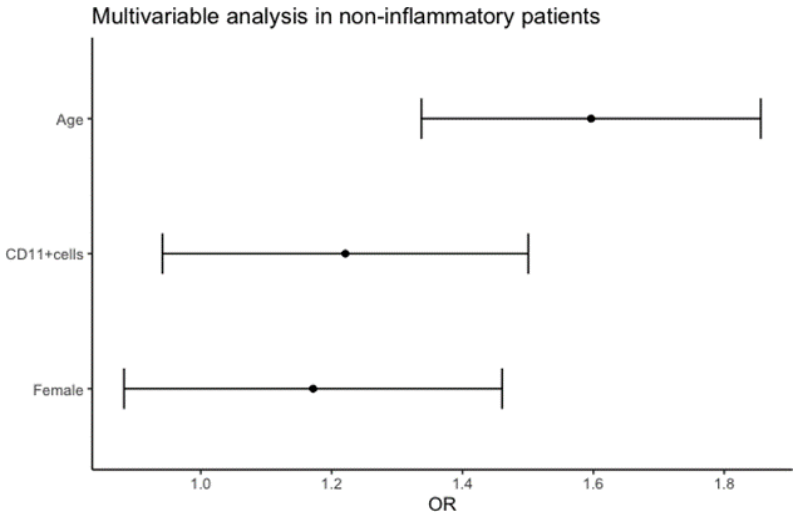

Figure 5: Forest plot showing the odds ratio (OR) and 95% confidence interval (CI) values for each observation included in the multivariable analysis of patients without inflammatory processes.

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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

Plappert C, et al., Cardiol Cardiovasc Med 2024
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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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