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Association between low-grade chronic inflammation and depressed left atrial compliance in heart failure with preserved ejection fraction: A retrospective analysis

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Abstract: Background: A novel paradigm of diastolic heart failure with preserved ejection fraction (HFpEF) proposed the induction of coronary microvascular dysfunction by HFpEF comorbidities via a systemic pro-inflammatory state and associated oxidative stress. The consequent nitric oxide deficiency would increase diastolic tension and favor fibrosis of adjacent myocardium, which implies not only left ventricular (LV), but all-chamber myocardial stiffening. Our aim was to assess relations between low-grade chronic systemic inflammation and left atrial (LA) pressure-volume relations in real-world HFpEF patients.
Methods: We retrospectively analyzed medical records of 60 clinically stable HpEFF patients in sinus rhythm with assayed high-sensitive C-reactive protein (CRP) during the index hospitalization. Subjects with CRP >10 mg/L or coexistent diseases, including coronary artery disease, were excluded. LV and LA diameters and mitral E/E' ratio (an index of LA pressure) were extracted from routine echocardiographic

records. A surrogate measure of LA stiffness was computed as the averaged mitral E/e' ratio divided by LA diameter.

R e s u l t s: With ascending CRP tertiles, we observed trends for elevated mitral E/e' ratio ($p < 0.001$), increased relative LV wall thickness ($p = 0.01$) and higher NYHA functional class ($p = 0.02$). The LA stiffness estimate and log-transformed CRP levels (log-CRP) were interrelated ($r = 0.38$, $p = 0.003$). On multivariate analysis, the LA stiffness index was independently associated with log-CRP ($\beta \pm SEM: 0.21 \pm 0.07$, $p = 0.007$) and age ($\beta \pm SEM: 0.16 \pm 0.07$, $p = 0.03$), which was maintained upon adjustment for LV mass index and relative LV wall thickness.

C o n c l u s i o n s: Low-grade chronic inflammation may contribute to LA stiffening additively to age and regardless of the magnitude of associated LV hypertrophy and concentricity. LA stiffening can exacerbate symptoms of congestion in HFpEF jointly with LV remodeling.

Key words: heart failure with preserved ejection fraction, low-grade chronic inflammation, left atrium, left ventricle, echocardiography.

Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for almost half of heart failure (HF) patients and is the most prevalent form of HF in the elderly. HFpEF has been traditionally attributed to excessive left ventricular (LV) afterload [1]. A recent novel HFpEF paradigm highlights the induction of a systemic pro-inflammatory state in HFpEF by coexistent comorbidities such as hypertension, obesity, diabetes or chronic kidney disease [1]. The pro-inflammatory state and associated oxidative stress in turn cause coronary microvascular endothelial dysfunction, i.e. deficient bioavailability of endothelium-derived nitric oxide. Depressed nitric oxide bioavailability lowers protein kinase G activity in adjacent cardiomyocytes, which subsequently slows down LV relaxation, increases resting tension of cardiomyocytes, stimulates collagen deposition and favors cardiomyocyte hypertrophy [1, 2].

This novel conceptualization of HFpEF implies a contribution of low-grade chronic systemic inflammation not only to LV stiffening but also to depressed left atrial (LA) and right atrial compliance [1]. Recent analyses of atrial pressure-volume relations support the notion that myocardial stiffening in HFpEF is not chamber-specific, including both atria [3–5]. Assuming this inflammatory model of HFpEF, the degree of chronic low-level systemic inflammatory activation is expected to impact both LA and LV stiffness in HFpEF. Associations among hypertensive subjects have been reported between C-reactive protein (CRP) levels and both LV hypertrophy and its concentricity [6–8] as well as reduced compliance of the large arteries [9]. Similar relationships were also observed in cohorts recruited from the general population [10, 11]. However, LA pressure-volume relations according to the degree of systemic inflammatory activation in HFpEF have so far not been described to the best of our knowledge.

Therefore, our aim was to assess associations between CRP levels and a surrogate measure of LA stiffness derived from medical records of real-world patients with HFpEF.

Methods

Patients

We retrospectively analyzed medical records of patients hospitalized at a cardiology department for a planned coronary angiography across a period of about 4 years. Coronary angiography was performed in order to exclude coronary artery disease, owing to inconclusive exercise ECG or stress imaging.

First, we selected the records of patients with clinically suspected HF and preserved sinus rhythm, in whom serum CRP was assessed with a high-sensitivity assay during the index hospitalization as a part of routine blood analysis at admission. Then subjects with a final diagnosis of HFpEF were identified, on the basis of symptoms or signs typical of HF (New York Heart Association [NYHA] functional class II–III), LV ejection fraction (EF) ≥50% without LV dilation, echocardiographic evidence of LV hypertrophy/LA enlargement and/or LV diastolic dysfunction, and the absence of probable non-cardiac causes of symptoms suggestive of HF, in agreement with the 2016 European Society of Cardiology guidelines for the management of HF [12]. LV diastolic dysfunction was diagnosed in accordance with the 2016 joint recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging [13].

Exclusion criteria — in addition to unstable clinical conditions (acute coronary syndrome, marked congestion, hypotension, poorly controlled hypertension) — included coronary diameter narrowings ≥50%, congenital heart disease, more than mild valvular heart disease, CRP >10 mg/L, pulmonary diseases, estimated glomerular filtration rate <30 mL/min per 1.73 m^2 (using the Modification of Diet in Renal Disease [MDRD] Study formula), inflammatory, proliferative and other coexistent diseases (except for well-controlled diabetes), as well as significant abnormalities in routine blood and urine assays.

Procedure

The following parameters were extracted from cardiac ultrasound performed during the index hospitalization by a well-trained experienced sonographer according to a standard protocol: 2D-guided M-mode measurements of LV dimensions and LV wall thickness, end-systolic anteroposterior LA diameter, EF (by the modified Simpson's rule), peak early diastolic trans-mitral flow velocity (E) and mean mitral annular velocity (e') averaged from recordings taken at the lateral and septal region of

the mitral annulus [13, 14]. LV mass index was computed by the Devereux formula, and relative LV wall thickness was estimated as an index of LV concentricity [14].

Then, a surrogate measure of LA stiffness was calculated according to an approach described below. LA stiffness was previously approximated as the slope of the regression line that connects minimal and maximal pressure-volume coordinates on the LA pressure-volume diagram following a figure-of-eight pattern [5, 15]. Admittedly, we were not able to derive this slope from routine echocardiographic records. However, Melenovsky *et al.* [5] have shown that changes in the slope, reflecting altered LA stiffness, were accompanied by corresponding changes in the same direction in the LA pressure/volume ratio at the time of mitral valve opening, i.e. at maximal LA volume. Averaged mitral E/e' ratio is an index of LA pressure at mitral valve opening [16], while LA diameter, conventionally measured at end-systole [14], roughly reflects maximal LA volume. Accordingly, the mean mitral E/e' ratio divided by LA diameter can be treated as a surrogate estimate of LA pressure-volume relations at mitral valve opening, and, consequently, LA stiffness.

The ethics committee of our university approved the protocol (Approval No. 122.6120.228.2016) and the fact that patients' consent was not sought owing to a retrospective study design.

Statistical analysis

Data were presented as means (SD) or n (%). Patients' characteristics were compared between CRP tertiles by analysis of variance or chi-squared test for continuous and categorical data, respectively. Trend effects across CRP tertiles were assessed by Spearman's rank order correlation coefficient (rho) for both types of data. Pearson's correlation coefficients (r) were computed in search for univariate correlates of CRP levels and the LA stiffness estimate. CRP concentrations were log-transformed due to a non-normal distribution. A p-value below 0.05 was inferred as significant.

In order to identify independent determinants of the LA stiffness index, multiple linear regression was performed with forward stepwise selection of covariates; p-to enter and p-to-remove values were set at 0.10 and 0.15, respectively.

All analyses were performed by means of STATISTICA (data analysis software system), version 12 (StatSoft, Inc., Tulsa, OK, USA).

Results

Out of 323 potentially eligible patients, 60 clinically stable subjects with an established diagnosis of HFpEF entered the final analysis based on the exclusion criteria. Characteristics of the study patients according to CRP tertile are presented in Table 1.

Table 1. Clinical and echocardiographic patients' characteristics according to CRP tertile.

Characteristics	CRP tertile			p*	p for trend†
	I (<1.3) [mg/L]	II (1.3–2.4) [mg/L]	III (>2.4) [mg/L]		
Clinical characteristics					
Age, years	68 ± 9	71 ± 7	70 ± 7	NS	NS
Female gender, n (%)	10 (50%)	10 (50%)	12 (60%)	NS	NS
NYHA class, II/III, n	17/3	11/9	10/10	0.04	0.02
Diabetes, n (%)	7 (35%)	6 (30%)	7 (35%)	NS	NS
Hypertension, n (%)	17 (85%)	16 (80%)	18 (90%)	NS	NS
Hypertension duration, years	9 ± 7	12 ± 5	11 ± 5	NS	NS
Body-mass index, kg/m^2	28.8 ± 4.40	28.7 ± 4.7	29.5 ± 3.8	NS	NS
Mean blood pressure, mmHg‡	99 ± 9	97 ± 8	98 ± 10	NS	NS
eGFR, mL/min per 1.73 m^2	70 ± 10	69 ± 11	72 ± 12	NS	NS
Echocardiographic characteristics					
LVd at end-diastole, mm	49 ± 6	48 ± 6	48 ± 4	NS	NS
Ejection fraction, %	71 ± 6	71 ± 8	70 ± 8	NS	NS
LV mass index, g/m^2	106 ± 24	122 ± 37	123 ± 26	0.15	0.07
Relative LV wall thickness	0.46 ± 0.09	0.51 ± 0.08	0.52 ± 0.06	0.06	0.01
LAd at end-systole	44 ± 3	46 ± 3	46 ± 4	0.15	0.12
Mitral E/e' ratio	10.6 ± 2.6	12.8 ± 2.1	13.5 ± 3.0	0.002	<0.001
LA stiffness index, a.u.	2.4 ± 0.6	2.8 ± 0.4	3.0 ± 0.7	0.01	0.004

Data are presented as mean ± standard deviation or n (%).

* By analysis of variance or chi-squared test for continuous and categorical data, respectively.

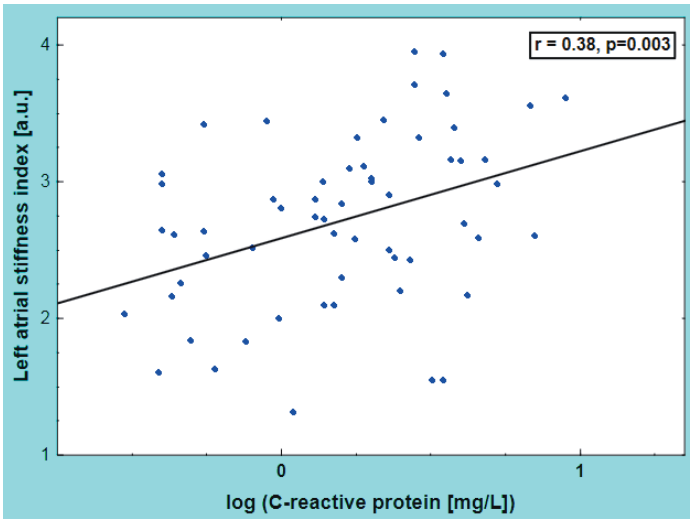
† By Spearman's rank order correlation coefficient (rho).

‡ Averaged from in-hospital blood pressure measurements.

a.u. — arbitrary units; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate by the MDRD Study formula; LA — left atrial; LAd — anteroseptal LA diameter in the parasternal long-axis view; LV — left ventricular; LVd — LV internal dimension in the parasternal long-axis view; Mitral E/e' ratio — peak early diastolic transmitral flow velocity divided by mean mitral annular velocity averaged from measurements taken at the lateral and septal region of the mitral annulus; NS — non-significant; NYHA — New York Heart Association.

With ascending CRP tertiles, we observed significant trends for elevated mitral E/e' ratio ($p < 0.001$), increased relative LV wall thickness ($p = 0.01$), and higher NYHA functional class ($p = 0.02$). Corresponding tendencies were weak for LV mass index ($p = 0.07$) and LA diameter ($p = 0.12$). Consequently, categorized CRP levels strongly correlated with the LA stiffness index (Table 1).

The LA stiffness estimate and log-transformed CRP levels (log-CRP) were interrelated (r = 0.38, p = 0.003) (Fig. 1). In addition, log-CRP correlated with relative LV wall thickness (r = 0.35, p = 0.007), LA diameter (r = 0.27, p = 0.04) and weakly with LV mass index (r = 0.24, p = 0.07). The LA stiffness index was related to age (r = 0.32, p = 0.01) and weakly to time elapsed since hypertension diagnosis (r = 0.22, p = 0.12).



a.u. — arbitrary units; r — Pearson's correlation coefficient.

Fig. 1. Left atrial stiffness surrogate index vs. log-transformed C-reactive protein levels.

Table 2. Forward stepwise multiple regression of the left atrial stiffness surrogate measure (adjusted R^2 for the regression equation: 0.18, p = 0.001).

Predictor variable	SD	β Mean ± SEM	p
Age, years	7.60	0.16 ± 0.07	0.03
log (CRP [mg/L])	0.37	0.21 ± 0.07	0.007

β — semi-standardized regression coefficient, equivalent to a rise in the LA stiffness index associated with 1-SD increase in each predictor; SD — standard deviation; SEM — standard error of the mean; other abbreviations as in Table 1.

On multivariable analysis, the LA stiffness index was independently associated with log-CRP and age (Table 2). The results virtually did not change after LV mass index, relative LV wall thickness, EF and body-mass index were also forced into the final regression model.

Discussion

We found a significant association between CRP and a surrogate measure of LA stiffness in a retrospective analysis of clinically stable real-world HFpEF patients. This association was particularly noteworthy for being additive to the effect of age and independent of CRP relations with the magnitude of LV hypertrophy or concentricity. Although a correlation does not imply a cause-and-effect relationship, our findings are consistent with the notion that chronic low-grade chronic systemic inflammation may contribute to all-chamber myocardial stiffening in HFpEF [1–5].

Mechanistic considerations

As early as 30 years ago, utilizing computer-based simulations Thomas *et al.* [17, 18] revealed that not only lower LV compliance but also depressed LA compliance might result in LA pressure elevation as a compensatory mechanism to keep LV filling volume (equal to LV stroke volume) relatively constant. This mechanism promotes pulmonary congestion and the development of pulmonary hypertension. These model-based theoretical predictions were elegantly verified in an in vitro analog of the left heart [17] and patients undergoing percutaneous balloon mitral valvuloplasty [19]. In the latter study [19], net atrioventricular compliance, determined by both LA and LV compliance, impacted trans-mitral pressure half-time independently of mitral valve area and the maximal early trans-mitral pressure gradient.

Net atrioventricular compliance has recently re-gained attention in mitral stenosis as a predictor of symptoms development irrespective of stenosis severity [20] and both persistent pulmonary hypertension and adverse outcome despite successful mitral valvuloplasty [21]. Additionally, LA stiffening accounts for the stiff LA syndrome, presenting as HF and pulmonary hypertension due to LA diastolic dysfunction [22]. The stiff LA syndrome had initially been described in a patient 7 years after mitral valve surgery despite normal prosthesis function [23], and later was identified as a rare complication of radiofrequency ablation for atrial fibrillation [22]. Finally, increased pre-procedural LA stiffness has recently been implicated in the recurrence of atrial fibrillation after ablation [24].

In regards to HFpEF, LA stiffening was found responsible for lower LA volume despite identical mean LA pressure compared to HF with reduced EF [5]. LA size is accordingly not only a barometer of an average effect of LV filling pressures over time and a predictor of incident HF and adverse outcome in various clinical settings [25, 26], but is also modulated by LA compliance. Notably, depressed LA compliance resulted in higher pulsatility of LA pressure with consequently increased variation of LA wall stress during the cardiac cycle [5]. This finding was suggested to underlie a higher risk of atrial fibrillation in this form of HF [5, 27].

LA stiffening may also play a role in the transition from asymptomatic LV diastolic dysfunction to overt HFpEF. Kurt *et al.* [28] observed that elevated LA stiffness index, calculated as the ratio of pulmonary capillary wedge pressure (or mitral E/e') to LA strain during ventricular systole, accurately distinguished HFpEF patients from subjects with asymptomatic LV diastolic dysfunction. Recently, in an animal model of early hypertensive HFpEF, Zakeri *et al.* [29] demonstrated a 2.5-fold increase in the modulus of LA chamber stiffness, which, jointly with LA myocyte hypertrophy, altered titin phosphorylation and endothelium-dependent LA microvascular dysfunction, is consistent with the notion that adverse LA remodeling contributes to HFpEF development.

Additionally, both systolic and diastolic LA function, quantified by speckle-tracking echocardiography, were more impaired in patients with HFpEF compared to those with asymptomatic diastolic dysfunction, and determined functional capacity [30]. Finally, low peak late mitral annular velocity, reflecting LA contractile function, was the only independent predictor of a composite of all-cause death or HF hospitalization in HFpEF [31]. Therefore, both systolic and diastolic LA dysfunction, corresponding to disturbed LA active contractile and passive reservoir function, respectively, are of clinical importance in HFpEF, thus explaining independent adverse prognostic effects of reduced active [5, 32] or total LA emptying fraction [5, 26, 32].

Study limitations

Owing to the study design, we estimated the magnitude of chronic low-level inflammatory activation through a single measurement of CRP, while a more reliable index index — e.g. averaging long term follow-up readings of an inflammatory marker — would be preferred. However, all patients were in stable clinical condition which, in addition to the application of a wide set of exclusion criteria, limited the heterogeneity of the study group, keeping in mind a high prevalence of multimorbidity in elderly HF subjects [33]. Moreover, prior to the index hospitalization and in-hospital CRP assay, virtually all patients (57 out of 60 analyzed subjects) — referred for a planned coronary angiography — were receiving standard medication according to practice guidelines, including statins and angiotensin-converting enzyme inhibitors, known to reduce serum inflammatory markers [34, 35].

Second, on the basis of available past medical records, we were able to calculate only a surrogate simplified measure of LA stiffness, which is an imprecise estimate of the LA pressure-volume relationship [5, 15]. In particular, strain imaging would have given a better insight into LA [28, 30] mechanics, nevertheless, this technique was not performed in the study subjects. Additionally, LA volume determinations are preferred over linear dimensions [13, 14], however, only anteroseptal LA diameter in

the parasternal long-axis view was available in the majority of the analyzed medical records.

Third, it would be appropriate to include additional covariates in multiple regression; nonetheless, the retrospective design and study size limited the number of potential confounders.

Conclusions

Low-grade chronic systemic inflammation may contribute to LA stiffening additively to age and regardless of the magnitude of associated LV hypertrophy and concentricity. LA stiffening can exacerbate symptoms of congestion in HFpEF jointly with LV remodeling. The utility of potential modulatory interventions remains to be studied in both counteracting global cardiac stiffening and slowing down HFpEF progression.

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Conflict of interest

None declared.

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