Left atrial structure and function in heart failure with reduced (HFrEF) versus preserved ejection fraction (HFpEF): systematic review and meta-analysis

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Abstract
Left atrial (LA) structure and function in heart failure with reduced (HFrEF) versus preserved ejection fraction (HFpEF) is only established in small studies. Therefore, we conducted a systematic review of LA structure and function in order to find differences between patients with HFrEF and HFpEF. English literature on LA structure and function using echocardiography was reviewed to calculate pooled prevalence and weighted mean differences (WMD). A total of 61 studies, comprising 8806 patients with HFrEF and 9928 patients with HFpEF, were included. The pooled prevalence of atrial fibrillation (AF) was 34.4% versus 42.8% in the acute inpatient setting, and 20.1% versus 33.1% in the chronic outpatient setting when comparing between HFrEF and HFpEF. LA volume index (LAVi), LA reservoir global longitudinal strain (LAGLSR), and E/e’ was 59.7 versus 52.7 ml/m2, 9.0% versus 18.9%, and 18.5 versus 14.0 in the acute inpatient setting, and 48.3 versus 38.2 ml/m2, 12.8% versus 23.4%, and 16.9 versus 13.5 in the chronic outpatient setting when comparing HFrEF versus HFpEF, respectively. The relationship between LAVi and LAGLSR was significant in HFpEF, but not in HFrEF. Also, in those studies that directly compared patients with HFrEF versus HFpEF, those with HFrEF had worse LAGLSR [WMD = 16.3% (22.05,8.61); p < 0.001], and higher E/e’ [WMD = −0.40 (−0.56, −0.24); p < 0.05], while LAVi was comparable. When focusing on acute hospitalized patients, E/e’ was comparable between patients with HFrEF and HFpEF. Despite the higher burden of AF in HFpEF, patients with HFrEF had worse LA global function. Left atrial myopathy is not specifically related to HFpEF.

Keywords LA structure · Function · HFrEF · HFpEF

Introduction
The left atrium can be considered a transporting chamber that optimizes left ventricular (LV) filling [1]. Left atrial (LA) hypertension with subsequent pulmonary venous congestion is the hallmark of HF regardless of LV ejection fraction (LVEF) [2, 3]. More recently, the significant pathophysiological role of LA dysfunction in HF has gained increasing attention, particularly in HF with preserved EF (HFpEF) [3–5]. Over the past decades, the incidence of HFpEF has risen relative to HF with reduced ejection fraction (HFrEF), accounting now for approximately 50% of cases of HF [6, 7]. Studies have shown that atrial fibrillation (AF), diabetes, and obesity are risk factors for the development of HFpEF, whereas coronary artery disease (CAD) and myocardial infarction are more predisposed to the development of HFrEF [6, 7]. The close link between AF and HFpEF might be explained by intrinsic LA myopathy underlying both HFpEF and AF [8].

However, information regarding differences in LA structure and function between HFrEF and HFpEF, particularly LA functional information assessed by strain analysis, is scarce and not fully understood. Thus, we aimed to conduct
a systematic review of LA structure and function assessed by echocardiography in patients with HFrEF versus HFpEF.

**Methods**

The systemic review and meta-analysis were conducted according to the Preferred Reporting items for Systemic Reviews and Meta-Analysis (PRISMA) statement [9]. The review protocol had been registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO).

**Literature search strategy**

We performed a systematic search in the MEDLINE and EMBASE database from inception through February 2021. Our search was restricted to studies in the English language. Additional studies were selected by reviewing and searching references of identified articles, which were not identified by the initial search. Search terms are mainly composed of the patient domain, including “heart failure,” “heart failure with preserved ejection fraction” and “heart failure with reduced ejection fraction,” and outcome domain as LA structure and function related terms, respectively. The detailed search strategy was described in the online supplementary Table S1.

**Study selection**

Studies were eligible if they were performed in a clearly defined group of patients with HFrEF or HFpEF or both. The study population had to have a clinical diagnosis of HF, based on signs and symptoms such as dyspnea, fatigue at rest or during exercise, or a previous HF hospitalization. At least one measure of LA structure and function assessed by echocardiography had to be reported. For HFrEF versus HFpEF categorization, the cutoff value of LVEF assessed by echocardiography had to be 45% or 50%. Elevated natriuretic peptides were recognized, but not mandatory for study inclusion. Two authors (XY.J, K.TH.T) independently screened the titles and abstracts of retrieved citations to identify potentially relevant studies. If abstracts were ambiguous, studies were reviewed at the full-text level. Citations were included when consensus between two authors was achieved.

**Data extraction**

For each included study, the following data of study participants were extracted: (1) baseline characteristics [i.e., publication year, the total number of study participants, the clinical setting of HF (i.e., inpatient vs outpatient setting), age, sex, body mass index (BMI), hypertension, ischemic heart disease (IHD), atrial fibrillation (AF), diabetes, and presence of more than moderate functional mitral regurgitation (MR)], (2) echocardiographic characteristics [i.e., LVEF, LV global longitudinal strain (GLS), the ratio of mitral valve peak velocity of early and late LV filling (E/A), mitral annulus e’ velocity (e’), E/e’ ratio, LA (reservoir, booster, conduit) GLS, software used for post-offline analysis]. When longitudinal studies reported cardiovascular outcomes (mortality and hospitalization), unadjusted and adjusted hazard ratio (HR) for the association between the LA-related parameter with outcomes were obtained. Follow-up time in months, outcome measure, and variables for which was adjusted were also obtained.

**Quality assessment**

To perform a quality assessment of included studies, the Newcastle–Ottawa scale adapted for observational studies [10] was used scoring each study on several items (i.e., selection process, comparability, and assessment of the outcome/exposure criterion). Moreover, the quality of the clinical trials was evaluated using the revised Cochrane risk-of-bias tool (RoB 2.0) [11], covering five domains (randomization, intervention, missing data, outcome measure, and reported results) of included studies.

**Statistical analysis**

Continuous variables were reported as mean ± standard deviation (SD), and categorical variables as percentage. When only medians and interquartile ranges were reported in the study, we translated those into means and SDs by an established formula based on previous recommendations [12].

The summary and pooled values of corresponding LA related echocardiographic parameters in both patients with HFrEF and HFpEF were pooled by the weighted average according to the number of patients among included studies and depicted in forest plots for HFrEF and HFpEF, respectively. The prevalence of comorbidities for included studies was pooled by the weighted average according to the number of patients for HFrEF and HFpEF, respectively. Data on LA related echocardiographic parameters in both patients with HFrEF and HFpEF were pooled to derive weighted mean differences (WMDs) and 95% confidence intervals (CI). Linear regression and the mixed-effects meta-regression model were applied to investigate the relationship of LAGLSR with LAVi and LVGLS in patients with HFrEF and HFpEF, respectively. Random effects model with inverse variance weighting was performed using the Cochrane I² statistic to account for heterogeneity across the studies. All statistical analyses were performed using RStudio version 1.1456.
Results

Study characteristics and quality assessment

The search strategy and study selection are summarized in the PRISMA flowchart [9] (Fig. 1). Of 1114 studies identified, a total of 61 studies were selected for the final quantitative and qualitative analysis. The quality assessment of included studies is shown in the supplementary material online (Tables S2 and S3). Reasons for exclusions were described in the supplementary Table S4. Among 61 studies, 27 studies (including 8806 patients with HFrEF and 38 studies including 9928 patients with HFpEF) reported LA structural and functional parameters by echocardiography. Nine out of 61 studies included both patients with HFrEF (n = 1877) and HFpEF (n = 3085). Nine out of 61 studies included patients with HF from an acute inpatient setting (HFrEF, n = 2749; HFpEF, n = 3319), whereas fifty-two studies included patients with HF from a chronic stable outpatient setting (HFrEF, n = 6057; HFpEF, n = 6714). The pooled clinical and echocardiographic characteristics in patients with HFrEF versus HFpEF in the acute inpatient versus chronic outpatient setting were described separately in Table 1. Moreover, the details of clinical and echocardiographic characteristics of included studies are described in Tables 2 and 3.

As compared to patients with HFrEF, patients with HFpEF appeared to be older, women, and had more often hypertension, AF and diabetes irrespective of inpatient or outpatient clinical setting (Table 1). The prevalence of IHD was 39.8% versus 30.7% in the acute inpatient setting and 49.8% versus 33.3% in the chronic outpatient setting when comparing patients with HFrEF versus HFpEF. Patients with HFrEF were more likely to be present with functional MR (27.2%) as compared to patients with HFpEF (12.0%) in the chronic ambulant setting of the study. The pooled mean value of BMI was 25.2 versus 25.6 kg/m² in the acute inpatient setting and 27.5 versus 29.8 kg/m² in the chronic outpatient in patients with HFrEF versus HFpEF. As expected by definition, patients with HFpEF had better LV systolic function as compared to patients with HFrEF with higher pooled LVEF and pooled absolute values of LVGLS irrespective of clinical setting of the study either acute inpatient or chronic outpatient (Table 1). Patients with HFpEF appeared to have higher pooled e’ (6.6 versus 7.5 cm/s in the acute inpatient versus chronic outpatient setting) than patients with HFrEF (4.7 versus 6.5 cm/s in the acute inpatient versus chronic outpatient setting). Conversely, the HFrEF group was characterized by higher E/e’ (18.5 versus 16.9 in the acute inpatient versus chronic outpatient setting) as compared to patients with HFpEF (14.0 versus 13.5 the acute inpatient versus chronic outpatient setting).

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Fig. 1 PRISMA flowchart of process for literature search and study selection. HF, heart failure; LA, left atrial, LVEF, left ventricular ejection fraction.
setting) irrespective of clinical setting of the study, indicating higher LV filling pressure in HFrEF.

**LA size and pressure estimated by LAVi and E/e’**

Twenty-nine studies reported LAVi in patients with HFrEF (n = 8726), and thirty-eight studies reported LAVi in patients with HFpEF (n = 9049). The pooled mean value of LAVi was 59.7 versus 48.3 ml/m² in the acute inpatient versus chronic outpatient setting for patients with HFrEF, and 52.7 versus 38.2 ml/m² in the acute inpatient versus chronic outpatient setting for patients with HFpEF. Eight out of 41 included studies reported E/e’ in both patients with HFrEF and HFpEF. In these studies, E/e’ was significantly higher in patients with HFrEF as compared to patients with HFpEF [15.9 versus 13.4 in HFrEF versus HFpEF; WMD = −0.40 (−0.56, −0.24); p < 0.05; I² = 77.6%]. However, in the acute inpatient setting, E/e’ was comparable between patients with HFrEF and HFpEF [17.7 versus 14.0 in HFrEF versus HFpEF; WMD = −0.40 (−0.56, −0.24); p = 0.15; I² = 77.6%], whereas E/e’ was significantly higher in patients with HFrEF as compared to patients with HFpEF in chronic HF setting [15.3 versus 13.3 in HFrEF versus HFpEF; WMD = −0.40 (−0.56, −0.24); p < 0.05; I² = 77.6%].

**LA function estimated by LA reservoir, booster, and conduit GLS**

Ten studies reported LA reservoir GLS (LAGLS_R) in patients with HFrEF (n = 3176), and seventeen studies reported LAGLS_R in patients with HFpEF (n = 4196). The pooled mean value of LAGLS_R was 9.0 versus 12.8% in the acute inpatient versus chronic outpatient setting for patients with HFrEF, and 18.9 versus 23.4% in the acute inpatient versus chronic outpatient setting for patients with HFpEF.
Table 2  Clinical characteristics of included studies

| Author/year | Study design | Study setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------|---------------|----------------------------------|-------------|------------------------|-------------|-----------------|------------------------|----------------------|----------------|--------------------------|------------|----------------------------------|-----------------------------------------------|
| Hoshida et al. [27] | Prospective multi-center observational study | CHF, inpatient setting | HFpEF ≥ 50% | 105 | 78.5 ± 10.2 | 53.3% | 41% | 88% | 24.3 ± 5.0 | LA, E/e' |
| Harada et al. [28] | Prospective single-center cohort study | AHF, compensatory inpatient setting | HFpEF ≥ 45% | 92 | 73.0 ± 12.8 | 59% | 47% | 27% | 72% | 34% | 22.3 ± 3.6 | LA, E/e', e' |
| Hwang et al. [29] | Prospective multi-center observational study | AHF, multi-center, inpatient setting | HFpEF ≥ 50% | 1105 | 76.0 ± 9.6 | 60.6% | 32.9% | 32.4% | 64.3% | 29.3% | 23.9 ± 3.7 | LA, E/e', LA reservoir strain |
| Shah et al. [30] | Retrospective cohort study | CHF, inpatient setting | HFpEF ≤ 40% | 67 | 49.5 ± 11.4 | 34.3% | 9% | 64.2% | 35.8% | 31.8 ± 7.0 | LA, E/e' |
| Tanaka et al. [31] | Retrospective cohort study | CHF, outpatient setting | HFpEF ≤ 40% | 69 | 57.5 ± 15.3 | 24.6% | 8.7% | 60.9% | 36.2% | 31.1 ± 7.3 | LA, E/e' |
| Castri- chim et al. [32] | Prospective single-center cohort study | CHF, outpatient setting | HFpEF < 40% | 77 | 65 ± 11 | 12.1% | 37.7% | 45.5% | 54.5% | 40.3% | 32% | LA, E/e', LA reservoir strain |
| Valentim et al. [33] | Prospective single-center cohort study | CHF, outpatient setting | HFpEF < 40% | 42 | 58.6 ± 11.1 | 17.1% | 40% | 31.4% | 42.9% | 28.1 ± 3.8 | LA, E/e' |
| Kurzawski et al. [34] | Retrospective single-center cohort | CHF, inpatient and outpatient settings | HFpEF < 25% | 63 | 61.9 ± 10.9 | 4.8% | 33.3% | 54% | 52.4% | 26.2 ± 4.5 | LA, E/e', LA reservoir strain |
### Table 2 (continued)

| Author/year | Study design | Study setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------|---------------|----------------------------------|-------------|-----------------------|-------------|----------------|------------------------|-----------------------|----------------|-----------------------------|------------|----------------------------------------|-------------------------------------------------|
| Park et al. [16] | Retrospective cohort study | AHF, multi-center, inpatient setting | HFpEF ≥ 50% | 1191 | 73.4 ± 13.3 | 60.3% | 35% | 31% | 62% | 27.4% | 23.8 ± 4.1 | LAVi, E/e', LA reservoir strain, e' |
| Deferm et al. [35] | Prospective single-center cohort study | ADHF (Acute decompensated HF), inpatient setting | HFpEF < 40% | 2036 | 68.4 ± 14.1 | 38.3% | 24.9% | 36.3% | 54.2% | 34.4% | 23.1 ± 4.3 | |
| Shah et al. [36] | Randomized, multi-center double-blind placebo controlled trial | CHF, multi-centers (752 sites in 43 countries), inpatients and outpatient settings | HFpEF ≥ 45% | 1097 | 74 ± 8 | 53% | 35% | 40% | 94% | 30% | 29.9 ± 4.9 | 12% | LAVi, E/e', E/A, e' |
| Reddy et al. [14] | Prospective single-center cohort study | CHF, single-center, outpatient setting | HFpEF ≥ 50% | 238 | 68 ± 10 | 62% | 17% | 29% | 90% | 32% | 32.9 ± 7.1 | LAVi, LA Reservoir, conduit and contractile strain |
| Modin et al. [18] | Retrospective single-center cohort study | CHF, outpatient setting | HFpEF ≤ 45% | 818 | 66.4 ± 11.4 | 26.6% | 15.3% | 11.4% | 41.2% | 55.9% | 26.4 ± 4.8 | 9% | LAVi, E/e', E/A, e' |
### Table 2 (continued)

| Author/year | Study design                          | Study setting          | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------------------------------|------------------------|---------------------------------|------------|------------------------|-------------|------------------|------------------------|------------------------|------------------|-------------------------------|-----------|----------------------------------------|-----------------------------------------------|
| Shintani et al. [37] | Retrospective single-center cross-sectional study | AHF, inpatient setting | HFpEF | ≥ 50% | 127 | 80.6 ± 8.1 | 50% | 52% | 41% | 67% | 23.2 ± 3.7 | LAVi |
| Wu et al. [38] | Prospective single-center cohort study | CHF, inpatient setting | HFpEF | ≥ 50% | 163 | 61.1 ± 15.3 | 61% | 30.1% | 60.1% | 3.5% | 25.9 ± 4.2 | LAVi, E/e', E/A, e' |
| Telles et al. [39] | Prospective single-center cohort study | CHF, inpatient setting | HFpEF | ≥ 50% | 49 | 69.4 ± 8.0 | 71.4% | 26.5% | 14% | 67% | 14% | 30.2 ± 5.0 | LAVi, E/e', LA reservoir strain, conduit, e', E/A |
| Sobirin et al. [40] | A single-center, unblind, randomized, controlled clinical trial | CHF, outpatient setting | HFpEF | > 50% | 30 | 62 ± 8 | 50% | 73.3% |
| Lundberg et al. [41] | Prospective single-center cohort study | CHF, inpatient setting | HFpEF | ≥ 50% | 92 | 73.0 ± 8.8 | 62% | 48% | 19% | 69% | 3% | 26.6 ± 5.2 | LAVi, E/e', LA reservoir strain, e', E/A |
| Saikhan et al. [42] | Prospective single-center cohort study | CHF, outpatient setting | HFpEF | ≥ 50% | 110 | 63 ± 11 | 38.1% | excluded | 48.1% | 82.7% | 60% | 27.8 ± 5.4 | LAVi, LA Reservoir, conduit and contractile strain |
| Author/year      | Study design            | Study setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|------------------|-------------------------|---------------|---------------------------------|-------------|------------------------|-------------|------------------|-------------------------|----------------------|----------------|-------------------------------|-------------|---------------------------------------------------------------|----------------------------------------------------------|
| Burns [43]       | Prospective single-center cohort study | CHF, outpatient setting | HFP EF with anemia                | ≥ 50%      | 224                    | 65 ± 12     | 56%              | 26%                     | 37%                  | 79%            | 50%                          | 32 ± 10      | LAVi, E/e', e'                                                            |
|                  |                         |               |                                 |            |                        |             |                  |                         |                      |                |                               |             |                                                                                             |
| Obokata et al. [44] | Prospective single-center cohort study | CHF, inpatient and outpatient settings | HFP EF without anemia              | ≥ 50%      | 195                    | 63 ± 13     | 69%              | 27%                     | 28%                  | 75%            | 46%                          | 33 ± 9       | LAVi, E/e', e'                                                            |
| Nagy et al. [45] | Subset of prospective, observational, multi-center study | CHF, inpatient setting | HFP EF                            | ≥ 45%      | 86                     | 72 ± 10     | 51%              | 60%                     | 33%                  | 79%            | 15%                          | 30 ± 5       | LAVi, E/e', LA reservoir strain, e, E/A ratio'                                      |
| Carluccio et al. [19] | Prospective single-center cohort study | CHF, outpatient setting | HFR EF                            | ≤ 40%      | 405                    | 65.2 ± 12.3 | 24%              | 26%                     | 38%                  | 26.6 ± 4.1   | LAVi, E/e', LA reservoir strain, e, E/A ratio'                                      |
| Malagoli et al. [46] | Prospective single-center cohort study | CHF, outpatient setting | HFR EF                            | < 40%      | 286                    | 67 ± 11     | 19%              | 64%                     |                      |                |                               |             | LAVi, LA reservoir strain                                                  |
| Eroglu et al. [47] | Retrospective cohort study | CHF, outpatient setting | HFR EF                            | < 50%      | 59                     | 57 ± 13     | 23%              | 84%                     |                      |                |                               |             | LAVi, E/e', E/A, e'                                        |
| Almeida et al. [48] | Retrospective case-control study | AHF, inpatient setting | HFP EF                            | ≥ 50%      | 65                     | 55%          | 47.7%            | 80%                     | 33.8%                |                |                               |             | LAVi, E/e'                                                                 |
|                  |                         |               |                                 | < 40%      | 65                     | 43.1%        | 70.8%            | 44.6%                   |                      |                |                               |             |                                                                                             |
Table 2 (continued)

| Author/year | Study design | Study setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------|---------------|----------------------------------|-------------|------------------------|-------------|----------------|-------------------------|------------------------|----------------|-------------------------------|-------------|--------------------------------|-------------------------------------------------|
| Liu et al. [49] | Prospective single-center study | CHF, inpatient setting | HFpEF | ≥ 50% | 55 | 61 ± 13 | 54.5% | 43% | 93% | 33% | LAVi, E/e', LA reservoir strain, e', E/A |
| Shah et al. [50] | Prospective multinational multi-center observational study | CHF, outpatient setting | HFpEF | ≥ 40% | 51 | 72.4 ± 9.0 | 63% | 35% | 25% | 92% | 16% | 32.5 ± 10.7 | LAVi, E/e', LA reservoir strain |
| Xu et al. [51] | Retrospective, single-center cohort | CHF, inpatient setting | HFpEF | < 40% | 28 | 38 ± 14 | 18% | 20.6 ± 3.2 | 57.1% | |
| Saha et al. [52] | Retrospective, single-center cohort | CHF, outpatient setting | HFpEF | < 40% | 49 | 72 ± 13 | 42% | 8% | 12% | 68% | E/e', LA reservoir strain |
| Abrahams et al. [53] | Prospective single-center observational study | CHF, inpatient setting | HFpEF | > 50% | 114 | 59 ± 8 | 55% | 64% | 64% | 16% | 27 ± 3 | LAVi, E/e' |
| Modin et al. [54] | Retrospective single-center cohort | CHF, outpatient setting | HFpEF | < 45% | 151 | 70.5 ± 9.2 | 21.2% | 9.2% | 43% | 26.7 ± 5.1 | LAVi, E/e' |
| Batalli [55] | Prospective single-center cohort | CHF | HFpEF | NA | 55 | 63.0 ± 6.8 | Excluded | 59% | 41% | 29 ± 4 | E/e' |

| | | | | | | | | | | | | | | | | | |
| Author/year       | Study design                      | Study setting                    | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|------------------|-----------------------------------|----------------------------------|----------------------------------|------------|------------------------|-------------|----------------|-------------------------|-------------------|----------------|--------------------------|-------------|---------------------------------------------|------------------------------------------------|
| Sugimoto et al. [56] | Prospective single-center study | CHF, outpatient setting         | HFpEF                            | > 50%      | 20                     | 72.6 ± 10.3 | 60%           | 42%                     | 74%               | 10%            | 28.3 ± 5.0                |             | LAVi, E/e', LA reservoir strain, E/A           |
| Hage et al. [57]   | Subset of prospective observational multicenter study | AHF, inpatient setting         | HFpEF                            | < 40%      | 49                     | 63.1 ± 12.9 | 31%           | 35%                     | 63%               | 52%            | 26.7 ± 4.5                |             | LAVi, E/e'                               |
| Sargento et al. [58] | Prospective single-center observational study | CHF, outpatient setting         | HFpEF                            | < 40%       | 203                   | 67.8 ± 12.5 | 26.6%          | 26.1%                   | 32%               | 88.7%         | 39.4%                     | 27.2 ± 4.4 | LAVi                              |
| Aung et al. [59]   | Prospective two center study      | CHF                             | HFpEF                            | ≥ 50%      | 38                     | 65.2 ± 5.7 | 50%           | 13.2%                   | 60.5%             | 47.4%         | 28.1 ± 2.0                |             | LAVi, E/e', LA reservoir strain, contractile, e' |
| Hung [60]          | Prospective single-center cohort study | CHF, outpatient setting         | HFpEF                            | ≥ 50%      | 58                     | 64.3 ± 12.4 | 53.4%          | 32.8%                   | 74.1%             |               | 27.2 ± 3.7                |             | E/e', LA reservoir strain, e', E/A           |
| Freed et al. [61]  | Prospective single-center cohort study | CHF, outpatient setting         | HFpEF                            | ≥ 50%      | 308                    | 65 ± 13    | 64%           | 26%                     | 75%               | 50%            | 31.5 ± 8.6                | 14%         | LAVi, LA Reservoir, conduit and contractile strain, E/e', E/A |
| Unger et al. [62]  | Prospective single-center cohort  | CHF, outpatient setting         | HFpEF with- out CKD               | > 50%      | 154                    | 60.9 ± 12.3 | 62%           | 22%                     | 21%               | 68%            | 46%                      | 31.8 ± 8.7 | LAVi, E/e', LA reservoir, conduit and booster strain |

Table 2 (continued)
| Author/year | Study design and setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------------------|---------------------------------|-------------|------------------------|-------------|----------------|------------------------|----------------------|----------------|-------------------------------|------------|------------------------------------------|-------------------------------------------------|
| Georgievskaa-Ismail et al. [63] | Prospective single-center, cross-sectional study | HFpEF > 50% | 145 | 69.3 ± 12.1 | 66% | 30% | 39% | 83% | 52% | 31.5 ± 8.4 | HFpEF with CKD | LAVi, E/e', LA reservoir, conduit and booster strain |
| Melenovksy et al. [17] | Retrospective single-center cohort study | HFpEF ≥ 50% | 101 | 71 ± 10 | 58% | 42% | 47% | 93% | 44% | 34.0 ± 8.6 | HFpEF > 50% | LAVi,e' |
| Gracia et al. [64] | Prospective single-center cohort study | HFpEF < 50% | 97 | 61 ± 13 | 20% | 26% | 41% | 56% | 46% | 31.0 ± 6.9 | HFpEF ≥ 50% | LAVi, E/e', E/A, e' |
| Hasselberg et al. [65] | Prospective single-center Cross-sectional study | HFpEF ≥ 50% | 37 | 58 ± 11 | 32.4% | 14% | 41% | 60% | 26 ± 4 | Sanchis et al. [15] | HFpEF ≥ 50% | LAVi, E/e', E/A, e' |
| Sanchis et al. [15] | Prospective single-center cohort | HFpEF ≥ 50% | 63 | 76 ± 8 | 71.4% | 39.7% | 23.8% | 85.7% | 30 ± 5 | CHF, outpatient setting | HFpEF ≥ 50% | LAVi, E/e', LA reservoir strain |
| Author/year | Study design | Study setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------|---------------|---------------------------------|-------------|------------------------|-------------|-----------------|------------------------|------------------------|----------------|-------------------------------|-----------|----------------------------------|----------------------------------|
| Shah et al. [66] | International, multi-center, randomized, double blind placebo-controlled trial (with an echo substudy) | CHF, multi-center (270 sites in 6 countries) | HFrEF (TOPCAT-ECHO) | ≥ 45% | 935 | 69.9±9.7 | 49% | 38% | 40% | 91% | 60% | 32.6±7.5 | LAVi, E/e', LA reservoir, conduit and contractile strain, E/A, e' |
| Santos et al. [67] | Echo substudy multicenter, international, randomized, double blind placebo-controlled trial | CHF, multicenters (65 centers in 13 countries) | HFrEF (PARAMOUNT trial) | ≥ 45% | 135 | 70±9 | 61% | 23% | 35% | 92% | 22% | 29.6±5.7 | LAVi, LA Reservoir, conduit and contractile strain, E/e', E/A |
| Donal et al. [68] | Prospective, multicenter international observational study | AHF inpatient setting | HFrEF | <40% | 32 | 74±12 | 37.5% | 50% | 43.8% | 78.1% | 43.5% | 29±6 | LAVi, E/e', E/A, e' |
| Burke et al. [69] | Prospective single-center cohort | CHF, outpatient setting | HFrEF | ≥ 50% | 419 | 65±13 | 62% | 26% | 33% | 77% | 48% | 33±9 | 14% | LAVi, E/e', e' |
| Motoki et al. [70] | Prospective single-center cohort | CHF, outpatient setting | HFrEF | ≤ 35% | 108 | 57±15 | 23% | excluded | 27% | 51% | 45% | | LAVi, E/e', LA reservoir strain, conduit and contractile strain, e' |
| Author/year          | Study design          | Study setting                                      | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|----------------------|-----------------------|----------------------------------------------------|----------------------------------|-------------|------------------------|-------------|----------------|------------------------|------------------------|----------------|-------------------------------|-------------|----------------------------------------|--------------------------------------------------|
| Obokata et al. [71]  | Prospective single-center cohort | CHF, out-patient setting | HFpEF ≥ 50%                        | 40          | 77 ± 13                | 65%         | 35%            | 88%                  | 22 ± 5                |                |                               |            | LA reservoir strain, E/e', e', E/A                              |
| Carluccio et al. [72]| Prospective single-center observational study | CHF, out-patient setting | HFrEF < 45%                        | 747         | 68 ± 12                | 22%         | 16%            | 22%                  | 48%                   | 26 ± 4          | 32%                           |            | LAVi, E/e'                                             |
| Gupta et al. [73]    | Prospective on-going multi-communities cohort | CHF, out-patient setting | HFpEF ≥ 50%                        | 85          | 61.6 ± 6.9             | 85%         | 42%            | 85%                  | 13%                   | 32.6 ± 5.9      | 0%                            |            | E/A                                                   |
| Oh et al. [23]       | International randomized trial | CHF, international (122 sites in 26 countries) | HFrEF ≤ 35%                       | 31          | 60.9 ± 8.0             | 65%         | 68%            | 84%                  | 32%                   | 33.7 ± 9.6      | 10%                           |            | LAVi, E/e', E/A, e'                                             |
| Zile et al. [74]     | Echo-cohort of placebo-controlled double-blind multi-center international parallel study | CHF, inpatient and out-patient settings | HFpEF (I-PRESERVE-Echo cohort) ≥ 45% | 745         | 72 ± 7                 | 62%         | 26%            | 25%                  | 33%                   | 30 ± 5          | E/e', LA area, e'                                |            |                                                        |
| Tan et al. [75]      | Prospective single-center cohort | CHF, out-patient setting | HFpEF ≥ 50%                        | 50          | 72 ± 8                 | 70%         | excluded       | 30%                  | 100%                  | 18%            | 31 ± 5                           |            | LAVi                                                  |
| Author/year | Study design | Study setting | Heart failure phenotype examined | LVEF cutoff | Number of patients (n) | Age (years) | Female sex (%) | Atrial fibrillation (%) | Diabetes mellitus (%) | Hypertension (%) | Ischemic heart disease (%) | BMI (kg/m²) | Moderate to severe mitral regurgitation | LA structure and functional parameters measured |
|-------------|--------------|---------------|----------------------------------|-------------|-----------------------|-------------|----------------|------------------------|-------------------|----------------|-----------------------------|-------------|-----------------------------------------------|-------------------------------------------------|
| Jaubert et al. [76] | Prospective single-center cohort | CHF, inpatient setting | HFrEF | ≥ 45% | 59 | 64 ± 12 | 37% | 36% | 58% | 49% | 27 ± 5 | LAVi, E/e', e' |
| Hinderliter et al. [77] | Prospective cohort | CHF, outpatient setting | HFrEF | ≤ 40% | 211 | 57 ± 12 | 31% | 19% | 44% | 77% | 43% | 31.2 ± 7.2 | LAVi |
| Donal et al. [78] | Prospective multicenter cohort | CHF, outpatient setting | HFrEF | < 35% | 75 | 59 ± 11 | 82.7% | - | 34.7% | LAVi |
| Jasiczpak et al. [79] | Prospective single-center cohort | CHF, outpatient setting | HFpEF without AF | ≥ 50% | 131 | 63.7 ± 8.0 | 73% | 0 | 37% | 89% | - | 29.4 ± 4.1 | LAVi, LA Reservoir, conduit and contractile strain, E/e', E/A |
| CarluccioE [80] | Prospective single-center cohort | CHF, outpatient setting | HFpEF with AF | ≥ 50% | 39 | 67.4 ± 8.9 | 72% | 100% | 49% | 97% | - | 30.4 ± 4.3 | - |

ADHF acute decompensated heart failure, AHF acute heart failure, CHF chronic heart failure, CKD chronic kidney disease, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, LA left atrial, LAVi left atrial volume index, e' mitral annular early diastolic velocity by tissue doppler, E/A the ratio between early and late mitral inflow velocity by doppler, E/e' the ratio between early mitral inflow velocity and mitral annular early diastolic velocity.
## Table 3  Echocardiographic characteristics of included studies

| Author/year | HF phenotype | Number of patients (n) | LAVi | LAGLSg (%) | LAGLSr (%) | LAGLSc (%) | E/e' | MV E/A | Mitral annulus e' | LVEF | LVGLS | Software for Speckle tracking analysis |
|-------------|--------------|------------------------|------|------------|------------|------------|------|--------|------------------|------|-------|-------------------------------------|
| Hoshida et al. [27] | HFpEF | 105 | 47.6 ± 24.2 | 14.4 ± 5.7 | 60.9 ± 6.9 |
| Harada et al. [28] | HFpEF | 92 | 54.6 ± 26.7 | 17.7 ± 3.7 | 57.8 ± 9.4 | −13.9 ± 4.4 | EchoPAC |
| Hwang et al. [29] | HFpEF | 1105 | 49.9(34.5-69.8) | 18.6 ± 11.6 | 59.3 ± 6.6 | −15.1 ± 5.0 | TomTec |
| Park et al. [16] | HFpEF | 1191 | 63 ± 48.8 | 19.1 ± 11.6 | 59.1 ± 5.9 | TomTec |
| Sobrin et al. [40] | HFpEF | 30 | 33.0 ± 8.0 | 18.6 ± 3.4 | 60.0 ± 7.0 | |
| Shah et al. [36] | HFpEF | 1097 | 38.9 ± 15.5 | 12.6 ± 5.7 | 58.6 ± 9.8 | |
| Reddy et al. [14] | HFpEF | 238 | 32 ± 15 | 29 ± 16 | 14 ± 6 | −15 ± 3 | Syngo |
| Shintani et al. [37] | HFpEF | 127 | 66.0 ± 27.4 | 14.6 ± 4.6 | 60.8 ± 9.0 | |
| Wu et al. [38] | HFpEF | 163 | 37.1 ± 8.1 | 16.5 ± 2.4 | 68.0 ± 9.0 | |
| Telles et al. [39] | HFpEF | 49 | 41.5 ± 15.2 | 12.9 ± 5.7 | 62.6 ± 6.1 | −18.7 ± 2.3 | TomTec |
| Lundberg et al. [41] | HFpEF | 92 | 43.0 ± 14.0 | 13.4 ± 6.6 | 60.7 ± 5.9 | −17.3 ± 4.4 | EchoPAC |
| Shah et al. [50] | HFpEF-absent CMD | 51 | 36.5 ± 11 | 19.8 ± 8.3 | 60.9 ± 6.4 | −17 ± 3.5 | TomTec |
| Shah et al. [50] | HFpEF-present CMD | 151 | 39.3 ± 13.4 | 15.0 ± 7.7 | 58.5 ± 8.1 | −15.7 ± 3.5 | TomTec |
| Abohammar et al. [53] | HFpEF | 114 | 47.0 ± 7.0 | 12.2 ± 2.0 | 61.0 ± 3.0 | −13.5 ± 1.5 | EchoPAC |
| Saikhan et al. [42] | HFpEF | 224 | 36.6 ± 15.8 | 16.1 ± 8.8 | 61.0 ± 7.0 | |
| Burns et al. [43] | HFpEF-Anemia | 195 | 31.3 ± 11.9 | 14.0 ± 7.3 | 61.0 ± 6.0 | |
| Obokata et al. [44] | HFpEF | 271 | 44 ± 15 | 16 ± 8 | 62.7 | |
| Nagy et al. [45] | HFpEF | 86 | 44 ± 16 | 13.3 ± 11.0 | 62.5 ± 7.0 | −15 ± 3.6 | TomTec |
| Almeida et al. [48] | HFpEF | 65 | 48.0 ± 19.4 | 16.0 ± 8.1 | 58.0 ± 5.9 | −14.0 ± 3.7 | EchoPAC |
| Liu et al. [49] | HFpEF | 55 | 37.5 ± 8.3 | 20.4 ± 7.4 | 59.5 ± 6.5 | EchoPAC |
| Batalli et al. [55] | HFpEF | 55 | 9.4 ± 4.7 | 0.8 ± 0.3 | 59.6 ± 8.7 | Philips iE33 |
| Sugimoto et al. [56] | HFpEF | 20 | 52.0 ± 24.0 | 20.0 ± 8.0 | 56.0 ± 11.0 | EchoPAC |
| Hage et al. [57] | HFpEF | 86 | 44.4 ± 11.6 | 11.0 ± 4.2 | 63.3 ± 7.4 | |
| Freed et al. [61] | HFpEF | 308 | 34 ± 13.7 | 18.3 ± 7.7 | 62.1 ± 6.3 | −15.7 ± 1.8 | EchoPAC |
| Aung et al. [59] | HFpEF | 38 | 43.7 ± 14.4 | 70.0 ± 2.5 | 62.9 ± 4.2 | |
| Hung et al. [60] | HFpEF | 58 | 28.2 ± 6.4 | 59.1 ± 19 | 61.6 ± 3.6 | "-9.1 ± 6.3 |
| Unger et al. [62] | HFpEF-no CKD | 154 | 32.5 ± 12.0 | 19.6 ± 8.9 | 61.5 ± 6.3 | −18.2 ± 4.0 | TomTec |
| Author/year | HF phenotype | Number of patients (n) | LAVi | LAGLSp (%) | LAGLSq (%) | LAGLSc (%) | E/e' | MV E/A | Mitral annulus e' | LVEF | LVGLS | Software for Speckle tracking analysis |
|-------------|--------------|------------------------|------|------------|------------|------------|------|--------|-----------------|------|-------|-----------------------------------|
| Shah et al. [66] | HFrEF-CKD | 145 | 36.5±15.4 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Melenovsky et al. [17] | HFrEF | 101 | 41.0±12.0 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Hasselberg et al. [65] | HFrEF | 37 | 45.0±22.0 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Gracia et al. [64] | HFrEF | 28 | 32.6±12.0 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Sandhis et al. [15] | HFrEF | 63 | 58.9±23.3 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Santos et al. [67] | HFrEF | 135 | 33.4±11.5 | 24.6±0.6 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Donal et al. [68] | HFrEF | 539 | 49.4±17.8 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Burk et al. [69] | HFrEF | 419 | 34.2±14.3 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Obokata et al. [71] | HFrEF | 40 | 22.7±6.6 | 12.3±5.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Gupta et al. [73] | HFrEF | 85 | 51.0±20.0 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Zile et al. [74] | HFrEF | 346 | 30.4±9.2 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Tan et al. [75] | HFrEF | 50 | 30.7±12.6 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Jaffet et al. [76] | HFrEF | 67 | 38.1±12.5 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Shah et al. [30] | HFrEF (recovered) | 69 | 47.1±11.7 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Tanaka et al. [31] | HFrEF | 205 | 51.0±20.0 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Castrichini et al. [32] | HFrEF | 77 | 57.0±26.0 | 10.3±6.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Valentim et al. [33] | HFrEF | 42 | 51.5±22.6 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Deferm et al. [35] | HFrEF | 63 | 69.0±26.0 | 6.4±2.2 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Park et al. [16] | HFrEF | 2036 | 58.1±28.8 | 11.7±8.1 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Kurzawski et al. [34] | HFrEF | 63 | 62.1±13.3 | 8.9±2.0 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Modini et al. [18] | HFrEF | 818 | 30.9±13.8 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Shimizu et al. [37] | HFrEF | 617 | 67±24.4 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Wu et al. [38] | HFrEF | 34 | 38.4±6.5 | 28.8±14.9 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Lundberg et al. [41] | HFrEF | 72 | 57.7±18.5 | 7.7±4.2 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
| Malagoli et al. [36] | HFrEF | 286 | 46.2±18.2 | 19.4±9.4 | 15.9±7.9 | 15.4±7.2 | 14.8±7.6 | 1.4±0.7 | 8.5±3.4 | 60.9±6.6 | −16.8±4.1 | TomTec |
### Table 3 (continued)

| Author/year | HF phenotype | Number of patients (n) | LAVi | LAGLSR (%) | LAGLSB (%) | LAGLSC (%) | E/e' | MV E/A | Mitral annulus e' | LVEF | LVGLS | Software for Speckle tracking analysis |
|-------------|--------------|------------------------|------|------------|------------|------------|------|--------|------------------|------|-------|--------------------------------------|
| Carluccio et al. [19] | HFrEF | 405 | 52.6±18.6 | 15.8±7.0 | 14.3±5.2 | 1.4±1.2 | 5.4±1.8 | 30.0±7.4 | −8.3±2.9 | EchoPAC |
| Eroglu et al. [47] | HFrEF | 59 | 42.7±22.1 | 17.0±6.0 | 1.7±1.7 | 5.3±1.3 | 33.3±10.4 | −9.7±4.4 | Philips QLAB |
| Almeida et al. [48] | HFrEF | 65 | 46.7±13.3 | 17.3±5.2 | 2.7±0.8 | 17.0±5.4 | 30.0±11.9 | −7.7±2.2 | EchoPAC |
| Xu et al. [51] | HFrEF-event | 28 | 71.0±22.0 | 19.3±10.7 | 2.1±1.2 | 19.0±5.6 | 30.0±11.1 | −7.7±2.2 | EchoPAC |
| Xu et al. [51] | HFrEF-event-free | 17 | 57.0±16.0 | 20.5±11.1 | 2.1±1.2 | 19.0±5.6 | 30.0±11.1 | −7.7±2.2 | EchoPAC |
| Saha et al. [52] | HFrEF | 49 | 11.6±11.6 | 15.0±10 | 31±8 | −7±3 | EchoPAC |
| Modin et al. [54] | HFrEF | 151 | 42.1±19.0 | 11.9±5.3 | 8.6±2.6 | 26.2±9.4 | −10.1±3.6 | EchoPAC |
| Batalii et al. [55] | HFrEF | 56 | 13.5±6.4 | 1.3±0.9 | 5.3±2.2 | 35±7.5 | EchoPAC |
| Sugimoto et al. [56] | HFrEF | 49 | 55.0±29.0 | 15.1±10.1 | 24.0±13.0 | 1.5±1.1 | 31.0±8.0 | EchoPAC |
| Sargento et al. [58] | HFrEF | 203 | 42.3±18.3 | 1.4±1.0 | 28.2±8.4 | −8.7±3.3 | EchoPAC |
| Melenovsky et al. [17] | HFrEF | 97 | 50.0±17.0 | 6.2±2.1 | 24±9.7 | EchoPAC |
| Sanchis et al. [15] | HFrEF | 32 | 57.8±20.8 | 6.5±5.4 | 11.6±7.6 | 34.0±10.0 | −9.5±4.5 | EchoPAC |
| Motoki et al. [30] | HFrEF | 108 | 42.0±15.0 | 14.5±8.2 | 7.7±5.7 | 20.0±12.0 | 1.7±1.4 | 7.2±4.5 | 25.0±6.0 | EchoPAC |
| Carluccio et al. [72] | HFrEF | 747 | 43.9±18.8 | 14.7±8.0 | 1.77±1.56 | 6.7±2.8 | 29.0±7.0 | Syngo |
| Gupta et al. [73] | HFrEF | 31 | 41.9±15.2 | 17.6±9.6 | 1.3±1.1 | 6.0±3.0 | 28.9±8.3 | EchoPAC |
| Oh et al. [23] | HFrEF | 2006 | 49±23 | 16.7±6.8 | 1.53±0.87 | 5.9±1.5 | 60±6 | −15.4±3.5 | EchoPAC |

**HFpEF** heart failure with preserved ejection fraction, **HFrEF** heart failure with reduced ejection fraction, **HF** heart failure, **CMD** coronary microvascular dysfunction, **CKD** chronic kidney dysfunction, **GLS** global longitudinal strain, **LVGLS** left ventricle global longitudinal strain, **LVEF** left ventricle ejection fraction, **LA** left atrial, **LAVi** left atrial volume index, **LAGLSR** left atrial global longitudinal strain at reservoir phase, **LAGLSB** left atrial global longitudinal strain at booster phase, **LAGLSC** left atrial global longitudinal strain at conduit phase, **e’** mitral annular early diastolic velocity by tissue Doppler, **MV E/A** the ratio between early and late mitral inflow velocity by Doppler, **E/e’** the ratio between early mitral inflow velocity and mitral annular early diastolic velocity.
versus chronic outpatient setting for HFrEF patients. Four out of 61 studies in the chronic outpatient setting reported LAGLSR in both patients with HFrEF (n = 3058) and HFrEF (n = 1877). LAGLSR was worse in patients with HFrEF as compared to patients with HFrEF [8.5% versus 23.6%; WMD = 16.3% (22.05, 8.61); p < 0.001, I² = 77.6%]. Besides, the relationship between LAVi and LAGLSR (Fig. 2) was significant in HFrEF (estimated coefficient −1.08, p = 0.009, R² = 0.525), but not in HFrEF (estimated coefficient −0.44, p = 0.06, R² = 0.447). On the other hand, the relationship between LAGLS with LVGLS was not significant in neither HFrEF (estimated coefficient 1.35, p = 0.30, R² = 0.01) nor HFrEF (estimated coefficient 2.81, p = 0.41, R² = 0.006). Two studies reported LA booster GLS (LAGLSB) in patients with HFrEF (n = 140), and ten studies reported LAGLSB in patients with HFrEF (n = 1320). The pooled mean value of LAGLSB was 7.7% versus 13.9% between patients with HFrEF and HFrEF. Five studies reported LA conduit GLS (LAGLSC) in patients with HFrEF (n = 1173) in the chronic ambulant clinical setting, and the pooled mean value LAGLSC was 15.8% in patients with HFrEF. No included studies reported LAGLSC in patients with HFrEF. Given the very limited number of studies comparing LA booster and conduit function in patients with HFrEF versus HFrEF, it is hard to determine how these two LA phasic function differ in patients with HFrEF versus HFrEF. Lastly, the details of prognostic information for each LA parameter and the adjusted covariates from included studies were summarized in supplementary online (Tables S5 and S6).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis assessing and comparing LA structural and functional echocardiographic parameters and their clinical relevance in patients with HFrEF versus HFrEF. It
A change in LA structure and function is a complex, dynamic and heterogeneous process that may be different between phenotypes of HF. LA dysfunction and increase of LA pressure have long been considered as hallmarks of HFrEF, whereas HFrEF is generally considered as a left ventricular disease [3, 20, 21]. This might explain the discrepancy in the number of studies focusing on LA dysfunction in HFrEF versus HFrEF. However, despite a greater burden of AF in patients with HFrEF, our data found that LA function was worse in patients with HFrEF than patients with HFrEF. This might be related to the greater burden of moderate to severe functional MR in patients with HFrEF. HFrEF is more associated with an eccentric ventricular remodelling, resulting in tethering of the mitral leaflets [22, 23]. In our review, we showed that in HFrEF patients functional MR was less prevalent, but not negligible, and may be more the result of mitral annular dilation due to the high incidence of AF in this subgroup.

LA reservoir peak longitudinal strain, inherent to its nature as a strain, is dependent on its baseline length, with maximal elongation of the LA during LV systole, suggesting its high dependence on LV longitudinal strain as well [24]. Carluccio et al. showed that LA reservoir GLS was more strongly associated with LVGLS beyond LA volume and E/e’ in patients with HFrEF, supporting the significant contribution of LV systolic dysfunction to LA dysfunction in patients with HFrEF [19]. Comparatively, LA mechanical dysfunction in patients with HFrEF, particularly in the setting of AF, is usually not accompanied by substantial changes of LV systolic function, which suggests LA mechanical dysfunction to be disproportionate to LV systolic dysfunction in such patients [8]. Hence, a decrease of LV longitudinal function, as we show in patients with HFrEF, might impact LA reservoir function more in patients with HFrEF than HFrEF [17, 20], suggesting that the concept of LA myopathy is not only subject to HFrEF, but to HFrEF as well.

Despite worse LA global function in HFrEF than HFrEF, the prevalence of AF was higher in patients with HFrEF than HFrEF. AF and HFrEF share many convergent metabolic risk factors, including obesity that promote systematic inflammatory processes. Expansion of epicardial fat tissue may act as a local source of inflammation, amplifying ongoing systemic inflammatory processes [20]. LA dysfunction in HFrEF is likely associated with a series of inflammatory cascades resulting in coupled LA endocrine and regulatory dysfunctions. This is supported by data from Patel et al. who showed that LA reservoir strain was associated with biomarkers of neurohormonal activation [25]. However, the exact mechanism of how the LA mechanical, regulatory, and endocrine functions are coupled together, and particular which factor is the main driving component of LA dysfunction in both settings of HFrEF and HFrEF remains unknown.
Although the prognostic value of LA reservoir strain has been described in several studies that were included in our systematic review both in patients with HFpEF and HFrEF [16, 18, 19], future prognostic studies are warranted to investigate whether LA dysfunction in HFrEF and HFpEF are two distinct processes. A better understanding of different forms of LA dysfunction in HFrEF versus HFpEF may have important clinical implications. Given the distinct LA reservoir GLS in patients with HFrEF versus HFpEF, this measurement might serve as a potential marker to better phenotype patients with HF. For patients with HFpEF, a novel therapeutic intervention which specifically targets the LA by creating a shunt at the atrial level to offload LA pressure looks promising from preliminary data [26]. Given our finding of higher LA pressure and worse LAGLS in HFrEF, we might cautiously postulate a potential benefit of this novel device in patients with HFrEF as well.

Limitations

There are several limitations of the current systematic review. First, our review has the inherent limitation of selection and reporting bias, which was minimized by a thorough selection procedure and quality assessment. Secondly, we only focused on primary echocardiographic parameters assessing LA structures and function that have been widely recommended in guidelines. Other echocardiographic parameters such as LAEF and other LA-related parameters assessed by other imaging modalities were not included in the current review. Thirdly, we were not able to account for all differences in clinical characteristics due to a lack of individual-level data. For example, the definition (and thus the extent) of ischemic cardiomyopathy varies study by study, which hampers a thorough analysis of its (possibly) confounding role. Fourth, we were unable to report the weighted HR of comprehensive LA structural and functional parameters except for LA reservoir GLS due to the limited numbers of studies, different outcome measures, and lack of confounder adjustments. Last but not least, the details of averaging the RR interval for the strain measurement in the setting of AF were not addressed in most of the studies.

Conclusion

Although left atrial abnormalities have been proposed as a hallmark of HFpEF, we found that LA structure and function are worse in patients with HFrEF than HFpEF. Thus, the significant pathophysiological insight of intrinsic LA myopathy should be equally emphasized in both patients with HFrEF and patients with HFpEF.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10741-021-10204-8.

Declarations

Conflict of interest The authors declare no competing interests.

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