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RESEARCH ARTICLE

Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis

**Muhammad Shahzeb Khan[1], Muhammad Mustafa Memon[2], Mohammad H. Murad[3], Muthiah Vaduganathan[4], Stephen J. Greene[5], Michael Hall[6], Filippos Triposkiadis[7], Carolyn S.P. Lam[8,9], Amil M. Shah[4], Javed Butler[10], and Sanjiv J. Shah[11]*

[1]Department of Internal Medicine, John H Stroger Jr. Hospital of Cook County, Chicago, IL, USA; [2]Department of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan; [3]Division of Preventive Medicine, Mayo Clinic, Rochester, MN, USA; [4]Harvard Medical School, Brigham and Women's Hospital Heart & Vascular Center, Boston, MA, USA; [5]Duke Clinical Research Institute and Duke University School of Medicine, Durham, NC, USA; [6]Department of Cardiology, University of Mississippi Medical Center, Jackson, MS, USA; [7]Department of Cardiology, Larissa University Hospital, Larissa, Greece; [8]National Heart Centre Singapore, Duke-National University of Singapore, Singapore; [9]Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands; [10]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; and [11]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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Aims Left atrial (LA) mechanical function may play a significant role in the development and progression of heart failure with preserved ejection fraction (HFpEF). We performed a systematic review and meta-analysis to evaluate association of impaired LA function with outcomes in HFpEF.

Methods and results Multiple databases were searched for original studies measuring different phases of LA function in HFpEF patients. Comparative LA function between HFpEF patients and healthy controls was assessed by pooling weighted mean differences (WMD). Adjusted hazard ratios (HRs) with 95% confidence intervals were pooled to evaluate the prognostic utility of LA function. Twenty-two studies (2 trials, 20 observational) comprising 1974 HFpEF patients and 751 healthy controls were included. HFpEF patients had decreased LA reservoir [WMD = −12.21% (−15.47, −8.95); $P < 0.001$], LA conduit [WMD = −5.68% (−8.56, −2.79); $P < 0.001$], and pump [WMD = −11.07% (−14.81, −7.34); $P < 0.001$] emptying fractions compared with controls. LA reservoir [WMD = −13.38% (−16.07, −10.68); $P < 0.001$], conduit [WMD = −4.09% (−6.77, −1.42); $P = 0.003$], and pump [WMD = −3.53% (−4.47, −2.59); $P < 0.001$] strains were also significantly lower in HFpEF patients. Decreased LA reservoir strain [HR 1.24 (1.02, 1.50); $P = 0.03$] was significantly associated with risk of composite all-cause mortality or heart failure hospitalization.

Conclusions Impaired LA function appears to have diagnostic and prognostic value in HFpEF, but whether indices of LA function truly refine discrimination for diagnosis or prognosis remains to be fully determined. Larger studies are needed to better evaluate associations between LA function and clinical outcomes and the role of LA function as a target for novel HFpEF therapies.

Keywords Left atrium • Heart failure with preserved ejection fraction • Meta-analysis • Remodelling

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for approximately half of all patients with HF,[1] and is increasingly becoming a global health problem.[2] Unfortunately, the biological basis and pathogenesis of HFpEF remain incompletely understood.[3] Initially, the pathophysiology of HFpEF was mainly described by increased left ventricular (LV) and vascular stiffness.[3]

*Corresponding author. Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 N St Clair St, Ste 600, Chicago, IL 60611, USA. Tel: +1 312 926-8294, Email: sanjiv.shah@northwestern.edu

However, increasing recognition of global myocardial and systemic abnormalities in HFpEF has recently shifted emphasis to understanding myocardial remodelling and dysfunction in other cardiac chambers.

Left atrial (LA) function is essential for optimal cardiac performance and modulates LV filling.[4] During the reservoir phase, the left atrium collects blood from the pulmonary veins. At this stage, atrial compliance ensures maintenance of normal filling pressures with increase in LA volume. Additionally, the LA reservoir phase is also influenced by LA relaxation, LA contractility, and LV characteristics such as descent of the LV base during systole. Subsequently, in early diastole, blood stored in the left atrium during the reservoir phase (atrial conduit volume) passively enters the left ventricle due to the pressure gradient between the left atrium and left ventricle and acts as a 'conduit' between pulmonary veins and the left ventricle. Finally, at end diastole, LA contraction occurs and further fills the left ventricle.[5] Thus, impaired LA compliance, conduit volume, or booster pump function should theoretically play a key role in HFpEF.

Multiple studies have shown that LA size is an independent predictor of mortality and morbidity in HFpEF.[6,7] However, diagnostic and prognostic data regarding different phases of LA function in HFpEF, especially in patients with normal LA size, are not well established.[8] LA remodelling in HFpEF is related to factors that are responsible for the development of HF and to abnormal LV performance. Thus, we performed a systematic review and meta-analysis of all available studies to assess the diagnostic and prognostic impact of LA functional changes in HFpEF patients.

Methods

Data sources and search strategy

This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[9] MEDLINE, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from database inception through March 2019. To identify grey literature, online libraries www.clinicaltrialresults.org, www.clinicaltrials.gov, www.cardiosource.org, www.escardio.org, and abstracts and presentations from major cardiovascular proceedings were also searched. Additional studies were selected by manually screening references of articles identified by the search. No restrictions were placed on time or language. A complete description of the search strategy used specific to each database is outlined in the online supplementary *Table S1*. All citations retrieved from the search were transferred to EndNote X7.5 (Clarivate Analytics, Philadelphia, PA, USA) Reference Manager and duplicates were removed.

Study selection

The citations were screened by two independent investigators (MSK and MMM). Non-relevant citations were excluded on the basis of title and abstract. Full texts of references were then screened for inclusion based on pre-determined criteria. Any disagreements were resolved by consensus. No disagreements required resolution by a third investigator. Randomized controlled trials (RCTs) or observational studies reporting at least one of the three LA volumetric phasic functions (total, passive, and active emptying fractions) or strain (reservoir, conduit, and booster pump strain) as measures of LA function in HFpEF patients were included in the meta-analysis. Presence of a control group was not necessary for the prognostic part of the analysis. Studies comparing HFpEF to HF with reduced ejection fraction (HFrEF) patients were excluded. Letters, editorials and review articles were also excluded.

Data extraction and risk of bias assessment

Two authors (MSK and MMM) independently abstracted data regarding year of publication, sample size, study design, baseline patient profiles, LA function measurement techniques, LA strain measurement software and platform, HFpEF diagnostic criteria, and follow-up time using a standardized data extraction form. LA functional outcomes included LA reservoir, conduit, and booster pump function in terms of strain and volumetric emptying components. LA reservoir, conduit and pump emptying fractions were calculated as previously described.[10] In brief, the following formulae were used: LA total (reservoir) emptying fraction, $(V_{max}-V_{min})/V_{max}$; LA passive (conduit) emptying fraction, $(V_{max}-V_{Pre\ A})/V_{max}$; LA active (pump) emptying fraction, $(V_{pre\ A}-V_{min})/V_{Pre\ A}$). Variables used were defined as follows: V_{max}, maximal LA volume just before the opening of the mitral valve; $V_{Pre\ A}$, LA volume at the onset of P-wave on the electrocardiogram; V_{min}, minimal volume at the closure of the mitral valve. LA strain parameters (online supplementary *Figure S1*) were calculated as defined by Hoit.[11] Only markers of LA function measured at rest were considered. Prognostic outcomes included all-cause mortality, HF hospitalization, and the combined endpoint of all-cause mortality and HF hospitalization. The methodological quality of RCTs was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) across five domains (randomization, intended intervention, missing data, outcome measurement, and reported results),[12] while the Newcastle–Ottawa scale was used for observational studies to evaluate methodological quality based on selection, comparability, and outcome/exposure criterion of included studies.[13]

Statistical analysis

Data on LA volumetric and strain function in both HFpEF patients and controls were pooled to calculate weighted mean differences (WMDs) and 95% confidence intervals (CIs). LA volumetric function was also separately pooled in hypertensive left ventricular hypertrophy (HLVH) patients and compared to HFpEF patients. A random effects model with inverse variance weighting was used to account for heterogeneity across studies, which was measured using the Cochrane I^2 statistic. I^2 values of <25–50%, 50–75%, or >75% indicated mild, moderate, or severe heterogeneity, respectively.[14] Adjusted hazard ratios (HRs) per one standard deviation (SD) increase or decrease in LA parameter with 95% CIs were pooled to evaluate prognosis. In only one case, HR per 1 SD increase in LA parameter was converted to HR per 1 SD decrease in LA parameter by exponentiating the negative logarithm of the HR and accompanying 95% CI. Random effects meta-regression analysis was performed to test the contribution of study covariates of mean age (years), mean LV mass index (kg/m^2), mean maximum LA volume index (mL/m^2) (as a measure of LA size), and mitral E/e' (as a surrogate of LV filling pressures) to heterogeneity in LA emptying fraction results. We also planned to include LV global longitudinal strain as a covariate

in meta-regression analysis; however, few studies ($n = 6$) reported the covariate, and thus it was not included.

We also conducted pre-specified subgroups analyses by mean age, mean baseline LV ejection fraction (LVEF), LA function measurement technique [echocardiography or cardiac magnetic resonance (CMR)], LA strain measurement software (EchoPAC or TomTec), HFpEF diagnosis LVEF cut-off (> 50% or > 45%), and prior history of atrial fibrillation (AF). We used median age and median baseline LVEF as cut-offs for subgroup analyses. For subgroup analyses by prior history of AF, for all LA parameters except LA reservoir strain, the included patients were in sinus rhythm at the time of echocardiography. Chi-square tests were used to assess subgroup differences.

To assess the impact of an individual study on functional and prognostic outcomes, a sensitivity analysis was conducted by stepwise exclusion of one study at a time. Sensitivity analysis was also performed by excluding studies with unmatched controls to determine the impact of matching controls based on demographic variables. Sensitivity analysis by restricting analyses to studies with healthy (non-co-morbid) control groups only was also carried out. An additional sensitivity analysis including patients with conditions related to HFpEF (HLVH) as part of the control group was also performed. The Egger's test and funnel plot were used to assess for publication bias. *P*-values < 0.05 were considered statistically significant in all cases. OpenMetaAnalyst (Brown University School of Public Health, Providence, RI, USA) was used for meta-regression and stepwise exclusion sensitivity analyses. RevMan (version 5.3; Cochrane Collaboration, Oxford, UK) was used for all other analyses.

Results

Study characteristics and quality assessment

The systematic review and study selection are outlined in the PRISMA flow chart (*Figure 1*). Of 1054 unique articles screened, 2 trials (one RCT, one randomized non-controlled) and 20 observational studies (3 retrospective, 17 prospective) including 1974 symptomatic HFpEF patients and 751 controls were included in the final analysis. Of the 16 studies with control groups, 6 selected age and sex-matched controls, 1 matched controls by age, sex, and race/ethnicity, 1 matched by age, sex, and body mass index, while 10 did not use matched controls. Six studies reported only LA volumetric emptying fractions, 7 reported only LA strain, and 10 reported both LA strain and volumetric emptying fractions. For the measurement of volumetric fractions, echocardiography was used by 13 studies (1259 HFpEF, 488 controls), while CMR was used by 2 studies (162 HFpEF, 60 controls). Similarly, for LA strain measurement, all studies used speckle-tracking echocardiography (819 HFpEF, 544 controls), except one that utilized CMR (10 HFpEF, 10 controls). Follow-up time across studies ranged from 11.5 to 44.4 months with a median of 31 months.

Seven studies excluded HFpEF patients with history of AF. In the remaining studies, a median of 24% of HFpEF patients had a history of AF, ranging from 10% to 42% across studies. All studies, except three, had data on patients in sinus rhythm at the time of echocardiography. The mean baseline LVEF between studies ranged from 56.5% to 72.0%. Most studies ($n = 19$) set a LVEF cut-off for HFpEF diagnosis of ≥ 50% while the remaining used ≥ 45% as their cut-off. Study characteristics and patient demographics of included studies are summarized in *Table 1*.[4,8,15–34] Methodological quality assessment showed low to moderate risk of bias among trials (online supplementary *Table S2*) and observational studies (online supplementary *Table S3*). Inspection of funnel plot and Egger's test showed no evidence of publication bias ($P = 0.07$) although the number of included studies was small to allow adequate power of this test (online supplementary *Figure S2*).

Left atrial volumetric function in HFpEF compared with hypertensive left ventricular hypertrophy

Three studies reported LA volumetric reservoir and pump function in HLVH patients (112 HFpEF, 90 HLVH). When compared with HFpEF patients, HLVH patients did not have significantly different LA reservoir [WMD = −3.84% (−10.14, 2.45); $P = 0.23$; $I^2 = 79\%$] and pump function [WMD = −1.97% (−8.59, 4.64); $P = 0.56$; $I^2 = 73\%$] (*Figure 2*). Only one study contained adequate data on LA conduit function in HLVH patients (37 HFpEF, 40 HLVH). LA conduit function was significantly decreased in HFpEF compared to HLVH.

Left atrial total emptying fraction (left atrial reservoir)

Twelve of the 22 included studies reported LA reservoir function (844 HFpEF, 500 controls) (*Figure 3*). LA reservoir function was significantly reduced in HFpEF patients [WMD = −12.21% (−15.47, −8.95); $P < 0.001$; $I^2 = 85\%$] compared with controls, although heterogeneity in the effect estimate was high. Online supplementary *Table S4* summarizes the results of meta-regression analysis. Mean age (coefficient −0.615; $P = 0.016$) and mean LV mass index (coefficient −0.127; $P = 0.017$) significantly contributed to the heterogeneity in the analysis for LA reservoir fraction. None of the other covariates were statistically significant in explaining heterogeneity after testing for differences in mean maximum LA volume index (coefficient −0.281; $P = 0.414$), and mean mitral E/E' (coefficient −0.598; $P = 0.322$) between studies. Restricting the analysis to studies using only demographically matched [WMD = −11.20 (−13.59, −8.81); $P < 0.001$; $I^2 = 50\%$] or healthy (non-co-morbid) [WMD = −9.06 (−12.96, −5.16); $P < 0.001$; $I^2 = 81\%$] control groups did not significantly change results (online supplementary *Table S5*). Similarly, sensitivity analysis including HLVH patients in the control group yielded similar results [WMD = −11.82 (−15.34, −8.29); $P < 0.001$; $I^2 = 87\%$].

Left atrial passive emptying fraction (left atrial conduit)

Out of the 22 studies, 8 included data on LA conduit function (655 HFpEF, 371 controls). A significantly lower LA conduit fraction was observed in HFpEF patients compared with controls [WMD = −5.68% (−8.56, −2.79); $P < 0.001$; $I^2 = 76\%$]. Heterogeneity in effect estimates was significant ($I^2 = 76\%$).

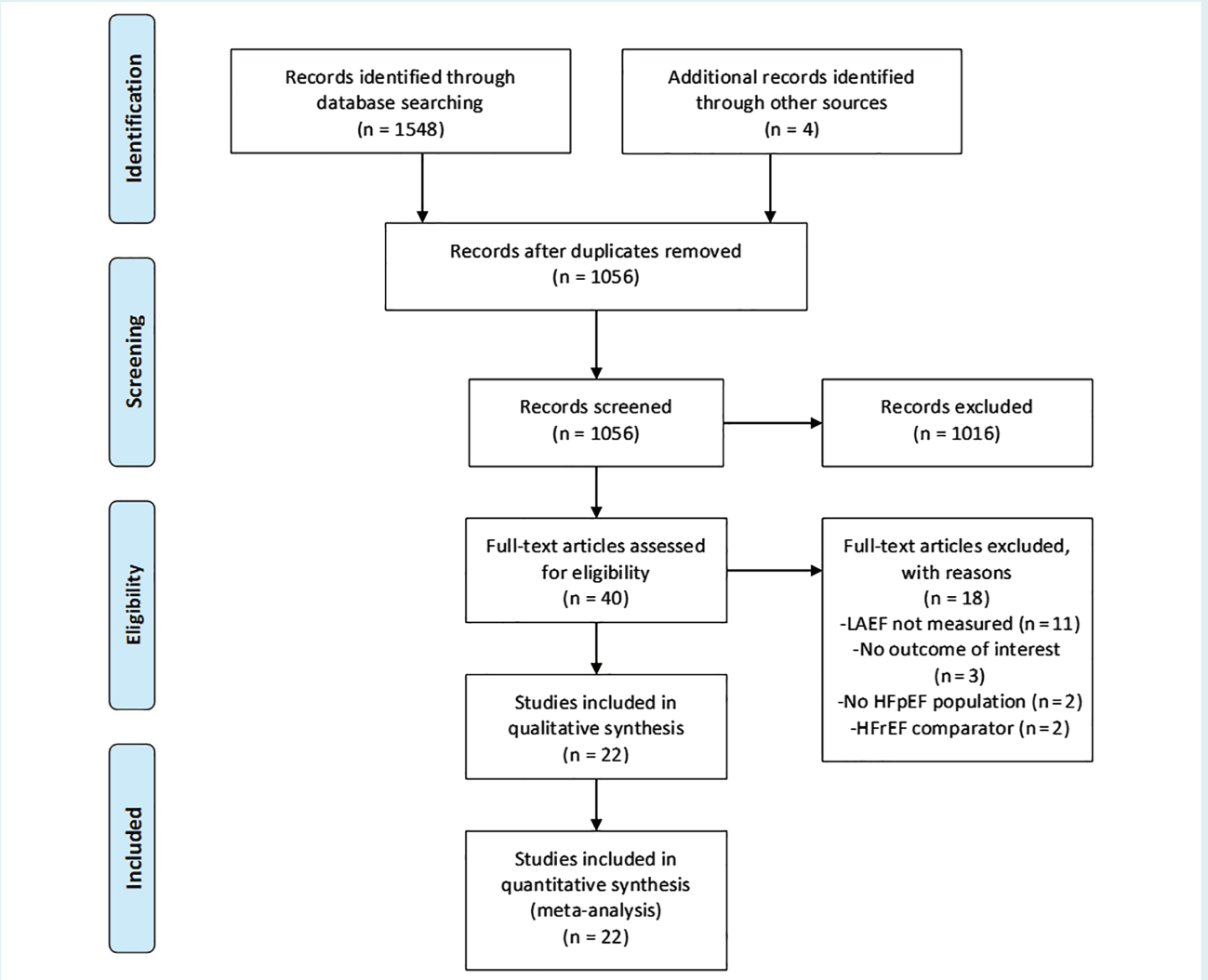

Figure 1 PRISMA flow chart outlining literature search process. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAEF, left atrial emptying fraction.

Meta-regression revealed that increasing age (coefficient 0.661; $P = 0.006$) and mean mitral E/E' (coefficient 2.060; $P = 0.004$) significantly contributed to the heterogeneity observed in LA conduit function. However, none of the other covariates had a significant effect on the results. Similarly, sensitivity analysis by excluding studies with unmatched controls [WMD = −8.35 (−12.08, −4.62); $P < 0.001$; $I^2 = 71\%$] or controls with co-morbidities [WMD = −7.20 (−11.24, −3.16); $P < 0.001$; $I^2 = 73\%$] did not significantly affect results. Sensitivity analysis adding HLVH to controls also did not significantly change the results [WMD = −5.59 (−8.43, −2.75); $P < 0.001$; $I^2 = 76\%$].

Left atrial active emptying fraction (left atrial pump)

Eleven studies provided data on LA pump function (870 HFpEF, 479 controls). LA pump fraction was significantly decreased in the HFpEF group [WMD = −11.07% (−14.81, −7.34); $P < 0.001$; $I^2 = 87\%$] compared with controls, albeit with high heterogeneity in the pooled result. None of the study covariates significantly contributed to explaining heterogeneity in pump function upon meta-regression analysis. Sensitivity analysis restricting the analysis to studies using only matched [WMD = −10.08 (−15.78, −4.38); $P < 0.001$; $I^2 = 89\%$] or healthy [WMD = −10.19 (−16.29, −4.09); $P < 0.001$; $I^2 = 88\%$] controls led to similar results. Additionally, sensitivity analysis by combining HLVH patients with controls did not significantly affect results [WMD = −10.29 (−13.82, −6.76); $P < 0.001$; $I^2 = 86\%$].

Left atrial total/sum/peak longitudinal strain (reservoir strain)

A total of 13 studies reported LA reservoir strain (781 HFpEF, 505 controls) (*Figure 4*). LA reservoir strain was significantly

Table 1 Study characteristics and patient demographics of included studies

Author, year	Type of study	HFpEF, *n*	Control, *n*	Controls matched by	Mean age, years (HFpEF/ Control)[a]	Men, % (HFpEF/ Control)	History of AF, % (HFpEF/ Control)	HTN, % (HFpEF/ Control)	DM, % (HFpEF/ Control)	BMI, kg/m^2 (HFpEF/ Control)[a]	LVEF, % (HFpEF/ Control)[a]	Obesity, % (HFpEF/ Control)	Measurement technique	LA strain measurement software/ platform	HFpEF diagnostic criteria; LVEF threshold	Follow-up, months
Reddy,[15] 2019	Prospective observational	238	125	Not matched	68 ± 10/58 ± 14	38/44	17/0	90/71	16/29	32.9 ± 7.1/ 28.4 ± 5.5	63 ± 6/63 ± 5	NR	Echocardiography	Syngo, Siemens Medical Solutions/NR	Clinical symptoms of HF (exertional dyspnoea, fatigue) and PCWP ≥15 mmHg at rest and/or ≥25 mmHg with exercise; LVEF ≥50%	NR
Telles,[16] 2019	Prospective observational	49	22	Not matched	69.4 ± 8.0/ 67.0 ± 9.9	28.6/22.7	26.5/4.5	67/73	14/23	30.2 ± 5.0/ 30.3 ± 5.4	62.6 ± 6.1/ 61.4 ± 6.8	51/50	Echocardiography	TomTec Image Arena 6.0	Dyspnoea and PCWP ≥15 mmHg at rest and/or ≥25 mmHg at maximal exertion; LVEF ≥50%	NR
Liu,[17] 2018	Prospective observational	55	33	Age and sex	61 ± 13/58 ± 11	45.5/36.4	NR	93/NR	43/NR	NR	59.6 ± 6.5/ 62.1 ± 4.4	9	Echocardiography	EchoPAC work station/Vivid 7 Dimension Ultrasound System	ASE criteria; LVEF >50%	NR
Issa,[18] 2017	Retrospective observational	40	40	Age and sex	72.1 ± 13.0/ 72.1 ± 12.7	50/50.0	0[b]	96/98	60/40	32.5 ± 11.3/ 27.7 ± 5.2	62.9 ± 3.56/ 64.3 ± 3.31	NR	Echocardiography	Echopac PC/Vivid 7 System	ACCF/AHA criteria; LVEF ≥50%	NR
Kanagala,[19] 2017	Prospective observational	140	48	Age and sex	73 ± 9/73 ± 5	49/50	31/NR	91/46	50/0	34 ± 7/25 ± 3	56 ± 5/58 ± 5	NR	CMR	N/A	Clinical or radiographic evidence of HF; LVEF >50%	20.3
von Roeder,[20] 2017	Prospective observational	22	12	Age	65 ± 9/58 ± 9	14/75	23/0	96/67	14/3	30.3 ± 4.1/ 26.8 ± 2.6	67 ± 8/63 ± 10	NR	Echocardiography and CMR	2-D Cardiac Performance Analysis Magnetic Resonance; TomTec Imaging Systems/NR	(1) signs and symptoms of HF (NYHA class ≥II) and (2) echocardiographic signs of DD according to ESC criteria; LVEF ≥50%	NR
Aung,[21] 2017	Prospective observational	38	45	Not matched	65.2 ± 5.7/ 64.2 ± 6.6	50/53.3	0[b]	60.5/55.6	13.2/13.3	28.1 ± 1.99/ 27.3 ± 1.97	62.9 ± 4.2/ 62.8 ± 4.1	NR	Echocardiography	EchoPAC/GE Vingmed Ultrasound AS	ESC criteria; LVEF >50%	NR
Sugimoto,[22] 2017	Prospective observational	20	32	Not matched	72.6 ± 10.3/ 56.5 ± 14.6	40/38	0[b]	74/66	42/6	28.3 ± 5.0/ 25.6 ± 4.3	56 ± 11/67 ± 6	NR	Echocardiography	QLAB, Philips/Philips IE33	ESC criteria and cardiologist-adjudicated HF diagnosis of >6 month duration; LVEF >50%	NR
Bytyci,[23] 2016	Prospective observational	74	29	Age and sex	61 ± 8/56 ± 9	28/44	9.9/NR	86.4/NR	54.6/NR	29.7 ± 4.0/ 27 ± 3.7	61.4 ± 8.8/ 61.0 ± 10	NR	Echocardiography	N/A	Clinical signs and symptoms of HF (NYHA class I–III), HFpEF patients with moderate DD (grade II) included; LVEF ≥45%	NR

Table 0 (Continued)

Author, year	Type of study	HFpEF, *n*	Control, *n*	Controls matched by	Mean age, years (HFpEF/Control)[a]	Men, % (HFpEF/Control)	History of AF, % (HFpEF/Control)	HTN, % (HFpEF/Control)	DM, % (HFpEF/Control)	BMI, kg/m^2 (HFpEF/Control)[a]	LVEF, % (HFpEF/Control)[a]	Obesity, % (HFpEF/Control)	Measurement technique	LA strain measurement software/platform	HFpEF diagnostic criteria; LVEF threshold	Follow-up, months
Freed,[24] 2016[c]	Prospective observational	308	0	N/A	65 ± 13.0	36	26	75	30	31.5 ± 8.6	61.0 ± 6.4	50	Echocardiography	2D Cardiac Performance Analysis, TomTec v4.5/Philips iE33 or 7500; Philips Medical Systems, Andover, MA; or Vivid 7; GE Healthcare	HF as defined by Framingham criteria; LVEF ≥50%	13.8
Hung,[25] 2016	Retrospective observational	40	27	Age, sex, BMI	61 ± 10.2/57.5 ± 7.7	47.5/59	NR	NR	NR	26.2 ± 2.6/24.6 ± 2	NR	NR	Echocardiography	EchoPAC workstation/GE VingMed Ultrasound	Discharge diagnosis record adjudicated by experienced cardiologists and should have documented pulmonary oedema on chest radiography; LVEF >50%	33.5
Sanchis,[26] 2016	Prospective observational	74	46	Not matched	76.6 ± 7.2/71.3 ± 11.4	26.7/23.9	39.2/0	86.5/63	23/11	NR	59.8 ± 5.2/60.8 ± 3.7	NR	Echocardiography	2D strain, EchoPAC/Vivid 7, GE Healthcare	ESC criteria; LVEF >50%	44.4
Santos,[27] 2016[c]	Randomized non-controlled trial	357	0	N/A	68.9 ± 9.7	43.3	21.6	93	41.6	32.9 ± 7.1	60.4 ± 7.7	59.8	Echocardiography	TomTec Imaging Systems/NR	Symptomatic HF, controlled systolic blood pressure, and a serum potassium level of <5 mmol/L; LVEF ≥45%	31.0
Melenovsky,[28] 2015	Retrospective observational	101	40	Not matched	71 ± 10/63 ± 7	42/47	42/0	93/57	47/0	NR	62 ± 5.9/62 ± 4.3	NR	Echocardiography	N/A	HF defined by cardiologist-adjudicated HF diagnosis (Framingham criteria) of >6 month duration and elevated pulmonary artery) wedge pressure (≥15 mmHg at rest or ≥25 mmHg at exercise); LVEF ≥50%	11.5
Wang,[29] 2015[c]	Prospective observational	80	0	N/A	66 ± 8	64	0[b]	47	27.3	NR	63	NR	Echocardiography	N/A	HFEA-ESC criteria; LVEF >50%	36.0
Sanchis,[30] 2015	Prospective observational	63	43	Not matched	76 ± 8/73 ± 8	18.6/23.3	39.7/9.3	85.7/65.1	23.8/18.6	29.62 ± 4.94/31.66 ± 4.36	60 ± 5/60 ± 4	NR	Echocardiography	2D strain, EchoPAC/Vivid 7, GE Healthcare	ESC criteria; LVEF >50%	NR

Table 0 (Continued)

Author, year	Type of study	HFpEF, *n*	Control, *n*	Controls matched by	Mean age, years (HFpEF/Control)[a]	Men, % (HFpEF/Control)	History of AF, % (HFpEF/Control)	HTN, % (HFpEF/Control)	DM, % (HFpEF/Control)	BMI, kg/m^2 (HFpEF/Control)[a]	LVEF, % (HFpEF/Control)[a]	Obesity, % (HFpEF/Control)	Measurement technique	LA strain measurement software/platform	HFpEF diagnostic criteria; LVEF threshold	Follow-up, months
Santos,[31] 2014	Randomized controlled trial	135	40	Age and sex	70 ± 9/68 ± 6	39/32	23/0	92/0	35/0	29.6 ± 5.7/25.2 ± 3.7	59 ± 7/60 ± 3	NR	Echocardiography	TomTec Imaging Systems/NR	Documented history of HF with NYHA class II–IV symptoms, and NT-proBNP levels >400 pg/mL at the baseline visit; LVEF ≥45%	NR
Kowallick,[32] 2014	Prospective observational	10	10	Not matched	69.7 (58–82)/40.6 (23–51)	70.0/50.0	0[b]	NR	NR	NR	63.6 ± 3.0/67.4 ± 6.4	NR	CMR	TomTec Imaging Systems, 2D CPA MR, Cardiac Performance Analysis/Philips Intera, Philips Achieva, Siemens Sonata or Siemens Symphony TIM	ESC criteria; LVEF >50%	NR
Obokata,[4] 2013	Prospective observational	40	46	Not matched	77 ± 13/75 ± 10	35.0/52.2	0[b]	88/100	35/22	21.4 ± 4.7/22.7 ± 3.6	60 ± 13/63 ± 7	NR	Echocardiography	EchoPAC/NR	ESC criteria and referred for pulmonary oedema due to HF; LVEF >50%	NR
Bilen,[33] 2012	Prospective observational	33	30	Age and sex	63.2 ± 11.9/60.3 ± 10.7	66.7/66.7	NR	72.7/50.0	27.3/20	NR	57.6 ± 5.5/61.5 ± 4.7	NR	Echocardiography	N/A	HFEA-ESC criteria; LVEF >50%	NR
Kurt,[34] 2009	Prospective observational	20	27	Not matched	58 ± 16/53 ± 20	70.0/37.0	0	90/NR	30/NR	NR	62 ± 6/64 ± 7	30	Echocardiography	EchoPac workstation/GE Vivid 7	DHF according to HFEA-ESC criteria; LVEF >50%	NR
Melenovsky,[8] 2007	Prospective observational	37	56	Age, sex and ethnicity	65 ± 10/65 ± 11	16/30	0[b]	100/34	61/3	37 ± 8/28 ± 5	72 ± 11/72 ± 10	NR	Echocardiography	N/A	HF defined by Framingham criteria and independently adjudicated by two cardiologists; LVEF >50%	NR

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; AF, atrial fibrillation; ASE, American Society of Echocardiography; BMI, body mass index; CMR, cardiac magnetic resonance; DD, diastolic dysfunction; DHF, diastolic heart failure; DM, diabetes mellitus; ESC, European Society of Cardiology; HF, heart failure; HFEA-ESC, Heart Failure and Echocardiography Associations of the European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; LA, left atrium; LVEF, left ventricular ejection fraction; NR, not reported; N/A, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure.

[a]Values presented as mean ± standard deviation or median (interquartile range).

[b]AF patients part of exclusion criteria.

[c]No control group.

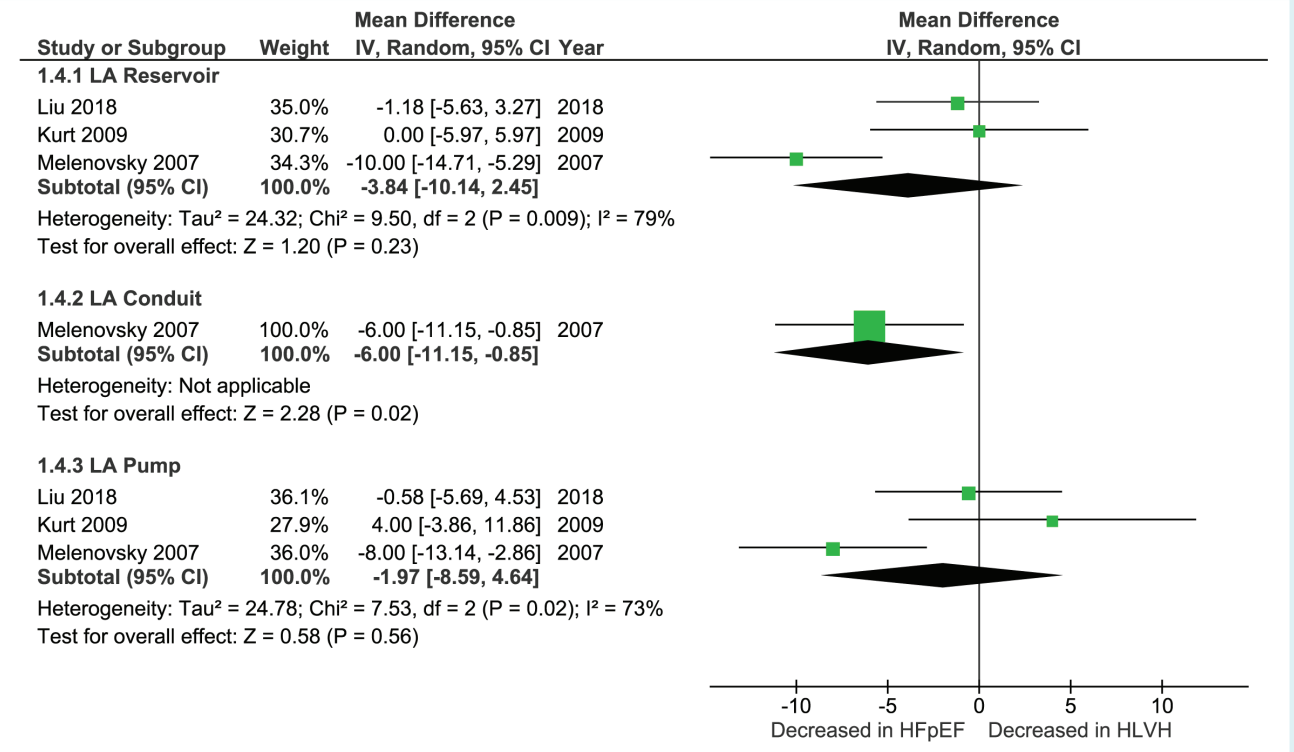

Figure 2 Forest plot for left atrial (LA) functional parameters of LA reservoir, conduit and pump emptying fractions in heart failure with preserved ejection fraction (HFpEF) patients compared with hypertensive left ventricular hypertrophy (HLVH) patients. CI, confidence interval; IV, inverse variance.

reduced in HFpEF patients [WMD = −13.38% (−16.07, −10.68); $P < 0.001$; $I^2 = 88\%$] compared with controls, though with high between-study heterogeneity.

Left atrial passive/longitudinal strain during early diastole (conduit strain)

Five studies reported data on LA conduit strain (344 HFpEF, 207 controls). HFpEF patients had significantly lower LA conduit strain [WMD = −4.09% (−6.77, −1.42); $P = 0.003$; $I^2 = 75\%$] than controls.

Left atrial active/longitudinal strain during late diastole (pump strain)

Left atrial pump strain values were provided by nine studies (497 HFpEF, 358 controls). LA pump strain was significantly lower in HFpEF patients [WMD = −3.19% (−4.23, −2.16); $P < 0.001$; $I^2 = 53\%$] compared with controls.

Subgroup analyses

For all three LA emptying fractions, subgroups analysis by mean age, mean baseline LVEF, HFpEF diagnosis LVEF cut-off, or by excluding studies which employed CMR, did not significantly change the results (online supplementary *Table S5*). However, the test for interaction between measurement technique ($P = 0.01$) subgroups was significant for LA conduit function. Subgroup analysis comparing patients with and without prior history of AF (but not in AF at the time of echocardiography for all LA parameters except reservoir strain) resulted in LA conduit function being no longer significantly reduced in HFpEF group without AF compared with controls [WMD = −4.54% (−11.40, 2.32); $P = 0.19$; $I^2 = 74\%$], although the test for interaction between these subgroups was non-significant ($P = 0.89$); results did not change significantly for the other two LA volumetric parameters with this subgroup. For LA strain parameters, subgroup analysis by strain measurement software also did not lead to significantly different results. Similarly, sensitivity analysis by stepwise exclusion of one study at a time did not lead to a significant change in results for any of the three volumetric or strain parameters except conduit strain function (online supplementary *Figures S3–S8*).

Prognosis and outcomes

Three studies provided data regarding the composite endpoint of all-cause mortality or HF hospitalization for LA pump fraction (577 HFpEF, 48 controls) with a mean follow-up time of 29 months (*Figure 5*). All AF patients had been excluded from this analysis. Increased LA pump fraction [HR per 1 SD increase in fraction = 0.88 (0.75, 1.03); $P = 0.11$; $I^2 = 40\%$] was not associated

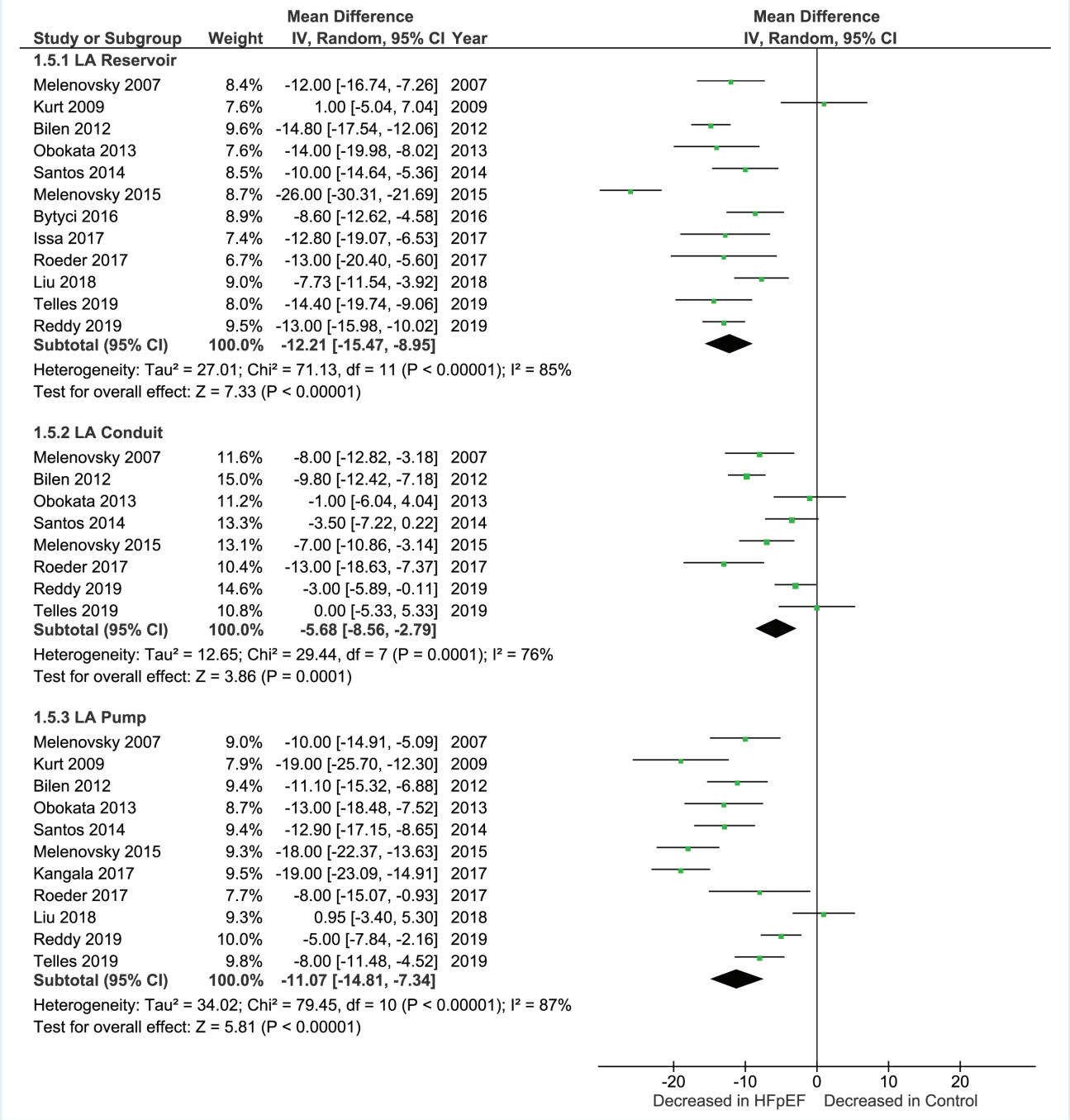

Figure 3 Forest plot for left atrial (LA) functional parameters of LA reservoir, conduit and pump emptying fractions in heart failure with preserved ejection fraction (HFpEF) patients compared with controls. CI, confidence interval; IV, inverse variance.

with decreased risk of this combined endpoint. For the other two fractions, only one study[27] contained data on the combined endpoint (357 HFpEF, zero controls), with a follow-up period of 31 months. Increased LA reservoir [HR per 1 SD increase in fraction = 0.91 (0.61, 1.21); $P = 0.52$] and conduit [HR per 1 SD increase in fraction = 0.97 (0.76, 1.24); $P = 0.84$] fractions were not significantly associated with decreased risk of composite all-cause mortality or HF hospitalization. Sensitivity analysis by stepwise exclusion of one study at a time did not change results significantly for LA pump function (online supplementary *Figure S9*). The other two parameters did not have enough studies for sensitivity analysis.

Two studies reported the composite endpoint of all-cause mortality or HF hospitalization in terms of HR per 1 SD change in LA parameter for LA reservoir strain (665 HFpEF, zero controls) and had a mean follow-up of 22.4 months. Decreased LA

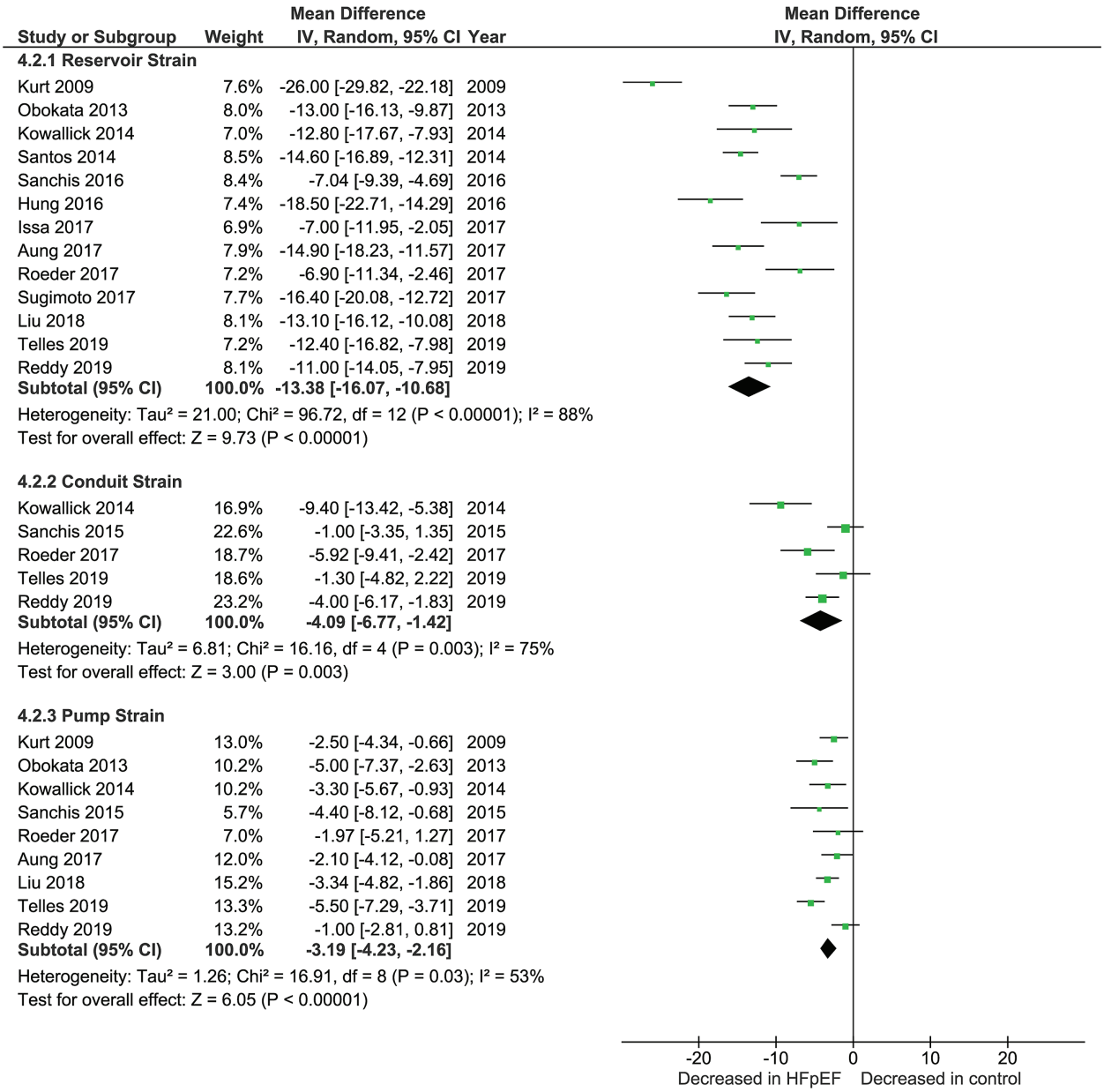

Figure 4 Forest plot for left atrial functional parameters of left atrial reservoir, conduit and pump strains in heart failure with preserved ejection fraction (HFpEF) patients compared with controls. CI, confidence interval; IV, inverse variance.

reservoir strain [HR per 1 SD decrease in strain = 1.24 (1.02, 1.50); $P = 0.03$; $I^2 = 0\%$] was significantly associated with the composite endpoint (online supplementary *Figure S10*). Only one study contributed data for the other two strain components (308 HFpEF, zero controls). Sensitivity analysis was not performed for the prognostic value of strain components due to low number of studies.

Discussion

This comprehensive systematic review and detailed meta-analysis of 22 studies and over 1900 symptomatic HFpEF patients shows that all LA volumetric and strain parameters are significantly reduced in HFpEF patients compared with healthy controls. In contrast, across three studies comparing 112 patients with HFpEF and 90 patients with HLVH patients, phases of LA volumetric function were not significantly different, suggesting that LA function may dynamically change in other pathological entities and with progression to symptomatic HFpEF.

Although LA dysfunction has been identified as one of the components of the multifactorial mechanism by which HFpEF occurs,[3] the exact process by which it contributes to the syndrome remains uncertain. Our analysis provides support of decreased

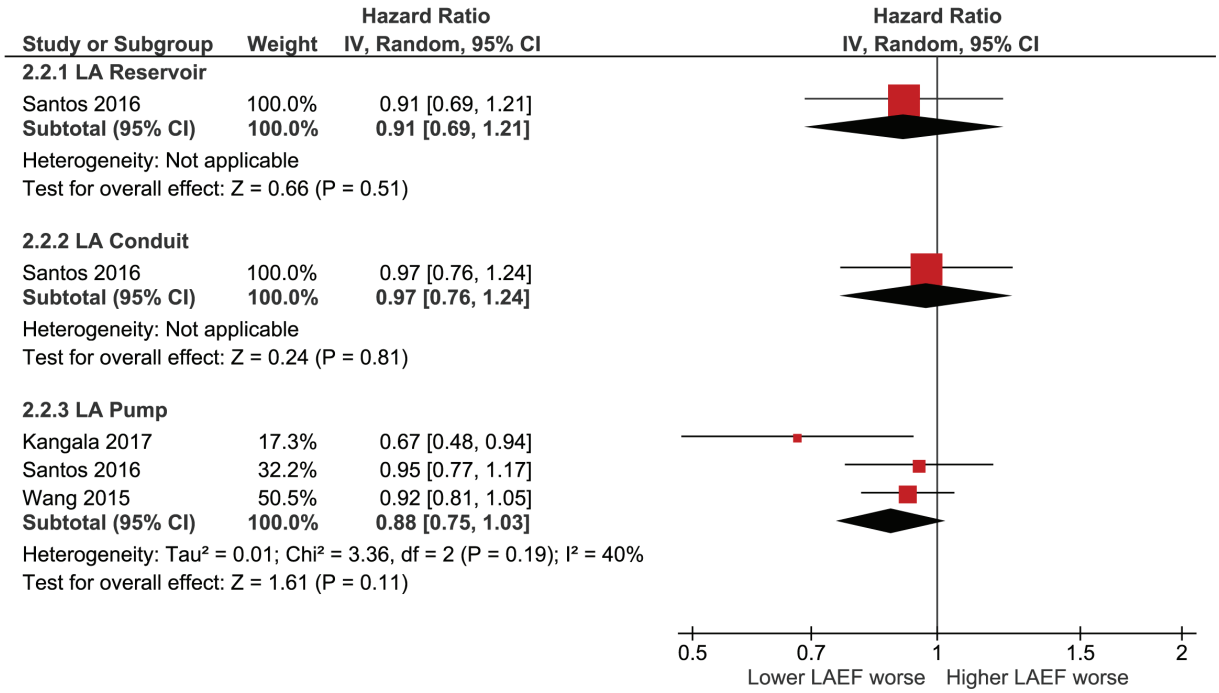

Figure 5 Forest plot for the association of decreased left atrial (LA) reservoir, conduit and pump emptying fractions with the combined endpoint of all-cause mortality and heart failure hospitalization. Adjusted variables: Santos 2016: age, sex, race, enrolment region (Americas vs. Russia/Georgia), randomization strata, history of atrial fibrillation, heart rate, New York Heart Association class, history of stroke, creatinine, haematocrit, left ventricular ejection fraction, LA volume index, and randomized treatment assignment; Kangala 2017: B-type natriuretic peptide, E/E', maximal indexed LA volume, and left ventricular mass; Wang 2015: E/e′ ratio during exercise, heart rate during exercise, global longitudinal strain during exercise. CI, confidence interval; IV, inverse variance; LAEF, left atrial emptying fraction.

LA reservoir function, signifying decreased atrial compliance and distensibility. As a consequence, the pressure gradient between the left atrium and left ventricle during early diastole is lowered and the volume of blood flowing into the left ventricle decreases considerably. This is best observed by the significantly reduced LA conduit function in our study. In addition to LA mechanical failure, LA endocrine failure [deficient atrial natriuretic peptide (ANP) and/or development of ANP resistance], LA regulatory failure (sympathetic overload, excessive vasopressin), and LA remodelling may also play a role in the complex pathophysiological mechanisms related to LA dysfunction of HFpEF.[35] Indeed, chronically elevated LV filling pressures have been shown to cause eccentric hypertrophy and remodelling of the left atrium,[36] which could in turn lead to decreased contractile ability and hence, impaired booster pump function in HFpEF. This understanding of the role of atrial dysfunction in HFpEF, along with formal investigations of sensitivity and specificity, could allow LA mechanical function to be used as a tool to ultimately reach a diagnosis. Indeed, recent studies have already demonstrated the predictive capacity of LA strain for distinguishing HFpEF from stages preceding HF, such as HLVH, to be superior than guideline-based parameters.[16] LA emptying function, however, did not significantly differ with regard to reservoir and pump fractions between HLVH and HFpEF patients in our study, suggesting that the impairment of volumetric LA function may precede progression to symptomatic HFpEF.

Since the left atrium is responsible for up to 30% of physiological stroke volume, substantial impairment of LA function may contribute to HF.[37] Maintenance of normal atrial function may have a protective effect against the development and progression of HFpEF. Although most HFpEF patients receive some type of therapy for symptomatic treatment (e.g. diuretics), there are no definitive therapies that improve outcomes in HFpEF, in contrast with HFrEF. Although some studies have found that HFrEF patients have larger LA volumes, HFpEF patients have higher LA peak pressures, higher LA stiffness, lower LA minimal pressures, and larger LA pulsatility at the same mean LA pressure.[28] Our findings, therefore, open a new avenue for targeted HFpEF therapy geared towards attenuating changes in LA mechanical parameters or directly unloading the left atrium, with the help of novel devices such as interatrial shunt devices.[38]

Left atrial functional indices have been corelated with adverse cardiovascular events and mortality in both the general population, as well as several clinical conditions including AF, cardiomyopathy, ischaemic heart disease, and valvular heart disease.[11] The data from this meta-analysis show the prognostic impact of LA reservoir strain on mortality and HF hospitalization. However, the other two strain components were not linked to increased mortality or morbidity, as reported previously.[24] Regardless of whether improvement in reservoir function could lead to better outcomes, LA reservoir strain holds prognostic significance that persists even

after accounting for common clinical risk factors, and therefore may be valuable in risk stratification in HFpEF. However, given the paucity of available studies, the incremental value of LA functional indices in discrimination of HFpEF diagnosis or prognosis above and beyond existing risk stratification models comprising clinical characteristics and/or other echocardiographic data has not yet been studied, and should be the focus of future research. Recent studies have also shown echocardiographic measures of LV diastolic function to be correlated to invasive haemodynamic measures and outcomes in HFpEF.[39,40] Similar studies assessing the correlation of echocardiographic LA functional parameters with invasively measured parameters could provide additional insights and should be undertaken.

Atrial fibrillation is a known cause of LA dysfunction and is a dominant co-morbidity in HFpEF.[1] The higher LA pressure pulsatility observed in HFpEF may indicate greater variation of wall stress, which may add to greater burden of AF observed in HFpEF.[28] The characteristic remodelling of the left atrium in HFpEF might also play a part in inducing AF by disrupting normal electrical conduction, while promoting re-entry and ectopic electrical activity.[41] It should be noted that though HFpEF, and HF in general, is a constantly evolving condition, patients are typically evaluated at one point during the course of this evolution. In HFpEF, LA remodelling is likely a manifestation of later stages of this disorder.[35] Nevertheless, recent studies have shown that HFpEF patients with AF exhibit diminished exercise capacity,[42] severe right ventricular dysfunction,[43] and an increased risk of mortality[2] when compared with patients in sinus rhythm. LA reservoir function has previously been proven to be a powerful independent predictor of first AF in older subjects in sinus rhythm.[44] While the predictive capacity of LA phasic functions for AF in HFpEF patients remains to be established, our subgroup analysis provides evidence of near normal LA conduit function in patients without prior history of AF, albeit without significant differences in reservoir or pump function.

Additionally, AF leaves the left atrium susceptible to dilatation, which in itself is an adaptive change in HFpEF due to heightened LV filling pressures.[45] Increased LA volumes have increasingly been associated with diastolic dysfunction,[6] as well as HF and death in previously asymptotic elderly subjects with preserved LVEF.[46] This interplay between AF, LA dilatation, and LA mechanical dysfunction could play a major role in defining, and therefore diagnosing, HFpEF in the future.

Limitations

Limitations of this systematic review should be noted. First, access to individual patient data was not available, so diagnostic accuracy tests of sensitivity and specificity for LA parameters could not be performed. Regression using aggregate data can be associated with ecological bias. Second, we observed high heterogeneity in our results, possibly due to large variation in HFpEF syndrome presentation and definition as well as varying baseline LVEF cut-offs used for HFpEF diagnosis across studies. Differences in methods of LA volume measurement and especially differences in vendor-specific analysis methods used for LA strain measurements could also have contributed to heterogeneity between studies. Third, only few studies reported prognostic outcomes, leading to reduced power. Additionally, the comparison of LA function in HFpEF to HLVH was based on only three studies enrolling about 200 patients, and hence may be underpowered to detect true differences between HFpEF and HLVH. Fourth, while LA size has been shown to affect LA function, we could not investigate LA functional parameters in HFpEF patients with normal LA sizes as none of the studies reported data specifically for patients with normal sized atria. Last, the effect of varying severity of HFpEF on LA function could not be explored.

Conclusion

Impaired LA function appears to have diagnostic and prognostic value in HFpEF, but whether indices of LA function truly refine discrimination for diagnosis or prognosis remains to be fully determined. Larger studies are needed to better evaluate associations between LA function and clinical outcomes and the role of LA function as a target for novel HFpEF therapies.

Supplementary Information

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

Table S1. Search strategy used in each database searched.

Table S2. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0).

Table S3. Quality assessment of observational studies.

Table S4. Results of multivariate meta-regression analysis on left atrial emptying fractions.

Table S5. Results of subgroups and sensitivity analyses on left atrial emptying fractions and left atrial strain.

Figure S1. Left atrial strain parameters measured by two-dimensional speckle-tracking echocardiography.

Figure S2. Funnel plot for left atrial reservoir function.

Figure S3. Sensitivity analysis of left atrial function between heart failure with preserved ejection fraction and controls by left atrial reservoir function using stepwise exclusion of one study at a time.

Figure S4. Sensitivity analysis of left atrial function between heart failure with preserved ejection fraction and controls by left atrial conduit function using stepwise exclusion of one study at a time.

Figure S5. Sensitivity analysis of left atrial function between heart failure with preserved ejection fraction and controls by left atrial booster pump function using stepwise exclusion of one study at a time.

Figure S6. Sensitivity analysis of left atrial function between heart failure with preserved ejection fraction and controls by left atrial reservoir strain using stepwise exclusion of one study at a time.

Figure S7. Sensitivity analysis of left atrial function between heart failure with preserved ejection fraction and controls by left atrial conduit strain using stepwise exclusion of one study at a time.

Figure S8. Sensitivity analysis of left atrial function between heart failure with preserved ejection fraction and controls by left atrial pump strain using stepwise exclusion of one study at a time.

Figure S9. Sensitivity analysis for prognosis of composite all-cause mortality and heart failure hospitalization by increased left atrial

pump emptying fraction using stepwise exclusion of one study at a time.

Figure S10. Forest plot for the association of decreased left atrial reservoir, conduit, and pump strain with the combined endpoint of all-cause mortality and heart failure hospitalization.

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