Cardiovascular Ultrasound

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Patients with chronic heart failure and predominant left atrial versus left ventricular myopathy

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Abstract

Background Left atrial (LA) and ventricular (LV) functional impairment often co-exist in patients with heart failure (HF). However, some patients with HF have a disproportionate LA or LV dysfunction. We aimed to characterize patients with predominant LA and LV myopathy in a cohort of patients with chronic HF across the spectrum of LV ejection fraction (LVEF).

Methods From a nationwide, prospective, multi-center, observational HF cohort, transthoracic echocardiographic examination was performed on each patient. LA reservoir strain and LV global longitudinal strain (LVGLS) were measured using dedicated software of the two-dimensional speckle tracking analysis to evaluate LA and LV function and to define the myopathy.

Results A total of 374 patients with chronic HF (mean age 58.9±11.5 years, 20% female, mean LVEF 39±17%) were included. By calculating the residuals from the linear regression between LA reservoir and LVGLS, we identified 47 patients with predominant LA myopathy, 271 patients with balanced LA/LV and 56 patients with predominant LV myopathy. Patients with predominant LA myopathy were older, had a higher prevalence of atrial fibrillation (AF), diabetes, higher plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP), Growth differential factor 15(GDF15), high sensitivity Troponin T (hs-TNT) as well as more dilated left and right atria, and worse right atrial function compared to other groups (all p-values < 0.05). Using multivariable logistic regression adjusted for LVEF and LA size, independent predictors of predominant LA myopathy were the presence of AF, diabetes, and higher GDF15, whereas absence of diabetes independently predicted predominant LV myopathy. Patients with predominant LA myopathy group had a lower probability of survival than the other groups (Log rank p-value = 0.01).

Conclusion While most patients with HF have balanced LA/LV myopathy, those with predominant LA myopathy are characterized by older age, more AF, more diabetes, higher circulating biomarkers of cardiac stress and injury, and worse outcomes.

Keywords Predominant LA myopathy, LV myopathy, Heart failure, LVEF

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Background

Heart failure (HF) is generally considered a left ventricular (LV) disease, typified by HF with reduced ejection fraction (HFrEF). But even in patients with HF with preserved EF (HFpEF), LV function, measured by LV global longitudinal strain (LVGLS), is impaired [1]. Atrial disease or myopathy might also play a significant pathophysiological role in HF, regardless of HF phenotype [2, 3]. Therefore, HF may be characterized not only by LV function, but also by left atrial (LA) function, as well as the relative function of both chambers. Yet, the concept of atrial myopathy is still underappreciated, especially in HFrEF [4].

Two-dimensional speckle tracking echocardiography (STE) enabling myocardial deformation assessment has emerged as a sensitive quantitative marker of LA and LV function [5, 6]. Importantly, both STE derived LA reservoir strain and LVGLS are strong and independent predictors of clinical outcome in patients with both HFpEF and HFrEF [2–7]. However, although LA and LV dysfunction are usually closely associated, some patients might have predominant LA dysfunction while others have predominant LV dysfunction. The clinical determinants of predominant LA or LV myopathy have not been fully elucidated.

Therefore, we studied the clinical and echocardiographic characteristics of patient with HF and predominant LA versus LV dysfunction across the spectrum of LVEF.

Methods

Study populations

Previously, details of the study design, criteria for the enrollment and selection of patients have been published [8, 9]. Briefly, the current study included a total of 469 patients with chronic HF from a nationwide, prospective, multi-center, observational HF study. Of these 469 patients, 95 patients were excluded due to ineligible DICOM format echocardiographic files for post-offline analysis or because LA reservoir or LVGLS to define the LA/LV myopathy phenotypes could not be obtained. Thus, a total number of 374 patients were included in the final analysis. All patients had either a history of hospitalization with a primary diagnosis of HF or outpatient treatment for decompensated HF within 6 months of enrollment. Patients with the primary cause of HF due to severe valve disease (i.e. aortic valve stenosis/regurgitation, mitral valve stenosis/regurgitation etc.), end-stage renal failure or receiving renal replacement therapy, primary diagnosis of acute coronary syndrome causing transient pulmonary edema, or specific subgroups of HF including constrictive pericarditis, complex adult congenital heart disease, hypertrophic cardiomyopathy, eosinophilic myocarditis, cardiac amyloid, and acute chemotherapy-induced cardiomyopathy were excluded. Each participant underwent comprehensive clinical assessment, blood test, and echocardiographic exams. N-terminal pro-B-type natriuretic peptide (NT-proBNP), Growth differential factor 15(GDF15), high sensitivity Troponin T (hs-TNT) and ST2 were measured from the blood sample given their contribution to the distinct pathophysiological mechanism to HF [8]. The study protocol was approved by the Institutional Review Boards in each hospital, and written Informed consent was acquired from all patients. All the participants were followed up for two years. Survival data was obtained through follow-up visits or telephone contact in the condition of missed visit. The primary endpoint of interest for this study was 2-year all-cause mortality. All study procedures were proceeded based on the guidelines of the Declaration of Helsinki.

Echocardiography

Each patient underwent comprehensive transthoracic echocardiography (TTE) according to the American Society of Echocardiography (ASE) guideline [5] by experienced sonographers using Vivid ultrasound systems (GE Healthcare, Chicago, IL). Subsequently, all DICOM files of echocardiographic images were stored and read offline using EchoPAC software (GE Vingmed Ultrasound, Horten, Norway). LV volume at end-diastole (LVEDV) and end-systole (LVESV), LVEF were obtained by the biplane Simpson method. LV mass was obtained using the Devereux formula. LA and right atrial (RA) volume were measured using the area-length method. Furthermore, LV mass, LA and RA volume were indexed for body surface area (BSA) to obtain LV mass index (LVMi), LA (LAVi) and RA volume index (RAVi). Tissue doppler imaging (TDI) was applied to record the mitral annular septal and lateral, tricuspid annular lateral (RV e') early diastolic velocity. Color Doppler was applied to obtain mitral valve inflow early (E) and late (A) diastolic velocity, and the ratio of mitral valve inflow E over A (E/A) velocity as well as peak velocity of tricuspid regurgitation (TRV). Pulmonary artery systolic pressure (PASP) was estimated based on the formula ($4^*[TRV]^2$ + RA pressure estimated by inferior vena cava diameter]). The ratio of mitral valve inflow E velocity over mean value of early diastolic mitral annular lateral and septal velocity (e') was derived (E/e') for LV filling pressure estimation. Furthermore, M-mode was applied in the apical four chamber view to obtain tricuspid annular plane systolic excursion (TAPSE).

STE was performed on each participant of echocardiographic image at a frame rate of 50–70 fps based on ASE/European association cardiovascular imaging (EACVI) guideline [5, 6]. Each LA reservoir, conduit, contractile strain was averaged from corresponding strain

components of apical four- and two chamber views, respectively. Similarly, LVGLS was averaged through the apical four, two and three chamber views. RA reservoir, conduit and contractile strain were obtained from the apical four chamber view. Right ventricle (RV) free wall strain was obtained by tracking the RV free wall in the apical four chamber view. LA compliance was calculated by the ratio of LA reservoir strain over E/e'. Absolute values of LVGLS and RVGLS were used for the final analyses in the current study.

Definition of LA/LV myopathy phenotypes

We defined three phenotypes of LA/LV myopathy by calculating residuals derived from the linear regression model between LA reservoir strain and LVGLS [10] and using the studentized residual (defined by the quotient derived from the division of a residual by an estimate of its standard deviation, Fig. 1). Predominant LA myopathy was defined as LA reservoir strain more than 1 studentized residual below the regression model. Predominant LV myopathy was defined as LA reservoir strain more than 1 studentized residual above the regression model. Balanced LA/LV myopathy was defined as LA reservoir GLS within 1 studentized residual from the regression model. A more detailed explanation of the method used to define LA/LV myopathy is provided in the supplementary material.

Statistical analysis

Baseline and echocardiographic characteristics of the patients were either presented as mean±SD for continuous variables or number (%) for categorical variables as appropriate. Differences of baseline and echocardiographic characteristics among different LA/LV myopathy phenotypes were tested using either linear regression for continuous variables, or logistic regression for categorical variables, both adjusted for age. Univariable linear regression was used for the relation between LA reservoir strain and LVGLS for the calculation of studentized residuals to define different phenotypes of LA/LV myopathy in the entire cohort. Univariable and multivariable logistic regression analysis were then performed to determine the clinical characteristics associated with predominant LA and LV myopathy, with odds ratios (OR) and corresponding 95% confidence intervals (CI) computed by logistic regression. All univariable predictors were entered into the multivariable model, with backward elimination used to determine the final model. Cumulative 2-year survival was calculated based on the Kaplan-Meier estimates and survival was compared among the 3 groups, with hazard ratios (HRs) and corresponding 95% CI computed by logistic regression. Stratified analysis based on HF subtypes were carried out for the logistic regression. Logistic regression was applied for the association between LA/LV myopathy phenotypes and combined HF hospitalization and 2-year mortality. All statistical analyses were performed using SPSS (version 26, SPSS Inc, Chicago, IL, USA) and RStudio version 1.2.5033. *P* value < 0.05 was considered statistically significant.

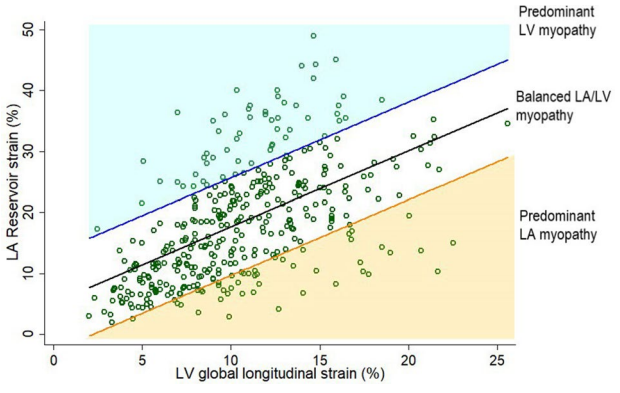

Fig. 1 The association between left ventricle (LV) global longitudinal strain and left atrial (LA) GLS at reservoir phase in heart failure. Predominant LA versus LV myopathy was defined as LA reservoir GLS more than 1 studentized residual below versus above the regression model

Results

From the 374 patients with HF included in the present study, we identified 47 (12.6%) patients with predominant LA myopathy, 271(72.4%) patients with balanced LA/LV myopathy and 56 (15%) patients with predominant LV myopathy.

Clinical characteristics among different phenotypes of LA/LV myopathy

Details of clinical characteristics and comparison between groups are depicted in Table 1.

Patients with predominant LA myopathy were older, had higher New York Heart Association (NYHA) functional class and more comorbidities (including AF, diabetes and hypertension) as compared to those with predominant LV myopathy (all $p<0.05$). Patients with predominant LA myopathy also had higher serum/plasma concentrations of creatinine, NT-proBNP, GDF15, hs-TNT and ST2 than those with predominant LV myopathy (all $p<0.05$). After adjusted for age, patients with predominant LA myopathy had more AF, diabetes, GDF15, and ST2 than those with predominant LV myopathy (all $p<0.05$). Similar trends in clinical characteristics were observed when comparing predominant LA versus balanced LA/LV myopathy groups (Table 1, all $p<0.05$). Patients with predominant LV myopathy were younger and had less AF, diabetes and coronary artery disease (CAD) as well as lower concentrations of NT-proBNP, GDF15, and ST2 compared to patients with balanced LA/LV myopathy (all $p<0.05$). However, these differences

Table 1 Clinical characteristics of patients with different phenotypes of LA Myopathy of HF

	Predominant LA myopathy (*n* = 47)	Balanced LA/LV myopathy (*n* = 271)	Predominant LV myopathy(*n* = 56)
Age, years	66.9 ±11.2*,†	58.2 ±11.1‡	51.7 ± 9.4
Male Sex (n, %)	38 (80.9%)	218 (80.4%)	42 (75.0%)
Heart rate (bpm)	74.7±11.4	74.9±13.6	74.4±12.6
Systolic blood pressure (mmHg)	129.5±19.7	127.2±21.1	126.1±23.2
Diastolic blood pressure (mmHg)	67.7±11.5†	72.7±13.7	73.4±13.6
NYHA class			
I/ II	38 (82.6%)	237 (89.1%)	54 (96.4%)
III/IV	8 (17.4%)	29 (10.9%)	2 (3.6%)
HFpEF (n, %)	19 (41.3%)	70 (26.0%)	16 (28.6%)
AF (n, %)	28 (63.6%) *,†	41 (15.7%)	4 (7.3%)
Diabetes (n, %)	34 (77.3%) *,†	139 (53.7%)	17 (30.9%)
Hypertension (n, %)	39 (86.7%) *	168 (64.6%)	34 (61.8%)
CAD (n, %)	26 (63.4%)	152 (63.3%)	24 (45.3%)
BMI, kg/m^2	27.9 ±5.5	27.5 ±5.9 ‡	26.5 ±6.1
Creatinine (μmol/ml)	114.0[95.0, 149.5]	97.0[84.0, 120.0]	96.5[77.5, 116.7]
NTproBNP	2227.5[1020.5, 6658.2]	924.3[321.6, 2332.0]	505.3[132.8, 963.2]
GDF15	3813.3[2523.5, 5898.0] *,†	1765.3[1104.9, 3248.9]	980.0[697.0, 1873.9]
hsTNT	31.0[19.7, 65.0] *	19.7[11.2, 34.5]	14.7[7.8, 34.1]
ST2	39.1[26.7, 48.4] †	27.8[22.7, 37.1]	24.7[19.9, 33.9]
Galectin3	10.3[8.2, 12.5]	8.7[6.9, 10.7]	9.0[7.1, 10.6]
History of Medication			
ACEi / ARB (n, %)	26 (63.4%)	152 (66.7%)	39 (76.5%)
βblocker (n, %)	29 (70.7%)	171(75.0%)	35 (68.6%)
MRA (n, %)	14 (34.1%)	137 (60.1%)	34 (66.7%)
Diuretics (n, %)	38 (92.7%)	206 (90.4%)	43 (84.3%)
Digoxin (n, %)	11 (26.8%) *	22 (9.6%)	3 (5.9%)

*Age–adjusted $p<0.05$ for comparison of Predominant LA myopathy vs. Balanced; †Age–adjusted $p<0.05$ for comparison of Predominant LA vs. LV myopathy; ‡Age–adjusted $p<0.05$ for comparison of Balanced vs. Predominant LV myopathy; NYHA, New York Heart Association; AF, atrial fibrillation; ACEi/ARB, angiotensin–converting enzyme/angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; MRA, mineralocorticoid receptor antagonist

between patients with predominant LV versus balance LA/LV myopathy were all attenuated after adjusted for age. The prevalence of HF subtypes (HFpEF/HFrEF) were not different among the three LA/LV myopathy groups, though.

Echocardiographic characteristics in patients with predominant LA or LV myopathy

Details of echocardiographic characteristics between the three groups are described in Table 2.

Patients with predominant LA myopathy had more enlarged LA size (64.7±25.3 versus 36.3±16.9 ml/m^2, $p<0.01$), higher LA pressure estimated by E/e' (17.8±8.8 versus 13.0±8.0, $p=0.01$), and, by definition, worse LA function, including LA reservoir (9.6±4.0 versus 33.1±6.4%, $p<0.01$), contractile (2.7±3.4 versus 17.4±5.0%, $p<0.01$) and conduit strain (6.9±4.4 versus 15.5±5.5%, $p<0.01$) as well as worse LA compliance (1.3±2.7 versus 3.1±1.5, $p<0.01$) as compared to those with predominant LV myopathy. Patients with predominant LA myopathy had smaller LV size (LVEDV, 107.3±46.5 versus 134.1±62.7ml, $p=0.03$) but similar LVGLS (12.7±4.3 versus 11.3±3.3%, $p=0.075$) and LVEF (45.5±13.2 versus 40.5±15.6%, $p=0.11$) as compared to those with predominant LV myopathy. Turning to the right side of the heart, patients with predominant LA myopathy had greater RA size (36.7±15.2 versus 20.0±8.4ml/m^2, $p<0.01$), worse RV free-wall strain (17.1±7.0 versus 20.9±6.1%, $p<0.01$) and RA function, including RA reservoir (13.6±10.4 versus 30.2±14.7%, $p<0.01$), contractile (6.0%) strain (6.0±9.0 versus 18.2±8.9%, $p<0.01$), and higher PASP (36.9 ±19.3 versus 20.0±11.8mmHg, $p<0.01$) than those with predominant LV myopathy. However, differences of RA size, LA pressure by E/e' and LA compliance in patients with predominant LA versus LV myopathy were attenuated after adjusted for age.

Patients with balanced LA/LV myopathy had the lowest LVGLS among the 3 groups, with LA, RA and RV echocardiographic characteristics intermediate between those with predominant LA myopathy and those with predominant LV myopathy.

Table 2 Echocardiographic characteristics of patients with different phenotypes of LA Myopathy of HF

	Predominant LA myopathy ($n=47$)	Balanced LA/LV myopathy ($n=271$)	Predominant LV myopathy($n=56$)
LVEDV (ml)	107.3±46.5	128.7±52.5	134.1±62.7
LVESV (ml)	63.9±36.0*	86.9±46.7	76.8±33.9
LVEF (%)	45.5 ±13.2*	37.2 ±16.2	40.5 ±15.6
LVGLS (%)	12.7 ±4.3*	10.0 ± 4.3‡	11.3 ± 3.3
LVMi (g/m^2)	114.7±53.6	124.5±38.1	122.2±47.8
LAVi (ml/m^2)	64.7 ± 25.3*,†	45.8 ± 22.3 ‡	36.3 ±16.9
LA reservoir GLS (%)	9.6 ±4.0 *,†	16.8 ±7.4‡	33.1 ± 6.4
LA contractile GLS (%)	2.7±3.4*,†	7.8±5.6‡	17.4±5.0
LA conduit GLS (%)	6.9±4.4*,†	9.1±5.2‡	15.5±5.5
MV e' lateral (cm/s)	7.5±3.7*,†	6.4±3.0	6.9±3.4
MV E/A ratio	3.0±2.0*,†	1.6±1.5	1.1±1.2
E/e'	17.8 ±8.8	15.3±8.0	13.0 ± 8.0
LA compliance	1.3 ±2.7	1.5 ±1.4 ‡	3.1 ±1.5
RAVi (ml/m^2)	36.7 ±15.2 *	26.0 ±12.2	20.0 ±8.4
RA reservoir GLS (%)	13.6 ±10.4 *,†	19.6 ±11.0‡	30.2 ±14.7
RA contractile GLS (%)	6.0±9.0*,†	11.0±6.9‡	18.2±8.9
RA conduit GLS (%)	6.6±4.8†	7.8±6.1‡	14.0±9.1
RVGLS (%)	17.1 ±7.0	17.9±7.0 ‡	20.9 ± 6.1
TAPSE (mm)	17.5±4.4	18.2±4.4	19.2±3.9
RV e'(cm/s)	10.0 ± 4.1*	8.1 ±3.2	8.1 ± 2.9
PASP (mmHg)	36.9 ±19.3*,†	25.0 ±11.8	20.0 ±10.8

*Age–adjusted $p<0.05$ for comparison of Predominant LA vs. Balanced LA/LV myopathy; †Age–adjusted $p<0.05$ for comparison of Predominant LA vs. LV myopathy; ‡Age–adjusted $p<0.05$ for comparison of Balanced LA/LV vs. Predominant LV myopathy; LVEDV, left ventricle end–diastolic volume; LVESV, left ventricle end–systolic volume; LVEF, left ventricle ejection fraction; LVGLS, left ventricle global longitudinal strain; LVMi, left ventricle mass index; LAVi, left atrial volume index; LA, left atrial; GLS, global longitudinal strain; RA, right atrial; RAVi, right atrial volume index; RV, right ventricle; RVGLS, right ventricle global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary artery systolic pressure

Clinical and echocardiographic determinants of predominant LA and LV myopathy

Details of significant univariable logistic regression for clinical determinants of predominant LA and LV myopathy were depicted in the Supplementary Tables 1, 2. After multivariable adjustments, most of the significant associations were attenuated. Using multivariable logistic regression and after adjustment for LVEF and LA volume index (LAVi), factors associated with predominant LA myopathy were presence of AF (OR 4.1 CI [1.68, 9.96], $p<0.01$) and diabetes (OR 4.01 CI [1.23,13.05], $p<0.05$), and higher plasma GDF15 concentrations (OR 2.19 CI [1.27, 5.46], $p<0.05$), whereas predominant LV myopathy was associated with absence of diabetes (OR 0.25 CI [0.12, 0.52], $p<0.01$). Given diabetes as a convergent determinant between predominant LA/LV myopathy, clinical and echocardiographic characteristics were further stratified based on the diabetes in the Supplementary Table 3.

Two-year mortality

Thirty patients died during the follow-up time period of 24 months. Kaplan-Meier survival curves showed a higher mortality in patients with predominant LA myopathy as compared to patients with predominant LV myopathy and balanced LA/LV myopathy (**Graphic Abstract**, Log rank $p=0.01$), with no significant difference in mortality between patients with predominant LV myopathy versus balanced LA/LV myopathy. Predominant LA myopathy was associated with an increased risk of age-adjusted 2-year all-cause mortality (HR 2.75, CI [1.03–7.37], $p=0.044$), whereas predominant LV myopathy (HR1.76, CI [0.56–5.59], $p=0.335$) was not (Supplementary Table 4). Stratified analysis showed that predominant LA myopathy was associated with an increased risk of 2-year all-cause mortality (HR 5.70, CI [2.11–15.4], $p<0.05$) in HFrEF, but not HFpEF (HR 5.70, CI [1.03–7.37], $p>0.05$). However, after adjusting for age, these differences did not remain statistically significant in HFrEF (Supplementary Table 5). Predominant LA or LV myopathy was not associated with combined HF hospitalization and 2-year mortality (Supplementary Table 6).

Discussion

The present study defined 3 heart failure phenotypes in an Asian cohort based on the predominance of either LA or LV myopathy, or a balanced phenotype, defined by LA reservoir strain and LVGLS. Patients with predominant LA myopathy were characterized by older age, more AF, more diabetes, higher circulating levels of NT-proBNP, GDF-15 and hsTnT, and poorer survival than those with either predominant LV or balanced LA/LV myopathy, although survival differences were rendered non-significant after adjustment for age.

There is a close coupling between the LA and LV during the cardiac cycle since the LA is directly exposed to changes in LV end-diastolic pressure (LVEDP) [8, 11]. Elevated LVEDP is the hallmark of HF, irrespective of LVEF [4]. Hence, functional derangements of the LA can be seen both in HFpEF as well as in HFrEF. The assessment of myocardial deformation (strain) imaging enabled us to identify those patients with either predominant LA dysfunction or LV dysfunction [2–6]. Previously, Patel et al. have shown that LA myopathy defined by reduced LA reservoir strain was associated with persistent increase of NTproBNP [12]. Furthermore, they demonstrated that disproportionate LA myopathy was associated with worse hemodynamics in patients with HFpEF from PROMISE-HFpEF study [10], which is in line with the findings of the current study. Furthermore, adding to the existing PROMISE-HFpEF research focusing on HFpEF solely, the present work fills in knowledge about LA myopathy across the spectrum of LVEF, especially in patients with HFrEF.

Whereas the notion of "LA myopathy" is underrecognized in the population with HFrEF, given atrial disease, more specifically LA disease, is still considered more HFpEF-related rather than pertaining to HF across the overall LVEF spectrum [4]. As such, the current study focused on more distinct characterizations of different types of LA/LV myopathy in patients with HF across the wide spectrums of LVEF, including predominant LV myopathy and provided additional outcome data as compared with those shown in the study by Patel et al. [12]. Nevertheless, some studies have shown that enlarged LA size was a significant predictor of mortality or HF hospitalizations in patients with HFrEF [13, 14]. Carluccio et al. showed that LA reservoir GLS was associated with adverse events in HFrEF independent of LAVi and LVGLS [2]. Previous studies showed that a few echocardiographic parameters including annular motion, LVGLS, LAVi, LA contractile strain, and LV filling pressure were the determinant of LA reservoir strain [15–18]. Cameli et al. showed that LA reservoir GLS was better correlated with pulmonary capillary wedge pressure than E/e' in patients with HFrEF [17]. A recent meta-analysis by our group demonstrated LAVi was associated with LA reservoir strain in HFpEF, but not in HFrEF [18]. As to which is the single most important determinant of LA reservoir strain in HF remained unestablished. Nonetheless, LA myopathy is not specific to HFpEF, but also to HFrEF with even worse global LA function despite less burden of AF [18]. In aggregate, the pathophysiological impacts of atrial disease should be recognized in patients with HF irrespective of LVEF, and the current study aimed to fill that gap. Indeed, we showed that patients with predominant LA myopathy present with a distinct clinical and echocardiographic profiles among patients with HF. According to the concept of a constant volume pump throughout the cardiac cycle, during LV systole, the descending mitral and tricuspid annuli stretch both atria so that atrial and ventricular volumes reciprocate, whereas total cardiac volume remains nearly constant. Therefore, the magnitude of LA expansion would be affected by the degree of LV longitudinal contraction and the two parameters are correlated. However, despite this correlation, LA relaxation phase may also be impaired by myocyte loss and atrial fibrosis, both of which likely present in patients with HF, potentially limiting atrial stretching (distension) independently of the degree LV longitudinal contraction. This finding might explain the predominant LA myopathy phenotype, as well as why LA reservoir strain may remain independently associated with the outcome, even after adjustment for GLS. Interestingly, right atrial myopathy is frequently observed in those patients with predominant LA myopathy of HF. The independent association of AF with predominant LA myopathy in the present study, which is also found in the prior study by Patel et al. [10] might help explain the common observation of bi-atrial myopathy in predominant LA myopathy.

The reciprocal relationship between AF and atrial myopathy is complex, involving structural remodeling along with electrophysiological remodeling [19–21]. Atrial fibrosis is responsible for the underlying substrate formation of atrial myopathy coupled with atrial electrical remodeling of alterations in ion channel function, calcium loading, excitation-contraction coupling as well as autonomic remodeling, which overall might contribute to the pathogenesis of AF [19–21]. This could explain the observed close association between the concurrent predominant LA myopathy and increased prevalence of AF in the present study.

Besides, the attenuated association between aging and predominant LA myopathy might also be explained by the close association of aging and increased prevalence of AF [19–22]. Furthermore, the intertwined link between age, HF, and AF might also explain the attenuated significance of the poor prognosis in predominant LA myopathy by age, which requires further elaboration in future studies. Although the exact mechanism of how diabetes modifies cardiac remodeling in HF, especially the left atrium in the context of AF warrants future investigation. However, the primary pathophysiological link connecting atrial myopathy, AF, and diabetes in HF is possibly inflammation [23]. With this in mind, it is interesting that GDF15, a biomarker expressed in systemic inflammation [24], was associated with the predominant LA myopathy phenotype.

Identification of a predominant LA myopathy phenotype in HF may carry clinical implications. Although speculative, therapeutic interventions targeting LA

myopathy may be explored [25–27]. In this regard, it is noteworthy that those with predominant LA myopathy also had the most RA and RV dysfunction, as well as highest PASP, which would imply a poorer response to interatrial shunt devices based on recent results of the REDUCE-LAP HF-II trial [28].

Limitations

The major limitation of current study is relatively small number of predominant LA and LV myopathy subgroup as compared to the balanced LA/LV myopathy phenotype. Secondly, conclusions regarding causality are not possible due to the cross-sectional design of the study. Selection bias resulting from the technical constraints inherent in imaging-based studies should be recognized. Moreover, information regarding functional mitral regurgitation and invasive hemodynamic parameters are not available.

Conclusions

Patients with HF and predominant LA myopathy are characterized by the presence of AF and diabetes, as well as larger LA volume and higher GDF-15 concentrations, worse NYHA functional status and survival. The recognition of these specific HF phenotypes that seem to be independent from left ventricular ejection fraction might lead to therapies specifically targeted to improve LA function in HF.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12947-024-00336-w.

Supplementary Material 1

Author contributions

X.J wrote and revised the main manuscript and prepared the Figures and tables; W.T.T. performed the statistical analysis and prepared the figure and tables; D.S, S.Y.L, S.L, D.S, F.J, L.H.L. A. M. R were in charge of patient recruitment and revised the paper; A.A.V, C.S.P.L, J.P.Vm supervised the manuscript, wrote and revised.

Funding

None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate

All patients included provided written informed consent, and this study was approved by the SingHealth Centralised Institutional Review Board (CIRB).

Competing interests

The authors declare no competing interests.

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Received: 11 October 2024 / Accepted: 17 December 2024
Published online: 03 February 2025

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