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ORIGINAL ARTICLE

Comparative analysis of phasic left atrial strain and left ventricular posterolateral strain pattern to discriminate Fabry cardiomyopathy from other forms of left ventricular hypertrophy

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Abstract

Background: "Classical" echocardiographic signs of Fabry cardiomyopathy (FC), such as left ventricular hypertrophy (LVH), posterolateral strain impairment (PLSI), and papillary muscle hypertrophy may be of limited diagnostic accuracy in clinical practice. Our aim was to evaluate the diagnostic value of left atrial (LA) strain impairment compared to "classical" echocardiographic findings to discriminate FC.

Methods: In standard echocardiographic assessments, we retrospectively analyzed the diagnostic value of the "classical" red flags of FC as well as LA strain in 20 FC patients and in 20 subjects with other causes of LVH. Receiver operating characteristic (ROC) curve analysis was performed to assess the respective diagnostic accuracy.

Results: FC was confirmed in 20 patients by genetic testing. In the LVH group, 12 patients were classified by biopsy to have hypertrophic cardiomyopathy, two had hypertensive heart disease, and six LVH combined with borderline myocarditis. Global and regional left ventricular (LV) strain was not significantly different between groups while LA strain was significantly impaired in FC (Left atrial reservoir strain (LASr) 19.1%±8.4 in FC and 25.6%±8.9 in LVH, $p = 0.009$; left atrial conduction strain (LAScd) -8.4%±4.9 in FC and -15.9%±8.4 in LVH, $p < 0.01$). LAScd, with an area under the curve (AUC) of .81 (95% confidence interval [CI] .66–.96) showed the highest diagnostic accuracy to discriminate FC. The PLSI pattern showed an AUC of .49, quantification of papillary muscle hypertrophy an AUC of .47.

Conclusion: Adding LA strain analysis to a comprehensive echocardiographic work-up of unclear LVH may be helpful to identify FC as a possible cause.

KEYWORDS
cardiomyopathy, Fabry Disease, left atrial deformation imaging, left atrial strain, left ventricular strain, speckle tracking echocardiography

1 | INTRODUCTION

Fabry Disease (FD) is a rare, X-linked lysosomal storage disease that leads to a deficient activity of the enzyme α-galactosidase and consequently progressive accumulation of sphingolipids in multiple organs, including the heart. This results in progressive concentric left ventricular (LV) hypertrophy (LVH),[1] making cardiovascular death the leading cause of mortality in patients with FD.[2,3] The prevalence of Fabry disease has been reported to be around 1% in hypertrophic cardiomyopathy population and 1:117.000 in general population based on clinical data,[4,5] although underdiagnosis is common and the true prevalence may be significantly higher.[6] Enzyme replacement therapy (ERT) and novel chaperone-based therapy is available for FD patients[7] and several treatments including modified enzymes, substrate reduction therapy, and gene therapy are in development. Studies have demonstrated a benefit when ERT is initiated early in the course of disease, but efficacy is uncertain when started after the development of advanced cardiomyopathy.[8] Early diagnosis of cardiac involvement as well as timely and effective treatment are therefore crucial to prevent irreversible cardiomyopathy. Guidelines currently suggest strict eligibility criteria of ERT, such as significant LVH, diastolic dysfunction, and increased indexed left atrial volume (LAVI).[9–11] In late stages of FC, reduced longitudinal systolic deformation, assessed by myocardial strain, could be predominately detected in the basal and mid posterolateral left ventricular (LV) segments combined with a progressive local myocardial thinning seen by magnetic resonance imaging (MRI).[12] This increase in myocyte mass, which subsequently causes LVH, is thought to be a combination of the intra-cellular accumulation of lipid and neurohormonal activation promoting hypertrophic activation.[1,13] Increase in myocyte mass is not only thought to affect ventricular walls but also the papillary muscles, causing a prominent papillary muscle often linked with FC. A prominent papillary muscle in FC becomes particularly obvious in the presence of a small left cavity due to hypertrophy.[14]

Beyond the known impairment of LVGLS in hypertrophic patients in many etiologies, including FC patients, compared to healthy controls,[15–17] impairment of phasic left atrial strain (LAS) compared to healthy controls was previously shown in FC[18,19] as well as in other storage diseases featuring increased myocardial wall thickness, such as cardiac amyloidosis (CA).[20] These findings suggest that FC may not only cause LVH and left ventricular fibrosis but may also impact on the thin-walled left atrium (LA) with consecutive impairment of LA mechanics. However, data investigating LA function and comparing its diagnostic value to parameters of regional LV function in FC, such as the posterolateral strain impairment (PLSI) pattern, are sparse.

In this study, we aimed to describe variations in phasic LA and regional LV strain in patients with FC compared to other causes of LVH and to assess their respective diagnostic accuracy in discriminating patients with FC.

2 | METHODS

2.1 | Study population

We retrospectively screened 51 patients with FC or LVH of other cause from our registry at the Department of cardiology at Charité–Universitätsmedizin Berlin. FC was confirmed by mutation analysis genetic testing and leukocyte α-galactosidase activity. Twenty patients had confirmed diagnosis of FC. Fabry patients were compared with a group of bi-optically confirmed LVH due to other causes ($n = 20$). LVH was defined as a septal or posterior wall thickness > 11 mm according to the European Society of Cardiology (ESC) guidelines.[21] All patients with LVH in the control group underwent endomyocardial biopsy to exclude infiltrative disease. All patients obtained a standardized transthoracic echocardiographic assessment between February 2013 and July 2020. Exclusion criteria were age < 18 years or insufficient imaging of the LA, such as foreshortening or bad acoustic window. Eleven patients had to be excluded due to insufficient imaging quality. Finally, we retrospectively analyzed clinical and echocardiographic data of 20 patients diagnosed with FC and of 20 patients in the LVH group. The collection of pseudonymized medical records and the conduction of the study were approved by the institutional ethics committee (registration number EA2/194/18).

2.2 | Echocardiography

A standardized transthoracic echocardiographic assessment was performed in 40 patients using a Vivid E9 (GE Vingmed, Horton, Norway) with an M5S 1.5–4.5 MHz transducer. LV dimensions, LV ejection fraction (LVEF), left ventricular global longitudinal strain (LVGLS), and LA volume index (LAVI) were analyzed in accordance with the recent recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).[21]

2.3 | Analysis of phasic LA and regional LV strain

Phasic LAS was retrospectively analyzed from a standard 2D apical four chamber view (offline analysis, EchoPAC PC, GE Vingmed, Horton, Norway), following the recent recommendations on standardization of left atrial deformation imaging.[22] LAS data was obtained as previously described[20]: In a QRS-triggered strain curve, with LAS set to zero at the beginning of QRS, global average LA reservoir, conduit, and contraction strain were defined as specific points: LA reservoir strain (LASr) was represented by the highest average LAS value, LA conduit strain (LAS during passive LV filling, LAScd) was calculated by average LAS value at the onset of the p-wave minus LASr. LA contraction strain (LAS during peak atrial contraction, LASct) was calculated by LAS value following maximum LA contraction minus LAS at the onset of the p-wave.

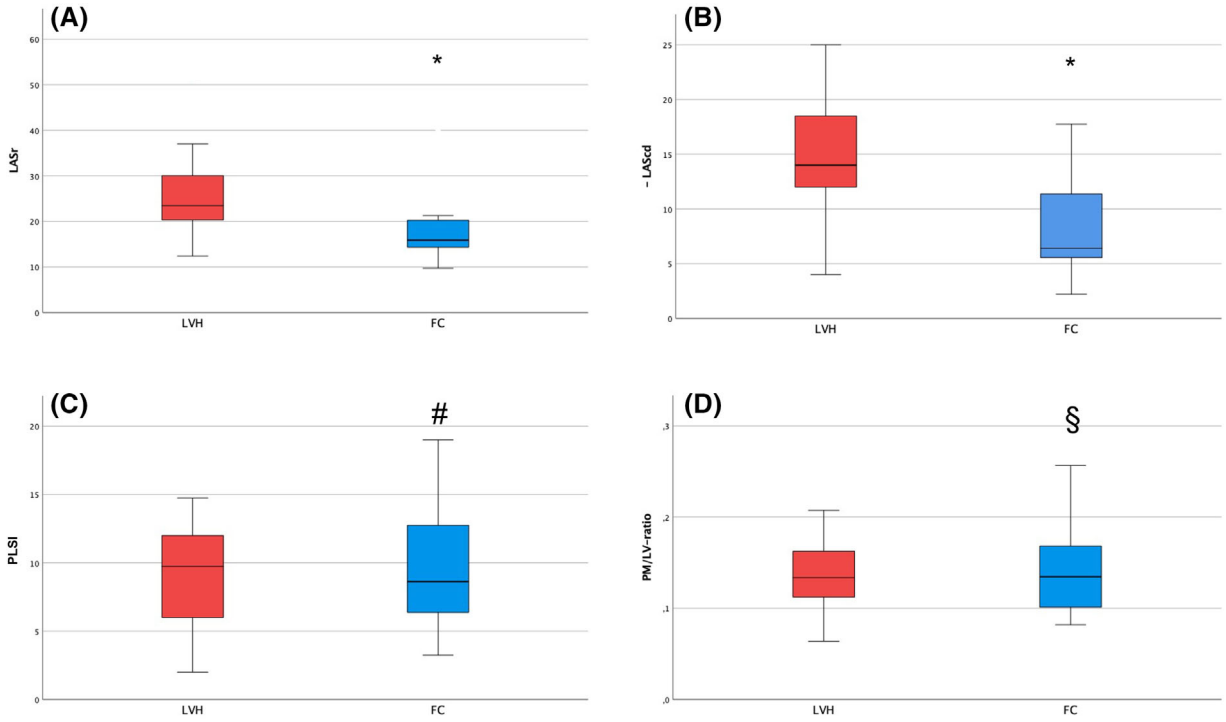

FIGURE 1 Differences of LA reservoir (A), conduit (B) strain, as well as of PLSI (C) and PM/LV-ratio (D) in patients with FC and LVH. *(*: $p < 0.05$; #: $p = 0.86$; §: $p = 0.93$; LASr: Left atrial strain rate; LAScd: Left atrial conduit strain; LA: left atrial; PLSI: posterolateral strain impairment; PM/LV-ratio: Ratio of papillary muscle area to left ventricular area; FC: Fabry cardiomyopathy; LVH: left ventricular hypertrophy)*

In patients with atrial fibrillation ($n = 5$), only LASr and LAScd were obtained, as proposed by the recent recommendations of the EACVI.[22] As proposed by the same recommendations, the arithmetic mean of three valid measurements was determined.

LVGLS was calculated offline as the average peak systolic longitudinal LV strain basing on LV strain analyses from three apical chamber views (17 segment LV model; EchoPAC software, GE, Vingmed, Horton, Norway). PLSI was obtained by the mean of deformation values in basal posterior and lateral segments as proposed by Kramer et al.[12]

Papillary muscle area to LV area ratio (PM/LV-ratio) was obtained at a transthoracic short axis view at end diastole and the areas were manually traced as proposed by Nieman et al.[14] Patients in whom only one papillary muscle was seen at this view were excluded; this applied to 16 patients.

Phasic LAS, as well as LVGLS and PM/LV-ratio measurements were all performed separately from the comprehensive echocardiographic baseline examination by an experienced observer blinded to the clinical data.

2.4 | Statistical analysis

Statistical analyses were performed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Macintosh Version 27.0. Armonk, NY, USA: IBM Corp). Data were expressed as mean ± standard deviation for continuous variables or in percentage for categorical variables. Significance of differences in clinical and echocardiographic data was calculated using the non-parametric Mann–Whitney U test for continuous variables, and the Fisher's exact test for categorical variables. Receiver operating characteristic curve (ROC) analyses were performed to compare the diagnostic value of phasic LAS and the PLSI.

To assess intra- and inter-observer variability, two experienced echocardiographers independently performed phasic LAS analyses of 10 randomly selected individuals. Intra- and inter-observer variability was then calculated using the intra-class correlation coefficient (ICC).

3 | RESULTS

3.1 | Clinical and echocardiographic characteristics

Of the 40 patients analyzed, 20 had FC proven by genetic testing. In the LVH group, twelve patients were classified by endomyocardial biopsy to have hypertrophic cardiomyopathy, two had hypertensive heart disease, and six expressed the pattern of LV hypertrophy combined with borderline myocarditis/myocardial inflammation by histopathological criteria. Possible confounders such as age, gender and Body mass index (BMI) showed homogenous distribution between the groups without significant differences. LV and LA geometry as well as LVEF were not different between groups. LV filling parameters such as E/A and E/e' showed slightly more advanced impairment in the LVH group. PM/LV-ratio showed no significant difference between groups (Figure 1). All clinical and echocardiographic characteristics can be inspected in Tables 1 and 2.

TABLE 1 Clinical characteristics of both groups

Clinical characteristics	FD with LVH ($n = 20$)	Control group with LVH ($n = 20$)	p-value
Age (years)	52.18 ± 11.4	53.5 ± 14.5	0.12
Female (%)	6 (30%)	9 (47,4%)	0.91
BMI (kg/m^2)	26.1 ± 3.1	27.4 ± 5.8	0.13
Heart rate (bpm)	61 ± 9	72 ± 13	0.11
Creatinine (mg/dl)	1.0 ± .2	1.5 ± 1.1	0.009
GFR (ml/min)	76.8 ± 13.7	59.3 ± 28,7	0.26
Diabetes (%)	24%	31,60%	0.9
Hypertension (%)	35%	52.6%	0.7
CAD (%)	10%	15,80%	0.7
aFib (%)	10%	15,80%	0.06
NTproBNP (ng/L)	1689 ± 3403	8280 ± 13708	0.001

Abbreviations: BMI, Body mass index; GFR, Glomerular filtration rate; CAD, Coronary artery disease; aFib, Atrial fibrillation; FD, Fabry disease; LVH, Left ventricular hypertrophy.

TABLE 2 Echocardiographic characteristics of both groups

Echocardiographic characteristics	FD with LVH ($n = 20$)	Control group with LVH ($n = 20$)	p-value
LVEF (%)	54.2 ± 9.8	52.5 ± 7.7	0.36
Septum (mm)	15.8 ± 3.4	17.9 ± 4.3	0.077
Posterior wall (mm)	14.9 ± 3.0	16.6 ± 5.1	0.21
LVEDD (mm)	46.8 ± 6.4	42.4 ± 8.3	0.18
VE/VA	1.2 ± .5	1.2 ± .7	0.92
E/e'	11.0 ± 4.9	13.2 ± 5.3	0.037
LAVI (ml/m^2)	37.1 ± 11.6	44 ± 16.8	0.405
PM/LV-ratio	.15 ± .06	.13 ± .04	0.931
Myocardial mechanics			
LVGLS (%)	−12.4 ± 3.7	−12.5 ± 3.8	0.972
Mean apical LV strain (%)	−16.3 ± 6.2	−17.4 ± 5.8	0.879
Mean mid LV strain (%)	−12.7 ± 4.2	−12.4 ± 3.4	0.727
Mean basal LV strain (%)	−10.9 ± 3.8	−9.0 ± 5.2	0.186
Mean basal posterolateral Strain (%)	−9.6 ± 4.2	−9.1 ± 3.8	0.863
LA reservoir strain (%)	19.1 ± 8.4	25.6 ± 8.9	0.009
LA conduit strain (%)	− 8.4 ± 4.9	−15.9 ± 8.4	0.02
LA contraction strain (%)	−10.7 ± 4.3	−13.0 ± 5.5	0.187

Abbreviations: LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic diameter; PE, Pericardial effusion; PM/LV-ratio, Ratio of papillary muscle area to left ventricular area; LVGLS, Left ventricular global longitudinal strain; LV, Left ventricular; LA, Left atrial; FD, Fabry disease; LVH, Left ventricular hypertrophy.

3.2 | Regional LV function and phasic LA strain

Global and regional LV function (LVGLS and PLSI) were not significantly different between groups (Table 2 and Figure 1). In contrast, LAS of reservoir and conduit, yet not contraction phase, was significantly reduced in FC compared to the LVH group (Table 2 and Figure 1). Figure 2 shows representative examples of regional LVGLS and phasic LAS analysis in a patient with FC and a patient of the LVH group.

3.3 | Diagnostic value of phasic LA strain in FC

A higher diagnostic accuracy could be shown for phasic LAS impairment in discriminating FC compared to parameters such as LVGLS and PLSI in ROC analyses (Table 3 and Figure 3). LAScd and LASr, with an area under the curve (AUC) of .81 (95% confidence interval [CI] .66–.96) for LAScd; and .76 (95% CI .58–.94) for LASr, respectively, showed the highest diagnostic accuracy, with a cut-off value of > -8.5% in LAScd

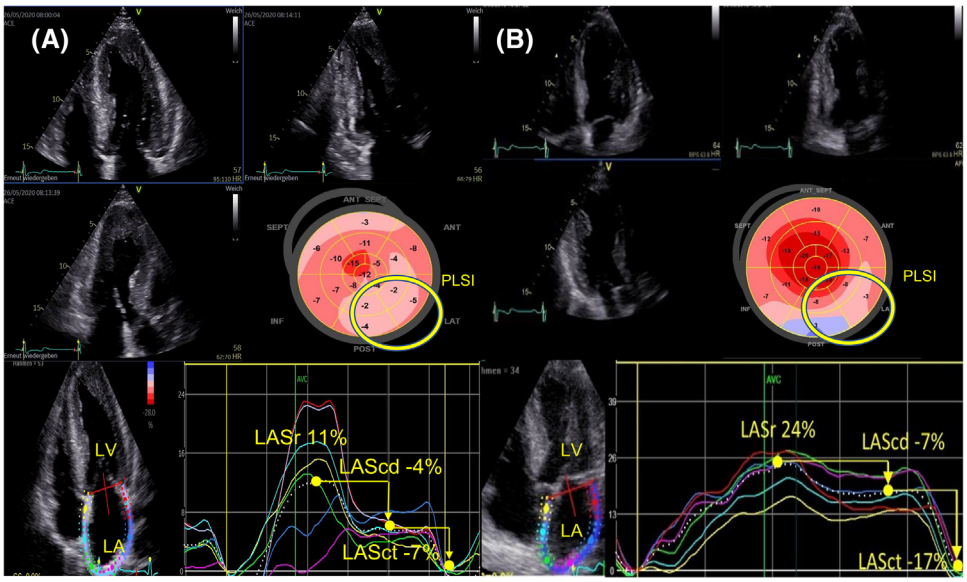

FIGURE 2 Representative examples of LVGLS in a 17 segment model and LAS analysis in two patients of the present cohort. (A) Patient with FC featuring the PLSI pattern (yellow circle) and impairment of LASr. (B) Patient with hypertrophic cardiomyopathy also demonstrating PLSI, while LASr is less impaired. *(LA: Left atrium; LV: Left ventricle; LASr: Left atrial strain rate; LAScd: Left atrial conduit strain; LASct: Left atrial contraction strain; PLSI: posterolateral strain impairment; FC: Fabry cardiomyopathy)*

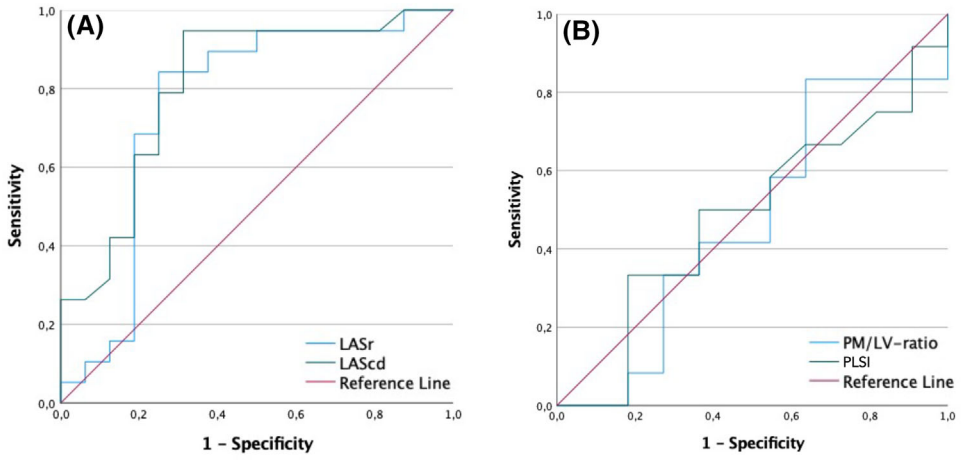

FIGURE 3 ROC analysis of LASr and LAScd (A) as well as of PLSI and PM/LV-ratio (B) to discriminate FC and LVH. (LASr: Left atrial strain rate; LAScd: Left atrial conduit strain; PLSI: posterolateral strain impairment; PM/LV-ratio: Ratio of papillary muscle area to left ventricular area; FC: Fabry cardiomyopathy; LVH: left ventricular hypertrophy)

(holding a Sensitivity of 94.7% and a Specificity of 68.7%, respectively) and < 16.8% in LASr (holding a Sensitivity of 89.5% and a Specificity of 62.5%, respectively). LASct showed an AUC of .65 (95% CI .46–.85). The PLSI, in contrast, showed an AUC of .49. LAVI also showed a poor diagnostic value to discriminate FC with an AUC of .58 (95% CI .35–.81; $p = 0.486$).

3.4 | Reproducibility of LA strain measurements

ICCs for intra-observer agreement of LASr, LAScd, and LASct were .94 (95% CI .86–.98), .91 (95% CI .77–.96), and .98 (95% CI .94–.99). Regarding inter-observer agreement, ICC of LASr, LAScd, and LASct were .94 (95% CI .86–.98), .88 (95% CI .69–.95), and .96 (95% CI .90–.98).

4 | DISCUSSION

In this study, we provide a comparative assessment of phasic LAS and LV mechanics, such as LVGLS and the PLSI pattern, in patients with FC and a group with LVH due to other causes. Results showed a significantly reduced phasic LAS in patients with FC compared to the LVH group. Beyond that, we describe a higher diagnostic value of LAS assessment, compared to that of LVGLS or PLSI, in discriminating patients with FC.

TABLE 3 Discriminative value of phasic LAS, LAVI, LVGLS, PLSI and PM/LV-ratio in Fabry cardiomyopathy; ROC analysis

	AUC	95% CI	*p*-value
LASr	.76	.58–.94	0.009
LAScd	.81	.66–.96	0.002
LASct	.65	.46–.85	0.138
PLSI	.49	.24–.73	0.902
PM/LV-ratio	.47	.22–.72	0.806
LAVI	.58	.345–.81	0.486
LVGLS	.54	.32–.76	0.71

Abbreviations: LASr, Left atrial strain rate; LAScd, Left atrial conduit strain; LASct, Left atrial contraction strain; PLSI, Posterolateral strain impairment; PM/LV-ratio, Ratio of papillary muscle area to left ventricular area; LAVI, Left atrial volume index; LVGLS, Left ventricular global longitudinal strain; AUC, Area under the curve; CI, Confidence interval.

Pichette et al.[18] published an extensive description of LAS alterations in FC and showed a significant impairment of phasic LAS in 50 patients with FC compared to 50 healthy controls. In contrast to these findings, we compared data of FC patients to those with LVH due to other causes; infiltrative disease was excluded by endomyocardial biopsy in all patients in the LVH group, a fact that is of growing importance due to the probable underreporting of infiltrative cardiomyopathy in patients with LVH during the past years.[23,24] Furthermore, we compared phasic LAS to more specific LV deformation parameters in FC since studies on this topic are yet scarce in cardiomyopathies, particularly in FC.

LVGLS impairment was earlier described in FC by echocardiography and MRI. Subsequently, Kramer et al.[12] described the phenomenon of PLSI in FC cardiomyopathy, concordant with posterolateral myocardial fibrosis seen in MRI; a finding which is since then thought to be the classic echocardiographic phenotype of FC.[10] Our study, however, showed a high diagnostic accuracy of phasic LAS impairment in discriminating FC, but a surprisingly low diagnostic accuracy for regional LVGLS and PM/LV-ratio, a fact that could be linked to power issues of our study on the one hand, and to the inclusion of patients featuring different staged FC forms with incomplete PLSI pattern combined with unspecific PLSI pattern in the LVH group on the other hand. These findings confirm the need for more reproducible research of such "classical" appearing phenotypes in comparison with other entities of LVH. Similarly, other LA parameters recommended for echocardiographic assessment in FC by the recent expert consensus recommendation,[10] such as LAVI, failed to discriminate FC as well, despite their proven correlation with phasic LAS.[25]

Another "classical" echocardiographic sign in FC, the PM/LV-ratio,[14] also failed to discriminate FC in our cohort.

In a widely underdiagnosed but treatable disease such as FD with proven benefit of treatment in early stages of disease, echocardiographic parameters yielding a higher diagnostic accuracy than the echocardiographic standard approach are urgently needed. Since Fabry disease is a systemic disease and sphingolipid accumulation is histologically proven to exceed the LV, it may be reasonable to integrate echocardiographic parameters exceeding LV geometry and function, such as impairment of LAS, into the diagnostic algorithm (Figure 4).

The mechanisms of the significant impairment of LAS in FC patients shown in our study are yet not thoroughly explained. The previously described pattern of PLSI is also matter of debate; previous data by Weidemann et al. and Kramer et al.[8,12] strongly suggest that impaired regional LV function may be caused by posterior and inferolateral LV wall thinning due to fibrosis following sphingolipid accumulation. Regarding the left atrium, impairment of LAS in many cardiomyopathies and thus also in FC could be partially explained by impaired diastolic LV function and consecutively elevated LV filling pressures, a hypothesis that was previously confirmed when assessing LA mechanics in general[26,27] and in FC.[18,19] LV filling pressures, LVGLS and LAVI were shown to be independent determinants of phasic LAS due to the anatomical connection of LV and LA.[27] However, phasic LAS showed significant reductions in the FC group while, in contrast, other parameters of LV systolic and diastolic function, that is, LVGLS, LAVI, E/e',

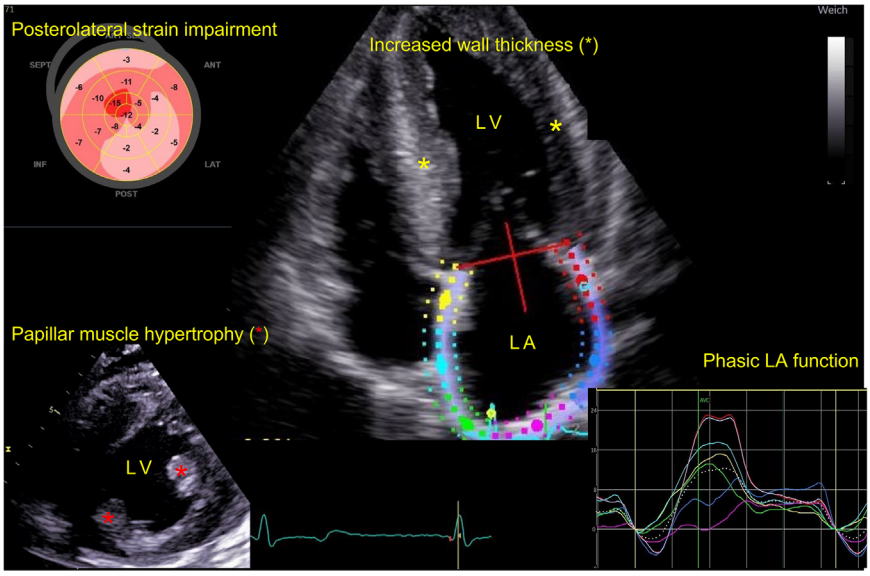

FIGURE 4 Classical' echocardiographic findings when examining patients with Fabry Cardiomyopathy. *(LA: Left atrium; LV: Left ventricle)*

TABLE 4 Reference ranges for atrial function parameters in different diseases

Population	Study	Parameter	Range with Median or IQR
Healthy population			
	EACVI NORRE study; Sugimoto et al., $n = 371$	LASr	42.5% (36.1 - 48.0)
		LAScd	−25.7% (20.4 - 31.8)
		LASct	−16.3% (12.9 - 19.5)
Hypertorphic cardiomyopathy			
	Debonnaire et al., $n = 242$	LASr	23.2% ± 8.0
	Paraskevaidis et al., $n = 43$	LASr	22.01% ± 8.18
		LAScd	−15.29% ± 6.84
		LASct	−8.05% ± 3.67
Cardiac amyloidosis			
	Nochioka et al., $n = 124$	LASr	18.8% ± 11.6
	Rausch et al., $n = 44$	LASr	11.0% ± 7.4 (ATTR)
		LAScd	9.8% ± 7.5 (AL)
		LASct	−5.9% ± 4.0 (ATTR)
			−6.9% ± 4.1 (AL)
			−5.7% ± 4.4 (ATTR)
			−6.6% ± 5.1 (AL)
	Brand et al., $n = 35$	LASr	9.7% ± 5.2
		LAScd	−6.5% ± 3.5
		LASct	−5.0% ± 4.1
Fabry Cardiomyopathy			
	Morris et al., $n = 50$	LASr	29.7% ± 9.9
	Pichette et al., $n = 50$	LASr	38.9% ± 14.9
		LAScd	−28.2% ± 10.1
		LASct	−12.6% ± 5.9
	Frumkin et al. (present study), $n = 20$	LASr	19.1% ± 8.4
		LAScd	− 8.4% ± 4.9
		LASct	−10.7% ± 4.3

Abbreviations: IQR, Inter-quartile range; LASr, Left atrial strain rate; LAScd, Left atrial conduit strain; LASct, Left atrial contraction strain; ATTR, Transthyretin amyloidosis; AL, Light chain amyloidosis.

were not different between groups. Furthermore, NTproBNP was significantly higher in the LVH group. Also, it is notable that LASr and LAScd show a higher impairment than LASct in the FC group, after previous studies about the determinants of impaired LAS showed a strong correlation between the LA reservoir (LASr) and pump (LASct) strain, both with LVGLS and LV filling pressures being the strongest determinants.[27] These findings suggest that intrinsic LA dysfunction, possibly through accumulation of sphingolipids, rather than reduced LVGLS and high filling pressures imposing on LA function, may be the leading cause of LAS impairment in this FC cohort.

As stated above in this cohort we see only a weak correlation of LV systolic and diastolic parameters with LA reservoir and conduit function, a finding that is well in line with the hypothesis of phasic LAS reductions due to intrinsic rather than secondary LA function. Next to our study, also data by Pichette et al suggest intrinsic LAS impairment in FC in a longitudinal speckle-tracking study[18] showing that after initiation of ERT therapy LA mechanics improved, whereas LVGLS remained stable. Similarly,[20] in another "thick heart pathology", that is, CA, concomitant LA myopathy was previously considered as well, questioning the isolated influence of systolic and diastolic LV function on impaired LA function.[20]

Boyd et al. previously suggested an additional atrial myopathy irrespective of LVH,[19] a suggestion we encourage with our results since accumulation of sphingolipids in the LA wall have been shown in autopsies.[28] Future prospective studies, however, assessing LA and LV dysfunction as well as tissue characterization in FC are needed to investigate whether sphingolipid accumulation into the thin-walled LA may be responsible for the observed significant mechanical LA impairment.

An overview of phasic LA strain reference values available in literature for different cardiomyopathies and a healthy cohort is depicted in Table 4.[18,20,29–34] As seen, impairment of LAS is a matter of

ongoing research in different cardiomyopathies accompanied with elevated filling pressures. It is noticeable that there are significant differences within singular cardiomyopathies, such as for cardiac amyloidosis and when comparing LAS values in our present study with the available values in FC in literature. In this particular case our cohort had significant higher values for LVH (15.8 mm ± 3.4 vs 11.7 mm ± 3,[34] respectively, another study had not significant elevated relative wall thickness in their FC cohort (.4 ± .12[18])) and LAVI (37.1 ml/m^2 ± 11.6 vs 25.9 ml/m^2 ± 10,[34] respectively) which could explain these differences and underscores that due to the scarce data collected so far in FC and in the face of differences in the selected cohorts it is difficult to make transferable cut-off values so far.

4.1 | Limitations

Our study was performed retrospectively, with all its inherent biases. Furthermore, echocardiographic images focusing of the LA are needed for LA strain analysis. However, this is neither part of standard transthoracic image acquisition beyond LA volume and area analysis nor feasible in all patients. Therefore, it contributes to the large number of exclusions. This could be avoided in future by a prospective study design with focus on LA image acquisition. The same applies for the poor feasibility of PM/LV-ratio of only 60% in our cohort.

The relatively low number of studied subjects is comparable to other Fabry disease studies[18,19] due to the rare nature of disease. Because the true prevalence of infiltrative disease is reported to be strongly underestimated,[23,24] we exclusively included patients in the control group in which no findings of infiltrative disease were detected by biopsy. Our results represent a first explorative description; they need to be confirmed in larger, prospective trials. Magnetic resonance imaging was not available in this cohort but should be used in future studies for further understanding of underlying pathophysiological mechanisms.

Our results suggest that adding phasic LA Strain analysis to the echocardiographic diagnostic work up of patients with unclear LV hypertrophy to discriminate FC. However, due to the small sample size of our cohort, and the limited sample size of our control group may impact on the discriminative value of our results. Because of the same reason it is beyond the aim of the study to calculate incremental values of different combinations of parameters. Therefore, our results should be interpreted as a first description that need to be confirmed in future prospective larger trials. Therefore, our conclusion was not the use of left atrial strain as highly accurate discriminative single parameter, but the use of multiple parameters as echocardiographic work up of unclear LVH. None of the parameters described in the present study has so far been validated in cohorts large enough to confirm a powerful discriminative value as single parameter.

5 | CONCLUSION

In this cohort of patients with FC and a control group with similar hypertrophic profile, global and regional left ventricular longitudinal strain showed low accuracy for discrimination. Adding LA strain analysis to a comprehensive echocardiographic work-up of unclear LVH may be helpful to identify FC as a possible cause.

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