Association and diagnostic utility of diastolic dysfunction and myocardial fibrosis in patients with Fabry disease

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ABSTRACT

Objective Current guidelines highlight important therapy implications of cardiac fibrosis in patients with Fabry disease (FD). However, association between morphological and functional impairments with cardiac fibrosis in hereditary cardiomyopathies remains elusive. We investigated the association between echocardiography-determined cardiac dysfunction and cardiac MRI (cMRI)-detected myocardial fibrosis (late gadolinium enhancement, LE) in patients with FD with preserved left ventricular ejection fraction (≥50%).

Methods 146 patients with FD (aged 39±14 years, 57 men) were analysed, all receiving echocardiography and cMRI within a 1 week interval. Longitudinal systolic strain (LS_sys), strain rate (LSr_sys) and diastolic strain rate (LSr_E) were assessed using speckle-tracking imaging. Receiver operating characteristic (ROC) analysis was performed to identify the diagnostic performance of various markers for LE.

Results LE was detected in 57 (39%) patients with FD. LV wall thickness, left atrial volume, septal E/e', diastolic dysfunction grade, global LS_sys and E/LSr_E, mid-lateral LS_sys and LSr_E, as well as N-terminal pro-brain natriuretic peptide were all associated with LE independent of age, sex, body mass index, New York Heart Association functional class and kidney function. In ROC curve analysis, septal E/e' performed best (area under the curve=0.86, 95% CI=0.79 to 0.92). Septal E/e'>14.8 was strongly associated with LE (specificity=97.8% and sensitivity=49.1%). In 9% of patients, localised LE was present even though no other cardiac or kidney abnormalities were detected.

Conclusions Echocardiography-derived diastolic dysfunction is closely linked to LE in FD. Septal E/e' ratio is the best echocardiographic marker suggestive of LE. Diastolic dysfunction is not a prerequisite for LE in FD, since LE can be detected in the absence of measurable cardiac functional impairments.

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INTRODUCTION

Fabry disease (FD) is an X-linked multisystem disorder characterised by alpha-galactosidase A enzyme deficiency leading to progressive accumulation of globotriaosylceramide in lysosome carrying cells.1 The occurrence of cardiomyopathy in FD is an ominous prognostic sign and today represents the leading cause of death in these patients.2-4 This cardiomyopathy is characterised by left ventricular (LV) hypertrophy, prominently hypertrophied papillary muscles, myocardial replacement fibrosis,5-8 right ventricular dysfunction9 and rhythm disorders.10

Fibrotic replacement of myocardial fibres is another hallmark of disease progression in FD. Replacement fibrosis can be detected by cardiac MRI (cMRI) through visualisation of late gadolinium enhancement (LE).11 Experimental and clinical studies showed that the extent of LE is associated with increased
myocardial stiffness and the degree of diastolic dysfunction in various cardiovascular diseases. Global systolic function often remains preserved in FD until its terminal stage; however, the development of more subtle alterations such as diastolic function frequently evades routine diagnostics. In particular, the association of diastolic dysfunction with myocardial replacement fibrosis in FD is not fully understood. Echocardiography plays a central role in the assessment of LV diastolic function. The diastolic strain rate measured by two-dimensional speckle-tracking imaging (STI) emerged as a feasible surrogate of LV filling pressure. For example, the ratio of early diastolic mitral inflow velocity to global early diastolic strain rate was particularly sensitive in detecting diastolic dysfunction in patients with acute myocardial infarction, superior to conventional diastolic indices.

Although clinical studies demonstrated that specific enzyme replacement therapy (ERT) successfully alleviated the symptom burden in FD, established Fabry cardiomyopathy was generally poorly responsive. Since treatment success critically depends on early therapy initiation, detection of subtle cardiac involvement might aid screening of patients with FD likely to benefit from early ERT.

We therefore investigated in patients with FD and preserved left ventricular ejection fraction (LVEF) the association between systolic/diastolic dysfunction as determined by echocardiography and myocardial fibrosis as detected by cMRI. We hypothesised that in these patients: (1) LE is linked not only to reduced longitudinal systolic strain (LS_sys) but also to diastolic dysfunction; (2) diastolic or systolic dysfunction is a prerequisite of replacement fibrosis indicated by LE; (3) STI-derived diastolic parameters might be superior to conventional diastolic indices for the staging of cardiac involvement.

METHODS

Study population

The database of the Würzburg Fabry Center for Interdisciplinary Treatment was searched for genetically proven patients with FD referred to the Center between 2006 and 2015. The structure of the center and the methodology of clinical phenotyping of patients with FD have been reported in detail elsewhere. All patients underwent both transthoracic echocardiography and cMRI within a 1 week interval. Out of 214 consecutive patients with FD, 165 had viable cMRI scans; 19 patients were excluded due to compromised LVEF (n=9) or diabetes; n=9 coronary artery disease), rendering 146 patients with echocardiographically measured LVEF ≥50% suitable for the current analysis (online supplementary eFigure 1). The study was conducted in accordance to the Declaration of Helsinki. Written informed consent was obtained from all patients or their guardians. cMRI was performed using a 1.5 Tesla full-body MRI scanner (Magnetom Symphony Quantum/Avanto; Siemens Medical Systems, Erlangen, Germany).

LE images were acquired 15 min after intravenous injection of 0.2 mmol/kg gadopentetate dimeglumine, using T1-weighted inversion recovery imaging sequences (field of view 240×320 mm², matrix size 165×256, slice thickness 8 mm, echo time 3.4 ms, repetition time 7.5 ms). LE was rated by two radiologists as described before who were kept blinded to all clinical data. Areas with signal intensity above the average of the normal myocardium plus 2 SDs were defined as LE positive.

Conventional echocardiography measurements

A standard echocardiographic examination was performed on a Vivid 7 or 9e echo machine (GE Vingmed, Horten, Norway). Measurements were performed offline by a single investigator (DL) according to recommended guidelines as previously described. Pulsed-wave Doppler and tissue Doppler were recorded and diastolic parameters including mitral inflow peak early (E-wave) and late (A-wave) velocities, E/A ratio, deceleration time (DT) of E velocity and isovolumetric relaxation time (IVRT) were measured. Diastolic filling patterns (ie, normal, impaired relaxation, pseudonormal and restrictive filling) were defined according to current guidelines. In brief, a normal filling pattern was defined as mitral inflow E/A ratio=0.8 to 2, DT=140 to 240 ms, IVRT=70 to 100 ms; impaired relaxation defined as the E/A ratio ≤0.8, DT ≥240 ms, IVRT>100 ms; pseudonormal filling defined as the E/A ratio=0.8 to 1.5, DT and IVRT<90 ms; restrictive pattern defined as the E/A ratio ≥2, DT <140 ms and IVRT≤70 ms. If necessary, a Valsalva manoeuvre was performed to distinguish between normal and pseudonormal filling. Tissue-Doppler derived mitral annular peak early velocity (e′) at the septal and lateral mitral annulus was acquired, and septal, lateral and averaged E/e′ ratios were calculated, respectively. Diastolic dysfunction was further graded by an integral approach based on the assessment of diastolic filling pattern, E/e′, and left atrial volume together with tricuspid regurgitation velocity.

Speckle-tracking imaging

STI analysis was performed using EchoPAC software (GE, Horten, Norway) as described previously. Longitudinal peak systolic strain rate (LSr_sys) and LS_sys, longitudinal early (LSr_E) and late (LSr_A) diastolic peak strain rates of each segment were measured. Global deformation values were acquired by averaging strain rate and strain values of all 16 segments. The ratio of E to global LSr_E (E/LSr_E) was calculated. Images and loops were analysed by an experienced echocardiographer (DL) with >6 years of experience in STI analysis, who was blinded to all patient information, including the final histopathological diagnosis.

Renal function

Glomerular filtration rate (GFR) was measured using technetium 99m-diethylene triamine penta-acetic acid aerosol clearance (Tc99m-DTPA) and estimated
according to the Modification of Diet in Renal Disease formula.

**Data analysis**

Continuous variables were expressed as mean±SD or median (quartiles). Categorical variables were presented as count (per cent). Differences on continuous data with normal distribution across groups were compared using unpaired Student’s t-test. Variables with skewed distribution were tested by Mann-Whitney U-test. Categorical data were compared using a similar approach employing χ² and Fisher’s exact test, as appropriate. Multivariable logistic regression was conducted to define the independent determinants for LE after adjustment for age, sex, body mass index, NYHA functional class and GFR. Receiver operating characteristic (ROC) analysis was performed to identify the diagnostic performance of markers for LE. For the determination of the cut-off values of septal E/e′, we used the cut-off value with maximum sensitivity (<7) to rule out the presence of LE, and the cut-off value with maximum specificity (>14.8) to predict the presence of LE. The respective cut-off values were determined by maximising sensitivity and specificity. Statistical significance was defined as p<0.05 (two-tailed test). Statistical analysis was performed using IBM SPSS, version 23 for Windows (IBM, New York, USA).

**RESULTS**

**Baseline clinical characteristics**

Clinical characteristics of patients with FD are summarised in table 1. LE was detected by cMRI in 57 out of 146 (39%) patients with FD with preserved LVEF. Patients were divided into two groups with and without LE. The mean age was 39±14 years, and 57 (39%) patients were men. Patients with LE were older than those without LE (48±11 vs 33±12 years, p<0.001). The percentage of patients with NYHA functional class III–IV was significantly higher in the LE group than in the no LE group (14.1% vs 2.2%, p<0.001). Prevalence of kidney dysfunction and levels of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) were significantly higher in the LE group than in the no LE group (both p<0.05).

**Cardiac MRI**

Mean LVEF as measured by cMRI was 64±8%, and similar between groups (table 2). LV mass index was higher in the LE group than in the no LE group (95±32 vs 71±19g/m², p<0.001). Table 2 shows an algorithm employing echocardiographic parameters suggestive of LE in patients with FD with preserved LVEF (area under the curve (AUC) 0.86; figure 1). LE was not detected in patients with septal E/e′<7 (sensitivity 100% and specificity 23.6%), while septal E/e′>14.8 was strongly associated with the presence of LE with a specificity of 97.8% and a sensitivity of 49.1% (table 5). LE was also detected in 29 out of 116 patients with septal E/e′≤14.8, indicating there is only a limited negative predictive value to exclude LE using a threshold of E/e′≤14.8.

Based on above findings, we established a framework for screening LE of patients with FD using echocardiography in the clinical setting. Figure 2 shows an algorithm employing echocardiographic parameters suggestive of LE in patients with FD with preserved LVEF.

In addition, we defined 45 patients with FD with neither kidney nor cardiac involvement, that is, normal renal function (Tr99m-DTPA clearance >90mL/min/1.73m²), normal NT-proBNP (<100pg/mL), normal systolic function (global longitudinal strain >18%), normal LV wall thickness (IVSd <11mm) and normal LA (LAVI<34mL/ m²). Local LE at basal inferior and lateral wall was still evidenced in four (8.9%) patients, indicating LE can be present even in the absence of measurable cardiac/renal dysfunction in patients with FD. On the other hand, LE was not detected in 41.9% of (18/43) patients with
a Tc99m-DTPA clearance of 60–90 mL/min/1.73 m² (mild renal dysfunction) and in 41.2% (7/17) of patients with a Tc99m-DTPA clearance of <60 mL/min/1.73 m² (moderate to severe renal dysfunction), reflecting vast pathological variance of FD.4 24

**DISCUSSION**

Our understanding of the pathogenesis of the Fabry cardiomyopathy significantly improved over the last two decades, but important features of Fabry cardiomyopathy, such as the inter-relationship between diastolic dysfunction, diagnostic criteria, and cardiovascular and neurological risk, remain elusive.4 24

### Table 1  Baseline clinical characteristics

|                      | Total n=146 | No LE n=89 | LE n=57 | P values |
|----------------------|-------------|------------|---------|----------|
| Age at baseline (years) | 39±14       | 33±12      | 48±11   | <0.001   |
| Male (n (%))         | 57 (39.0)   | 34 (38.2)  | 23 (40.4) | 0.795    |
| BMI (kg/m²)          | 24±5        | 23±4       | 25±5    | 0.006    |
| BSA (m²)             | 1.8±0.2     | 1.8±0.2    | 1.8±0.2 | 0.033    |
| Heart rate (beats/min) | 67±12      | 68±12      | 66±12   | 0.228    |
| Systolic blood pressure (mm Hg) | 123±19 | 120±19 | 127±19 | 0.040    |
| Diastolic blood pressure (mm Hg) | 80±12 | 79±11 | 83±12 | 0.035    |
| NYHA class (n (%))   |             |            |         | <0.001   |
| I                    | 112 (76.7)  | 79 (88.8)  | 33 (57.9) |          |
| II                   | 24 (16.4)   | 8 (9.0)    | 16 (28.1) |          |
| III                  | 9 (6.2)     | 2 (2.2)    | 7 (12.3)  |          |
| IV                   | 1 (0.7)     | 0          | 1 (1.8)   |          |
| Lyso-Gb3 (ng/mL)     | 9.5 (4.1–24.1) | 8.9 (2.8–63.0) | 10.6 (6.9–19.0) | 0.782   |
| Reduced enzyme activity (n (%)) | 123 (84.2) | 76 (85.4) | 47 (82.5) | 0.635    |
| Enzyme replacement therapy | 79 (54.1) | 42 (53.2) | 37 (46.8) | 0.036    |
| Kidney function      |             |            |         |          |
| GFR (DTPA) (mL/min)  | 105±32      | 112±28     | 93±35   | 0.001    |
| Creatinine (mg/dL)   | 0.8 (0.7–0.9) | 0.8 (0.7–0.9) | 0.9 (0.7–1.0) | 0.002    |
| Cystatin C (mg/L)    | 0.78 (0.70–0.90) | 0.76 (0.64–0.84) | 0.83 (0.73–1.08) | 0.001    |
| Proteinuria (n (%))  | 50 (35.0)   | 23 (25.8)  | 27 (50.0) | 0.003    |
| CKD stage III–V (n (%)) | 17 (11.6) | 9 (10.1) | 8 (14.0) | 0.471    |
| Dialysis (n (%))     | 7 (4.8)     | 2 (2.2)    | 5 (8.8)  | 0.110    |
| Kidney transplantation (n (%)) | 3 (2.1) | 0 | 3 (5.3) | 0.058    |
| NT-proBNP (pg/mL)    | 91 (41–261) | 69 (30–132) | 267 (81–773) | <0.001   |
| Cardiovascular history (n (%)) | 40 (27.4) | 18 (20.2) | 22 (38.6) | 0.015    |
| ICD/PM               | 1 (0.7)     | 0          | 1 (1.8)  | 0.390    |
| Neurological manifestions (n (%)) | 13 (8.9) | 4 (4.5) | 9 (15.8) | 0.034    |
| Depression            | 27 (18.5)   | 15 (16.9)  | 12 (21.1) | 0.524    |
| Tinnitus             | 53 (36.3)   | 28 (31.5)  | 25 (43.9) | 0.129    |
| Hearing loss          | 28 (19.2)   | 15 (16.9)  | 13 (22.8) | 0.373    |
| Dysarthria            | 4 (2.7)     | 0          | 4 (7.0)  | 0.011    |
| Heat intolerance      | 72 (49.3)   | 40 (44.9)  | 32 (56.1) | 0.235    |

Continuous variables are presented as mean±SD or median (quartiles), and categorical variables are presented with counts and percentages. P<0.05 vs no LE group.

BMI, body mass index; BSA, body surface area; CKD, chronic kidney disease; GFR (DTPA): glomerular filtration rate from 99mTc-diethylene triamine penta-acetic acid renography; ICD, implantable cardioverter defibrillator; LE, late gadolinium enhancement; Lyso-Gb3: plasma globotriaosylsphingosine; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; TIA, transient ischaemic attack.
systolic dysfunction, hypertrophy and myocardial fibrosis remain elusive. To the best of our knowledge, this is the first report focusing on the association of both classical and modern diastolic/systolic indices with the presence of myocardial replacement fibrosis in patients with FD with preserved LVEF. The major findings of the present study in patients with FD with preserved LVEF are (1) LE is significantly associated with age, kidney function, NT-proBNP, LV hypertrophy, and systolic and diastolic dysfunction; (2) septal E/e′ ratio appears to be the best echocardiographic marker associated with LE; (3) septal E/e′>14.8 is strongly associated with the presence of LE and (4) LE can sometimes be detected in FD in the absence of additional measurable cardiac/renal dysfunction.

**LE in patients with FD with preserved LVEF**

The appearance of myocardial replacement fibrosis is an acknowledged key feature in the cardiac pathophysiology of FD. It has been postulated that tissue ischaemia secondary to endothelial accumulation of glycosphingolipids in the microvasculature might accelerate the development of myocardial fibrosis in FD, with the inferolateral wall representing the predominantly affected segment. Previous cMRI studies from our group found that LE was present in 33% of female and 48% of male patients with FD. In line with previous findings from others as well as from our own group, we here confirmed that LE mostly presented at basal and mid-segments of the inferolateral wall, and mid-lateral LS_sys was often significantly reduced despite preserved global LS_sys (figure 1). However, a recent biopsy study revealed that interstitial myocardial fibrosis was already detectable at very early stages of the Fabry cardiomyopathy. Accordingly, the current study confirmed that LE can be detected at least in some patients with FD in the absence of measurable cardiac and renal dysfunction, suggesting that LE may appear at very early stages of the disease and is neither necessarily related to prior larger-scale morphological nor functional impairments. Pathophysiological explanation might be provided in a current study using cMRI T2 mapping, showing that (chronic) inflammation might contribute to the development of LE in FD. In line with these findings, we could just recently show that LE is not necessarily progressive, but might even regress slightly under appropriate therapy. These observations might not be specific or limited to FD, since similar phenomena were evidenced recently also in patients with aortic stenosis undergoing aortic valve replacement.

**Association of systolic and diastolic dysfunction with LE**

Progressive LV hypertrophy, diastolic dysfunction and preserved systolic function have been described as the major echocardiographic features of Fabry cardiomyopathy. Pieroni et al demonstrated that diastolic dysfunction can already exist prior to the development of LV hypertrophy or systolic dysfunction in patients with Fabry cardiomyopathy, suggesting that diastolic dysfunction might be an early sign of cardiac involvement in patients with FD. In line with these findings, we found that diastolic dysfunction was already present in 19% (17/88) of patients with FD with normal LS_sys (>18%) and normal LVEF in the current patient cohort.

Previous studies also indicated that the tissue Doppler derived diastolic index (ie, e′) could provide satisfactory preclinical evidence for diastolic dysfunction in patients with Fabry cardiomyopathy. Shanks et al further showed that STI-derived longitudinal systolic strain and diastolic isovolumetric strain rate were superior to other classic echocardiographic parameters for the risk stratification and disease staging in patients with FD. Our results indicate that despite a preserved systolic function (LVEF: mean value 66%, range 52% to 80%), a significant proportion of patients with FD (35%) presented with at least mild diastolic dysfunction, as shown by abnormal conventional and STI-derived diastolic deformation indices (LSr_E and E/LSr_E). Moreover, increased LV wall thickness, left atrium volume, septal E/e′, E/LSr_E and reduced septal and lateral e′ were evidenced in the LE group compared with the no LE group, reflecting that diastolic dysfunction is closely linked to LE. Our results further revealed that serum and echocardiographic biomarkers reflecting diastolic function (including the myocardial stress biomarker NT-proBNP, LV wall thickness, LA volume, e′ and E/e′) remained predictive of LE, supporting the close relationship between diastolic dysfunction and replacement myocardial fibrosis in FD. However, the STI-derived diastolic index was not superior to the conventional echocardiographic diastolic index. Indeed, our results showed that e′ and E/e′ were the best echocardiographic markers suggestive of LE in FD, superior to E wave, E/A, and DT, and STI-derived global LSr_E and E/LSr_E.

A recent study demonstrated that E/e′ was associated with myocardial fibrosis detected by cMRI in children with hypertrophic cardiomyopathy. In line with these findings, our data showed a close correlation between E/e′ and LE in patients with FD and preserved LVEF. Septal

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**Table 2** Cardiac MRI characteristics

|                | Total n=146 | No LE n=89 | LE n=57 | P values |
|----------------|-------------|------------|---------|----------|
| LVEF (%)       | 64±8        | 62±7       | 66±7    | 0.004    |
| LVMI (g/m²)    | 80±28       | 71±19      | 95±32   | <0.001   |
| EDVI (mL/m²)   | 76±18       | 77±15      | 74±21   | 0.281    |
| ESVI (mL/m²)   | 28±10       | 29±9       | 25±11   | 0.037    |
| SVI (mL/m²)    | 48±12       | 48±10      | 47±15   | 0.779    |
| CI (L/min/m²)  | 3.2±0.8     | 3.3±0.8    | 3.1±0.9 | 0.073    |

Continuous variables are presented as mean±SD. P<0.05 vs no LE group. CI, cardiac index; EDVI, end-diastolic volume indexed to body surface area; ESVI, end-systolic volume indexed to body surface area; LE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass indexed to body surface area; SVI, stroke volume indexed to body surface area.
### Table 3  Echocardiographic characteristics

|                      | Total  | No LE | LE     | P values |
|----------------------|--------|-------|--------|----------|
|                      | n=146  | n=89  | n=57   |          |
| **Cardiac dimensions** |        |       |        |          |
| LVEDD (mm)           | 47±5   | 47±5  | 46±6   | 0.150    |
| LVESD (mm)           | 29±4   | 30±4  | 28±5   | 0.012    |
| IVSd (mm)            | 10.0±2.4 | 9.0±1.5 | 11.7±2.6 | <0.001 |
| LVPWd (mm)           | 9.9±2.4 | 8.9±1.7 | 11.5±2.5 | <0.001 |
| LVMi (g/m²)          | 92±30  | 82±23 | 108±32 | <0.001  |
| RWT                  | 0.43±0.13 | 0.38±0.08 | 0.51±0.15 | <0.001 |
| RVD_middle (mm)      | 27±4   | 27±5  | 26±5   | 0.478    |
| RAA (cm²)            | 14±3   | 14±3  | 14±3   | 0.458    |
| LAVI (mL/m²)         | 24±9   | 21±6  | 28±11  | <0.001   |
| **RV function**      |        |       |        |          |
| TAPSE (mm)           | 23.0±3.9 | 23.8±3.7 | 21.8±4.0 | 0.002   |
| sPAP (mm Hg)         | 26±7   | 25±5  | 27±9   | 0.136    |
| **LV systolic function** |        |       |        |          |
| LVEF (%)             | 66±6   | 65±6  | 68±6   | 0.007    |
| **LV diastolic function** |       |       |        |          |
| E wave (cm/s)        | 87±19  | 86±16 | 89±21  | 0.343    |
| E/A ratio            | 1.47±0.54 | 1.5±0.5 | 1.4±0.6 | 0.653    |
| DT (ms)              | 207±50 | 203±43 | 214±58  | 0.173   |
| IVRT (ms)            | 89±24  | 79±17 | 104±27 | <0.001   |
| Septal e’ (cm/s)     | 8.6±3.3 | 10.1±2.9 | 6.3±2.3 | <0.001   |
| Septal E/e’ ratio    | 11.7±5.8 | 9.1±3.1 | 15.8±6.7 | <0.001   |
| Lateral e’ (cm/s)    | 11.9±4.2 | 13.7±3.8 | 9.2±3.1  | <0.001   |
| Lateral E/e’ ratio   | 8.3±3.7 | 6.7±2.0 | 10.7±4.3 | <0.001   |
| **Diastolic dysfunction** | <0.001 |<0.001 |<0.001 |<0.001 |
| Normal               | 95 (65.1) | 76 (58.5) | 19 (33.3) |          |
| Mild                 | 24 (16.4) | 10 (11.2) | 14 (24.6) |          |
| Moderate             | 19 (13.0) | 3 (2.1)  | 16 (28.1) |          |
| Severe               | 8 (5.5)  | 0      | 8 (14.0) |          |
| **Speckle-tracking imaging** (18 segments averaged) | <0.001 |<0.001 |<0.001 |<0.001 |
| LS_sys (%)           | −17.9±3.3 | −18.9±2.5 | −16.3±3.7 | <0.001 |
| LSr_sys (s⁻¹)        | −0.99±0.16 | −1.03±0.15 | −0.94±0.17 | 0.001   |
| LSr_E (s⁻¹)          | 1.36±0.41 | 1.49±0.39 | 1.16±0.36 | <0.001   |
| LSr_A (s⁻¹)          | 0.66±0.23 | 0.66±0.22 | 0.65±0.25 | 0.938    |
| E/LSr_E (cm)         | 69.0±25.3 | 60.5±16.3 | 82.6±30.8 | <0.001   |

Continuous variables are presented as mean±SD, and categorical variables are presented with counts and percentages. P<0.05 vs no LE group. DT, deceleration time of E wave; E wave, mitral inflow early diastolic filling velocity; E/A ratio, the ratio of mitral inflow early filling velocity to late diastolic filling velocity; E/e’, the ratio of early diastolic mitral inflow velocity to mitral annular tissue velocity; E/LSr_E, the ratio of mitral inflow early diastolic filling velocity to LSr_E; e’, tissue Doppler-derived mitral annular early diastolic velocity; IVRT, isovolumetric relaxation time; IVSd, end-diastolic interventricular septal thickness; LAVI, left atrial volume indexed to body surface area; LE, late gadolinium enhancement; LS_sys, longitudinal systolic strain; LSR_A, longitudinal late diastolic strain rate; LSR_E, longitudinal early diastolic strain rate; LSR_sys, longitudinal systolic strain rate; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass indexed to body surface area; LVPWd, end-diastolic posterior wall thickness; RAA, end-diastolic right atrial area; RV, right ventricle; RVD, end-diastolic mid-right ventricular diameter; RWT, relative wall thickness sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
Even though the presence of myocardial fibrosis can influence the management of patients with FD, therapeutic approaches might be affected not only by the presence, but more importantly the absolute amount of LE. In the current study, we only investigated the presence or absence of LE and the severity of LE was not analysed. This study limitation particularly needs to be clarified in future studies aiming to observe the clinical outcome of patients with FD with various degrees of LE severity and therapy regimens.

**Clinical implications**

Both echocardiography and MRI examinations are valuable tools for monitoring the cardiac involvement in patients with FD. Even though a close correlation of LE with diastolic functional parameters was found, the current results also show that LE can be detected even in the absence of measurable cardiac involvement at least in some patients with FD. It has been reported that ERT can reduce glycosphingolipid accumulation in the kidney of patients with FD and even clean intracellular deposits. ERT also improves outcome, however, is presumably less effective in patients with FD who already developed myocardial fibrosis. As a result, our study results strongly support additional routine examinations both by echocardiography as well as by cMRI in patients with FD at risk of organ involvement in order to facilitate a therapy start as early as possible to avoid permanent organ damage. In patients not feasible to undergo MRI, diastolic function as acquired by echocardiography might additionally be used as a surrogate for the presence or absence of LE and the severity of LE.

### Table 4: Independent determinants for LE in patients with Fabry disease with preserved LVEF

| Clinical marker | Spearman’s r | P values | OR* | 95% CI | P values | AUC | 95% CI | P values |
|----------------|-------------|----------|-----|--------|----------|-----|--------|----------|
| NT-proBNP (pg/mL)† | 0.47 | <0.001 | 1.85 | 1.18 to 2.92 | 0.008 | 0.78 | 0.70 to 0.85 | <0.001 |
| Echocardiographic markers | | | | | | | | |
| IVSD (mm) | 0.55 | <0.001 | 1.65 | 1.25 to 2.18 | <0.001 | 0.82 | 0.75 to 0.89 | <0.001 |
| LVMi (g/m²) | 0.42 | <0.001 | 1.03 | 1.01 to 1.05 | 0.002 | 0.75 | 0.66 to 0.83 | <0.001 |
| EF (%) | 0.23 | <0.001 | 1.05 | 0.97 to 1.13 | 0.222 | 0.63 | 0.49 to 0.73 | 0.006 |
| LAVI (mL) | 0.39 | <0.001 | 1.10 | 1.03 to 1.18 | 0.004 | 0.73 | 0.64 to 0.82 | <0.001 |
| Septal E/e’ | 0.60 | <0.001 | 1.30 | 1.13 to 1.49 | <0.001 | 0.86 | 0.79 to 0.92 | <0.001 |
| Lateral E/e’ | 0.54 | <0.001 | 1.34 | 1.11 to 1.62 | 0.002 | 0.82 | 0.75 to 0.89 | <0.001 |
| Diastolic dysfunction grading | 0.56 | <0.001 | 2.98 | 1.61 to 5.526 | 0.001 | 0.78 | 0.70 to 0.86 | <0.001 |
| STI markers | | | | | | | | |
| Global LS Sys (%) | 0.38 | <0.001 | 1.16 | 1.00 to 1.34 | 0.047 | 0.73 | 0.65 to 0.81 | <0.001 |
| E/LSr_E (cm) | 0.42 | <0.001 | 1.03 | 1.00 to 1.05 | 0.015 | 0.74 | 0.65 to 0.82 | <0.001 |
| Mid-lateral LS Sys (%) | 0.51 | <0.001 | 1.20 | 1.07 to 1.34 | 0.002 | 0.83 | 0.75 to 0.90 | <0.001 |
| Mid-lateral Lsr_E (s⁻¹) | −0.44 | <0.001 | 0.38 | 0.15 to 0.95 | 0.034 | 0.76 | 0.68 to 0.84 | <0.001 |

*Adjusted for age, sex, BMI, NYHA functional class, GFR (DTPA).
†Ln transformed.

AUC, area under the curve; BMI, body mass index; E/e’, the ratio of early diastolic mitral inflow velocity to mitral annular tissue velocity; EF, ejection fraction; GFR (DTPA), glomerular filtration rate from 99mTc-diethylene triamine penta-acetic acid; IVSd, end-diastolic interventricular septal thickness; LAVI, left atrial volume indexed to body surface area; LE, late gadolinium enhancement; LS_sys, longitudinal systolic strain; LVMI, left ventricular mass indexed to body surface area; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; STI, speckle-tracking imaging.

E/e’<7 indicated absence of LE in patients with FD. On the other hand, LE was detected in 93% of patients with septal E/e’>14.8. In patients presenting with mid-ranged septal E/e’ (7–14.8), an increased lateral E/e’ (>13) might provide additional information suggestive of LE.

**Limitations**

The patient sample was relatively small in this retrospective study, which could have introduced overoptimism regarding the proposed cut-off values of index test. Future prospective studies are warranted to verify the clinical value of the proposed algorithm, in particular as segmental STI has technical limitations specifically regarding interobserver and intraobserver variability. In our algorithm, we used reduced segmental longitudinal strain/strain rate at mid-lateral wall (ie, LS_midLat and Lsr_E_midLat) as one screening criteria suggestive of LE, since related changes in this segment belong to pathological feature of cardiac involvement of FD. Of note, however, previous studies showed that single segmental strain values are associated with higher variability in contrast to global longitudinal strain. Additionally, potential misclassification in some groups of patients with ‘grey zone’ E/e’ could be as high as 20% according to our proposed algorithm. This scenario further implies the importance of cMRI examination in patients with FD with preserved LVEF.

Even though the presence of myocardial fibrosis can influence the management of patients with FD, further studies are required to delineate the clinical implications of the proposed algorithm.
**Figure 1** Receiver operating characteristic analyses of NT-proBNP and echocardiographic determinants for late gadolinium enhancement (LE) in patients with Fabry disease with preserved left ventricular ejection fraction. AUC, area under curve; $E/e'$, the ratio of early diastolic mitral inflow velocity to mitral annular tissue velocity; IVSd, end-diastolic interventricular septal thickness; NT-proBNP, N-terminal pro-brain natriuretic peptide; LS$_{sys}$, longitudinal systolic strain; LS$_{r_E}$, longitudinal early diastolic strain rate; E/LS$_{r_E}$, the ratio of mitral inflow early diastolic filling velocity to LS$_{r_E}$; LS$_{r_{ivr}}$, longitudinal peak strain rate during isovolumetric relaxation time.
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Table 5  Diagnostic performance of septal E/e’ for LE in patients with Fabry disease

|                  | No LE (n=89) | LE (n=57) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|------------------|--------------|-----------|----------------------|----------------------|--------------|--------------|
| Septal E/e’<7    | 21           | 0         | 100 (92.1 to 100)    | 23.6 (15.5 to 34.0)  | 45.6 (36.7 to 54.7) | 100 (80.7 to 100) |
| Septal E/e’≥7    | 68           | 57        |                      |                      |              |              |
| Septal E/e’<10   | 62           | 11        | 80.7 (67.7 to 89.5)  | 69.7 (58.9 to 78.7)  | 63.0 (50.9 to 73.8) | 84.9 (74.2 to 91.9) |
| Septal E/e’≥10   | 27           | 46        |                      |                      |              |              |
| Septal E/e’<14   | 84           | 25        | 56.1 (42.4 to 69.0)  | 94.4 (86.8 to 97.9)  | 86.5 (70.4 to 94.9) | 77.1 (67.8 to 84.3) |
| Septal E/e’≥14   | 5            | 32        |                      |                      |              |              |
| Septal E/e’≤14.8 | 87           | 29        | 49.1 (35.8 to 62.6)  | 97.8 (91.3 to 99.6)  | 93.3 (76.5 to 98.8) | 75.0 (65.9 to 82.4) |
| Septal E/e’>14.8 | 2            | 28        |                      |                      |              |              |

E/e’, the ratio of early diastolic mitral inflow velocity to mitral annular tissue velocity; LE, late gadolinium enhancement; PPV, positive predictive value; NPV, negative predictive value.

CONCLUSIONS

LE is significantly associated with age, kidney function, NT-proBNP, LV hypertrophy, and systolic and diastolic dysfunction in patients with FD with preserved LVEF. In these patients, septal E/e’ ratio is the best echocardiographic marker associated with prevalence of LE. However, diastolic dysfunction is not a prerequisite for LE in FD, since LE can precede measurable functional impairments as very early marker of cardiac involvement.

Figure 2  Screening algorithm by the use of echocardiographic parameters suggestive of late gadolinium enhancement (LE) in patients with Fabry disease with preserved left ventricular ejection fraction. 95% CI for proportions was calculated according to the efficient-score method (corrected for continuity) described by R. Newcombe, based on the procedure outlined by E. B. Wilson in 1927. E/e’, the ratio of early diastolic mitral inflow velocity to mitral annular tissue velocity; IVSd, end-diastolic interventricular septal thickness; LSr_E, longitudinal early diastolic strain rate.
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