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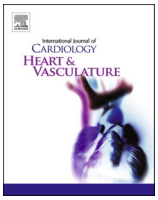

Clinical determinants and biomarkers associated with cardiac fibrosis after heart transplantation as assessed by magnetic resonance: Size matters

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ABSTRACT

Background: Cardiac fibrosis is increasingly recognized as a marker of worse outcomes in long-term follow-up after heart transplantation (HTX). We investigated the clinical determinants and biomarkers of focal and interstitial cardiac fibrosis as assessed with cardiac magnetic resonance (CMR).

Methods: Consecutive HTX recipients underwent CMR with late gadolinium enhancement for focal myocardial fibrosis and T1 mapping for interstitial fibrosis. We calculated the correlations of these findings with clinical parameters, history, biomarkers of fibrosis (B-type natriuretic peptide (BNP), growth differentiation factor-15, galectin-3 and soluble ligand ST2) and echocardiography.

Results: Forty-eight HTX patients were included: median age 63 ± 13 years, 11 ± 6 years after heart transplantation. Only donor weight (p 0.044) and the rate of a > 30 % mismatch between donor and recipient weight (p 0.02) were significantly different in patients with vs. without late LGE. Extracellular volume (ECV) was correlated with the weight mismatch between donor and recipient (r = 0.32, p 0.04), resulting in a higher ECV for oversized donors. BNP was the only biomarker of the four studied that was correlated with interstitial fibrosis as assessed by ECV (r = 0.35, p 0.04). T1 relaxation time was correlated with treated acute cellular rejection grade ≥ 2 (ISHLT grading) (r = 0.34, p 0.02).

Conclusion: Both focal and interstitial fibrosis, as determined by CMR, after heart transplantation are correlated with donor and recipient weight mismatch. BNP was the only biomarker clinically relevant to interstitial cardiac fibrosis.

1. Introduction

Cardiac fibrosis after heart transplantation is increasingly recognized as a marker of worse outcomes in long-term follow-up. [1] Little is known about the clinical determinants and causes of this fibrosis. Cardiac magnetic resonance (CMR) is a noninvasive, accessible tool to investigate cardiac fibrosis and has recently become increasingly popular in the research literature and hence clinical practice. Focal cardiac fibrosis, assessed by late gadolinium enhancement (LGE) on CMR, is described in up to 18 % of recipients after heart transplantation and is independently associated with the long-term risks of all-cause death and major adverse cardiac events (see Fig. 1). [1] Interstitial fibrosis, as measured by native T1 mapping on MRI, is also prevalent after heart transplantation and is linked to prognosis (see Fig. 2). [2] Despite the interest in the prognostic value of CMR-detected cardiac fibrosis after heart transplantation, only coronary artery vasculopathy (CAV) has been identified as a major source of focal fibrosis. [1] Other determinants of cardiac fibrosis have not been addressed in depth. We investigated focal and interstitial cardiac fibrosis after adult heart transplantation with CMR and attempted to translate the CMR findings into clinical practice. We studied determinants of cardiac fibrosis in clinical care, such as clinical parameters and history, biomarkers, and echocardiographic findings.

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2. Methods

This study was designed as a single-center cross-sectional study. Consecutive adult heart transplant recipients in regular follow up at the Antwerp University Hospital in Belgium were screened to take part in the present study. The study protocol was approved by the local ethics committee, and written informed consent was given. In 2018, in total eighty-two potentially eligible patients were invited for enrolment in the study. All CMR scans were performed from November 2018 until November 2019, during their annual post-transplant evaluation. Thirteen patients were unable to be scheduled for CMR due to non-compatible pacemakers and twenty-one patients did not provide informed consent. The final study population consisted of forty-eight subjects. Eight patients had incomplete CMR: six patients only had native T1 mapping due to chronic kidney disease with an eGFR<30 ml/min/m^2, precluding the use of contrast, while T1 mapping was not performed in two patients.

CMR scans were performed on a 3-T Siemens Skyra scanner. The CMR protocol consisted of localizers, a balanced steady-state free-precession cine short-axis stack and 3 long-axis views (4-, 2- and 3-chamber view) and native T1 mapping (basal, mid and apical short-axis) using a modified Look-Locker inversion recovery sequence. Ten minutes after intravenous injection of 0.2 mmol/kg gadoterate meglumine (Dotarem), LGE imaging was performed of the left ventricular short-axis stack and 3 apical long-axis views. Fifteen minutes postcontrast, T1 mapping was repeated. Contrast administration was skipped in patients with severe kidney insufficiency (eGFR≤30 ml/min/1.73 m2) to avoid the risk of nephrogenic systemic fibrosis. All CMR images were analyzed using CVI42 software (Circle Cardiovascular Imaging) by a single Level III observer who was blinded to clinical characteristics and transplant history. Ventricular volumes and function were derived from the short-axis cine stack. LGE was scored as present when seen in two orthogonal planes according to international recommendations (2013 SCMR Position Statement). LGE at the right ventricular insertion point was not regarded as significant myocardial fibrosis. The presence of significant fibrosis on LGE images was re-analysed in a blinded fashion and verified by a second experienced observer (NS). T1 values were averaged over basal and mid short-axis slices, excluding areas of ischemic scar (n = 1). ECV was calculated from native and postcontrast T1 maps according to the formula: $ECV = (1 - haematocrit)(1/(post\ \ contrast\ T1\ myocardium - native\ T1\ myocardium)/1/(post\ contrast\ T1\ \ blood - native\ T1\ blood))$.

Clinical data were obtained from patient records (see Fig. 1). Demographic data were collected from patients (recipients, R) and donors (D) (see Fig. 1A). Transplant-related data, current medication and comorbidities were recorded. The history of rejection was assessed by the number of rejections on endomyocardial biopsy and was described according to the International Society of Heart and Lung Transplantation (ISHLT) grading system. Only in the case of immunosuppressant intensification (grade ≥ 2) was the rejection held as significant. The presence of CAV was determined according to standardized ISHLT nomenclature from previous angiography proceedings.

At the time of CMR, transthoracic echocardiography was performed. Standard measurements were made (see figure appendix).

Blood samples for biomarkers were taken at the same time as the CMR and stored at −80 °C for later analysis. For B-type natriuretic peptide (BNP), the triage device and the Quidel triage BNP test were used. An enzyme-linked immunosorbent assay was used to quantify human galectin-3. For the quantification of growth differentiation factor-15 (GDF-15), an electrochemiluminescence immunoassay with the sandwich principle using the Cobas e801 system, an analytical unit, was used. The soluble ST2 determinations were determined using QUANTA-lyser, a system that performs high-throughput enzyme-linked immunoassays and immunofluorescence assays.

Statistical analysis was performed by using IBM SPSS Statistics (version 26). Normally distributed continuous variables are stated as mean ± standard deviation (SD). Nonnormally distributed continuous variables are presented as median with interquartile range. Categorical variables are listed as count (percentage). Functional CMR parameters were indexed to body surface area. The donor-recipient mismatch was calculated as [(donor X —recipient X)/donor X] x 100 for weight, BMI, and height. Cutoffs for subgroup analysis were based on transplantation guidelines, recommending against a weight mismatch larger than −30 % or −20 % in the case of a female or male recipient, respectively (i.e. undersized donors). [3] To determine if a difference existed between the means of two independent groups in a continuous dependent variable, for normally distributed variables (Shapiro-Wilk > 0.05), the independent *T* test was used, and for nonnormally distributed variables (Shapiro-Wilk < 0.05), the Mann–Whitney *U* test was used. Categorical variables were examined for independence via the chi-square test or, in cases where the expected cell count was less than five, Fisher's exact test. To define associations between two normally distributed continuous variables, the Pearson product-moment correlation was calculated to evaluate the strength and direction of the relationship between normally distributed continuous variables. In the case of nonnormally distributed data, Spearman's rank-order correlation was calculated. Finally, after multicollinearity assessment, correlated parameters with p

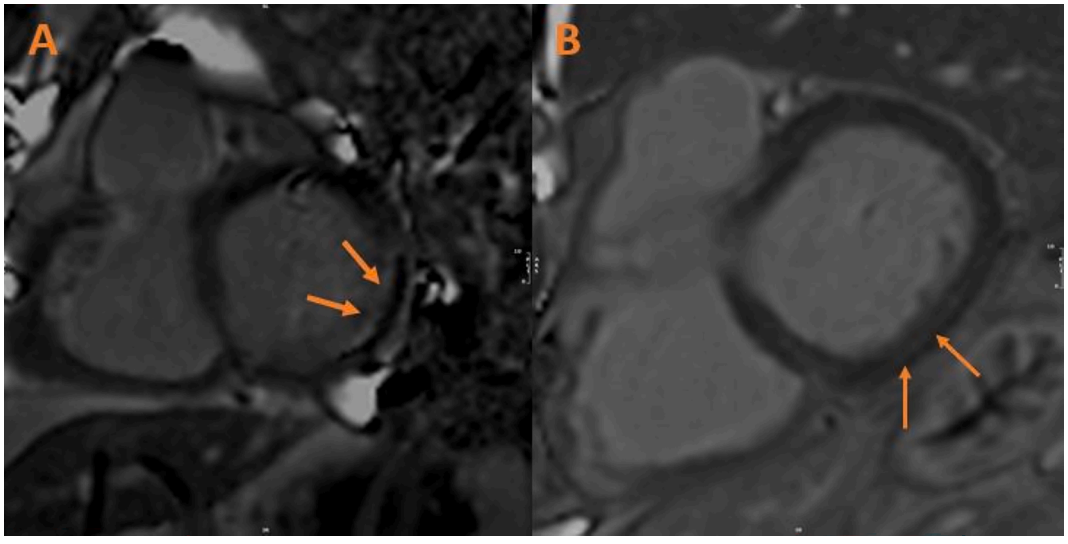

Fig. 1. Panel A shows a patient after heart transplantation with subendocardial LGE of the basal inferolateral wall (=infarction-like pattern). Panel B depicts a patient with subepicardial LGE of the basal inferolateral wall (=myocarditis-like pattern).

< 0.1 were included in a multiple linear regression analysis to determine the independence of correlations observed on simple linear regression. A two-sided $p < 0.05$ was used to denote statistical significance.

3. Results

Forty-eight transplant patients were included. Their median age was 63 ± 13 years, 23 % were female, and the time after heart transplantation was 11 ± 6 years.

LGE was detected in seventeen patients (40 %) on CMR. Not counting right ventricular insertion point enhancement, significant LGE was present in 9 patients. LGE patterns were predominantly nonischemic (n = 8), resembling myocarditis-like findings: mid-wall septum (n = 4) and/or subepicardial basal inferior to lateral walls (n = 6). Two patients had a patchy LGE distribution. Only one subject displayed ischemic LGE. Table 1A shows the clinical determinants of the patients and donors in relation to the presence of LGE. Only donor weight and a > 30 % mismatch between donor and recipient weight (both at the time of transplantation) were significantly different in patients with vs. without late LGE. No biomarker was correlated with CMR parameters of focal cardiac fibrosis (see table 1B). No echocardiographic measurements were correlated with LGE on CMR (see fig appendix).

Native T1 mapping was employed to identify interstitial fibrosis by quantifying absolute T1 relaxation times and calculating extracellular volume (ECV): 1230 ± 56 ms for native T1 values and 26.4 ± 2.9 % for ECV (reference values at our institution: 1190 ± 40 ms for native T1 and 24 ± 2 % for ECV). The same clinical determinants as studied for LGE were evaluated for correlations with T1 and ECV. ECV was correlated with the weight mismatch between donor and recipient (r = 0.32, p 0.04), ECV being higher in oversized donors. BNP was the only biomarker of the four studied that was correlated with interstitial fibrosis as expressed by ECV (r = 0.35, p 0.04). T1 relaxation time was correlated with treated acute cellular rejections grade ≥ 2 (ISHLT grading) (r = 0.34, p 0.02). For ECV, the significance criterion was not reached (r = 0.30, p 0.058).

4. Discussion

After heart transplantation, chronic allograft failure results in decreased overall survival. Chronic allograft failure is the result of many synergistically active mechanisms, such as pressure and volume overload, ischemia, inflammation and immunological processes. Cardiac fibrosis can be seen as the final result of these processes. [4] CMR is emerging as an easy, noninvasive technique to document myocardial fibrosis of the cardiac allograft and is histologically validated. [5,6] The translation of this fibrosis to a clinical treatment approach has been difficult. With this work, we tried to translate the CMR findings into clinical practice and searched for determinants of cardiac fibrosis among donor and recipient variables, transplant procedure-related parameters, clinical history, biomarkers of fibrosis and echocardiography findings.

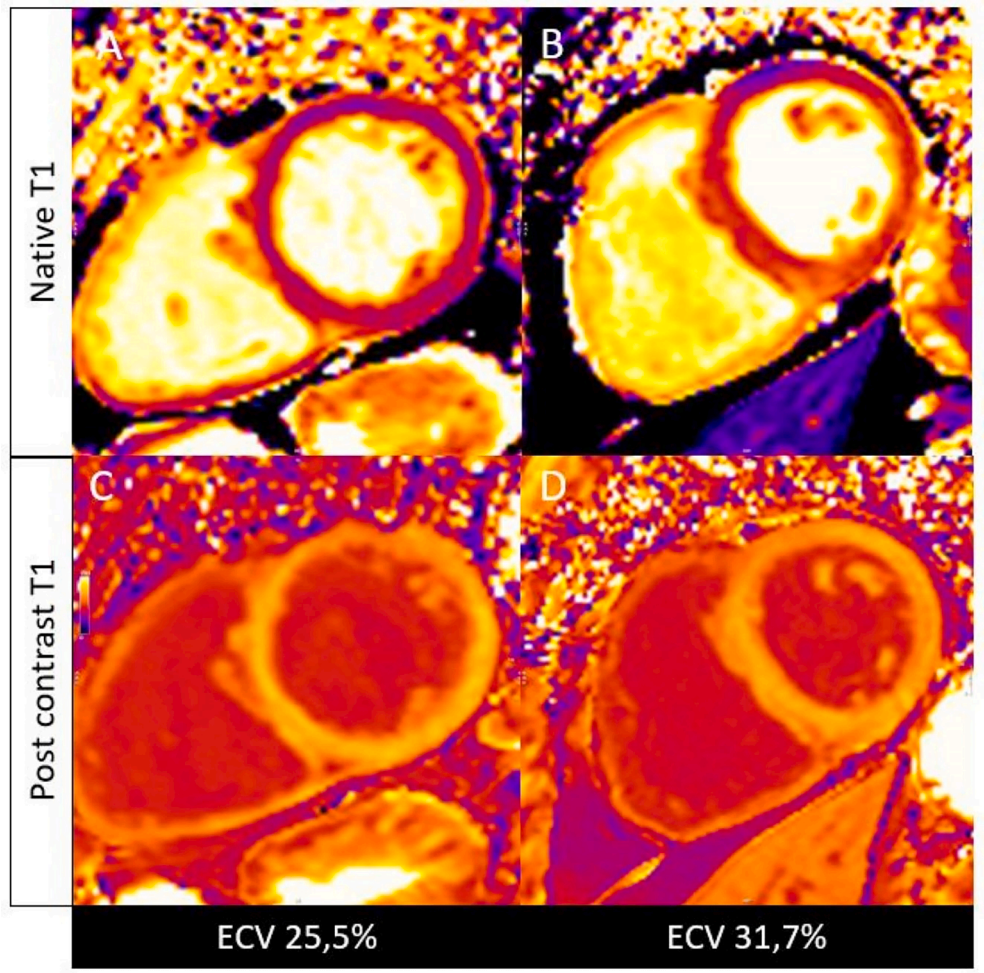

Fig. 2. Upper row panels (A+B) show pre-contrast T1 mapping; A. Patient 1 with normal native T1 values at 3 T; B. Patient 2 with abnormal T1 values; Lower row panels (C+D) show postcontrast T1 mapping; C. Patient 1 with a normal calculated ECV 25.5 %; D. Patient 2 with a high calculated ECV of 31.7 %, which is in keeping with a higher level of interstitial fibrosis..

Table 1A
Clinical determinants and late gadolinium enhancement in magnetic resonance imaging.

	LGE- (n = 34)	LGE+ (n = 9)	p
Demographics, recipients			
Weight (kg)	79,7 ± 12,3	96,7 ± 22,5	0.056
Height (cm)	175 ± 8	178 ± 15	0.619
BMI (kg/m^2)	25,8 ± 3,7	30,4 ± 6,3	0.064
Age (years)	64 [57–73]	61 [49–70]	0.547
Sex (male)	28 (82,4%)	7 (77,8%)	1
Comorbidities, recipients			
Hypertension	29 (85,3%)	8 (88,9%)	1
Atrial Fibrillation	4 (11,8%)	1 (11,1%)	1
Coronary artery vasculopathy	9 (26,5%)	2 (22,2%)	1
Rejection (ISHLT≥2)	10 (29,4%)	4 (44,4%)	0.442
eGFR (ml/min/1.73 m2)	66 ± 23	76 ± 18	0.217
eGFR<60 ml/min/1.73 m2	16 (47,1%)	2 (22,2%)	0.263
Medication, recipients			
ACE-I/ARB	14 (41,2%)	5 (55,6%)	0.477
Tacrolimus	28 (82,4%)	9 (100,0%)	0.315
Cyclosporine	6 (17,6%)	0 (0,0%)	0.315
Mycophenolic acid	25 (73,5%)	8 (88,9%)	0.659
Methylprednisolone	17 (50 %)	4 (44,4%)	1
Azathioprine	6 (17,6%)	1 (11,1%)	1
Transplantation data			
Time since HTx at CMR (y)	10,9 ± 5,6	8,8 ± 5,6	0.344
Allograft age at CMR (y)	45,9 ± 12,7	52,2 ± 12,1	0.192
Ischemia at HTx (min)	195 ± 54	208 ± 59	0.533
Time since HTx at CMR (y)	10,9 ± 5,6	8,8 ± 5,6	0.344
Treated cellular rejections	10 (29 %)	4 (44 %)	0.404
Donor data			
Age at HTx (y)	34,7 ± 12,0	43,3 ± 12,4	0.064
Weight (kg)	76,6 ± 9,8	84,1 ± 8,7	**0.044**
Height (cm)	177 ± 7	181 ± 6	0.210
BMI (kg/m^2)	24,3 ± 2,9	25,7 ± 2,9	0.064
Sex (male)	26 (76,5%)	9 (100 %)	0.171
Smoking	8 (25,0%)	2 (25,0%)	1
Hypertension	1 (3,0%)	1 (14,3%)	0.323
Donor–recipient mismatch			
Male to female or F to M	10 (29,4%)	2 (22,2%)	1
−10 % < BMI < + 10 %	23 (67,7%)	6 (66,6%)	1
BMI<-10 %	15 (44,1%)	5 (55,6%)	0.711
BMI > + 10 %	7 (20,6%)	1 (11,1%)	1
Weight mismatch > 30 %	2 (6 %)	3 (33 %)	**0.02**
Weight mismatch (%)	−5 (18)	−16 (29)	0.179

Data are mean ± SD or median with interquartile range. The p values denote significance between LGE-positive and LGE-negative groups.
HTx= heart transplantation.
BMI= body mass index.
LGE=late gadolinium enhancement.
Ns= not statistically significant.

Table 1B
Biomarkers of fibrosis and late gadolinium enhancement.

Biomarkers	**LGE- (n=27)**		**LGE+ (n=8)**		p
	Mean	± SD	Mean	± SD	
BNP (pg/ml)	116,23	104,11	66,78	59,81	0.212
Gal-3 (ng/ml)	8,28	2,86	9,34	4,19	0.418
GDF-15 (pg/ml)	2350,19	1958,06	1246,13	431,50	0.126
ST2 (µg/l)	36,59	18,68	29,34	10,37	0.304

Although we studied many parameters, donor weight and, in particular, a mismatch between donor and recipient weight was most relevant to cardiac fibrosis after heart transplantation. Hearts from heavier donors have significant LGE, and oversized donors also have a higher ECV. This result corroborates the work by Dolan et al., who found that several donor-recipient mismatch characteristics, particularly weight mismatch, were correlated with an increase in ECV. [7] Whether this cardiac fibrosis is due to obesity in the donor or due to the size mismatch itself is debated. Oversized hearts are often used to overcome pulmonary hypertension in transplant recipients. [8,9] Obesity-associated cardiac fibrosis has been extensively documented and is associated with a wide range of pathophysiological alterations, such as volume overload, metabolic dysregulation and systemic inflammation, all contributing to cardiac fibrosis. [10] An increased risk of mortality in overweight recipients as well as recipients of oversized-donor hearts has been described. [11,12] Other clinical variables described in the literature, such as female sex, increased age, hypertension in the donor, and ischemia time during the transplant procedure, were not linked to cardiac fibrosis in our work. [7,5].

Unsurprisingly, severe rejection is associated with an increase in the extracellular matrix, as demonstrated here by the correlation of native T1 and ECV with a history of ISHLT≥2 grade rejection. A relationship between cardiac fibrosis on CMR and rejection history has been described before. [13] Pathophysiologically, transforming growth factor β overexpression is frequently implicated in chronic rejection as a mechanism of fibrogenesis through the differentiation of cardiac myofibroblasts, and biomarkers of inflammation and fibrosis could be of interest. [14].

Biomarkers are the easiest and therefore preferred way to identify heart disease and determine prognosis in clinical care. Unfortunately, biomarkers of cardiac fibrosis are difficult to confirm and are rarely used in clinical practice despite the abundant literature on them. BNP, upregulated in pressure and volume overload, is the most robust marker for the detection and prognostic prediction of clinical heart failure. Here and in the literature, it is also the only biomarker related to interstitial fibrosis as expressed by ECV. [6] Galectin-3, involved in scarring and fibrogenesis, has been studied in heart transplantation but has no implications for disease. [15,16] The IL-33/ST2L signaling pathway is important in cardiac hypertrophy and fibrosis, and GDF-15 is elevated in cardiac remodeling. [17,19] Both galectin-3 and GDF-15 could be of interest in heart transplantation but showed no relevance in our study. In our opinion, biomarkers fail to show correlations with disease because, although these biomarkers all well predict fibrosis in research studies, they have no robust cutoff point in clinical care, besides BNP. Interactions with other disease states are also common. [16,18] A multimarker strategy, as in heart failure, could be considered. [19,20] The heart transplant population is not large. As long as there are no strong correlations between biomarkers and cardiac fibrosis in the context of other, far more prevalent diseases, the use in smaller populations will be difficult.

The use of echocardiography for the detection of cardiac fibrosis was not successful in our transplant population. The effects on systolic and diastolic function are subtle in the early phase of myocardial fibrosis and are not detected in conventional routine echocardiographic examination. [21] The best way to detect cardiac fibrosis is by speckle-tracking echocardiography, [22] a technique not always available in clinical care.

About donor selection not much is proven. A common practice to overcome elevated pulmonary artery pressure in the recipient is to choose overweight donors. Our study signalizes problems with this strategy. To overcome one problem, other issues are raised. Because of the shortage of donors, older donors and donors with more comorbidities are increasingly accepted. This practice is however not well documented. We advise centers to report on outcomes and encourage scientific societies to invest in clinical research.

The main limitation of our study is the limited number of transplant recipients and the high number of potential determinants studied. The determinants of cardiac fibrosis are not clear due to the multitude of possible causes and confounding factors. Since most data in the literature are reports from single centers, only small groups have been studied. (Inter)national registries are the preferred way to study possible determinants of fibrosis in larger heart transplant populations. Although these registries exist, the data assembled are limited. Another limitation is the lack of a baseline CMR, therefore we cannot rule out that myocardial fibrosis was present in the transplanted heart at the start of the transplant journey. At our institution, we aim for young donors

without major comorbidities, and thus a low likelihood of pre-existing cardiac fibrosis, although this is increasingly challenging in the current era of donor shortage.

5. Conclusion

At present, CMR is the most robust non-invasive method to determine cardiac fibrosis and prognosis after heart transplantation. We identified donor weight and oversized donors as major contributors to this fibrosis. BNP was the only biomarker in clinical care that was linked to cardiac fibrosis after transplantation. Standard echocardiography offered no benefit in detecting fibrosis.

CrediT authorship contribution statement

Anne Vorlat: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jeroen van Eijk:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Sjoerd Wiersma:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft. **Leroy Smid:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft. **Sofie Depooter:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft. **Bernard Paelinck:** Data curation, Investigation, Validation, Visualization. **Khadija Guerti:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation. **Bart Peeters:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Validation. **Nicole Sturkenboom:** Data curation, Formal analysis, Investigation, Software, Visualization. **Emeline Van Craenenbroeck:** Conceptualization, Data curation, Methodology, Supervision, Validation. **Hein Heidbuchel:** Conceptualization, Resources, Software, Supervision, Validation. **Caroline Van De Heyning:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix

Table appendix
Echocardiographic measurements, mean ± SD. The p value denotes the statistical significance of the comparison between late gadolinium enhanced (LGE)-positive and -negative groups. Data are mean ± SD. The p values denote the significance between LGE-positive and LGE-negative groups.

Echocardiography	LGE – (n=34)	LGE + (n = 9)	p
EDV (ml)	84.4 (22.8)	90 (18)	0.397
ESV (ml)	32 (10)	35 (11)	0.469
LVEF (%)	61 (7)	59 (5)	0.631
IVS (mm)	12 (2)	13 (1)	0.576
PW (mm)	10 (2)	10 (2)	0.676
LVEDD (mm)	45 (5)	47 (6)	0.371
LVESD (mm)	29 (5)	29(5)	0.372
E (cm/s)	80 (17)	84 (17)	0.371
A (cm/s)	38 (11)	39 (9)	0.411
Dt (ms)	148 (35)	154 (30)	0.368
s' sept (cm/s)	6.8 (1.1)	6.4 (1.1)	0.399
e' sept (cm/s)	7.5 (1.9)	7.3 (1.9)	0.636
E/e' sept	11 (3)	11 (4)	0.420
IVRT (ms)	78 (16)	73 (11)	0.662
LA vol (ml)	83 (35)	105 (19)	0.411
Tapse (mm)	15 (4)	19 (2)	0.679
FAC (%)	43 (10)	43 (10)	0.516
PAT (ms)	114 (26)	90 (19)	0.399
PAPs (mmHg)	25.3 (5.9)	28.6 (7.2)	0.417

Abbreviations: end-diastolic volume (EDV); end-systolic volume (ESV); left ventricular ejection fraction (LVEF); intraventricular septum (IVS); posterior wall (PW); left ventricular end-diastolic diameter (LVEDD); left ventricular end-systolic diameter (LVESD); E, A and deceleration time (Dt) of the mitral inflow; systolic and early diastolic movement of the left ventricular septal annulus (s' and e'); intraventricular relaxation time (IVRT); left atrial volume (LA vol); tricuspid annular plane systolic excursion (Tapse); right ventricular fractional area change (FAC); pulmonary acceleration time (PAT); systolic arterial pressure (PAPs).

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