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INFLUENCE OF MIDWALL FIBROSIS ON DIASTOLIC DYSFUNCTION IN NON-ISCHEMIC CARDIOMYOPATHY

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Until recently, myocardial fibrosis could only be identified by histology; however, now it can be non-invasively detected by late post-gadolinium myocardial enhancement cardiac magnetic resonance (LGE-CMR), as validated against histology.¹ In nonischemic cardiomyopathy (NICM), midwall myocardial fibrosis is a major component of pathological remodeling, and a predictor of adverse outcome.² Since severity of diastolic dysfunction increases with extent of fibrosis in various cardiac conditions³, it is important to investigate the relationship between fibrosis and diastolic function in NICM; however, data available are conflicting and/or inconclusive^{4–6}.

We investigated the influence of midwall myocardial fibrosis on diastolic dysfunction in NICM patients subjected to evaluation of cardiac fibrosis (by LGE-CMR) and diastolic function (by echocardiography).

METHODS

Population

All patients undergoing LGE-CMR and echocardiography within 30 days at Ohio State University (January 2007–March 2008) with NICM (having excluded other causes of LV dysfunction). The study was Institutional Review Board approved. Authors comply with the Principles of Ethical Publishing in the International Journal of Cardiology.⁷

CMR

Scans were acquired with 1.5T MAGNETOM Avanto (Siemens, Germany). Multislice short-axis cine imaging used ECG-triggered, steady-state free-precession (slice thickness 8 mm, interslice gap 2 mm). LGE was performed 10 min after gadolinium-DTPA administration (0.2 mmol/kg i.v.) using T1-weighted inversion-recovery gradient echo sequence, optimizing inversion time for adequate myocardial suppression and scar visualization. Scans were analyzed by an experienced physician blinded to patients' clinical

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and echocardiographic data. LV volumes, mass, and ejection fraction (EF) were measured from contiguous short-axis cine images using endocardial and epicardial contours and end-systole and end-diastole and Simpson's rule, where the volumes from each short-axis slice were summed to obtain global measures. In NICM, fibrosis typically shows midwall localization, which distinguishes it from infarction scar because of its sparing the subendocardium; similarly, subepicardial enhancement indicates epi-myocarditis. Midwall fibrosis was considered present when LGE positivity showed all the following: midmyocardium distribution; endocardial/epicardial sparing; non-coronary territory distribution. For each of the 17 LV segments LGE was rated as 0=absent, 1=present, and the sum of ratings was computed.

Echocardiography

Exams were analyzed by investigators unaware of CMR results. General Electric Vivid-7 (Milwaukee, WI), and Philips ie33 (Andover, MA), with a 3.5 MHz probe were used. Diastolic inflow was interrogated using pulsed-wave Doppler from apical 4- chamber view with sample volume placed at the tip of mitral leaflets; velocity of mitral early diastolic peak (E-wave) and late-diastolic peak (A-wave), E/A ratio, and deceleration time (DT) of mitral early velocity were measured. Tissue Doppler (TDI) was obtained in apical 4- chamber view with sample volume placed at lateral mitral annulus. Early-diastolic mitral annulus peak velocity was measured, and the transmitral diastolic peak velocity/mitral annular diastolic peak velocity ratio (E/E') calculated to index LV filling pressure; E/E' cut-off value of 10 categorized patients as having normal or increased LV filling pressure.^{8,9}

Statistics

Continuous variables are expressed as mean±standard deviation (SD). Differences between groups were compared with Student's t-test, or Mann-Whitney U-test, as appropriate; Fisher's exact-test was used for categorical variables. Multiple-group differences were tested by ANOVA with Bonferroni correction. Associations between variables were tested by linear regression analysis. Only variables significant by univariable analysis entered multivariable logistic regression, with enter-forward procedure. P<0.05 was considered significant. Analyses were performed with SPSS-13.0 for Windows (Chicago, Ill).

RESULTS

Characteristics

Fifty-four patients were included. Overall, LVEF averaged 30±13%, and LV dilation was present (see Table I for demographic and imaging characteristics).

CMR

All 17 segments were analyzable in each patient, for a total of 918 segments. Midwall LGE was present in 31 patients (57%), for a total of 105 segments (3.4±2.9 segment/patient). All patients had midwall fibrosis in septal segments; 19 showed it also in inferior and/or inferolateral segments, and 7 also in anterior and/or anterolateral segments. This prevalence is consistent with prior autopsy studies¹⁰ and with CMR findings in NICM patients.¹¹

Diastolic Function

Abnormal diastolic filling pattern was present in 44 patients (82%), as impaired relaxation (n=11), pseudonormal (n=17), restrictive filling (n=16); 31 patients (57%) had E/E'>10.

Increasing severity of filling impairment was associated with increased prevalence of midwall fibrosis (Fig. 1). Similarly, midwall fibrosis was significantly more frequent in

patients having elevated LV filling pressures by E/E' (Fig. 2). E' and E/E' were also significantly different between patients with and without midwall fibrosis (Table 1).

By univariable analysis, E/E' significantly correlated with midwall fibrosis, EF, and end-diastolic volume (Table 2). After multivariable analysis only midwall fibrosis remained significantly correlated with diastolic dysfunction (Table 2).

DISCUSSION

In patients with NICM, severity of LV diastolic dysfunction was associated with the extent of cardiac midwall fibrosis, also after adjusting for known factors influencing diastolic dysfunction.

That cardiac fibrosis affects diastolic function had been established through direct evaluation of collagen deposition by histology in experimental models,^{12,13} and in patients.¹⁴ However, use of tissues biopsies obviously limits investigating this issue in patients. Myocardial fibrosis can now be reliably and non-invasively assessed by LGE-CMR.^{15–17}

Recent investigations of fibrosis and diastolic function in NICM by combined echo and LGE-CMR yielded conflicting results^{5–6,18}. Of two studies in which cardiac fibrosis correlated with impaired diastolic function, one had 81% of patients showing substitution scar, and therefore other pathophysiological alterations were present; another study¹⁸ investigated only 17 patients, and deceleration time was the only index of diastolic function. Finally, Malaty et al⁶ reported lower LV filling pressure in NICM patients with LGE-CMR positivity, paradoxically indicating preserved diastolic function in presence of fibrosis. This goes opposite to our findings and to data obtained through direct examination of cardiac biopsies^{12–14}; however, there are major differences with our study. First, they included patients in whom LGE positivity could be found as midwall, or as patchy pattern, or both; instead, we purposely focused on “pure” midwall fibrosis, to investigate a population possibly free of confounders. Also, they did not evaluate whether diastolic function was similarly affected by different fibrosis patterns. Secondly, the paradoxical relationship between fibrosis and diastolic function was when TDI was measured in LV septum was lost when assessed at the lateral wall⁶. As all our LGE-positive patients showed septal fibrosis, we avoided measuring tissue function in an area affected by fibrosis; thus, we purposely measured TDI in the lateral wall and this may contribute to the seemingly divergence.

While LGE-CMR is accurate at measuring myocardial replacement fibrosis, its sensitivity to assess diffuse interstitial fibrosis is limited; quantitative T1 mapping¹⁹ may demonstrate diffuse interstitial fibrosis in future studies. Finally, as fibrosis is not the only factor affecting myocardial stiffness,²⁰ our findings cannot entirely explain the pathophysiology of diastolic dysfunction in NICM.

In conclusion, in patients with NICM, midwall myocardial fibrosis identified by LGE-CMR is a frequent finding, and it is significantly correlated with diastolic dysfunction.

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Figure 1.

Diastolic function according to the presence of midwall fibrosis. $p=0.0001$ between groups; post hoc comparison: normal vs pseudonormal and restrictive $p=0.0001$ and $p=0.002$, respectively; impaired relaxation vs pseudonormal $p=0.04$.

Figure 2.
Relationship between the presence of midwall fibrosis and the E/E' ratio. $p=0.0001$

Table 1

Demographic and Imaging Characteristics

	All	Absence Midwall (23, 43%)	Presence Midwall (31, 57%)	P
Male	31(57%)	16 (70%)	15 (48%)	0.17
Age, years	49±16	45±14	52±17	0.11
Diabetes	7 (13%)	0	7 (23%)	0.02
Hypertension	24 (44%)	10 (43%)	14 (45%)	1
<i>Cardiac magnetic resonance</i>				
End-diastolic volume indexed, ml/m ²	96±41	81±24	109±48	0.052
End-systolic volume indexed, ml/m ²	69±40	52±24	84±46	0.009
Ejection fraction, %	30±13	35±12	26±13	0.01
LV mass index, g/m ²	90±49	69±28	108±56	0.01
<i>Echocardiography</i>				
E wave, cm/s	0.90±0.26	0.81±0.21	0.97±0.27	0.02
A wave, cm/s	0.60±0.27	0.59±0.23	0.61±0.31	0.89
Mitral E/A ratio	1.79±1.02	1.59±0.89	1.94±1.09	0.25
Mitral deceleration time, ms	189±52	204±54	178±49	0.07
Mitral annular E', cm/s	0.09±0.03	0.10±0.03	0.08±0.03	0.005
E/E'	11.7±4.8	8.6±3.2	13.9±4.6	0.0001

Table 2

Univariate and Multivariate Analysis of Variables Associated with Increased E/E' ratio

	β	<i>P value</i>
Univariate		
Age	0.059	0.15
Diabetes	1.40	0.48
Hypertension	2.307	0.08
Ejection fraction	−0.138	0.005
End-diastolic volume indexed	0.032	0.03
Midwall fibrosis (y/n)	5.274	0.0001
Multivariate		
Ejection fraction	−0.005	0.92
End-diastolic volume indexed	0.015	0.34
Midwall fibrosis (y/n)	3.794	0.002

 β indicates linear regression coefficient