Influence of Myocardial Fibrosis on Left Ventricular Diastolic Function

Noninvasive Assessment by Cardiac Magnetic Resonance and Echo

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Background—Fibrosis is a common end point of many pathological processes affecting the myocardium and may alter myocardial relaxation properties. By measuring myocardial fibrosis with cardiac magnetic resonance and diastolic function with Doppler echocardiography, we sought to define the influence of fibrosis on left ventricular diastolic function.

Methods and Results—Two hundred four eligible subjects from 252 consecutive subjects undergoing late postgadolinium myocardial enhancement (LGE) cardiac magnetic resonance and Doppler echocardiography were investigated. Subjects with normal diastolic function exhibited no or minimal fibrosis (median LGE score, 0; interquartile range, 0 to 0). In contrast, the majority of patients with cardiomyopathy (regardless of underlying cause) had abnormal diastolic function indices and substantial fibrosis (median LGE score, 3; interquartile range, 0 to 6.25). Prevalence of LGE positivity by diastolic filling pattern was 13% in normal, 48% in impaired relaxation, 78% in pseudonormal, and 87% in restrictive filling ($P<0.0001$). Similarly, LGE score was significantly higher in patients with deceleration time $<150$ ms ($P<0.012$), and it progressively increased with increasing left ventricular filling pressure estimated by tissue Doppler imaging–derived E/E' ($P<0.0001$). After multivariate analysis, LGE remained significantly correlated with degree of diastolic dysfunction ($P=0.0001$).

Conclusions—Severity of myocardial fibrosis by LGE significantly correlates with the degree of diastolic dysfunction in a broad range of cardiac conditions. Noninvasive assessment of myocardial fibrosis may provide valuable insights into the pathophysiology of left ventricular diastolic function and therapeutic response. (Circ Cardiovasc Imaging. 2009;2:437-443.)

Key Words: diastole ■ myocardium ■ collagen ■ MRI ■ echocardiography

Clinical Perspective on p 443

Diastolic dysfunction significantly influences prognosis in chronic heart disease across multiple etiologies; it is present in virtually all patients with heart failure1-4 as well as in less severe conditions.5-7 From a mechanistic point of view, it can be traced to abnormalities of left ventricular (LV) distensibility, filling, or relaxation.8 These alterations may coexist and act in synergy to influence LV diastolic function.8

Accumulating evidence indicates that myocardial fibrosis contributes to the pathogenesis of diastolic dysfunction.9,10 This is conceivable because the structural properties of the heart are determined not only by the myocyte network but also by interstitial connective tissue. Thus, changes in the amount and composition of the extracellular matrix should affect the diastolic properties of the LV.11 However, our ability to investigate this issue in patients has long been hampered by lack of suitable methodology, because investigations thus far have been restricted to evaluating cardiac fibrosis in tissue biopsies or at autopsy.12-14

Late postgadolinium myocardial enhancement (LGE) by cardiac magnetic resonance (CMR) has long been used to detect the presence of scar after myocardial infarction.15 More recently, LGE-CMR has been shown to provide an accurate noninvasive means of detecting myocardial fibrosis due to various forms of nonischemic cardiomyopathy and has been validated against histopathologic examination.16,17 Distinct hyperenhancement patterns occur in different myocardial disorders that all share tissue disarray, fibrosis, and inflammation.18-22 Regardless of initial etiology, myocyte injury ultimately leads to increased myocardial collagen content and expanded interstitial space.23 Extracellular contrast agents such as gadolinium chelates accumulate in such regions, leading to hyperenhancement on imaging that takes advantage of gadolinium’s T1-shortening effects.
In the present study, we used LGE-CMR combined with established Doppler flow and tissue velocity measurement techniques\textsuperscript{24} to investigate noninvasively whether myocardial fibrosis influences diastolic function.

**Methods**

The study population comprised patients referred for CMR with LGE and in whom echocardiography with Doppler assessment of transmval flow and tissue Doppler imaging was performed within 30 days of CMR. All patients were in stable sinus rhythm. Of 252 patients screened, 22 were excluded because of complex congenital heart disease, 12 had mitral stenosis or valve prosthesis, 12 had constrictive pericarditis or significant pericardial effusion, and 2 had prior surgical ventricular restoration. CMR and echo studies were independently analyzed by expert investigators unaware of imaging and clinical data. This study was performed with institutional review board approval.

**CMR Acquisition and Analysis**

All scans were acquired with a 1.5-T magnetic resonance scanner (MAGNETOM Avanto, Siemens Medical Solutions, Inc, Erlangen, Germany). Multislice short-axis cine imaging used ECG-triggered, steady-state free precession (slice thickness, 8 mm; interslice gap, 2 mm) acquired from the atrioveentricular ring to the apex.\textsuperscript{25} Late gadolinium imaging was performed 5 to 10 minutes after intravenous gadolinium-DTPA contrast administration (0.2 mmol/kg) using a T1-weighted inversion-recovery gradient echo sequence,\textsuperscript{25} optimizing the inversion time for adequate myocardial suppression and scar visualization. Magnetic resonance examinations were analyzed by an experienced CMR physician blinded to patient history and echocardiographic data. LV volumes, mass, and ejection fraction (EF) were measured from contiguous short-axis cine images using endocardial and epicardial contours at end-systole and end-diastole with Simpson’s rule, in which the volumes from each short-axis slice were summed to obtain global measures. Wall motion score index (WMSI) was calculated using a standard 17-segment model\textsuperscript{27} and 4-point scoring system (0, normal/hyperkinetic; 1, hypokinetic; 2, akinetic; 3, paradoxical/dyskinetic). Regional WMSIs were obtained by summing the basal, mid, and apical segment scores in each region, as follows: anterior (anterior and anterolateral), septal (anteroseptal and inferoseptal), and inferior (inferior and inferolateral).

Similarly, LGE was rated by visual assessment blinded to echocardiographic and clinical data as 0 (none), 1 (nontransmual), or 2 (transmural) in each of the 17 myocardial segments. The LGE score was computed for each patient as the 17-segment sum of these scores. One hundred four (51%) patients demonstrated LGE positivity in 1 or more segments; of the 515 patients screened, 22 were excluded because of complex congenital heart disease; 12 had mitral stenosis or valve prosthesis; 12 had constrictive pericarditis or significant pericardial effusion; and 2 had prior surgical ventricular restoration. CMR and echo studies were independently analyzed by expert investigators unaware of imaging and clinical data. This study was performed with institutional review board approval.

**Echocardiography Acquisition and Analysis**

Standard echocardiographic and Doppler recordings were performed by experienced sonographers. Echo images were stored in digital format for subsequent off-line analysis by experienced investigators unaware of CMR results. The Vivid-7 System (Vingmed-General Electric, Milwaukee, Wis), Sonos 5500 (Philips Medical Systems, Andover, Mass), and ie33 (Philips Medical Systems) with a 3.5-MHz probe were used for echocardiography. Mitral diastolic inflow was interrogated using pulsed-wave Doppler from the apical 4-chamber view with the sample volume placed at the level of the mitral leaflet tips. Mitral early diastolic peak (E-wave) and late peak (A-wave) velocities, E/A ratio, and deceleration time (DT) of mitral early velocity were measured.\textsuperscript{5,28,29} Tissue Doppler was obtained at the apical 4-chamber view with the sample volume placed at the lateral mitral annulus. Early diastolic mitral annulus peak velocity was measured, and ratio of transmural mitral diastolic peak velocity to the mitral annular diastolic peak velocity (E/E') was calculated.\textsuperscript{24,30} Data were averaged over 3 cardiac cycles. Classification of diastolic function as normal, mild dysfunction (impaired relaxation), moderate dysfunction (pseudonormal), and severe dysfunction (restrictive filling pattern) was performed according to standard criteria.\textsuperscript{5,28,29} The E/E' ratio was used to estimate LV filling pressures. Based on the E/E' cutoff value of 10, patients were categorized as having normal or elevated filling pressure.\textsuperscript{30}

**Statistical Analysis**

Continuous variables are expressed as median and interquartile ranges (IQRs) or mean ±95% confidence intervals. Differences between groups were compared using Student t test and Mann–Whitney U test when the distribution of the variable was asymmetrical; the Fisher exact test was used for categorical variables. Spearman correlation was used to test the correlation between continuous variables; differences between groups were tested by ANOVA with Bonferroni post hoc test. Association between E/E' or E' and LGE was first evaluated by quadratic model (LGE = β0 + β1E'E + β2E'2). Then, associations between E/E' and age, echocardiographic, and CMR data were evaluated by linear regression analysis. Only variables significant at univariate analysis were entered into a multiple linear regression analysis. Statistical significance was set at a probability value <.05. Statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Ill) release 13.0 for Windows.

**Results**

**Patient Characteristics**

From January to August 2007, 204 suitable subjects were identified. Of these, 42 (20%) had no evidence of structural heart disease; these patients were typically referred for CMR because of a questionable abnormality seen on echocardiography or to rule out arhythmogenic right ventricular cardiomyopathy in the setting of isolated ventricular premature beats. The remaining patients had various cardiac diagnoses; their clinical and demographic characteristics are summarized in Table 1.

**CMR Findings**

In the overall population, CMR-derived median LVEF was 50% (IQR, 27% to 58%), end-diastolic and end-systolic volumes indexed to body surface area were 72 (59 to 97) mL/m\(^2\) and 36 (26 to 63) mL/m\(^2\), respectively, and LV mass index was 65 (50 to 89) g/m\(^2\).

All cardiac segments were adequately visualized by CMR in every patient. One hundred four (51%) patients demonstrated LGE positivity in 1 or more segments; of the 515 LGE-positive segments, distribution pattern of LGE was transmural in 216 segments (42%), and nontransmural in 299 (58%). Importantly, no LGE-positive segments were detected in subjects without structural heart disease. In contrast, LGE positivity was common in patients with cardiomyopathy, being present in 89% of patients with ischemic cardiomyopathy, in 59% of those with dilated cardiomyopathy, and in 67% of those with hypertrophic cardiomyopathy. The median LGE score was 0 (IQR, 0.00 to 0.00) in subjects without structural heart disease compared with 3 (IQR, 0 to 6.25) in patients with cardiomyopathy (P < .0001). Severity of LGE score showed a significant inverse correlation with LV EF (r = −.51; P < .0001).

**Echocardiographic Findings**

A pattern of abnormal diastolic filling based on mitral inflow velocities was seen in 113 patients (51%); furthermore, 26
(16%) had severely impaired diastolic filling, as indicated by a DT < 150 ms.5,28,29

Assessment of LV diastolic function was completed by measuring E/E’ by tissue Doppler, as this parameter provides an accurate, relatively load-independent estimate of LV filling pressure31,32; diastolic impairment with increased LV filling pressure (E/E’>10)30 was present in 80 patients (39%).

### Diastolic Function and LGE

Overall, 63 (31%) subjects had normal diastolic function by concomitant presence of all 3 criteria, that is, normal mitral inflow pattern, DT ≥ 150 ms, and E/E’ ≤ 10. Importantly, no LGE was detected in the majority (87%) of these subjects with entirely normal diastolic function; overall, median LGE score in these patients was 0 (IQR, 0.00 to 0.01). Across the entire study population, LGE positivity was significantly associated with all parameters of diastolic dysfunction. Median LGE score in subjects who showed normal filling was 0 (IQR, 0.00 to 0.01), but it significantly and progressively increased with increasing severity of filling impairment, reaching 4 (IQR, 2 to 10) in patients with restrictive filling pattern (Figure 1; P<0.0001). Similarly, mean±SD LGE scores progressively increased from normal (0.3±0.1) to impaired relaxation (2.8±0.6), pseudonormal (6.2±0.8) and restrictive filling (7.2±1.3). Similarly, LGE was significantly higher in patients in whom deceleration time was <150 ms, compared with patients with normal deceleration time (Figure 2; P=0.012). Finally, degree of fibrosis as assessed by LGE score also significantly increased with increasing severity of LV filling pressure estimated by E/E’ (≤10 versus >10) (Figure 3; P<0.0001). Conversely, of the 100 LGE-negative patients, 86 had normal diastolic function by E/E’ ≤ 10.

At the individual level, fibrosis by LGE was directly and significantly correlated with E/E’ (LGE = −1.477+0.538E/E’−0.003 E/E’; SE of β0 = 1.325, β1 = 0.203, β2 = 0.006; r = 0.444; P<0.001); similarly, LGE was also significantly related to the E’ component (LGE = 11.006 to 102.935 E’+257.109 E’2; SE of β0 = 1.989, β1 = 35.625, β2 = 143.547; r = 0.356; P<0.001). Analysis of patients divided into those with EF ≥ 50% and those with EF < 50% showed that the relationship between LGE and diastolic function remained statistically significant in both groups (P<0.001; r = 0.28 and 0.44, respectively). Additional plots of the individual LGE scores and diastolic function parameters are shown in Figure 4.
analysis showed a significant association between LGE positivity and presence or absence of any diastolic dysfunction ($\chi^2 = 53, P < 0.0001$). Univariate analysis showed significant correlations between diastolic dysfunction assessed by E/E' and age, diabetes, hypertension, type of heart disease, EF, WMSI, and LGE score ($P < 0.05$ for all). After multivariate analysis, only age, diabetes, and LGE score remained significantly and independently correlated with the degree of diastolic dysfunction (Table 2). We checked collinearity for variables, and the tolerance was near 0.9 for all variables.

Discussion

In a large cross-sectional study that included a broad range of cardiac conditions as well as patients without structural heart disease, we found that the presence and severity of LV diastolic dysfunction was consistently associated with myocardial enhancement on LGE-CMR. Intact cardiomyocytes do not show LGE positivity, underscoring the ability of LGE to demonstrate altered myocardial composition that contributes to impaired diastolic function. Previous reports had shown a relationship between degree of cardiac fibrosis and diastolic dysfunction10–13,33; however, those studies relied on evaluation of collagen deposition as assessed by histological examination of tissue specimens. Although accurate, those investigations were obviously limited with respect to number of patients studied and because of relative exclusion of subjects with no structural heart disease. To our knowledge, ours is the first study to investigate the relationship between LV diastolic dysfunction and severity and location of myocardial fibrosis in a large cohort of patients with cardiac impairment.

LV filling and myocyte relaxation show a complex interplay during diastole, which is influenced by many factors including loading conditions, systolic emptying, myocardial ischemia, heart rate, and intracellular calcium cycling.34 Physical properties of the myocardium also play a very relevant role in dictating LV behavior during diastole.9 In this respect, collagen is an important constituent of the myocardial extracellular matrix, and changes in its structure can affect diastolic function. Increased tissue collagen deposition alters the viscoelasticity of the myocardium impairing relaxation, diastolic recoil (ie, "suction"), and passive stiffness. The collagen network of the heart consists of epimysial, perimysial, and endomysial components, around which muscle fibers are oriented.9 The LV develops a negative diastolic pressure (suction) when coiled perimysial fibers release the energy stored during systolic compression; this contributes to diastolic filling that is not entirely passive. Microdisarray and macrodisarray of these components, especially of perimysial fibers, have been implicated in the pathogenesis of diastolic dysfunction.33 Although undoubtedly relevant to understanding
the pathophysiology of diastole, systematic investigation of cardiac fibrosis and of its relationship with diastolic function has long been hampered by lack of suitable methodology.

LGE-CMR is a well-established technique to noninvasively detect foci of collagen deposition in vivo. Importantly, it has been documented that LGE results show a good correlation with direct histological findings. Although originally associated with infarct scar visualization in ischemic heart disease, distinct patterns of hyperenhancement have subsequently been described in dilated cardiomyopathy, hypertrophic cardiomyopathy, and other myocardial diseases. Our population included subjects without structural heart disease as well as patients with a wide spectrum of heart diseases of different etiology; the percentages of LGE positivity that we found in those various conditions compares well with what has been previously reported.

By using a noninvasive approach, we were able to explore subjects spanning across a wide range of cardiac fibrosis and, at the same time, a wide range of degrees of diastolic function. This is important because impaired diastolic function can be found in many subjects with no overt cardiac disease or even as the initial cardiac manifestation of aging. We confirmed in our study the well-known correlation between aging and myocardial relaxation impairment, demonstrating that age was correlated with diastolic function in multivariate analysis.

Because the degree of diastolic impairment may vary with the severity of disease, it is crucial to be able to detect and differentiate severity of diastolic dysfunction. We investigated diastolic function by a multipronged approach based on well-established echocardiographic techniques. One is pulsed-wave Doppler evaluation of transmitral inflow velocities; by this approach, distinct filling patterns have been described representing various degrees of diastolic impairment, from normal LV filling to restrictive physiology. The most benign alteration, termed impaired relaxation (grade I) and characterized by prolonged deceleration time of early diastolic filling and decreased E/A, is associated with delayed relaxation in the presence of normal LV filling pressures. At the other end of the spectrum, a restrictive filling pattern (grade III) is characterized by shortened deceleration time, increased E/A, and shortened relaxation time and reflects high LV filling pressures. The pseudonormal filling pattern (grade II) is considered a condition of intermediate severity.

Our data are consistent with this concept of a gradient of severity in diastolic dysfunction, paralleled by a relationship between degree of diastolic impairment and extent of myocardial fibrosis by LGE-CMR (Figure 1). This finding was confirmed when impairment of diastolic filling dynamics was established with respect to deceleration time of early atrial emptying. It is well established that DT<150 ms denotes a condition of severe impairment of diastolic emptying associated with increased atrial pressures and poor systolic function. Our data indicated that patients with DT<150 ms have significantly greater myocardial fibrosis (Figure 2).

Doppler evaluation of LV filling may be influenced by both preload and afterload. To overcome this limitation, we simultaneously assessed diastolic function using mitral annular velocity by tissue Doppler imaging (TDI)—a sensitive, reliable, and relatively load-independent index of diastolic function. Again, we demonstrated progressive increase in extent of fibrosis with progressive increase in LV filling pressure as estimated by TDI (Figure 3). Indeed, there was a significant correlation between either E' or E/E' and the degree of LGE enhancement.

We did not find any significant correlation between E/E' and etiology of heart disease; in addition to the severity of fibrosis, only its location in the septum was significantly and
independently associated with E/E', and this regardless of etiology. We have no immediate explanation for the observed correlation between E/E' and septal fibrosis, although it may underscore the role of the septum in LV filling, either directly or as a consequence of altered interventricular dependence, which in turn may affect diastolic function.\(^{39}\)

**Limitations**

In the present study, we did not attempt to dissect out the various components of diastole, as analysis of how fibrosis affects precise mechanisms of diastolic function was beyond the scope of this study. Absence of invasive measurement of atrial and ventricular pressures is another limitation because LV diastolic filling is sensitive to loading conditions. However, among noninvasive surrogates, TDI-derived E' and E/E' have been shown to correlate well with direct pressure-volume measurements obtained through conductance catheters.\(^{24}\) Furthermore, we examined subjects in stable hemodynamic and clinical conditions. This, along with the fact that the relationship between LGE and diastolic function was consistently reproduced when using either LV filling patterns by pulsed-wave Doppler or TDI parameters, indicates that our findings were unlikely to be an effect of different loading conditions. Distinction among specific cardiac conditions was not done; rather, the goals of this work were to (1) consider diastolic function as a common end point in patients with a broad spectrum of disorders and those with normal cardiac structure and (2) demonstrate altered myocardial tissue characterization as potential substrate for diastolic dysfunction. We did not use techniques such as myocardial tagging to assess diastolic function by CMR\(^{40}\); these could be used in future studies.

Whereas we used a semiquantitative LGE score for practical implementation, direct signal intensity–based measurements would represent true quantification of LGE data. Age probably affects fibrosis even in the absence of cardiac disease; however, our patients without cardiac disease were relatively young, precluding further analysis of this relationship. Although accumulating histopathologic studies indicate that LGE probably represents fibrosis in patients with stable cardiac disease,\(^{36–38,41}\) accruing microscopy correlates may expand our understanding of the precise histopathologic signature responsible for LGE positivity. Finally, the current resolution of CMR can detect only areas of fibrosis that are macroscopically visible; thus, collagen infiltration at the microscopic level goes undetected, though it also probably contributes to diastolic dysfunction. Diffuse interstitial fibrosis, not readily appreciated by visual inspection of LGE images, may have been present in those patients deemed LGE negative but found to have some degree of diastolic dysfunction. Future studies using CMR-based T1 mapping, a quantitative approach to measuring collagen volume fraction noninvasively, may overcome this limitation.\(^{42}\)

**Implications**

There is increasing recognition of the importance in assessing diastolic function for both diagnosis and prognosis across a broad spectrum of cardiac conditions. Common to these conditions is reactive or replacement fibrosis that alters myocardial architecture and mechanical properties, and, as indicated in our work, produces measurable changes in diastolic function. Noninvasive evaluation of myocardial fibrosis allows analysis of a much larger number of patients than is feasible with direct tissue examination. In addition, this approach lends itself well to serial measurements in investigating disease progression as well as treatment effects. Another implication of our findings is the observation that etiology, in and of itself, appears to be less relevant than the presence and distribution of myocardial fibrosis in the pathophysiology of fibrosis-mediated diastolic impairment, because presence and severity of diastolic dysfunction were associated with presence and extent of fibrosis in various forms of underlying cardiac disease.

**Conclusions**

In patients with various degrees of cardiac impairment, the extent of cardiac fibrosis reliably predicts the degree of diastolic dysfunction. LGE-CMR provides a powerful means to noninvasively assess extent and location of myocardial fibrosis caused by a variety of cardiac diseases. This, coupled with classification of diastolic function by echocardiography, provides insights into the mechanism of LV diastolic dysfunction.

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**Disclosures**

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**References**

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Myocardial Fibrosis and LV Diastolic Function

Myocardial fibrosis develops as a final common end point in response to a broad range of cardiac pathologies such as ischemia, inflammation, hypertension, and valvular heart disease. Clinically, these conditions may produce signs and symptoms related to increased myocardial stiffness that may result from replacement or reactive fibrosis. This study used late gadolinium enhancement cardiac magnetic resonance to noninvasively quantify myocardial fibrosis and Doppler echocardiography to detect and classify severity of left ventricular diastolic dysfunction. Regardless of etiology, the presence and severity of diastolic dysfunction increased with the greater extent of myocardial fibrosis. This work suggests that late gadolinium enhancement cardiac magnetic resonance may be useful to identify the myocardial substrate for impaired relaxation and provides a rationale for its use as an end point in developing novel therapeutics for diastolic dysfunction.

CLINICAL PERSPECTIVE

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