Aortic Stiffness and Interstitial Myocardial Fibrosis by Native T1 Are Independently Associated With Left Ventricular Remodeling in Patients With Dilated Cardiomyopathy

Valentina O. Puntmann, Eduardo Arroyo Ucar, Rocio Hinojar Baydes, Ning Binti Ngah, Yen-Shu Kuo, Darius Dabir, Alexandra Macmillan, Ciara Cummins, David M. Higgins, Nicholas Gaddum, Phil Chowienczyk, Sven Plein, Gerry Carr-White, Eike Nagel

Abstract—Increased aortic stiffness is related to increased ventricular stiffness and remodeling. Myocardial fibrosis is the pathophysiological hallmark of failing heart. We investigated the relationship between noninvasive imaging markers of myocardial fibrosis, native T1, and late gadolinium enhancement, respectively, and aortic stiffness in ventricular remodeling. Consecutive patients with known dilated cardiomyopathy (n=173) underwent assessment of cardiac volumes and function, T1 mapping, scar imaging, and pulse wave velocity, a measure of aortic stiffness. Asymptomatic healthy volunteers served as controls (n=47). Controls and patients showed an increase in pulse wave velocity with age, which was accelerated in the presence of cardiovascular disease. On the contrary, native T1 increased with age in patients, but not in controls. Pulse wave velocity was associated with native T1 in the presence of disease, but not in health. Native T1 showed a strong relationship with markers of structural and functional left ventricular remodeling and diastolic impairment. Ischemic and nonischemic pathophysiology of ventricular remodeling showed a similar slope of relationship between pulse wave velocity and native T1. However, in nonischemic patients, increase in pulse wave velocity was associated with greater increase in native T1. Aortic stiffness is related to age, and this process is accelerated in the presence of disease. On the contrary, increase in interstitial myocardial fibrosis is associated with age in the presence of disease. Patients with ischemic and nonischemic dilated cardiomyopathy have a similar relationship between native T1 and pulse wave velocity, which is stronger in the latter group. (Hypertension. 2014;64:762-768.) ● Online Data Supplement

Key Words: cardiomyopathy, dilated ▪ endomyocardial fibrosis ▪ vascular stiffness

Aging influences the structural and functional properties of the arterial and ventricular system: the central arteries dilate and their walls become thicker and stiffer, adding onto the cardiac workload. Increased aortic stiffness impedes forward displacement of left ventricular (LV) stroke volume as well as efficient diastolic filling, leading to LV dysfunction and stiffness, remodeling, and heart failure. Pulse wave velocity (PWV), a measure of aortic stiffness, is a marker of aortic characteristic impedance and LV afterload. Increase in aortic stiffness is associated with traditional cardiovascular risk factors and independently predictive of adverse cardiovascular events. Evidence suggests that increased aortic stiffness relates to adverse extracellular matrix turnover and LV remodeling in dilated cardiomyopathies and relates to poorer prognosis.

Myocardial dysfunction and remodeling is associated with its pathophysiological hallmark—myocardial fibrosis. Diffuse interstitial or replacement myocardial fibrosis has been demonstrated as a common feature in a broad variety of heart conditions, leading to ventricular remodeling and dilated cardiomyopathy (DCM). Cardiovascular magnetic resonance (CMR) can uniquely characterize the extent of replacement fibrosis by late gadolinium enhancement (LGE; Figure 1). Myocardial T1 mapping is an emerging technique for assessment of interstitial diffuse myocardial fibrosis. Both markers have been associated with adverse outcome in patients with heart failure. In this study, we examined whether noninvasive measures of myocardial fibrosis by T1 mapping and LGE, respectively, relate to the increase in aortic stiffness in DCM and whether this relationship differs by the cause of underlying DCM, because of ischemic and nonischemic pathophysiology.

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Methods

Consecutive patients with established DCM in accordance with the
criteria of the World Health Organization/International Society and
Federation of Cardiology of ≤6 months’ duration were eligible for
inclusion. Patients were classified as ischemic heart disease (IHD) if
they had at least 1 of the following: (1) significant documented coro-
nary artery disease, (2) previous coronary revascularization, (3) pre-
vious history of myocardial infarction, (4) evidence of ischemic-type
LGE or significant inducible ischemia on CMR. Diagnosis of non-
ischemic DCM (NICM) was based on the evidence of (1) increased
LV end-diastolic volume indexed to body surface area, (2) reduced
LV ejection fraction compared with published reference ranges nor-
malized for age and sex, (3) absence of subendocardial LGE indica-
tive of previous myocardial infarction, and (4) absence of any specific
identifiable underlying cause (eg, aortic or valvular disease, myocar-
ditis, amyloid, hypertrophic cardiomyopathy). Asymptomatic and normotensive subjects taking no regular medi-
ation and with no significant medical history (and consequently normal
CMR findings, including volumes and mass) served as controls. Age,

Figure 1. Ischemic and nonischemic cardiomyopathies and their phenotypic equivalents by cardiovascular magnetic resonance.

Figure 2. Measurement of proximal pulse wave velocity using an inplane gradient echo sequence (A, cine; B, phase contrast readout) by dividing
the distance between the 2 locations with a measurement of the time delay required for the
arrival of the pulse wave between the 2 locations. Transit time was defined as the temporal shift of the
wave foot (C) and required the location of both the local velocity minima at end diastole and the highest
blood acceleration during the systolic upslope.
Table 1. Results of Cardiac Function and Structure and Tissue Characterization by Cardiovascular Magnetic Resonance and Diastolic Parameters by Echocardiography

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=47)</th>
<th>Ischemic Heart Disease (n=91)</th>
<th>NICM (n=82)</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVED index, mL/m²</td>
<td>76±13</td>
<td>125±35*</td>
<td>123±26*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVES index, mL/m²</td>
<td>46±8</td>
<td>85±23*</td>
<td>92±30*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>56±10</td>
<td>89±28*</td>
<td>87±19*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>61±6</td>
<td>33±15*</td>
<td>39±18*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>57±9</td>
<td>56±11</td>
<td>56±26</td>
<td>0.83</td>
</tr>
<tr>
<td>LA area, cm²</td>
<td>19±3</td>
<td>28±4*</td>
<td>31±6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>5.4±1.3</td>
<td>8.1±2.5*</td>
<td>7.9±2.3*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGE (present), n (%)</td>
<td>0 (0)</td>
<td>62 (68)*</td>
<td>27 (23)*†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61±6</td>
<td>61±11</td>
<td>61±12</td>
<td>0.83</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>56±10</td>
<td>89±28*</td>
<td>87±19*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVES index, mL/m²</td>
<td>46±8</td>
<td>85±23*</td>
<td>92±30*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e′</td>
<td>6.9±1.4</td>
<td>9.2±1.6*</td>
<td>9.8±2.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>222±19</td>
<td>192±29*</td>
<td>192±74*</td>
<td>0.025</td>
</tr>
</tbody>
</table>

FWHM indicates full-width half-maximum; LA, left atrial; LGE, late gadolinium enhancement; LVED, left ventricular (LV) end diastolic; LVES, LV end-systolic; NICM, nonischemic dilated cardiomyopathy; PWV, pulse wave velocity; RV, right ventricular; and SAX, short axis.

P<0.05 is considered statistically significant. One-way ANOVA with Bonferroni post hoc tests or Kruskal–Wallis for the differences from controls (*). Comparisons of means were performed using Student t test for continuous variables and χ² test for categorical variables. The associations were analyzed using uni- and multivariate linear regression analyses and compared by Fisher r-to-z transformation. Multivariate binary logistic regression was used to determine whether the variables independently discriminate between health and disease. Collinearity diagnostics was used to examine the variance inflation factor analysis. Inter- and intraobserver reproducibility and agreement of postprocessing approaches has been determined using Bland–Altman procedures. All tests were 2-tailed, and P value <0.05 was considered statistically significant.

Image Analysis

Assessment of cardiac volumes, function, and mass has been described previously (see the online-only Data Supplement).27 The LGE images were visually examined for the presence of regional scar tissue in 2 phase–encoding directions. LGE was defined as present when regions of brightness with signal intensity >6 SDs from normal regions.27 The extent of myocardial fibrosis was quantified as a percentage of LV mass using the full-width half-maximum technique and semiautomated software (CVI42; Circle Cardiovascular Imaging Inc).29 T1 mapping analysis was performed using the PRIDE Relaxation Maps Tool (version 2.1.1; Philips Healthcare) as previously described.22,23,26 In addition to T1 values of native and postcontrast myocardium, we also report partition coefficient λ, a marker of interstitial contrast agent accumulation (details in the the online-only Data Supplement). PWV was calculated by dividing the length of the aorta between the locations used for aortic flow measurements with the time difference between the arrival of the pulse wave at these locations (Figure 2) as described previously26 (details in the online-only Data Supplement).

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL; version 21.0). Departures from normality were detected using Kolmogorov–Smirnov test. Results for normally distributed continuous variables are expressed as meansSD and categorical data are expressed as counts (%). Comparisons of means were performed using Student t test for continuous variables and χ² test for categorical variables. The associations were analyzed using uni- and multivariate linear regression analyses and compared by Fisher r-to-z transformation. Multivariate binary logistic regression was used to determine whether the variables independently discriminate between health and disease. Collinearity diagnostics was used to examine the variance inflation factor analysis. Inter- and intraobserver reproducibility and agreement of postprocessing approaches has been determined using Bland–Altman procedures. All tests were 2-tailed, and P value <0.05 was considered statistically significant.

Results

Table with details on subject characteristics is provided in the online-only Data Supplement. All patients took a variety of cardiac medication, including aspirin (n=148; 86%), clopidogrel (n=38; 22%), renin–angiotensin system blockers (n=163; 94%), aldosterone inhibitors (n=114; 66%), β-blockers (n=159; 92%), lipid-lowering treatment (n=123; 71%), and anticoagulant therapy (n=42; 24%).

The results of imaging parameters are listed in Table 1. Compared with controls, patients had larger indexed LV volumes and mass and reduced global systolic function by CMR. Compared with controls, patients also had higher PWV (Figure 3A) and abnormal parameters of diastolic function by echocardiography (P<0.01), with no significant difference between the patient groups. Results of reproducibility assessments are provided in the online-only Data Supplement.

Figure 3. Box-and-whisker plots for pulse wave velocity (A) and native T1 (B) values in subgroups. HHD indicates ischemic heart disease; and NICM, nonischemic dilated cardiomyopathy.
Native T1 was raised in both patient groups compared with controls (Figure 3B). Native T1 was significantly higher in NICM group compared with patients with IHD ($P<0.001$), $\lambda$ was higher in patients compared with controls ($P=0.002$), but did not differ between the patient groups ($P=0.51$).

Sixty-two patients with IHD had ischemic-type LGE (68%), whereas 27 (33%) patients with NICM showed nonischemic-type LGE ($P<0.01$), predominantly as midmyocardial septal stria ($n=18$) followed by patchy diffuse intramyocardial LGE ($n=9$). The mean extent of LGE (%) when present was not different between the groups, irrespectively of the LGE type.

In the IHD group, patients with LGE were older and predominantly men (age $P=0.04$; sex $P=0.04$). In the NICM group, patients with LGE were older ($P=0.01$) and had a higher PWV ($P=0.03$). All other parameters did not differ significantly between patients with and without LGE.

**Analysis of Relationships**

There was a positive association between PWV and age in all groups ($r=0.51$; $P<0.001$; Figure 4A; Table 2). This relationship was accelerated in the presence of cardiovascular disease as indicated by steeper slopes in DCM group. Contrasting PWV, increase in native T1 was age-independent in controls ($r=0.21$; $P=0.17$), but associated with age in patient groups (Table 2; Figure 4B). In patients, native T1 ($r=0.53$; $P<0.01$) and $\lambda$ ($r=0.34$; $P<0.01$), extent of LGE by full-width half-maximum ($r=0.36$; $P<0.01$) and $E/e'$ ($r=0.67$; $P<0.001$) were positively associated with PWV. In contrast, controls showed no relationship between native T1 or global LV parameters and PWV.

Controlling for age, sex, body surface area, systolic blood pressure, presence of hypertension, and diabetes mellitus, native T1 showed a stronger relationship with markers of structural and functional LV remodeling and diastolic impairment compared with PWV. Group-specific associations are shown in Table 2 and Figure 5. Dichotomizing for the presence of LGE, the association between PWV and native T1 was not significantly different in the presence of LGE (LGE-negative versus LGE-positive: $r=0.36$; $P<0.01$ versus $r=0.57$; $P<0.001$ for all subjects; $z=-1.33$; $P=0.18$) as well as in the IHD group (IHD: $z=-0.24$; $P=0.81$; NICM: $z=-0.49$; $P=0.62$). Associations between PWV and native T1 showed a trend in the presence of hypertension and diabetes mellitus in IHD group (hypertension—IHD: $z=1.79$; $P=0.08$; NICM: $z=0.20$; $P=0.84$; diabetes mellitus—IHD: $z=0.93$; $P=0.18$; NICM: $z=0.81$; $P=0.42$).

**Table 2. Bivariate Correlations of PWV With Subject Characteristics, LV Geometry and Function, and Tissue Characterization**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ischemic Heart Disease</th>
<th>NICM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivariate correlations, $r_p$</td>
<td>PWV    Native T1_{sax}</td>
<td>PWV Native T1_{sax}</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>1                    0.52*</td>
<td>1                    0.59*</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.49*                0.29*</td>
<td>0.52*                0.33*</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.06                 0.26†</td>
<td>0.29†                0.29†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.37*                0.22†</td>
<td>0.11                 0.12</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.29*                 0.26†</td>
<td>0.10                 0.11</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.23†                 0.12</td>
<td>0.18                 0.20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.31†                 0.21†</td>
<td>0.12                 0.09</td>
</tr>
<tr>
<td>NYHA</td>
<td>0.29†                 0.34*</td>
<td>0.36*                0.41*</td>
</tr>
<tr>
<td>$E/e'$</td>
<td>0.41*                 0.39*</td>
<td>0.45*                0.64*</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>-0.29*               -0.42*</td>
<td>0.21†                0.42*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>0.11                 0.18</td>
<td>0.11                 0.12</td>
</tr>
<tr>
<td>LV EDV index, mL/m²</td>
<td>0.49*                 0.56*</td>
<td>0.42*                0.39*</td>
</tr>
<tr>
<td>LV ESV index, mL/m²</td>
<td>0.39*                 0.29†</td>
<td>0.34*                0.26*</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>0.36*                 0.54*</td>
<td>0.40†                0.52*</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>-0.32*               -0.36*</td>
<td>-0.37*               -0.29†</td>
</tr>
<tr>
<td>Native T1_{sax}</td>
<td>0.29†                 0.69*</td>
<td>0.21                 0.65*</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>0.22†                 0.55†</td>
<td>0.29*                0.49*</td>
</tr>
<tr>
<td>LGE (presence)</td>
<td>0.14                 0.19</td>
<td>0.19                 0.29†</td>
</tr>
<tr>
<td>LGE FWHM</td>
<td>0.29†                 0.49*</td>
<td>0.13                 0.32†</td>
</tr>
</tbody>
</table>

Pearsons ($r$) and Spearman ($\rho$) coefficient, as appropriate for the type of the data. FWHM indicates full-width half-maximum; LGE, late gadolinium enhancement; LV, left ventricular; LV EDV, left ventricular end-diastolic volume; LV ESV, LV end-systolic volume; NICM, nonischemic dilated cardiomyopathy; NYHA, New York Heart Association; and PWV, pulse wave velocity.

*$P<0.01$; †$P<0.05$. 

Figure 4. Association between pulse wave velocity (A) and native T1 (B) with aging with fit-lines for subgroups and 95% confidence intervals for means. DCM indicates dilated cardiomyopathy; IHD, ischemic heart disease; and NICM, nonischemic dilated cardiomyopathy.
In multivariate stepwise linear regression analysis, native T1 was independently associated with $E/e'$ (adjusted $R^2=0.32; F=83.5$), followed by the models that also included PWV (adjusted $R^2=0.42; F=61.6$), LV end-diastolic volume (adjusted $R^2=0.45; F=47.9$), and LGE full-width half-maximum ($R^2=0.48; F=32.8; P<0.001$ for all models). Subgroup analyses for underlying cardiomyopathy, presence of hypertension, or diabetes mellitus revealed no significant differences in above predictive associations. Age was not an independent predictor of native T1 in any group.

**Discussion**

Our findings provide novel mechanistic insights by showing that in health ventricular tissue characteristics as determined by native T1 measurements with CMR are not associated with aging and afterload, as measured by PWV. In contrast, in the presence of disease, native T1 follows an increase in PWV and aging. Furthermore, native T1 shows a stronger relationship with markers of structural and functional LV remodeling and diastolic impairment compared with PWV, suggesting that increase in interstitial fibrosis in LV remodeling is partially afterload-independent.

These observations are important because they expand on the current understanding of the concept of aortoventricular interdependence, which postulates ventricular dependence and injury as a consequence of the increased afterload caused by increased aortic stiffness. Our findings confirm this concept in the presence of disease, as evidenced by relationship between parameters of LV remodeling and aortic stiffness in patients with ischemic and nonischemic DCM; however, this is not evident in healthy volunteers. As such, it is much more likely that the observed abnormalities in aortic stiffness, ventricular myocardium, and myocardial function are a pathophysiological commonality shared by a similar underlying disease process. The accelerated deterioration of vascular and ventricular function with age would thus be a function of the accumulated damage of both systems. Of note, in patients with DCM, the myocardial damage is more pronounced than in patients with IHD, resulting in a higher native T1 at a given PWV. However, the relationship between both parameters remains similar, that is, the same amount of change in PWV is related to the same amount of change of native T1 in both disease entities.

Interestingly, the presence of replacement fibrosis by LGE shows no association to vascular stiffening in DCM in any of the groups, whereas the extent of replacement fibrosis by LGE full-width half-maximum relates to an increase in PWV. Similarly, the extent of replacement fibrosis relates to increased diffuse fibrosis, whereas the presence of fibrosis does not.

**Figure 5.** Associations between native T1 and pulse wave velocity (A) and markers of left ventricular (LV) remodeling, LV mass (B) and LV end-diastolic volume (EDV) (C) and echocardiographic parameter of diastolic impairment (D) with fit-lines for subgroups. DCM indicates dilated cardiomyopathy; IHD, ischemic heart disease; and NICM, nonischemic dilated cardiomyopathy.
This finding suggests that the pure presence of replacement fibrosis may be a more random and sporadic finding, whereas the extent is more directly related to the overall disease burden and accumulated myocardial damage.

Increased central arterial stiffness is the hallmark of age-related vascular remodeling. We demonstrate that this process is accelerated in the presence of cardiovascular disease, such as in DCM, compared with controls, as shown by the steeper slope of relationship between aortic stiffness and age. Results of our study concur with previous knowledge on the associations between aortic PWV and age in previous reports (current study in overall cohort; \( r=0.51; \) \( P<0.001 \) versus Rogers et al\(^{24} \) \( r=0.57 \) versus Vaitkevicius et al\(^{13} \) \( r=0.55 \)). A previous study determined that the best markers of subclinical large artery stiffening were ascending aortic distensibility in younger and proximal PWV in older individuals,\(^{32} \) corroborating our choice for PWV as the better measure of vascular aging in the current population.

We demonstrate that increase in native T1 is independent of aging: controls show no relationship between age and native T1. This result concords with our own findings in a larger and multicenter cohort of healthy subjects,\(^{33} \) as well accords with the subanalysis in subjects with low prevalence of cardiovascular risk factors in Multiethnic Study of Atherosclerosis (MESA) study (albeit reporting on extracellular volume fraction).\(^{34} \) Piechnik et al\(^{15} \) showed a mild inverse relationship between native T1 and age. Contrary to controls, native T1 increases with age in the presence of disease, suggesting a cumulative effect of disease process with time. Again, this finding is concordant with our own previous results in DCM\(^{22} \) and those of others.\(^{35} \) This finding may be explained by composite information reflected in native T1, which relates to the components of intra- and extracellular space, as well as the water content in addition to the myocardial fibrosis. In-depth characterization of extracellular matrix in health and disease and cross-correlation with the imaging is required to separate these signals by the tissue influences.\(^{37} \)

Limitations

This is a hypothesis-generating proof-of-concept study and a few limitations apply. T1 mapping in a midventricular short axis slice is based on the assumption that it is representative of diffuse interstitial involvement of the whole myocardium. Because both potential mechanisms of myocardial damage (effects of vascular afterload because of increased aortic stiffness or primary myocardial remodeling) likely affect the myocardium globally, the effect of sampling in a single slice compared with complete myocardial coverage is likely to be negligible. Because we intended to separately inform on the interstitial and replacement fibrosis, areas of visualized LGE within the corresponding midventricular slice (see the online-only Data Supplement for details) were excluded from the T1 mapping regions of interest.\(^{29} \) Because stress perfusion testing has only been performed in symptomatic patients, a small number of patients with silent inducible ischemia may have not been included. Whereas it is recognized that gadolinium partition coefficients reflect extracellular space with higher fidelity compared with native T1, they are also influenced by the variability of T1 measurements of native and postcontrast blood T1,\(^{28} \) which can explain the reduced ability of \( \lambda \) to detect the separation between disease groups, as well as the weaker associations.

Perspectives

We demonstrate that in patients with DCM increase in PWV is primarily associated with age, and this process is accelerated in the presence of cardiovascular disease. On the contrary, increase in markers of interstitial myocardial fibrosis by native T1 is associated with the presence of disease and paralleled by structural and functional markers of LV remodeling and diastolic impairment. PWV is associated with markers of diffuse interstitial myocardial fibrosis in the presence of disease, but not health. This association has a similar course, but is stronger in NICM compared with IHD, suggesting a common disease pathway, which is more noxious in NICM.

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Disclosures

None.

References

We provide a novel concept by showing that increase in pulse wave velocity relates to myocardial remodeling via accumulation of myocardial fibrosis in the presence of cardiovascular disease, but not health. We also show that this relationship is potentiated in the presence of nonischemic heart disease.

We demonstrate that increase in pulse wave velocity is primarily related to aging and this process is accelerated in the presence of cardiovascular disease. On the contrary, increase in markers of interstitial myocardial fibrosis by native T1 is associated with age in the presence of disease and paralleled by markers of structural and functional markers of left ventricular remodeling and diastolic impairment. Pulse wave velocity is associated with markers of diffuse interstitial myocardial fibrosis in the presence of disease, but not health. This association has a similar course, but is stronger in nonischemic dilated cardiomyopathies compared with ischemic heart disease, suggesting a common disease pathway, which is more noxious in nonischemic dilated cardiomyopathy.

**What Is Relevant?**

- Means of noninvasive phenotyping by cardiovascular magnetic resonance provide an imaging biosignature, which can serve to determine whether the effects of antiremodeling medications would alter this relationship and reduce the interrelated pathophysiology.
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Supplementary material

Full title: Aortic stiffness and interstitial myocardial fibrosis by native T1 are independently associated with left ventricular remodeling in patients with dilated cardiomyopathy
Short title: Aortic stiffness and myocardial fibrosis in DCM
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Methods
MRI sequence imaging parameters
1. Cine imaging
All cine-images were acquired using balanced steady-state free precession in combination with parallel imaging (SENsitivity Encoding, factor 2) and retrospective gating during a gentle expiratory breath-hold (TE/TR/flip-angle: 1.7msec/3.4msec/60°, acquired spatial resolution 1.8x1.8x8 mm).

2. LGE imaging
LGE imaging was performed using gapless whole heart coverage of short axis slices ~20 minutes after administration of 0.2 mmol/kg body weight gadobutrol gadobutrol using a mid-diastolic inversion prepared 2-dimensional gradient echo sequence (TE/TR/flip-angle 2.0 msec/3.4 msec/25°, acquired voxel size 1.4x1.4x8mm) with an individually adapted prepulse delay to achieve optimally nulled myocardium.

3. T1 mapping
Balanced steady state free precession single breath-hold modified Look-Locker Imaging (MOLLI) was used for T1 mapping and performed in a single midventricular short axis slice at mid-diastole, prior to contrast administration and to scar imaging, respectively (TE/TR/flip-angle: 1.64msec/3.3msec/50°, acquired voxel size 1.8 x 1.8 x 8 mm, phase encoding steps n=166, 11 images corresponding to different inversion times (3+3+5 MOLLI scheme), adiabatic prepulse to achieve complete inversion.

4. PWV measurements
Central aortic PWV was employed as a measure of aortic stiffness and obtained with an in-plane sagittal oblique acquisition of the ascending and descending aorta and aortic arch, using a retrospectively gated free-breathing phase-contrast gradient echo pulse sequence and signal averaging (Figure 2) [24-26]. Imaging parameters included TR/TE/flip-angle: 3.7msec/2.2msec/15°; acquired spatial resolution 2.3 mm x 2.3 mm x 10 mm; velocity encoding 200 cm/s with 120 acquired phases per cardiac cycle.
**Results**

**Supplemental table S1.** Subject characteristics. Student T test, one-way ANOVA with Bonferroni post-hoc tests or Kruskal-Wallis * for the differences from controls; † for the differences between patient groups; p<0.05 is considered statistically significant.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=47)</th>
<th>IHD (n=91)</th>
<th>NICM (n=82)</th>
<th>Sig. (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51±15</td>
<td>56±13</td>
<td>52±16</td>
<td>0.11</td>
</tr>
<tr>
<td>Gender (male, n)</td>
<td>24 (52)</td>
<td>51 (56)</td>
<td>43 (53)</td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25±5</td>
<td>27±5</td>
<td>27±5</td>
<td>0.36</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>66±11</td>
<td>71±12</td>
<td>70±13</td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120±10</td>
<td>139±21*</td>
<td>128±19†</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76±5</td>
<td>78±10</td>
<td>78±8</td>
<td>0.56</td>
</tr>
<tr>
<td>NYHA class ≥2 (n, %)</td>
<td>0 (0)</td>
<td>77 (87)*</td>
<td>55 (68)* †</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NYHA class ≥3 (n, %)</td>
<td>0 (0)</td>
<td>14 (13)*</td>
<td>26 (32)* †</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension (n,%)</td>
<td>0 (0)</td>
<td>77 (87)*</td>
<td>32 (42)* †</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>7 (15)</td>
<td>46 (50)*</td>
<td>26 (32)*</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia on treatment (n, %)</td>
<td>0 (0)</td>
<td>66 (72)*</td>
<td>23 (27)* †</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>0 (0)</td>
<td>57 (63)*</td>
<td>25 (31)*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Reproducibility and variability of measurements
T1 mapping showed excellent intra-observer (r=0.98, p < 0.01) and inter-observer (r=0.96, p < 0.01) agreement for all subject groups. In comparison to native myocardial T1 values, λ showed consistently higher intra-observer coefficient of variation (CoV, native T1: 1.0%; λ: 6.6%) and inter-observer coefficient of variation (native T1: 1.8%; λ: 7.7%) of for all subject groups. Native myocardial T1 and λ values produced a lower CoV for NICM patients in comparison to IHD for inter-observer variability (NICM: native T1: 0.6%; λ: 2.6%; IHD: native T1: 1.0%; λ: 3.1%) as well as for inter-observer variability (NICM: native T1: 1.4%; λ: 3.9%; IHD: native T1 2.4%; λ: 24.1%). PWV showed high intra-observer (r=0.89, p < 0.01) and inter-observer (r=0.78, p < 0.01) agreement for all subject groups with the lowest CoV in the control group, followed by DCM and IHD patients, (controls 3.1%, DCM, 4.8%, IHD 6.1%).