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## Association Between Extracellular Matrix Expansion Quantified by Cardiovascular Magnetic Resonance and Short-Term Mortality

Timothy C. Wong, MD; Kayla Piehler, BS; Christopher G. Meier, BS; Stephen M. Testa, BS; Amanda M. Klock, BS; Ali A. Aneizi; Jonathan Shakesprere; Peter Kellman, PhD; Sanjeev G. Shroff, PhD; David S. Schwartzman, MD; Suresh R. Mulukutla, MD; Marc A. Simon, MD, MS; Erik B. Schelbert, MD, MS

**Background**—Extracellular matrix expansion may be a fundamental feature of adverse myocardial remodeling, it appears to be treatable, and its measurement may improve risk stratification. Yet, the relationship between mortality and extracellular matrix is not clear because of difficulties with its measurement. To assess its relationship with outcomes, we used novel, validated cardiovascular magnetic resonance techniques to quantify the full spectrum of extracellular matrix expansion not readily detectable by conventional cardiovascular magnetic resonance.

**Methods and Results**—We recruited 793 consecutive patients at the time of cardiovascular magnetic resonance without amyloidosis or hypertrophic cardiomyopathy as well as 9 healthy volunteers (ages 20–50 years). We measured the extracellular volume fraction (ECV) to quantify the extracellular matrix expansion in myocardium without myocardial infarction. ECV uses gadolinium contrast as an extracellular space marker based on T1 measures of blood and myocardium pre- and post-gadolinium contrast and hematocrit measurement. In volunteers, ECV ranged from 21.7% to 26.2%, but in patients it ranged from 21.0% to 45.8%, indicating considerable burden. There were 39 deaths over a median follow-up of 0.8 years (interquartile range 0.5–1.2 years), and 43 individuals who experienced the composite end point of death/cardiac transplant/left ventricular assist device implantation. In Cox regression models, ECV related to all-cause mortality and the composite end point (hazard ratio, 1.55; 95% confidence interval, 1.27–1.88 and hazard ratio, 1.48; 95% confidence interval, 1.23–1.78, respectively, for every 3% increase in ECV), adjusting for age, left ventricular ejection fraction, and myocardial infarction size.

**Conclusions**—ECV measures of extracellular matrix expansion may predict mortality as well as other composite end points (death/cardiac transplant/left ventricular assist device implantation). (*Circulation*. 2012;126:1206-1216.)

**Key Words:** collagen ■ magnetic resonance imaging ■ mortality ■ myocardial fibrosis

The relationship between mortality and extracellular matrix (ECM) expansion is not well established. ECM expansion appears to be a fundamental feature of adverse myocardial remodeling, which can occur diffusely throughout the myocardium.<sup>1,2</sup> Although ECM expansion may be common in human heart disease,<sup>1–7</sup> the scarcity of human ECM data ante mortem renders the association with subsequent mortality unclear. Conventional imaging techniques cannot robustly quantify the full spectrum of ECM expansion. ECM expansion often may not be evident on late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR)<sup>8</sup> or other modalities. Several studies suggest that ECM expansion, in part from a disproportionate accumulation of collagen,<sup>1,2</sup> alters mechanical, electric, and

vasomotor function,<sup>1,2,6,7,9–13</sup> so ECM expansion may represent a key intermediate phenotype that precedes cardiac morbidity and mortality.<sup>14,15</sup> Further data are needed to establish an association with mortality and assess its role in risk stratification. Because ECM expansion in humans appears to be treatable and represents a potential therapeutic target,<sup>6,7,16,17</sup> quantifying ECM expansion may ultimately provide a foundation to improve care through targeted treatment.

**Editorial see p 1179**  
**Clinical Perspective on p 1216**

Novel CMR techniques using gadolinium (Gd) contrast can detect and quantify the full spectrum of ECM expansion

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noninvasively, regardless of whether it is apparent by LGE CMR. Flett et al<sup>8</sup> validated a robust and fully quantitative CMR measure of the ECM expansion, the extracellular volume fraction (ECV) that correlates highly with the collagen volume fraction in human myocardium ( $R^2=0.8$ ). Collagen appears to be an important element of ECM expansion.<sup>1,2</sup> Furthermore, LGE microscopy data ex vivo at 7 Tesla reveal that Gd tracks collagen strands with high fidelity at the cellular level.<sup>18</sup> The ECV technique used in this study to quantify ECM expansion exploits the extracellular nature of Gd and measures Gd uptake in the myocardium relative to plasma. ECV is reproducible between CMR scans<sup>19</sup> and sensitive,<sup>8,19</sup> and it can be integrated into CMR workflow easily,<sup>19</sup> suggesting that routine CMR may possess the ability to detect prognostically relevant ECM expansion.

The specific aim of our study was to examine the association between mortality and ECV in myocardium without myocardial infarction (MI) in routine clinical CMR practice. We hypothesized that in a large consecutive series of patients, ECV would predict (1) mortality, or (2) a combined end point of mortality/cardiac transplant/ventricular assist implantation in Cox regression models, even after adjustment for other key variables. Such data may advance significantly our understanding of ECM expansion.

## Methods

### Patient Population

After approval from the Institutional Review Board, we recruited 840 consecutive adult patients referred for clinical CMR who provided informed consent before CMR scanning. This cohort was formed at its inception specifically to examine whether novel measures of ECM expansion collected during the baseline CMR scan could incrementally improve prediction of subsequent patient outcomes such as mortality. Inclusion criteria were the provision of informed consent and the ability to undergo a complete contrast-enhanced CMR scan, which required a glomerular filtration rate  $\geq 30$  mL/min/1.7m<sup>2</sup> and no other contraindications to CMR (eg, implanted devices). Because other factors besides the accumulation of excess collagen can expand the ECM, we attempted to limit the cohort to those with ECM expansion and outcomes that may be attributable to ostensible myocardial fibrosis. Thus, exclusion criteria were as follows: (1) known or suspected cardiac amyloidosis (n=12), a unique disorder that markedly expands the interstitium independent of myocardial fibrosis (unpublished data), and (2) known or suspected hypertrophic cardiomyopathy (by known genotype or phenotype) and its phenocopies (n=35), a distinct genetic disorder with intrinsic clinical characteristics where outcome may be affected by factors beyond acquired myocardial fibrosis. We could not identify and exclude individuals with phenotype-negative HCM whose genotype was not known. None in our cohort had known Wegener's granulomatosis, Fabry's disease, Danon's disease, or Friedreich's ataxia; 18 individuals carried a diagnosis of sarcoidosis. To maximize generalizability, we chose not to exclude those with MI because MI size can vary greatly and because we measured ECV specifically in myocardium without MI. ECM expansion can occur in myocardium remote from the infarction and is an important feature of ischemic cardiomyopathy.<sup>3</sup>

The final cohort used for analysis thus included 793 patients. Comorbidity data were determined according to the medical record. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Pittsburgh.<sup>20</sup> Vital status was ascertained by Social Security Death Index queries and medical record review. To identify individuals who received cardiac transplant, we cross referenced our database with the University of Pittsburgh Medical Center Cardiothoracic Transplantation Program's Transplant Patient Management

System, which collects data for all transplant patients and is IRB approved.

### CMR Scans

#### Cine CMR

All patients received clinical CMR scans by dedicated CMR technologists with a 1.5-Tesla Siemens Magnetom Espree (Siemens Medical Solutions, Erlangen, Germany) and a 32-channel phased array cardiovascular coil. The examination included standard breath held segmented cine imaging with steady state free precession.<sup>21</sup> Left ventricular dimensions, myocardial mass (indexed to body surface area), left ventricular volume indices, and ejection fraction (EF) were measured without geometric assumptions from short axis stacks of end diastolic and end systolic cine frames.<sup>21</sup>

#### Late Gadolinium Enhancement

LGE imaging<sup>21</sup> was performed at least 10 minutes after a 0.2 mmol/kg intravenous gadoteridol bolus (Prohance, Bracco Diagnostics, Princeton, NJ). To optimize LGE, we used a phase-sensitive inversion recovery segmented gradient echo pulse sequence to increase signal to noise ratios, correct for surface coil intensity variation, and render signal intensity proportional to T1 recovery.<sup>22</sup> When patients could not breath hold, or in the presence of arrhythmia, single-shot, steady-state free precession motion-corrected, averaged phase-sensitive inversion recovery images were acquired.<sup>23</sup> MI size was measured blinded to clinical data as described previously.<sup>24</sup>

### T1 Measurement

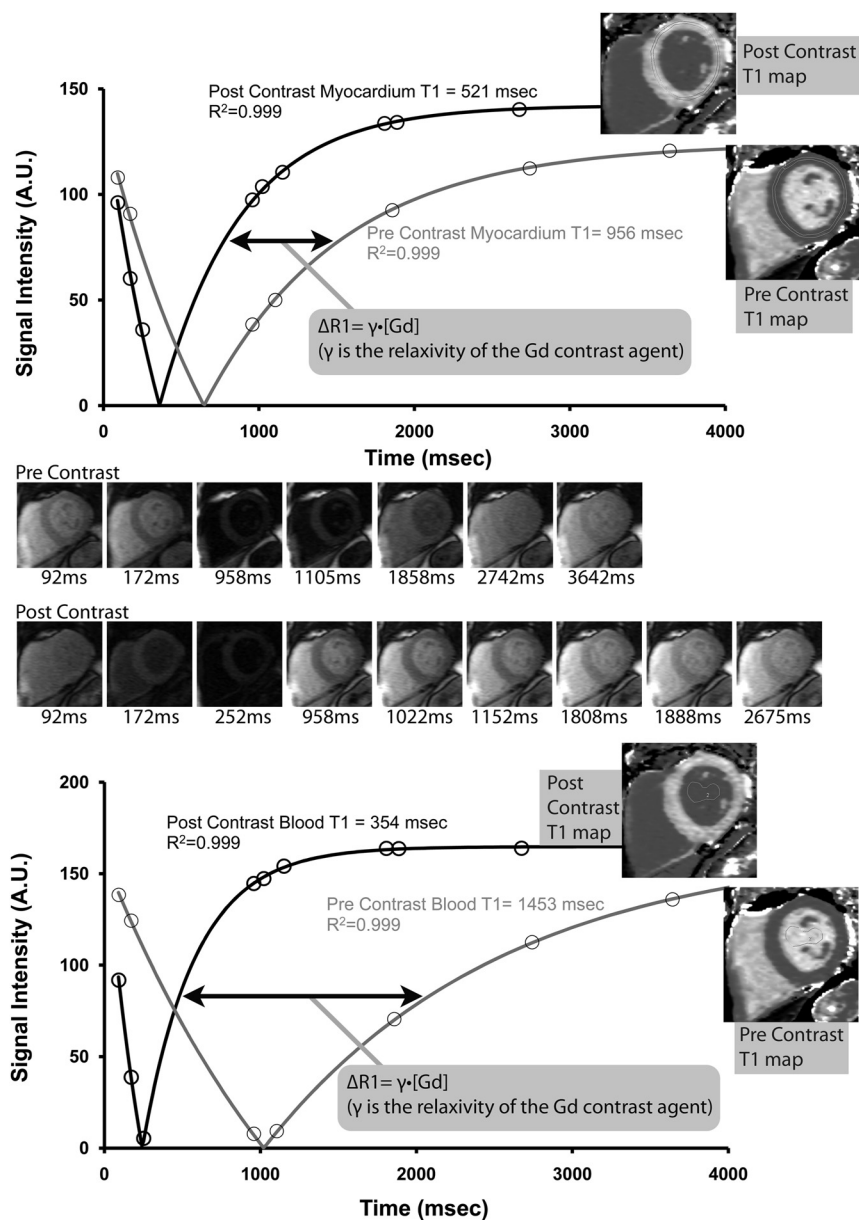
ECV measures depend on T1 measurement before and after Gd contrast. We used methods described previously that yield highly reproducible ECV measures in noninfarcted myocardium 12 to 50 minutes after a gadolinium bolus with minimal variation related to heart rate.<sup>19,25</sup> We validated T1 measures using an ECG-gated single-shot modified Look Locker inversion recovery (MOLLI) sequence against CuSO<sub>4</sub> phantoms with physiological T1 and T2 values for myocardium and blood pre- and postcontrast described previously.<sup>19</sup> To obtain T1 values from CMR data, we used a 3-parameter model to describe signal intensity (SI) as a function of exponentiated inversion time (TI):  $SI = A - B \cdot e^{(-TI/T1^*)}$ , where  $T1 = T1^* \times ((B/A) - 1)$ .<sup>26</sup> For longer precontrast T1 recovery of myocardium and blood ( $\approx 950$  and  $\approx 1500$  ms, respectively), we used 2 nonselective adiabatic inversion pulses with a 5- and 2-sampling scheme (5+2=7 images total) with 3 additional dummy heart beats separating inversion pulses. For postcontrast T1 recovery that demonstrates faster relaxation rates (300–550 ms), we used 3 inversion pulses with a 4-, 3-, and 2-sampling scheme (4+3+2=9 images total), with 1 additional dummy heart beat separating inversion pulses. Examples are shown in Figures 1 and 2.

T1 values were mostly obtained from regions of interest from motion-corrected T1 maps<sup>27</sup> (Figures 1 and 2). The sampling scheme for T1 mapping differs slightly from our previous work using a 5+1 and 4+2+1 sampling scheme in that an additional image is acquired for the inversion pulses after the initial inversion pulse. We have found that the additional data points minimize the noise associated with pixelwise curve fitting (ie, regions of interest for pixelwise curve fitting are by definition small and therefore have a smaller signal-to-noise ratio). Phantom experiments and repeated measures on patients indicated that T1 measures are nearly identical with either technique, but T1 maps speed the process of T1 measurement from which the ECV measures are derived. When the maps exhibited artifact (eg, from poor coregistration of images), we fit the T1 curves manually as shown in Figures 1 and 2, where least square estimates of model parameters were obtained using the Levenberg-Marquardt algorithm in Matlab (The MathWorks, Inc., Natick, Massachusetts).<sup>19</sup>

### ECV Measures

We quantified ECV with the formula used by other recent publications<sup>8,25,28,29</sup> as shown in Figure 3:

$$\text{Extracellular Volume Fraction} = \lambda \times (1 - \text{hematocrit})$$



**Figure 1.** Myocardial and blood pool T1 relaxation curves from a surviving individual who had a normal ECV. Signal intensity for myocardium and blood pool in the thumbnail images are plotted against inversion time, and T1 values are derived from a 3-parameter fit. The accumulation of Gd contrast is reflected by the (nonlinear) shift of T1 curves (ie,  $\Delta R1$ ; arrow). T1 data can be measured from regions of interest taken from individual thumbnail images or from a T1 map (inset), where the curve fitting occurs on a pixelwise basis from motion-corrected, registered images<sup>27</sup> (see text for details). With a hematocrit of 45.2%, the ECV was computed at 22.8%. ECV indicates extracellular volume fraction; Gd, gadolinium.

where  $\lambda = [\Delta R1_{\text{myocardium}}] / [\Delta R1_{\text{bloodpool}}]$  pre- and post-Gd (where  $R1 = 1/T1$ ). Regarding nomenclature, note that the extracellular volume fraction (ECV)<sup>25,29</sup> term is synonymous with the myocardial contrast volume of distribution ( $Vd(m)$ )<sup>8</sup> and the myocardial fibrosis index<sup>28</sup> and is a linear transformation of the extravascular extracellular volume fraction ( $Ve$ ).<sup>19,30</sup> Each ECV measurement for a short axis slice location was derived from a single precontrast T1 acquisition and a single postcontrast acquisition occurring after clinical LGE images (usually 20–25 minutes after the contrast bolus). We averaged ECV measures from basal and midventricular short axis slices to yield the final measurement. Apical slices were avoided because of concerns of error related to partial volume averaging.<sup>31</sup> Unlike ECV, which has been shown to be reproducible,<sup>19</sup> isolated postcontrast T1 measures as surrogates for ECV are confounded by the following: (1) variable weight-based Gd doses, (2) kidney function, (3) time elapsed since bolus, (4) myocardial steatosis, and (5) the displacement of Gd by the hematocrit. Hematocrit measures were acquired on the day of scanning (eg, during intravenous line insertion for outpatients or during morning labs for inpatients) specifically to compute ECV.

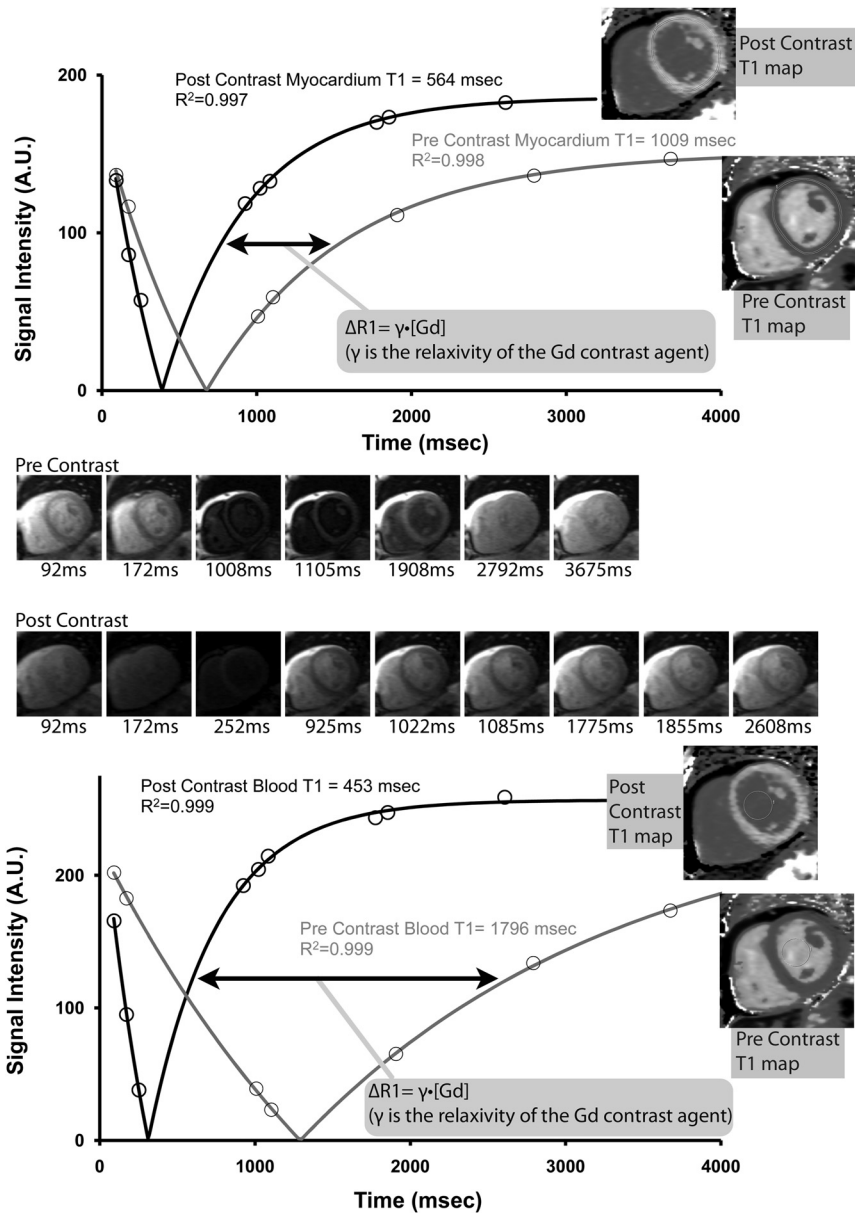
ECV measurement occurred blinded to outcome and comorbidity. The cut-off for an elevated ECV was estimated to be  $>28.5\%$ .

Assuming a normal distribution, these cut-offs represent  $>99$ th percentile in 9 healthy volunteers with an age range of 21–50 years. ECV measures included myocardium potentially containing scar in myocardium without MI on LGE images. Although LGE for measuring presence and extent of MI has excellent histological validation, using LGE to quantify ECM expansion in myocardium without MI at clinical resolution does not and has important limitations. We did not exclude foci of LGE in myocardium free of MI from quantitative ECV measures. We did not want spatial variation of ECM expansion, which renders it potentially detectable on an LGE image<sup>32</sup> to confound its quantification. Spatial heterogeneity of ECM expansion has a continuous spectrum between diffuse and focal, and we simply quantified its extent. We excluded myocardium in the vicinity of infarcted or edematous<sup>33</sup> myocardium from ECV measures and traced the middle third of myocardium to avoid partial volume effects.

### Statistical Analysis

Categorical variables were summarized as percentages, and continuous variables were summarized as median and interquartile range. ECV data were expressed as continuous variables and tertiles. Hazard ratios for ECV measures were expressed according to 3%





**Figure 2.** Myocardial and blood pool T1 relaxation curves from an individual with a high ECV who died unexpectedly. Despite a longer postcontrast myocardial T1 value compared with the individual from Figure 1, with a hematocrit of 25.0%, ECV was computed at 35.5%, which is considerably higher than the individual from Figure 1. The increased ECV is not apparent from the images unless a parametric ECV map is created from fully coregistered images that also incorporate hematocrit data. ECV indicates extracellular volume fraction.

increments reflecting the 95% confidence intervals for repeated measurements ( $\pm 1.4\%$ ).<sup>19</sup> MI size was expressed as tertiles with an additional category of no MI being the referent category. Statistical tests were 2 sided, and  $P < 0.05$  was considered significant. Chi square tests compared associations between categorical variables. Wilcoxon rank sum tests compared associations between continuous variables, because continuous variables exhibited skewed distributions on visual inspection and the Shapiro Wilk test indicated non-normal distributions. Survival analysis for all-cause mortality used the log rank test and Cox regression. The number of events limited the number of predictor variables to permit roughly 10 events per predictor variable.<sup>34</sup> Proportional hazards assumptions were verified by Schoenfeld residuals<sup>35</sup> and nonsignificant time interaction terms for EF and LGE. There was no statistical interaction in Cox regression models between ECV and other variables (age, MI size, or EF). Statistical analyses were performed using SAS 9.2 (Cary, NC).

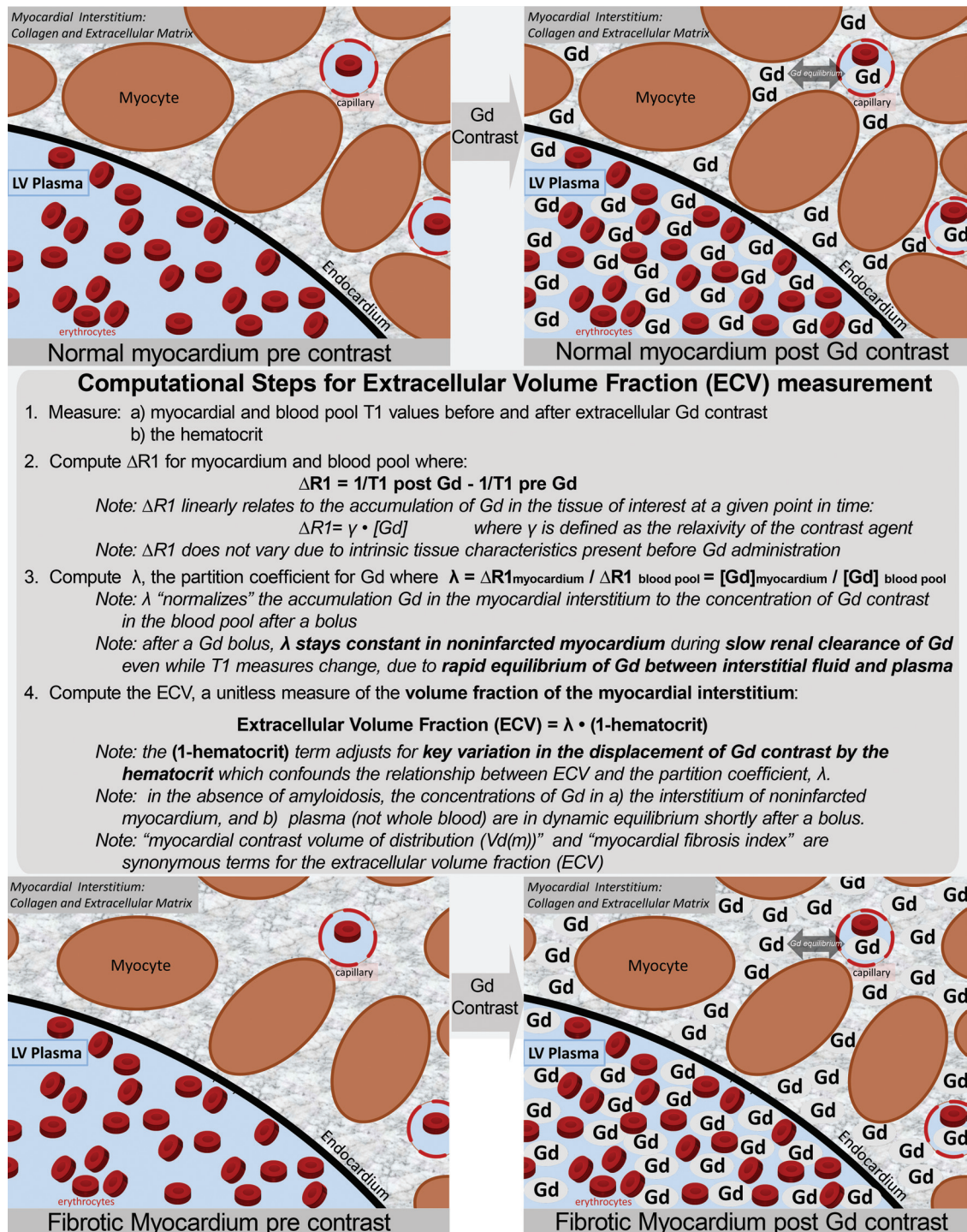
## Results

### Baseline Characteristics

The characteristics of the patient sample as well as the subsets of individuals who died or survived are summarized in Table 1.

Those who died during the follow-up period had higher comorbidity. They were significantly older, had higher prevalence of diabetes mellitus, previous coronary bypass surgery, renal dysfunction, systolic dysfunction, left ventricular enlargement, and myocardial scarring evident in myocardium without MI on LGE images. In addition, they were more likely to be hospitalized at the time of CMR scanning, have an acute MI, and require loop diuretics.

There was a spectrum of cardiac disease manifest by the range of EF (7% to 79%); 33% of the overall sample was hospitalized. There were 138 patients with MI evident on LGE images. ECV measures ranged from 21.0% to 45.8%. Using an approximate 99th percentile cut-off of 28.5% estimated from normal volunteers (range 21.7% to 26.2%), 42% (n=317) of the sample had elevated ECV as shown in Figure 4. There were some differences between the base and midslice ECV measures, which were correlated ( $R = 0.84$ ,  $P < 0.001$ ). Yet, Bland-Altman analysis revealed no evidence



**Figure 3.** Simplified schematic diagram indicating how extracellular matrix expansion increases the ECV with accumulation of Gd contrast in the myocardial extracellular matrix relative to the plasma. Erythrocytes, plasma, myocytes, myocardial capillaries, collagen and extracellular matrix, and molecules of Gd contrast are shown. The top panels are analogous to the individual from Figure 1 with a low ECV, and the lower panels are analogous to the individual from Figure 2 with a high ECV. Computational steps are also defined. ECV indicates extracellular volume fraction; Gd, gadolinium.

of bias (1 slice having more ECM expansion than the other) with mean differences of only  $0.2\% \pm 5.8\%$  (ie, mean difference  $\pm 1.96SD$ ). The variation reflects true variation in ECV as well as intrinsic error in the measurement itself. We have previously reported the 95% confidence interval for repeated ECV measures on different days to be  $\pm 1.4\%$ .<sup>19</sup>

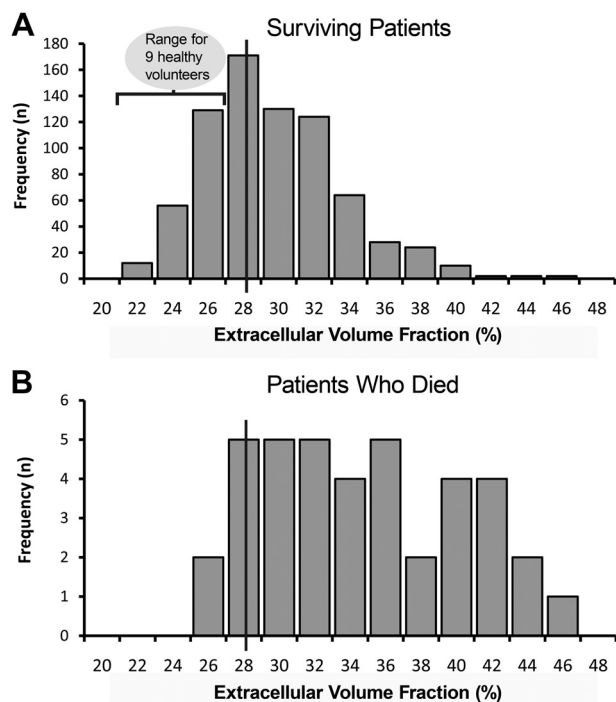
ECV correlated weakly with left ventricular ejection fraction ( $R=0.32$ ,  $P<0.001$ ), but there was no correlation with MI size whether acute or chronic ( $R<0.13$ ,  $P>0.6$  for all). Those with nonischemic scar on LGE had a higher ECV, but there was considerable overlap (27.5%, interquartile range, 23.8% to 31.5%, versus 24.8%, interquartile range, 22.6% to

**Table 1. Patient Characteristics (n=793)**

Variable	Entire Cohort Frequency or Median (Interquartile Range)	Patients Who Survived (n=754)	Patients Who Died (n=39)	P Value
<b>Demographics</b>				
Age, y	54 (41–64)	54 (41–64)	63 (55–72)	<0.001
Female	42%	42%	31%	0.16
White race	88%	88%	92%	0.61
Black race	9%	9%	5%	0.57
<b>General indication for CMR exam</b>				
Known or suspected cardiomyopathy	36%	36%	36%	0.94
Possible coronary disease/viability/ vasodilator stress testing	35%	35%	38%	0.64
Evaluation for arrhythmia substrate	26%	27%	18%	0.23
Mass or thrombus	4%	4%	0%	0.63
Syncope evaluation	4%	3%	5%	0.64
<b>Comorbidity</b>				
Hypertension	46%	45%	46%	0.94
Diabetes	19%	18%	36%	0.004
Dyslipidemia	36%	36%	44%	0.32
Current cigarette smoking	14%	14%	23%	0.10
Body mass index, kg/m <sup>2</sup>	28 (24–33)	28 (24–33)	27 (23–32)	0.44
Atrial fibrillation or flutter	7%	6%	13%	0.17
In-patient status at time of CMR	33%	32%	72%	<0.001
Previous percutaneous intervention	12%	12%	13%	0.80
Previous coronary artery bypass surgery	7%	6%	21%	0.003
Previous stroke	3%	3%	3%	0.63
Acute myocardial infarction	5%	4%	18%	<0.001
<b>Medications</b>				
ACE inhibitors/angiotensin receptor blockers/aldosterone/eplerenone	40%	40%	44%	0.65
Beta-blockers	46%	45%	51%	0.46
Aspirin	42%	42%	49%	0.38
Clopidogrel	11%	10%	21%	0.03
Thiazide diuretics	8%	9%	3%	0.24
Loop diuretics	18%	17%	38%	<0.001
<b>Laboratory and CMR characteristics</b>				
Creatinine, mg/dL*	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.1 (0.8–1.4)	0.002
Glomerular filtration rate, mL/min/1.73m <sup>2</sup> *	83 (68–104)	84 (69–104)	68 (49–103)	0.004
Ejection fraction, %	58 (46–64)	58 (48–64)	31 (22–54)	<0.001
Left ventricular mass index, g/m <sup>2</sup>	57 (47–71)	56 (46–70)	66 (52–80)	0.006
End diastolic volume index, mL/m <sup>2</sup>	81 (67–99)	80 (66–98)	102 (77–135)	<0.001
Scar in myocardium without myocardial infarction evident on late gadolinium enhancement images	22%	21%	54%	0.001
Myocardial infarction evident on LGE images	17%	17%	28%	0.07
Myocardial infarction size among those with MI, % of left ventricular mass	12% (5%–25%)	12% (4%–24%)	11% (7%–37%)	0.47

\*Serum creatinine was available for 638 patients all within 24 hours of scanning. Individuals at low risk for kidney disease (age <60, no hypertension, diabetes, known renal disease or diuretic use) did not have creatinine routinely checked. CMR indicates cardiovascular magnetic resonance; ACE, angiotensin-converting enzyme; and LGE, late gadolinium enhancement.





**Figure 4.** The 39 individuals who died had higher ECV in myocardium without MI. Frequency histograms of ECV in 793 consecutive patients referred for clinical CMR exams are shown according to whether they survived (**A**) or died (**B**). Based on 9 healthy volunteers without evident cardiovascular disease or risk factors whose ECV ranged 21.7% to 26.2%, an ECV >28.5% was estimated to be abnormally elevated (ie, beyond the 99th percentile assuming a normal distribution) represented by the black vertical lines (**A**). Among surviving individuals, a considerable burden of extracellular matrix expansion reflected by ECV appears evident for a significant proportion, suggesting risk for adverse outcomes. ECV indicates extracellular volume fraction; MI, myocardial infarction; and CMR, cardiovascular magnetic resonance.

27.7%). Left ventricular mass index and quantitative ECV measures were weakly correlated ( $R \leq 0.13$ ) with or without inclusion of subjects with MI ( $P < 0.001$ ). Of note, this correlation between ECV and myocardial mass was positive, suggesting that extracellular matrix expansion does not occur solely at the expense of the myocyte compartment.

### Association Between the Extracellular Volume Fraction and Outcomes

Among the 793 individuals there were 39 deaths (11 in those with previous MI, 28 in those without MI) that occurred over a median follow-up of 0.8 years (interquartile range, 0.5–1.2 years). There were 43 individuals who experienced the composite end point of death/cardiac transplant/left ventricular assist device implantation (2 individuals received transplants who subsequently died; 5 surviving individuals received left ventricular assist devices, of which 1 also received a transplant). Only 1 individual with sarcoidosis died. In univariable Cox regression models, ECV related to all-cause mortality and the composite end point (hazard ratios, 1.81; 95% confidence interval, 1.53–2.13; and hazard ratios, 1.77; 95% confidence interval, 1.51–2.07; respectively, for every 3% increase in ECV). Kaplan–Meier curves for the sample stratified by ECV tertiles are shown in Figure 5.

ECV remained associated with adverse outcomes in multivariable models (Table 2 and Figure 6). Nearly identical results were obtained when MI was expressed as either a dichotomous variable or a continuous variable (percent of myocardial mass infarcted). Left ventricular ejection fraction and ECV were similar in terms of the magnitude of their association with outcomes. There was no significant interaction between ECV and (1) ejection fraction measurements or (2) the presence of foci of LGE in myocardium without infarction. ECV remained significantly associated with mortality in multivariable Cox models, even when limiting the analysis to the following: (1) the subgroup with overt nonischemic scar on LGE images, or (2) the subgroup without overt nonischemic scar on LGE images (data not shown). When a stepwise selection process ( $P = 0.05$  criterion to enter and remain in the model) was used to select variables associated with mortality among those with significant differences between survivors and nonsurvivors in Table 1, ECV remained significantly associated with mortality in the model (data not shown).

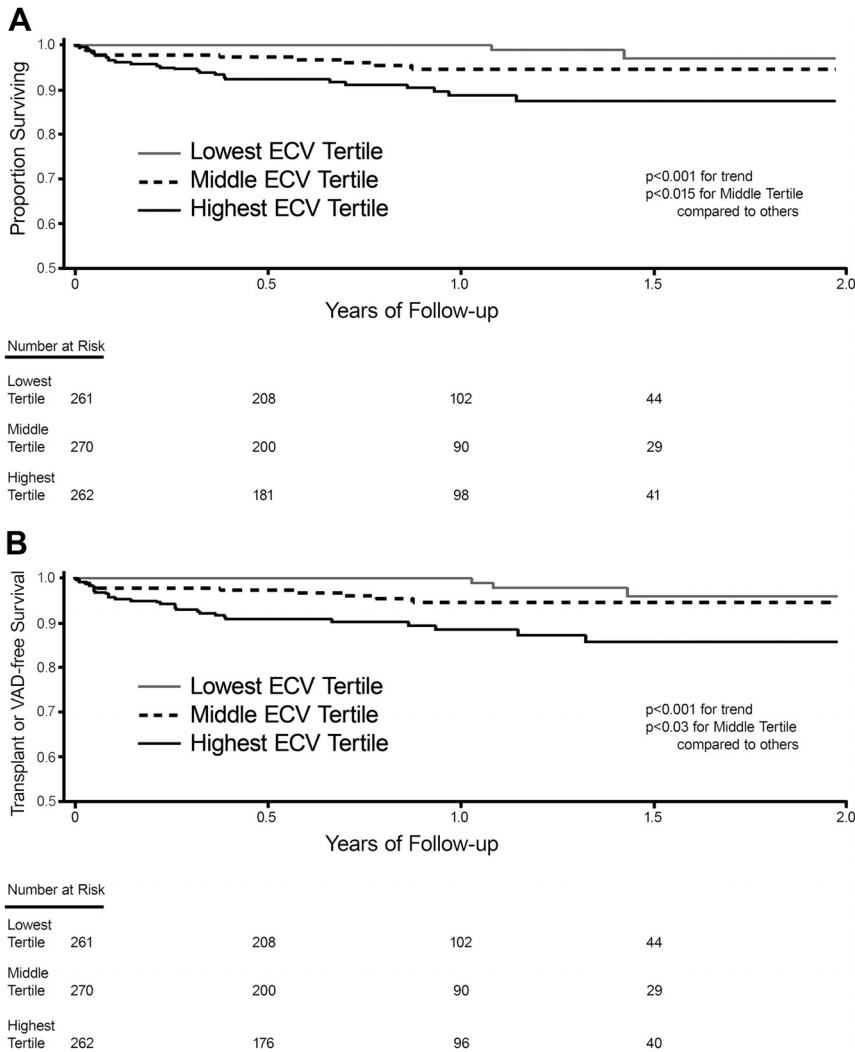
### Discussion

In this study, we used novel CMR techniques to measure ECV and quantify the full spectrum of ECM expansion that may not be evident on conventional CMR scans with LGE. We measured ECV only in myocardium without evident MI by LGE. The principal finding of our study is the significant relationship between quantitative ECV measures and mortality, even after adjusting for key characteristics such as age, EF, and MI size. Similar results were observed when using a combined end point of death, cardiac transplant, or mechanical support with a left ventricular assist device. There was no interaction between ejection fraction and ECV. Thus, novel quantitative metrics of ECM expansion such as ECV appear to have promise as biomarkers for risk stratification.

The incremental prognostic value of ECV is uncertain and will have to be determined in future studies. Yet, advances in CMR now permit the rapid and routine assessment of ECV in the clinical setting as we implemented in our study,<sup>8,19,25,27</sup> which fosters further exploration of ECM expansion. Interestingly, we noted that in our cohort the prognostic ability of fully quantitative ECV measures appeared comparable with the prognostic ability of EF, a traditional and historically robust stratifier of risk that governs many treatment decisions in clinical practice. Although provocative, this finding is unconfirmed, but we hope it will stimulate further investigation of ECM expansion and ECV.

ECV appears to be a promising measure of extracellular matrix expansion but is still under investigation. Nonetheless, the relationship between ECV and mortality appears to support the importance of the extracellular matrix expansion asserted by Weber and Brilla >20 years ago.<sup>1</sup> Although many components constitute the ECM, its expansion beyond baseline may occur in part from myocardial fibrosis.<sup>1,2,8,18</sup> In the context of previous associations of ECM expansion with altered mechanical, electric, and vasomotor function,<sup>1,6,7,9,10</sup> our data may further support the concept that ECM expansion may represent an important intermediate phenotype. Intermediate phenotypes permit an opportunity to modulate or even





**Figure 5.** ECV in myocardium without MI is associated with all-cause mortality (A) and also a composite end point of death, cardiac transplant, or left ventricular assist device (B). When the sample was divided into tertiles based on quantitative ECV measures, those with higher ECV experienced a significantly higher incidence of adverse events. The relationship between ECV and adverse outcomes remained significant after risk adjustment in multivariable models (see text). ECV indicates extracellular volume fraction; MI, myocardial infarction.

reverse disease progression before the onset of full-blown disease. In our study, we speculate that increased ECV may indicate a transition from healthy myocardium to diseased myocardium, which is associated with increased mortality risk. The risk of death appeared to increase with higher degrees of ECV. The lack of statistical interaction between ECV and either EF or extent of MI suggests that this phenomenon may occur across the EF and MI size spectrum. The minimal change in the hazard ratio for ECV with or

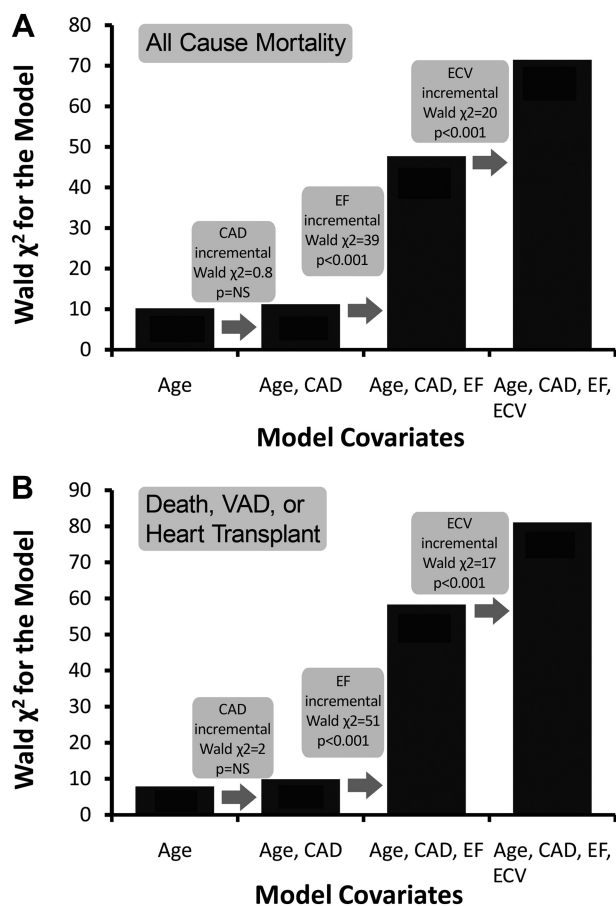
without risk adjustment suggests that the metric may add independent prognostic information beyond that captured by other covariates in the model, but further study is needed to evaluate this claim given the limited risk adjustment in our study.

Supporting the potential importance of ECM expansion cardiac disease when it is attributable to myocardial fibrosis, Thum et al<sup>9</sup> demonstrated in rodents that sole activation of fibroblasts to create myocardial fibrosis yields a dilated

**Table 2. The ECV Was Associated With Outcomes in Multivariable Models**

Variable	Mortality Outcome (n=39)		Death, Cardiac Transplant, or Left Ventricular Assist Device Outcome (n=43)	
	Hazard Ratio (95% Confidence Interval)	Wald $\chi^2$	Hazard Ratio (95% Confidence Interval)	Wald $\chi^2$
ECV (for every 3% increase)	1.55 (1.27–1.88)	18.6	1.48 (1.23–1.78)	16.6
Left ventricular ejection fraction (for every 5% decrease)	1.23 (1.11–1.37)	14.7	1.29 (1.16–1.43)	23.0
Myocardial infarction size tertile	1.13 (0.81–1.57)	0.5	1.15 (0.86–1.55)	0.9
Age (for every 10-y increase)	1.29 (1.02–1.64)	4.4	1.17 (0.94–1.46)	1.9

The  $\chi^2$  statistic measures the strength of association between the predictor variable and the outcome. ECV indicates extracellular volume fraction.



**Figure 6.** To demonstrate the sequence in which information becomes clinically available for risk stratification, the global Wald  $\chi^2$  are shown for separate Cox regression models predicting death (A) or death/VAD/cardiac transplant (B), whereby age, coronary disease (MI or previous revascularization), left ventricular EF, and finally the ECV are each added in succession ( $P<0.01$  for all global Wald  $\chi^2$  for each model). The incremental Wald  $\chi^2$  (type 3 tests) and probability values attributable to the addition of the new variable are also shown in the shaded gray boxes to demonstrate the magnitude of incremental information introduced by each additional variables in the model accounting for the variables already present in the model. EF and ECV each add significant additional prognostic information beyond the variables that preceded them. ECV indicates extracellular volume fraction; MI, myocardial infarction; VAD, left ventricular assist device; and EF, ejection fraction.

cardiomyopathy phenotype and that inhibition of fibroblasts could prevent the cardiomyopathy phenotype. They advanced a paradigm that assigns a primary role to cardiac fibroblast activation in the development of myocardial disease,<sup>9</sup> as opposed to a secondary, reparative phenomenon after apoptosis or necrosis. Although further work is undoubtedly needed to understand the complex interplay between fibroblasts, the extracellular matrix, collagen, and the myocyte compartment, we observe that the positive correlation between ECV and myocardial mass may support their concept and may suggest that extracellular matrix expansion does not simply occur to replace myocyte loss. In our cohort, it is possible that ECM expansion may reflect some degree of myocardial fibrosis based on the validation data from Flett et al,<sup>8</sup> who reported an  $R^2$  of 0.8 for the correlation between ECV and the collagen

volume fraction in humans. Yet, we lack the histological confirmation in our sample needed to support this hypothesis, which remains unproven because it would require invasive biopsies and postmortem assessment. Still, we excluded patients with known or suspected amyloidosis as well as potentially edematous myocardium in the vicinity of infarcted myocardium, which are other explanations for increased ECV.

We speculate that our data may support an expanded paradigm of cardiac dysfunction to include not only myocyte dysfunction (represented by ejection fraction) and myocyte loss (represented by MI), but also expansion of the ECM<sup>3–5</sup> (ie, the environment in which myocytes reside [ECV]). Because ECV remained associated with mortality after adjusting for EF and MI size (as well as patient age), we speculate that the ECM may constitute an important component of cardiac dysfunction and subsequent risk. In the context of previous work associating ECM expansion with electric dysfunction,<sup>11–13</sup> ECM expansion might contribute to vulnerable myocardium previously summarized by Naghavi et al.<sup>36</sup>

A comparison of the spectrum of ECV in our sample with healthy volunteers suggests the possibility that there may be a considerable burden of ECM expansion in our cohort (Figure 4). In support of this observation, there are considerable data indicating that ECM expansion may be a final common pathway in many types of myocardial disease.<sup>3–7,11</sup> Although further work is needed to identify the causes, consequences, and natural history of ECM expansion—particularly the role of myocardial fibrosis in ECM expansion—it may be a marker of disease progression and adverse myocardial remodeling that culminates in increased risk of mortality. It is conceivable that treatment strategies may need to be developed for individuals with ECM expansion because mortality risks appear to increase with the extent of ECM expansion. We hope our findings will stimulate interest in further supporting this premise and pursuing such work.

### Limitations

Our study has limitations. First, the incremental prognostic value of ECV remains uncertain and will have to be determined in future studies, ideally from other cohorts that permit more extensive risk adjustment. Risk adjustment was limited in our study as a result of limited event rates constraining the number of variables in the model. Second, in the patients with known or occult coronary disease, ECV measures may have inadvertently included areas of MI in apparently noninfarcted myocardium. Although we lack histological confirmation, the sensitivity and specificity for LGE patterns to distinguish MI from other nonischemic etiologies has been reported to be >90%.<sup>32</sup> Third, like other publications assessing ECV, we did not quantify the extracellular matrix in all myocardial segments. Nonetheless, we typically measured ECM expansion in 12 of 17 myocardial segments (ie, 71% of the myocardium if there were no segments with MI that were excluded from ECV measures). Despite any imperfections in ECV measurement that would likely obscure relationships with mortality, we still obtained significant results. Fourth, our data come from a referred sample in a single center, not

a population study, with abbreviated follow-up and limited risk adjustment, so our results may not generalize. We are uncertain how referral bias affects our results, which should be replicated by others. Still, our event rates were similar to other large cohorts of CMR patients.<sup>37</sup> ECV cannot otherwise be ascertained clinically, and no cases were specifically referred for ECV measurement. To maximize generalizability of our data, we enrolled large numbers of consecutive patients and minimized exclusions. Although the sample was clinically heterogeneous, ECM expansion is believed to represent a final common pathway of myocardial disease,<sup>1,3–7,11</sup> so we believe it is reasonable to study ECV in a diverse sample. Examining how ECV varies across disease processes with differing disease severity is beyond the scope of our work. Finally, the mechanism of death was not clear in sufficient numbers to permit inference about how ECV may have affected cause of death (eg, heart failure or malignant arrhythmia).

## Conclusions

Quantitative and validated ECV measures of ECM expansion may predict short-term mortality and other adverse events (such as cardiac transplantation or left ventricular assist device implantation) after adjusting for left ventricular EF, age, and MI size. Quantifying ECV may improve risk stratification in patients, but further study is needed to ascertain incremental prognostic value. ECM expansion as measured by ECV appears prevalent in those referred for routine CMR scans. Further work is needed to advance our understanding of the causes, consequences, and treatment of ECM expansion.

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## Disclosures

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### CLINICAL PERSPECTIVE

Extracellular matrix expansion may be ubiquitous in chronically diseased viable myocardium as shown by histopathologic studies in humans and animals. It is associated with mechanical, vasomotor, and electrical dysfunction and is treatable, but the relationship with outcomes has remained poorly understood. Historically, there has not been a robust noninvasive method to quantify the extent of extracellular matrix expansion in myocardium, which is often diffuse and not detectable by conventional late gadolinium enhancement imaging. Thus, the presence and extent of extracellular matrix expansion has mostly been invisible to clinicians. We employed novel cardiovascular magnetic resonance techniques to quantify extracellular matrix expansion by measuring the extracellular volume fraction in myocardium without myocardial infarction in a consecutive cohort of individuals referred for cardiovascular magnetic resonance. These techniques require: i) robust blood pool and myocardial T1 measurement before and after gadolinium contrast, and ii) hematocrit measurement. Extracellular volume fraction measures of the interstitial space can be embedded in clinical protocols easily and correlate highly with the collagen volume fraction in viable myocardium in most settings. In our study, extracellular matrix expansion appeared prevalent, and the extracellular volume fraction predicted both mortality and the composite endpoint of death/cardiac transplant/left ventricular assist device implantation even after adjusting for age, ejection fraction and myocardial infarction size. The apparent statistical independence of the extracellular volume fraction measure suggests a potential to improve risk stratification in patients. Further work is needed to advance our understanding of the causes, consequences, and treatment of extracellular matrix expansion and myocardial fibrosis.