JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2015

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2014.09.020

Increased Extracellular Volume and Altered Mechanics Are Associated With LVH in Hypertensive Heart Disease, Not Hypertension Alone

Sujith Kuruvilla, MD,* Rajesh Janardhanan, MD,* Patrick Antkowiak, PhD,† Ellen C. Keeley, MD,* Nebiyu Adenaw, BA,† Jeremy Brooks, BS,† Frederick H. Epstein, PhD,†‡ Christopher M. Kramer, MD,*† Michael Salerno, MD, PhD*†‡

ABSTRACT

OBJECTIVES The goal of this study was to assess the relationship among extracellular volume (ECV), native T1, and systolic strain in hypertensive patients with left ventricular hypertrophy (HTN LVH), hypertensive patients without LVH (HTN non-LVH), and normotensive controls.

BACKGROUND Diffuse myocardial fibrosis in HTN LVH patients, as reflected by increased ECV and native T1, may be an underlying mechanism contributing to increased cardiovascular risk compared with HTN non-LVH subjects and controls. Furthermore, increased diffuse fibrosis in HTN LVH subjects may be associated with reduced peak systolic and early diastolic strain rate compared with the other 2 groups.

METHODS T1 mapping was performed in 20 HTN LVH (mean age, 55 ± 11 years), 23 HTN non-LVH (mean age, 61 ± 12 years), and 22 control subjects (mean age, 54 ± 7 years) on a Siemens 1.5-T Avanto (Siemens Healthcare, Erlangen Germany) using a previously validated modified look-locker inversion-recovery pulse sequence. T1 was measured pre-contrast and 10, 15, and 20 min after injection of 0.15 mmol/kg gadopentetate dimeglumine, and the mean ECV and native T1 were determined for each subject. Measurement of circumferential strain parameters were performed using cine displacement encoding with stimulated echoes.

RESULTS HTN LVH subjects had higher native T1 compared with controls ($p < 0.05$). HTN LVH subjects had higher ECV compared with HTN non-LVH subjects and controls ($p < 0.05$). Peak systolic circumferential strain and early diastolic strain rates were reduced in HTN LVH subjects compared with HTN non-LVH subjects and controls ($p < 0.05$). Increased levels of ECV and native T1 were associated with reduced peak systolic and early diastolic circumferential strain rate across all subjects.

CONCLUSIONS HTN LVH patients had higher ECV, longer native T1 and associated reduction in peak systolic circumferential strain, and early diastolic strain rate compared with HTN non-LVH and control subjects. Measurement of ECV and native T1 provide a noninvasive assessment of diffuse fibrosis in hypertensive heart disease. (J Am Coll Cardiol Img 2015;■:■-■) © 2015 by the American College of Cardiology Foundation.

From the *Department of Medicine (Cardiology), Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, Virginia; †Department of Radiology, Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, Virginia; and the ‡Department of Biomedical Engineering, Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, Virginia. Dr. Kuruvilla has received grant support from National Institutes of Health (NIH) T32 5T32EB003841. Dr. Salerno has received grant support from NIH K23 HL112910. Dr. Keeley has received grant support from NIH HL97074 and American Heart Association G13IRG14560018. Drs. Salerno and Kramer have received research support from Siemens Healthcare. Dr. Kramer is a consultant with Bristol-Myers Squibb. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Nathaniel Reichek, MD, FACC, FAHA, served as Guest Editor for this paper.

Manuscript received July 31, 2014; revised manuscript received September 24, 2014, accepted September 26, 2014.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ECV = extracellular volume

EF = ejection fraction

FOV = field of view

Hct = hematocrit

HTN = hypertension

LGE = late gadolinium enhancement

LV = left ventricle

LVH = left ventricular hypertrophy

LVMI = left ventricular mass index

MOLLI = modified look-locker inversion recovery

TE = echo time

TR = repetition time

Hypertension (HTN) is a common cause of morbidity and mortality in the United States affecting 1 in 3 adults (1). Patients with long-standing or poorly controlled HTN are at increased risk for developing left ventricular hypertrophy (LVH) and diastolic dysfunction (2). LVH is an independent risk factor for cardiovascular morbidity and mortality in hypertensive patients (3,4). Diffuse fibrosis has been detected in subjects with HTN with LVH in both biopsy (5) and autopsy studies (6) and has been linked to the development of LVH and diastolic dysfunction (7). Concentric LVH portends higher cardiovascular morbidity and mortality compared with other hypertrophy subtypes (8). The presence of diffuse fibrosis may confer increased cardiovascular risk in HTN LVH patients.

Diffuse myocardial fibrosis in hypertensive LVH is not detected by conventional late gadolinium enhanced (LGE) cardiac magnetic resonance (CMR). T1 mapping is a novel CMR approach that is able to detect diffuse fibrosis in diseases such as aortic stenosis and hypertrophic cardiomyopathy as validated against myocardial biopsy (9). By measuring the T1 relaxation times of the blood and myocardium both pre- and post-contrast, one can determine the partition coefficient (λ) of gadolinium and, subsequently, the extracellular volume (ECV).

We hypothesized that HTN LVH patients would show diffuse myocardial fibrosis as measured by T1 mapping and ECV compared with HTN non-LVH and normotensive controls. We also postulated that subjects with HTN LVH would have greater fibrosis and reduced systolic strain, and early diastolic strain rate compared with the other 2 groups.

METHODS

Twenty subjects with HTN LVH (mean age, 55 ± 11 years), 23 subjects with HTN non-LVH (mean age, 61 ± 12 years), and 22 normotensive controls (mean age, 54 ± 7 years) were enrolled between November 2010 and October 2013 under an institutional review board-approved protocol. All subjects signed informed consent. Patients with a history of HTN and evidence of LVH by any imaging modality were considered for this study. Patients with any other causes of LVH, known coronary disease, significant valvular disease, renal impairment with glomerular filtration rate <45 ml/min/1.73 m^2 or reduced systolic function (ejection fraction [EF] <45%) were excluded. Subjects with a history of HTN with systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg on at least 2 office readings (10), or taking 1 or more medications for hypertension, were included. Subjects were then classified as having LVH if their left ventricular mass indexed by body surface area (LVMI) as measured by cardiac magnetic resonance imaging was >81 g/m^2 for men or >61 g/m^2 in women as defined by Olivotto et al. (11). Hypertensive subjects not meeting criteria for LVH as defined in the preceding text were included in the HTN non-LVH group. Healthy volunteers who were normotensive and did not have a history of HTN were enrolled in the control arm.

CMR PROTOCOL. CMR was performed on a 1.5-T magnetic resonance scanner (Siemens Avanto, Erlangen, Germany).

Cine Imaging. Left ventricular (LV) mass and function were assessed by steady-state free-precession cine imaging using the following sequence parameters: repetition time (TR) 2.7 ms, echo time (TE) 1.3 ms, flip angle 70°, field of view (FOV) 300 to 350 mm, and in-plane resolution 1.8 × 1.4 mm, TR 40 to 50 ms, slice thickness 8 mm. Images were obtained in short-axis and standard long-axis orientations. Analyses were performed (R.J., S.K.) using Argus software (Siemens Healthcare, Princeton, New Jersey) on a Leonardo workstation (Siemens Healthcare, Erlangen, Germany). End-diastolic and end-systolic endocardial and epicardial cavity areas were planimetered for each short-axis slice. The LV mass, end-diastolic volume, and end-systolic volumes were determined and indexed to body surface area. LV mass was measured from the end-diastolic image frames using the validated Q-Mass (Medis 7.5 version, Medis Medical Imaging, Leiden, the Netherlands) program (12). Papillary muscles were included when measuring LV mass as per recent Society for Cardiovascular Magnetic Resonance guidelines (13).

T1 mapping. T1 mapping was performed using a reduced breath-hold variant of the modified look-locker inversion recovery (MOLLI) technique (14), which was previously validated by our group (15). This protocol yields 8 T1-weighted source images over 11 heartbeats. The starting TI (to the first image readout) was chosen to be 100 ms, with an increment of 80 ms for the subsequent look-locker trains. The pulse sequence parameters included: TE 1.1 ms, TR 2.5 ms, flip angle 35°, FOV 340 × 260 mm, resolution 1.8 × 1.8 mm and slice thickness of 8 mm.

T1 maps (**Figure 1**) were obtained in basal and mid-ventricular short axis slices pre-contrast and at 10, 15, and 20 min after a bolus intravenous injection of 0.15 mmol/kg gadopentetate dimeglumine (Gd-DTPA)

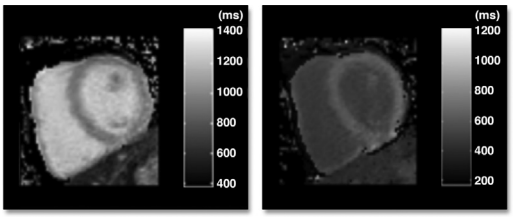

FIGURE 1 Example T1 Maps

T1 maps pre-contrast **(left)** and post-contrast **(right)**. T1 maps are generated from a collection of T1 images obtained at different inversion times during the same phase of the cardiac cycle.

(Magnevist, Bayer Healthcare, Berlin, Germany). Hematocrit (Hct) was measured in all subjects.

Late gadolinium enhancement. LGE images were acquired approximately 10 to 15 min after bolus injection of 0.15 mmol/kg of Gd-DTPA. A phase sensitive inversion recovery sequence was used (TR 7.1 ms, TE 3.4 ms, flip angle 25°, FOV 300 to 340 mm, resolution 1.8 × 1.3, slice thickness 8 mm). LGE images were scored visually by 2 experienced observers (S.K., M.S.).

Strain imaging. A spiral cine displacement encoding with stimulated echoes-pulse sequence was used to quantify circumferential strain and strain rate. Sequence parameters included: TR 17 ms, TE 1.8 ms, flip angle 20°, FOV 350 mm^2, resolution 2.5 mm × 2.5 mm, slice thickness 8 mm, number of spiral interleaves 6, temporal resolution 34 ms (16,17). Images were obtained in basal and mid short-axis locations.

Data analysis. T1 maps were calculated from the MOLLI data using a nonlinear least squares fit of the signal intensity versus TI on a pixel-by-pixel basis, and the endocardial and epicardial borders of the myocardium were manually segmented using a previously validated custom MATLAB script (MathWorks, Natick, Massachusetts) (15). The mean T1 in a region of interest in the ventricular cavity was taken as the blood T1. The partition coefficient (λ) was determined from the slope of a plot of 1/T1 of the myocardium versus 1/T1 of the blood. Data from both the mid and basal slices pre-contrast and at time points 10, 15, and 20 min post-contrast were used for the fitting. The ECV was calculated as $(1 - Hct) \cdot \lambda$.

Peak systolic circumferential strain and early diastolic strain rates were computed offline from cine displacement encoding with stimulated echo images with a custom MATLAB script using previously described methods (18,19).

STATISTICAL ANALYSIS. All continuous variables are expressed as their mean and standard deviation. All statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, New York). Values were compared between groups using 1-way analysis of variance, the Scheffe method was used to control for multiple pairwise corrections. Age and number of blood pressure medications for the 3 groups as shown in Table 1 were reported as median scores with interquartile ranges. Comparisons between groups of non-normally distributed variables were perfomed using the Kruskal-Wallis test. Correlation analysis used the Pearson's correlation coefficient for linear associations, and the Spearman's rank correlation coefficient for monotonic nonlinear associations. A p value <0.05 was considered significant.

RESULTS

Table 1 shows the baseline characteristics of the 3 groups. The groups had similar values for heart rate, LVEF, and Hct. The systolic and diastolic blood pressures were significantly higher in the HTN LVH group than the HTN non-LVH and control subjects. LV mass was higher in the HTN LVH group by study design. Two subjects (both in the HTN non-LVH group) had focal areas of late enhancement: 1 subject had right ventricular insertion site hyperenhancement, and the other had a focal area of midwall enhancement in the distal inferior wall, considered to be nonischemic in origin. These regions were not included on T1 mapping analysis to minimize potential bias from including regions with focal fibrosis. Left ventricular mass/volume ratios for the

TABLE 1 Baseline Characteristics of HTN LVH Subjects, HTN Non-LVH Subjects, and Controls

	Normotensive Controls (n = 22)	Hypertensive Non-LVH (n = 23)	Hypertensive LVH (n = 20)
Sex	15 F; 7 M	13 F; 10 M	14 F; 6 M
Age (yrs)*	54 (48-61)	64 (56-71)	55 (44-66)
Systolic BP (mm Hg)	123 ± 14	135 ± 16*	151 ± 21*†
Diastolic BP (mm Hg)	71 ± 11	77 ± 11	84 ± 16*
Heart rate	73 ± 12	73 ± 14	71 ± 10
Number of HTN medicines	0	2.1 ± 1.1*	3.6 ± 1.2*†
LV mass (g)	92 ± 20	115 ± 31	171 ± 39*†
LVMI (g/m^2)	49 ± 7	55 ± 9	83 ± 14*†
LV mass/volume ratio	0.71 ± 0.19	0.87 ± 0.21	1.30 ± 0.40*†

Values are n, median (interquartile range), mean ± SD. *p < 0.05 vs. controls. †p < 0.05 vs. non-LVH groups.

BP = blood pressure; F = female; HTN = hypertension; LV = left ventricular; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; M = male.

TABLE 2 ECV, Partition Coefficient, and Native T1 Values in HTN LVH Subjects Versus Non-LVH and Controls

	Normotensive Controls (n = 22)	Hypertensive Non-LVH (n = 23)	Hypertensive LVH (n = 20)
Extracellular volume	0.26 ± 0.02	0.27 ± 0.02	0.29 ± 0.03*†
Native T1 (ms)	967.4 ± 35.0	974.0 ± 33.6	996.0 ± 32.5†
Partition coefficient (λ)	0.43 ± 0.03	0.45 ± 0.03	0.48 ± 0.04*†

*p < 0.05 vs. non-LVH groups. †p < 0.05 vs. controls.
ECV = extracellular volume; HTN = hypertensive; LVH = left ventricular hypertrophy.

3 groups were calculated. Left ventricular mass/volume ratios were higher in the HTN LVH groups compared with other 2 groups (Table 1) (Online Appendix).

ECV. ECV was significantly higher in HTN LVH subjects versus controls (0.29 ± 0.03 vs. 0.26 ± 0.02, p < 0.01) and HTN non-LVH subjects (0.29 ± 0.03 vs. 0.27 ± 0.02, p = 0.05) (Table 2; Figure 2). There were no differences in ECV (p = 0.6) between HTN non-LVH and control subjects. Similar findings were seen with partition coefficient (λ) (Table 2) (Online Appendix).

NATIVE T1. The native T1 of the patients with HTN LVH was longer than that of control subjects (996 ± 32 vs. 967 ± 35, p = 0.007) (Table 2). Although the point estimate of native T1 in the HTN non-LVH group was higher than that of controls, this difference was not statistically significant (Table 2). Post-contrast T1 values are provided in the data supplement.

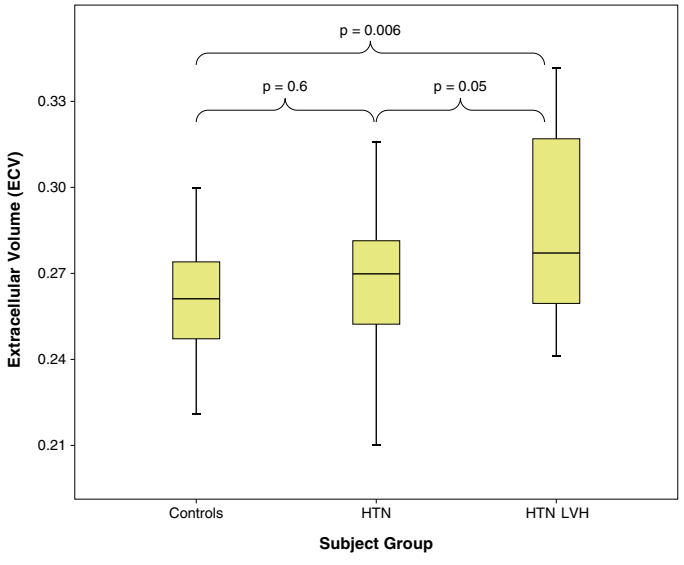

FIGURE 2 ECV of Gadolinium Among the 3 Groups

Box plot showing the distribution of ECV among the 3 study groups. Boxes represent the 25th to 75th percentiles, and horizontal lines within the boxes represent the median values. ECV = extracellular volume; HTN = hypertension; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index.

RELATIONSHIP AMONG ECV, NATIVE T1, AND LVMI. A positive association was noted between LVMI and ECV (Figure 3A) (Spearman rho = 0.26, p = 0.03). However, ECV was not linearly related to an increase in LVMI. HTN non-LVH subjects had similar LVMI and ECV levels to those of controls. HTN LVH subjects had higher LVMI levels as expected and had higher ECV levels. However, subjects with the highest LVMI did not show a proportional increase in ECV. Furthermore, certain HTN LVH subjects with relatively lower LVMI had significantly higher levels of ECV (>0.30). Similarly, a positive association was noted between native T1 levels and LVMI (Figure 3B) (Spearman rho = 0.36, p = 0.03).

ECV, NATIVE T1, CIRCUMFERENTIAL STRAIN, AND STRAIN RATE. Figure 4A shows average circumferential strain-time curves from the 3 groups. Peak circumferential strain at both base and mid-ventricular levels was reduced in HTN LVH subjects compared with both controls and HTN non-LVH subjects (Table 3). ECV correlated with peak circumferential strain (R = 0.26, p = 0.05) (Figure 5A).

Figure 4B shows average circumferential strain rate versus time curves in the 3 groups. The average early diastolic circumferential strain rate (e'_{SR}) was reduced in HTN LVH subjects compared with both controls and HTN non-LVH subjects (0.49 ± 0.26 vs. 0.82 ± 0.16, p < 0.0001 and 0.49 ± 0.26 vs. 0.71 ± 0.18, p = 0.02, respectively) (Table 3). The results were similar for early diastolic circumferential strain rates at both the basal and mid-ventricular levels (Table 3). ECV correlated significantly with average early diastolic circumferential strain rate (R= −0.34, p = 0.01) (Figure 5B). Radial strain measurements were also performed and are presented in the data supplement. Native T1 correlated significantly with peak systolic circumferential strain (R = 0.44, p < 0.0001) (Figure 6A). Native T1 also correlated significantly with e'_{SR} (R= −0.40, p <0.01) (Figure 6B).

LV MASS TO VOLUME RATIO, ECV, AND CIRCUMFERENTIAL STRAIN. Left ventricular mass to volume ratio correlated significantly with ECV (R = 0.337, p = 0.006) and native T1 (R = 0.341, p = 0.006). Circumferential strain and strain rate correlated significantly with LV mass to volume ratio (R = 0.733, p < 0.0001 and R = −0.642, p < 0.0001, respectively).

DISCUSSION

In this study, T1 mapping by CMR showed greater diffuse fibrosis as measured by ECV in subjects with

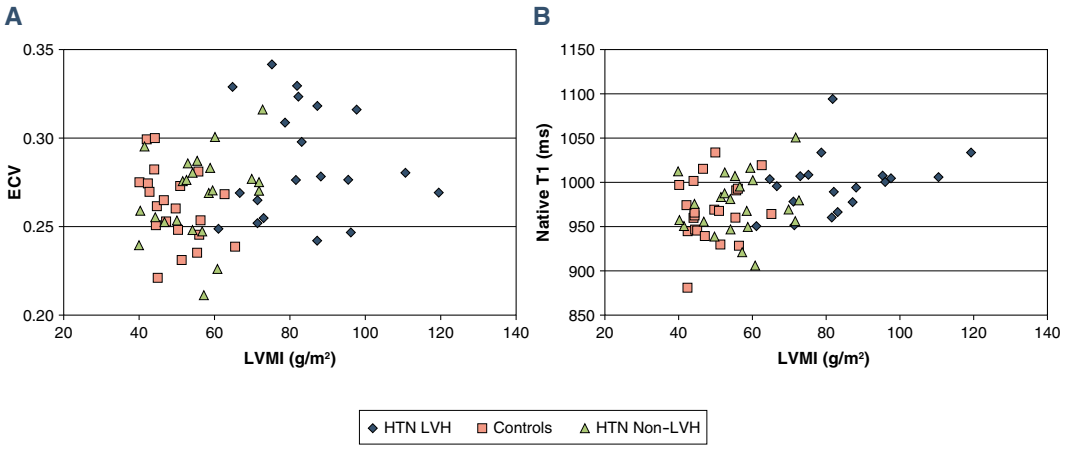

FIGURE 3 Correlation of ECV and Native T1 With LVMI

(A) ECV versus LVMI. Spearman correlation shows a positive association (Spearman rho = 0.26, p = 0.03) between ECV and LVMI. **(B)** Native T1 and LVMI. Spearman correlation shows a positive association (Spearman rho = 0.36, p = 0.03) between native T1 levels and LVMI. Abbreviations as in Figure 2.

HTN LVH compared with HTN non-LVH and control subjects. Higher ECV values were associated with reduced peak systolic circumferential strain and early diastolic circumferential strain rate across all subjects. Furthermore, native T1 levels were found to be longer in HTN LVH subjects compared with normotensive controls. Similarly, increased native T1 was associated with reductions in peak circumferential systolic strain and early diastolic strain rate. Left ventricular mass to volume ratio also correlated with strain and strain rate with increased mass to volume ratio associated with increased ECV, increased native T1, and reduced circumferential strain and strain rate.

ECV and native T1 have different sensitivity to the underlying changes in the intracellular and extracellular spaces within the myocardium. Native T1 is a

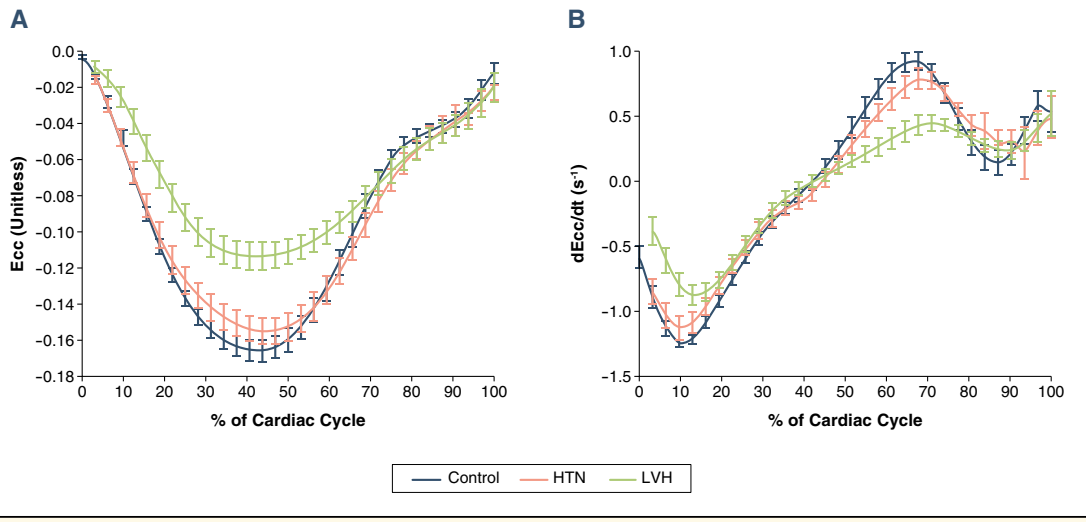

FIGURE 4 Circumferential Strain and Strain Rates in the 3 Groups

(A) Circumferential strain curves. **(B)** Circumferential strain rates in the 3 study groups. Average circumferential and circumferential strain rates for the 3 groups are shown. Ecc = circumferential strain; other abbreviations as in Figure 2.

TABLE 3 Strain and Strain Rate Among the 3 Groups

	Normotensive Controls (n = 22)	Hypertensive Non-LVH (n = 23)	Hypertensive LVH (n = 20)
Peak base circumferential strain	−0.17 ± 0.03	−0.15 ± 0.03	−0.12 ± 0.03*
Peak mid-circumferential strain	−0.17 ± 0.03	−0.17 ± 0.03	−0.12 ± 0.03*
Peak average circumferential strain	−0.17 ± 0.02	−0.16 ± 0.03	−0.12 ± 0.02*
Base e'_{SR} (s^{-1})	0.81 ± 0.17	0.68 ± 0.17	0.48 ± 0.27*
Mid e'_{SR} (s^{-1})	0.83 ± 0.19	0.72 ± 0.23	0.43 ± 0.22*
Average e'_{SR} (s^{-1})	0.82 ± 0.16	0.71 ± 0.18	0.49 ± 0.26*

Values are mean ± SD. *p < 0.05 vs. non-LVH groups and controls.
e'_{SR} = early diastolic circumferential strain rate; LVH = left ventricular hypertrophy.

function of the relaxation of water in both the extracellular and intracellular compartments and may reflect both changes in cellular hypertrophy or extracellular fibrosis. As there is fast water exchange between these compartments, without giving contrast the contribution of the intracellular and extracellular compartments cannot be separated. Because gadolinium contrast agents accumulate only in the extracellular space, the post-contrast T1 shortening is primarily due to a shortening of T1 relaxation time in the extracellular space (although the measured T1 is still affected by water exchange with the intracellular compartment) (20). The ECV is calculated from a combination of native and post-contrast measurements and reflects the volume fraction of extracellular space on a pixel-wise basis. Thus, native T1 and ECV are sensitive to different compartments within the myocardium and may each reflect different aspects of the pathological changes of hypertensive heart disease.

MYOCARDIAL FIBROSIS IN HYPERTENSION. Myocardial fibrosis is a common end point of many cellular and noncellular pathological processes in hypertensive heart disease. The pathogenesis of hypertensive heart disease involves remodeling of the myocardium with fibrosis of the muscle and perivascular space, medial hypertrophy of intramyocardial coronary vasculature, and cardiomyocyte hypertrophy (21). The mechanisms responsible for the development, progression, and pattern of LVH are incompletely defined but include the severity and duration of hypertension, effects of growth factors, cytokines and neurohormones, and genetic predisposition (22). Myocardial fibrosis predisposes patients to diastolic and systolic dysfunction, myocardial ischemia, and atrial and ventricular arrhythmias (23). A strong correlation has been noted between increased myocardial collagen content and left ventricular diastolic dysfunction by echocardiography (24). This study also showed that treatment with losartan reduced the collagen content and left ventricular stiffness. This suggests that diffuse fibrosis seen in hypertensive patients is reversible in response to certain antihypertensive therapies. Reduction in diffuse fibrosis can result in improvement of diastolic function, systolic function, and perhaps outcomes. Thus, measurement of diffuse fibrosis levels could serve as a therapeutic target to

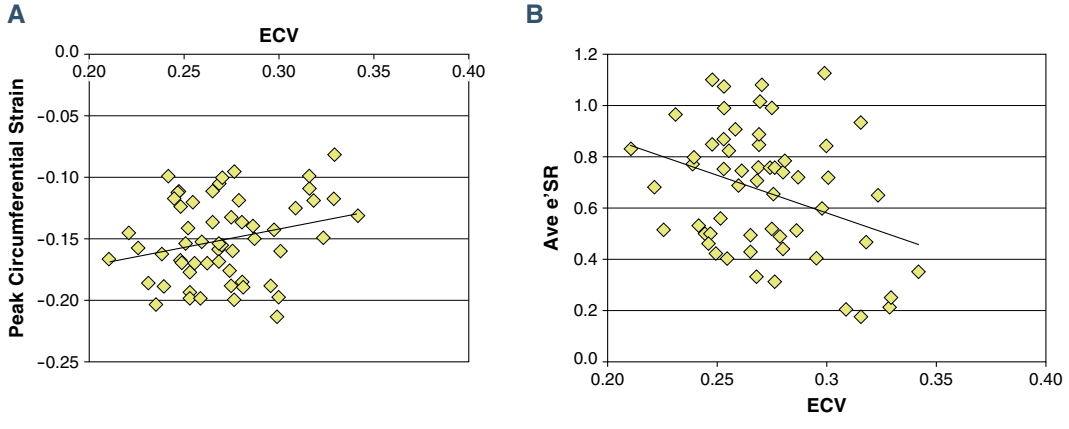

FIGURE 5 Correlation Between ECV and Circumferential Strain and Strain Rate

(A) Peak circumferential strain versus ECV. Pearson's correlation shows a linear association between ECV and peak circumferential strain (Pearson's correlation coefficient of 0.26, p = 0.05). **(B)** Average early diastolic circumferential strain rate versus ECV. Pearson's correlation shows a linear association between ECV and peak circumferential strain rate (Pearson's correlation coefficient of −0.34, p = 0.01). Ave e'SR = average early diastolic circumferential strain rate; other abbreviations as in Figure 2.

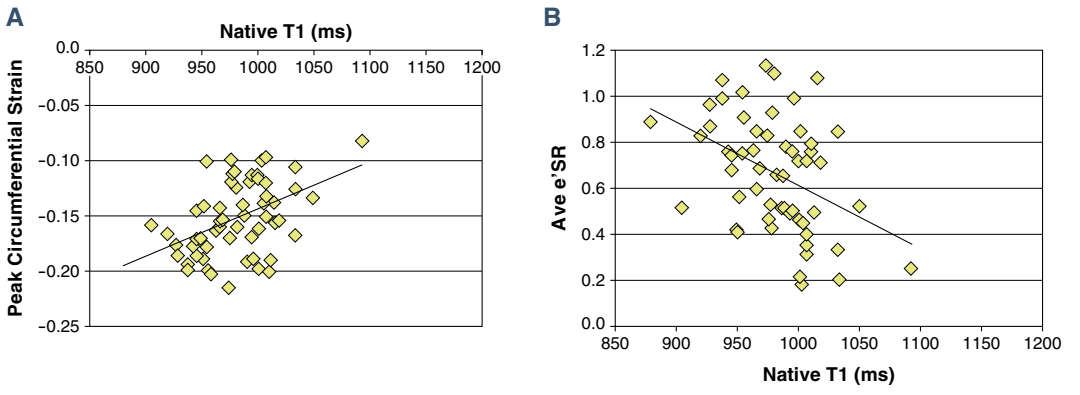

FIGURE 6 **Correlation Between Native T1 and Circumferential Strain and Strain Rate**

(A) Peak circumferential strain versus native T1. Pearson's correlation shows a linear association between native T1 levels and peak circumferential strain (Pearson's correlation coefficient of 0.44, $p < 0.0001$) and **(B)** average early diastolic circumferential strain rate versus native T1. Pearson's correlation shows a linear association between native T1 levels and average early diastolic circumferential strain rate (Pearson's correlation coefficient of -0.40, $p < 0.01$). Abbreviations as in Figure 5.

measure the efficacy of antihypertensive and other therapies.

Initial animal studies in mice with hypertensive heart disease have shown that measurement of ECV as quantified by CMR T1 measurements can detect extracellular matrix expansion due to underlying interstitial fibrosis (20). Our study likewise uses the measurement of ECV of gadolinium as a surrogate marker for underlying diffuse fibrosis among the study groups.

This is the first study to measure the level of diffuse fibrosis using ECV in HTN LVH subjects compared with HTN non-LVH subtypes using a noninvasive imaging method. HTN LVH subjects in this study had greater diffuse fibrosis as measured by ECV. The presence of diffuse fibrosis may be an underlying mechanism contributing to the increased cardiovascular risk in HTN LVH subjects, and therapies that modify diffuse fibrosis may affect the risk. The link between diffuse fibrosis and increased cardiovascular risk was examined in a recent study (25) of heart failure patients with preserved EF and found that shortened post-contrast T1 times, a marker of diffuse fibrosis, was associated with increased cardiac events.

Although there is greater diffuse fibrosis in HTN LVH subjects, the association between ECV and LVMI is nonlinear suggesting that there may be differential stimulation of fibrosis and myocyte hypertrophy in these patients. The HTN non-LVH subjects had better controlled blood pressures, and their LV mass was not significantly higher than that of control subjects. Fibrosis in these subjects was similar to that of controls, and the lack of fibrosis may be related to the lower risk of cardiovascular events for this group.

NATIVE T1. Native T1 of HTN LVH subjects in this study were significantly higher than that of HTN non-LVH or control subjects. Native T1 as discussed in the preceding text is affected by both intracellular myocardial tissue and the extracellular space. The extracellular fibrosis and myocardial cell hypertrophy seen in HTN LVH patients contribute to elevated native T1 levels. The measurement of native T1 as a potential predictor of increased cardiovascular events in LVH may have added value in that it does not require contrast administration, which may otherwise be contraindicated in those with stage 4 or 5 chronic kidney disease.

DIFFUSE FIBROSIS AND SYSTOLIC STRAIN. Earlier studies have shown reduced peak longitudinal and radial systolic strain in hypertensive patients using echocardiography and correlated the reduction in strain with increased collagen synthesis and reduced collagen degradation (26). Studies using CMR myocardial tagging have shown reduction in both circumferential and longitudinal strain in HTN patients with LVH (27). In this study, HTN LVH subjects were found to have significantly reduced peak systolic circumferential strain and e'_{SR}. We have also shown a positive correlation among the peak systolic circumferential strain, average e'_{SR}, and increasing levels of diffuse fibrosis as measured by ECV and native T1 levels, consistent with the expected

relationship between myocardial function and fibrosis. Reduced systolic strain has been previously described in heart failure patients with preserved EF, many of whom have HTN LVH and similar characteristics (28). A possible mechanism linking ECV to reduced systolic strain in such patients may be increased extracellular matrix deposition leading to increased LV stiffness, resulting in reduced end-diastolic muscle fiber length and, by Frank-Starling's law, reduced cardiac muscle contraction and LV systolic strain. Indeed, prior studies have also shown that diffuse fibrosis has been linked with worsening systolic/diastolic function and adverse LV remodeling (23). However, further studies are needed to verify this hypothesis.

STUDY LIMITATIONS. The study is limited by a relatively small sample size; however, this is the largest study to date evaluating ECV in hypertensive heart disease and LVH. Given the small sample size of this study, the effect of variables such as age, gender, diabetes, hypertension duration, or antihypertensive medications such as renin-angiotensin inhibitors on ECV and native T1 could not be evaluated. Although the severity of LVH by CMR was relatively mild in this study, it was associated with increased levels of ECV and higher native T1, suggesting significantly greater diffuse fibrosis in the HTN LVH group compared with the other groups. There are differing methods of T1 mapping, and although consensus guidelines have recently been published regarding use of T1 mapping, further research is needed before establishing a standardized method of T1 mapping for clinical use (29). The method that we used in this study was previously compared with that of the standard MOLLI technique and produced similar results (15). Also, the applicability of results to an individual subject is less certain given the higher variability of T1 relaxation times and thus ECV when only measured in a single subject. The use of multiple points for the calculation of partition coefficient and ECV in our study is advantageous a because it allows us to check the assumption of linearity at different time points to verify the equilibrium assumption and enables an assessment of the uncertainty in determining λ. The use of only 2 time points (1 pre- and 1 post-contrast) does not permit the measure of uncertainty of the fit and may be more sensitive to measurement outliers. Two of our control subjects as mentioned in the preceding text had elevated ECV levels, and it is unclear whether these results are due to normal variation or due to undetermined pathologies.

FUTURE DIRECTIONS. There are limited data on the prognostic value of diffuse fibrosis as measured by ECV in hypertensive subjects. Additionally, the prognostic value of native T1 levels has yet to be studied in this study population. Although diffuse fibrosis in HTN LVH subjects may be an underlying mechanism that explains the increased cardiovascular morbidity and mortality seen in these subjects, further studies are needed to conclusively link the presence of diffuse fibrosis with hard outcomes in these patients. Currently only 1 study has evaluated the prognostic capability of T1 mapping in predicting cardiovascular events in a similar study population (25).

CONCLUSIONS

The present study shows that HTN LVH patients have greater diffuse fibrosis and reduced circumferential strain and circumferential strain rate compared with HTN non-LVH and control subjects. Although diffuse fibrosis is linearly related to worsening circumferential strain, variations in ECV among patients with LVH may provide insight into the differential expression of fibrosis and myocyte hypertrophy among patients with hypertensive heart disease. Measurement of ECV and native T1 levels may serve as a useful novel target to monitor the efficacy of therapies for HTN patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Michael Salerno, Department of Medicine, Cardiovascular Division, University of Virginia Health System, 1215 Lee Street, Box 800158, Charlottesville, Virginia 22908. E-mail: ms5pc@virginia.edu.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127:e6–245.

2. Janardhanan R, Desai AS, Solomon SD. Therapeutic approaches to diastolic dysfunction. Curr Hypertens Rep 2009;11:283–91.

3. Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham Study. Ann Intern Med 1970;72:813–22.

4. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.

5. Querejeta R, Varo N, López B, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. Circulation 2000;101:1729–35.

6. Rossi MA. Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. J Hypertens 1998;16:1031–41.

7. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.

8. Cuspidi C, Giudici V, Negri F, et al. Left ventricular geometry, ambulatory blood pressure and extra-cardiac organ damage in untreated essential hypertension. Blood Press Monit 2010;15:124–31.

9. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138–44.

10. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 2005;111:697–716.

11. Olivotto I, Maron MS, Autore C, et al. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008;52:559–66.

12. Van der Geest RJ, Buller VG, Jansen E, et al. Comparison between manual and semiautomated analysis of left ventricular volume parameters from short-axis MR images. J Comput Assist Tomogr 1997;21:756–65.

13. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees' task force on standardized post processing. J Cardiovasc Magn Reson 2013;15:35.

14. Messroghli DR, Greiser A, Fröhlich M, Dietz R, Schulz-Menger J. Optimization and validation of a fully-integrated pulse sequence for modified look-locker inversion-recovery (MOLLI) T1 mapping of the heart. J Magn Reson Imaging 2007;26:1081–6.

15. Salerno M, Janardhanan R, Jiji RS, et al. Comparison of methods for determining the partition coefficient of gadolinium in the myocardium using T1 mapping. J Magn Reson Imaging 2013;38:217–24.

16. Kim D, Gilson WD, Kramer CM, Epstein FH. Myocardial tissue tracking with two-dimensional cine displacement-encoded MR imaging: development and initial evaluation. Radiology 2004;230:862–71.

17. Zhong X, Spottiswoode BS, Meyer CH, Kramer CM, Epstein FH. Imaging three-dimensional myocardial mechanics using navigator-gated volumetric spiral cine DENSE MRI. Magn Reson Med 2010;64:1089–97.

18. Spottiswoode BS, Zhong X, Lorenz CH, Mayosi BM, Meintjes EM, Epstein FH. Motion-guided segmentation for cine DENSE MRI. Med Image Anal 2009;13:105–15.

19. Spottiswoode BS, Zhong X, Hess AT, et al. Tracking myocardial motion from cine DENSE images using spatiotemporal phase unwrapping and temporal fitting. IEEE Trans Med Imaging 2007;26:15–30.

20. Coelho-Filho OR, Mongeon FP, Mitchell R, et al. Role of transcytolemmal water-exchange in magnetic resonance measurements of diffuse myocardial fibrosis in hypertensive heart disease. Circ Cardiovasc Imaging 2013;6:134–41.

21. Díez J, González A, López B, Querejeta R. Mechanisms of disease: pathologic structural remodeling is more than adaptive hypertrophy in hypertensive heart disease. Nat Clin Pract Cardiovasc Med 2005;2:209–16.

22. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med 2008;358:1370–80.

23. McLenachan JM, Dargie HJ. Ventricular arrhythmias in hypertensive left ventricular hypertrophy. Relationship to coronary artery disease, left ventricular dysfunction, and myocardial fibrosis. Am J Hypertens 1990;3:735–40.

24. Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512–7.

25. Mascherbauer J, Marzluf BA, Tufaro C, et al. Cardiac magnetic resonance postcontrast t1 time is associated with outcome in patients with heart failure and preserved ejection fraction. Circ Cardiovasc Imaging 2013;6:1056–65.

26. Plaksej R, Kosmala W, Frantz S, et al. Relation of circulating markers of fibrosis and progression of left and right ventricular dysfunction in hypertensive patients with heart failure. J Hypertens 2009;27:2483–91.

27. Palmon LC, Reichek N, Yeon SB, et al. Intramural myocardial shortening in hypertensive left ventricular hypertrophy with normal pump function. Circulation 1994;89:122–31.

28. Kraigher-Krainer E, Shah AM, Gupta DK, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447–56.

29. Moon JC, Messroghli DR, Kellman P, et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. J Cardiovasc Magn Reson 2013;15:92.

KEY WORDS cardiac magnetic resonance, extracellular volume, hypertension, hypertensive heart disease, left ventricular hypertrophy, myocardial fibrosis, T1 mapping

APPENDIX For supplementary tables and figures, please see the online version of this article.