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Title

Left Ventricular Extracellular Volume Fraction and Atrio-Ventricular Interaction in Hypertension

Abstract

Objectives

Left atrial enlargement (LAE) predicts cardiovascular morbidity and mortality. Impaired LA function also confers poor prognosis. This study aimed to determine whether left ventricular (LV) interstitial fibrosis is associated with LAE and LA impairment in systemic hypertension.

Methods

Following informed written consent, a prospective observational study of 86 hypertensive patients (49±15 years, 53% male, office SBP 168±30mmHg, office DBP 97± 4 mmHg) and 20 normotensive controls (48±13 years, 55% male, office SBP 130±13 mmHg, office DBP 80±11 mmHg) at 1.5T cardiovascular magnetic resonance was conducted. Extracellular volume fraction (ECV) was calculated by T1 mapping. LA volume (LAV) was measured with biplane area-length method. LA reservoir, conduit and pump function were calculated with the phasic volumetric method.

Results

Indexed LAV correlated with indexed LV mass (R=0.376, p<0.0001) and ECV (R=0.359, p=0.001). However, ECV was the strongest significant predictor of LAE in multivariate regression analysis (odds ratio [95th confidence interval]: 1.24 [1.04–1.48], p=0.017).

Indexed myocardial interstitial volume was associated with significant reductions in LA reservoir (R=-0.437, p<0.0001) and conduit (R=-0.316, p=0.003) but not pump (R=-0.167, p=0.125) function. Multiple linear regression, correcting for age, gender, BMI, BP and diabetes, showed an independent decrease of 3.5% LA total emptying fraction for each 10ml/m^2 increase in myocardial interstitial volume (standard β coefficient: -3.54, p=0.002).

Conclusions

LV extracellular expansion is associated with LAE and impaired LA reservoir and conduit function. Future studies should identify if targeting diffuse LV fibrosis is beneficial in reverse remodeling of LA structural and functional pathological abnormalities in hypertension.

Key words

Cardiac Imaging Techniques; Magnetic Resonance Imaging; Hypertension; Fibrosis; Strain

Key points

- Left atrial enlargement (LAE) and impairment are markers of adverse prognosis in systemic hypertension but their pathophysiology is poorly understood.
- Left ventricular extracellular volume fraction was the strongest independent multivariate predictor of LAE and was associated with impaired left atrial reservoir and conduit function.

- LV interstitial expansion may play a central role in the pathophysiology of adverse atrio-ventricular interaction in systemic hypertension.

Abbreviations

LA	-	Left atrial
LAE	-	Left atrial enlargement
LVH	-	Left ventricular hypertrophy
LV	-	Left ventricular
CMR	-	Cardiovascular magnetic resonance
SBP	-	Systolic blood pressure
DBP	-	Diastolic blood pressure
SSFP	-	Steady state free precession
LVM	-	Left ventricular mass
LAV	-	Left atrial volume
LAVmin	-	Minimal left atrial volume
LAVpre-A	-	Left atrial volume just prior to left atrial contraction
LAVmax	-	Maximal left atrial volume
EDV	-	End-diastolic volume
ESV	-	End-systolic volume
SV	-	Stroke volume
ROI	-	Region of interest
ECV	-	Extracellular volume fraction
ANOVA	-	Analysis of variance
BMI	-	Body mass index
ESC	-	European Society of Cardiology

Introduction

Left atrial (LA) enlargement (LAE) is common in hypertension[1] and postulated to be compensatory to left ventricular hypertrophy (LVH) associated diastolic dysfunction. However, LAE may develop before LVH in hypertension[2] and LAE is an independent predictor of cardiovascular morbidity and mortality[3].

Atrio-ventricular interaction is important; LA function is intimately related to left ventricular (LV) compliance. As LV compliance falls, LA pump function contributes proportionately more to LV filling[4]. However, as LV compliance falls further, LA pump function declines and the LA reverts to mainly functioning as a passive conduit[5]. In hypertension, LA pump function has been shown to be an independent predictor of adverse cardiac events[6].

However, the pathophysiology of LA dilatation and dysfunction in hypertension remains poorly understood. This assessed atrio-ventricular interaction using multi-parametric cardiovascular magnetic resonance (CMR), to investigate the relationship between LV interstitial expansion, a surrogate for diffuse LV fibrosis, and LA size/function. The hypothesis was that increasing LV interstitial expansion would be associated with LAE and impaired LA function.

Methods

Ethics approval and participants

A prospective, observational study of hypertensive patients from a tertiary hypertension clinic undergoing CMR was performed (February 2013–April 2016). The local research ethics committee confirmed the study conformed to governance arrangements. Subjects provided informed, written consent. Baseline demographic and clinical characteristics were recorded. Average office systolic (SBP) and diastolic blood pressures (DBP) were acquired in accordance with International hypertension guidelines[7]. Exclusion criteria were: atrial fibrillation, concomitant myocardial pathology that may confound LAE (e.g. moderate-severe valvular disease and acquired/inherited cardiomyopathy) and estimated glomerular filtration rate <30ml/min/1.73m^2. Normotensive healthy volunteers acted as controls, but did not receive intravenous gadolinium chelate due to ethics approval constraints.

CMR cine protocol

1.5T CMR was performed (Avanto, Siemens Healthineers). Short-axis steady-state free precession (SSFP) cines with whole LV coverage (8mm slice thickness, no slice gap, temporal resolution 38.1ms, echo time 1.07ms, representative field of view 300mm, image matrix 152x192, in-plane pixel size 1.6x1.6mm) were used to measure LV mass (LVM) and volumes, which were indexed to body surface area (Mosteller formula) as before[8].

LA enlargement and function analysis

LA volume (LAV) was measured by biplane area-length[9](**Figure 1**) as follows:

$$LAV = 0.85 \times A_{4c} \times A_{2c} / L$$

Where:

A4c = LA area on 4-chamber cine at end-systole

A2c = LA area on 2-chamber cine at end-systole

L = shortest LA length on either 4-chamber or 2-chamber at end-systole

LA function was assessed using the phasic-volumetric method[10](**Figure 2**) that measures LAV at 3 phases of the cardiac cycle reliably[6]:

1) Minimal LAV (**LAVmin**) at LV end-diastole at mitral valve closure

2) Just prior to LA contraction (**LAVpre-A**)

3) Maximal LAV (**LAVmax**) at end-systole just prior to mitral valve opening.

LA function was estimated as[10]:

1) **LA reservoir function:**

LA total emptying fraction = (LAVmax – LAVmin) / LAVmax x 100%

2) **LA conduit function:**

LA passive emptying fraction = (LAVmax – LAVpre-A) / LAVmax x 100%

3) **LA pump function:**

LA active emptying = (LAVpre-A – LAVmin) / LAVpre-A x 100%

LA expansion index was defined as previously[11][12][13] as:

(LAVmax – LAVmin) / LAVmin x 100%

LAE was defined as indexed LAVmax ≥55ml/m^2, which is larger than echocardiographic cut-off values[14] but more appropriate for CMR as it represents 2 standard deviations above the CMR mean of healthy subjects[15][16]. Furthermore, a recent publication of 804 normal volunteers confirmed indexed LAVmax 55ml/m^2 as the upper limit of normal for men and women[17].

LV volume, mass and functional analysis

A validated and highly reproducible[18] threshold-detection software (CMR42, Circle Cardiovascular Imaging Inc.) was used to include papillary muscles and LV trabeculae in LVM estimation and then include them in blood-pool volume for end-diastolic (EDV), end-systolic (ESV) and stroke (SV) volume measurements as before[8]. CMR analysis was performed blinded to all other data.

CMR T1-mapping protocol and analysis

Myocardial T1-mapping was performed using a modified look-locker inversion recovery sequence with native and post-contrast sequences dependent upon heart rate at acquisition (**Table 1**). Constant scan parameters were: flip angle 35°, GRAPPA acceleration factor 2, bandwidth 1085 Hz/Px, number of inversions 2, starting TI 120ms, TI increment 80ms. Regions of interest (ROI) were drawn within mid-septum on short-axis, motion-corrected, native T1-maps and copied onto corresponding 15 minutes post-contrast maps, adjusting for partial-voluming and/or artifact, as previously described[19]. Argus software (Siemens, Germany) was used for T1 analysis, as previously described[19]. Extracellular volume fraction (ECV) was calculated using an established formula[19]:

$$ECV = (\Delta R1_{myocardium} / \Delta R1_{blood\text{-}pool}) \times (1 - \text{haematocrit})$$

Where:

$\Delta R1 = (1/\text{post-contrast } T1 - 1/\text{native } T1)$.

Haematocrit measured from peripheral venous blood sample.

Indexed interstitial volume was calculated by multiplying the ECV by indexed myocardial volume (indexed LVM divided by myocardial specific gravity 1.05g/ml). Myocardial cell volume fraction was defined, as previously[20], as (1–ECV), and multiplied by indexed LV myocardial volume to generate an estimation of indexed myocardial cell volume. Excellent reproducibility was demonstrated in a subset of 50 subjects (native T1-mapping intra-class correlation coefficient (ICC): 0.968 (95^{th} confidence interval: 0.951–0.984) and ECV ICC: 0.988 (95^{th} confidence interval: 0.979–0.993).

CMR strain imaging

Strain imaging was performed offline by software (Tissue Tracking, CMR42, Circle Cardiovascular Imaging Inc.) that tracks myocardial voxels through the cardiac cycle in 2D, based on a previously described algorithm[21][22]. Briefly, the endocardial and epicardial borders (excluding papillary muscles and trabeculae) and the mitral valve annular plane at end-diastole were defined on LV 4-chamber, LV 2-chamber and whole LV short-axis SSFP cine images. Circumferential strain and strain rates were calculated from mean values of mid LV myocardial segments from the short-axis 2-dimensional strain model. Srain analysis was performed blinded to all other data.

Statistical analysis

Statistical analysis was performed in SPSS (v.21, IBM Corp). A power calculation could not be performed for this exploratory observational study because there are no previous studies assessing the atrio-ventricular interaction using non-invasive measures of LV diffuse interstitial fibrosis and LA phasic volume function using any cardiac imaging modality. Normally distributed continuous variables were expressed as mean ± standard deviation and compared using analysis of variance (ANOVA) with Bonferroni post-hoc correction. Categorical variables were expressed as percentages and interrogated with Chi-square tests. Correlations were assessed with Pearson's coefficient. General linear models were used to correct for differences in baseline covariates of age, gender, body mass index (BMI), diabetes, office SBP, office DBP and number of anti-hypertensive medications between cohorts. Multiple linear regression was preformed to quantify independent impact of indexed interstitial and myocardial cell volumes on indexed LAVmax, LAVmin and LA total emptying fraction, accounting for covariates. Univariate logistic regression identified predictors of LAE and significant univariate variables were tested in a multivariate model to determine independent associations. $P<0.05$.

Results

Participant demographics

116 hypertensive patients were assessed for eligibility. 30 patients were excluded(**Figure 3**), with final sample size of 86 (49±15 years, 53% male, office SBP 168±30mmHg, office DBP 97±4mmHg). 20 normotensive control subjects were recruited (48±13 years, 55% male, office SBP 130±13mmHg, office DBP 80±11mmHg). Hypertensive and normotensive subjects were age- and sex-matched(**Table 2**). LAE was present in 27% (n=23).

LA size and LV mass

Indexed LVM correlated with indexed LAVmax (R=0.376, P<0.0001)(**Figure 4A**) and with indexed LAVmin (R=0.616, P<0.0001)(**Figure 4B**).

Hypertensive subjects with LAE had higher: 1) indexed LVM mass (97±33g/m^2 vs 84±22g/m^2, P=0.044), 2) indexed EDV (89±17ml/m^2 vs 73±16ml/m^2, P<0.0001) and 3) indexed ESV (34±17ml/m^2 vs 24±10ml/m^2, P<0.0001) compared to hypertensive subjects without LAE(**Table 3**), which persisted after correcting for covariates(**Table 4**).

LA size, LV fibrosis and LV strain

There was a positive correlation between ECV and 1) indexed LAVmax (R=0.359, P=0.001)(**Figure 4C**) and 2) indexed LAVmin (R=0.390, P<0.0001)(**Figure 4D**). Hypertensives with LAE had higher ECV (30±4% vs 27±3%, P=0.003)(**Table 2**) and larger indexed LV interstitial volume (28±12ml/m^2 vs 21±7ml/m^2, P=0.043) than hypertensives without LAE(**Table 3**), which persisted after correcting for covariates

(**Table 4**). However, there was no significant difference in indexed LV myocardial cell volume between hypertensive subjects with LAE and those without LAE (64±21ml/m^2 vs 57±15ml/m^2, P=0.106)(**Table 3**).

Accounting for the covariates of age, gender, BMI, diabetes, office SBP and office DBP, each 10ml/m^2 increase in indexed LV interstitial volume, a significant independent increase in 1) indexed LAVmax of 4.9ml/m^2 (standard β coefficient: 4.88, P<0.0001) and 2) indexed LAVmin of 5.6ml/ m^2 occurs (standard β coefficient: 5.61, P<0.0001). In a separate model, each 10ml/m^2 increase in indexed LV myocardial cell volume, was also associated with a significant independent increase in 1) indexed LAVmax of 3.2ml/m^2 (standard β coefficient: 3.20, P<0.0001) and 2) indexed LAVmin of 4.7ml/ m^2 (standard β coefficient: 4.74, P<0.0001).

Indexed interstitial volume correlated with peak circumferential strain (R=0.454, p<0.0001), peak systolic strain rate (R=0.342, p=0.001) and peak diastolic strain rate (R=-0.380, p<0.0001). Indexed myocardial cell volume also correlated with peak circumferential strain (R=0.509, p<0.0001), systolic strain rate (R=0.267, p=0.013) and diastolic strain rate (R=-0.501, p<0.0001). In turn, indexed LAVmin correlated with peak circumferential strain (R=0.275, p=0.01), systolic strain rate (R=0.438, p<0.0001) and diastolic strain rate (R=-0.273, p=0.011). However, LAVmax only correlated with systolic strain rate (R=0.405, p<0.0001) and not with peak circumferential strain (R=0.067, p=0.537) or diastolic strain rate (R=-0.136, p=0.212).

Predictors of LAE

Indexed LVM, ECV and peak circumferential strain rate were significant predictors of LAE in univariate logistic regression(**Table 5**). ECV and peak circumferential strain rate remained significant predictors in the multivariate model and ECV was the strongest predictor (**Table 5**).

LA function and LV fibrosis

Indexed LV interstitial volume inversely correlated with LA total reservoir function (R=-0.437, P<0.0001)(**Figure 5A**). Likewise, indexed LV interstitial volume inversely correlated with LA passive conduit function (R=-0.316, P=0.003)(**Figure 5B**). However, there was no significant correlation between indexed LV interstitial volume and LA pump function (R=-0.167, P=0.125)(**Figure 5C**). There was a significant decrease in LA expansion index with increasing interstitial volume (R=-0.377, P<0.0001)(**Figure 5D**).

Accounting for the covariates of age, gender, BMI, diabetes, office SBP and office DBP, each 10ml/m^2 increase in indexed LV interstitial volume, a significant independent decrease in LA total reservoir function of 3.5% occurs (standard β coefficient: -3.54, P=0.002). In a separate model, each 10ml/m^2 increase in indexed LV myocardial cell volume, was associated a significant independent decrease in LA total reservoir function of 3.2% (standard β coefficient: -3.20, P=0.006).

Discussion

We demonstrate the relationship between LV interstitial expansion and LA structure and function in hypertension using CMR. Previous studies have investigated using with T1 mapping techniques in hypertensive patients[23][24][25][26][27], but all have focused exclusively on the LV, with no focus on atrio-ventricular interaction, which has been addressed in the current study. Our novel findings are: 1) increasing LV interstitial volume is associated with increasing LAVmax and LAVmin. 2) increasing LV interstitial volume is also associated with impaired circumferential systolic and diastolic strain rate that are in turn correlate with LAVmin, 3) Increasing LV ECV was the strongest independent multivariate predictor of LAE, and 4) LV interstitial fibrotic burden significantly inversely correlates with LA total reservoir function and in LA passive conduit function but not with LA active pump function.

Atrio-ventricular interaction

Hypertensive LV changes are intimately related to LA dynamics. A recent echocardiographic study showed that LV systolic and diastolic dysfunction were associated with increased LAV and LA diastolic stiffness, even in asymptomatic patients[28]. Our study provides further insight at the LV myocardial intra/extracellular level. Although both increases in indexed myocardial cell volume and indexed interstitial volume were independently associated with LAE, the regression coefficient was larger for indexed interstitial volume. Furthermore, ECV was the only independent predictor of LAE in multivariate regression analysis.

*Potential for LA reverse remodeling***.**

We demonstrated no significant relationship between LA pump function and indexed LV interstitial volume. This may suggest a greater LV fibrotic burden is required to cause LA pump dysfunction than is required to cause LA conduit or reservoir dysfunction. A prior CMR study in 210 hypertensive subjects[6] support this notion where, during a median 19 month follow-up, contractile atrial dysfunction was an independent predictor of major adverse clinical events(MACE)[6]. Furthermore, preservation of the proportion of LA contraction to total LV diastolic filling was strongly associated with lower MACE[6]. Decreased LA contractile function may identify those with the most LV diastolic dysfunction and conceivably these are the patients with the most diffuse LV fibrosis. It is therefore possible that failure of LA pump function fails heralds near end-stage hypertensive cardiac end-organ damage, accounting for the correlation of this imaging biomarker with mortality[6]. Therefore, therapeutic targeting of diffuse LV myocardial fibrosis prior to the onset of overt LA contractile dysfunction may offer the best chance of achieving LA reverse remodeling. Treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers have been associated with LA reserve remodeling in both the spontaneously hypertensive rat[29] and in hypertensive humans[30]. The putative mechanisms by which these agents result in LA reverse remodeling are incompletely understood, potentially include downstream effects of BP reduction or improved LV diastolic function. However, direct suppression of the renin-angiotensin-aldosterone system is also implicated. Our results, showing a correlation between LV fibrosis and LA volume, may offer further pathophysiological insights. Such agents have been demonstrated to result in regression of LV fibrosis in murine models of hypertension[31], which could be a common driver of the LV diastolic functional improvement and improvement in LA function and structure. Although not assessed in the current study, it is possible that these drugs cause direct regression of LA fibrosis, having been associated with a reduction in the percentage of fibrosis of LA tissue in spontaneously hypertensive rats treated with Olmesartan compared to controls[29].

Clinical implications

The clinical prognostic importance of LAV independent to LV diastolic dysfunction is debated. In a study of 1,160 elderly patients with cardiovascular disease referred for routine clinical echocardiography, both LV diastolic dysfunction and indexed LAVmax were independent predictors of cardiovascular events[32]. In a younger cohort of 484 subjects in sinus rhythm referred for echocardiography, an elevated indexed LAVmax was the only independent predictor of cardiovascular death and events, and indices of LV diastolic dysfunction were not[33]. Many previous studies have focused on LAVmax but in a study of 41 patients undergoing invasive pressure measurements via left heart cardiac catheterization and CMR on the same day, increased LAVmin had the best ability to predict elevated LV end-diastolic filling pressure[34]. Furthermore, a prior echocardiographic study showed that LAVmin significantly increased with worsening LV diastolic dysfunction and in multivariate models, increasing LAVmin was independently associated with decreasing echocardiographic indices of LV diastolic function, but LAVmax was not[35]. Our study helps explain this by demonstrating a statistically stronger correlation between ECV and indexed LAVmin, than with LAVmax. We also found significant correlation between peak circumferential strain, peak circumferential systolic strain rate and peak circumferential diastolic strain rate and indexed LAVmin. These findings support the notion that diffuse LV fibrosis is associated with LV diastolic dysfunction, elevated LV end-diastolic filling pressure and in turn LAVmax and LAVmin dilatation. However, whether the fibrotic process starts in the LV and that drives the LA changes, or whether the same fibrotic process occurs simultaneous in the LV and LA remains unanswered.

LA function is also of prognostic importance. In the Dallas Heart CMR study of 1,802 subjects, decreasing LAEF, defined as (LAVmax – LAVmin)/LAVmax x 100), was independently associated with mortality[36]. We show a correlation between declining total LA emptying fraction and diffuse LV fibrosis. Furthermore, we demonstrate a significant decrease in LA expansion index, a parameter that predicts LV filling pressure[12], severe LV diastolic dysfunction[13] and all-cause mortality[11], with increasing LV interstitial volume.

Our study highlights the central pathophysiological role of LV diffuse myocardial fibrosis in hypertension. The LV fibrotic burden has associations with structural and functional changes beyond the LV. This suggests that targeting LV fibrosis should be a key therapeutic target but effective anti-fibrotic treatments have proven to be an elusive until very recently. New insights into both the understanding of the development of myocardial fibrosis and novel ways in which to abrogate this process, such as inhibition of interleukin-11[37], at least in animal models, offers hope that the effective therapies for blocking/reversing myocardial fibrosis may be on the horizon, which may improve LV and LA structure and function in hypertension.

Study limitations

The study was performed in a specialist hypertension clinic population. Further study is required in a larger, more diverse population to enable further analyses such as impact of duration of hypertension and anti-hypertensive regimens on LV diffuse myocardial fibrosis and LA structure/function.

T1 values were recorded in mid-septum owing to lower intra-observer, inter-observer and inter-study variability previously reported in the lateral wall, likely related to a number of confounders, e.g. magnetic susceptibility artifact, receiver coil sensitivity and distance from the receiver coil elements[38]. Nevertheless, more comprehensive segmental T1 quantification has been described[39], but not performed in the current study. Hypertensive remodeling may begin in the septum[40] and therefore only measuring T1 relaxation values here could theoretically result in a overestimation of the degree of interstitial expansion.

LA conduit function was defined as passive emptying fraction. This is an index of one component of conduit function as it only describes the flow that results from change in LA volume during this time interval rather than the entire flow from the pulmonary veins through the LA into the LV during that phase of diastole.

Contemporaneous comprehensive echocardiographic assessment was not available in all study subjects. CMR strain rates have been provided but may be limited by inferior temporal resolution of CMR to echocardiography. Future work could investigate whether diffuse LV myocardial fibrosis is the underlying pathophysiological abnormality, which independently causes both LV diastolic dysfunction and LA dilatation and dysfunction.

LA replacement fibrosis assessment, with LGE or T1 mapping, was not investigated, but may be potentially important[41].

Conclusion

In hypertension, increasing LV interstitial fibrosis is associated with LAE and impaired LA function. ECV was the strongest significant independent predictor of LAE in multivariate analysis, and increasing indexed LV interstitial volume significantly and independently resulted in worsening LA reservoir function. Diffuse LV fibrosis may represent a key therapeutic target for reverse remodeling of both LA and LV structural and functional abnormalities in hypertension.

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Conflicts of interest

All authors have no conflicts of interest to declare.

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Figure legends

Figure 1: The biplane area-length method to measure LAV. LAVmax was measured at maximal atrial dilatation occurring at LV end-systole just before mitral valve opening, as before. Briefly, the image on **A)** LV long-axis 4-chamber (A1 = atrial area, L1 = atrial length) and **B)** 2-chamber SSFP cines (A2 = atrial area, L2 = atrial length) immediately preceding the opening of the mitral valve was used for analysis of LAVmax. First, LA length was measured from the mitral annular plane to the posterior aspect of the LA wall, parallel to the LV long-axis on both 4-chamber and 2-chamber SSFP cines. The endocardial border of the LA was also manually contoured at LAVmax, excluding the LA appendage and pulmonary venous confluence. RA=right atrium, RV=right ventricle, LV=left ventricle

Figure 2: The phasic volumetric method for assessing left atrial function. A) LAVmin measured at mitral valve closure. B) LAVpre-A measured just prior to left atrial contraction. C) LAVmax measured just before mitral valve opening. RA = right atrium, RV = right ventricle, LV = left ventricle

Figure 3: Study design and exclusions. *Image artifact from implantable loop recorder device precluding volumetric assessment from LV short axis SSFP cine stack.

Figure 4: **A & B)** The relationship between LV mass and LA volume in 86 hypertensive patients (n=23 with LAE, n=63 without LAE) and 20 controls. **A)** Scatterplot demonstrates positive correlation between indexed LV mass and indexed LAVmax (R=0.376, P<0.0001). **B)** Scatterplot demonstrates positive correlation between

indexed LV mass and indexed LAVmin (R=0.616, P<0.0001). **4 C & D)** The relationship between LAVmax and LV fibrosis in 86 hypertensive patients (n=23 with LAE, n=63 without LAE). **C)** Scatterplot demonstrates positive correlation between ECV and indexed LAVmax (R=0.359, P=0.001). **D)** Scatterplot demonstrates positive correlation between ECV and indexed LAVmin (R=0.390, P<0.0001).

Figure 5: Relationship between LA function and LV fibrosis in 86 hypertensive patients (n=23 with LAE, n=63 without LAE). **A)** Scatterplot demonstrates negative correlation between indexed myocardial interstitial volume and LA total reservoir function (R=-0.437, P<0.0001). **B)** Scatterplot demonstrates negative correlation between indexed myocardial interstitial volume and LA passive conduit function (R=-0.316, P=0.003). **C)** There was no significant correlation between indexed interstitial volume and LA contractile pump function (R=-0.167, P=0.125). **D)** Scatterplot demonstrates negative correlation between indexed myocardial interstitial volume and LA expansion index (R=-0.377, P<0.0001).

Table 1: Scan parameters for native and post contrast T1-mapping sequences

	Native T1-mapping		Post contrast T1-mapping	
	HR < 90 bpm	**HR > 90 bpm**	**HR < 90 bpm**	**HR > 90 bpm**
TR (ms)	314.85	374.95	394.85	374.95
TE (ms)	1.12	1.00	1.12	1.00
Slice thickness (mm)	8	8	8	8
Voxel size (mm)	2.1 x 1.4 x 8	2.4 x 1.9 x 8	2.1 x 1.4 x 8	2.4 x 1.9 x 8
Matrix	144 x 256	128 x 192	144 x 256	128 x 192
No. acquired heart beats	5	5	4	4
No. recovery heart beats	3	3	1	1

HR = heart rate, bpm = beats per minute, TR = repetition time, TE = echo time, ms = milliseconds, mm = millimetres

Table 2: Demographic and CMR data

		Hypertensive	
	Controls (n=20)	**No LAE** (n=63)	**LAE** (n=23)
Age (year)	48 ± 13	48 ± 14	52 ± 14
Gender (% male)	55	60	48
BMI (kg/m^2)	28 ± 5	31 ± 6	30 ± 6
Diabetes mellitus (%)	0	13	9
Heart rate (beats/min)	71 ±10	73 ± 13	64 ± 10^^^
Office systolic blood pressure (mmHg)	130 ± 13	166 ± 27 §§§	169 ± 35 ***
Office diastolic blood pressure (mmHg)	80 ± 11	96 ± 12 §§§	97 ± 17 ***
ESH/ESC office BP grade			
- Controlled (%)	…	6	13
- High normal (%)	…	3	4
- Grade 1 (%)	…	30	26
- Grade 2 (%)	…	32	13
- Grade 3 (%)	…	27	39
- Isolated systolic (%)	…	3	4
No. antihypertensive medications (n)	0	2 ± 2	3 ± 2 ***
ACEi/ARB (%)	0	76	83 ***

One-way ANOVA with Bonferonni post-hoc correction or Chi squared test as appropriate:

Controls vs LAE: *** p < 0.001

Controls vs No LAE : §§§ p < 0.001

LAE vs No LAE: ^^^ p <0.001, LAE vs No LAE

Table 3: Demographic and CMR data

		Hypertensive	
	Controls (n=20)	**No LAE** (n=63)	**LAE** (n=23)
LV data			
EF (%)	66 ± 8	68 ± 8	64 ± 11
Indexed EDV (ml/m^2)	70 ± 12	73 ± 16	89 ± 17 *** ^^^
Indexed ESV (ml/m^2)	24 ± 7	24 ± 10	34 ± 17 * ^^^
Indexed SV (ml/m^2)	46 ± 9	49 ± 10	56 ± 10 ** ^
Cardiac output (l/min^1)	6.3 ± 1.4	6.6 ± 3.0	6.7 ± 2.1
Mass : volume (g/ml)	0.82 ± 0.13	1.16 ± 0.30 §§§	1.12 ± 0.41 **
Indexed LV mass (g/m^2)	56 ± 8	84 ± 22 §§§	97 ± 33 *** ^
LV strain data			
Peak circumferential strain (%)	-17.6 ± 2.7	-16.8 ± 3.2	-15.7 ± 4.2
Peak circumferential systolic strain rate (%/sec)	-102.7 ± 13.4	-108.7 ± 29.7	-86.4 ± 24.8 ^^
Peak circumferential diastolic strain rate (%/sec)	102.3 ± 26.9	94.5 ± 24.9	83.3 ± 31.9

Continued…

Table 3: Demographic and CMR data continued

		Hypertensive	
	Controls (n=20)	**No LAE** (n=63)	**LAE** (n=23)
LV T1 mapping data			
Native T1 (ms)	1030 ± 42	1039 ± 36	1044 ± 52
ECV (%)	…	27 ± 3	30 ± 4 ^^
Indexed interstitial volume (ml/m^2)	…	21 ± 7	28 ± 12 ^
Indexed myocardial cell volume (ml/m^2)	…	57 ± 15	64 ± 21
LA data			
Indexed LAVmax (ml/m^2)	38 ± 8	42 ± 8	65 ± 8 ***
Indexed LAVmin (ml/m^2)	16 ± 3	20 ± 6 §	34 ± 10 ***
Reservoir function (%)	57 ± 9	51 ± 9 §	47 ± 11 **
Conduit function (%)	35 ± 10	28 ± 12	26 ± 9 *
Pump function (%)	33 ± 9	31 ± 13	30 ± 11
Expansion index (%)	133 ± 31	114 ± 38	96 ± 37 **

One-way ANOVA with Bonferonni post-hoc correction:

Controls vs LAE:	* p < 0.05, Controls vs LAE	** p < 0.01, Controls vs LAE	*** p < 0.001, Controls vs LAE
Controls vs No LAE:	§ p < 0.05, Controls vs No LAE	§§ p < 0.01, Controls vs No LAE	§§§ p < 0.001, Controls vs No LAE
LAE vs No LAE:	^ p < 0.05 LAE vs No LAE	^^ p < 0.01, LAE vs No LAE	^^^ p <0.001, LAE vs No LAE

Table 4: CMR data corrected for covariates[¶]

		Hypertensive	
	Controls (n=20)	**No LAE** (n=63)	**LAE** (n=23)
LV data			
EF (%)	65 ± 2	68 ± 1	64 ± 2
Indexed EDV (ml/m^2)	74 ± 2	72 ± 16	89 ± 3 * ^^^
Indexed ESV (ml/m^2)	28 ± 3	24 ± 2	33 ± 2 ^^
Indexed SV (ml/m^2)	47 ± 3	49 ± 1	56 ± 2 * ^
Cardiac output (l/min^1)	6.9 ± 0.8	6.4 ± 0.3	6.7 ± 0.6
Mass : volume (g/ml)	0.94 ± 0.09	1.12 ± 0.04	1.12 ± 0.06
Indexed LV mass (g/m^2)	72 ± 6	79 ± 2	95 ± 4 ** ^^
LV strain data			
Peak circumferential strain (%)	-15.8 ± 0.8	-17.3 ± 0.4	-15.9 ± 0.6
Peak circumferential systolic strain rate (%/sec)	-89.5 ± 6.6	-111.2 ± 3.3 [§]	-90.0 ± 7.4 ^^
Peak circumferential diastolic strain rate (%/sec)	89.5 ± 6.6	97.6 ± 2.9	86.2 ± 4.8

Continued…

Table 4: CMR data corrected for covariates¶ continued

		Hypertensive	
	Controls (n=20)	**No LAE** (n=63)	**LAE** (n=23)
LV T1 mapping data			
Native T1 (ms)	1047 ± 12	1036 ± 5	1042 ± 9
ECV (%)	…	27 ± 4	30 ± 6 ^^^
Indexed interstitial volume (ml/m^2)	…	21 ± 1	29 ± 2 ^^^
Indexed myocardial cell volume (ml/m^2)	…	57 ± 2	65 ± 3 ^
LA data			
Indexed LAVmax (ml/m^2)	40 ± 2	42 ± 1	64 ± 2 *** ^^^
Indexed LAVmin (ml/m^2)	19 ± 2	20 ± 1	34 ± 1 *** ^^^
Reservoir function (%)	53 ± 3	52 ± 1	48 ± 2
Conduit function (%)	32 ± 3	29 ± 1	26 ± 2
Pump function (%)	30 ± 3	32 ± 1	30 ± 2
Expansion index (%)	124 ± 11	115 ± 5	103 ± 7

¶General linear models accounting for the covariates of age, gender, BMI, diabetes, office SBP and DBP and number of anti-hypertensive medications. Data are presented as mean ± standard error.

One-way ANOVA with Bonferonni post-hoc correction:

Controls vs LAE:	* p < 0.05, Controls vs LAE	** p < 0.01, Controls vs LAE	*** p < 0.001, Controls vs LAE
Controls vs No LAE:	§ p < 0.05, Controls vs No LAE	§§ p < 0.01, Controls vs No LAE	§§§ p < 0.001, Controls vs No LAE
LAE vs No LAE:	^ p < 0.05 LAE vs No LAE	^^ p < 0.01, LAE vs No LAE	^^^ p <0.001, LAE vs No LAE

Table 5: Determinants of LAE

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.02 [0.98–1.05]	=0.309	…	…
Male gender	1.66 [0.63–4.34]	=0.302	…	…
BMI (kg/m^2)	0.97 [0.88–1.05]	=0.427	…	…
Office SBP (mmHg)	1.00 [0.99–1.02]	=0.688	…	…
Office DBP (mmHg)	1.01 [0.97–1.04]	=0.784	…	…
Diabetes mellitus	1.53 [0.30–7.79]	=0.610	…	…
Indexed LV mass (g/m^2)	1.02 [1.00–1.04]	=0.034*	1.00 [0.98–1.02]	=0.938
ECV (%)	1.30 [1.10–1.54]	=0.002*	1.24 [1.04–1.48]	=0.017*
Peak circ systolic strain rate (%/sec)	1.04 [1.01–1.07]	=0.003*	1.04 [1.01–1.07]	=0.022*

OR=odds ratio, CI=confidence interval, * P<0.05