Hypertension

ORIGINAL ARTICLE

Markers of Focal and Diffuse Nonischemic Myocardial Fibrosis Are Associated With Adverse Cardiac Remodeling and Prognosis in Patients With Hypertension: The REMODEL Study

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BACKGROUND: The prognostic significance of focal and diffuse myocardial fibrosis in patients with cardiovascular risk factors is unclear.

METHODS: REMODEL (Response of the Myocardium to Hypertrophic Conditions in the Adult Population) is an observational cohort of asymptomatic patients with essential hypertension. All participants underwent cardiovascular magnetic resonance to assess for myocardial fibrosis: nonischemic late gadolinium enhancement (LGE), native myocardial T1, postcontrast myocardial T1, extracellular volume fraction including/excluding LGE regions, interstitial volume (extracellular volume×myocardial volume), and interstitial/myocyte ratio. Primary outcome was a composite of first occurrence acute coronary syndrome, heart failure hospitalization, strokes, and cardiovascular mortality. Patients were recruited from February 2016 and followed until June 2021.

RESULTS: Of the 786 patients with hypertension (58±11 years; 39% women; systolic blood pressure, 130±14 mm Hg), 145 (18%) had nonischemic LGE. Patients with nonischemic LGE were more likely to be men, have diabetes, be current smokers, and have higher blood pressure ($P<0.05$ for all). Compared with those without LGE, patients with nonischemic LGE had greater left ventricular mass (66±22 versus 49±9 g/m^2; $P<0.001$), worse multidirectional strain ($P<0.001$ for all measures), and elevated circulating markers of myocardial wall stress and myocardial injury, adjusted for potential confounders. Twenty-four patients had primary outcome over 39 (30–50) months of follow-up. Of all the cardiovascular magnetic resonance markers of myocardial fibrosis assessed, only nonischemic LGE (hazard ratio, 6.69 [95% CI, 2.54–17.60]; $P<0.001$) and indexed interstitial volume (hazard ratio, 1.11 [95% CI, 1.04–1.19]; $P=0.002$) demonstrated independent association with primary outcome.

CONCLUSIONS: In patients with hypertension, myocardial fibrosis on cardiovascular magnetic resonance is associated with adverse cardiac remodeling and outcomes. (***Hypertension*. 2022;79:1804–1813. DOI: 10.1161/HYPERTENSIONAHA.122.19225.)** • **Supplemental Material**

Key Words: blood pressure ■ contrast media ■ humans ■ prognosis ■ smokers

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NOVELTY AND RELEVANCE

What Is New?

In patients with hypertension, nonischemic late gadolinium enhancement on cardiovascular magnetic resonance is associated with adverse left ventricular remodeling: greater left ventricular mass and concentricity, worse function, and elevated circulating markers of wall stress and myocardial injury.

As markers of focal and diffuse myocardial fibrosis, nonischemic late gadolinium enhancement and indexed interstitial volume assessed on cardiovascular magnetic resonance are independently associated with worse prognosis.

What Is Relevant?

Myocardial fibrosis is a pathological hallmark of heart failure. Reactive interstitial fibrosis is potentially reversible with targeted therapies.

The study highlights the potential role of using imaging markers to improve risk stratification, monitor disease progression, and guide antifibrotic therapies.

Clinical/Pathophysiological Implications?

The current study highlights the potential of cardiovascular magnetic resonance markers of focal and diffuse myocardial fibrosis. Nonischemic fibrosis can be used to improve risk stratification of patients with hypertension. Indexed interstitial combined with myocyte volume (calculated from the difference between indexed myocardial and interstitial volume) can track compartmental changes in the myocardium over time, assessing disease progression and treatment response. The potential of using these imaging markers to assess antifibrotic therapies in patients with hypertension is currently being investigated (Role of ARNi in Ventricular Remodelling in Hypertensive LVH [REVERSE-LVH]; https://www.clinicaltrials.gov; unique identifier: NCT03553810).

Nonstandard Abbreviations and Acronyms

CMR	cardiovascular magnetic resonance
ECV	extracellular volume
hsTnI	high-sensitivity cardiac troponin I
LGE	late gadolinium enhancement
LV	left ventricle
NT-proBNP	N-terminal pro-B type natriuretic peptide
REMODEL	Response of the Myocardium to Hypertrophic Conditions in the Adult Population

Hypertension is a major cause of ischemic heart disease, strokes, and heart failure.[1–3] About 30% of the burden associated with hypertension occurred in individuals with well-controlled blood pressures.[3] This presupposes that despite the substantial benefits in blood pressure lowering, conventional treatment does not normalize risks of cardiovascular events. One reason can be attributed to the heterogeneous myocardial response to hypertension. We have recently demonstrated systolic blood pressure (on 24-hour ambulatory monitors) accounted for about 20% of the variance observed in left ventricular (LV) mass.[4] Moreover, LV hypertrophy represents a spectrum from adaptation to decompensation. In an individual patient, the extent of hypertrophy when adaptive LV hypertrophy transitions to decompensation is not well-defined.

Myocardial fibrosis is a pathological hallmark of a failing heart.[5,6] Cardiovascular magnetic resonance (CMR) has emerged as the noninvasive imaging tool to characterize the myocardium. Gadolinium-based contrast agents have an increased volume of distribution in regions of myocardial fibrosis, which are characterized by an increased extracellular space. This technique of late gadolinium enhancement (LGE) imaging identifies regions of focal replacement fibrosis in the myocardium that appear bright compared with the surrounding black-appearing normal myocardium.[7] More recent development using T1 mapping techniques combined with gadolinium-based contrast agents allows robust quantification of the extracellular space.[8,9] These validated CMR approaches have demonstrated prognostic value in diverse patient populations.[10–17]

REMODEL (Response of the Myocardium to Hypertrophic Conditions in the Adult Population; https://www.clinicaltrials.gov; unique identifier: NCT02670031) was designed to investigate the significance of focal or diffuse myocardial fibrosis on CMR in asymptomatic patients with hypertension. We hypothesize CMR markers of nonischemic myocardial fibrosis are associated with adverse cardiac remodeling and have prognostic value in patients with hypertension.

METHODS

The data that support the findings of this study are included in this article or available from the corresponding author upon reasonable request.

Patient Population

REMODEL is a prospective, observational study of asymptomatic patients (≥21 years of age) with essential hypertension. The diagnosis of hypertension was guided by contemporary recommendations at the time of study initiation: (1) physician-diagnosed

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Table 1. Baseline Clinical and Cardiovascular Magnetic Resonance Characteristics in Asymptomatic Patients With and Without Nonischemic LGE

Participant characteristics	All participants (n=786)	No LGE (n=641)	Nonischemic LGE (n=145)	*P* value
Clinical				
Age, y	58±11	58±10	58±12	0.841
Men, n (%)	479 (61)	380 (59)	99 (68)	0.045
Body mass index, kg/m²	26.4±4.5	26.2±4.6	26.7±5.7	0.259
Diabetes, n (%)	162 (21)	116 (18)	46 (32)	<0.001
Dyslipidemia, n (%)	375 (48)	296 (46)	79 (55)	0.071
Smoking, n (%)	50 (6)	29 (5)	21 (15)	<0.001
Duration of hypertension, y	10±9	10±9	11±9	0.748
Antihypertensive medications, n	1 (1–2)	1 (1–2)	2 (1–2)	<0.001
Medications*				
ACE inhibitor/ARB, n (%)	428 (54)	339 (53)	89 (61)	0.064
CCB/β-blockers, n (%)	541 (69)	438 (68)	103 (71)	0.526
Others,† n (%)	98 (12)	79 (12)	19 (13)	0.798
Ambulatory SBP, mm Hg	130±14	129±14	137±16	<0.001
Ambulatory DBP, mm Hg	79±10	79±9	81±11	0.015
Laboratory				
Serum creatinine, μmol/L	77 (62–91)	76 (61–89)	81 (66–96)	0.003
HbA1c in diabetes, %	7.0 (6.6–7.7)	7.0 (6.6–7.5)	7.2 (6.6–8.1)	0.216
NT-proBNP, pg/mL	42 (19–84)	36 (17–73)	74 (34–166)	<0.001
hsTnI, ng/L	2.0 (0.9–4.0)	1.7 (0.6–3.2)	3.7 (2.0–8.4)	<0.001
Cardiovascular magnetic resonance				
Indexed LV mass, g/m²	52±14	49±9	66±22	<0.001
Indexed LV EDV, mL/m²	72±13	71±12	78±17	<0.001
Indexed LV ESV, mL/m²	29±9	28±7	34±15	<0.001
Indexed LV SV, mL/m²	43±8	43±7	44±9	0.473
LV ejection fraction, %	60±7	61±6	57±9	<0.001
LV mass/EDV ratio	0.73±0.15	0.70±0.11	0.85±0.21	<0.001
Maximal wall thickness, mm	8.9±1.9	8.5±1.4	10.7±2.7	<0.001
LV hypertrophy, n (%)	217 (28)	132 (21)	85 (59)	<0.001
Indexed RV EDV, mL/m²	73±13	73±13	73±14	0.891
Indexed RV ESV, mL/m²	30±9	30±9	29±11	0.685
Indexed RV SV, mL/m²	43±8	43±8	43±8	0.808
RV ejection fraction, %	60±8	60±7	60±9	0.279
Indexed LA volume, mL/m²	50±14	49±13	53±17	0.004
Global circumferential strain, %	−21.3±3.3	−21.8±2.9	−19.5±4.2	<0.001
Global radial strain, %	42.0±12.1	43.1±11.6	37.0±13.0	<0.001
Global longitudinal strain, %	−17.9±3.2	−18.4±2.9	−15.9±3.7	<0.001
Native T1, ms	1016 (998–1035)	1014 (997–1031)	1027 (1009–1049)	<0.001
Postcontrast T1, ms	540 (517–562)	542 (518–565)	538 (512–554)	0.021
ECV, %	25.7 (24.0–27.5)	25.6 (23.8–27.3)	26.6 (24.8–28.7)	<0.001
ECV (excluding LGE), %	25.5 (23.8–27.3)	25.6 (23.8–27.3)	25.1 (23.5–27.0)	0.220
Indexed interstitial volume, mL/m²	12.8±3.9	12.0±2.6	15.9±6.2	<0.001
Interstitial/myocyte ratio	0.35±0.05	0.34±0.05	0.37±0.06	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; ECV, extracellular volume fraction; EDV, end-diastolic volume; ESV, end-systolic volume; HbA1c, hemoglobin A1c; hsTnI, high-sensitivity cardiac troponin I; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricle; SBP, systolic blood pressure; and SV, stroke volume.

*Patients may be taking >1 medication.

†Diuretics, α_1 blockers, mineralocorticoid antagonists, hydralazine, and methyldopa.

essential hypertension, receiving at least 1 medication for blood pressure control or (2) newly diagnosed hypertension with office blood pressure ≥140/90 mm Hg at at least 2 separate clinic visits.[18–20] Exclusion criteria were secondary causes of hypertension (such as pheochromocytoma, bilateral renal artery stenosis, and polycystic kidney disease), cardiovascular diseases (such as ischemic heart disease and heart failure), previous strokes, atrial fibrillation, and contraindications to gadolinium contrast and CMR.[4] Patients with incidental myocardial infarction and cardiomyopathies (such as cardiac amyloidosis, sarcoidosis, and hypertrophic and dilated cardiomyopathy) on CMR were excluded from the current analysis.

Ambulatory blood pressure was measured with the OnTrak 90227 device (SpaceLabs Healthcare, Snoqualmie, WA). A properly sized cuff was selected and placed with the monitor for the patient on the day of CMR, after scan was performed. Resting BP was obtained after the monitor was placed to confirm correct function of the monitor. Measurements were obtained every 20 minutes from 6 AM to 10 PM and 30 minutes from 10 PM to 6 AM.

Ethics approval was obtained from the local centralized institutional review board, and all participants provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical Outcomes

The primary outcome was a composite of first occurrence of hypertension-related adverse events: acute coronary syndromes, acute decompensated heart failure (first heart failure hospitalization), strokes, and cardiovascular mortality (see the Supplemental Material for more details in defining clinical outcomes). Recruitment started in February 2016, and patients were followed until June 2021. Data in patients who were lost to follow-up were censored at the date when patient was last known to be alive and event free. Outcomes were adjudicated from reviewing patients' medical records by a cardiologist, who was blinded to the imaging data.

CMR Imaging and Analysis

All participants underwent standardized CMR (Siemens Aera 1.5T; Siemens Healthineers, Erlangen, Germany). Balanced steady-state free precession cine images were acquired in the long-axis 2-, 3-, and 4-chamber views (acquired voxel size, 1.6×1.3×8.0 mm; 30 phases per cardiac cycle). Short-axis cines extending from the mitral valve annulus to the apex were also acquired (acquired voxel size, 1.6×1.3×8.0 mm; 30 phases per cardiac cycle).

Myocardial fibrosis was assessed using 2 approaches: LGE imaging for nonischemic focal replacement fibrosis and myocardial T1 mapping for more quantitative assessment of diffuse interstitial myocardial fibrosis. LGE imaging was performed 8 minutes after 0.1 mmol/kg of gadobutrol (Gadovist; Bayer Pharma AG, Germany). An inversion-recovery fast gradient echo sequence was used, and the inversion time was optimized to achieve appropriate nulling of the myocardium. The modified Look-Locker inversion-recovery sequence was used for myocardial T1 mapping. Native and postcontrast myocardial T1 maps (15 minutes after contrast administration) were acquired using a heartbeat acquisition scheme of 5(3)3 and 4(1)3(1)2, respectively.

Deidentified imaging data were analyzed at the National Heart Research Institute Singapore (NHRIS) CMR Core Laboratory using a dedicated software (CVI42; Circle Cardiovascular Imaging, Calgary, Canada) by individuals who were blinded to the clinical and outcome data. Cardiac volumes, function, LV mass, and myocardial strain were analyzed according to standardized

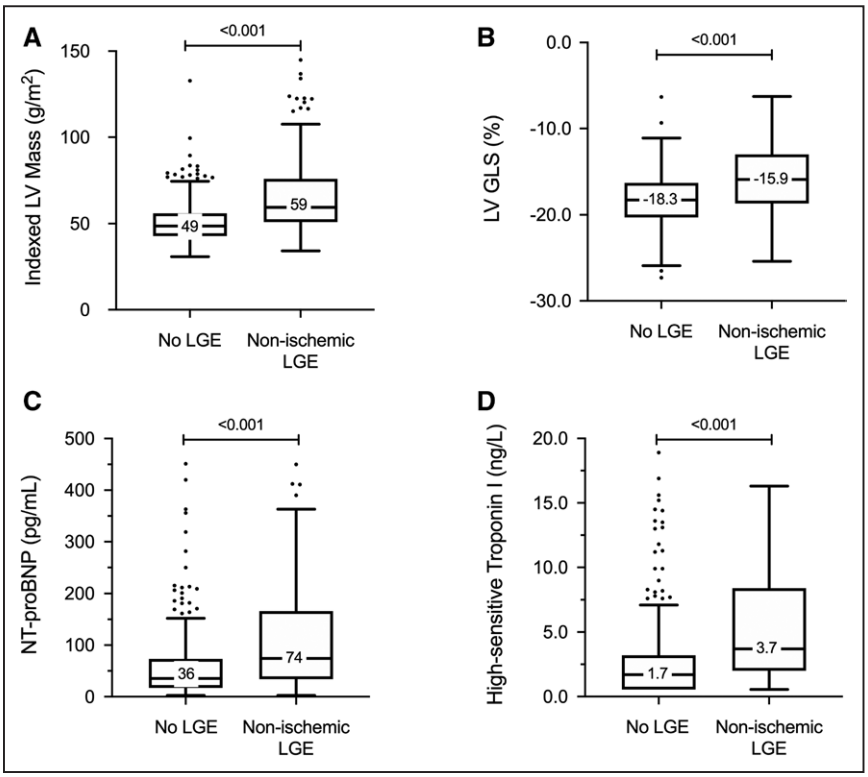

Figure 1. Association between nonischemic late gadolinium enhancement (LGE) and cardiac remodeling.
Nonischemic LGE was associated with greater left ventricular (LV) mass (**A**), worse LV global longitudinal strain (GLS; **B**), and elevated circulating markers of wall stress (NT-proBNP [N-terminal pro-B-type natriuretic peptide]; **C**) and myocardial injury (high-sensitivity troponin I; **D**). Results presented in box and whiskers (Tukey method).

protocols.[21,22] LGE was assessed qualitatively by 2 readers according to the recommendations by the Society of CMR.[23] Concentricity was defined as a ratio of LV mass and end-diastolic volume (M/V). Extracellular volume (ECV) fraction was assessed as a mean of the basal and midventricular slices (including regions of nonischemic LGE) using the T1 mapping module in CVI42 (Circle Cardiovascular Imaging; see the Supplemental Material for more background on ECV calculation). In a separate analysis, we also calculated ECV that excluded regions of nonischemic LGE in the pre- and postcontrast myocardial T1 maps. Interstitial volume was defined as ECV×myocardial volume, where myocardial volume (mL) is defined as myocardial mass (g)/1.05 g/mL. Of all the T1 measures of fibrosis examined, this measure demonstrated the strongest association with fibrosis on histology (r=0.87; $P<0.001$).[24] In this study, we used ECV that excluded regions of focal LGE to calculate interstitial volume to avoid any potential confounding by LGE.

Cardiac Biochemical Markers

Blood samples were collected on the day of CMR and stored at −80 °C. Biochemical analyses were performed in a single freeze-thaw cycle over 2 assay runs at a laboratory accredited by the College of American Pathologists (Changi General Hospital, Singapore). Serum NT-proBNP (N-terminal pro-B-type natriuretic peptide; proBNP II STAT; Roche Diagnostics, Pensberg, Germany) was assayed using electrochemiluminescence immunoassay on the Cobas E602 analyzer (Roche Diagnostics Asia Pacific, Singapore). Serum high-sensitivity cardiac troponin I (hsTnI; ARCHITECT STAT high-sensitivity troponin I; Abbott Diagnostics, Abbott Park, IL) was determined using chemiluminescent microparticle immunoassay on the ARCHITECT i2000SR analyzer (Abbott Laboratories, Singapore). The manufacturer-reported lower limit of detection NT-proBNP and hsTnI was 5 pg/mL and 1.1 ng/L, respectively.[25,26] All biochemical concentrations lower than the detection levels in the participants were assigned a value equivalent to half the limit of detection.

Statistical Analysis

For continuous variables, normality was assessed using the Shapiro-Wilk test. Normally distributed data are presented as mean±SD. Non-normally distributed data are presented as median (interquartile range). Continuous data were compared between groups using either the parametric Student *t* test or nonparametric Mann-Whitney *U* test, depending on normality of the distribution. Categorical data were compared using the χ^2 test.

Univariable Cox proportional-hazards models were used to examine the prognostic importance of clinically relevant (age, sex, diabetes, dyslipidemia, smoking, antihypertensive medications, blood pressure, creatinine, NT-proBNP, and hsTnI) CMR markers cardiac remodeling and myocardial fibrosis: nonischemic LGE, native myocardial T1, postcontrast myocardial T1, ECV (including and excluding LGE regions), indexed interstitial volume, and interstitial/myocyte ratio. Event-free survival curves associated with CMR markers of fibrosis were examined using the Kaplan-Meier method and compared with the log-rank test. These CMR markers were stratified into 2 groups, either the presence/absence (for nonischemic LGE) or with an interval of 1 SD above the mean of the cohort (for continuous variables).

Table 2. Univariable Cox Analyses of Clinical and Cardiovascular Magnetic Resonance Predictors of Cardiovascular Events

Participant characteristics	HR (95% CI)	*P* value
Clinical		
Age (per 10-y increment)	1.04 (0.69–1.57)	0.844
Men	2.11 (0.77–5.77)	0.145
Diabetes	1.09 (0.37–3.24)	0.881
Dyslipidemia	2.38 (0.96–5.90)	0.061
Smoking	2.60 (0.77–8.83)	0.126
Antihypertensive medications, n	2.35 (1.46–3.77)	<0.001
Ambulatory SBP (per 10 mm Hg increment)	1.49 (1.14–1.97)	0.004
Creatinine (per 10 µmol/L increment)	1.27 (1.09–1.48)	0.002
NT-proBNP (per 10 pg/mL increment)	1.01 (0.99–1.03)	0.191
hsTnI	1.00 (0.99–1.02)	0.746
Cardiovascular magnetic resonance		
Indexed LV mass (per 10 g/m² increment)	1.48 (1.28–1.69)	<0.001
Indexed LV EDV (per 10 mL/m² increment)	1.57 (1.31–1.88)	<0.001
LV ejection fraction (per 10% decrement)	0.52 (0.39–0.70)	<0.001
Indexed LA volume (per 10 mL/m² increment)	1.25 (0.97–1.61)	0.087
LV mass/EDV ratio (per 10% increment)	1.24 (1.10–1.40)	<0.001
Global longitudinal strain	1.28 (1.13–1.44)	<0.001
Presence of nonischemic LGE	8.44 (3.49–20.39)	<0.001
Native T1 (per 10 ms increment)	1.20 (1.13–1.28)	<0.001
Postcontrast T1 (per 10 ms decrement)	0.93 (0.82–1.06)	0.286
ECV	1.28 (1.11–1.47)	0.027
ECV (excluding LGE)	1.20 (1.02–1.41)	0.027
Interstitial volume index	1.15 (1.10–1.21)	<0.001
Interstitial/myocyte ratio (per 10% increment)	1.55 (1.22–1.96)	<0.001

ECV indicates extracellular volume; EDV, end-diastolic volume; HR, hazard ratio; hsTnI, high-sensitivity cardiac troponin I; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SBP, systolic blood pressure.

The proportional-hazards assumption was tested by including a time-dependent covariate representing the interaction between CMR markers of fibrosis and follow-up time. A nonsignificant *P* for this covariate ($P>0.20$) was taken as evidence that the proportional-hazards assumption has been satisfied.

Statistical analyses were performed using SPSS, version 24 (SPSS; IBM, Inc, Armonk, NY), and GraphPad Prism 8.1.2 (GraphPad Software, Inc, San Diego, CA). Unless otherwise stated, a 2-sided $P<0.05$ was considered as statistically significant.

RESULTS

In the cohort of 786 participants (58±11 years; 61% men; 130±14 mm Hg), 145 patients (18%) had nonischemic LGE (see the Supplemental Material for patient flowchart). Compared with those without LGE, patients

with nonischemic LGE were more likely to be men (68% versus 59%; P=0.045), have diabetes (32% versus 18%; P<0.001), be current smokers (15% versus 5%; P<0.001), and have worse renal function (81 [66–96] versus 76 [61–89] µmol/L; P=0.003). The patients with nonischemic LGE also had higher 24-hour systolic blood pressure (137±16 versus 129±14 mm Hg; P<0.001) and took more antihypertensive medications (P<0.001). There was no difference in age, body mass index, and duration of hypertension between the 2 groups (P>0.05; Table 1).

The presence of nonischemic LGE was associated with adverse LV remodeling: greater LV mass and concentricity, worse LV function, and elevated circulating markers of cardiac wall stress and myocardial injury (Table 1; Figure 1). Indexed left atrial volumes were larger in patients with nonischemic LGE compared with those without LGE (53±17 versus 49±13 mL/m^2; P=0.004). These observations remained significant after adjusting for potential confounding from clinical variables that were significantly different between the 2 groups: systolic blood pressure, creatinine levels, diabetes, and smoking status (P≤0.001 for all analyses after adjusting). Of note, RV volumes and function were similar between patients with and without nonischemic LGE.

CMR Markers of Myocardial Fibrosis as Predictors of Adverse Outcomes

There were 24 patients with primary outcome over 39.2 (30.1–50.3) months of follow-up (0.9 events per 100 patient-years): myocardial infarction (ST-segment and non–ST-segment elevation), n=7; unstable angina, n=3; incident heart failure, n=6; strokes, n=5; cardiovascular mortality, n=3.

Clinical parameters such as systolic blood pressures, number of antihypertensive medications, and creatinine and CMR markers of remodeling such as indexed LV mass, concentricity, LV ejection fraction, and multidirectional strain were associated with primary outcome. All CMR measures of myocardial fibrosis, except postcontrast myocardial T1 (hazard ratio, 0.93 [95% CI, 0.82–1.06]; P=0.286), were significant predictors of primary outcome in the univariable analyses (Table 2). Increased interstitial volumes defined as ≥17.0 mL/m^2 (corresponding to 1 SD above the mean indexed interstitial volume of the cohort) also predicted worse cardiovascular outcome (hazard ratio, 9.41 [95% CI, 4.00–22.17]; P<0.001). Only the presence of nonischemic LGE (hazard ratio, 6.69 [95% CI, 2.54–17.60]; P<0.001) and indexed interstitial volume (hazard ratio, 1.11 [95% CI, 1.04–1.19]; P=0.002) were independently associated with primary outcome (Figure 2; see the Supplemental Material for more detailed analyses).

In an exploratory post hoc analysis to examine the incremental prognostic value of nonischemic LGE and interstitial volume, we stratified the measures into the following categories: (1) absence of LGE and no increased interstitial volume, (2) presence of nonischemic LGE only, (3) presence of increased interstitial volume only, and (4) presence of both nonischemic LGE and increased interstitial volume. Patients without LGE and no increased interstitial volume had the best prognosis (0.3 events/100 patient-years), whereas those with both nonischemic LGE and increased interstitial volume had the worst (5.0 events/100 patient-years). The event rates were similar in those with nonischemic LGE only (1.6 events/100 patient-years) and those with increased interstitial volume only (2.4 events/100 patient-years; pairwise log-rank P=0.802; Figure 3). Across the 4 groups of patients, those with the presence of both nonischemic LGE and increased interstitial volume had consistently the worst cardiac remodeling—highest concentration of circulating markers of wall stress (NT-proBNP) and myocardial injury (hsTnI), largest LV mass, increased left atrial volumes—and the worst multidirectional strain (Figure 4). Furthermore, nearly all patients in

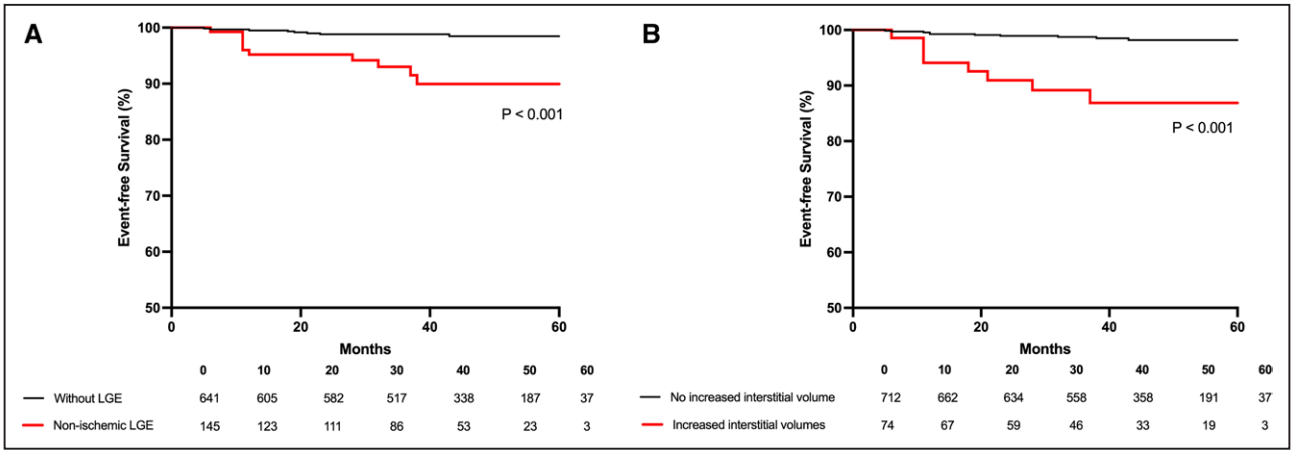

Figure 2. Event-free survival of primary outcome in asymptomatic hypertensive patients.
Survival curves demonstrating worse prognosis in patients with nonischemic late gadolinium enhancement (LGE; **A**) or increased interstitial volume (≥17.0 mL/m^2 corresponding to 1 SD above the mean indexed interstitial volume of the cohort; **B**).

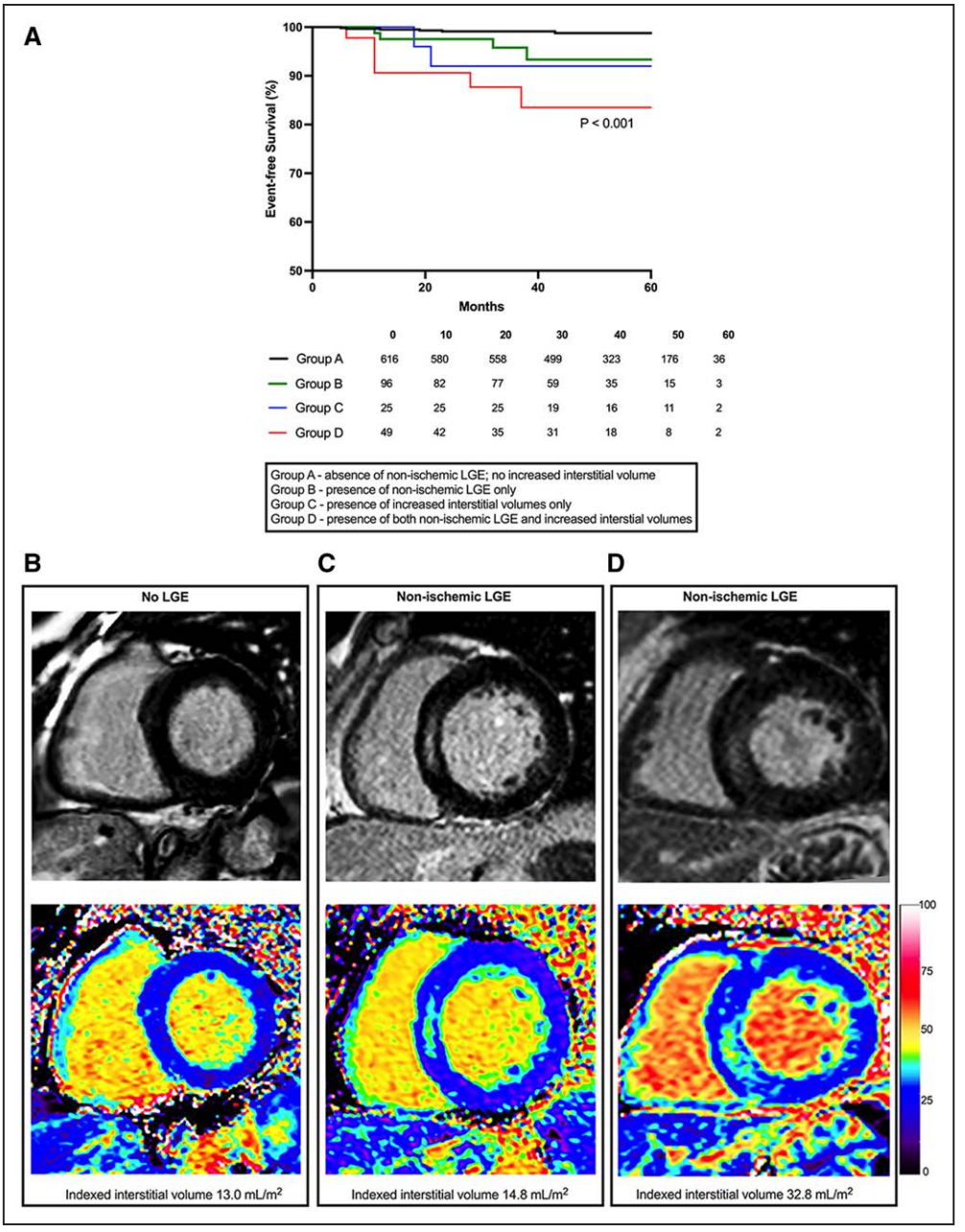

Figure 3. Event-free survival curves of primary outcome and representative images of asymptomatic hypertensive patients with nonischemic late gadolinium enhancement (LGE) and increased interstitial volume.
Event-free survival curves demonstrating worst prognosis in those with both nonischemic LGE and increased interstitial volume. Individuals with either nonischemic LGE or increased interstitial volume had similar outcomes (**A**). LGE images and extracellular volume maps of patients without LGE (**B**) and with nonischemic LGE (**C** and **D**). In this study, increased interstitial volume was defined as ≥17.0 mL/m^2 (**D**), corresponding to 1 SD above the mean indexed interstitial volume of the cohort.

this group had LV hypertrophy, defined by sex- and age-specific Asian thresholds. Similar findings were observed with interstitial volumes calculated based on ECV that included LGE regions.

DISCUSSION

The main finding of the study is nonischemic LGE in asymptomatic patients with hypertension is associated with adverse hypertrophic response, worse LV function (including diastolic function using left atrial volumes), and elevated circulating markers of cardiac wall stress (NT-proBNP) and myocardial injury (hsTnI). This is the first report to systematically evaluate the prognostic value of known CMR markers of myocardial fibrosis in patients with cardiovascular risk factors. Of all the measures assessed, conventional nonischemic LGE and novel ECV-based indexed interstitial volume are identified as independent predictors of adverse outcomes in this large cohort of patients with hypertension.

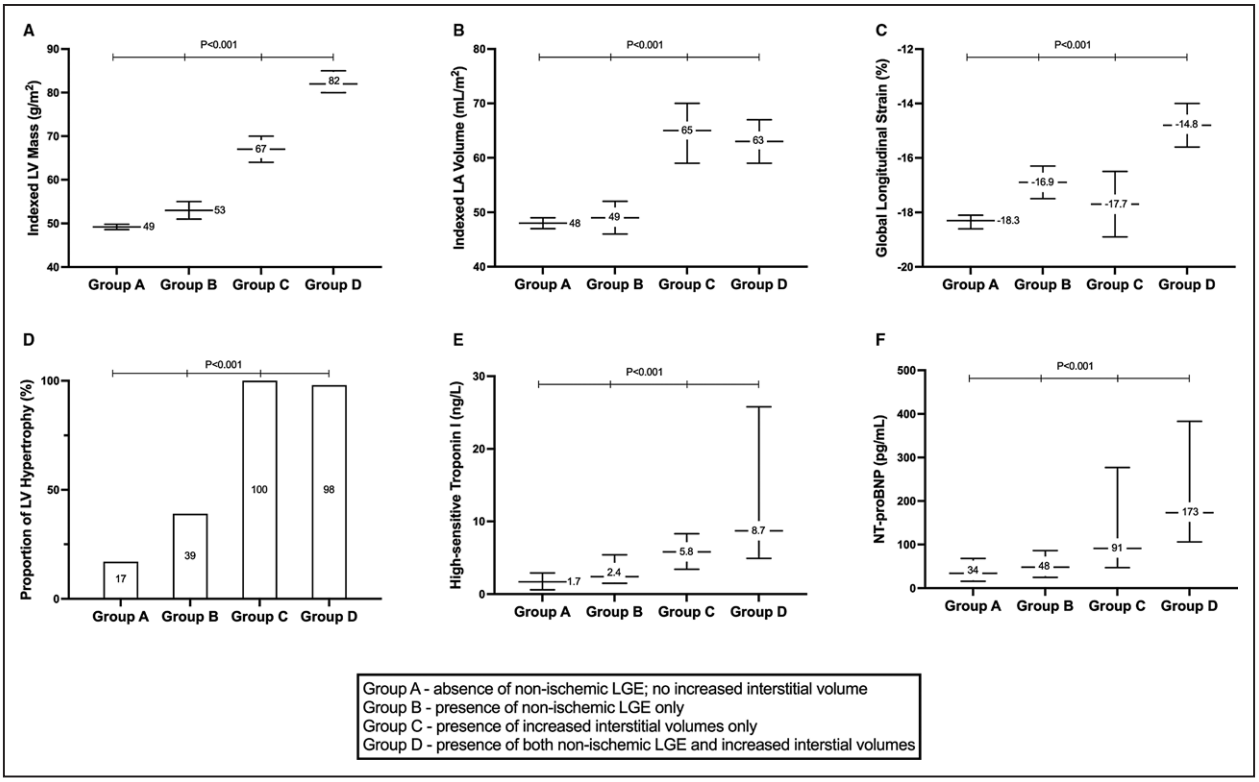

Figure 4. Circulating and cardiovascular magnetic resonance markers of cardiac remodeling in asymptomatic hypertensive patients with nonischemic late gadolinium enhancement and increased interstitial volume.
Compared with patients in the other groups, patients in group D had the highest left ventricular (LV) mass (**A**), increased left atrial (LA) volumes (**B**), and worst LV global longitudinal strain (GLS; **C**). Nearly all patients in group D had LV hypertrophy (**D**). Circulating markers of myocardial injury (high-sensitivity troponin I; **E**) and myocardial wall stress (NT-proBNP [N-terminal pro-B-type natriuretic peptide]; **F**) were also elevated in patients in group D. Data in **A**–**C** were presented in mean and 95% CI, adjusted for age, sex, and systolic blood pressure; data in **D** were presented in proportions; and data in **E** and **F** were presented in median and interquartile range.

In the study, patients with hypertension and nonischemic LGE were more likely to be men, have diabetes, be current smokers, and have worse renal function. They also had higher blood pressures and took more antihypertensive medications. This profile likely predisposes patients to higher risk of myocardial fibrosis due to the activation of the renin-angiotensin-aldosterone system, β-adrenergic system, inflammatory/immune pathways, and metabolic disturbances induced by hyperglycemia/insulin resistance.[27,28] As a consequence, they also have worse cardiac function and advanced hypertrophy, including elevated circulating biomarkers of myocardial wall stress and cardiac injury, which concurred and extended previous studies.[4,29–31]

Although nonischemic myocardial fibrosis has been reported in patients with hypertension,[30,32,33] the prognostic significance is not well understood. We observed that most CMR measures of nonischemic myocardial fibrosis (native T1, nonischemic LGE, ECV, and indexed interstitial volume) demonstrated prognostic associations in univariable analyses. Only nonischemic LGE and indexed interstitial volume remained as independent prognostic predictors. Nonischemic LGE implies replacement fibrosis. Replacement fibrosis follows myocyte necrosis, and it is believed to be more advanced and nonmodifiable.[27] Reactive interstitial fibrosis is characterized by the diffuse accumulation of collagen within the interstitium and perivascular space. This pattern of fibrosis has generated intense interest as a marker of intermediate disease severity that is potentially reversible.[34–37] The intrinsic differences in CMR assessment of interstitial fibrosis may partly account for the independent prognostic value observed with indexed interstitial volume over ECV and native T1. Native T1 reflects the combined interstitial and myocyte compartments; theoretically it is not considered a true measure of the interstitial space. ECV assesses the interstitium as a proportion of the total LV myocardial volume, whereas indexed interstitial volume estimates the absolute ECV (indexed to body surface area). Of note, indexed interstitial volume had the strongest correlation with myocardial fibrosis on histology compared with ECV and native T1.[24]

Nonischemic LGE was a much stronger independent predictor compared with indexed interstitial volume. These findings also provide pathophysiological insights, supporting the notion that focal replacement fibrosis (nonischemic LGE) and diffuse interstitial fibrosis (indexed interstitial volume) are related but independent

markers of different stages of myocardial fibrosis. In the exploratory analysis, the presence of both expanded interstitial volume and nonischemic LGE was associated with the worst features of cardiac remodeling and prognosis compared with those with either expanded interstitial volume or nonischemic LGE alone. Expansion in the extracellular compartment due to interstitial fibrosis is a transition from healthy myocardium to subclinical decompensation. In the presence of an expanded interstitium, focal replacement fibrosis is believed to result from the progression of interstitial fibrosis, and it is associated with a more advanced stage of cardiac decompensation. Because of the low event rates, these findings should be interpreted with caution and requires further validation. In particular, more studies are needed to compare the prognostic significance of the different T1 or ECV measures and the incremental value it can offer to nonischemic LGE.

Study Limitations

The is a single-center study, and the findings will need to be confirmed in other cohorts of patients with hypertension and cardiovascular risk factors. The duration of follow-up period accounted for the relatively small numbers of events that precluded further detailed subgroup and multivariable analyses, avoiding potential overfitting of the models.

Conclusions

The study demonstrated that both focal and diffuse myocardial fibrosis assessed on CMR is associated with adverse cardiac remodeling and prognosis and underscores its potential as a therapeutic target. Further studies are needed to investigate the potential role of using these imaging biomarkers to guide targeted therapies.

Perspectives

Cardiovascular complications remain high in patients with hypertension, even those with well-controlled blood pressure. In a cohort of 786 patients with hypertension, CMR markers of nonischemic myocardial fibrosis are independently associated with adverse cardiac remodeling and worse prognosis. The study highlights the role of these imaging markers to improve risk stratification and monitor disease progression in hypertension. As a pathological hallmark of heart failure, myocardial fibrosis is also a potential therapeutic target. These imaging markers have potential to guide and monitor treatment response.

ARTICLE INFORMATION

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Disclosures

None.

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