

## Novel Index of Maladaptive Myocardial Remodeling in Hypertension

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**Background**—Hypertensive left ventricular hypertrophy (HTN-LVH) is a leading cause of heart failure. Conventional patterns of cardiac geometry do not adequately risk-stratify patients with HTN-LVH. Using cardiovascular magnetic resonance, we developed a novel Remodeling Index (RI) that was designed to detect an exaggerated hypertrophic response to hypertension and tested its potential to risk-stratify hypertensive patients.

**Methods and Results**—The RI was derived using LaPlace's Law ( $\frac{\sqrt[3]{\text{end-diastolic volume}}}{\text{max wall thickness}}$ ), and normal RI ranges were

established in 180 healthy volunteers. The utility of the RI was examined in 256 asymptomatic hypertensive patients and 10 patients with heart failure with preserved ejection fraction. Hypertensive patients underwent multimodal cardiac assessment: contrast-enhanced cardiovascular magnetic resonance, echocardiograms, 24-hour blood pressure monitoring, and cardiac biomarkers (high-sensitivity cardiac troponins, NT-proBNP [N-terminal pro-B-type natriuretic peptide], and galectin-3). Blood pressure accounted for only 20% of the variance observed in LV mass. Although there was no association between blood pressure and myocardial fibrosis, LV mass was independently associated with fibrosis. Compared with hypertensive patients without LVH (n=191; 74.6%) and those with HTN-LVH and normal RI (n=50; 19.5%), patients with HTN-LVH and low RI (HTN-LVH/low RI; n=15, 5.9%) had an amplified myocardial response: elevated indexed LV masses ( $83 \pm 24$  g/m<sup>2</sup>), more fibrosis (73%), and higher biomarkers of myocardial injury and dysfunction ( $P < 0.05$  for all). RI was similar in HTN-LVH/low RI and heart failure with preserved ejection fraction (4.1 [3.4–4.5] versus 3.7 [3.4–4.0], respectively;  $P = 0.15$ ).

**Conclusions**—We suggest that RI provides an approach for stratifying hypertensive patients and is suitable for testing in other disease cohorts to assess its clinical utility.

**Clinical Trial Registration**—URL: <https://clinicaltrials.gov>. Unique identifier: NCT02670031.

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**Key Words:** blood pressure ■ heart diseases ■ hypertrophy, left ventricular ■ magnetic resonance imaging ■ natriuretic peptide, brain

Hypertensive heart disease is a syndrome characterized by left ventricular hypertrophy (LVH), systolic and diastolic dysfunction alongside the clinical manifestations of heart failure.<sup>1</sup> In susceptible patients, the myocardium progressively thickens in response to elevated arterial pressure to minimize myocardial wall stress ( $\sigma$ ) according to the LaPlace's Law:  $\sigma = [P \times r] / 2h$ , where  $P$  is the left ventricular (LV) pressure,  $r$  is the LV radius, and  $h$  is the myocardial wall thickness. These changes are initially adaptive to maintain cardiac output and function. Over time, the LV can decompensate and fail.<sup>1–3</sup> Two major processes drive the transition from ventricular adaptation to decompensation: cardiac

myocyte dysfunction/death and myocardial fibrosis.<sup>4</sup> Myocyte dysfunction/death occurs in response to chronic exposure to neurohormonal factors and progressive myocardial ischemia associated with elevated wall stress.<sup>5,6</sup> Myocardial fibrosis, a common final pathology in all heart failure causes, is characterized by an increase in collagen volume fraction of myocardial tissue that can be assessed noninvasively using contrast-enhanced cardiovascular magnetic resonance (CMR) techniques.<sup>7</sup>

**See Editorial by Aurigemma and Salerno  
See Clinical Perspective**

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Hypertensive LVH is associated with adverse prognosis, above and beyond the effects of blood pressure (BP).<sup>8–14</sup> Four LV geometric patterns have conventionally been described: normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy,<sup>15</sup> but the 3-dimensional (3D) phenotype of LVH shows the true situation to be far more nuanced.<sup>16</sup> Both concentric and eccentric LVH patterns are associated with increased cardiovascular events. LV geometry has limited incremental prognostic value when LV mass and other cardiovascular risk factors are considered.<sup>10,17–22</sup> Therefore, a better marker of adverse remodeling is needed to identify high-risk hypertensive LVH phenotypes.

Ventricular dilatation and myocardial thickening are 2 important determinants of increased LV mass and myocardial wall stress. We hypothesize that an index of LV end-diastolic volume (EDV) and wall thickness (Remodeling Index [RI]) may provide a more clinically relevant readout of adverse ventricular remodeling by combining the effects of LV volumes and wall thickness in a single metric. Using multi-imaging techniques (CMR and echocardiography), ECG, comprehensive BP assessment (office and 24-hour ambulatory), and cardiac biomarkers (high-sensitive cardiac troponin I/T [hsTnI/T], NT-proBNP [N-terminal pro-B-type natriuretic peptide], and galectin-3), we aim to examine the myocardial response and the potential role of RI in hypertensive patients.

## Methods

### Derivation of the Novel RI

The Law of LaPlace states the factors that determine LV generated wall stress,  $\sigma$ , as:

$$\sigma = \frac{PR}{2t}, \quad (1)$$

where  $P$  is intra-LV pressure generated during passive filling (at end of diastole),  $R$  is LV radius, and  $t$  is LV wall thickness.<sup>23,24</sup> Assuming LV to be spherical, LV volume is related to radius ( $R$ ):

$$V = \frac{4}{3}\pi R^3, \text{ where } V = \text{EDV} \quad (2)$$

$$R = \sqrt[3]{\frac{3}{4\pi}\text{EDV}} \quad (3)$$

Substituting Equation 3 into Equation 1, we have

$$\sigma = c \cdot P \frac{\sqrt[3]{\text{EDV}}}{t}, \text{ where } c = \frac{\sqrt[3]{3}}{2} \quad (4)$$

We define  $\frac{\sqrt[3]{\text{EDV}}}{t}$  as the RI, which describes the geometric relationship between LVEDV and wall thickness and it is proportionate to the LV generated wall stress ( $\sigma \propto P \cdot \text{RI}$ ). LVEDV and maximum wall thickness (across the 16 segments) were used in the calculation of RI.

### Patient Population

The REMODEL study (Response of the Myocardium to Hypertrophic Conditions in the Adult Population) consists of adults with essential hypertension. We excluded individuals with known secondary causes of hypertension; those with previously diagnosed significant coronary artery disease (previous myocardial infarction,  $\geq 70\%$  luminal stenosis on invasive angiography, or positive cardiac stress tests), cerebrovascular events, heart failure, atrial fibrillation; and those with contraindications to gadolinium contrast and CMR (implantable

devices, cerebral aneurysmal clips, cochlear implants, estimated glomerular filtration rate  $< 30$  mL/min per  $1.73\text{m}^2$ , severe claustrophobia, and women who are pregnant or breastfeeding).

Healthy volunteers between 20 and 69 years old ( $n=180$ ) without cardiac symptoms, coronary artery risk factors, and clinical and family history of cardiovascular disease were prospectively recruited from the community. The inclusion and exclusion criteria of this cohort have been described in detail previously.<sup>25</sup>

Patients in the REMODEL cohort did not have heart failure. We examined the role of RI in patients with hypertension and heart failure with preserved ejection fraction (HFpEF) who had been referred for CMR evaluation. These patients did not have other diagnoses that could account for heart failure, such as ischemic heart disease, valvular heart disease, or infiltrative cardiomyopathies.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local research ethics committee. Written informed consent was obtained from all participants.

## Cardiovascular Procedures and Biochemical Markers

All participants in REMODEL underwent comprehensive cardiovascular assessment including 24-hour ambulatory BP, ECG, echocardiography, CMR, and cardiac biochemical markers.

### Electrocardiography

A standard 12-lead ECG was obtained in all participants. ECGs were scored according to the Romhilt–Estes score that includes voltage criteria, ST-T abnormalities, QRS duration and other variables to diagnose LVH on ECG.<sup>26</sup>

### Echocardiography

Echocardiography was performed in all hypertensive patients (ProSound F75; Hitachi Aloka Medical Ltd., Tokyo, Japan). Cardiac dimensions, function, and severity of valvular heart disease (if present) were assessed according to the European Association of Echocardiography/American Society of Echocardiography guidelines.<sup>15,27,28</sup> Diastolic function was assessed using pulse-wave and tissue Doppler imaging. Trans-mitral early (E), late diastolic velocities, and deceleration time of early filling velocity were measured at the tips of the mitral valve leaflets in the apical 4-chamber view. Early diastolic velocities ( $e'$ ) of the medial and lateral mitral annulus were measured using tissue Doppler imaging. Diastolic function was assessed using the E/ $e'$  ratio.

### Cardiovascular Magnetic Resonance

CMR was performed in all participants (Siemens Ingenia 1.5T; Siemens AG, Healthcare Sector, Erlangen, Germany). Balanced steady-state free precision cine images of the vertical and horizontal long-axis planes and the sagittal LV outflow tract view were acquired (acquired voxel size  $1.6 \times 1.3 \times 8.0$  mm; 30 phases per cardiac cycle). Short-axis cines were obtained from the mitral valve annulus to the apex (acquired voxel size  $1.6 \times 1.3 \times 8.0$  mm; 30 phases per cardiac cycle). Image analysis was performed in our dedicated research laboratory using standardized protocols for measuring cardiac volumes, function and LV mass (CMR42; Circle Cardiovascular Imaging, Calgary, Canada).<sup>25</sup> End-diastolic myocardial wall thickness was measured semiautomatically in the short-axis views (50 chords per myocardial slice), according to the standard 16-segment model (Data Supplement). Short-axis slices that did not have complete ring of myocardium were excluded in the wall thickness analysis.

Myocardial fibrosis was assessed using 2 approaches: late gadolinium-enhanced imaging (focal replacement fibrosis) and myocardial T1 mapping (diffuse myocardial fibrosis). Late gadolinium-enhanced imaging started 8 minutes after  $0.1$  mmol/kg of gadobutrol (Gadovist; Bayer Pharma AG, Germany). An inversion-recovery fast gradient echo sequence was used. The inversion time was optimized to achieve appropriate nulling of the myocardium. Myocardial T1 mapping was performed using the Modified Look-Locker inversion-recovery sequence (flip angle  $35^\circ$ ; minimum TI 100 ms; TI increment of 80 ms). Native and postcontrast myocardial

T1 (15 minutes after contrast administration) were acquired using a heartbeat acquisition scheme of 5(3)3 and 4(1)3(1)2, respectively. Extracellular volume fraction was quantified using an approach as described previously.<sup>29</sup> Recently, we have demonstrated an excellent correlation between interstitial volume on CMR and the amount of histological fibrosis that had an adverse prognostic impact on patients with aortic stenosis.<sup>30</sup> Interstitial volume was defined as extracellular volume fraction  $\times$  myocardial volume, where myocardial volume (mL)=myocardial mass (g)/1.05 g/mL.

### Cardiac Biochemical Markers

All biochemical analyses were performed in a single freeze–thaw cycle  $>3$  assay runs using the same lot of reagents in an accredited laboratory (Changi General Hospital, Singapore). Serum NT-proBNP (proBNP II STAT; Roche Diagnostics, Pensberg, Germany) and hsTnT (STAT; Roche Diagnostics, Pensberg, Germany) were assayed using electrochemiluminescence immunoassay on the Cobas E602 analyzer (Roche Diagnostics Asia-Pacific, Singapore). Serum hsTnI (ARCHITECT STAT High-Sensitive Troponin-I; Abbott Diagnostics, Abbott Park, IL) and galectin-3 (ARCHITECT Galectin-3; Abbott Diagnostics) were determined using chemiluminescent microparticle immunoassay on the ARCHITECT i2000SR analyzer (Abbott Laboratories [Diagnostics], Singapore). Blood samples were collected on the day of CMR.

The manufacturer-reported lower limit of detection (LOD) and the 99th percentile upper reference limit for NT-proBNP were 5 and 135 pg/mL, respectively.<sup>31</sup> The LOD and 99th percentile upper reference limit for hsTnT were 5 and 14 pg/mL, respectively.<sup>32</sup> The LOD for hsTnI was 1.1 ng/L. We have determined previously that the 99th percentile upper reference limit for hsTnI was 26 ng/L.<sup>33</sup> Serum galectin-3 had a manufacturer-reported LOD of 1.0 ng/mL.<sup>34</sup> All biochemical concentrations lower than the detection levels were assigned a value equivalent to half the LOD.

### Statistical Analysis

Continuous variables were assessed for normal distribution using the Shapiro–Wilk test. Data were presented in either mean $\pm$ SD or median (interquartile range), as appropriate. Depending on the normality of the data, parametric Student *t* test and 1-way ANOVA or the nonparametric Mann–Whitney *U* test and Kruskal–Wallis test were used to compare groups of continuous data. Categorical data were compared using the  $\chi^2$  tests. We used multivariable linear and logistic regression models to assess association between variables, adjusting for potential confounders (age, sex, systolic BP [SBP], treatment duration, and where appropriate, LV mass, and LV concentricity). Log-transformed NT-proBNP, hsTnT/I, and galectin-3 concentrations were used in correlations and regression analyses because of non-normal distribution.

Normal RI ranges were established in healthy volunteers using the 95% prediction interval: mean  $\pm t_{0.975, n-1} (\sqrt{(n+1)/n}) \cdot (SD)$ . To account for the effects of sample size on the reference range, 95% confidence intervals of the upper and lower reference limits were estimated.<sup>35</sup> Values within these confidence limits were considered indeterminate/borderline.<sup>25</sup>

Analyses were performed using GraphPad Prism 6 (GraphPad Software, Inc., San Diego) and STATA/MP version 13.0 (StataCorp, TX). Statistical significance was taken as a 2-sided  $P < 0.05$ .

## Results

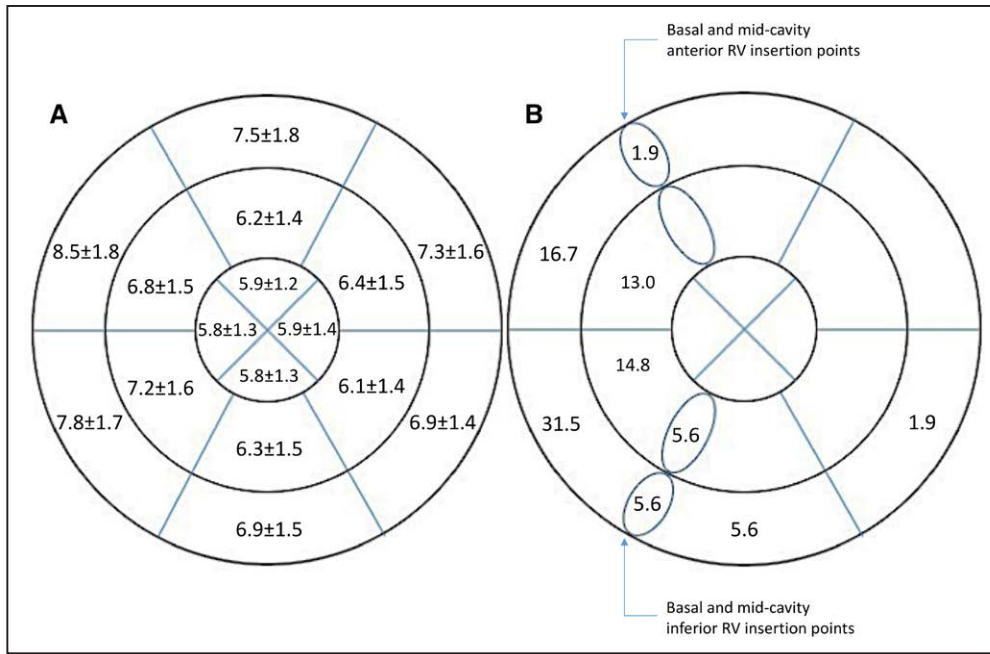
### Baseline Characteristics

Patients in REMODEL ( $n=256$ ; men=66%) were older and had higher body mass index compared with healthy volunteers ( $n=180$ ; men=51%). Hypertensive patients in REMODEL had close to normal BPs as they were receiving antihypertensive treatment (Table 1). Twelve patients had moderate valvular heart disease diagnosed on echocardiography and corroborated

**Table 1. Baseline Characteristics of Healthy Volunteers and Patients with Hypertension**

	Healthy Volunteers (n=180)	REMODEL (n=256)	P Value
Clinical characteristics			
Age, y	45 $\pm$ 13	58 $\pm$ 11	<0.001
Males, n (%)	91 (51)	169 (66)	<0.01
Hyperlipidemia, n (%)	...	93 (36)	...
Diabetes mellitus, n (%)	...	28 (11)	...
24-h SBP, mm Hg	...	130 $\pm$ 13	...
24-h DBP, mm Hg	...	80 $\pm$ 10	...
Office SBP, mm Hg	130 $\pm$ 16	142 $\pm$ 19	<0.001
Office DBP, mm Hg	79 $\pm$ 11	81 $\pm$ 13	0.07
Heart rate, bpm	75 [67–83]	68 [60–77]	<0.001
Body surface area, m <sup>2</sup>	1.70 $\pm$ 0.20	1.79 $\pm$ 0.21	<0.001
Romhilt–Estes ECG score	...	3 [1–4]	...
Myocardial structure and function			
LV end-diastolic volume, mL/m <sup>2</sup>	75 $\pm$ 12	74 $\pm$ 15	0.25
LV end-systolic volume, mL/m <sup>2</sup>	30 $\pm$ 7	28 $\pm$ 9	0.07
LV stroke volume, mL/m <sup>2</sup>	45 $\pm$ 7	45 $\pm$ 8	0.92
LV ejection fraction, %	60 $\pm$ 5	62 $\pm$ 6	0.02
RV end-diastolic volume, mL/m <sup>2</sup>	84 $\pm$ 15	74 $\pm$ 13	<0.001
RV end-systolic volume, mL/m <sup>2</sup>	39 $\pm$ 11	30 $\pm$ 9	<0.001
RV stroke volume, mL/m <sup>2</sup>	45 $\pm$ 7	45 $\pm$ 8	0.85
RV ejection fraction, %	54 $\pm$ 7	61 $\pm$ 7	<0.001
LV mass, g/m <sup>2</sup>	45 $\pm$ 9	53 $\pm$ 15	<0.001
Interstitial volume, mL/m <sup>2</sup>	...	12.5 [11.0–14.3]	...
Max. wall thickness, mm	7.6 $\pm$ 1.5	8.9 $\pm$ 1.9	<0.001
LA volume, mL/m <sup>2</sup>	45 $\pm$ 11	51 $\pm$ 14	<0.001
RA area, cm/m <sup>2</sup>	11.4 $\pm$ 2.0	12.1 $\pm$ 2.3	<0.01
Diastolic function E/e'	...	8.0 $\pm$ 2.1	...
Biochemical markers			
Serum creatinine, $\mu$ mol/L	76 $\pm$ 18	82 $\pm$ 19	<0.01
NT-proBNP, pg/mL	26.5 [13.1–41.1]	35.6 [14.1–76.7]	<0.01
High-sensitive troponin T, pg/mL	2.5 [2.5–2.5]	5.5 [2.5–7.8]	<0.001
High-sensitive troponin I, ng/L	0.5 [0.5–1.9]	1.7 [0.8–3.4]	<0.001
Galectin-3, ng/mL	11.4 [10.0–13.2]	12.6 [10.6–14.6]	<0.001

DBP indicates diastolic blood pressure; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RA, right atrial; RV, right ventricular; and SBP, systolic blood pressure.



**Figure 1.** Maximal wall thickening were predominantly localized in the basal anterior segments and septum (A). Midwall myocardial fibrosis was predominantly present in the basal and midventricular septum (B). Maximal wall thickness (mm) and proportion of segments (%) with midwall fibrosis are presented in A and B, respectively.

on CMR (aortic regurgitation, n=5; tricuspid regurgitation, n=5; mitral regurgitation, n=2). No patients had aortic stenosis.

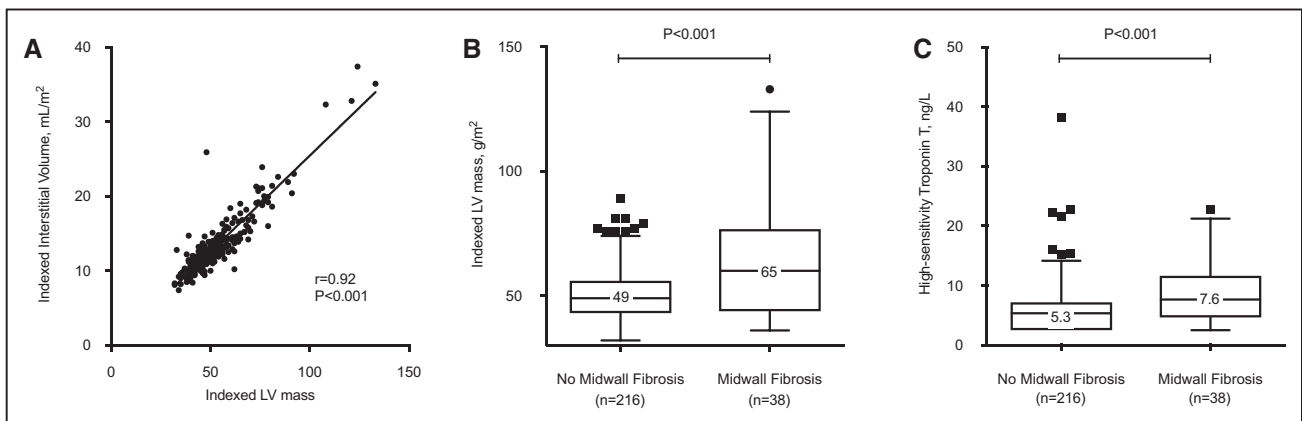
**Hypertensive LVH and Myocardial Fibrosis**

The thickest LV segments were predominantly localized in the basal septum in the majority (74.2%) of patients with hypertension (Figure 1A), with an asymmetrical ratio of 1.36 (1.27–1.48). Conversely, only 4 patients (1.6%) had maximal wall thickening in the apical segments. Regardless of the methods of assessment, SBP accounted for only 5% to 20% of the variance in LV mass (24-hour SBP:  $r=0.44$ ,  $P<0.001$ ; office SBP:  $r=0.22$ ,  $P<0.01$ ) and maximal wall thickness.

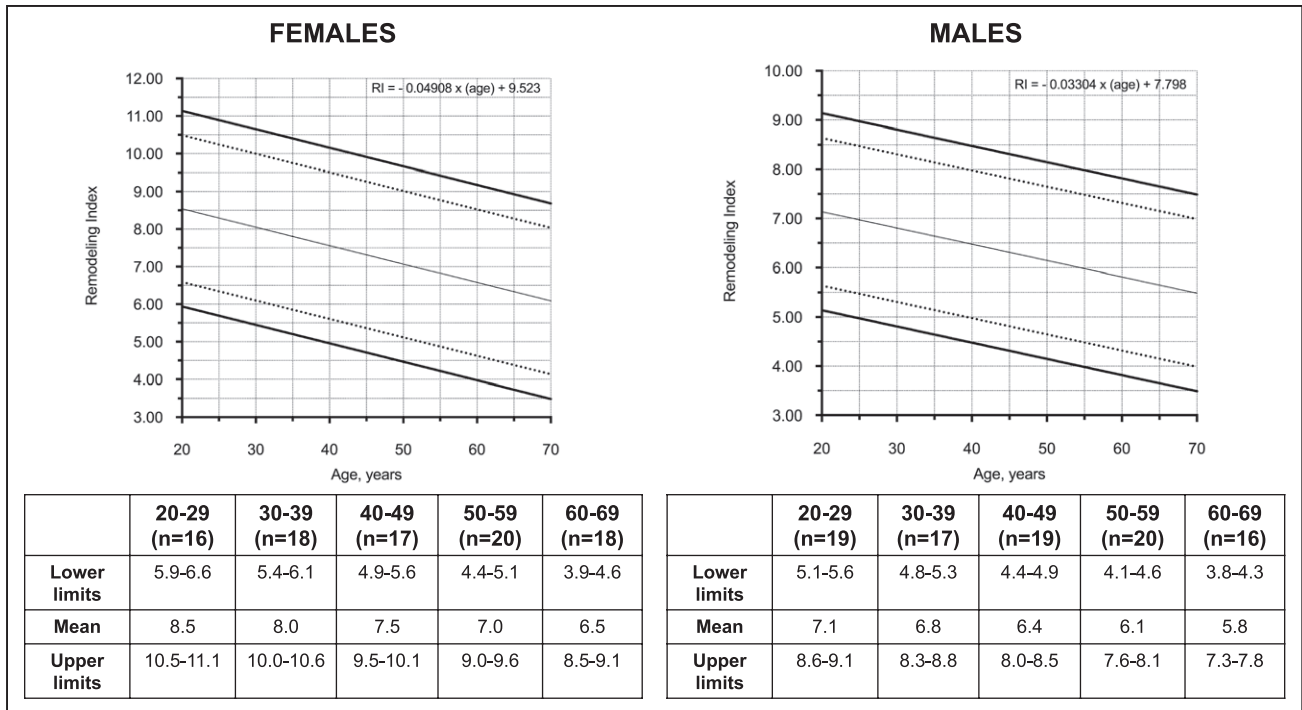
Thirty-eight patients had midwall fibrosis and 2 had incidental myocardial infarction. Midwall fibrosis was predominantly present in the basal and midventricular septum and can

involve the RV insertion points (Figure 1B). Positive correlations were observed between SBP and interstitial volume (24-hour SBP:  $r=0.36$ ,  $P<0.001$ ; office SBP:  $r=0.21$ ,  $P<0.01$ ), and there were small differences in BPs between those without and with myocardial midwall fibrosis (24-hour SBP:  $129\pm 13$  versus  $134\pm 16$  mm Hg, respectively;  $P=0.04$ ). Conversely, LV mass correlated strongly with myocardial interstitial volume ( $r=0.91$ ;  $P<0.001$ ) and was higher in those with midwall fibrosis ( $65\pm 25$  versus  $51\pm 11$  g/m<sup>2</sup>;  $P<0.001$ ; Figure 2). Indeed, LV mass was an independent determinant of myocardial fibrosis (using either CMR approaches) after adjusting for age, sex, SBP, and treatment duration (Data Supplement).

Indexed LV mass and myocardial fibrosis were independently associated with serum cardiac troponin T and I (Figure 2; Data Supplement). As a marker of cardiac wall



**Figure 2.** Indexed left ventricular (LV) mass correlated positively with interstitial volume assessed on cardiovascular magnetic resonance (A). Compared with those without midwall myocardial fibrosis, hypertensive patients with midwall fibrosis had increased left ventricular mass index (B) and high-sensitive cardiac troponin I concentrations, a marker of myocardial injury (C). Results in B and C presented in box-and-whiskers plot (Tukey method).



**Figure 3.** Sex- and age-specific reference ranges of Remodeling Index (RI) in a healthy population.

stress, NT-proBNP was associated with increased indexed LA and LV volumes, LV mass, and myocardial fibrosis (but not RV volumes) independent of age, sex, SBP, and creatinine levels (Data Supplement). Conversely, no correlations were observed between galectin-3 and LV mass ( $r=-0.07$ ;  $P=0.35$ ), myocardial interstitial volume ( $r=-0.03$ ;  $P=0.71$ ) and LV volumes.

### RI as a Marker of Advanced Hypertrophy

We established age- and sex-specific RI reference ranges in healthy volunteers (Figure 3). Women had increased RI when compared with men ( $7.3\pm 1.3$  versus  $6.3\pm 1.0$ ;  $P<0.001$ ) and RI correlated inversely with age ( $r=-0.43$ ;  $P<0.001$ ).

Based on these normal values, 15 patients in the REMODEL cohort had RI values below the normal range. All 15 patients had LVH as defined by age- and sex-specific CMR criteria.<sup>25</sup> Compared with patients with hypertension without LVH ( $n=191$ ;  $RI=6.1\pm 1.0$ ) and those with hypertensive LVH and normal RI ( $n=50$ ;  $RI=5.7\pm 0.8$ ), patients with hypertensive LVH and low RI ( $n=15$ ;  $RI=4.0\pm 0.7$ ) were the youngest ( $45\pm 16$  years old;  $P<0.001$ ) and had a relatively short duration of hypertensive treatment (2.0 years [0.3–3.8 years]; Table 2).

Hypertensive patients with low RI values represented a group with advanced LVH: highest Romhilt–Estes ECG scores, increased LV mass index, most myocardial fibrosis (assessed by interstitial volumes and proportion of patients with replacement fibrosis), impaired diastolic function, and elevated cardiac biochemical markers of cardiac injury and decompensation (Table 2; Figure 4). We further demonstrated the incremental value of RI and the novel classification (normal, hypertensive LVH with normal RI, and hypertensive LVH with low RI) compared with conventional geometric classification (Data Supplement).

One patient with hypertension had a higher than normal RI (man=73 years;  $RI=9.1$ ). Indexed LVEDV was increased for age, whereas LV mass, stroke volume, and systolic function were normal. He had no valvular heart or history of coronary artery disease.

### Discussion

To date, this is the largest prospective study to systematically examine the effects of BP on ventricular remodeling using multi-imaging and biochemical approaches. BP correlated only modestly with LV mass (accounting for <20% of the variance observed), and it was not associated with myocardial fibrosis. Instead, LV mass was positively and independently associated with myocardial fibrosis, and both LV mass and myocardial fibrosis were independently associated with circulating markers of myocardial injury and cardiac dysfunction. The novel RI, derived from the biophysical model of myocardial wall stress, risk stratified patients with hypertensive LVH. A lower than normal RI was associated with LVH on CMR, increased myocardial fibrosis and injury and heart failure.

Currently, the diagnosis and management of hypertension relies primarily on brachial BP. However, the difficulties associated with all noninvasive techniques of measuring BP are well recognized.<sup>36,37</sup> Contemporary management places great emphasis on achieving BP targets, but the specific targets (particularly in older patients) remain controversial. Compared with previous recommendations, less stringent but different BP targets were recently proposed by all major organizations.<sup>38–40</sup> Adding to this complexity, a more recent trial demonstrated a significant reduction in mortality in patients (including >75 years) intensely treated to achieve SBP <120 mmHg,<sup>41</sup> challenging the new targets and increasing

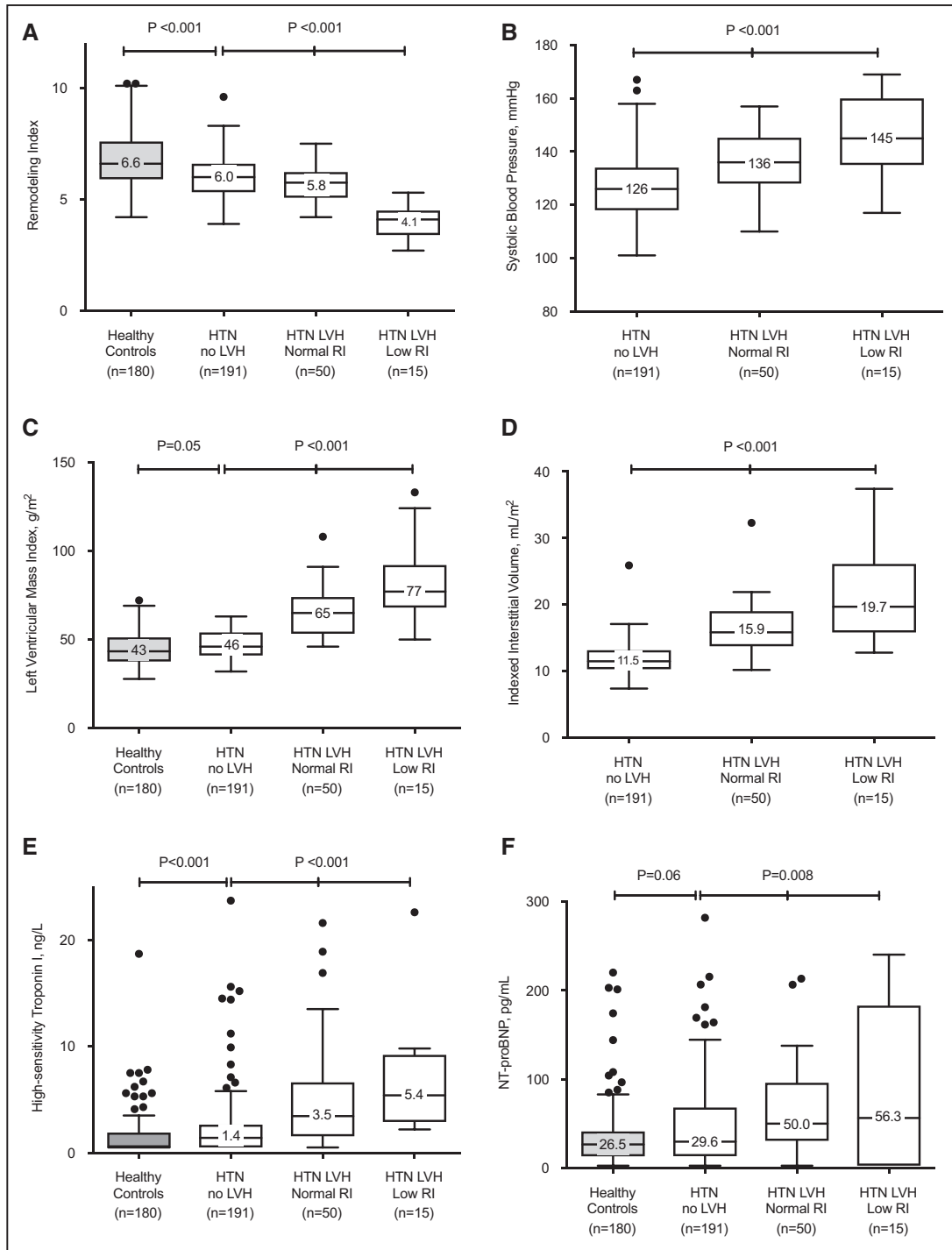
**Table 2. Characteristics of Patients With Hypertension Stratified by the Presence of Left Ventricular Hypertrophy and Remodeling Index**

	HTN no LVH (n=191)	HTN-LVH Normal RI (n=50)	HTN-LVH Low RI (n=15)	PValue
<b>Clinical characteristics</b>				
Age, y	59±10	58±11	45±16	<0.001
Male, n (%)	128 (67)	30 (60)	11 (73)	0.54
Hyperlipidemia, n (%)	72 (38)	16 (32)	5 (32)	0.74
Diabetes mellitus, n (%)	24 (13)	3 (6)	1 (7)	0.36
Duration of treatment, y	6.9 [3.7–15.5]	10.3 [3.7–18.7]	2.0 [0.3–3.8]	<0.001
Antihypertensive Medications, n	1.0 [1.0–2.0]	2.0 [1.0–2.0]	2.0 [1.0–2.0]	0.35
24-h SBP, mm Hg	127±12	136±12	145±16	<0.001
24-h DBP, mm Hg	79±9	82±11	89±14	<0.001
Office SBP, mm Hg	140±17	148±20	152±33	<0.01
Office DBP, mm Hg	80±11	82±15	90±21	0.02
Body surface area, m <sup>2</sup>	1.79±0.19	1.78±0.21	1.88±0.33	0.23
Romhilt–Estes ECG score	1 [0–4]	4 [3–4]	6 [4–7]	<0.001
ECG strain pattern, n (%)	0	0	7 (46%)	<0.001
<b>Myocardial structure and function</b>				
Remodeling Index	6.1±1.0	5.7±0.8	4.0±0.7	<0.001
LV end-diastolic volume, mL/m <sup>2</sup>	70±10	87±19	77±21	<0.001
LV end-systolic volume, mL/m <sup>2</sup>	27±6	34±13	34±15	<0.001
LV stroke volume, mL/m <sup>2</sup>	43±7	53±10	43±11	<0.001
LV ejection fraction, %	62±6	61±7	57±9	0.01
RV end-diastolic volume, mL/m <sup>2</sup>	72±11	84±16	70±16	<0.001
RV end-systolic volume, mL/m <sup>2</sup>	29±8	32±11	27±9	0.04
RV stroke volume, mL/m <sup>2</sup>	43±6	52±9	42±11	<0.001
RV ejection fraction, %	60±7	62±8	62±9	0.17
Max wall thickness, mm	8.3±1.3	9.5±1.5	13.2±2.3	<0.001
LV mass, g/m <sup>2</sup>	47±7	65±13	83±24	<0.001
Interstitial volume, mL/m <sup>2</sup>	11.5 [10.3–13.1]	15.9 [13.8–19.0]	19.7 [15.8–26.1]	<0.001
Late gadolinium enhancement, n (%)	18 (9)	9 (18)	11 (73)	<0.001
LA volume, mL/m <sup>2</sup>	48±11	59±15	55±23	<0.001
RA area, cm/m <sup>2</sup>	12±2	13±2	11±2	<0.001
Diastolic function E/e'	7.8±1.9	8.6±2.2	9.7±3.2	<0.001
<b>Biochemical markers</b>				
Serum creatinine, μmol/L	82±19	82±21	84±23	0.90
NT-proBNP, pg/mL	29.6 [13.2–68.1]	50.0 [30.6–96.0]	56.3 [2.5–182.9]	<0.01
High-sensitive troponin T, pg/mL	5.1 [2.5–6.7]	7.1 [2.5–11.1]	8.5 [7.2–12.0]	<0.001
High-sensitive troponin I, ng/L	1.4 [0.5–2.7]	3.5 [1.6–6.6]	5.4 [2.9–9.2]	<0.001
Galectin-3, ng/mL	12.4 [10.5–14.4]	12.6 [10.4–14.5]	15.7 [13.1–18.0]	0.05

DBP indicates diastolic blood pressure; HTN, hypertensive; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RA, right atrial; RI, Remodeling Index; RV, right ventricular; and SBP, systolic blood pressure.

uncertainty among physicians. These limitations signal a critical need of a more reliable marker to monitor the progression of hypertensive heart disease.

The myocardium thickens to minimize myocardial wall stress in the presence of elevated BP.<sup>2</sup> However, excessive LVH carries an increased risk of adverse cardiac events,



**Figure 4.** The Remodeling Index (RI) identifies a subgroup of hypertensive (HTN) patients with advanced left ventricular hypertrophy (LVH; **A**). These patients had the highest blood pressures (**B**), left ventricular mass (**C**), more myocardial fibrosis (**D**), and elevated markers of myocardial injury and cardiac decompensation (**E** and **F**). Results presented in box-and-whiskers plot (Tukey method).

independent of BP.<sup>8-11</sup> Myocardial fibrosis is an important mediator in the transition between adaptive hypertrophy and cardiac decompensation,<sup>4</sup> and it is a common histological hallmark of cardiac decompensation.<sup>7,42</sup> Indeed, LV mass and myocardial fibrosis demonstrated significant and independent associations with circulating biomarkers of myocardial injury and cardiac decompensation, over and above the effects of increased BPs. This relationship between the myocardium

and adverse outcomes justifies the complementary role of assessing the myocardium in the management of hypertensive LVH.

This study examined a novel myocardial marker, the RI that incorporates LVEDV and myocardial wall thickness. Both are important determinants of myocardial mass and wall stress. In the absence of invasive pressure measurements, myocardial wall stress is estimated based on a spherical

biophysical model. The advantage of using a spherical model is the ease of application and its ability to reflect the effects of cardiac geometry on function.<sup>45</sup> Exaggerated wall thickening from pressure-overloaded conditions such as hypertension would result in a low RI. In this cohort, ≈6% of all hypertensive patients (23% of those with hypertensive LVH) had low RI according to the normal age- and sex-specific ranges established in 180 healthy volunteers. Hypertensive patients with low RI have LVH, myocardial fibrosis, and elevated biochemical markers of cardiac injury and dysfunction. All patients with ECG strain pattern had low RI. This ECG pattern is highly specific for myocardial fibrosis and has been shown to be associated with worse outcomes in aortic stenosis and hypertension.<sup>46–48</sup> The RI provided incremental value to hypertensive LVH in the association with markers of cardiac decompensation.

When LV dilatation exceeds the relative effects of wall thickening to maintain wall stress, RI increases. In this study, only 1 hypertensive patient had a higher than normal RI. Of note, in patients with dilated cardiomyopathy and systolic dysfunction, a higher than normal RI was associated with increased cardiovascular events (Data Supplement).

### Clinical Implications

We examined the role of RI in 10 patients with hypertensive HFpEF (7 men; median, 57 years [range, 37–75 years]). All patients with hypertensive HFpEF had LVH and low RI values. The RI values were not significantly different between asymptomatic patients with hypertensive LVH and low RI in REMODEL and those with hypertensive HFpEF (4.1 [3.4–4.5] versus 3.7 [3.4–4.0], respectively;  $P=0.15$ ). Two patients with hypertensive LVH and low RI developed hypertension-related events over 5.2-month [3.0–7.8-month] follow-up: one was in the emergency department for hypertensive emergency and the other had an acute myocardial infarction. No events occurred in the other patients groups.

The RI is an index easily derived on routine CMR. It holds potential as a marker to monitor progression of disease and response to therapies targeted at the myocardium.<sup>49</sup> Hypertensive patients with HFpEF had lower than normal RI, highlighting the potential role of differentiating patients with dyspnea and suspected HFpEF.

### Study Limitations

A longer follow-up with higher event rates would be necessary to clearly demonstrate the incremental prognostic value of RI over traditional predictors. The RI was derived using a spherical model according to the LaPlace's Law. In the spherical model, the radius (R in the wall stress formula) is estimated from LVEDV, which can be measured accurately on routine CMR. Conversely, the ellipsoid model requires 2 to 3 linear measurements in 1 to 2 cardiac views to estimate R (depending on the specific model used). This will not only increase the complexity but also introduce more variation and error in the measurements and calculations. Regardless of the model used, each was associated with systematic differences in assessing wall stresses.<sup>45</sup> We have excluded hypertensive patients with impaired estimated glomerular

filtration rate <30 mL/min per 1.73 m<sup>2</sup> because of the risks of nephrogenic systemic fibrosis. In large population-based studies, the prevalence of stages 4 and 5 chronic kidney disease in hypertensive patients was <5%.<sup>50,51</sup> Therefore, the impact of excluding these individuals, if any, is likely small.

### Conclusions

The RI is a marker of advanced hypertrophy in patients with hypertensive LVH. Its true potential should be examined in larger cohorts with long-term follow-up.

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### Disclosures

None.

### References

1. Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011;123:327–334. doi: 10.1161/CIRCULATIONAHA.108.845792.
2. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation*. 2000;102:470–479.
3. Chin CW, Vassiliou V, Jenkins WS, Prasad SK, Newby DE, Dweck MR. Markers of left ventricular decompensation in aortic stenosis. *Expert Rev Cardiovasc Ther*. 2014;12:901–912. doi: 10.1586/14779072.2014.923307.
4. Hein S, Arnon E, Kostin S, Schönburg M, Elsässer A, Polyakova V, Bauer EP, Klövekorn WP, Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation*. 2003;107:984–991.
5. Fortuño MA, Ravassa S, Fortuño A, Zalba G, Díez J. Cardiomyocyte apoptotic cell death in arterial hypertension: mechanisms and potential management. *Hypertension*. 2001;38:1406–1412.
6. Cramariuc D, Gerds E. Epidemiology of left ventricular hypertrophy in hypertension: implications for the clinic. *Expert Rev Cardiovasc Ther*. 2016;14:915–926. doi: 10.1080/14779072.2016.1186542.
7. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2011;57:891–903.
8. Vakil BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. *Am Heart J*. 2001;141:334–341. doi: 10.1067/mhj.2001.113218.
9. 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;322:1561–1566. doi: 10.1056/NEJM199005313222203.
10. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991;114:345–352.
11. Verdecchia P, Carini G, Circo A, Dovellini E, Giovannini E, Lombardo M, Solinas P, Gorini M, Maggioni AP; MAVI (MASSA Ventricolare sinistra nell'Ipertensione) Study Group. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. *J Am Coll Cardiol*. 2001;38:1829–1835.
12. Schillaci G, Verdecchia P, Porcellati C, Cuccurullo O, Cosco C, Perticone F. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension*. 2000;35:580–586.
13. Missault LH, De Buyzere ML, De Bacquer DD, Duprez DD, Clement DL. Relationship between left ventricular mass and blood pressure in treated hypertension. *J Hum Hypertens*. 2002;16:61–66. doi: 10.1038/sj.jhh.1001295.



14. Devereux RB, Pickering TG, Harshfield GA, Kleinert HD, Denby L, Clark L, Pregibon D, Jason M, Kleiner B, Borer JS, Laragh JH. Left ventricular hypertrophy in patients with hypertension: importance of blood pressure response to regularly recurring stress. *Circulation*. 1983;68:470–476.
15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003.
16. de Marvao A, Dawes TJ, Shi W, Minas C, Keenan NG, Diamond T, Durighel G, Montana G, Rueckert D, Cook SA, O'Regan DP. Population-based studies of myocardial hypertrophy: high resolution cardiovascular magnetic resonance atlases improve statistical power. *J Cardiovasc Magn Reson*. 2014;16:16. doi: 10.1186/1532-429X-16-16.
17. Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. *J Am Coll Cardiol*. 1995;25:879–884. doi: 10.1016/0735-1097(94)00473-4.
18. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, Santucci A, Santucci C, Reboldi G, Porcellati C. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *J Am Coll Cardiol*. 1995;25:871–878. doi: 10.1016/0735-1097(94)00424-0.
19. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S. Left ventricular mass and geometry and the risk of ischemic stroke. *Stroke*. 2003;34:2380–2384. doi: 10.1161/01.STR.0000089680.77236.60.
20. Ghali JK, Liao Y, Cooper RS. Influence of left ventricular geometric patterns on prognosis in patients with or without coronary artery disease. *J Am Coll Cardiol*. 1998;31:1635–1640.
21. Katz DH, Beussink L, Sauer AJ, Freed BH, Burke MA, Shah SJ. Prevalence, clinical characteristics, and outcomes associated with eccentric versus concentric left ventricular hypertrophy in heart failure with preserved ejection fraction. *Am J Cardiol*. 2013;112:1158–1164. doi: 10.1016/j.amjcard.2013.05.061.
22. Paoletti E, De Nicola L, Gabbai FB, Chiodini P, Ravera M, Pieracci L, Marre S, Cassottana P, Lucà S, Vettoretti S, Borrelli S, Conte G, Minutolo R. Associations of Left Ventricular Hypertrophy and Geometry with Adverse Outcomes in Patients with CKD and Hypertension. *Clin J Am Soc Nephrol*. 2016;11:271–279. doi: 10.2215/CJN.06980615.
23. Yin FC. Ventricular wall stress. *Circ Res*. 1981;49:829–842.
24. Sandler H, Dodge HT. Left ventricular tension and stress in man. *Circ Res*. 1963;13:91–104.
25. Le TT, Tan RS, De Deyn M, Goh EP, Han Y, Leong BR, Cook SA, Chin CW. Cardiovascular magnetic resonance reference ranges for the heart and aorta in Chinese at 3T. *J Cardiovasc Magn Reson*. 2016;18:21. doi: 10.1186/s12968-016-0236-3.
26. Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J*. 1968;75:752–758.
27. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M; American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009;22:1–23; quiz 101. doi: 10.1016/j.echo.2008.11.029.
28. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802. doi: 10.1016/S0894-7317(03)00335-3.
29. Chin CW, Semple S, Malley T, White AC, Mirsadraee S, Weale PJ, Prasad S, Newby DE, Dweck MR. Optimization and comparison of myocardial T1 techniques at 3T in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2014;15:556–565. doi: 10.1093/ehjci/jet245.
30. Chin CW, Everett RJ, Kwienecinski J, Vesey AT, Yeung E, Esson G, Jenkins W, Koo M, Mirsadraee S, White AC, Japp AG, Prasad SK, Semple S, Newby DE, Dweck MR. Myocardial fibrosis and cardiac decompensation in aortic stenosis [published online ahead of print December 8, 2016]. *JACC Cardiovasc Imaging*. doi:10.1016/j.jcmg.2016.10.007.
31. Roche NT-pro BNP assay [Package insert]. 2006.
32. Troponin T hs STAT [Package insert]. 2013.
33. Aw TC, Phua SK, Tan SP. Measurement of cardiac troponin I in serum with a new high-sensitivity assay in a large multi-ethnic Asian cohort and the impact of gender. *Clin Chim Acta*. 2013;422:26–28. doi: 10.1016/j.cca.2013.03.034.
34. ARCHITECT Gal3 [Package Insert]. 2016.
35. International Federation of Clinical Chemistry, Scientific Committee, Clinical Section. Expert Panel on Theory of Reference Values (EPTRV). The theory of reference values. Part 5. Statistical treatment of collected reference values. Determination of reference limits. *Clin Chim Acta* 1984;137:97F–114F.
36. Marshall T. Blood pressure measurement: the problem and its solution. *J Hum Hypertens*. 2004;18:757–759. doi: 10.1038/sj.jhh.1001753.
37. Pater C. Beyond the Evidence of the New Hypertension Guidelines. Blood pressure measurement - is it good enough for accurate diagnosis of hypertension? Time might be in, for a paradigm shift (I). *Curr Control Trials Cardiovasc Med*. 2005;6:6. doi: 10.1186/1468-6708-6-6.
38. Mancía G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357. doi: 10.1097/01.hjh.0000431740.32696.cc.
39. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Oggedge O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427.
40. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CV, Cohen DL, Cadet JC, Jean-Charles RR, Taler S, Kountz D, Townsend RR, Chalmers J, Ramirez AJ, Bakris GL, Wang J, Schutte AE, Bisognano JD, Touyz RM, Sica D, Harrap SB. Clinical Practice Guidelines for the Management of Hypertension in the Community. *J Clin Hypertens* 2014;16:14–26.
41. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103–2116.
42. de Leeuw N, Rüter DJ, Balk AH, de Jonge N, Melchers WJ, Galama JM. Histopathologic findings in explanted heart tissue from patients with end-stage idiopathic dilated cardiomyopathy. *Transpl Int*. 2001;14:299–306.
43. Khouri MG, Peshock RM, Ayers CR, de Lemos JA, Drazner MH. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: the Dallas heart study. *Circ Cardiovasc Imaging*. 2010;3:164–171. doi: 10.1161/CIRCIMAGING.109.883652.
44. Bang CN, Gerds E, Aurigemma GP, Boman K, de Simone G, Dahlöf B, Køber L, Wachtell K, Devereux RB. Four-group classification of left ventricular hypertrophy based on ventricular concentricity and dilatation identifies a low-risk subset of eccentric hypertrophy in hypertensive patients. *Circ Cardiovasc Imaging*. 2014;7:422–429. doi: 10.1161/CIRCIMAGING.113.001275.
45. Huisman RM, Sipkema P, Westerhof N, Elzinga G. Comparison of models used to calculate left ventricular wall force. *Med Biol Eng Comput*. 1980;18:133–144.
46. Chin CW, Shah AS, Vassiliou V, Cowell SJ, Doris M, Kwok TC, Semple S, Zamvar V, White AC, McKillop G, Boon NA, Prasad SK, Mills NL, Newby DE, Dweck MR. Left ventricular hypertrophy with strain and aortic stenosis. *Circulation*. 2014;130:1607–1616.
47. Rodrigues JC, Amadu AM, Ghosh Dastidar A, McIntyre B, Szantho GV, Lyen S, Godsave C, Ratcliffe LE, Burchell AE, Hart EC, Hamilton MC, Nightingale AK, Paton JF, Manghat NE, Bucciarelli-Ducci C. ECG strain pattern in hypertension is associated with myocardial cellular expansion and diffuse interstitial fibrosis: a multi-parametric cardiac magnetic resonance study. *Eur Heart J Cardiovasc Imaging*. 2017;18:441–450. doi: 10.1093/ehjci/jew117.
48. Greve AM, Boman K, Gohlke-Baerwolf C, Kesäniemi YA, Nienaber C, Ray S, Egstrup K, Rossebø AB, Devereux RB, Køber L, Willenheimer R, Wachtell K. Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis:

- the Simvastatin and Ezetimibe in Aortic Stenosis study. *Circulation*. 2012;125:346–353. doi: 10.1161/CIRCULATIONAHA.111.049759.
49. Gyöngyösi M, Winkler J, Ramos I, Do QT, Firat H, McDonald K, González A, Thum T, Díez J, Jaisser F, Pizard A, Zannad F. Myocardial fibrosis: biomedical research from bench to bedside. *Eur J Heart Fail*. 2017;19:177–191. doi: 10.1002/ejhf.696.
50. Crews DC, Plantinga LC, Miller ER III, Saran R, Hedgeman E, Saydah SH, Williams DE, Powe NR; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States. *Hypertension*. 2010;55:1102–1109. doi: 10.1161/HYPERTENSIONAHA.110.150722.
51. Krittayaphong R, Rangsin R, Thinkhamrop B, Hurst C, Rattanamongkolgul S, Sripaiboonkij N, Wangworatrakul W. Prevalence of chronic kidney disease associated with cardiac and vascular complications in hypertensive patients: a multicenter, nationwide study in Thailand. *BMC Nephrol*. 2017;18:115. doi: 10.1186/s12882-017-0528-3.

### CLINICAL PERSPECTIVE

Longstanding hypertension ultimately leads to heart failure. In response to the increased afterload, cardiac hypertrophy is initially compensatory to maintain wall stress and cardiac function. Over time, cardiac decompensation occurs. The transition from adaptive hypertrophy to cardiac decompensation is mediated by myocyte death and myocardial fibrosis. We have

developed a novel risk marker (Remodeling Index =  $\frac{\sqrt[3]{EDV}}{WT}$ , where EDV is the left ventricular end-diastolic volume and

WT is the maximal myocardial wall thickness) based on a spherical model of LaPlace's wall stress. Normal Remodeling Index values were established in 180 healthy volunteers. With advanced hypertrophy from wall thickening, Remodeling Index values will be lower than normal. In 256 patients with hypertension, patients with hypertensive left ventricular hypertrophy and low Remodeling Index (n=15) had more advanced hypertrophy: increased mass, most myocardial fibrosis, impaired diastolic function, and elevated cardiac biochemical markers of myocardial injury and decompensation. This marker holds important potential in identifying patients with hypertensive LVH at risk of cardiac decompensation.