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The remodelling index risk stratifies patients with hypertensive left ventricular hypertrophy

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Aims

Hypertensive left ventricular hypertrophy (LVH) is associated with increased cardiovascular events. We previously developed the remodelling index (RI) that incorporated left ventricular (LV) volume and wall-thickness in a single measure of advanced hypertrophy in hypertensive patients. This study examined the prognostic potential of the RI in reference to contemporary LVH classifications.

Methods and results

Cardiovascular magnetic resonance was performed in 400 asymptomatic hypertensive patients. The newly derived RI ($\frac{2EDV}{t}$, where EDV is LV end-diastolic volume and t is the maximal wall thickness across 16 myocardial segments) stratified hypertensive patients: no LVH, LVH with normal RI (LVH_{Normal-RI}), and LVH with low RI (LVH_{Low-RI}). The primary outcome was a composite of all-cause mortality, acute coronary syndromes, strokes, and decompensated heart failure. LVH_{Low-RI} was associated with increased LV mass index, fibrosis burden, impaired myocardial function and elevated biochemical markers of myocardial injury (high-sensitive cardiac troponin I), and wall stress. Over 18.3 ± 7.0 months (601.3 patient-years), 14 adverse events occurred (2.2 events/100 patient-years). Patients with LVH_{Low-RI} had more than a five-fold increase in adverse events compared to those with LVH_{Normal-RI} (11.6 events/100 patient-years vs. 2.0 events/100 patient-years, respectively; log-rank $P < 0.001$). The RI provided incremental prognostic value over and above a model consisting of clinical variables, LVH and concentricity; and predicted adverse events independent of clinical variables, LVH, and other prognostic markers. Concentric and eccentric LVH were associated with adverse prognosis (log-rank $P = 0.62$) that was similar to the natural history of hypertensive LVH (5.1 events/100 patient-years).

Conclusion

The RI provides prognostic value that improves risk stratification of hypertensive LVH.

Keywords

hypertensive heart disease • left ventricular hypertrophy • cardiac remodelling • cardiovascular magnetic resonance

Introduction

Left ventricular hypertrophy (LVH) is prevalent in 16–74% of patients with essential hypertension and it is well-established that hypertensive LVH is associated with adverse cardiovascular outcomes, above and beyond blood pressure effects.^{1–3}

Conventionally, four geometric patterns have been recommended to describe the left ventricular (LV) response to

hypertension: normal, concentric remodelling, concentric, and eccentric hypertrophy.^{4,5} Although both concentric and eccentric hypertrophy were associated with worse outcomes, the incremental value of geometry beyond LV mass remains uncertain.^{6–11} Moreover, both concentric and eccentric hypertrophy were associated with similar LV mass index, fibrosis burden, and biochemical markers of myocardial injury and cardiac decompensation.¹² These observations may suggest that the risk of adverse cardiovascular

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outcomes is increased once hypertensive LVH develops, regardless of the geometric patterns. However, it also raises the question of whether there are other strategies to improve risk stratification of hypertensive LVH.

Recently, we have derived a cardiovascular magnetic resonance (CMR) marker of advanced hypertrophy (*remodelling index*; $RI = \frac{\sqrt[3]{EDV}}{t}$, where EDV is the end-diastolic volume and t is the maximal wall thickness across 16 myocardial segments; *Figure 1*) from a biophysical model of LaPlace's Law of wall stress.¹² This measure is distinctive from conventional measures of concentricity. In patients with hypertensive LVH, an abnormally low RI was associated with the highest LV mass, increased non-ischaemic myocardial fibrosis, impaired diastolic function, and elevated biochemical markers of myocardial injury and cardiac decompensation. These findings demonstrated the potential of the RI in risk stratifying hypertensive patients. In this study, we aim to examine the mechanistic and prognostic potential of the RI in asymptomatic patients with hypertension in reference to conventional LVH classifications. We hypothesize that the RI is a measure that reflects the heterogeneous remodelling process of hypertensive LVH; and it can improve LVH risk stratification.

Methods

Patient populations

Asymptomatic patients with essential hypertension comprised of participants from the *REMODEL* observational study (clinicaltrials.gov identifier: NCT02670031). Patients with secondary causes of hypertension, clinically diagnosed coronary artery disease (previous myocardial infarction, $\geq 70\%$ stenosis on invasive angiography, or positive cardiac stress tests), previous cerebrovascular events, atrial fibrillation, and heart failure were excluded. Patients with incidental myocardial infarction and significant valvular heart disease (\geq moderate severity in valvular regurgitation or aortic stenosis) on CMR were excluded from this study. Blood pressure in the *REMODEL* cohort was recorded with 24-h ambulatory blood pressure monitors.

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

Clinical outcomes

The primary outcome was a composite of all-cause mortality, acute coronary syndromes (unstable angina and myocardial infarction), strokes and acute decompensated heart failure (first heart failure hospitalization diagnosed based on contemporary guidelines). Patients were followed between February 2016 and December 2018. An experienced cardiologist (C.W.L.C.) who was blinded to the imaging data, adjudicated all events by independent review of patient's healthcare records.

CMR protocol and image analysis

CMR was performed in all hypertensive patients with a standardized imaging protocol (Siemens Aera 1.5 T, Siemens Healthineers, Erlangen, Germany). Balanced steady-state free precision cines were acquired in the standard long-axis (two-, three-, and four-chamber) planes, and right ventricular (RV) long-axis view aligned with the tricuspid inflow and RV outflow tract. Short-axis cines extending from the atrioventricular ring to the apex were obtained to cover the entire left and right ventricles (acquired voxel size: 1.6 mm \times 1.3 mm \times 8.0 mm; 2 mm gap; 30 phases

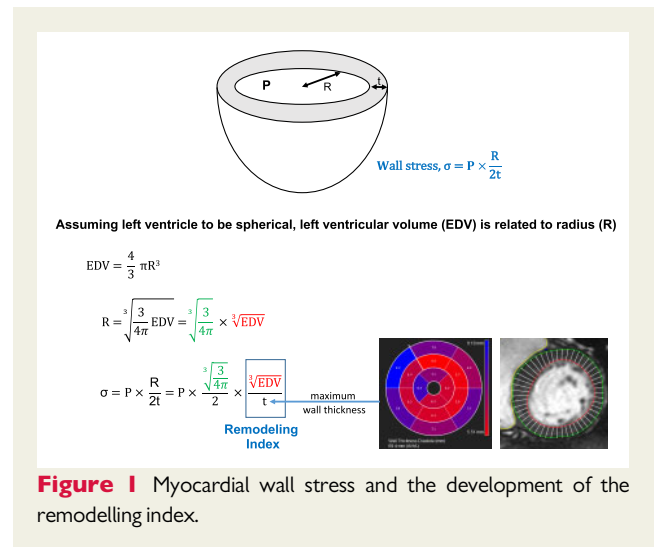


Figure 1 Myocardial wall stress and the development of the remodelling index.

per cardiac cycle). Flow at the ascending aorta was assessed using standard through-plane breath-hold segmented phase-contrast imaging at the level of the pulmonary artery bifurcation (acquired voxel size: 1.8 mm \times 1.8 mm \times 6.0 mm; 50 phases per cardiac cycle). The encoding velocity was individually adjusted according to the velocity of blood flow starting from 150 cm/s.

Myocardial fibrosis was assessed using two approaches: late gadolinium-enhanced imaging and myocardial T1 mapping. For the assessment of non-ischaemic replacement fibrosis, late gadolinium-enhanced imaging was performed ~ 8 min after administration of 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. Myocardial T1 mapping based on the Modified Look-Locker inversion-recovery sequence was used as a more sensitive measure of diffuse myocardial fibrosis.^{13,14} Extracellular volume fraction (ECV) was estimated from the native and 15-min post-contrast T1 map,¹⁵ analysed using the T1 mapping module (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). Interstitial volumes were defined as a product of ECV and myocardial volume (myocardial volume = LV mass/1.05 g/mL). We had previously demonstrated its excellent correlation with histological fibrosis and prognostic value in patients with aortic stenosis.¹⁶

Cardiac volumes, function, LV mass, and myocardial strain were analysed using CVI42 (Circle Cardiovascular Imaging, Calgary, Canada) at our *NHRIS CMR Core Laboratory*. Myocardial mass was estimated at end-diastole and corroborated at end-systole: (total epicardial volume - total endocardial volume) \times 1.05 g/mL. Circumferential and radial strain were measured in the short-axis cine images, while longitudinal strain was measured in the long-axis views.¹⁷ Aortic peak flow acceleration values were the first derivative of the instantaneous flow measurements. Peak flow acceleration was validated as a non-invasive marker of LV contractility in echocardiographic studies.^{18,19} All image analyses were performed by three trained investigators (V.Z.K.L., M.T., and R.I.) who were blinded to the other clinical and outcome data.

Echocardiography

Echocardiography (ProSound F75; Hitachi Aloka Medical Ltd., Tokyo, Japan) was performed in the patients. Cardiac dimensions and function were assessed according to the European Association of Echocardiography/American Society of Echocardiography guidelines.²⁰

Relative wall thickness (RWT) was estimated as two times posterior wall thickness divided by LV diastolic diameter on M-mode, measured by a single trained sonographer.²⁰

Classifications of LVH

We examined the prognostic value of two LVH classifications in this study. The conventional approach classified LV geometry based on LV mass and concentricity (LV mass/end-diastolic volume; M/V ratio): normal geometry, concentric remodelling, concentric, and eccentric hypertrophy.²⁰ The second approach stratified hypertensive LVH based on the RI. Three remodelling patterns were described: no LVH, hypertensive LVH with normal RI, and hypertensive LVH with low RI.¹² LVH and abnormal M/V were diagnosed according to age- and sex-specific reference ranges we had established in Asians.²¹

Cardiac biochemical markers

Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP; proBNP II STAT, Roche Diagnostics, Pensberg, Germany) was assayed using electrochemiluminescence immunoassay on the Cobas E602 analyzer (Roche Diagnostics Asia-Pacific, Singapore). Serum high-sensitive cardiac troponin I (hsTnI; ARCHITECT STAT high-sensitive Troponin-I; Abbott Diagnostics, Abbott Park, IL) was determined using chemiluminescent microparticle immunoassay on the ARCHITECT i2000SR analyzer (Abbott Laboratories, Singapore). The lower limit of detection (LOD) for NT-proBNP and hsTnI was 5 pg/mL and 1.1 ng/L, respectively.^{22,23} All biochemical concentrations lower than the detection levels were assigned a value equivalent to half the LOD.

Statistical analysis

Distribution of continuous variables was assessed using the Shapiro–Wilk test. Data were presented in either mean \pm standard deviation or median (interquartile range), as appropriate. Depending on the normality of the distribution, parametric Student's *t*-test and one-way analysis of variance (ANOVA; with *post hoc* Bonferroni adjustment for pairwise comparison) or the non-parametric Mann–Whitney *U* test and Kruskal–Wallis test were used to compare groups of continuous data. Categorical data were compared using the χ^2 test.

Event-free survival curves associated with LVH patterns were estimated using the Kaplan–Meier method and compared with the log-rank test. The incremental prognostic values of RI (categorical) and CMR concentricity (categorical) over a model consisting of LVH (categorical), age, sex, and systolic blood pressure (SBP) were assessed using a change in the global χ^2 value for each model. Multivariable Cox proportional hazards models were used to adjust for potential confounders (age, sex, and SBP) and known markers of prognostic significance (wall thickness, CMR concentricity, global longitudinal strain, and echocardiographic RWT).

Statistical analyses were performed using GraphPad Prism Version 8 (GraphPad Software, Inc., San Diego, CA, USA) and SPSS Version 24 (IBM Corp., Armonk, NY, USA). A two-sided *P*-value <0.05 was considered as statistically significant.

Results

A total of 400 hypertensive patients (57 ± 11 years; 58% males; SBP 132 ± 15 mmHg) were recruited in this study. There were 176 patients with hypertensive LVH: 121 patients with normal RI and 55 with low RI. No patients with hypertensive LVH had higher than normal RI values in this cohort (Table 1).

Geometric profiles of hypertensive LVH

In patients with hypertensive LVH, concentric hypertrophy was the more prevalent geometric pattern ($n = 110$; 62.5%; Table 2). LV dilatation (based on age- and sex-specific reference ranges we have established in Asians²¹) was not a common feature, present in only 33 patients (18.8%) with hypertensive LVH. A similar number of patients with dilated LV had concentric ($n = 14$) and eccentric ($n = 19$) hypertrophy. Dilated concentric hypertrophy was most prevalent in younger males and associated with adverse features of LVH (highest LV mass, fibrosis burden, increased myocardial injury, and worst myocardial deformation). Conversely, non-dilated eccentric hypertrophy was most prevalent in older females and associated with more favourable characteristics of cardiac remodelling (Figure 2; Supplementary data online).

In a single measure, the RI describes the complex relationship between LV dilatation and concentricity associated with cardiac remodelling (Figure 2). In those with normal RI, 47.9% and 52.1% had concentric and eccentric hypertrophy, respectively. About 17% of these patients with normal RI had dilated LV. Concentric hypertrophy was the most common pattern in patients with hypertensive LVH and low RI ($n = 52$; 94.5%). Approximately one in five patients with low RI had a dilated LV, all of them had dilated concentric LVH pattern. Hypertensive LVH and low RI was more prevalent in younger males and associated with elevated blood pressures. Patients with hypertensive LVH and low RI had increased LV mass index, non-ischaeamic myocardial fibrosis, reduced myocardial deformation, and elevated biochemical markers of myocardial injury (hsTnI) and cardiac decompensation (Table 1). Similar findings were observed after adjusting for age, sex, and SBP ($P < 0.001$ for all analyses).

Increasing severity of hypertensive LVH was associated with abnormalities in myocardial mechanics despite similar LV ejection fraction, a global measure of LV function. In early hypertensive LVH (normal RI), an initial reduction in myocardial deformation was associated with an increased in aortic peak flow acceleration; in more severe hypertensive LVH (low RI), further impairment in myocardial deformation was associated with no significant change in aortic peak flow acceleration, after adjusting for the effects of age, sex, and SBP (Figure 3).

Adverse cardiovascular outcomes

Complete follow-up data were available in all patients. During the 18.3 ± 7.0 months (601.3 patient-years) of follow-up, 14 adverse events occurred (2.2 events/100 patient-years): all-cause death ($n = 2$), non-fatal myocardial infarction ($n = 3$), non-fatal strokes ($n = 2$), decompensated heart failure ($n = 2$), and unstable angina (medical therapy, $n = 3$; invasive revascularization, $n = 2$).

The RI improved risk stratification of hypertensive LVH by identifying patients with high- and low-event rates. High-risk patients identified using the RI (corresponding to the 5th percentile for age and sex) had more than a five-fold increase in adverse events (11.6 events/100 patient-years vs. 2.0 events/100 patient-years, respectively; log rank $P < 0.001$; Figure 4), with 50% of the events occurring within the first year of follow-up. Hypertensive LVH and low RI was associated with increased rates of primary endpoint [hazard ratio (HR) 22.0; 95% confidence interval: 3.8–127.3], but hypertensive

Table 1 Clinical and cardiovascular magnetic resonance characteristics of hypertensive patients stratified by the remodelling index

	Hypertensive patients			P-value
	No LVH (n = 224)	LVH normal RI (n = 121)	LVH low RI (n = 55)	
Clinical characteristics				
Age (years)	58 ± 10 ^a	57 ± 11 ^b	50 ± 13	<0.0001
Males, n (%)	147 (66)	50 (41)	35 (64)	<0.0001
Height (m)	1.66 ± 0.08 ^c	1.63 ± 0.08 ^b	1.66 ± 0.10	0.006
Weight (kg)	71 ± 14 ^a	71 ± 17 ^b	78 ± 22	0.009
BSA (m ²)	1.79 ± 0.20	1.76 ± 0.21 ³	1.86 ± 0.27	0.012
Diabetes mellitus, n (%)	28 (13)	13 (11)	10 (18)	0.385
Hyperlipidaemia, n (%)	85 (38)	57 (47)	23 (42)	0.255
Systolic blood pressure (mmHg)	127 ± 13 ^{a,c}	134 ± 14 ^b	145 ± 16	<0.0001
Diastolic blood pressure (mmHg)	79 ± 9 ^a	80 ± 10 ^a	88 ± 10	<0.0001
Echo relative wall thickness	0.35 ± 0.07 ^a	0.36 ± 0.09 ^b	0.48 ± 0.11	<0.0001
HbA1c (%)	7.0 (6.7–7.6)	7.1 (6.6–8.6)	7.9 (7.0–8.4)	0.100
NT-proBNP (pg/mL)	30.2 (13.5–64.2)	41.8 (18.2–87.5)	110.5 (39.0–268)	<0.0001
High-sensitive troponin I (ng/L)	1.5 (0.9–3.0)	3.2 (1.6–5.8)	5.5 (2.8–10.5)	<0.0001
Cardiovascular magnetic resonance characteristics				
Indexed LV mass (g/m ²)	47 ± 7 ^{a,c}	59 ± 13 ^b	78 ± 22	<0.0001
Indexed LV mass (g/height ^{1.7})	36 ± 7 ^{a,c}	45 ± 12 ^b	61 ± 19	<0.0001
Indexed LV mass (g/height ^{2.7})	22 ± 4 ^{a,c}	28 ± 6 ^b	36 ± 11	<0.0001
Indexed LVEDV (mL/m ²)	69 ± 10 ^{a,c}	81 ± 17	79 ± 17	<0.0001
Indexed LVESV (mL/m ²)	27 ± 6 ^{a,c}	33 ± 14	33 ± 13	<0.0001
Indexed LVSV (mL/m ²)	43 ± 7 ^{a,c}	48 ± 8	46 ± 9	<0.0001
LVEF (%)	62 ± 6 ^a	60 ± 8	59 ± 9	0.021
LV mass/LVEDV ratio	0.69 ± 0.10 ^{a,c}	0.73 ± 0.10 ^b	0.98 ± 0.16	<0.0001
Maximal wall thickness (mm)	8.4 ± 1.4 ^{a,c}	9.0 ± 1.4 ^b	12.5 ± 2.1	<0.0001
Remodelling index	6.1 ± 1.0 ^a	5.9 ± 0.8 ^b	4.3 ± 0.6	<0.0001
Remodelling index, percentile specific for age and sex	47.3 ± 26.5 ^{a,c}	34.3 ± 19.4 ^b	3.8 ± 2.8	<0.0001
Circumferential strain (%)	-22.6 ± 3.0 ^{a,c}	-21.6 ± 3.6 ^b	-20.1 ± 4.4	<0.0001
Radial strain (%)	48.2 ± 12.6 ^{a,c}	43.7 ± 13.0	40.4 ± 15.0	<0.0001
Longitudinal strain (%)	-20.5 ± 12.1 ^{a,c}	-18.2 ± 3.1 ^b	-15.8 ± 3.9	<0.0001
Native T1 (ms)	1004 ± 24 ^{a,c}	1020 ± 28 ^b	1037 ± 34	<0.0001
ECV (%)	25.9 ± 2.2 ^a	26.5 ± 2.8	26.9 ± 3.0	0.018
Non-ischaemic myocardial fibrosis, n (%)	22 (10)	25 (21)	35 (65)	<0.0001
Interstitial volume (mL/m ²)	11.7 ± 2.0 ^{a,c}	14.9 ± 3.9 ^b	20.0 ± 6.3	<0.0001

BSA, body surface area; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; SV, stroke volume; ECV extracellular volume.

^aANOVA *post hoc* Bonferroni adjustment: $P < 0.05$ between no LVH and LVH low RI.

^bANOVA *post hoc* Bonferroni adjustment: $P < 0.05$ between LVH normal RI and LVH low RI.

^cANOVA *post hoc* Bonferroni adjustment: $P < 0.05$ between no LVH and LVH normal RI.

LVH and normal RI was not (HR 4.5; 95% confidence interval: 0.7–28.0; [Supplementary data](#) online).

Although the survival distributions across the four conventional geometric patterns (normal, concentric remodelling, concentric, and eccentric hypertrophy) were statistically significant (log rank $P < 0.01$), both concentric and eccentric LVH had similar event rates (4.5 events/100 patient-years vs. 6.0 events/100 patient-years, respectively; log rank $P = 0.62$) compared to the natural history of LVH (5.1 events/100 patient-years; [Figure 4](#)). Eccentric hypertrophy was associated with increased rates of primary outcomes (HR 8.8; 95% confidence interval 1.6–48.3) but concentric hypertrophy was not

after adjusting for potential confounders (HR 4.7; 95% confidence interval 0.8–28.1; [Supplementary data](#) online).

Potential incremental prognostic value of the RI

Concentricity did not provide incremental prognostic value to LVH and other clinical variables: age, sex, and SBP. Conversely, the RI provided incremental prognostic value over and above the clinical model, LVH, and CMR concentricity ([Figure 4](#)). Similar findings were observed with RWT analysed in place of CMR concentricity. Furthermore, multivariable cox regression models

Table 2 Clinical and cardiovascular magnetic resonance characteristics of hypertensive patients stratified by the left ventricular mass and concentricity

	Hypertensive patients				P-value
	Normal (n = 182)	Concentric remodelling (n = 42)	Concentric LVH (n = 110)	Eccentric LVH (n = 66)	
Clinical characteristics					
Age (years)	59 ± 9 ^a	55 ± 10	54 ± 12	57 ± 10	0.001
Males, n (%)	120 (66)	27 (64)	57 (52)	28 (42)	0.003
Height (m)	1.66 ± 0.08	1.65 ± 0.07	1.64 ± 0.09	1.63 ± 0.08	0.215
Weight (kg)	70 ± 14 ^{a,b}	78 ± 15	75 ± 20	70 ± 16	0.004
BSA (m ²)	1.77 ± 0.20	1.85 ± 0.19	1.81 ± 0.25	1.75 ± 0.20	0.048
Diabetes mellitus, n (%)	24 (13)	4 (10)	15 (14)	8 (12)	0.913
Hyperlipidaemia, n (%)	69 (38)	16 (38)	48 (44)	32 (49)	0.441
Systolic blood pressure (mmHg)	126 ± 12 ^{a,b}	133 ± 15 ^c	141 ± 14 ^d	131 ± 16	<0.0001
Diastolic blood pressure (mmHg)	78 ± 9 ^{a,b}	83 ± 10	84 ± 11 ^d	79 ± 11	<0.0001
Echo relative wall thickness	0.34 ± 0.07 ^a	0.36 ± 0.07 ^c	0.43 ± 0.12 ^d	0.35 ± 0.08	<0.0001
HbA1c (%)	6.9 (6.6–7.4)	7.3 (6.9–8.0)	7.6 (7.0–8.2)	6.8 (6.6–8.9)	0.251
NT-proBNP (pg/mL)	30.2 (14.9–68.3)	30.3 (6.1–53.3)	66.3 (23.3–182.9)	42.9 (28.1–109.3)	<0.0001
High-sensitive troponin I (ng/L)	1.5 (0.6–2.9)	1.7 (1.3–3.4)	3.9 (2.3–8.7)	3.7 (1.5–6.6)	<0.0001
Cardiovascular magnetic resonance characteristics					
Indexed LV mass (g/m ²)	46 ± 7 ^{a,e}	51 ± 8 ^{c,f}	69 ± 20 ^d	58 ± 13	<0.0001
Indexed LVEDV (mL/m ²)	71 ± 9 ^{a,b,e}	62 ± 7 ^{c,f}	77 ± 16 ^d	87 ± 17	<0.0001
Indexed LVESV (mL/m ²)	28 ± 6 ^{a,b,e}	23 ± 6 ^{c,f}	31 ± 13 ^d	37 ± 15	<0.0001
Indexed LVSV (mL/m ²)	44 ± 7 ^{b,e}	39 ± 6 ^{c,f}	46 ± 8 ^d	50 ± 9	<0.0001
LVEF (%)	61 ± 6	63 ± 7 ^f	60 ± 9	59 ± 9	0.017
LV mass/LVEDV ratio	0.66 ± 0.08 ^{a,b}	0.83 ± 0.09 ^{c,f}	0.89 ± 0.15 ^d	0.67 ± 0.08	<0.0001
Maximal wall thickness (mm)	8.1 ± 1.2 ^{a,b,e}	9.6 ± 1.4 ^c	10.8 ± 2.4 ^d	8.9 ± 1.7	<0.0001
Remodelling index	6.3 ± 0.9 ^{a,b}	5.1 ± 0.6 ^f	4.9 ± 0.9 ^d	6.1 ± 0.9	<0.0001
Circumferential strain (%)	-22.6 ± 2.9 ^a	-22.7 ± 3.4 ^c	-20.9 ± 4.1	-21.4 ± 3.8	<0.0001
Radial strain (%)	48.1 ± 12.0 ^a	48.6 ± 15.4	42.3 ± 14.2	43.1 ± 13.0	0.001
Longitudinal strain (%)	-19.8 ± 3.0 ^a	-19.2 ± 3.8 ^c	-17.0 ± 3.7	-18.0 ± 3.3	<0.0001
Native T1 (ms)	1004 ± 25 ^{a,e}	1007 ± 22 ^{c,f}	1026 ± 32	1023 ± 28	<0.0001
ECV (%)	26.1 ± 2.2	25.2 ± 2.4 ^{c,f}	26.6 ± 3.0	26.6 ± 2.7	0.013
Non-ischaeamic myocardial fibrosis, n (%)	15 (8)	7 (17)	48 (44)	12 (18)	<0.0001
Interstitial volume (mL/m ²)	11.5 ± 1.8 ^{a,e}	12.3 ± 1.7 ^{c,f}	17.5 ± 5.8 ^d	14.9 ± 3.9	<0.0001

BSA, body surface area; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; SV, stroke volume; ECV extracellular volume.

^aANOVA post hoc Bonferroni adjustment: $P < 0.05$ between no LVH and concentric LVH.

^bANOVA post hoc Bonferroni adjustment: $P < 0.05$ between no LVH and concentric remodelling.

^cANOVA post hoc Bonferroni adjustment: $P < 0.05$ between concentric remodelling and concentric LVH.

^dANOVA post hoc Bonferroni adjustment: $P < 0.05$ between concentric and eccentric LVH.

^eANOVA post hoc Bonferroni adjustment: $P < 0.05$ between no LVH and eccentric LVH.

^fANOVA post hoc Bonferroni adjustment: $P < 0.05$ between concentric remodelling and eccentric LVH.

demonstrated that the RI was associated with worse prognosis independent of age, sex, SBP and LVH, and other prognostic markers, such as CMR concentricity, RWVT, wall thickness, and (trend towards statistical significance) global longitudinal strain (Table 3; Supplementary data online).

Discussion

The RI is an integrated measure that describes the heterogeneous remodelling effects of hypertensive LVH. In a large CMR cohort of

400 well-characterized hypertensive patients, we demonstrated that LVH with low RI was associated with features of maladaptive cardiac remodelling: increased LV mass, non-ischaeamic myocardial fibrosis, impaired myocardial deformation, elevated biochemical markers of myocardial injury (hsTnI) and cardiac wall stress. Unlike the conventional LVH classification (concentric and eccentric hypertrophy), the RI improved risk stratification of hypertensive LVH. Hypertensive patients with LVH and low RI had more than five-fold increase in event rates compared to those with LVH and normal RI. The RI provided incremental prognostic value to an established model of clinical variables and LVH; and predicted

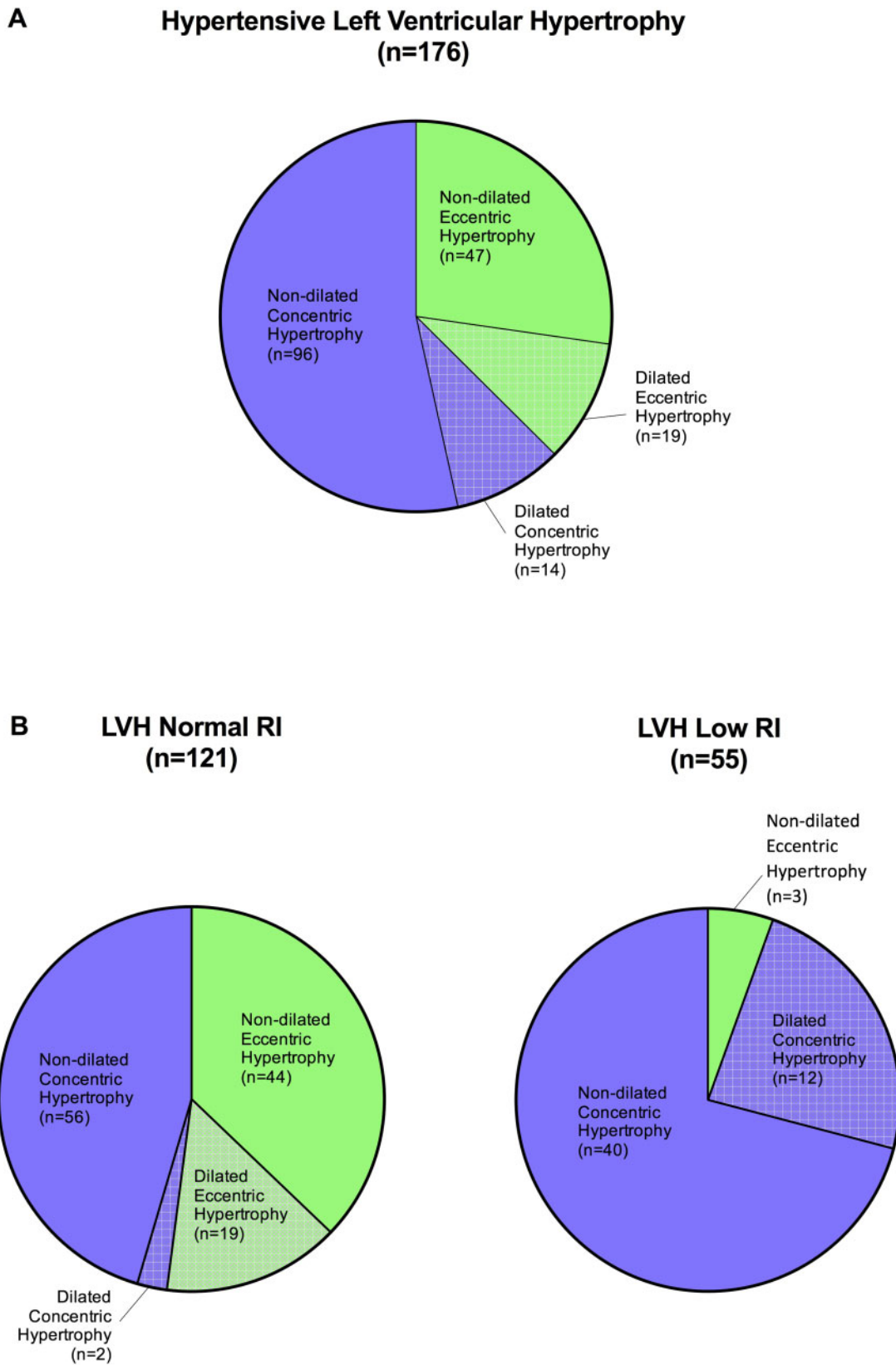


Figure 2 Geometric patterns of hypertensive left ventricular hypertrophy (A) and after classification by the remodelling index (B).

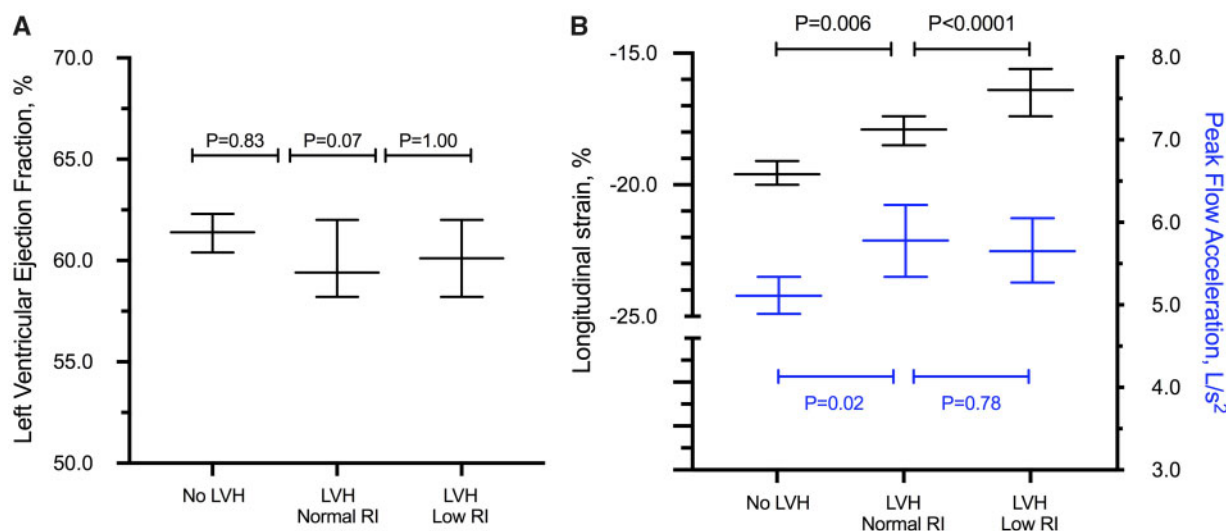


Figure 3 Myocardial function in hypertensive left ventricular hypertrophy assessed using left ventricular ejection fraction (A) and myocardial deformation and peak flow acceleration (B). Results were presented in mean and 95% confidence interval, adjusted for age, sex, and systolic blood pressure.

adverse cardiovascular outcomes independent of clinical variables, LVH, and other prognostic markers.

LVH is conventionally classified into two groups based on concentricity: increased in concentric hypertrophy and normal in eccentric hypertrophy.²⁰ However, cardiac remodelling is far more nuanced and the conventional classification may not completely reflect the complex interaction between LV dilatation and concentricity. To address this limitation, several studies have examined an expanded four-group to include LV dilatation: dilated and non-dilated concentric LVH, as well as, dilated and non-dilated eccentric LVH.^{24–27}

We have recently developed a measure, the RI, based on the principles of the LaPlace's Law of wall stress. This Index incorporates LV volume and wall-thickness in a single measure, with sex- and age-specific thresholds previously established in healthy volunteers.¹² We examined how the classification by the RI relates to this proposed four-group LVH classification. In this cohort, the RI classified hypertensive LVH into two categories: LVH with normal RI and LVH with low RI. No patients had LVH with high RI. The geometric patterns after classification by the RI were diverse. It was perhaps not surprising that non-dilated concentric hypertrophy was the most prevalent pattern associated with low RI because of increased wall thickening. Of note, one in five patients with low RI had dilated concentric hypertrophy, and three patients had non-dilated eccentric hypertrophy. Conversely, LVH with normal RI consisted of both eccentric and concentric hypertrophy; and 17% of these patients had dilated LV. These findings support the RI as a measure that reflects the complex geometrical alterations in hypertensive LVH.

In the presence of increased afterload from elevated pressures, LVH was initially adaptive to minimise wall stress and maintain cardiac output. Subsequently, the LV decompensates.²⁸ While the conventional LVH classification is meaningful to describe mechanical wall

stress due to pressure (concentric hypertrophy) or volume (eccentric hypertrophy) overloaded cardiovascular conditions, it may not be adequate to accurately reflect the mechanical stress on the heart before decompensation occurs. Using the RI, we characterized changes in LV mechanics related to hypertension. In hypertensive patients with LVH and normal RI, the initial reduction in myocardial deformation was associated with an increase in aortic peak flow acceleration, suggesting a compensatory phase. With more severe remodelling (low RI), there was further reduction in myocardial deformation without any improvement in aortic peak flow acceleration. Indeed, hypertensive LVH with low RI was associated with features of advanced hypertrophy: increased LV mass, myocardial fibrosis, elevated markers of myocardial injury (hsTnI), and cardiac decompensation, findings consistent with our previous study.¹²

In addition to being a marker of advanced hypertrophy, the RI improved risk stratification of hypertensive LVH by identifying patients at high and low risk for adverse cardiovascular events. Patients with LVH and low RI had over a five-fold increase in event rate compared to those with normal RI. Moreover, the RI (but not concentricity or RWT) provided incremental prognostic value over clinical variables and LVH. In the proposed four-group LVH classification, dilated concentric had the highest risk and non-dilated eccentric hypertrophy was associated with the most favourable prognosis.^{24–27} Consistent with these observations, in our study, all but two patients with dilated concentric hypertrophy (85.7%) had low RI, our classification of high-risk phenotype; conversely, all but three patients with non-dilated eccentric hypertrophy (93.8%) had normal RI (low-risk phenotype).

Clinical implications

Hypertensive LVH is a heterogeneous condition and the individual risk of adverse outcomes is variable. Therefore, it is critical to

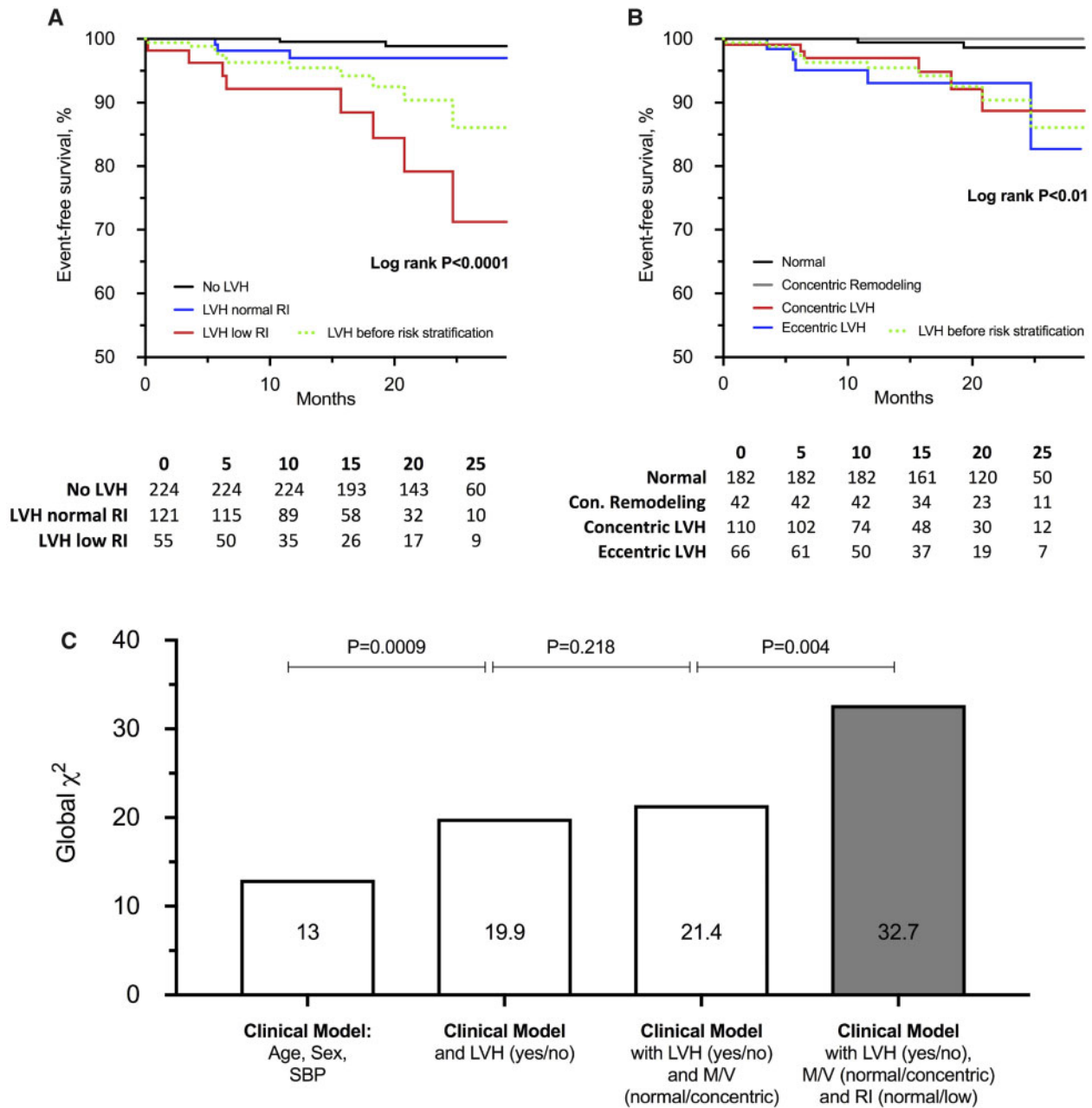


Figure 4 Event-free survival associated with left ventricular hypertrophy stratified by the remodelling index (A) and conventional geometric classification (B). Incremental prognostic value of the remodelling index compared with conventional markers (C).

efficiently identify and prioritise high-risk patients for intensified therapies. Our study supports existing evidence and endorses the importance of assessing LV dilatation and concentricity as important mediators of cardiac remodelling. The RI simplifies the four-group LVH classification into a single measure that is easy to apply.

In the previous studies, the two highest risk groups in the proposed four-group LVH classification accounted for 8–37% of all the adverse events observed,^{25,27} with a lack of incremental value demonstrated in one study.²⁶ Using the RI, about 30% of patients with hypertensive LVH were stratified as high risk that accounted

for more than 60% of the events observed. These high-risk patients may potentially derive the most benefits from aggressive management and targeted treatment, while unnecessary treatment and investigations can be avoided in the lower risk patients. The application of the RI and these findings should be validated in other populations.

Recommending CMR in all patients with hypertensive LVH is not practical. Cost-effective strategies to integrate the RI into clinical practice and its role with other more widely available biomarkers of cardiac remodelling should be investigated in future studies.

Table 3 Hazard ratios predicting adverse cardiovascular events for the remodelling index in adjusted and unadjusted analyses

Model	Hazard ratio (95% confidence interval)
Unadjusted model	5.96 (2.77–12.83)
Model 1: Age, sex, systolic blood pressure, LVH (categorical)	3.55 (1.13–11.18)
Model 2: Model 1 + CMR concentricity (categorical)	5.03 (1.62–15.59)
Model 3: Model 1 + RWT (echo)	4.84 (1.32–17.78)
Model 4: Model 1 + wall thickness	4.11 (1.33–12.65)
Model 5: Model 1 + global longitudinal strain	3.16 (0.91–10.95)

Study limitations

The number of events is relatively small due to the low-risk cohort of asymptomatic hypertensive patients that was studied. However, the event rate observed in our study (2.0 events/100 patient-years) was comparable to those reported in previous studies.^{2,3} We were not able to examine the prognostic interactions between LV dilatation and concentricity because of the limited number of patients with dilated LV in our cohort. The RI assumes a spherical LV that may be insensitive to the effects of chamber dilatation. We had used a spherical model because the radius can be estimated accurately from LVEDV on routine CMR. Conversely, the use of an ellipsoid model requires at least two linear measurements in 1–2 cardiac views to estimate radius. This will not only increase the complexity but also introduce variations in measurements and calculations. Regardless of the model used, we acknowledged that each was associated with systematic differences in estimating wall stresses.

Conclusions

Hypertensive LVH is a heterogeneous remodelling process mediated by increased concentricity and LV dilatation. The RI provides mechanistic insights and as a single measure, it is a convenient approach of risk stratifying patients with hypertensive LV hypertrophy.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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