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ORIGINAL ARTICLE

Endothelial dysfunction is associated with left ventricular mass (assessed using MRI) in an adult population (MESA)

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Brachial flow-mediated dilation (FMD) is a measure of endothelial nitric oxide bioavailability. Endothelial nitric oxide controls vascular tone and is likely to modify the ventricular muscle coupling mechanism. The association between left ventricular mass and FMD is not well understood. We assessed the association between left ventricular mass index (LVMI) and FMD in participants of the Multi-Ethnic Study of Atherosclerosis (MESA). MESA is a population-based study of 6814 adults free of clinical cardiovascular disease at baseline who were recruited from six US clinics. LVMI (left ventricular mass per body surface area) and FMD were measured in 2447 subjects. Linear regression analysis was used to evaluate the association. The subjects had a mean age of 61.2 ± 9.9 years, 51.2% females with 34.3% Caucasians, 21.6% Chinese, 19.4% African Americans and 24.7% Hispanics. The mean body mass index (BMI) was 27.4 ± 4.8 kg m^{-2}, 9.4% had diabetes, 11% were current smokers and 38% hypertensives. The mean ± s.d. LVMI was 78.1 ± 15.9 g m^{-2} and mean ± s.d. FMD was 4.4% ± 2.8%. In univariate analysis, LVMI was inversely correlated with FMD ($r = -0.20$, $P < 0.0001$). In the multivariable analysis, LVMI was associated with FMD (β coefficient (se) = −0.50 (0.11), $P < 0.001$ (0.5 g m^{-2} reduction in LVMI per 1% increase in FMD)) after adjusting for age, gender, race/ethnicity, systolic blood pressure, diabetes mellitus, smoking, weight, statin use, antihypertensive medication use, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. The association between brachial flow mediated dilation and LVMI maybe independent of traditional CV risk factors in population based adults.
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Introduction

Nitric oxide has been shown to modulate the cardiac inotropic state[1] and sarcolemmal calcium homoeostasis,[2] as well as inhibits direct and β-adrenergic growth-promoting effects of catecholamines on cardiac myocytes through its autocrine and paracrine effects.[3] Brachial flow-mediated dilation (FMD), a measure of endothelial nitric oxide release by the brachial endothelium in response to transient shear stress, is a measure of vascular health.[4] Endothelial nitric oxide also controls vascular tone[5] and is likely to modify the ventricular muscle coupling mechanism, systemic vascular resistance and cardiac workload.

Increased left ventricular (LV) mass has also been shown to be an important prognostic factor for cardiovascular mortality and morbidity in both normotensive and hypertensive populations.[6–10] Cardio protective therapy such as ACE inhibitors and HMG CoA reductase inhibitors have all been shown to reduce LV mass[11,12] through mechanisms that may be independent of their direct effects on blood pressure.

Brachial FMD, a physiological measure of endothelial function, has also been associated with cardiovascular morbidity and mortality,[13,14] and ACE inhibitors and HMG CoA reductase inhibitors have also been shown to improve endothelial function.[15,16]

Although the current theory supports an association between endothelial dysfunction and LV mass, the existing evidence on this association is limited

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and reflects mixed results.[17–20] Although some studies have shown associations between endothelial function and LV mass,[17–19] other studies[20] have failed to demonstrate such an association. Current published data on the association between FMD and LV mass were obtained from small and highly selected cohorts of hypertensive individuals with or without LV hypertrophy. In addition, most of the limited data used echocardiography,[17,19,20] a modality that has been shown to be both imprecise and inaccurate compared with magnetic resonance imaging (usually considered a reference standard), to measure LV mass. Therefore, the association between brachial FMD and LV mass is currently assumed to exist only in hypertensive individuals and whether this association exists in other populations is unclear.

To address some of these limitations in our understanding of this potential association, we assessed the relationship between brachial FMD and LV mass in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study population and data collection

The study design for MESA has been published elsewhere.[21] In brief, MESA is a prospective cohort study that began in July 2000 to investigate the prevalence, correlates and progression of subclinical CVD in individuals without known CVD at baseline. The cohort includes 6814 women and men aged 45–84 years old recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St Paul, MN). MESA cohort participants were 38% white ($n=2624$), 28% black ($n=1895$), 22% Hispanic ($n=1492$) and 12% Chinese ($n=803$). Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke or transient ischaemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement or other vascular surgeries) were excluded from participation. This study was approved by the Institutional Review Boards of each study site and written informed consent was obtained from all participants.

Demographics, medical history, anthropometric and laboratory data for this study were taken from the first examination of the MESA cohort (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as fasting glucose $\geqslant 126\,\mathrm{mg\,100\,ml^{-1}}$ or the use of hypoglycaemic medications. Use of antihypertensive and other medications was based on the review of prescribed medication containers. Resting blood pressure was measured three times in seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure $\geqslant 140$ mm Hg, diastolic blood pressure $\geqslant 90$ mm Hg or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height (m^2). Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein cholesterol was estimated by the Friedewald equation.[22]

Brachial FMD measurement

Brachial FMD was measured in the MESA cohort during the first examination. Participants were excluded if they had uncontrolled hypertension (158 MESA participants were excluded), blood pressures in the left and right arms that differed by more than 15 mm Hg, or if they had a history of Raynaud's phenomenon (55 MESA participants were excluded), a congenital abnormality of the arm or hand (12 MESA participants were excluded), or a radical mastectomy on either side (100 MESA participants were excluded). Thus, 6489 MESA participants had brachial FMD measured during the first examination period. Participants were examined in the supine position after 15 min rest and after at least a 6-h fast. An automated sphygmomanometer (Dinamap device) was used to monitor blood pressure and pulse in the left arm at 5-min intervals throughout the exam. A standard blood pressure cuff was positioned around the right arm, 2 inches below the antecubital fossa and the artery was imaged 5–9 cm above the antecubital fossa. A linear-array multifrequency transducer operating at 9 MHz (GE Logiq 700 Device) was used to acquire images of the right brachial artery. After obtaining baseline images, the cuff was inflated to 50 mm Hg above the participant's systolic blood pressure for 5 min. Images of the right brachial artery were captured continuously for 30 s before cuff inflation, and for 2 min beginning immediately before cuff deflation to document the vasodilator response. Images of the brachial artery diameters were captured in diastole (gated with electrocardiograph R-wave). A detailed description of the scanning and reading protocol can be found at the MESA website (www.mesa-nhlbi.org).

Videotapes of the acquired images of the brachial artery were analysed at the Wake Forest University Cardiology Image Processing Laboratory using a previously validated semi-automated system.[23] The semi-automated readings of these digitized images generated the baseline and maximum diameters of the brachial artery from which % FMD was computed.

$$\%\mathrm{FMD} = [(\mathrm{Maximum\ diameter} - \mathrm{Baseline\ diameter}) / \mathrm{Baseline\ diameter}] \times 100\%$$

Intra-reader reproducibility for baseline diameter, maximum diameter and % FMD was evaluated by

comparing an original and a blinded quality control re-read of ultrasounds from 40 MESA participants (32 males, 18 Caucasians, 2 Chinese, 10 African–American and 10 Hispanics). The intra-class correlation coefficients were 0.99, 0.99 and 0.93, respectively. Intra-subject variability was evaluated by comparing results from repeated examinations of 19 subjects on 2 days a week apart. The intra-class correlation coefficients for baseline diameter, maximum diameter and % FMD were 0.90, 0.90 and 0.54, respectively. Percent technical error of measurement for baseline diameter measurement was 1.39%, maximum diameter measurement was 1.47 and %FMD measurement was 28.4%.

Even though 6489 participants had FMD measured, for cost reason only a subset ($n=3026$), a randomly selected sample of 2843 and 182 subjects who had a cardiovascular event including incident myocardial infarction, definite angina, coronary revascularization (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or other revascularization), stroke, resuscitated cardiac arrest and CVD death after 5 years of follow up, had their tapes read and were included in the MESA FMD ancillary study.

Magnetic resonance imaging (MRI)
Consenting participants underwent a cardiac MRI scan a median of 16 days after the baseline evaluation; 95% were completed by 11 weeks after the baseline examination. Participation in the MRI exam was voluntary. The MRI exams were carried out using scanners with 1.5-T magnets as previously described.[24] All the imaging was carried out with a four-element phased-array surface coil positioned anteriorly and posteriorly, electrocardiographic gating and brachial artery blood pressure monitoring. Imaging consisted of fast gradient echo cine images of the left ventricle with time resolution <50 ms. Functional parameters and mass were determined by volumetric imaging. Imaging data were read using MASS software (version 4.2, Medis, Leiden, the Netherlands) at a single reading center by readers trained in the MESA protocol and without knowledge of risk factor information. Papillary muscles were included in the LV volumes and excluded from LV mass. The reliability of the MRI readings was determined by calculating for a set of 155 duplicate readings the intra-class correlation (ICC) as the ratio of the variance of the variable if precisely measured (without measurement error) over the observed variance of the variable (with measurement error). An intra-class correlation reliability estimate of 0.95 means that 5% of the total variability is attributed to reader measurement error. For LV mass, intra-class correlation was 0.97 (95% confidence interval 096–0.98).

Statistical analysis
Demographic data are reported as mean ± s.d. for continuous variables and frequency/percentages for categorical variables. LV mass index (LVMI) was computed using the formula:

$$\text{LVMI} = \text{LV mass}/\text{body surface area}$$

Pearson's correlation was used to examine the relationship between LVMI and brachial FMD. The association between LVMI and brachial FMD was examined in a univariate linear regression model and also in multivariable models adjusting for covariates that have been associated with FMD/LVMI in previous studies and also showed an association with FMD/LVMI in our univariate regression models including age, gender, race/ethnicity, systolic and diastolic blood pressure, cigarette smoking, weight, high-density lipoprotein and low-density lipoprotein cholesterol, diabetes mellitus, HMG CoA reductase inhibitor use and antihypertensive medication use. Above analyses were repeated using LV mass and adjusting for height and weight in models. Our full model was then stratified by hypertension status (defined as BP $\geqslant$ 140/90 mm Hg). A two-tailed value of $P<0.05$ was considered significant. Statistical analysis was carried out using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Out of the 3027 participants in the MESA brachial FMD ancillary study, 2447 also had cardiac MRI-assessed LV mass and were therefore included in this cross-sectional analysis. The mean age of the subset was 61 years, 51.2% females, 9.4% were diabetics, 11% were current smokers, 28.3% were on antihypertensive medications and 13.7% were on HMG CoA reductase inhibitors (Table 1).

LVMI and covariates
The distribution of LV mass was approximately normal. Mean LV mass was 144.4 ± 38.8 g and the mean LVMI was $78.1 \pm 15.9\,\text{g}\,\text{m}^{-2}$.

Less than 4% of the cohort had either LVMI or LV mass greater than the mean + 2 (s.d.). However, based on MRI criteria by Alfakih *et al.*,[25] 24.4% had LV hypertrophy. Correlation coefficient of LVMI and age, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, weight, heart rate, waist circumference and fasting blood glucose were 0.01, $P=0.59$; 0.29, $P<0.0001$; 0.29, $P<0.0001$; 0.01, $P=0.59$; -0.24, $P<0.0001$; 0.51, $P<0.0001$; -0.13, $P<0.0001$; 0.18, $P<0.0001$; and 0.11, $P<0.0001$ respectively.

Brachial FMD and covariates
The mean FMD was 4.4 ± 2.8 (%). Correlation coefficient of FMD and age, systolic blood pressure,

Table 1 Demographics of the MESA ancillary study cohort

Variables	*Mean ± s.d.* n = *2447*
Age (years)	60.8 ± 9.8
Female gender (%)	1252 (51.2)
Race (%)	
Caucasian	838(34.3)
Chinese	528 (21.6)
African–Americans	478 (19.4)
Hispanics	603(24.7)
Body mass index (kg m^{-2})	27.4 ± 4.8
Systolic blood pressure (mm Hg)	123.8 ± 19.6
Diastolic blood pressure (mm Hg)	71.8 ± 10.1
Hypertension (%)	932(38)
Heart rate (beats per min)	62.5 ± 9.1
Waist circumference (cm)	95.5 ± 13.1
Fasting glucose level (mg 100 ml^{-1})	95.1 ± 25.8
Diabetes mellitus (%)	229 (9.4)
Cholesterol (mg 100 ml^{-1})	
Total	193.4 ± 34.7
HDL	51.1 ± 14.6
LDL	116.2 ± 30.3
Triglycerides	132.2 ± 89.3
Glomerular filtration rate	81.7 ± 16.6
Cigarette smoking (%)	
Never	1334 (54.5)
Former	844 (34.5)
Current	268 (11)
LVMI (gm m^{-2})	78.1 ± 15.9
LVH (>mean ± 2 s.d.)	82 (3.5%)
LVH (MRI criteria)	570 (24.4%)
LV mass (grams)	144.4 ± 38.8
LV systolic function (%)	69.4 ± 7.2
Body surface area (m^2)	1.85 ± 0.22
Brachial FMD (%)	4.4 ± 2.8
Blood pressure medication use (%)	692 (28.3)
ACE inhibitor use (%)	231(9.4)
α-blocker use (%)	90 (3.7)
β-blocker use (%)	208 (8.5)
Calcium channel blocker use (%)	254 (10.4)
Diuretics (%)	240 (9.8)
HMG CoA reductase inhibitors (%)	335 (13.7)

Abbreviations: FMD, flow-mediated dilation; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.

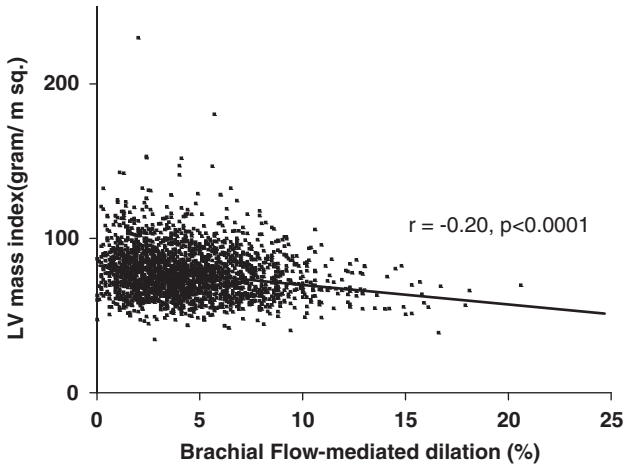

Figure 1 Association of LVMI(g m^{-2}) and brachial FMD (%) in MESA ($n = 2447$).

Table 2 Multivariable model for the association of LVMI* (g m^{-2}) and brachial FMD (%) in MESA FMD ancillary study

Variable	*β coefficient*	*s.e.*	P *value*
Brachial FMD (%)	−0.50	0.10	<0.001
Age (years)	−0.18	0.03	<0.0001
Caucasian	0.78	0.23	<0.001
Male gender	13.6	0.67	<0.0001
SBP	0.20	0.03	<0.001
Weight	0.04	0.01	0.001
Diabetes mellitus	0.55	0.63	0.39
BP medication use	3.22	0.65	<0.001
HDL	0.03	0.02	0.20
LDL	0.004	0.001	0.62
Smoking	2.25	0.41	<0.001

Abbreviations: BP, blood pressure; FMD, flow-mediated dilation; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
LVMI* = LV mass/body surface area. R-square for the model was 0.45.
NB: Race/ethnicity was dichotomized into Caucasian vs non-Caucasian (Chinese, Hispanics and African–Americans). Similarly smoking status was dichotomized into never smokers and smokers (current and former smokers).

diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, weight, heart rate, waist circumference and fasting blood glucose were −0.31, $P<0.0001$; −0.21, $P<0.0001$; −0.11, $P<0.0001$; −0.03, $P=0.63$; 0.03, $P=0.20$; and −0.05, $P=0.01$; 0.10, $P<0.0001$; −0.09, $P<0.001$; −0.09, $P<0.001$, respectively.

Association between FMD and LVMI

In the univariate analysis, LVMI was significantly associated with brachial FMD (Pearson's $r=-0.20$, $P<0.0001$) and Figure 1. Similar Pearson coefficients were obtained when the association between LVMI and brachial FMD was stratified by race/ethnicity (Caucasians: $r=-0.21$, $P<0.0001$; Chinese: $r=-0.13$, $P=004$; African–Americans $=-0.17$, $P=0.0006$; and Hispanics: $r=-0.14$, $P=0.0001$). LVMI was independently associated with brachial FMD after adjusting for systolic blood pressure, diastolic blood pressure and antihypertensive medication use (β coefficient $=-0.75\pm0.11$, $P<0.0001$, translate to 0.75 g m^{-2} reduction in LVMI per 1% increase in FMD). In the full multivariable linear regression model, LVMI was also significantly associated with FMD (β coefficient $=-0.50\pm0.11$, $P<0.001$) (Table 2). This translated into a 0.5 g m^{-2} reduction in LVMI per 1% increase in FMD in this cohort. Age, Caucasian race, male gender, systolic blood pressure, weight (kg), cigarette smoking and

antihypertensive medication use were also independently associated with LVMI in our multivariable model (Table 2). LVMI was independently associated with FMD after forcing brachial artery diameter into the full multivariable model (β coefficient = -0.23 ± 0.11, $P = 0.03$). LVMI and brachial FMD were significantly different in subjects with hypertension compared with subjects without hypertension (data not shown). We stratified the full multivariable model by the presence or absence of hypertension (defined as blood pressure >140/90 mm Hg or use of blood pressure medication) (no hypertension ($n = 1515$, β coefficient -0.27 ± 0.12, $P = 0.02$) and hypertension ($n = 932$, β coefficient -0.76 ± 0.20, $P = 0.002$)). Similarly, subjects with LV hypertrophy by the MRI criteria[25] had a stronger negative association compared with subjects without LV hypertrophy (no LVH ($n = 1877$, β coefficient -0.26 ± 0.07, $P = 0.009$) and LVH ($n = 570$, β coefficient -0.47 ± 0.10, $P = 0.001$)).

Adjusting for height and weight in models containing LV mass instead of LVMI produced similar results (data not shown).

Further evaluation of the independent association between LVMI and cigarette smoking status in the multivariable model revealed no significant difference between the mean LVMI of never smokers and former smokers (77.2 ± 0.27 vs 77.6 ± 0.32, P for difference = 0.34). There was a significant difference between the LVMI of current smokers and never/former smokers ($77.2 \pm 0.27/77.6 \pm 0.32$ vs 82.2 ± 0.54, P for difference <0.001 for each comparison).

Discussion

The aim of this study was to assess the cross-sectional association between brachial FMD, a validated physiologic measure of endothelial function and LV mass index. The current study used a large sample of a multi ethnic population based cohort without clinical cardiovascular disease to show that brachial FMD has a modest but significant negative association with LV mass index independent of cardiovascular risk factors.

There is paucity but mixed data on the association between endothelial dysfunction and LV mass.[17–20] In addition to the small sample sizes of previous studies, they were all conducted in hypertensives with or without LV hypertrophy. The lack of data on non-hypertensives may be because of publication bias but has erroneously created the impression that the association between endothelial dysfunction and LV mass exists only in hypertensives and thus implies that the common mechanism is hypertension. Cardiovascular risk factors such as diabetes mellitus, high-density lipoprotein cholesterol, smoking and HMG CoA reductase inhibitors have all been shown to be associated with both LV mass and brachial FMD. In our multivariable model, the association between brachial FMD and LVMI persisted after adjusting for these factors.

Recent studies have alluded to the heritability of both LV mass and endothelial function.[26,27] It appears that a portion of the variance in LV mass and endothelial function is inherited and this by itself could position an individual at a higher or lower cardiovascular risk. More studies on the underlying molecular/genetic basis of the differences in LV mass are warranted and may lead to avenues for cardiovascular risk reduction in populations.

Left ventricular hypertrophy by electrocardiography has been well documented to be a cardiovascular risk factor.[28] Echocardiographic and MRI-assessed increased LV mass have also been documented to be a cardiovascular risk factor.[6] It is possible that the vascular endothelium may serve as a 'barometer' for the cumulative insults to the cardiovascular system,[29] and that endothelial dysfunction may be a measure of the cumulative cardiovascular risk. This study highlights the fact that even though the association between LVMI and cardiovascular risk appears to be stronger in subjects with LV hypertrophy, it also exist in subjects without LV hypertrophy. Thus the association between LVMI and endothelial dysfunction exist in subjects with or without LV hypertrophy.

Cigarette smoking is a cardiovascular risk factor and cigarette smoking cessation has been shown to be associated with a reduction in cardiovascular risk and prognosis.[30] However, the underlying mechanism is unclear. The result of this study is consistent with a reduction in LV mass in former smokers compared with current smokers. In addition to the proposed hypotheses such as improvement in endothelial function and reduction in inflammation with cigarette smoking cessation, a reduction in LV mass may also be a potential mechanism. Similar potentially beneficial effects of cigarette smoking cessation have been shown in hypertensives with respect to pulse wave velocity and arterial stiffness.[31] Longitudinal studies are needed to delineate the role of cigarette smoking in the development of increased LVMI.

This study has the following limitations. Even though after adjusting for most cardiovascular risk factors in our multivariable model, LVMI was still significantly associated with endothelial dysfunction; our result may still be because of residual confounding. Covariates such as antihypertensive medication use, race/ethnicity and smoking status were all introduced into the model as binary variables and the duration of antihypertensive medication use was not included in the analysis. It is unclear how these may have affected the results of this study. Endothelial independent vasodilation (smooth muscle dilation) was not evaluated. Thus it is unclear the effect that smooth muscle dysfunction had on the brachial FMD measurements. Duration of hypertension was not collected and therefore was not included in our multivariable model. It is

unclear the effect that duration of hypertension would have on the association of brachial FMD and LVMI. However, our stratified analysis showed that this independent association between brachial FMD and LVMI exist in subjects with hypertension and those without hypertension, even though the association seems to be stronger in hypertensives than in non-hypertensives. Ambulatory blood pressure measurements were also not done in the MESA cohort. It is unclear how ambulatory blood pressure instead of the average of two seated blood pressure used in this study may have affected our findings.

Finally, even though sonographers were centrally trained and standardized FMD measuring protocols were employed at all study sites, the re-test and re-read performance measures indicate considerable within-subject variability. This variability limits the resolution possible for estimating effect sizes and likely obscures other important relationships between FMD, conventional CVD risk factors and LVMI.

Conclusion

The association between LVMI and endothelial dysfunction (brachial FMD) maybe independent of cardiovascular risk factors, which include blood pressure and antihypertensive medication use. Half percent reduction in endothelial dysfunction is associated with $1\,g\,m^{-2}$ increase in LV mass in asymptomatic adults without the history of clinical cardiovascular disease. More studies are needed in this area of research.

What is known about this topic

- Impaired brachial flow-mediated dilation (FMD) and increased left ventricular (LV) mass are cardiovascular risk markers.[10,14]
- Limited and mixed data on the association between brachial FMD and LV mass in hypertensive patients,[17–20]
- Most of the previous studies used echocardiogram derived LV mass. Echocardiogram-derived LV mass has been shown to be inaccurate compared with MRI-derived LV mass.

What this study adds

- Brachial FMD is associated with LV mass (assessed using MRI) independent of cardiovascular risk factors in large multi ethnic population based adults.
- Current cigarette smokers have higher LV mass compared with former/never smokers.

Conflict of interest

The authors declare no conflict of interest.

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