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Correlation of Trabeculae and Papillary Muscles With Clinical and Cardiac Characteristics and Impact on CMR Measures of LV Anatomy and Function

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OBJECTIVES The goal of this study was to assess the relationship of left ventricular (LV) trabeculae and papillary muscles (TPM) with clinical characteristics in a community-based, free-living adult cohort and to determine the effect of TPM on quantitative measures of LV volume, mass, and ejection fraction (EF).

BACKGROUND Hypertrabeculation has been associated with adverse cardiovascular events, but the distribution and clinical correlates of the volume and mass of the TPM in a normal left ventricle have not been well characterized.

METHODS Short-axis cine cardiac magnetic resonance images, obtained using a steady-state free precession sequence from 1,494 members of the Framingham Heart Study Offspring cohort, were analyzed with software that automatically segments TPM. Absolute TPM volume, TPM as a fraction of end-diastolic volume (EDV) (TPM/EDV), and TPM mass as a fraction of LV mass were determined in all offspring and in a referent group of offspring free of clinical cardiovascular disease and hypertension.

RESULTS In the referent group (mean age 61 ± 9 years; 262 men and 423 women), mean TPM was 23 ± 3% of LV EDV in both sexes ($p = 0.9$). TPM/EDV decreased with age ($p < 0.02$) but was not associated with body mass index. TPM mass as a fraction of LV mass was inversely correlated with age ($p < 0.0001$), body mass index ($p < 0.018$), and systolic blood pressure ($p < 0.0001$). Among all 1,494 participants (699 men), LV volumes decreased 23%, LV mass increased 28%, and EF increased by 7.5 EF units ($p < 0.0001$) when TPM were considered myocardial mass rather than part of the LV blood pool.

CONCLUSIONS Global cardiac magnetic resonance LV parameters were significantly affected by whether TPM was considered as part of the LV blood pool or as part of LV mass. Our cross-sectional data from a healthy referent group of adults free of clinical cardiovascular disease demonstrated that TPM/EDV decreases with increasing age in both sexes but is not related to hypertension or obesity. (J Am Coll Cardiol Img 2012;5:1115–23) © 2012 by the American College of Cardiology Foundation

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Left ventricular (LV) "hypertrabeculation" has been associated with adverse cardiovascular outcomes (1–3) and with extracardiac disease, including neuromuscular disorders (4), but the normal range of trabeculation and papillary muscle mass on cardiac magnetic resonance (CMR) imaging has not been fully characterized. In addition, the effect of the trabeculae and papillary muscles (TPM) on determination of LV volume, mass, and ejection fraction (EF) has not been assessed in a large, community-dwelling population. Cine steady-state free precession (SSFP) CMR provides high-resolution imaging of the left ventricle, with excellent visual contrast between myocardium and LV blood pool (5,6). These desirable attributes emphasize the papillary muscles and the trabeculae carnae, which were less well-visualized with other CMR sequences. There is variability in the treatment of TPM with respect to quantification of LV mass (LVM) and EF, important indexes with diagnostic and prognostic value. The TPM are often considered part of the LV cavity volume (i.e., blood pool) because this simplifies analysis and has been shown to improve observer reproducibility, particularly with manual tracing of endocardial contours (7). Although this is a reasonable approach for many patients, the proportional impact of TPM may be greater in select patient groups, such as those with hypertrophic cardiomyopathy (8) or markedly impaired LV EF (9).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index
CMR = cardiac magnetic resonance
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
+HTN = participants with history of hypertension
ICC = intraclass correlation coefficient
LV = left ventricular
LVM = left ventricular mass
SBP = systolic blood pressure
SSFP = steady-state free precession
TPM = trabeculae and papillary muscles
TPMm = calculated mass of trabeculae and papillary muscles
+WMA = participants with wall motion abnormalities

The goal of this study was to determine the relation of TPM to global LV cavity size, mass, and global systolic function metrics in a cohort of free-living adults and to assess the effect of treating TPM as LV blood pool, versus as myocardial mass, on those LV metrics. We also sought to determine whether TPM varies with sex, age, body mass index (BMI), and history of hypertension or previous adverse cardiovascular events.

METHODS

Study population. The Framingham Heart Study Offspring cohort was initiated in 1971 and comprises 5,124 participants who are the children of the original cohort or the spouses of those children (10). Offspring cohort members were eligible for participation in the CMR substudy if they attended the seventh offspring cycle examination (1998 to 1999, N = 3,799), were in sinus rhythm, and had no contraindications to CMR. A total of 1,794 offspring underwent CMR from 2002 to 2006. All participants provided written informed consent, and the study was approved by the institutional review boards of the Beth Israel Deaconess Medical Center and the Boston University Medical Center.

Clinical covariates and medication information (blood pressure, height, weight, BMI, and antihypertensive drug treatment) were collected in a structured examination by a physician during the seventh cycle examination. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on the mean of 2 measurements by a physician or use of antihypertensive medication. Data regarding cardiovascular disease events, such as myocardial infarction and heart failure, were collected and reviewed. All cardiovascular disease events were adjudicated by a panel of 3 physicians who were blinded to participant CMR data and who used standardized criteria (11).

CMR imaging. Participants underwent supine CMR scanning using a 1.5-T system with a 5-element cardiac array coil for radiofrequency signal reception (Gyroscan NT, Philips Healthcare, Best, the Netherlands). After scout imaging to determine the orientation of the heart within the thorax, a contiguous stack of short-axis two-dimensional SSFP cine images, encompassing the left ventricle from apex to base, was obtained. Imaging parameters included: TR = 3.2 ms, TE = 1.6 ms, and flip angle = 60°. Slice thickness was 10 mm (no interslice gap) with 1.9- × 1.6-mm^2 in-plane spatial resolution.

Image analysis. Images were transferred to a dedicated workstation (Extended MR Workspace 2009, Philips Healthcare) for analysis. Epicardial and endocardial LV contours were delineated across the cardiac cycle using an automated contour detection algorithm followed by manual correction as needed. The automated contour detection method was applied to the LV short-axis images only and has been previously described (12). Briefly, it models the short-axis myocardium as a ribbon of variable width, with the inner (endocardial) and outer (epicardial) contours described by interpolation of a minimal number of splines for each. An energy-

minimizing criterion that favors smooth, circular shapes, combined with regional constraints favoring homogeneous segmentation, results in contours that treat TPM as part of the LV blood pool. The automated analysis (which can be manually corrected as needed) agrees well with fully manual analysis, with correlation coefficients of 0.99 for LV end-diastolic volume (EDV) and end-systolic volume (ESV), 0.96 for LVM, and 0.97 for LV EF (12).

The initial segmentation (INIT), which considered TPM as part of the LV blood pool, was used to determine EDV_{INIT}, ESV_{INIT}, EF_{INIT}, and LVM_{INIT}. The TPM volume was then quantified using a fuzzy thresholding algorithm (12) based on the difference between bright blood pool and darker myocardial intensities; the threshold was determined on the basis of image characteristics. Thresholds are examination specific; there are no pre-determined global cutpoints for myocardium versus blood pool. Figure 1 shows 2 examples of TPM segmentation. Although the sample figures are posterized (black or white) to emphasize trabecular fine details, the actual algorithm used to determine TPM volume accounts for partial volume effects. Finally, LV parameters were adjusted (ADJ) by subtracting TPM volume from LV volume at each phase, yielding EDV_{ADJ} and ESV_{ADJ}, and the calculated mass of TPM (TPMm = TPM volume × 1.05 g/ml) was added to LVM, yielding LVM_{ADJ}. LV EF_{ADJ} was computed from EDV_{ADJ} and ESV_{ADJ}. All image data were analyzed by a single experienced operator (C.J.S.) who was unaware of participant characteristics.

Statistical analysis. Data were analyzed using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). Continuous data were checked for normality and summarized as mean ± SD. Pearson correlation was used to assess linear relationships between TPM and clinical characteristics. We defined a healthy referent group, free of any history of prior myocardial infarction or heart failure, any wall

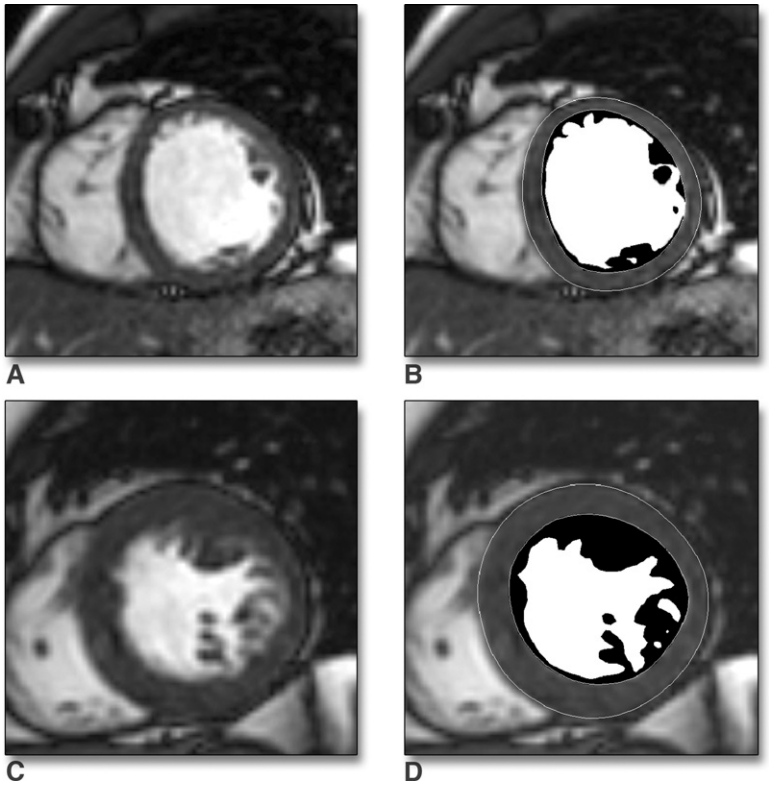

Figure 1. Examples of TPM Quantitation

(A) End-diastolic mid–left ventricular (LV) slice from a relatively lightly trabeculated participant. **(B)** The same slice after endocardial and epicardial border detection and segmentation of trabeculae and papillary muscles (TPM); TPM are shown in **black** and the residual blood pool (slice end-diastolic volume $[EDV]_{ADJ}$) is shown in **white**. For this slice, EDV_{INIT} = 24.6 ml and left ventricular mass $(LVM)_{INIT}$ = 12.5 g, whereas slice EDV_{ADJ} =19.9 ml and LVM_{ADJ} = 17.5g. **(C and D)** A more heavily trabeculated participant with slice EDV_{INIT} = 21.5 ml and LVM_{INIT} = 17.4 g; after TPM segmentation slice EDV_{ADJ} = 12.1 ml and LVM_{ADJ} = 27.3 g.

motion abnormality (of ≥2 anatomically contiguous segments) on CMR, and any history of hypertension to determine the amount of TPM, and its effect on LV EF and LVM, in this putatively normal group. Global LV and TPM measures were compared between the sexes and within-sex between referent and nonreferent participants using the 2-sample *t* test with equal or unequal variance as indicated. Pairs of unadjusted and adjusted LV parameters were compared using the paired *t* test. Linear correlations were assessed using Pearson correlation coefficients. Reproducibility was assessed by intraclass correlation coefficient (ICC) on a subsample of 48 participants randomly selected from equal strata of sex and age-tertile. A p value <0.05 was considered statistically significant.

RESULTS

Study cohort. Data from 1,494 consecutive offspring undergoing CMR were analyzed for this study. In this cohort, 53 (3.6%) had a documented prior myocardial infarction or heart failure, 125 (8.4%) had a focal LV wall motion abnormality on CMR, and 785 (52.5%) had documented hypertension or use of antihypertensive medication. Application of these exclusion criteria left 262 men (38.2%) and 423 women (61.8%) in the healthy referent group. A particular participant could have >1 criterion for exclusion from the referent group. The clinical characteristics of the referent and nonreferent groups, as well as the study population as a whole, are shown in Table 1. There were differences between men and women in anthropometric and blood pressure measures, as expected.

Global LV and TPM measures. Table 2 displays the global LV parameters in referent-group men and women. In the referent group, EDV_{INIT}, ESV_{INIT}, and LVM_{INIT} were greater in men than in women, whereas EF_{INIT} was greater in women. LVM_{INIT} was linearly correlated with SBP in referent men ($r = 0.26$) and women ($r = 0.26$) ($p < 0.0001$ for both) and across all participants (men: $r = 0.21$, women: $r = 0.31$; $p < 0.0001$ for both). TPM was greater in men than in women, but TPM volume as a fraction of EDV_{INIT} (TPM/EDV) did not differ between sexes. TPMm as a fraction of LVM_{INIT} (TPMm/LVM) was slightly but significantly greater in women than men.

After subtraction of TPM volume (ADJ) we expected EDV to decrease, and LVM to increase with the addition of TPMm. In the referent group, EDV decreased by an average of 23% in both sexes, whereas LVM increased 30% and LV EF increased by 7.5 EF units after ADJ. Changes of the same direction and similar magnitude were seen post-ADJ across the study group as a whole (Table 2). Post-ADJ LV volumes and mass remained greater in men versus women. LV EF increased after ADJ in both sexes, and EF_{ADJ} remained greater in women than in men. EF_{INIT} and EF_{ADJ} were highly correlated with one another among men ($r = 0.95$, $p < 0.0001$) and among women ($r = 0.92$, $p < 0.0001$).

Reproducibility of TPM measures. Intraobserver ICCs were 0.99, 0.99, 0.99, and 0.97 for EDV_{ADJ}, ESV_{ADJ}, LVM_{ADJ}, and EF_{ADJ}, respectively. Interobserver ICCs were 0.99 for EDV_{ADJ}, 0.98 for ESV_{ADJ}, 0.99 for LVM_{ADJ}, and 0.96 for EF_{ADJ}.

Table 1. Clinical Characteristics of the REF Group and the Entire Study Population

	Men (REF) (n = 262)	Women (REF) (n = 423)	Men (Non-REF) (n = 437)	Women (Non-REF) (n = 372)	Men, All (n = 699)	Women, All (n = 795)
Age, yrs	60.6 ± 8.5	61.7 ± 8.6*	67.4 ± 8.6†	67.8 ± 8.3†	64.9 ± 9.1	64.6 ± 9.0‡
Height, m	1.76 ± 0.07	1.62 ± 0.06‡	1.74 ± 0.06§	1.60 ± 0.06†	1.75 ± 0.06	1.61 ± 0.06‡
Weight, kg	84.6 ± 14.0	67.9 ± 12.4‡	88.7 ± 14.0†	74.7 ± 16.5†	87.2 ± 13.4	71.1 ± 14.8‡
BMI, kg/m^2	27.2 ± 3.5	25.8 ± 4.4‡	29.1 ± 4.3†	29.0 ± 6.0†	28.4 ± 4.1	27.3 ± 5.4‡
SBP, mm Hg	117 ± 10	114 ± 12*	132 ± 17†	135 ± 19†	126 ± 17	124 ± 19*
DBP, mm Hg	73 ± 11	70 ± 8‡	77 ± 11†	75 ± 11†	76 ± 10	72 ± 10*
+HTN, %	NA	NA	96.3	97.8	60.2	45.8
+WMA, %	NA	NA	21.7	8.1	13.6	3.8
+MIHF, %	NA	NA	9.8	2.7	6.2	1.3

Values are mean ± SD or %. *$p < 0.05$ between men and women of corresponding groups (e.g., Men [REF] versus Women [REF]); †$p < 0.001$ within-sex difference between REF and non-REF; ‡$p < 0.001$ between men and women of corresponding groups (e.g., Men [REF] versus Women [REF]); §$p < 0.05$ within-sex difference between REF and non-REF.

BMI = body mass index; DBP = diastolic blood pressure; +HTN = presence of any antecedent hypertension or use of antihypertensive medications; +MIHF = positive history of adjudicated myocardial infarction or heart failure; NA = not applicable; non-REF = participants not in the referent group; REF = healthy referent group (members were free of HTN, WMA, and MIHF by definition); SBP = systolic blood pressure; +WMA = having a cardiovascular magnetic resonance focal wall motion abnormality.

Table 2. Global LV Parameters in Men and Women in the REF Group and Among All Participants

Parameter	REF Men (n = 262)	REF Women (n = 423)	p Value: Men Versus Women	All Men (n = 699)	All Women (n = 795)	p Value: Men Versus Women
EDV_{INIT} (ml)	143 ± 25	107 ± 18	<0.0001	146 ± 29	108 ± 20	<0.0001
EDV_{ADJ} (ml)	111 ± 19	83 ± 15	<0.0001	113 ± 24	84 ± 16	<0.0001
ESV_{INIT} (ml)	49 ± 13	35 ± 9	<0.0001	52 ± 19	34 ± 11	<0.0001
ESV_{ADJ} (ml)	30 ± 10	20 ± 7	<0.0001	32 ± 15	20 ± 8	<0.0001
LV EF_{INIT} (%)	66.0 ± 5.3	68.0 ± 5.0	<0.0001	65 ± 7	69 ± 6	<0.0001
LV EF_{ADJ} (%)	73.4 ± 6.5*	75.6 ± 5.9*	<0.0001	72 ± 9*	76 ± 7*	<0.0001
LVM_{INIT} (g)	123 ± 22	81 ± 15	<0.0001	129 ± 26	86 ± 17	<0.0001
LVM_{ADJ} (g)	157 ± 26	107 ± 18	<0.0001	163 ± 30	112 ± 20	<0.0001
TPM (ml)	33 ± 8	24 ± 5	<0.0001	33 ± 9	24 ± 6	<0.0001
TPM/EDV	0.23 ± 0.03	0.23 ± 0.03	0.90	0.22 ± 0.04	0.23 ± 0.04	0.22
TPMm/LVM	0.28 ± 0.07	0.32 ± 0.06	<0.0001	0.27 ± 0.07	0.30 ± 0.07	<0.0001
TPM/BSA (ml/m^2)	16.2 ± 3.9	13.9 ± 2.6	<0.0001	16.7 ± 4.3	14.4 ± 3.1	<0.0001

*$EF_{ADJ} > EF_{INIT}$, $p < 0.0001$.
ADJ = trabecular and papillary muscles considered as myocardial mass; BSA = body surface area; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; INIT = trabecular and papillary muscles considered as part of left ventricular blood pool; LVM = left ventricular mass; TPM = trabecular and papillary muscles; TPMm = calculated mass of trabeculae and papillary muscles; other abbreviations as in Table 1.

Variation in global LV and TPM measures with hypertension and focal LV dysfunction. Sex-specific comparisons of referent participants to those with history of hypertension (+HTN) and those with wall motion abnormalities (+WMA) are presented in Table 3. In each sex, the referent-group participants were younger than those in the +HTN and +WMA groups. As expected, referent participants also had lower BMI and had lower SBP than the +HTN or the +WMA groups. EDV_{INIT}, ESV_{INIT}, and LVM_{INIT} were greater in the +WMA versus referent groups for both men and women, whereas EF_{INIT} was lower in the +WMA group. The +HTN group had greater LVM_{INIT} than the referent group; EF_{INIT} was slightly higher in referent women versus +HTN women but did not differ among men.

Absolute TPM volume was significantly greater in +WMA versus referent men ($p = 0.0002$); a similar pattern was seen among women, but this finding was only of borderline significance ($p = 0.03$). TPM/EDV was similar in magnitude among both men and women, with at most borderline decreases associated with +HTN or +WMA. TPMm/LVM was significantly lower in men ($p = 0.0003$) and women ($p < 0.0001$) with +HTN

Table 3. Global LV Parameters in Men and Women With Hypertension or CMR LV Wall-Motion Abnormality Compared With the REF Group

	Men: REF (n = 262)	Men: +HTN (n = 421)	Men: +WMA (n = 95)	Women: REF (n = 423)	Women: +HTN (n = 423)	Women: +WMA (n = 30)
Age, yrs	60.6 ± 8.5	67.6 ± 8.5*	67.6 ± 9.1*	61.7 ± 8.6	67.9 ± 8.3*	69.1 ± 8.6*
BMI, kg/m^2	27.2 ± 3.5	29.2 ± 4.3*	29.0 ± 4.3*	25.8 ± 4.4	29.2 ± 6.0*	28.6 ± 6.3†
SBP, mm Hg	117 ± 10	132 ± 17*	128 ± 19*	114 ± 12	136 ± 18*	132 ± 21*
EDV_{INIT}, ml	143 ± 25	147 ± 31	166 ± 34*	107 ± 18	110 ± 21	127 ± 32†
EDV_{ADJ}, ml	111 ± 19	115 ± 26†	129 ± 29*	83 ± 15	85 ± 18	100 ± 26†
ESV_{INIT}, ml	49 ± 13	52 ± 21†	76 ± 28*	35 ± 9	33 ± 12	53 ± 20*
ESV_{ADJ}, ml	30 ± 10	33 ± 17†	52 ± 24*	20 ± 7	19 ± 9	35 ± 14*
EF_{INIT}, %	66.0 ± 5.3	65.3 ± 8.4	55.2 ± 9.6*	68.0 ± 5.0	70.2 ± 6.4*	59.7 ± 8.4*
EF_{ADJ}, %	73.4 ± 6.5	72.4 ± 9.7	61.1 ± 11.7*	75.6 ± 5.9	77.6 ± 7.5*	65.8 ± 8.8*
LVM_{INIT}, g	123 ± 22	132 ± 27*	144 ± 29*	81 ± 15	92 ± 18*	103 ± 27*
LVM_{ADJ}, g	157 ± 26	166 ± 32*	182 ± 34*	107 ± 18	118 ± 22*	132 ± 32*
TPM, ml	33 ± 8	33 ± 9	37 ± 10*	24 ± 5	25 ± 6	27 ± 7†
TPM/EDV	0.23 ± 0.03	0.22 ± 0.04†	0.23 ± 0.05	0.23 ± 0.03	0.22 ± 0.04	0.22 ± 0.04†
TPMm/LVM	0.28 ± 0.07	0.26 ± 0.07*	0.28 ± 0.08	0.32 ± 0.06	0.28 ± 0.07*	0.28 ± 0.07†
TPM/BSA, ml/m^2	16.2 ± 3.9	15.7 ± 4.1	18.0 ± 4.8*	13.9 ± 2.6	13.5 ± 3.2	15.0 ± 3.8†

*$p < 0.001$, †$p < 0.05$ versus REF within each sex. (Some participants overlap in both the +HTN and +WMA groups.)
EF = ejection fraction; other abbreviations as in Tables 1 and 2.

versus their referent counterparts. TPMm/LVM was also lower in +WMA versus referent women ($p = 0.0046$) but not in men. EF_{ADJ} was consistently greater than EF_{INIT} in the referent group as well as in the +HTN and +WMA groups.

Correlation of clinical characteristics and LV indexes with TPM. Linear correlations between TPM measures and age, SBP, BMI, and global LV parameters are presented in Table 4. Absolute TPM volume was inversely and significantly correlated with age in both sexes for referent participants and for the offspring as a whole, but the correlation coefficient was attenuated in the referent group compared with all participants. TPM/EDV was also inversely correlated with age in both sexes, but this was attenuated in the referent group compared with all participants. TPM/EDV was not associated with BMI in either sex. There was an inverse correlation between TPM/EDV and SBP in men but not in women.

With respect to LV parameters, absolute TPM increased with greater EDV_{INIT} and ESV_{INIT} in both sexes. TPM/EDV was weakly and inversely correlated with EDV_{INIT} and ESV_{INIT} in referent men but not in men overall or in women overall. Absolute TPMm increased with LVM_{INIT} in both sexes, but TPMm/LVM was significantly inversely correlated with LVM_{INIT} in both men and women. Finally, TPM was inversely correlated with EF_{INIT} in both sexes ($r = -0.30$ in men and $r = -0.31$ in women [$p < 0.0001$ for both]), but TPM/EDV was not correlated with EF_{INIT} in either men or women.

Table 5. Median (50th) and 90th and 95th Percentile Cutpoints for TPM, TPM/EDV, and TPMm/LVM Among REF Group Participants

	Men			Women		
	50th	90th	95th	50th	90th	95th
TPM, ml	32.3	42.7	45.6	23.9	30.1	33.2
TPM/EDV	0.23	0.27	0.28	0.23	0.27	0.28
TPMm/LVM	0.28	0.38	0.40	0.31	0.40	0.42
TPM/BSA, ml/m^2	16.7	21.8	24.2	14.3	18.4	19.5

Abbreviations as in Tables 1 and 2.

Distribution of TPM measures. Table 5 shows the median and 90th and 95th percentile cutpoints, according to sex, for TPM, TPM/EDV, and TPMm/LVM among referent-group offspring. The 90th and 95th percentile cutpoints of TPM/EDV ratios were similar across the sexes, whereas TPMm/LVM was slightly greater in women than in men for both thresholds. There was minimal difference between referent-group participants and the study group as a whole (data not shown). We elected not to present age-specific percentiles due to

Table 4. Pearson Correlation Coefficients Between Clinical Characteristics, LV Parameters by CMR, and TPM Measures in Men and Women in the REF Group and the Entire Study Sample

	Age	BMI	SBP	EDV	ESV	LVM	EF
Referent-group men (n = 262)							
TPM	−0.33*	−0.004	−0.13*	0.80*	0.70*	0.33*	−0.30*
TPM/EDV	−0.15†	−0.08	−0.22*	0.14†	0.15†	−0.12	−0.12
TPMm/LVM	−0.23*	0.023*	−0.31*	0.39*	0.43*	−0.37*	−0.30*
Referent-group women (n = 423)							
TPM	−0.36*	0.27*	−0.017	0.75*	0.65*	0.51*	0.31*
TPM/EDV	−0.11†	0.0096	−0.090	−0.077	−0.022	−0.050	−0.054
TPMm/LVM	−0.24*	−0.12†	−0.27*	0.20*	0.28*	−0.33*	0.46*
All men (n = 699)							
TPM	−0.21*	0.087†	−0.054	0.72*	0.57*	0.34*	0.030*
TPM/EDV	−0.13*	−0.054	−0.10†	−0.024	−0.027	−0.14*	−0.001
TPMm/LVM	−0.19*	−0.17*	−0.20*	0.29*	0.26*	−0.39*	−0.20*
All women (n = 795)							
TPM	−0.28*	0.27*	−0.004	0.70*	0.58*	0.43*	−0.28*
TPM/EDV	−0.12*	0.023	−0.055	−0.07†	−0.04	−0.11†	−0.017
TPMm/LVM	−0.28*	−0.13*	−0.28*	0.17*	0.25*	−0.39*	−0.26*
All study participants (n = 1,494)							
TPM	−0.19*	0.20*	0.007	0.79*	0.68*	0.57*	−0.37*
TPM/EDV	−0.13*	−0.013	−0.079†	−0.053†	−0.043	−0.11*	−0.0001
TPMm/LVM	−0.23*	−0.17*	−0.25*	0.055*	0.10*	−0.42*	−0.15*

*$p < 0.001$, †$p < 0.05$.
Abbreviations as in Tables 1 and 2.

limited sample size in several of the age-specific and sex-specific categories.

DISCUSSION

In this CMR study of nearly 1,500 community-dwelling members of the Framingham Heart Study Offspring cohort, we found that LVM and EF increased significantly when the TPM were considered as myocardial mass, whereas EDV and ESV significantly decreased, compared with the corresponding quantities obtained when the TPM were considered as part of the LV blood pool. We further found that TPM decreased with advancing age, and TPMm/LVM decreased with increasing BMI and SBP, in both sexes, in a healthy referent cohort strictly free of obesity, hypertension, and any history of myocardial infarction or heart failure.

In the context of the current literature. Our average TPM volume of 23% of LV EDV is consistent with the literature. However, the majority of previous reports have considered either papillary muscle volume or trabecular volume in isolation, and have not combined them. A canine CMR study by François et al. (13) found papillary muscle volume represented 7.7% of LVM. In a 100-participant subset of the Multi-Ethnic Study of Atherosclerosis CMR trial, Vogel-Claussen et al. (14) found that papillary muscles comprised 8.9 ± 0.1% of LVM. In terms of LV trabeculae, in a study of 20 healthy controls and 20 patients with decreased LV EF, Papavassiliu et al. (7) found that trabeculae comprised approximately 10% of LVM in healthy subjects and 14% in patients with systolic dysfunction. Jacquier et al. (15) compared the percentage of trabecular mass with global LVM in 16 controls (12 ± 5%) and the same number of patients in each group with hypertrophic cardiomyopathy (12 ± 4%), with dilated cardiomyopathy (11 ± 4%), and those with LV noncompaction (32 ± 10%). Combining the published 8% to 9% for papillary muscles and approximately 12% for trabeculations resulted in findings similar to our data.

As expected, exclusion of TPM from the LV blood pool and their inclusion with LVM resulted in lower LV volumes and greater mass. These findings are similar to the results of Weinsaft et al. (9) and Papavassiliu et al. (7), who found that EF was significantly greater when TPM were considered myocardial mass, but the magnitude of increase was larger in the current study, at about 7 EF units versus previous results of 3 to 4 EF units. However, these earlier studies included subjects with advanced systolic dysfunction, a group not represented in the current study; therefore, direct comparisons of change in EF may not be warranted. Han et al. (8) found a 17% increase in indexed LVM, a 20% decrease in indexed EDV, and an average 9-unit increase in EF among a cohort of 30 patients with hypertrophic cardiomyopathy. These results are broadly comparable to those of the current study. Also consistent with previous work, we found that TPM increased with greater LVM, and now extend this finding by considering TPMm as a proportion of total LVM, which actually decreased with greater overall mass.

Areas for additional study. Because this was a cross-sectional study, it is not possible to determine whether changes in total LVM are accompanied by proportional changes in TPM. For example, although it is possible that TPM increase more slowly in response to a pressure stimulus, such as hypertension or aortic stenosis, than the remainder of myocardium, it is also possible that those with an initially lower proportion of TPM are more responsive to that stimulus. Although causality cannot be inferred from our cross-sectional study, we note that TPM volume (and thus TPMm) did not correlate with SBP either in the referent group or in the study group as a whole, although overall LVM was significantly correlated with SBP. This suggests that TPMm may be less responsive to hypertension than overall myocardial mass. The lack of association between TPMm and SBP in our study is consistent with the MESA (Multi-Ethnic Study of Atherosclerosis) results (14).

We examined LV mass (and TPM volume) only at end-diastole, as is common practice. Some readers may consider that because TPM is the difference between EDV_{INIT} and EDV_{ADJ}, a similar relation should hold between TPM, ESV_{INIT}, and ESV_{ADJ} due to incompressibility of myocardium, but this was not the case (Table 2). The numerical difference and apparent discrepancy are resolved when one considers that at end-systole, a substantial proportion of the trabeculae are already tightly apposed against the compacted myocardium, so that the initial putative endocardial contours already classify some portion of the trabeculae as myocardium. Thus, the adjustment for TPM at end-systole captures only a portion of the TPM identified at end-diastole.

Currently, LV noncompaction is diagnosed using CMR based on maximal ratio of noncompacted-to-compacted layer thickness. The results of this study do not provide insight as to whether global measures of trabecular burden, such as the TPM mea-

sures presented here, or regional measures (e.g., the aforementioned ratio of noncompacted-to-compacted thicknesses, the maximal thickness of the trabeculated layer, the number/location of "hypertrabeculated" segments in the standard 17-segment model) will have greater value for diagnosis and prognosis of hypertrabecular disorders of the myocardium.

Clinical implications. The greater temporal and spatial resolution of current noninvasive imaging techniques, regardless if they are SSFP in CMR or second-harmonic imaging in echocardiography (16,17), generally result in better visualization of LV trabeculae compared with older techniques (e.g., segmented k-space gradient-echo sequences in the case of CMR). This can lead to concerns regarding possible LV noncompaction, particularly when first adopting the newer techniques. Thus, it is important to determine what constitutes a "normal range" of trabeculation.

Petersen et al. (18) have shown that the majority (approximately 60%) of healthy individuals, as well as fit athletes, have marked trabeculations, principally in the apical and select mid-LV segments on SSFP CMR. Interestingly, they noted a somewhat lower proportion of patients with hypertensive heart disease who had segmental hypertrabeculation, an observation that seems broadly in accord with our finding that TPMm/LVM is inversely associated with SBP. Dawson et al. (19) used SSFP CMR to study a cohort of 120 healthy subjects 20 to 80 years of age. A trabeculated endocardial layer was present in at least 1 segment in all subjects, and they found that the end-diastolic thickness of the trabeculated layer decreased with advancing age, which is broadly consistent with our finding of decreased TPM with greater age. These investigators also found that the epicardial compacted layer was thinner in women versus men, but that there was no difference between sexes in the thickness of the trabeculated layer. This finding is consistent with the greater TPMm/LVM ratio in women in the current study.

Although our study was based on a large community sample without any participants suspected of having LV noncompaction, we present 90th and 95th percentile upper limits of TPM/EDV and TPMm/LVM in a healthy referent group. This information may be useful in future studies of LV noncompaction or other disorders associated with abnormal trabecular or papillary muscle volume.

Study limitations. The Framingham Heart Study Offspring cohort is overwhelmingly white, and the majority of subjects were middle-aged or older. Thus, although our results are valid in white subjects in the community, they may not be generalizable to other age ranges or ethnic groups. In addition, our study population did not include subjects with advanced systolic dysfunction. Finally, our CMR findings may not apply to results obtained with non-SSFP CMR sequences and are unlikely to apply directly to echocardiographic data (20).

CONCLUSIONS

Among adults free of clinical cardiovascular disease, LV trabeculations and papillary muscles occupy 23% of LV EDV in both men and women. Considering TPM as myocardial mass (as opposed to LV blood pool) increased LV EF significantly across the entire study cohort. Reference standards for "normal values" and comparisons across serial CMR examinations must take into account not only the CMR imaging sequence used (6) but also the image analysis protocol and its treatment of trabeculations and papillary muscles.

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Key Words: cardiac magnetic resonance ■ left ventricular ejection fraction ■ papillary muscle ■ population study ■ trabeculae.