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Prediction of Mortality Risk by Different Methods of Indexation for Left Ventricular Mass

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Objectives. **We sought to compare the predictive value of echocardiographically determined left ventricular hypertrophy on death from all causes and cardiac mortality using various methods of indexation for left ventricular mass.**

Background. **Considerable controversy exists regarding the optimal method for indexing left ventricular mass to body size in the clinical setting.**

Methods. **The study included 988 consecutive patients who had both coronary angiograms and echocardiographic examinations in an inner-city public hospital in Chicago, Illinois. Patients were followed up for a mean of 7 years (range 2 to 11).**

Results. **Various left ventricular mass indexes (e.g., mass indexed for height, height^2, height$^{2.13}$, height$^{2.7}$, body surface area and body surface area$^{1.5}$ were highly correlated (r = 0.90 to 0.99). Used as a continuous measure, an increase in any left ventricular mass index was associated with similar risk of death from all causes and cardiac diseases. Although left ventricular hypertrophy assessed by mass indexed for body surface area using the published conventional partition values provided somewhat better prediction, the adjusted relative risk was in general not significantly different from hypertrophy based on other indexes. Patients with left ventricular hypertrophy defined concordantly by indexes based on both body surface area and height (or height$^{2.7}$) had, by definition, the highest average mass indexes among all groups and experienced as much as a threefold greater risk of death than those without hypertrophy. A small proportion of patients (12%) who were classified into the hypertrophy group by height-based indexes alone, but not by body surface area, had a moderate increase in mass and showed no increase in risk, even though being overweight was extremely prevalent in this group.**

Conclusions. **Because of the high correlation among various body size indexes, left ventricular hypertrophy, defined by different indexes for left ventricular mass, similarly confers increased risk of mortality in patients with or without coronary artery disease.**

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Echocardiographically determined left ventricular hypertrophy indexed for either body surface area or height has been shown to be an independent predictor of cardiovascular morbidity and mortality (1–5). Recently, height$^{2.0}$ (6), height$^{2.13}$ (7,8), height$^{2.7}$ (7–9), height^3 (10) and body surface area$^{1.5}$ (9) have also been proposed as the appropriate measure of body size to normalize left ventricular mass. This study compares the impact of various methods of indexation for left ventricular mass on mortality in a hospital-based patient series.

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Methods

Study patients. Between January 1983 and June 1991, 2,971 consecutive patients underwent cardiac catheterization for diagnostic evaluation of presumed coronary artery disease in Cook County Hospital, a public general hospital in Chicago, Illinois, serving a primarily minority population. A satisfactory echocardiogram had been performed on 1,317 patients. This analysis excluded 295 patients with impaired systolic function (ejection fraction <45%) to eliminate the confounding effect of impaired contractility of the left ventricle on the relation between left ventricular mass and prognosis. Patients with asymmetric septal hypertrophy (n = 10) and with missing data on body surface area (n = 24) were also excluded. The final analytic cohort for this study thus consisted of a total of 988 patients.

Body surface area was calculated using the formula: $0.0001 \times 71.84 \times (\text{weight [kg]})^{0.425} \times (\text{height [cm]})^{0.725}$. Overweightness was defined according to the National Institutes of Health Consensus Panel (11) as body mass index (weight in kilogram per square meter of height) >27.8 in men and 27.3 in women.

Measurements. Coronary cineangiograms were obtained in multiple projections, including angulated views in the sagit-

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Abbreviations and Acronyms

ASE = American Society of Echocardiography
CI = confidence interval

tal plane. Significant coronary artery disease was defined as ≥50% reduction in the diameter of any major coronary artery. Two-dimensionally guided M-mode echocardiograms were obtained according to the recommendations of the American Society of Echocardiography (ASE) using a leading edge to leading edge convention (12). Left ventricular posterior wall thickness, ventricular septal thickness and left ventricular internal dimension were measured at end-diastole, as defined by the onset of the QRS complex. Left ventricular mass was calculated using the modification by Devereux et al. (13) of the ASE cube formula:

$$0.8(1.04\,[\text{Left ventricular internal diameter} + \text{Left ventricular septal thickness} + \text{Posterior wall thickness}]^3 - [\text{Left ventricular internal diameter}]^3) + 0.6.$$

This formula has been anatomically validated, and values obtained using this formula were similar to those obtained with the Penn cube method (13). There are currently more than a dozen criteria with various left ventricular indexation and partition values used to define the presence of left ventricular hypertrophy (14). In this report we selected the criteria originally derived from the same population samples and widely used in cohort studies (1,2,4,5,7–9,15,16). In the Framingham Heart Study, the mean values ± 2 SD were 131 and 100 g/m^2 for men and women, respectively, for left ventricular mass indexed by body surface area (15). The corresponding values were 143 and 102 g/m, respectively, for mass/height, and 259 and 166 g, respectively, for unindexed mass. The partition values reported by de Simone et al. (8) for 97.5 percentile of mass/body surface area, mass/height and mass/height$^{2.7}$ were 117 g/m^2, 126 g/m and 50 g/m$^{2.7}$ for men and 104 g/m^2, 105 g/m and 47 g/m$^{2.7}$ for women, respectively. The nongender-specific upper limit of 51 g/m$^{2.7}$ has also been suggested for mass indexed by height$^{2.7}$ (8). In addition, the partition value of 125 g/m^2 for both men and women has been used for mass indexed by body surface area in several studies (1,4).

Follow-up. An attempt was made to contact all patients either during an outpatient visit, by telephone or by review of medical records of clinic attendance. In addition, the data base provided by the National Death Index, which contains a standard set of identifying data for each decedent of the nation, was searched annually until December 31, 1993, for all members of the original cohort (17). Death certificates of the decedents were obtained from the Department of Public Health in the states where the patients died. Patients who were not contacted and thus not confirmed to be alive and who were not matched to a death certificate were considered alive as of the last date included in the National Death Index File.

Data analysis. The relations among continuous variables (e.g., various left ventricular mass indexes) were examined using Pearson correlation analyses. A Cox proportional hazards model was used to examine the risk of all causes of death and cardiac death for different mass indexes in the following manner: First, each left ventricular mass index was entered in the Cox regression models as a continuous measurement. To assure the comparable scales for all mass indexes, the measurements were log-transformed and standardized into a Z score. The relative risks and their 95% confidence intervals were calculated for each Z score (a standardized unit) increase in left ventricular mass index. Then, risks were estimated for left ventricular hypertrophy defined by each mass indexation and published partition value. Finally, left ventricular hypertrophy defined by two different mass indexations (e.g., body surface area and height or body surface area and height$^{2.7}$) were considered simultaneously. The definitions of left ventricular hypertrophy for various indexes were derived from the same population sample (8). We cross-classified patients by body surface area and height (or height$^{2.7}$) and examined the pattern of relative risk among those in the concordant and discordant cells. Three indicator variables representing four different combinations of the two dichotomized measures were tested in the Cox regression model.

The analyses were first performed separately for men and women. As previously reported (18), the excess risk of mortality associated with increasing left ventricular mass was greater in women than in men among patients without coronary artery disease. However, risk comparisons among different mass indexes within the same gender followed similar patterns for men and women. Hence, combined data were presented in the report with adjustment for gender.

Left ventricular mass indexed for various measures of body size are highly correlated and are not independent from each other. Hence, devising a formal test to compare the two relative risks associated with different indexes is complex. We used a computer-intensive method—bootstrap resampling (19)—to test whether the observed differences between two Cox coefficients were unusually large. We randomly drew samples (with replacement) from the study cohort and computed the difference between two Cox coefficients. This procedure was repeated 1,000 times and the variance of the difference in Cox coefficients was estimated. The null hypothesis was rejected if the 95% confidence interval of the difference did not include 0.

Results

Baseline data. The demographic and clinical characteristics by angiographically-defined coronary anatomy are shown in Table 1. Of 988 patients, 531 (54%) had one or more obstructed coronary vessels. Most of the patients were black (82%) and had a history of hypertension (83%). More than half of the patients were overweight. Left ventricular hyper-

Table 1. Baseline Characteristics of Patients With or Without Coronary Artery Disease

	Without CAD (n = 457)	With CAD (n = 531)
Age (yr)	53.5 ± 9.6	56.9 ± 9.0
Female (%)	65.2	47.1
Black (%)	86.7	78.2
Hypertension (%)	81.8	83.4
Diabetes (%)	18.6	31.5
Overweight (%)	60.8	53.5
Body mass index (kg/m^2)	29.7 ± 6.1	28.4 ± 5.4
Ejection fraction (%)	70 ± 10	65 ± 11
Echocardiographic data		
Posterior wall thickness (cm)	1.1 ± 0.2	1.2 ± 0.2
Interventricular septal thickness (cm)	1.2 ± 0.2	1.2 ± 0.2
LV end-systolic dimension (cm)	3.0 ± 0.8	3.3 ± 0.9
LV end-diastolic dimension (cm)	4.7 ± 0.7	4.9 ± 0.8
LV mass (g)	208 ± 75	230 ± 83
LV mass index/BSA (g/m^2)*	109 ± 39	122 ± 42
LV mass index/height (g/m)*	125 ± 44	137 ± 48
LV mass index/height$^{2.7}$ (g/m$^{2.7}$)*	53 ± 20	57 ± 21
Prevalence of LV hypertrophy [no. (%)]		
Corrected for BSA	177 (39%)	255 (48%)
Corrected for height	223 (49%)	295 (56%)
Corrected for height$^{2.7}$	190 (42%)	278 (52%)

*Definitions of left ventricular (LV) hypertrophy are left ventricular mass/body surface area (BSA) ≥131 g/m^2 in men and ≥100 g/m^2 in women; left ventricular mass/height ≥143 g/m in men and ≥102 g/m in women; and left ventricular mass/height$^{2.7}$ ≥51 g/m$^{2.7}$ for both men and women. Data presented are mean value ± SD, unless otherwise indicated. CAD = coronary artery disease.

trophy was present in 41% to 50% of the patients without coronary artery disease and in 49% to 57% of those with coronary artery disease, depending on the criteria used to define hypertrophy. The various mass indexes were highly correlated with the Pearson correlation coefficients (r) ranging from 0.92 to 0.99 among height-based indexes, and from 0.90 to 0.97 between height-based and body surface area-based indexes. The coefficients were 0.81 to 0.98 between unindexed and indexed mass. Among patients with coronary artery disease there was a weak but statistically significant correlation (r = 0.09 to 0.14) between mass indexes and age, which was itself strongly associated with mortality. Thus, further analyses were done with adjustment for age.

Left ventricular mass indexes as continuous measures. During a mean follow-up of 7 years (range 2 to 11), 202 patients died (142 patients with and 60 patients without coronary artery disease at baseline), among whom 127 died from cardiac diseases (95 patients with and 32 patients without coronary artery disease). The multivariate-adjusted relative risks and 95% confidence intervals for the two fatal end points associated with each Z-score increase in left ventricular mass and mass indexes are presented in Table 2. All the standardized relative risks were similar regardless of the indexes used. None of the risk estimates was significantly different by the computer-intensive method.

Predictive values of left ventricular hypertrophy based on different indexes. Table 3 shows the relative risks by left ventricular hypertrophy defined by various criteria. With only a few exceptions, all the relative risks were significantly different from 1.0 ($p < 0.05$). In Table 3, criteria to define left ventricular hypertrophy by unindexed mass (item 1), mass/body surface area (item 2) and mass/height (item 5) were derived from the Framingham Study (16). Mass/body surface area (item 3); mass/height (item 6); mass/height$^{2.7}$, nongender-specific criteria (item 7); and mass/height$^{2.7}$, gender-specific criteria (item 8) were from the same adult samples reported by de Simone et al. (8). Pairwise comparisons across criteria within the same study samples showed that most of the

Table 2. Adjusted* Relative Risk (95% confidence interval) Associated With Each Standardized Unit Increase in Various Left Ventricular Mass Indexes

	Without CAD		With CAD	
Indexation for LV Mass	All-Cause Death	Cardiac Death	All-Cause Death	Cardiac Death
Unindexed LV mass	1.80 (1.43–2.26)	1.92 (1.41–2.62)	1.39 (1.18–1.63)	1.38 (1.14–1.69)
LV mass indexed for height	1.71 (1.35–2.15)	1.79 (1.31–2.46)	1.38 (1.17–1.63)	1.39 (1.14–1.70)
LV mass indexed for height^2	1.60 (1.27–2.03)	1.66 (1.20–2.28)	1.36 (1.15–1.61)	1.39 (1.13–1.70)
LV mass indexed for height$^{2.13}$	1.59 (1.26–2.01)	1.64 (1.19–2.26)	1.36 (1.15–1.61)	1.39 (1.13–1.70)
LV mass indexed for height$^{2.7}$	1.53 (1.21–1.93)	1.56 (1.13–2.15)	1.34 (1.13–1.59)	1.38 (1.12–1.69)
LV mass indexed for BSA	1.74 (1.38–2.18)	1.82 (1.34–2.46)	1.43 (1.22–1.69)	1.47 (1.21–1.79)
LV mass indexed for BSA$^{1.5}$	1.69 (1.35–2.12)	1.75 (1.29–2.37)	1.44 (1.22–1.70)	1.49 (1.23–1.82)

*Adjustment for age and gender; all relative risks are significantly different from 1.0 ($p < 0.01$). Abbreviations as in Table 1.

Table 3. Adjusted* Relative Risk (95% confidence interval) in Patients With Left Ventricular Hypertrophy Defined by Various Left Ventricular Mass Indexations and Partition Values

LV Hypertrophy	Without CAD		With CAD	
	All-Cause Death	Cardiac Death	All-Cause Death	Cardiac Death
1. Defined by unindexed LV mass ≥259 g in men, 166 g in women	2.7 (1.6–4.8)	2.8 (1.3–6.0)	2.0 (1.4–2.9)	1.9 (1.2–3.1)
Defined by LV mass/BSA				
2. ≥131 g/m^2 in men, ≥100 g/m^2 in women	3.5 (2.0–6.1)	3.7 (1.8–7.9)	2.1 (1.5–3.0)	2.1 (1.3–3.2)
3. ≥117 g/m^2 in men, ≥104 g/m^2 in women	3.8 (2.2–6.6)	3.7 (1.8–7.9)	1.9 (1.3–2.6)	2.1 (1.4–3.3)
4. ≥125 g/m^2 in both men and women	3.9 (2.3–6.5)	4.5 (2.2–9.2)	1.9 (1.4–2.7)	1.7 (1.2–2.6)
Defined by LV mass/height				
5. ≥143 g/m in men, ≥102 g/m in women	2.9 (1.7–5.1)	2.6 (1.2–5.6)	1.7 (1.2–2.5)	1.7 (1.1–2.7)
6. ≥126 g/m in men, ≥105 g/m in women	2.8 (1.6–5.0)	2.4 (1.1–5.1)	1.6 (1.1–2.3)	1.7 (1.1–2.7)
Defined by LV mass/height$^{2.7}$				
7. ≥51 g/m$^{2.7}$ in both men and women	3.0 (1.7–5.1)	3.3 (1.5–6.9)	1.5 (1.1–2.1)	1.5† (1.0–2.3)
8. ≥50 g/m$^{2.7}$ in men, ≥47 g/m$^{2.7}$ in women	2.3 (1.3–4.0)	2.6 (1.2–5.5)	1.4† (1.0–2.0)	1.4‡ (0.9–2.2)

*Adjustment for age and gender; all relative risks are significantly different from 1.0 except for †$p < 0.10$ and $p > 0.05$ and ‡$p > 0.05$. Abbreviations as in Table 1.

observed differences in relative risk were not statistically significant. A few exceptions were identified. Relative risks in item 3 (hypertrophy defined by mass/body surface area) were significantly greater than those in item 8 (mass/height$^{2.7}$, gender-specific criteria). Significant differences were also found when comparing body surface area indexation with that indexed by height for cardiac death among patients without coronary artery disease (relative risk 3.7 in item 3 vs. 2.4 in item 6 and 3.7 in item 2 vs. 2.6 in item 5).

Left ventricular hypertrophy cross-classified by two indexes. When patients were cross-classified as having left ventricular hypertrophy by two indexes, two concordant and two discordant groups were identified. The number of patients in each of the four groups varied according to the indexes and the partition values for hypertrophy used. Table 4 shows selected variables for the four groups using mass/body surface area and mass/height with the definitions for hypertrophy derived from a recent study (8). Patients classified as having hypertrophy simultaneously by two indexes had the highest average left ventricular mass and mass indexes (Table 4 and Fig. 1). They had a significantly increased risk of mortality compared with those without hypertrophy by both indexes (adjusted relative risk was 3.5 (95% confidence interval [CI] 2.0 to 6.3) and 3.1 (95% CI 1.5 to 6.6) for all causes of death and cardiac death, respectively, among patients without coronary artery disease. For patients with coronary artery disease, the relative risk was 1.8 (95% CI 1.2 to 2.6) and 2.0 (95% CI 1.2 to 3.2), respectively. In a small proportion of patients, hypertrophy was detected by mass indexed for height but not for body surface area. By definition, these patients had only moderate increases in ventricular mass and had the highest body mass index and prevalence of overweightness among all groups ($p < 0.01$) (Table 4). No increased risk of either fatal end point was observed (relative risk 0.1 to 0.8, $p > 0.05$). The number of patients classified with hypertrophy only by mass indexed for body surface area was very small and no inference could be derived. The results followed a similar pattern when mass indexed for body surface area and for height$^{2.7}$ were considered together (data not shown). Again, left ventricular hypertrophy identified by both indexes was associated with a significantly increased risk of death. Little evidence of an increase in risk was found in patients with hypertrophy detected by mass indexed for height$^{2.7}$ but not for body surface area.

Discussion

Indexation of left ventricular mass to body size. Since the 19th century, many aspects of human metabolism and organ growth have been "normalized" by body surface area (20). This indexation has subsequently been applied to cardiovascular measurements, including ventricular mass (21–24). Height was chosen as a measure of body size because it is obesity independent (25), and the linear growth determined by height was the major factor influencing left ventricular mass in children and young adults (26). Recently, many other indexes have been proposed as the more appropriate measure of body

Table 4. Selected Characteristics According to Presence or Absence of Left Ventricular Hypertrophy Defined by Left Ventricular Mass Indexed for Body Surface Area* and Mass Indexed for Height†

LVH Defined by Mass/BSA:	No	Yes	No	Yes
LVH Defined by Mass/Height:	No	No	Yes	Yes
		Patients Without CAD		
No. of pts	218	3	57	179
Body mass index (kg/m^2)	28.8 ± 5.4	22.5 ± 1.9	33.1 ± 5.4	29.9 ± 6.8
Overweight (%)	54	0	91	60
LV mass (g)	156 ± 27	182 ± 22	198 ± 26	271 ± 76
LV mass/BSA (g/m^2)	81 ± 14	111 ± 8	100 ± 8	143 ± 39
LV mass/height (g/m)	92 ± 15	112 ± 12	119 ± 11	163 ± 43
		Patients With CAD		
No. of pts	199	10	58	264
Body mass index (kg/m^2)	26.6 ± 4.6	20.4 ± 2.6	32.5 ± 4.7	29.1 ± 5.4
Overweight (%)	37	0	91	59
LV mass (g)	166 ± 31	186 ± 22	202 ± 28	283 ± 81
LV mass/BSA (g/m^2)	89 ± 14	113 ± 9	100 ± 8	150 ± 40
LV mass/height (g/m)	98 ± 16	111 ± 9	120 ± 11	169 ± 45

*Defined as left ventricular (LV) mass/body surface area (BSA) ≥117 g/m^2 in men and ≥104 g/m^2 in women. †Defined as left ventricular mass/height ≥126 g/m in men and ≥105 g/m in women. Data presented are mean value ± SD, unless otherwise indicated. CAD = coronary artery disease; LVH = left ventricular hypertrophy.

size to use in normalizing left ventricular mass (6–10). Residual relations of mass/body surface area to body surface area and of mass/height to height were markedly reduced by normalization of ventricular mass for height$^{2.7}$. However, a weak inverse association between mass/height$^{2.7}$ and height has also been demonstrated (6,9), which may indicate possible overadjustment. In fact, intragroup variability of ventricular mass was essentially the same regardless of the indexes used, except for height, where it was somewhat greater (9). Different methods of indexation had a minimal effect on the observed association between left ventricular mass and systolic blood pressure (6).

Predictive values of different methods of indexation. Left ventricular hypertrophy defined by mass indexed for body surface area or height has long been known to be an independent predictor of cardiovascular morbidity and mortality (1–5). Recently, de Simone et al. (8) reported that height-based indexes of left ventricular mass at least maintained or perhaps enhanced risk prediction; the former but not the latter outcome was supported by this study. Given the high degree of correlation between the different indexes of left ventricular mass, it is not surprising that we found no differences in the mortality risks for the different indexes when considered as continuous measures. Only when partition values were used to define hypertrophy did any indication of prognostic differences arise. This outcome is a result of the fact that the normal limits for these different indexes were mostly derived from the studies with small sample sizes in each gender group (8,22).

Impact of overweight. Many studies have suggested that normalization of left ventricular mass for body surface area or height introduces artifacts into the relation between heart size and body size and underestimates the impact of overweight (6,7,9,15,25,27). The prevalence rates of left ventricular hypertrophy, correcting mass for body surface area, were less than those when correction was made for height or height$^{2.7}$ (7,9,15,27). The allometric signal for height was proposed as the optimal index for body size, which would prevent erroneously categorizing obesity-induced left ventricular hypertrophy as normal. However, use of body surface area correction attenuated but did not eliminate the observed relations between obesity and echocardiographic left ventricular variables (27–29). Except for "obesity cardiomyopathy," which occurs in very obese patients (30), the clinical course and prognostic implication of minor or moderate changes in left ventricular size, assumed to be caused by obesity, are not yet clear (6,28).

Study limitations. The data for this study were obtained from a hospital registry and may be subject to a certain degree of selection bias. All the patients had undergone angiographic and echocardiographic examination. The patients were predominantly blacks and had a high prevalence of hypertension, overweightness and left ventricular hypertrophy. The generalizability of the results needs to be examined in separate populations. Morbidity data were not available for patients in this cohort. This study therefore cannot exclude the possibility that obesity-related left ventricular hypertrophy may increase morbid cardiovascular events before an overt survival disadvantage becomes apparent.

Conclusions. These data from a clinical setting indicate that left ventricular hypertrophy, defined by various body size indexes for left ventricular mass, similarly confers increased risk of mortality in patients with or without coronary artery disease. Patients with hypertrophy defined by both a body surface area index and a height-based index had the greatest mass indexes and hence the greatest risk. No increased mortality was found for hypertrophy detected by height-based indexes in the absence of hypertrophy based on criteria that indexed for body surface area. These patients were usually overweight and had a lower degree of hypertrophy. The

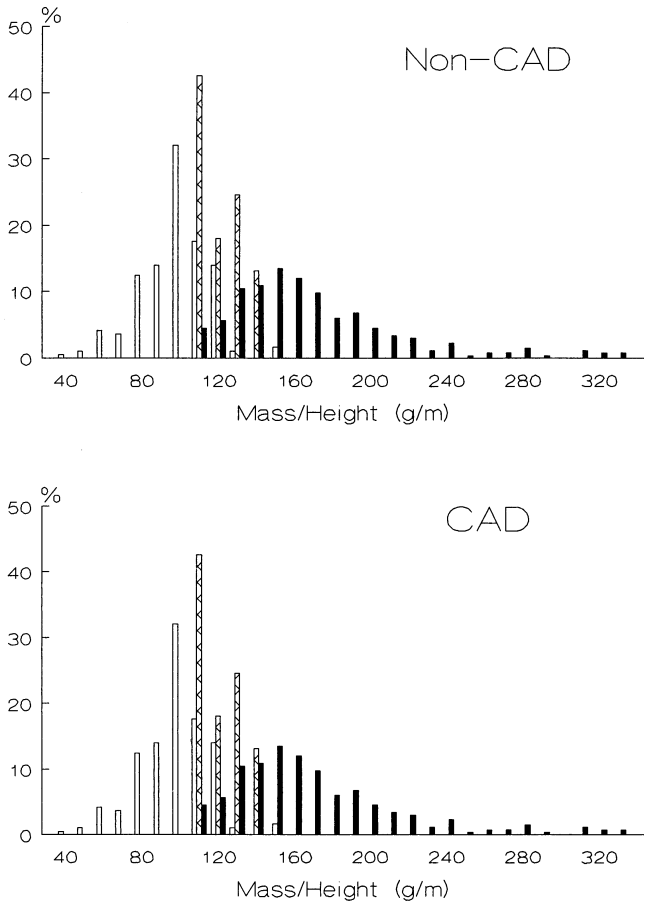

Figure 1. Joint distribution of left ventricular mass indexed for height by left ventricular hypertrophy (LVH) defined by mass indexed for body surface area (mass/BSA ≥117 g/m^2 in men and ≥104 g/m^2 in women) and mass indexed for height (mass/height ≥126 g/m in men and ≥105 g/m in women) in patients with and without coronary artery disease (CAD):

	Open Bars	Not Shown	Hatched Bars	Solid Bars
LVH defined by mass/BSA	No	Yes	No	Yes
LVH defined by mass/height	No	No	Yes	Yes

prognostic implication of ventricular hypertrophy in this small subset of patients deserves further investigation.

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