Importance of Overweight in Studies of Left Ventricular Hypertrophy and Diastolic Function in Mild Systemic Hypertension

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The relations of Metropolitan Life Insurance Co. Relative Weight values and blood pressure (BP) to minimal forearm vascular resistance, ventricular septal and posterior wall thickness, left ventricular (LV) mass index and cardiac diastolic function were assessed in 31 men, 37 ± 2 (mean ± standard error of the mean) years of age. Eighteen patients with untreated mild hypertension were compared with 13 normotensive control subjects of similar age and weight. The hypertensives had higher clinic (137 ± 3/96 ± 2 vs 121 ± 4/81 ± 3 mm Hg, p <0.001/<0.001) and home (p <0.001) BP. Despite higher BP, the hypertensives did not have significantly greater values than normotensives, respectively, for minimal forearm vascular resistance (2.20 ± 0.12 vs 2.04 ± 0.11 U), ventricular septal (9.9 ± 0.5 vs 10.2 ± 0.3 mm) and posterior wall thickness (10.2 ± 0.4 vs 10.0 ± 0.3 mm) or LV mass index (106 ± 6 vs 107 ± 6 g/m²). Furthermore, diastolic peak filling rate, an index of LV diastolic function, was virtually identical in the 2 groups (2.71 ± 0.14 vs 2.69 ± 0.07 liters/s, difference not significant). Correlates of peak filling rate included relative weight (r = −0.62, p <0.001), posterior wall thickness (r = −0.51, p <0.01) and age (r = −0.45, p <0.05). Relative weight also correlated significantly with posterior wall (r = 0.59, p <0.005), ventricular septal (r = 0.47, p <0.005) and LV mass index (r = 0.38, p <0.05). Although clinic systolic BP correlated directly with posterior wall thickness (r = 0.45, p <0.05), neither systolic nor diastolic BP in the clinic or at home correlated significantly with peak filling rate (r = −0.26 to +0.02, difference not significant).

The results suggest that relative weight is an important determinant of diastolic function and LV dimensions. These findings highlight the importance of controlling for weight in comparative studies of cardiovascular structure and function.

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Most untreated patients with mild hypertension do not experience complications over a mean follow-up period of 5 years.[1] In fact, most patients with mild hypertension and minimal funduscopic change may die from diseases unrelated to hypertension.[2] In an effort to more selectively target intervention, extensive efforts have been directed toward identifying evidence of cardiovascular injury that increases the probability of future complications. Funduscopic,[2] electrocardiographic[3] and echocardiographic[4,5] changes in hypertensive patients are examples of abnormalities that predict a higher incidence of subsequent clinical events. Additional subclinical abnormalities identified in the mild hypertensive state include reduced maximal vasodilator capacity[6,7] and decreased cardiac compliance.[8-10] The identification of impaired diastolic function, which may precede abnormalities in left ventricular (LV) wall thickness, systolic function or both,[10-12] offers an opportunity for very early detection of a potentially high risk subgroup.

One confounding variable in assessing structural and functional cardiovascular changes in hypertensive patients is weight. Overweight is a significant risk factor for hypertension.[13] Hypertensive patients are generally heavier than normotensive control subjects. Furthermore, overweight is an independent risk factor for cardiovascular disease.[14] Overweight may induce cardiovascular changes[15] that are possible harbingers of later cardiovascular problems. Consequently, evidence of cardiovascular injury in mildly hypertensive patients compared with normotensive control subjects may partially reflect weight differences rather than disparities only of blood pressure (BP). This study determines if previously noted abnormalities of cardiovascular structure and function in hypertensives persist when patients are compared with normotensive control subjects of similar age and weight.

METHODS

Patients: All hypertensive patients were untreated for a minimum of 6 months. The exception was 1 patient who went without therapy for 1 month. Patients had a BP >140 mm Hg systolic or 90 mm Hg diastolic, or both, on ≥2 consecutive clinic visits preceding the study. The normal volunteers had no prior history of hypertension and had clinic BP values <140/90 mm Hg. All subjects provided a history and underwent physical and laboratory examinations to exclude the presence of medical problems, high BP excepted.

Measurements: Height and weight were measured conventionally. The Metropolitan Life Insurance Co. Relative Weight values were used in the calculations.[16] BP during casual sitting was measured in triplicate. The mean of the second and third readings was used to determine systolic and diastolic BP values. Self-determined home BP was obtained twice daily by patients and normal volunteers in the week before the study. Maximal forearm vasodilator capacity in response to 10 minutes of ischemic exercise was assessed by venous occlusion plethysmography.[7] Minimal forearm vascular resistance was calculated as mean BP divided by maximal forearm blood flow.

LV internal diastolic dimension, ventricular septal and posterior wall thickness were measured from 2-dimensional M-mode echocardiograms as previously described.[17] The M-mode beam was set to transect the left ventricle just distal to the inferior edge of the mitral valve leaflets during diastole. LV muscle mass was calculated using the Penn convention.[18]

LV diastolic function was determined as peak LV filling rate. Data were obtained by electrocardiographically gated radionuclide ventriculograms. The results were analyzed by forward gating of the time activity curves as described previously.[19]

Protocol: Subjects arriving at the Clinical Research Center had their BP measured in triplicate. In the next 4 hours, the volunteers underwent echocardiography, radionuclide ventriculography and plethysmography.

Data analysis: Data for the hypertensive patients and normotensive control subjects are reported as mean ± standard error of the mean. Differences between the 2 groups for the measured and calculated variables were assessed with the Student t test. Pearson correlation coefficients (r values) were obtained to assess interactions between BP, weight, age and measurements of cardiovascular injury. Multivariate analysis was used to examine the independent contributions of relative weight, age and posterior wall thickness to peak filling rate. All p values <0.05 were accepted as the level at which the null hypothesis was rejected.

RESULTS

Descriptive data for the hypertensive and normotensive groups are listed in Table I. The results indicate that the 2 groups were statistically similar for age, height, weight and relative weight. Based on the selection process, the hypertensive group had significantly higher BP values both in the clinic and at home.

The indexes of cardiovascular injury are listed in Table II. The 2 groups had statistically indistinguishable values for minimal forearm vascular resistance, ventricular septal and posterior wall thickness, LV muscle mass and diastolic peak filling rate.

The relations of BP, relative weight and age to the various measures of cardiovascular change are listed in Table III. Because home BPs did not provide stronger correlation coefficients than clinic BPs with the various measures of cardiovascular change, only the latter are reported. As listed in Table III, relative weight, posterior wall thickness and age were significant correlates of

TABLE I Baseline Data for Hypertensive Patients and Normotensive Subjects

	Normotensive (n = 13)	Hypertensive (n = 18)	p Value
Age (yrs)	37 ± 2	36 ± 2	NS
Height (cm)	179 ± 2	182 ± 1	NS
Weight (kg)	87 ± 4	92 ± 4	NS
MRW (%)	125 ± 7	128 ± 3	NS
Sytolic BP (clinic) (mm Hg)	121 ± 4	137 ± 3	<0.001
Diastolic BP (clinic) (mm Hg)	81 ± 3	96 ± 2	<0.001
Systolic BP (home) (mm Hg)	119 ± 3	137 ± 2	<0.001
Diastolic BP (home) (mm Hg)	75 ± 2	91 ± 2	<0.001

BP = blood pressure; MRW = Metropolitan Life Insurance Co. Relative Weight values; NS = not significant.

TABLE II Indexes of Cardiovascular Injury in Hypertensive Patients Versus Normotensive Subjects

	Normotensive (n = 13)	Hypertensive (n = 19)	p Value
Minimum vascular resistance (U)	2.03 ± 0.11	2.20 ± 0.11	NS
Septal thickness (mm)	10.2 ± 0.3	9.9 ± 0.4	NS
Posterior wall (mm)	10.0 ± 0.3	10.2 ± 0.4	NS
LV muscle mass (g)	223 ± 16	227 ± 14	NS
LV mass index (g/m²)	107 ± 6	106 ± 6	NS
Peak filling rate (liters/s)	2.69 ± 0.07	2.71 ± 0.14	NS

LV = left ventricular; NS = not significant.

TABLE III Correlation* Between Blood Pressure, Relative Weight, Age and Indexes of Cardiovascular Injury

	PFR (liters/s)	IVS (mm)	PW (mm)	LVMM (g)	LVMI (g/m²)	MFAVR (U)
Systolic BP (clinic)	0.02	0.44[†]	0.45[†]	0.29	0.25	0.28
Diastolic BP (clinic)	−0.02	0.35[†]	0.29	0.26	0.22	0.26
Relative weight	−0.62[‡]	0.47[‡]	0.59[‡]	0.54[‡]	0.38[†]	0.19
Age	−0.45[†]	0.23	0.22	0.14	0.08	0.35[†]

* r values; [†] p <0.05; [‡] p <0.005.
IVS = interventricular septal thickness; LVMI = left ventricular mass index; LVMM = left ventricular muscle mass; MFAVR = minimal forearm vascular resistance; PFR = peak filling rate; PW = posterior wall thickness.

peak filling rate, an index of diastolic function. Relative weight (partial r = −0.47) and age (partial r = −0.36) retained a significant (p <0.05) independent relation to peak filling rate in multivariate analysis, while the relation to posterior wall disappeared (partial r = −0.18, difference not significant). The significant negative correlation between relative weight and peak filling rate is shown in Figure 1.

DISCUSSION

The data listed in Table I indicate that the 2 groups had similar values for age, height, weight and relative weight. Despite higher clinic and home BP levels, the hypertensive group, in comparison with normotensive subjects, did not have significantly different values for maximal vasodilator capacity, septal or posterior wall

thickness, LV muscle mass or mass index, or peak diastolic filling rate as listed in Table II.

Minimal forearm vascular resistance: The vascular resistance persisting after 10 minutes of ischemic forearm exercise is a measure of structural arteriolar cross-sectional area.[6,7] Several investigators observed elevated values for minimal vascular resistance in patients with borderline and mild hypertension compared with normotensive control subjects.[6,7] Although the mean minimal forearm resistance was higher in the hypertensive group, the difference was not significant. In 1 of our previous studies,[7] hypertensive patients, compared with age- and weight-matched normotensive control subjects, had significantly higher minimal forearm vascular resistance. In the largest study,[6] BP was a significant, albeit relatively weak ($r^2 = 0.16$) determinant of minimal forearm vascular resistance. Thus, the dichotomy of the minimal resistance results in our 2 studies may be explained by smaller mean BP differences between hypertensives and normotensives in the present investigation.

Left ventricular wall thickness and muscle mass: Abnormally high values for ventricular septal and posterior wall thickness as well as LV muscle mass in subjects with borderline and mild hypertension are well documented.[20-22] The increased LV wall thickness and mass also are found in children and adolescents with minimal abnormalities of BP.[21,22] Although posterior wall and ventricular septal thickness correlated significantly with clinic systolic BP as listed in Table III, neither posterior wall or ventricular septal thickness nor LV muscle mass was significantly elevated in hypertensive patients (Table II). This finding is at variance with many published studies. Relative weight correlated significantly with posterior wall, ventricular septal, LV muscle mass and mass index. Thus, our deliberate weight matching of hypertensive patients and normotensive control subjects may have obliterated the influence of very mild hypertension on ventricular morphology.

This conclusion is consistent with the observations by Messerli et al,[23] who indicated that both overweight and hypertension increase LV wall thickness. LV wall thickness was higher in lean hypertensive versus lean normotensive persons. However, posterior and septal wall thickness were not significantly increased in overweight hypertensive patients compared with overweight normotensive control subjects. Consequently, weight was more important than BP in determining cardiac structure in obese patients with mild hypertension.[23]

Left ventricular diastolic function: In this study, peak LV filling rate at rest assessed by radionuclide ventriculography served as the measure of cardiac diastolic function. Our data show that the peak filling rate was virtually identical in hypertensive patients compared with normotensive control subjects of similar age and weight. These findings are in direct contrast to several previous studies in which evidence was found of reduced ventricular diastolic function in untreated patients with mild hypertension.[8-12] The majority of studies did not report values for weight in either the hypertensive patients or normotensive control subjects.[8-11] The weight data reported in 1 study indicated that the group with higher BP also had higher mean weight values.[14] The potential importance of weight in determining diastolic function was suggested in 1981 by De-Devitis et al.[24] This group observed a significantly positive correlation between overweight and both LV end-diastolic pressure and amplitude of the A waves in the pulmonary wedge pressure tracing in obese normotensive men. Our findings, listed in Table III and shown in Figure 1, confirm that overweight is associated with impaired diastolic function. The study was not designed to determine the physiologic basis for this association. The data extend previous findings by showing that over-
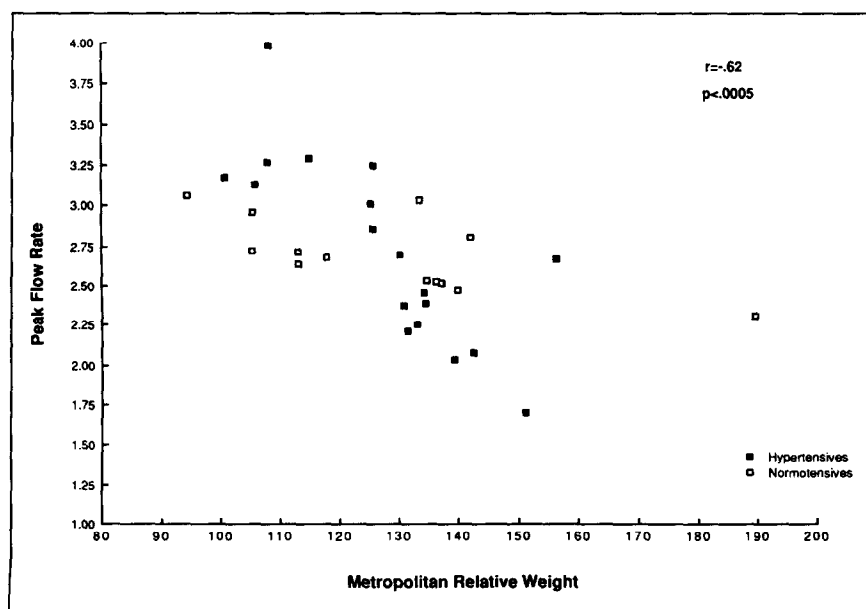
FIGURE 1. The significantly negative relation between data obtained from the Metropolitan Life Insurance Co. Relative Weight values and LV peak diastolic flow rate (liters/s) is shown for hypertensive patients (*closed squares*) and normotensive subjects (*open squares*).

weight predominates over very mild elevations of BP in determining diastolic function. This conclusion is further substantiated by multivariate analysis, which indicates that relative weight is the single best predictor of peak filling rate.

After relative weight, age was the only other variable significantly and independently correlated with diastolic function. These data are consistent with the observations of Spirito and Maron,[25] who reported that LV relaxation is impaired with aging. Although posterior wall thickness correlated with diastolic function, the relation was insignificant in multivariate analysis when accounting for the effects of relative weight and age. A brief review of published studies also suggests a complex and somewhat variable relation between LV anatomy and cardiac diastolic function. Some studies found that ventricular wall thickness and LV muscle mass were the main correlates of diastolic function.[26,27] However, trained athletes with various degrees of LV hypertrophy observed in pathologic states had supranormal diastolic function.[28] Thus, the influence of LV hypertrophy on diastolic function must be interpreted in the context of factors inducing the morphologic change. Furthermore, abnormalities of diastolic function in hypertension may exist in the absence of increased LV wall thickness or muscle mass.[8,10,12] In these cases, disordered cellular calcium metabolism, perhaps an integral feature of hypertension,[29] may contribute to reduced diastolic function independently of structural changes.[30]

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