

# Left Ventricular Hypertrophy in Severe Obesity

## Interactions Among Blood Pressure, Nocturnal Hypoxemia, and Body Mass

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**Abstract**—Obese subjects have a high prevalence of left ventricular (LV) hypertrophy. It is unclear to what extent LV hypertrophy results directly from obesity or from associated conditions, such as hypertension, impaired glucose homeostasis, or obstructive sleep apnea. We tested the hypothesis that LV hypertrophy in severe obesity is associated with additive effects from each of the major comorbidities. Echocardiography and laboratory testing were performed in 455 severely obese subjects with body mass index 35 to 92 kg/m<sup>2</sup> and 59 nonobese reference subjects. LV hypertrophy, defined by allometrically corrected (LV mass/height<sup>2.7</sup>), gender-specific criteria, was present in 78% of the obese subjects. Multivariable regression analyses showed that average nocturnal oxygen saturation <85% was the strongest independent predictor of LV hypertrophy ( $P<0.001$ ), followed by systolic blood pressure ( $P<0.015$ ) and then body mass index ( $P<0.05$ ). With regard to LV mass, there were synergistic effects between hypertension and body mass index ( $P$  interaction  $<0.001$ ) and between hypertension and reduced nocturnal oxygen saturation. Severely obese subjects had normal LV endocardial fractional shortening ( $35\pm 6\%$  versus  $35\pm 6\%$ ) but mildly decreased midwall fractional shortening ( $15\pm 2\%$  versus  $17\pm 2\%$ ;  $P<0.001$ ), indicating subtle myocardial dysfunction. In conclusion, more severe nocturnal hypoxemia, increasing systolic blood pressure, and body mass index are all independently associated with increased LV mass. The effects of increased blood pressure seem to amplify those of sleep apnea and more severe obesity. (*Hypertension*. 2007;49:34-39.)

**Key Words:** obesity ■ echocardiography ■ left ventricular hypertrophy ■ myocardial contraction ■ hypertension ■ diabetes ■ metabolic syndrome ■ obstructive sleep apnea

Obesity is associated with an increased risk of developing heart failure,<sup>1</sup> as well as an increased overall risk of death.<sup>2</sup> The association between obesity and heart failure could result from direct adverse effects of obesity on cardiac structure and function or could occur indirectly because obese patients have a high prevalence of coexisting disorders, such as coronary artery disease, diabetes, hypertension (HTN), and sleep-disordered breathing.<sup>3,4</sup> Many studies have shown that obesity is associated with left ventricular (LV) hypertrophy, a potential contributor to heart failure.<sup>5-10</sup> However, because obesity rarely exists in isolation, it has been a challenge to dissect out the relative contributions of various obesity-associated conditions.

The majority of published works show a positive, independent relationship between body mass index (BMI) and LV mass.<sup>5,6,9</sup> Several studies also show additive effects of increasing blood pressure and BMI on LV mass.<sup>11,12</sup> The impact of diabetes, glucose intolerance, and insulin resistance on LV hypertrophy has been seen less consistently,<sup>13-17</sup> and this relationship may depend on the population being studied. Obstructive sleep apnea (OSA), a frequent condition in obese

patients, is linked with HTN and causes increased sympathetic tone.<sup>18</sup> Sleep apnea has been recognized as a risk factor for and a potential contributor to heart failure<sup>19</sup> and other cardiovascular diseases.<sup>20</sup> However, whether OSA contributes directly to LV hypertrophy is controversial.<sup>21-24</sup>

We hypothesized that in severe obesity, the presence and severity of several coexisting conditions, including OSA, would determine the extent and pattern of LV remodeling. We tested this hypothesis in a large cohort of patients who met criteria for gastric bypass surgery.<sup>25</sup> Extensive clinical testing was performed in a controlled setting at the same time that echocardiography was performed.

### Methods

The University of Utah Institutional Review Board approved this study. All of the subjects gave informed consent. Severely obese subjects ( $n=1156$ ) who met criteria for bariatric surgery (BMI  $>40$  kg/m<sup>2</sup> or  $>35$  kg/m<sup>2</sup> with  $\geq 2$  complications of obesity) were recruited into a study examining the cardiovascular, metabolic, and pulmonary effects of weight loss achieved by Roux en Y gastric bypass surgery (details are available in an online supplement at <http://hyper.ahajournals.org>).<sup>25</sup> The subjects consisted of 3 groups: (1) subjects studied prior to surgery

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(n=417); (2) subjects who did not have surgery (generally because the procedure was not covered by their insurance policy; n=418); and (3) obese subjects not seeking gastric bypass surgery who were randomly selected from the population (n=321). A subset of subjects were admitted overnight to the General Clinical Research Center at the University of Utah where they underwent resting blood pressure monitoring, overnight oximetry and polysomnography without sleep staging, echocardiography, and measurement of fasting glucose, insulin, glycosylated hemoglobin (Hgb A1C), electrolytes, and serum lipids (please see <http://hyper.ahajournals.org> for additional details).<sup>25</sup> The study group reported herein consisted of 455 obese subjects with echo windows that were suitable for analysis. Of these, 355 subjects had interpretable overnight sleep studies available. A referent group with BMI <30 kg/m<sup>2</sup> (n=59) also underwent echocardiography with history and physical examination, but was not admitted to the General Clinical Research Center and did not have the sleep study or laboratory tests.

HTN was defined as a resting blood pressure >140/90 mm Hg recorded during the admission to the General Clinical Research Center and/or the use of antihypertensive medications (please see <http://hyper.ahajournals.org> for details of blood pressure measurements). Diabetes was defined as blood sugar >126 mg% measured after an overnight fast and/or use of insulin or an oral hypoglycemic agent. Insulin resistance was calculated by means of the homeostasis model assessment that compares fasting insulin and glucose levels.<sup>26</sup> OSA was considered to be present if the apnea-hypopnea index was >5 per hour.<sup>27</sup>

### Echocardiography

2D images and M-mode and Doppler recordings were obtained from standard imaging windows (Sequoia 256, Siemens). All of the data were stored in digital format and analyzed offline in a blinded fashion by 1 of 2 observers (E.A. and S.E.L.). LV dimensions were determined from 2D or M-mode images according to established criteria,<sup>28,29</sup> and these were used to calculate LV mass using the modified cube formula.<sup>30</sup> Because none of the patients had regional wall motion abnormalities, global LV systolic function was assessed using LV endocardial fractional shortening (FS), and myocardial function was assessed with midwall FS.<sup>28,31</sup> LV hypertrophy was defined using gender-specific criteria with LV mass corrected for height raised to the allometric power of 2.7 (LV mass index; male: >48 g/m<sup>2.7</sup>; female: >44 g/m<sup>2.7</sup>).<sup>32</sup> This correction has been shown to minimize gender differences in LV mass and to improve the prediction of adverse cardiovascular events in a population with a high prevalence of obesity.<sup>33,34</sup> LV geometry was categorized based on LV mass/height<sup>2.7</sup> and relative wall thickness (see the online supplement).

### Respiratory Measures During Sleep

Limited polysomnography consisted of nasal airflow (using a pressure transducer), thoracic and abdominal effort, snoring, activity, body position, peripheral arterial O<sub>2</sub> saturation and heart rate (see the online supplement). Records were scored blindly. Patients with an apnea-hypopnea index >5 per hour were considered to have OSA.<sup>27</sup>

### Statistical Analysis

BMI was treated as a continuous variable. For pairwise comparisons of continuous variables between the reference and obese groups, unpaired *t* tests were performed. For categorical variables, pairwise comparisons were analyzed with a  $\chi^2$  test or Fisher's exact test as appropriate. Pearson correlation was used to determine the univariate associations between individual continuous variables and LV mass index. Multivariate linear regression analysis was used to identify independent predictors of LV mass index. We used interaction terms to test whether OSA, diabetes, or HTN had synergistic or additive effects with BMI on LV mass index.

## Results

### Clinical Characteristics

The study population was 94% white, 4% Hispanic, 1.7% Native American, <1% other races, and predominantly female (83%) with a mean age of 43 years (Table 1). For the

obese group as a whole, systolic and diastolic blood pressures, fasting glucose, HgbA1C, and low-density lipoprotein cholesterol were all at the upper end of the reference range (Table 1). Forty-three percent of the subjects were hypertensive, and 21% had diabetes. Most patients with diabetes or HTN were so categorized on the basis of medical treatment for these conditions (70% and 71%, respectively). Although fasting glucose values were overall in the reference range, insulin resistance as assessed by the homeostasis model assessment was very common (Table 1).

### LV Geometry and Systolic Function in Severe Obesity

Despite the presence of severe obesity, echocardiographic image quality was adequate for quantitative analysis of LV mass in  $\approx$ 80% of subjects (455 of 569). The subjects with poor echo windows were excluded from additional analysis. Interobserver variability was 10.6 $\pm$ 1.8% for interventricular septal thickness, 10.9 $\pm$ 1.8% for posterior wall thickness, and 14.6 $\pm$ 2.4% for LV internal dimension. The excluded subjects had similar characteristics (age, gender, and BMI) compared with the ones used for analysis (data not shown). Diastolic interventricular septum thickness, posterior wall thickness, LV internal diameter, relative wall thickness, LV mass/height<sup>2.7</sup>, and left atrial diameter were all significantly increased in the severely obese subjects compared with the reference group (Table 2). The majority of nonobese subjects in the reference group (60%) had a normal LV geometry, whereas the majority of obese subjects (67%) had abnormal LV geometry (Figure 1). LV concentric hypertrophy was the most common pattern in the severely obese group, although eccentric hypertrophy was also present in significant numbers. LV endocardial FS was not different in the reference group and the severely obese group (Table 2). However, myocardial function, as estimated by midwall FS, was significantly decreased in the obese subjects (Table 2).

### OSA

Of subjects undergoing sleep study, 83% met criteria for OSA as defined by an apnea-hypopnea index  $\geq$ 5 per hour (Table 3). Patients with OSA were younger, more frequently male and had significantly higher BMIs and waist circumference, a higher prevalence of HTN, and higher heart rate than subjects without OSA (Table 3). LV mass index, relative wall thickness, LV endocardial FS, and midwall FS were not different between subjects with and without OSA (Table 3).

### Predictors of LV Hypertrophy

Within the group of severely obese subjects, univariate analysis showed significant correlations between LV mass index and average nocturnal O<sub>2</sub> saturation, systolic blood pressure, BMI, age, and log apnea-hypopnea index (Table 4). Diabetes, glycosylated hemoglobin, and fasting glucose did not have significant associations with LV mass index. Gender was not included in the analysis, because the allometric indexing method for indexing minimizes gender differences in LV mass. In the multivariate regression model, average nocturnal O<sub>2</sub> saturation, systolic blood pressure, and BMI maintained independent associations with LV mass index (Table 4).

**TABLE 1. Clinical Characteristics of the Severely Obese Subjects**

Variable	Entire Cohort (n=455)	Males (n=78)	Females (n=377)	P (Male vs Female)
Age	44±11	47±10	44±10	0.005
BMI, kg/m <sup>2</sup>	43±10	43±13	43±10	0.96
Diabetes, %	21	22	18	0.12
Diabetes meds, %	15	17	14	0.32
Hypertension, %	40	45	34	0.01
Hypertension meds, %	28	36	26	0.03
Heart rate, bpm	78±11	81±11	77±11	0.02
SBP, mm Hg	123±18	130±19	121±18	<0.001
DBP, mm Hg	70±10	75±10	68±10	<0.001
Waist, cm	129±24	134±30	128±22	0.02
Waist/hip ratio	0.97±0.08	1.0±0.06	0.94±0.08	<0.001
Weight, kg	132±27	148±42	122±27	<0.001
Height, cm	168±8	179±7	165±6.5	<0.001
Cholesterol, mg/dL	186±35	177±32	188±34	0.008
HDL, mg/dL	46±11	40±10	47±11	<0.001
LDL, mg/dL	106±27	101±25	108±27	0.05
Triglycerides, mg/dL	181±101	183±91	186±102	0.80
HbA1C, %	5.8±0.97	6.1±1.3	5.7±0.87	0.04
Glucose, mg/dL	103±35	109±43	102±33	0.10
Plasma insulin, IU	19±18	20±18	19±17	0.66
HOMA-IR	5.1±4.9	5.8±5.3	5.0±4.8	0.18
AHI, events per hour	22±24	40±30	19±21	<0.001

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, index of insulin resistance; AHI, apnea-hypopnea index; HbA1C, glycosylated hemoglobin; meds, medications.

HTN seemed to produce additive effects with respect to LV mass index when it was present in conjunction with higher tertiles of BMI or with nocturnal hypoxemia (Figure 2). We formally tested for additive or synergistic effects on LV mass index between BMI and HTN, BMI and OSA, and BMI and diabetes using linear regression analysis with 2 interaction terms added into the model. This analysis showed a significant interaction of BMI with HTN on LV mass index. As well, there was a significant interaction between HTN and average nocturnal O<sub>2</sub> saturation <85%.

## Discussion

Our results in a large cohort of severely obese subjects confirm previous reports showing that obesity is associated with a high prevalence of LV hypertrophy.<sup>9,11,12</sup> This study expands on the previous works by examining the combined contributions of sleep-disordered breathing, blood pressure, and the major components of the metabolic syndrome. Our main findings are that more severe nocturnal hypoxemia, increasing systolic blood pressure, and increasing BMI were independently associated with increased LV mass index, whereas diabetes, fasting glucose, and fasting insulin levels were not. Importantly, HTN seems to amplify the prohypertrophic effects of both nocturnal hypoxemia and increasing BMI.

### Patterns of LV Remodeling in Obesity

The most common pattern of LV geometry in our group of severely obese subjects was concentric LV hypertrophy.

Obesity is often considered to produce a state of chronic “volume overload,” because the heart is required to continuously circulate blood through the large and relatively low resistance depot of adipose tissue. In keeping with this hypothesis, some investigators have found evidence of eccentric LV hypertrophy (an increase in cavity volume that is greater than the increase in wall thickness) in obese subjects.<sup>35–37</sup> However, other studies of obese subjects have found a predominance of concentric hypertrophy.<sup>6,9</sup> We observed both patterns, but the concentric pattern was more frequent. The predominance of concentric LV hypertrophy suggests that sympathetic activation, elevated blood pressure, or intermittent heavy lifting could contribute to the hypertrophy. In addition, it is also possible that the allometric method of indexing LV mass allowed us to detect cases of concentric hypertrophy that might have been missed if LV mass were normalized to body surface area, because the latter method tends to underestimate hypertrophy in obese subjects.<sup>37</sup>

### Possible Factors Contributing to LV Remodeling in Obesity

In our subjects, relatively severe nocturnal hypoxemia had the strongest correlation with LV mass index. OSA has been proposed to contribute to LV hypertrophy because of increased heart rate, blood pressure, sympathetic tone, intermittent hypoxia, and large negative intrathoracic pressure changes during periods of airway obstruction.<sup>19</sup> The presence of HTN in patients with OSA likely contributes to the

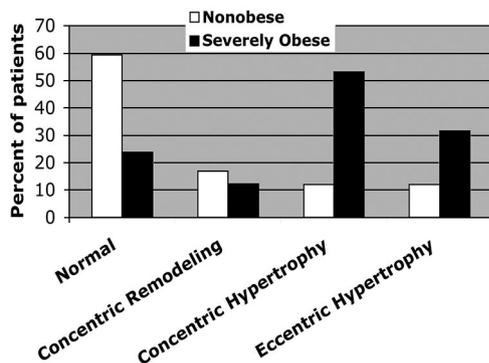
**TABLE 2. Cardiac Geometry and Function in Nonobese and Severely Obese Subjects**

Variable	Nonobese (n=59)	Severely Obese (n=455)	P
Age	43±10	44±11	0.36
Gender, % female	73	83	0.06
BMI, kg/m <sup>2</sup>	24±3	45±9	<0.001
SBP, mm Hg	113±17	123±18	0.001
DBP, mm Hg	69±12	70±10	0.70
Heart rate, bpm	67±10	78±11	<0.001
IVSd, cm	0.9±0.1	1.1±0.2	<0.001
PWd, cm	0.8±0.1	1.0±0.1	<0.001
LVIDd, cm	4.4±0.5	4.7±0.5	0.001
RWT	0.40±0.08	0.46±0.08	<0.001
LV mass, g	160±38	234±65	<0.0001
LV mass/height <sup>2.7</sup> , g/m <sup>2.7</sup>	40±10	58±14	<0.001
Endocardial FS, %	35±6	35±6	0.91
Midwall FS, %	17±2	15±2	<0.001
LA dimension, cm	3.3±0.4	3.6±0.4	<0.001

IVSd indicates interventricular septum thickness in diastole; PWd, posterior wall thickness in diastole; LVIDd, left ventricular internal dimension in diastole; RWT, relative wall thickness; LA, left atrial; SBP, systolic blood pressure; DBP, diastolic blood pressure.

association with LV hypertrophy or increased wall thickness.<sup>38</sup> Data supporting a possible cause and effect relationship between OSA and LVH were published by Cloward et al,<sup>24</sup> who found that 6 months of nocturnal positive airway pressure administration to patients with severe OSA was associated with a significant reduction in LV wall thickness. Some, but not all, previous studies have found OSA to be associated with LV hypertrophy.<sup>21–24,38</sup> Our patient population is somewhat unique in that the subjects were predominantly female. Most studies of OSA have a male predominance, because this disease affects men much more frequently than women.<sup>39</sup> Nonetheless, our data show that in severely obese women, like men, OSA is common. Our data suggest that the degree of sustained hypoxemia, rather than the

**Pattern of LV Geometry**



**Figure 1.** LV geometry in nonobese (n=59) and obese (n=455) subjects. Normal LV geometry is the most common in the nonobese referent group, whereas eccentric and concentric LV hypertrophy become more prevalent in the severely obese subjects. Concentric hypertrophy is the most frequent pattern in the obese subjects.

**TABLE 3. Clinical and Echocardiographic Characteristics in Severely Obese Subjects With and Without Obstructive Sleep Apnea**

Variable	Obese Subjects Without Sleep Apnea (n=57)	Obese Subjects With Sleep Apnea (n=298)	P
Age	44±6	38±10	<0.001
Gender, % female	94	83	0.05
BMI, kg/m <sup>2</sup>	44±6	47±8	0.01
Height, cm	166±6.1	167±8.5	0.54
Weight, kg	121±19	131±26	0.002
Waist, cm	129±16	135±17	0.006
Hypertension, %	21	43	0.001
Diabetes, %	14	19	0.22
Heart rate, bpm	74±9	78±11	0.005
SBP, mm Hg	116±15	126±19	0.001
DBP, mm Hg	66±10	70±10	0.008
Glucose, mg/dL	103±43	105±32	0.61
Endocardial FS, %	35±5	35±6	0.89
Midwall FS, %	15±2	15±2	0.89
LV mass/height <sup>2.7</sup> , g/m <sup>2.7</sup>	57±11	59±15	0.36
RWT	0.45±0.07	0.46±0.09	0.78
Average nocturnal SpO <sub>2</sub> , %	93	90	<0.001
AHI, events per hour	2.6±1.2	26±25	<0.001

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; RWT, relative wall thickness; SpO<sub>2</sub>, peripheral arterial oxygen saturation; AHI, apnea–hypopnea index.

number of apneic and hypopneic episodes, may contribute to the development of LV hypertrophy.

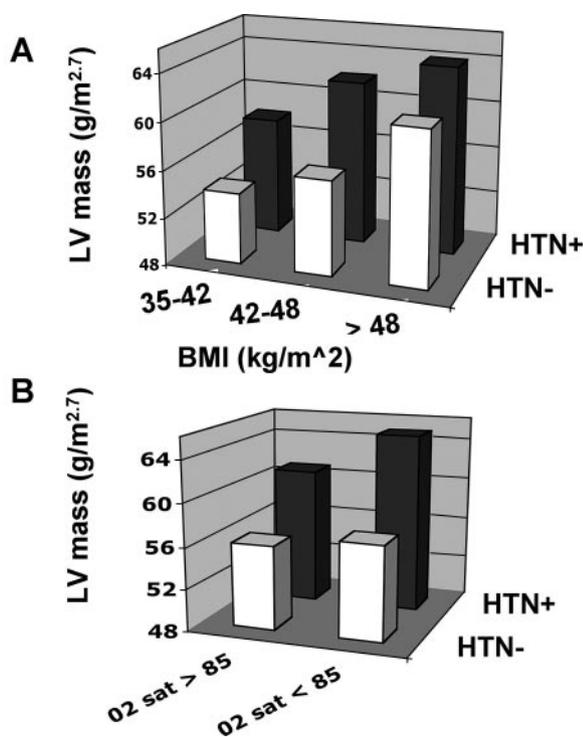
Systolic blood pressure had the second strongest independent correlation with LV mass index. Although a history of HTN was common, measured blood pressure was within the reference range (<140 mm Hg) in most of the obese subjects, presumably because of the common use of antihypertensive medications. Nonetheless, our findings imply that even mild increases in blood pressure that still fall within the reference range may have exaggerated effects on LV mass in obese subjects.

**TABLE 4. Univariate and Multivariate Predictors of LV Mass Index in Severely Obese Subjects**

Variable	Univariate		Multivariate	
	Pearson's Correlation Coefficient	P	Standardized Coefficient (β)*	P
Average nocturnal O <sub>2</sub> saturation, %	−0.27	<0.0001	−0.25	<0.0001
SBP, mm Hg	0.27	<0.0001	0.21	0.001
BMI, kg/m <sup>2</sup>	0.21	<0.0001	0.18	0.002
Age	0.17	0.001	0.074	0.21
Log AHI	0.17	0.002	0.08	0.17
Glucose, mg/dL	−0.023	0.64		
HbA1c, %	−0.028	0.67		

Left ventricular mass index indicates LV mass/height<sup>2.7</sup>; SBP, systolic blood pressure; AHI, apnea–hypopnea index; HbA1C, glycosylated hemoglobin.

\*Standardized slope in the same units of measure.



**Figure 2.** A, Interaction of BMI and HTN with respect to LV mass/height<sup>2.7</sup>. LV mass/height<sup>2.7</sup> increases consistently as BMI increases. However, the increase in LV mass/height<sup>2.7</sup> is more pronounced in patients with HTN than in those without. Formal testing showed a synergistic interaction of BMI and systolic BP on LV mass index. B, Relationship between the degree of nocturnal hypoxemia and LV mass/height<sup>2.7</sup> in subjects with and without HTN. The effects of nocturnal hypoxemia on LV mass index were amplified in subjects with HTN.

Fasting glucose, glycosylated hemoglobin, serum insulin levels, and homeostasis model assessment were not independently associated with increased LV mass in our study. The lack of association between LV mass and diabetes may reflect the very well controlled glucose levels in our subjects (Table 2). However, insulin resistance was common, and this also did not show an independent correlation in our subjects. In other populations, such as those examined in the Strong Heart Study, the presence of the metabolic syndrome does seem to have a significant influence on LV mass.<sup>40</sup> Other potential causes of LV hypertrophy in obese subjects include trophic effects of fat-secreted hormones<sup>41,42</sup> or a “training effect” on the heart because of the extreme amount of body weight that has to be lifted during normal activities.

The duration of obesity may be an important consideration when assessing the effects of BMI on the heart.<sup>8</sup> Our subjects reported that, on the average, they became overweight at the age of 23 years. Thus, the mean duration of obesity in our study is 20 years. This clearly represents a considerable exposure to the effects of obesity. On the average, the subjects with the highest BMIs in our study had earlier onset of obesity (top tertile of BMI; mean age at onset: 19 years) compared with the less obese subjects (bottom tertile; mean age at onset: 28). The subjects in the top tertile also reported higher body weight at age 20 to 25 than those in the bottom tertile (209±61 versus 156±39 lb). These findings emphasize the importance of preventing and treating obesity at young ages or earlier stages.

### Systolic Function in Severe Obesity

Although LV endocardial FS was preserved in our obese subjects, midwall FS, a better index of myocardial function in hypertrophied hearts, was reduced. These findings are in keeping with recent publications showing normal LV ejection fractions in obese subjects, whereas subtle abnormalities of systolic function were detected with the more sensitive techniques of tissue Doppler and strain imaging.<sup>5,6</sup> It is unknown whether these abnormalities progress or lead to clinical heart failure in the absence of coronary artery disease.

### Limitations

The cross-sectional nature of the current data set does not permit us to directly draw inferences about the factors that cause LV hypertrophy in obesity. Our data can only show that associations and conclusions about causality remain inferential. Future longitudinal studies in obese subjects or subjects who lose weight after being obese will be required to clarify this question. Selection bias resulting from the recruitment criteria that were used in this study may have affected our conclusions. Almost all of our severely obese subjects had well-controlled blood pressure and normal fasting glucose and glycosylated hemoglobin levels. The favorable level of control in our population may have minimized or “masked” some of the untoward effects of metabolic syndrome that have been reported in other series.<sup>13,14</sup> On the other hand, the low frequency of measured HTN and overt diabetes in our population may have allowed us to more directly and independently assess the cardiac effects of obesity.

### Perspectives

In our population, a diagnosis of HTN or increasing systolic blood pressure amplified the increased LV mass associated with nocturnal hypoxemia and more severe obesity. These findings raise the possibility that antihypertensive or vasodilator therapy should be initiated at lower levels of blood pressure, perhaps even pressures within the “normal” range, in obese patients. Second, our data support the importance of diagnosing and treating OSA in obesity. Lastly, onset of obesity during the teenage years resulted in greater total weight gain and increased LV hypertrophy by the mid-40s. Greater efforts need to be directed toward prevention and treatment of childhood and adolescent obesity.

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### Disclosures

None.

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