

Sudden death is more common in those who are naturally fat than in the lean.

HIPPOCRATES¹

Overweight and Sudden Death

Increased Ventricular Ectopy in Cardiopathy of Obesity

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• Obesity has been documented to be an independent risk factor for sudden death and other cardiovascular mortality. The present study was designed to monitor and quantify cardiac arrhythmias in obese subjects with and without eccentric left ventricular hypertrophy, who were matched with regard to arterial pressure, age, sex, and height with lean subjects. Prevalence of premature ventricular (but not atrial) contractions was 30 times higher in obese patients with eccentric left ventricular hypertrophy compared with lean subjects. Similarly, obese patients with left ventricular hypertrophy scored higher with regard to the classification of Lown and Wolf than those without left ventricular hypertrophy and lean subjects having the same level of arterial pressure. Patients' class in the Lown and Wolf system correlated with ventricular diastolic diameter and left ventricular mass. Thus, heart enlargement of the eccentric type as a consequence of obesity predisposes to excessive ventricular ectopy. Echocardiographic assessment and electrocardiographic monitoring allow us to identify the patients who are at highest risk of more serious arrhythmias or possibly sudden death and to subject them to the most specific preventive and therapeutic measures.

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More than half a century ago Smith and Willius at the Mayo Clinic attempted to untangle the cardiac effects of obesity from those of hypertension.² They reported average normal heart weight values of 272 g in their autopsy study compared with heart weights averaging 376 g in obese subjects with no evidence of other cardiovascular disease and 467 g in subjects who were both obese and hypertensive.² We recently showed that cardiac adaptation to obesity results in cardiac hypertrophy of the *eccentric* type, ie, an increase in myocardial mass combined with chamber dilatation.³⁻⁵ In contrast, left ventricular hypertrophy as a consequence of longstanding hypertension is most often of the *concentric* type, ie, an increase in myocardial mass at the expense of chamber volume.⁵⁻⁸ Concentric left ventricular hypertrophy has been documented to give rise to increased ventricular ectopy and to put the patient at risk

for more serious arrhythmias.⁹⁻¹¹ Indeed, data from the Framingham cohort identify left ventricular hypertrophy as a pressure-independent risk factor for sudden death and other cardiovascular mortality.¹² However, since the Framingham Study also established that obesity *per se* increases the risk of dying suddenly,^{13,14} we wondered whether 24-hour electrocardiographic monitoring would allow us to identify those patients with cardiopathy of obesity who are at the highest risk. The present study was designed to monitor and quantify cardiac arrhythmias in obese subjects with and without eccentric left ventricular hypertrophy who were matched with regard to arterial pressure, age, and sex with the same number of lean subjects.

PATIENTS AND METHODS

The study population consisted of a total of 53 patients, of whom 24 were lean and 29 obese with uncomplicated established essential hypertension. Patients were classified as obese when their body weight exceeded 150% of the ideal weight and as lean when they were less than 105% of the ideal weight according to the Metropolitan Insurance Weight Tables.¹⁵ Established essential hypertension was said to be present if diastolic pressures measured in the outpatient department were consistently higher than 90 mm Hg. All patients had appropriate clinical and laboratory evaluation to exclude secondary forms of hypertension. We also excluded patients with coronary artery disease or other organic heart disease as evidenced by clinical criteria and, when indicated, by exercise testing and/or thallium scintigraphy. Antihypertensive therapy was discontinued at least four weeks before the study. All patients provided informed consent to the protocol which was previously approved by our institution's review committee.

Obese patients were enrolled into the study in a prospective, randomized way. Only patients with uncomplicated moderately severe obesity in whom a good echocardiographic window was obtained were included. According to echocardiographic criteria, obese patients were further subdivided into a group with and one without eccentric left ventricular hypertrophy. Eccentric left ventricular hypertrophy was said to be present if posterior wall thickness exceeded 1.1 cm and the left ventricular internal diameter was greater than 5.0 cm. Both obese patient groups were matched with regard to systolic, diastolic, and mean arterial pressure with 24 lean subjects who were selected from our investigational data bank. The match also took age, sex, and race of the three patient groups into consideration.

Electrocardiographic tracings were recorded during one 24-hour period starting and ending at 9 AM, as previously described.¹⁶ Each tape was initially scanned at high speed and subsequently reviewed for a detailed analysis by two independent investigators. Left ventricular function and structure were assessed by M-mode

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Table 1.—Clinical Characteristics of Lean and Obese Patients With and Without Left Ventricular Hypertrophy (LVH)

Characteristic	Lean	Obese	
		Without Eccentric LVH	With Eccentric LVH
No. of patients	24	15	14
Age, y	50 ± 12	44 ± 5	46 ± 7
Sex (M:F)	18:6	12:3	10:4
Race (W:B)	21:3	8:7	9:5
Weight, kg	63 ± 8	104 ± 11	108 ± 7
Height, cm	1.67 ± 0.08	1.68 ± 0.09	1.69 ± 0.05
Body surface area, m ²	1.88 ± 0.19	2.01 ± 0.21	2.05 ± 0.13
Systolic blood pressure, mm Hg	152 ± 12	150 ± 6	158 ± 18
Diastolic blood pressure, mm Hg	97 ± 4	98 ± 4	99 ± 7
Mean arterial pressure, mm Hg	115 ± 5	115 ± 6	118 ± 5
Heart rate, beats per minute	77 ± 5	77 ± 4	75 ± 3

echocardiography, as previously reported.⁶ Left ventricular mass was calculated according to the formula of Bennett and Evans.¹⁷ The relative wall thickness and the ratio between left ventricular internal diameter and body surface area were calculated by standard formulas.

Differences between the three groups were evaluated by a one-way analysis of variance, followed by the Bonferroni correction method.¹⁸ Statistical significance of prevalence of ectopic beats as well as differences between the three groups with regard to the classification of Lown and Wolf were evaluated by χ^2 tests.¹⁸

RESULTS

The three groups of hypertensive patients, the lean and the obese with and without eccentric left ventricular hypertrophy, were comparable with regard to age, sex, race, heart rate, and arterial pressure (Table 1). Echocardiographic measurements were different between lean and obese subjects, as previously reported⁵ (Table 2). Obese patients were characterized by a higher left ventricular mass and increased posterior wall thickness and left ventricular internal diastolic diameter. These changes were most pronounced (by design of the study) in those with eccentric left ventricular hypertrophy. Relative wall thickness (Table 2), ejection fraction, fractional fiber shortening, as well as isovolumetric stress were similar in the three groups, but end-systolic wall stress was elevated ($P < .001$) in patients with eccentric left ventricular hypertrophy (Table 3). Obese subjects had a higher cardiac output, a lower total peripheral resistance, and a higher end-systolic wall stress than lean subjects with the same arterial pressure (Table 3).

No significant difference with regard to premature atrial beats was found in the three populations. In contrast, prevalence of premature ventricular contractions distinctly increased with body weight, and was more than ten times higher in obese patients without eccentric left ventricular hypertrophy, and even 30 times higher in patients with eccentric left ventricular hypertrophy compared with lean subjects (Figure). When subdivided according to the classification of Lown and Wolf, obese patients with eccentric left ventricular hypertrophy scored distinctly higher ($P < .005$) than patients without eccentric left ventricular hypertrophy and lean subjects having the same arterial pressure (Table 4). Short runs of ventricular tachycardia lasting a few seconds occurred in two patients with eccen-

Table 2.—Echocardiographic Measurements (Mean ± SD) of Lean and Obese Patients With and Without Left Ventricular Hypertrophy (LVH)

Echocardiographic Measurements	Lean	Obese	
		Without Eccentric LVH	With Eccentric LVH
Septal thickness, cm	1.18 ± 0.2	1.12 ± 0.1	1.16 ± 0.1
Posterior wall thickness, cm	0.97 ± 0.1	1.13 ± 0.1*	1.22 ± 0.1*
Relative wall thickness	0.43 ± 0.1	0.45 ± 0.3	0.44 ± 0.3
Left ventricular diastolic diameter, cm	4.46 ± 0.4	4.99 ± 0.6*	5.54 ± 0.5*
Left ventricular diastolic diameter/body surface area	2.34 ± 0.2	2.47 ± 0.3	2.7 ± 0.3†
Left ventricular systolic diameter, cm	2.70 ± 0.4	3.0 ± 0.5	3.35 ± 0.3
Left ventricular mass, g	185 ± 29	308 ± 100	370 ± 80
Left ventricular mass index, g/m ²	98 ± 14	152 ± 5.0*	175 ± 37*

* $P < .02$ between lean and both other groups.

† $P < .05$ between lean and obese with eccentric LVH.

Table 3.—Cardiac Function and Systemic Hemodynamics of Lean and Obese Patients With and Without Left Ventricular Hypertrophy (LVH) (Mean ± SD)

Cardiac Function and Systemic Hemodynamics	Lean	Obese	
		Without Eccentric LVH	With Eccentric LVH
Cardiac output, L/m	5.04 ± 1.7	6.2 ± 2.1	7.65 ± 1.3*
Total peripheral resistance, U	27.9 ± 2	24.0 ± 5.0*	16 ± 3†
Ejection fraction, %	70 ± 0.8	70 ± 0.7	70 ± 0.6
Fractional fiber shortening, %	39 ± 1	38 ± 7.0	39 ± 1.0
End-systolic wall stress, 10 ³ dynes/cm ²	44.5 ± 1	46 ± 2†	55 ± 1†
End-isovolumetric wall stress, 10 ³ dynes/cm ²	122 ± 9	117 ± 9	123 ± 7

* $P < .001$ between lean and obese with eccentric LVH.

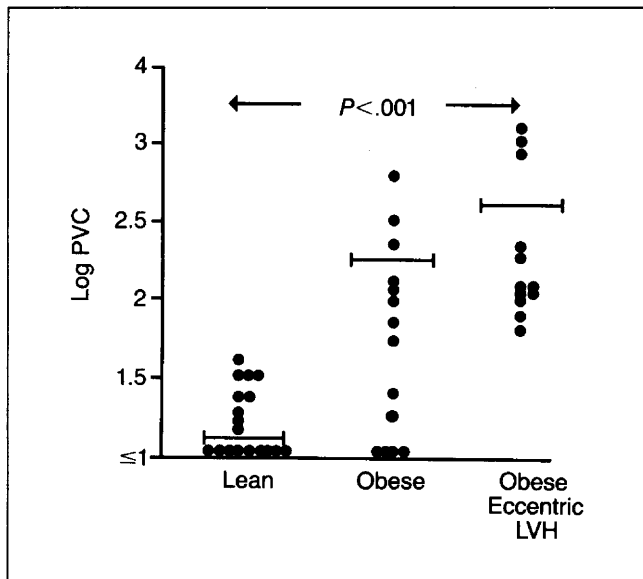
† $P < .01$ between lean and obese with eccentric LVH and between obese without eccentric LVH and obese with eccentric LVH.

tric left ventricular hypertrophy. Trigeminy and quadrigeminy, as well as periods of idioventricular rhythm, occurred in another patient in the same group. The highest values of left ventricular mass and left ventricular diastolic diameters were found in these three patients. All patients were asymptomatic throughout the 24-hour monitoring period.

The patients' classification according to Lown and Wolf correlated closely with left ventricular diastolic diameter ($r = .46$; $P < .001$) as well as with left ventricular mass ($r = .48$; $P < .001$). No correlation was observed between body measurement (height, weight, percentage overweight), other echocardiographic or hemodynamic findings, and the prevalence or the degree of severity of the arrhythmia as evidenced by the number of premature ventricular beats or classification of Lown and Wolf.

COMMENT

An increase in body mass by adipose tissue requires a higher cardiac output and an expanded intravascular vol-



Prevalence of premature ventricular contractions (logarithmic scale) in lean subjects and obese patients with and without eccentric left ventricular hypertrophy. LVH indicates left ventricular hypertrophy; PVC, premature ventricular contractions.

Table 4.—Classification of Lown and Wolf of Lean and Obese Patients With and Without Left Ventricular Hypertrophy (LVH)

Maximal Classification of Lown and Wolf	Obese		
	Lean	Without Eccentric LVH	With Eccentric LVH*
0	19	7	1
I	4	4	3
II	0	4	2
III	1	0	4
IV	0	0	4

* $P < .005$ between obese with eccentric LVH and both other groups.

ume to meet the higher metabolic demands. Left ventricular filling pressure and volume increase, shifting left ventricular function to the left on the Frank-Starling curve and giving rise to chamber dilatation.³⁻⁵ This inappropriately increases wall stress and, in an attempt to bring wall stress back to normal, the myocardium will adapt by adding contractile elements. Thus, myocardial mass increases and left ventricular hypertrophy of the eccentric type (wall thickening and chamber dilatation) ensues.³⁻⁵ Indeed, left ventricular diameter, posterior-wall and septal thickness, as well as left ventricular mass, were distinctly elevated in our obese subjects when compared with lean ones having the same arterial pressure, corroborating previous findings. Patients with left ventricular hypertrophy from longstanding hypertension have more premature ventricular contractions and higher grade arrhythmias than hypertensive patients without hypertrophy or normotensive subjects.⁹⁻¹¹ The present study documents that the corollary obese patients with distinct eccentric left ventricular hypertrophy also are prone to increased ectopy when compared with those without left ventricular hypertrophy or slender subjects. Patients with the largest hearts had the highest prevalence of ventricular ectopy and scored highest with regard to classification of Lown and Wolf. Although the

causal relationship between ventricular ectopy and sudden death is not firmly established, common sense dictates that in a population at risk, those patients with the highest degree of electric instability are also the most vulnerable.

Why should an increase in myocardial mass give rise to increased ventricular irritability? Several possible electrophysiologic mechanisms must be considered: First, enlarged myocytes, multiple intercalated disks, and electrically silent (ie, fibrotic) areas in fibrotic regions disturb intercellular current flow and wave propagation, thereby giving rise to reentry mechanisms.^{19,20} Second, mechanical stretching of isolated myocytes has been shown to increase excitability threshold.²¹ Volume overload states such as seen in obesity produce chamber dilation and increase ventricular wall stress (as in the present study), thereby possibly enhancing the arrhythmogenic potential by this mechanism. Third, the increased wall stress and stroke work of the left ventricle in obesity increases myocardial oxygen requirements and could lead to subendocardial ischemia. Experimental and clinical data indicate that ectopic activity increases with progressive underperfusion of the myocardium.²² Although none of our patients had clinical evidence of coronary artery disease, it must be remembered that left ventricular hypertrophy by itself diminishes coronary reserve and may give rise to relative ischemia.²³⁻²⁵ Thus, the hypertrophied myocardium, whether the result of chronic volume or pressure overload, provides a fertile soil for the sprouting of ventricular arrhythmias.

Excessive weight loss with ketogenic (high protein–low carbohydrate) diets has been shown to be associated with prolongation of the QT interval, ventricular tachycardia, and sudden death.^{26,27} The exact electrophysiologic mechanisms leading to these arrhythmias are unknown although they have been related to myocardial potassium or magnesium depletion secondary to diet-induced lactic acidosis or natriuresis. Clearly, this dire complication must be considered before obese patients are allowed to embark on a weight reduction program without medical supervision. Particularly, those obese patients who have preexisting ventricular ectopy secondary to cardiac enlargement and cardiomyopathy can be expected to be vulnerable to serious arrhythmias during weight loss. Electrocardiographic monitoring allows us to identify the patients who are at the highest risk and should, therefore, be carried out in all obese subjects with eccentric left ventricular hypertrophy.

Can weight reduction improve the grave outlook of cardiopathy of obesity? Alpert et al²⁸ did not find a distinct regression of eccentric left ventricular hypertrophy in morbidly obese patients who lost more than 50 kg of body weight after gastric resection. In contrast, MacMahon et al²⁹ recently demonstrated that a small weight loss of merely 8 kg in mildly obese and hypertensive patients was associated with a decrease in posterior wall and septal thickness, as well as in left ventricular mass.¹⁷ It still remains to be shown, however, whether or not such a regression of left ventricular hypertrophy ultimately will diminish ventricular ectopy and, even more important, lower the risk of sudden death.

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