0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(5):2080–2083

COMMENT

FFAs and QT Intervals in Obese Women with Visceral Adiposity: Effects of Sustained Weight Loss Over 1 Year

GRAZIA MARIA CORBI, SCIPIONE CARBONE, PATRIZIA ZICCARDI, GIOVANNI GIUGLIANO, RAFFAELE MARFELLA, FRANCESCO NAPPO, GIUSEPPE PAOLISSO, KATHERINE ESPOSITO, AND DARIO GIUGLIANO

Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples 80138, Italy

We evaluated 66 obese patients grouped by waist-to-hip ratio (WHR) into group A (WHR > 0.85, n = 30) and group B (WHR ≤ 0.85, n = 36), before and after 1 yr of diet-induced weight loss compared with 25 nonobese women. Before diet, the longest values of QT intervals and the highest levels of FFA and catecholamines were in group A ($P < 0.01$). In obese women (both groups), the corrected QT (QTc); interval correlated with plasma FFA ($P < 0.01$) and catecholamine ($P < 0.02$) concentrations. After 1 yr of diet, at the same levels of body weight reduction, the decrement of the QTc interval ($P < 0.02$), FFA ($P < 0.01$) and catecholamine ($P < 0.02$) levels were significantly greater in-group A than group B. In multivariate analysis, the decline of the QTc interval after weight loss was associated with changes in plasma FFA independently of changes in WHR and plasma catecholamines. Our data suggest that the QTc interval is tightly correlated with plasma FFA levels; shortening of cardiac repolarization times in the course of long-lasting weight reduction may reduce the risk of ventricular electrical instability, especially in women with abdominal adiposity. (*J Clin Endocrinol Metab* 87: 2080–2083, 2002)

OBESITY CAUSES OR exacerbates many health problems, both independently and in association with other diseases (1). Obese individuals with excess fat in intraabdominal depots are at particular risk of cardiovascular and metabolic diseases (2). Prolongation of the QT interval represents delayed repolarization of the ventricular myocardium and is considered a precursor of malignant arrhythmias and sudden death (3, 4). Although QT lengthening has been found to be associated with both obesity (5, 6) and abdominal fat deposition (7, 8), the mechanism responsible for such association remains elusive. Recent evidence demonstrating that raised plasma FFA concentrations increase QT intervals in normal subjects (9) and are an independent risk factor for sudden death in middle-aged men (10) might offer a plausible link between obesity, ventricular repolarization times, and sudden death.

The aims of the present study were to determine whether 1) differences in body fat distribution were associated with abnormalities of the QT interval in obese patients; 2) circulating plasma FFA concentrations could be implicated in the association; and 3) a substantial weight loss over a long period could influence the QT interval.

Materials and Methods

Obese premenopausal women, aged 25–44 yr, were recruited among 200 women attending our outpatient department for weight loss. Sixty-six were eligible based on the following exclusion criteria: type 2 diabetes mellitus, hypertension, cardiovascular disease, psychiatric problems, a history of alcohol abuse (at least 500 g alcohol/week in the last year), or if they smoked or took any medication known to have a cardiac effect. Twenty-five nonobese women, matched for age to the obese women, recruited from the paramedical staff of our department, volunteered to serve as control group. All women had laboratory data (urea nitrogen, creatinine, electrolytes, liver function tests, uric acid, tiroxine, complete blood count), chest x-ray, and electrocardiogram normal. Each subject gave informed written consent to participate in this study, which was approved by the institutional committee of ethical practice of our institution.

According to the waist-to-hip circumference ratio (WHR), obese subjects matched for age and body mass index (BMI) were divided into two groups. Group A consisted of 30 women with a WHR > 0.85 and group B of 36 women with a WHR ≤0.85. The cut-off value was based upon the evidence indicating high metabolic risk in women with a WHR > 0.85 (11). All subjects were studied after a 14-h overnight fast and were required to refrain from drinking alcohol in the previous 10 d.

Intervention

To ensure the greatest adherence to the treatment program, obese women were treated with a multidisciplinary approach consisting of diet, exercise, and behavioral and nutritional counseling. The prescribed daily caloric intake was 1300 kcal, ranging from 1250–1350 kcal/d according to the personal food questionnaire that each women had to complete at least 2 d for each month of follow-up. The composition of the dietary regimen was: carbohydrates 178 g (53%), proteins 73 g (23%), saturated fat 9 g (6.3%), monounsaturated fat 17 g (12%), polyunsaturated fat 8 g (5.7%), sodium 1.1 g, potassium 3 g, calcium 0.5 g, phosphorus 1.2 g, fiber 25 g. This regimen was very similar to the Mediterranean-style Step I diet, which is under active evaluation by the American Heart Association as a possible tool to lower cardiovascular risk in the population (12). All women were encouraged to have a physical activity (at least 1 h walk three times a week). Women were followed on an outpatient basis, at 1 month intervals. Testing was repeated at 6 and 12 months, at least 1 d after the last bout of exercise. There were no drop-outs from this 1-yr study.

Parameters

Subjects were measured to the nearest 0.5 cm for height and 100 g for weight. Height was determined using a stadiometer, weight in stocking-

Abbreviations: BMI, Body mass index; QTc, corrected QT; WHR, waist-to-hip ratio.

feet using a mechanical scale. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). WHR was calculated as waist circumference in centimeters divided by hip circumference in centimeters.

Electrocardiograms were recorded with a standard resting 12-lead electrocardiogram at a paper speed of 50 mm/sec. The QT interval was measured from the earliest onset of the QRS complex to the terminal portion of the T wave where it met the baseline. The RR interval from the preceding cardiac cycle was measured from the peaks of the R waves to correct the QT interval for heart rate (QTc). QT intervals were corrected with Bazett's formula (QTc = QT/$\sqrt{}$R-R) (13). QTc dispersion was calculated as interlead variability of the QTc interval (QTc dispersion = QTcmax-Qtcmin). A cardiologist who was blinded from other information did the QT interval analysis with the aid of calipers and magnifying lens for seven consecutive beats in lead II.

Assays for serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma FFA concentrations were determined according to Dole and Meinertz (14). To avoid *in vitro* lypolysis, plasma FFA levels were determined in chilled plasma containing EDTA and 0.275 mg/ml paroxon, a lipoprotein lipase inhibitor. Blood samples for catecholamines were drawn with the patient at rest for 30 min; the samples were immediately placed on ice, before determination by HPLC.

Statistics

Data are presented as group mean (SD). Baseline levels represent the mean of two measurements made at a 2-wk interval before intervention. A preliminary ANOVA was used to assess the significance within and between groups. One-sample *t* tests were used to compare values obtained before and after intervention, and two-samples *t* tests were used for between-group comparisons. Pearson's simple correlation allowed studying the association between two variables. Multivariate regression analysis tested the independent association and contribution of changes in WHR, plasma FFA, and catecholamines with the dependent variable (the QTc interval, and QTc dispersion). $P < 0.05$ was considered significant. All calculations were made on an IBM PC computer (SPSS, Inc., Chicago, IL; version 9.0).

Results

Clinical and laboratory characteristics of study women are reported in Table 1. Compared with nonobese women, obese women (all) had higher systolic blood pressure ($P < 0.05$), glucose ($P < 0.01$), triglyceride ($P < 0.05$), FFA ($P < 0.01$), norepinephrine ($P < 0.02$), and epinephrine ($P < 0.05$) levels. Compared with women of group B (WHR < 0.85), women of group A presented higher levels of blood pressure, glucose, triglyceride, FFA, and catecholamines, as well as increased values of the QTc interval and QTc dispersion. Group A had the longest QTc interval and dispersion, nonobese group had the shortest, and group B had intermediate values.

TABLE 1. Clinical and metabolic characteristics of the study women[a]

Parameters	Group A (n = 30)	Group B (n = 36)	Nonobese (n = 25)
Age (yr)	34.4 (5.1)	35.2 (5.0)	34.5 (4.7)
BMI (kg/m^2)	37.4 (2.6)	36.9 (2.5)	23 (2.0)[b]
Body weight (kg)	97.4 (8.1)	95.2 (9.3)	63.5 (5.7)[b]
WHR	0.90 (0.04)	0.78 (0.04)[c]	0.73 (0.04)[b]
SBP (mm Hg)	126 (9)	122 (8)[c]	121 (9)[b]
DBP (mm Hg)	84 (5)	80 (6)[c]	81 (5)
Glucose (mmol/liter)	5.9 (0.5)	5.4 (0.6)[c]	5.0 (0.6)[b]
TC (mmol/liter)	4.9 (0.6)	4.8 (0.6)	4.8 (0.7)
HDL-C (mmol/liter)	0.9 (0.3)	1.0 (0.4)	1.1 (0.3)
TGL (mmol/liter)	1.9 (0.3)	1.6 (0.4)[c]	1.5 (0.5)[b]
FFA (mmol/liter)	657 (43)	443 (58)[c]	405 (46)[b]
NE (nmol/liter)	2.5 (0.5)	2.0 (0.4)[c]	1.8 (0.4)[b]
E (pmol/liter)	350 (56)	285 (39)[c]	272 (43)[b]
QTc (msec)	427 (13)	408 (17)[c]	395 (18)[b]
QTc-d (msec)	60 (9)	52 (8)[c]	46 (7)[b]

[a] Data are presented as mean (SD). SBP, Systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TGL, triglycerides; NE, norepinephrine; E, epinephrine; QTc-d, QTc dispersion.

[b] $P < 0.05$ compared with obese women.

[c] $P < 0.05$ compared with group A.

In obese women (both groups), the QTc interval correlated with plasma FFA (r = 0.56, $P < 0.01$) (Fig. 1), epinephrine (r = 0.45, $P < 0.02$), and norepinephrine (r = 0.42, $P < 0.02$) concentrations, but not with triglyceride (r = 0.08, $P = 0.5$) or blood pressure values ($P = 0.09$). Similarly, QTc dispersion showed a correlation with plasma FFA (r = 0.51, $P < 0.01$), epinephrine (r = 0.44, $P < 0.02$) and norepinephrine (r = 0.40, $P < 0.02$) concentrations. Moreover, there was a correlation between WHR and both the QTc interval (r = 0.53, $P < 0.01$) and QTc dispersion (r = 0.50, $P < 0.01$).

Except for HDL cholesterol concentrations, anthropometric, metabolic, and cardiovascular parameters decreased in all women at 6 and 12 months of intervention (Table 2). The reduction of BMI and the increment of HDL cholesterol were similar in both groups; on the other hand, the decrement of systolic blood pressure ($P < 0.05$), glucose ($P < 0.05$), triglyceride ($P < 0.05$), FFA ($P < 0.01$), norepinephrine ($P < 0.05$), and epinephrine ($P < 0.05$) levels was significantly greater in group A. Similarly, the decrease of the QTc interval ($P < 0.01$) and QTc dispersion ($P < 0.02$) was greater in women of group A than in those of group B (Fig. 2). The decline in weight loss was correlated with the decline in plasma FFA (r = 0.42, $P < 0.01$) and QTc (r = 0.37, $P < 0.01$). After intervention, the decline in plasma glucose, epinephrine, and norepinephrine levels, and the QTc interval was positively correlated with the decline in plasma FFA.

For evaluating the independent association of changes in the QTc interval with changes in plasma FFA levels, a multivariate analysis was performed in which the QTc interval was the dependent variable, and WHR, BMI, plasma FFA, epinephrine, norepinephrine, and glucose levels were the independent variables. The model explained near 70% ($R^2 = 0.69$) of the variability in the changes of the QTc interval with changes in plasma FFA and catecholamine levels, independently and significantly associated with changes in the QTc interval. Moreover, changes in plasma FFA, norepinephrine and epinephrine levels explained 30%, 17%, and 12%, respectively, of the QTc interval variability. There was no significant change in the electrolyte balance after intervention.

Discussion

The main findings of our study are that the QTc interval on the surface electrocardiogram positively correlated with circulating plasma FFA levels in obese women, and that reduction of body weight resulted in significant shortening of the QTc interval and QTc dispersion strictly correlated with reduction in plasma FFA concentrations. On the other hand, it has to be emphasized that the duration of the QTc interval for all women was normal at baseline considering

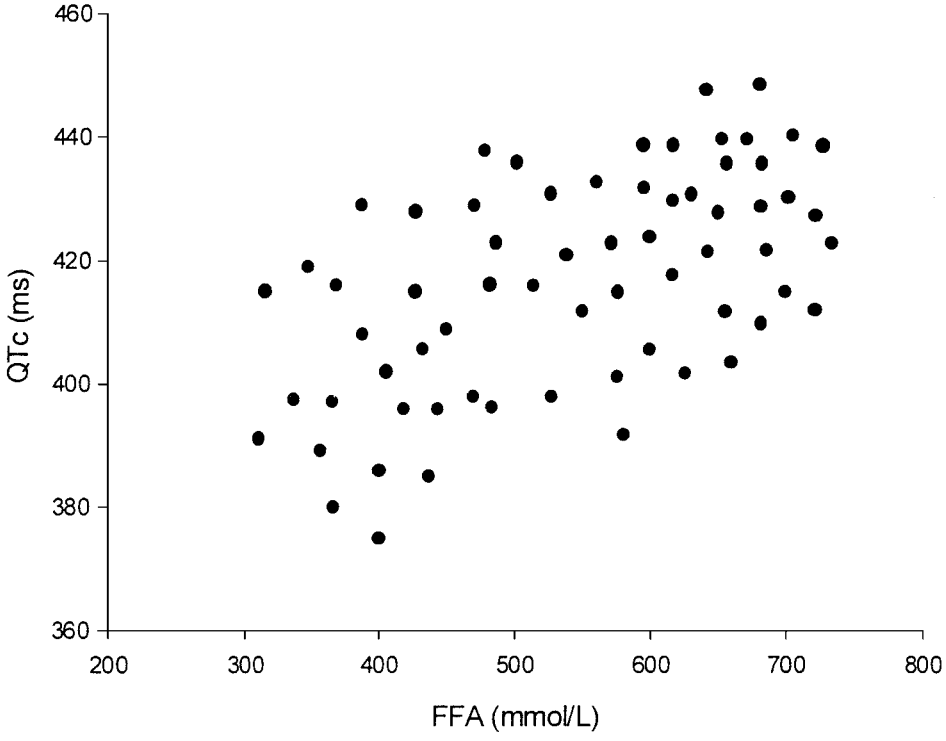

FIG. 1. Simple correlation between the QTc interval and plasma FFA levels in 66 obese women (r = 0.56).

TABLE 2. Clinical and metabolic parameters in obese women before and after intervention

Variables	Group A (n = 30)			Group B (n = 36)		
	Baseline	6 months	12 months	Baseline	6 months	12 months
Body weight (kg)	97.4 (8.1)	89.6 (6.7)[b]	84.1 (8.0)[b]	95.2 (9.3)	88.3 (8.2)[b]	83.4 (9)[b]
BMI (kg/m^2)	37.4 (2.6)	34.3 (2.3)[b]	32.4 (2.2)[b]	36.9 (2.5)	34.1 (2.4)[b]	32.3 (2.2)[b]
WHR	0.90 (0.04)	0.85 (0.04)[b]	0.83 (0.04)[b]	0.78 (0.04)	0.76 (0.04)	0.75 (0.04)[b]
SBP (mm Hg)	126 (9)	121 (8)[b]	118 (8)[b]	122 (8)	120 (8)	119 (7)[b]
DBP (mm Hg)	84 (5)	82 (6)	81 (5)[b]	80 (6)	79 (5)	78 (6)
Glucose (mmol/liter)	5.9 (0.5)	5.5 (0.5)[b]	5.4 (0.4)[b]	5.4 (0.5)	5.4 (0.5)	5.2 (0.4)[b]
TC (mmol/liter)	4.9 (0.6)	4.3 (0.7)[b]	4.3 (0.6)[b]	4.8 (0.6)	4.4 (0.7)[b]	4.3 (0.6)[b]
HDL-C (mmol/liter)	0.9 (0.3)	1.1 (0.4)	1.2 (0.4)[b]	1.0 (0.4)	1.1 (0.3)	1.2 (0.4)[b]
TGL (mmol/liter)	1.9 (0.5)	1.5 (0.4)[b]	1.4 (0.5)[b]	1.6 (0.5)	1.5 (0.6)	1.4 (0.5)
FFA (mmol/liter)	657 (43)	579 (45)[b]	431 (49)[b]	443 (58)	388 (49)[b]	363 (41)[b]
NE (nmol/liter)	2.5 (0.5)	2.0 (0.4)[b]	1.8 (0.4)[b]	2.0 (0.4)	1.8 (0.5)	1.6 (0.4)[b]
E (pmol/liter)	350 (56)	287 (50)[b]	231 (45)[b]	285 (39)	261 (45)	237 (31)[b]

[a] Data are presented as mean (SD). For abbreviations, see legend to Table 1.
[b] $P < 0.05$ or less compared with baseline.

that the generally accepted upper limit of the QTc interval is 440 msec.

Although prolongation of the QT interval is the most important electrocardiographic abnormality found in human obesity (5), cardiac arrhythmias and sudden deaths have been reported among dieters using very low energy dietary regimens (15, 16). In accord with previous findings (7, 8), our data confirm the association between the QTc interval, QTc dispersion and intraabdominal deposition of fat as measured by the WHR in obese women independent of body weight and BMI.

The novel finding of our study was the significant relationship we found between QTc intervals, WHR, plasma FFA, epinephrine, and norepinephrine concentrations, suggesting autonomic nervous system dysfunction as a possible mechanism of the prolonged QTc interval in visceral obesity. The QT interval is influenced by the autonomic tone: sympathetic stimulation unopposed by vagal activity might induce ventricular electrical instability, resulting in a risk of arrhythmia and sudden death (17), as reported to occur in obese patients (18). Interestingly enough, cardiac parasympathetic activity increases with weight loss in obese women (19).

Several lines of thought support a role for raised FFA concentrations to induce autonomic nervous system dysfunction in obesity. First, elevated plasma FFA levels have a stimulatory effect on sympathetic nervous system (20); second, raising plasma FFA levels with infusion of lipid emulsion in normal subjects stimulates cardiac sympathetic nervous activity (21) and prolongs the QTc interval and QTc dispersion (9); third, elevated FFA concentrations may inhibit Na/k-ATPase activity resulting in a disturbed myocar-

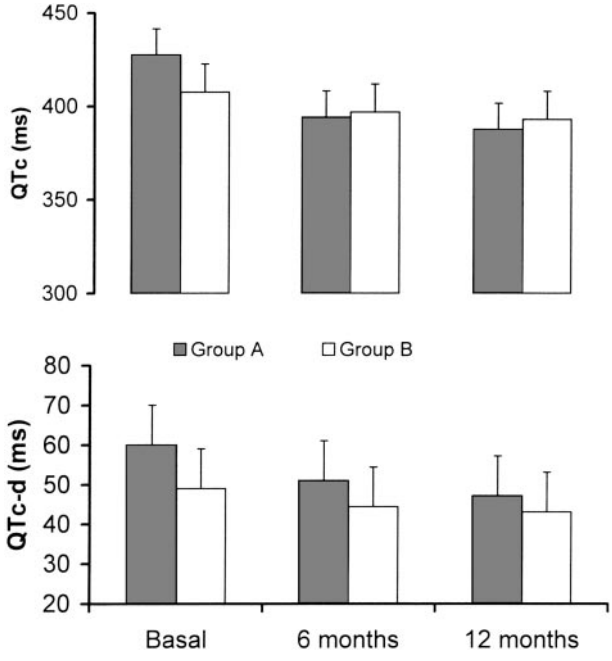

FIG. 2. Changes of the QTc interval and QTc dispersion at 6 and 12 months following the weight loss treatment program in obese women of Group A (WHR >0.85) and Group B (WHR ≤0.85). In group A, the changes of the QTc interval and the QTc dispersion are significantly different from baseline at both 6 and 12 months ($P < 0.01$); in group B, the significance levels are $P < 0.025$ at 6 months and $P < 0.02$ at 12 months.

dial membrane function (22); finally, FFA overload of myocardium may cause heart disease via induction of nitric oxide-mediated lipotoxicity and lipoapoptosis (23, 24).

The results obtained after the sustained weight loss in obese subjects also support this line of reasoning. In fact, at the same level of body weight and BMI reduction, women with the highest degree of visceral obesity had the greatest decrease of the QTc interval, QTc dispersion, WHR, plasma FFA and catecholamine levels. On the other hand, the multivariate analysis of data showed that changes in plasma FFA concentration were associated with change in the QTc interval independently of the changes in BMI, WHR, plasma norepinephrine, and epinephrine levels. Although we did not measure insulin resistance in our patients, it cannot be excluded that the improved insulin sensitivity associated with reduction of visceral fat might have contributed to the results obtained (25).

This study shows that, in obese women, the QTc interval and QTc dispersion are associated with increased abdominal fat deposition at the same level of BMI. A likely mechanism for this association is through the plasma FFA levels, which correlated with cardiac repolarization times both at baseline and after sustained weight loss. Shortening of the QTc interval and QTc dispersion in the course of a long-lasting weight reduction program, especially in women with visceral obesity, may be of clinical significance by reducing the cardiovascular risk profile, including the risk of potentially fatal arrhythmias and sudden death.

Acknowledgments

Received September 25, 2001. Accepted February 12, 2002.

Address all correspondence and requests for reprints to: Dario Giugliano, M.D., Ph.D., Department of Geriatrics and Metabolic Diseases, Second University of Naples, Piazza L. Miraglia, Naples 80138, Italy. E-mail: dario.giugliano@unina2.it.

References

1. **Kopelman PG** 2000 Obesity as a medical problem. Nature 404:635–643
2. **Lemarche B** 1998 Abdominal obesity and its metabolic complications: implication for the risk of ischaemic heart disease. Coron Artery Dis 9:473–481
3. **Vlay SC, Mallis GI, Brown EJ, Cohn PF** 1984 Documented sudden cardiac death in prolonged QT syndrome. Arch Intern Med 144:833–835
4. **Moss AJ** 1993 Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol 72:23B–25B
5. **Blunberg VS, Alexander J** 1992 Obesity and the heart. In: Bjorntrop P, Brodoff BN, eds. Obesity. Philadelphia: Lippincott; 517–531
6. **El-Gamal A, Gallagher D, Nawras A, Gandhi P, Gomez J, Allison DB, Steinberg JS, Shumacher D, Blank R, Heymsfield SB** 1995 Effects of obesity on QT, RR and QTc intervals. Am J Cardiol 75:956–959
7. **Peiris AN, Thakur RK, Sothman MS, Gustafson AB, Hennes MI, Wilson CR, Kissebah AH** 1991 Relationship of regional fat distribution and obesity to electrocardiographic parameters in healthy premenopausal women. South Med J 84:961–965
8. **Park J-J, Swan PD** 1997 Effect of obesity and regional adiposity on the QTc interval in women. Int J Obes 21:1104–1110
9. **Marfella R, De Angelis L, Nappo F, Manzella D, Siniscalchi M, Paolisso G, Giugliano D** 2001 Elevated plasma free fatty acid concentrations prolong cardiac repolarization in healthy subjects. Am J Clin Nutr 73:27–30
10. **Jouven X, Charles MA, Desnos M, Ducimetière P** 2001 Circulating nonesterified fatty acid level as a predictive risk factor for sudden death in the population. Circulation 104:756–761
11. **Bray G** 1989 Obesity: basic considerations and clinical approaches. Dis Mon 35:460–540
12. **Robertson RM, Smaha L** 2001 Can a Mediterranean-style diet reduce heart disease? Circulation 103:1821–1822
13. **Bazzett HC** 1920 An analysis of the time relations of electrocardiograms. Heart 7:353–367
14. **Dole VP, Meinertz H** 1960 Micro-determination of long-chain fatty acids in plasma and tissues. J Biol Chem 235:2595–2599
15. **Spencer IOB** 1968 Death during therapeutic starvation for obesity. Lancet 1:1288–1290
16. **Pringle TH, Scobie IN, Kosson CM, Maccuish AC** 1983 Prolongation of the QT interval during therapeutic starvation: a substrate for malignant Arrhythmias. Int J Obes 7:253–261
17. **Zipes DP** 1992 The long QT syndrome: a Rosetta stone for sympathetic related ventricular tachyarrhythmias. Circulation 84:1414–1419
18. **Messerli FH, Nunez BD, Ventura HO, Snyder DW** 1987 Overweight and sudden death: increased ventricular ectopy in cardiopathy of obesity. Arch Intern Med 147:1725–1728
19. **Rissanen P, Franssila-Kallunki A, Rissanen A** 2001 Cardiac parasympathetic activity is increased by weight loss in healthy women. Obes Res 9:637–643
20. **Grekin RJ, Vollmer AP, Sider RS** 1995 Pressor effect of portal venous oleate infusion. A proposed mechanism for obesity hypertension. Hypertension 25: 195–198
21. **Paolisso G, Manzella D, Rizzo MR, Ragno E, Barbieri M, Varricchio G, Varricchio M** 2000 Elevated plasma free fatty acid concentrations stimulate the cardiac autonomic nervous system in healthy subjects. Am J Clin Nutr 72: 723–730
22. **Kelly RA, O'Hara, Micth WE, Smith TW** 1986 Identification of Na-K-ATPase inhibitors in human plasma as non-esterified fatty acids and lysophospholipids. J Biol Chem 261:11704–11711
23. **Mjos OD** 1971 Effect of free fatty acids on myocardial function and oxygen consumption in intact dogs. J Clin Invest 50:1386–1389
24. **Unger RH, Orci L** 2001 Lipotoxic diseases of nonadipose tissues in obesity. Int J Obes Relat Metab Disord 24(Suppl 4):S28–S32
25. **Oliver MF, Opie LH** 1994 Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. Lancet 343:155–158