

Effect of Weight Loss on Cardiac Synchronization and Proinflammatory Cytokines in Premenopausal Obese Women

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OBJECTIVE — Obesity is an important risk factor for heart failure in both women and men. Dyssynchrony between right and left ventricular contraction and relaxation has been identified as an independent predictor of heart failure. We examined the relationship of ventricular synchronization abnormalities with the concentration of proinflammatory cytokines in obese women at baseline and after sustained weight loss.

RESEARCH DESIGN AND METHODS — Echocardiographic parameters of ventricular dyssynchrony, circulating levels of tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-18, and C-reactive protein (CRP) were investigated in 67 healthy, premenopausal obese women and 40 age-matched normal-weight women.

RESULTS — Compared with nonobese women, obese women had increased concentrations of CRP ($P < 0.01$), TNF- α ($P < 0.01$), IL-6 ($P < 0.01$), and IL-18 ($P < 0.01$). Moreover, obese women had a higher myocardial performance index ($P < 0.02$) and lower transmitral Doppler flow ($P < 0.05$), pulmonary venous flow analysis ($P < 0.02$), and ejection fraction ($P < 0.05$), indicating ventricular dyssynchrony. Concentrations of CRP, TNF- α , and IL-6 were related to anthropometric indexes of obesity and to echocardiographic parameters of ventricular dyssynchrony. After 1 year of a multidisciplinary program of weight reduction, obese women lost at least 10% of their original weight. This was associated with reduction of cytokine ($P < 0.01$) and CRP ($P < 0.02$) concentrations and with improvement of echocardiographic parameters of ventricular dyssynchrony, which correlated with changes in adiposity, particularly visceral adiposity.

CONCLUSIONS — In obese women, ventricular dyssynchrony correlates with body fat, possibly through inappropriate secretion of cytokines. Weight loss represents a safe method for downregulating the inflammatory state and ameliorating cardiac function in obese women.

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Dyssynchrony between right and left ventricular contraction and relaxation has been identified as an independent predictor of cardiac mortality in patients with heart failure (1,2). Moreover, cardiac resynchronization reduces mortality from progressive heart failure in patients with symptomatic left ventricular

dysfunction and ventricular dyssynchrony (3). Because approximately one-half of all deaths among patients with heart failure occur because of progressive cardiac dysfunction, it may be important to evaluate heart function among people at risk of heart failure.

Obesity is an important risk factor for heart failure in both women and men. Approximately 11 and 14% of heart failure cases among men and women in the community, respectively, are attributable to increased BMI (4). This is associated with altered left ventricular remodeling, possibly owing to increased hemodynamic load, neurohormonal activation, and increased cytokine production (5). Adipocytes synthesize and secrete several cytokines, including tumor necrosis factor (TNF)- α (6) and interleukin (IL)-6 (7). Elevated levels of IL-6, TNF- α , and IL-18 as well as the sensitive marker of inflammation, C-reactive protein (CRP), have been found to be associated with proxy indicators of elevated body fat (8) and with risk of heart failure (9,10). To the best of our knowledge, no previous study has evaluated the relationships among obesity, ventricular dyssynchrony, and circulating proinflammatory cytokines; neither has there been any study investigating the influence of weight reduction. Therefore, the aim of the present study was to evaluate, in premenopausal obese women, whether ventricular synchronization abnormalities were associated with body weight and whether circulating proinflammatory cytokines were involved in this association. Moreover, the effect of sustained weight loss (at least 10% of the initial body weight) was also investigated.

RESEARCH DESIGN AND METHODS

Obese and nonobese premenopausal women, aged 25–44 years, were recruited from the outpatient department of the teaching hospital at the Second University of Naples, Italy. All

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Abbreviations: CRP, C-reactive protein; ET, ejection time; HOMA, homeostasis model assessment; ICT, isovolumetric contracting time; IL, interleukin; IRT, isovolumetric relaxation time; MPI, myocardial performance index; PVF, pulmonary vein flow; RV-RT_m, right ventricular relaxation time; TNF, tumor necrosis factor; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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obese women ($n = 67$) were sedentary (<1 h/week of physical activity), with no evidence of participation in diet-reduction programs within the last 6 months. Women were asked to complete a personal health and medical history questionnaire that served as a screening tool. Women were excluded from the study if they had type 2 diabetes, hypertension, cardiovascular disease, psychiatric problems, a history of alcohol abuse, or if they smoked or took any medication. All women had normal results for laboratory data (urea nitrogen, creatinine, electrolytes, liver function tests, uric acid, thyroxin, and complete blood count), chest X-rays, and electrocardiograms. Forty nonobese women, matched for age to the obese women, served as the control group. All women (both groups) had normal glucose tolerance (2-h postload plasma glucose <7.8 mmol/l) and were studied in the same phase of the menstrual cycle. Each woman provided informed written consent to participate in this study, which was approved by the institutional committee of ethical practice of our institution.

All women were studied after a 14-h overnight fast and were required to refrain from drinking alcohol over the previous 10 days. Women were measured to the nearest 0.5 cm in height and 100 g in weight. Height was determined with the subject standing without shoes and weight with the subject in stockinged feet, using a mechanical scale. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-to-hip ratio (WHR) was calculated as waist circumference in centimeters divided by hip circumference in centimeters.

Obese women were treated with a multidisciplinary approach consisting of diet, exercise, and behavioral and nutritional counseling. The mean recommended daily caloric intake was 1,300 kcal, ranging from 1,250 to 1,350 kcal. The recommended composition of the dietary regimen was 178 g carbohydrates, 73 g proteins, 9 g saturated fat, 17 g monounsaturated fat, 8 g polyunsaturated fat, 1.1 g sodium, 3 g potassium, 0.5 g calcium, 1.2 g phosphorus, and 25 g fiber. This regimen was very similar to the Mediterranean-Style Step 1 diet (11), which is under active evaluation by the American Heart Association as a possible tool to lower cardiovascular risk in the population. Physical activity was encour-

aged in all women (i.e., to walk for at least 1 h three times a week).

All women underwent two-dimensional and Doppler echocardiography before starting the intervention, with measurements taken according to the American Society of Echocardiography recommendations (12). Only frames with optimal visualization of interfaces and simultaneously showing septum, left ventricular internal diameter, and posterior wall were used for reading. Two observers read the tracings, and the mean value from at least five measurements per observer were computed. Left ventricular mass was calculated according to Troy et al. (13) and was normalized by both body surface area and height (14) to correct for the effect of overweight. The ejection fraction was calculated from area measurements using the area-length method applied to the average apical area (12). Left ventricular internal dimension and interventricular septal were measured at end diastole and end systole by American Society of Echocardiography recommendations (12). Myocardial synchronization was evaluated by diastolic filling time, mitral regurgitation time (the ratio of velocity time intervals of mitral early [E] and late [A] diastolic flows [E/A ratio]), pulmonary vein flow analysis (PVFs/PVFD ratio), the effective ejection time (ET) (ejection fraction), right ventricular relaxation time (RV-RT_m), and myocardial performance index (MPI). Doppler velocities and time intervals were measured from mitral inflow and left ventricular outflow recordings. Isovolumetric relaxation time (IRT) was the time interval from cessation of left ventricular outflow to onset of mitral inflow. ET was the time interval from the onset and cessation of left ventricular outflow, and mitral early diastolic flow deceleration time was the time interval between the peak early diastolic velocity and the end of early diastolic flow. Total systolic time interval was measured from the cessation of one mitral flow to the beginning of the following mitral inflow. Isovolumetric contracting time (ICT) was calculated by subtracting ET and IRT from the total systolic time interval. The ratio of velocity time intervals of mitral early and late diastolic flows was calculated. MPI was calculated by using the formula $MPI = (IRT + ICT)/ET$. Right ventricular function (RV-RT_m) was evaluated by Doppler tissue imaging of the right ventricular tricuspid anulus (15).

Serum samples for cytokine and CRP levels were stored at -80°C until assayed. Serum concentrations of TNF- α , IL-6, and IL-18 were determined in duplicate using a highly sensitive quantitative sandwich enzyme assay (Quantikine HS; R&D Systems, Minneapolis, MN). High-sensitivity CRP was assayed by immunonephelometry on a Behring Nephelometer 2 (Dade Behring, Marburg, Germany). Assays for serum total and HDL cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono, Italy). Insulin sensitivity in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated with the following formula: fasting plasma glucose (millimoles per liter) times fasting serum insulin (microunits per milliliter) divided by 25, as described by Matthews et al. (16).

Data are presented as group means \pm SD. One-way ANOVA was used to compare baseline data, followed by Scheffé's test for pairwise comparisons. Multiple comparisons were made with ANOVA, followed by post hoc analysis (Student-Newmann-Keuls test) to locate the significant difference indicated with ANOVA. Linear regression and correlation were used to evaluate relationships between variables. Multivariate regression analysis tested the independent association and contribution of changes in BMI, WHR, HOMA, CRP, and plasma cytokine concentrations with the dependent variables (indexes of cardiac function). A value of $P < 0.05$ was considered significant. All calculations were made on an IBM PC (version 9.0; SPSS, Chicago, IL).

RESULTS— The characteristics of women are shown in Table 1. The mean age was similar in the two groups, and BMI and WHR were significantly higher in the obese group. Compared with nonobese women, obese women had higher fasting glucose and insulin concentrations and HOMA scores. By contrast, serum lipid and blood pressure levels were not different between the two groups (Table 1). As expected for an obese female population, serum TNF- α ($P < 0.01$), IL-6 ($P < 0.01$), IL-18 ($P < 0.01$), and CRP ($P < 0.01$) levels were higher than those of nonobese women (Table 1). Electrocardiogram parameters were not dif-

Table 1—Clinical characteristics of the study women

	Obese	Nonobese	P
n	67	40	
Age (years)	36.5 ± 4.6	35.1 ± 5.1	NS
BMI (kg/m ²)	37.6 ± 2.1	23.6 ± 1.5	<0.001
WHR	0.84 ± 0.07	0.73 ± 0.04	<0.001
Systolic blood pressure (mmHg)	124.6 ± 5.9	122.8 ± 5.1	NS
Diastolic blood pressure (mmHg)	83.8 ± 3.8	82.6 ± 3.5	NS
Fasting glucose (mmol/l)	5.5 ± 0.5	4.9 ± 0.4	<0.05
Fasting insulin (μU/ml)	16.5 ± 3.2	8.1 ± 2.3	<0.001
HOMA	3.6 ± 0.4	1.7 ± 0.2	<0.001
Total cholesterol (mmol/l)	4.9 ± 0.4	4.8 ± 0.6	NS
LDL cholesterol (mmol/l)	3.4 ± 0.4	3.3 ± 0.4	NS
HDL cholesterol (mmol/l)	1.0 ± 0.3	1.1 ± 0.3	NS
Triglyceride (mmol/l)	1.4 ± 0.6	1.3 ± 0.3	NS
TNF-α (pg/ml)	5.8 ± 1.5	3.5 ± 0.7	<0.001
IL-6 (pg/ml)	4.2 ± 0.9	1.7 ± 0.5	<0.001
IL-18 (pg/ml)	227.5 ± 27.4	129.3 ± 25.8	<0.001
CRP (mg/l)	3.4 ± 0.7	1.2 ± 0.3	<0.001
LVM/BSA (g/m ²)	94.1 ± 11	72.2 ± 10	<0.05
LVM/h ² (g/m ²)	63.4 ± 8	47.3 ± 8	<0.001
Fractional shortening (%)	31 ± 3	37 ± 6	<0.05
LVIDD (mm)	51.7 ± 5.1	41.1 ± 4.9	<0.05
IVS (mm)	10.9 ± 1.6	8.2 ± 1.1	<0.05
LVPW (mm)	10.1 ± 1.3	7.5 ± 1.8	<0.05
Mitral deceleration (ms)	156 ± 13	195 ± 19	<0.001
E/A ratio	0.9 ± 0.2	1.3 ± 0.3	<0.001
MPI	0.57 ± 0.08	0.38 ± 0.04	<0.001
PVFs/PVFD ratio	1.41 ± 0.08	1.60 ± 0.5	<0.001
RV-RT (ms)	42.4 ± 5	10.3 ± 4	<0.001
Ejection fraction (%)	50 ± 7	66 ± 11	<0.02

Data are group means ± SD. IVS, interventricular septum; LVM/BSA, left ventricular mass index/body surface area; LVM/h², left ventricular mass index/height squared; LVIDD, left ventricular internal diastolic diameter; LVPW, left ventricular posterior wall.

ferent between the two groups (data not shown).

Echocardiographic/Doppler measurements are presented in Table 1. Compared with nonobese women, obese women had longer left ventricular internal diastolic diameter ($P < 0.01$), thicker interventricular septum ($P < 0.05$) and left ventricular posterior wall ($P < 0.04$), but lower ejection fraction ($P < 0.05$) (Table 1). Moreover, obese women had lower PVFs/PVFD ($P < 0.02$) and E/A ratios ($P < 0.02$) and higher MPI ($P < 0.02$) and RV-RT_m ($P < 0.02$), indicating ventricular dyssynchrony (Table 1).

Serum cytokine and CRP levels and HOMA scores were related to measures of total (BMI) and, particularly, central (WHR) obesity (Table 2). Measures of total and central adiposity were inversely related to ejection fraction, E/A ratio, and PVFs/PVFD ratio and directly related to MPI and RV-RT_m (Table 2). Concentra-

tions of TNF-α, IL-6, and CRP were inversely related to ejection fraction, E/A ratio, and PVFs/PVFD ratio and directly related to MPI and RV-RT_m (Table 2). Insulin levels and HOMA scores were not

related to indexes of cardiac function (ejection fraction, MPI, RV-RT_m, E/A ratio, and PVFs/PVFD ratio). To investigate which variables might account for the association between cardiac function and circulating IL-6, TNF-α, and CRP levels, multiple regression analysis was performed. The independent variables were those significantly correlated with MPI in univariate analysis. Only BMI ($P < 0.05$) and WHR ($P < 0.02$) were independently and significantly associated with MPI and levels of IL-6, TNF-α, and CRP.

Effects of weight loss

All obese women lost at least 10% of their initial body weight, with a mean decrease of 9.8 ± 1.5 kg (range 7.5–13). This was associated with significant reductions in BMI, WHR, fasting glucose, insulin levels, HOMA scores, and IL-6, IL-18, TNF-α, and CRP concentrations (Table 3). Echocardiographic parameters of cardiac function improved after weight loss (Table 3). Serum total cholesterol, cholesterol subfractions, triglycerides, and blood pressure values were not significantly decreased after the same period. Changes in cytokine and CRP concentrations after weight loss were related to changes in BMI and WHR (Table 4). Changes in BMI and WHR after weight loss were associated with improvements of cardiac function indexes (MPI, RV-RT_m, E/A ratio, and PVFs/PVFD ratio) (Table 4). After weight loss, the decline in serum TNF-α, IL-6, and CRP levels correlated with the changes in ejection fraction, RV-RT_m, E/A ratio, PVFs/PVFD ratio, and MPI. For evaluating the independent association of changes in echocardiographic parameters of cardiac function with changes in serum

Table 2—Relationships of anthropometric measures of obesity and concentrations of proinflammatory cytokines with echocardiographic parameters in obese women

	BMI	WHR	TNF-α	IL-6	IL-18	CRP
TNF-α*	0.29†	0.41‡	—	0.10	0.14	0.09
IL-6*	0.42‡	0.54§	0.10	—	0.21†	0.20†
IL-18*	0.27†	0.51§	0.14	0.21†	—	0.14
CRP*	0.29†	0.33‡	0.09	0.20†	0.14	—
HOMA	0.31‡	0.51§	0.35‡	0.28†	0.33‡	0.28†
Ejection fraction	-0.25†	-0.39‡	-0.31‡	-0.21†	-0.10	-0.34‡
E/A ratio	-0.20†	-0.33‡	-0.27†	-0.19†	-0.06	-0.32‡
MPI	0.29†	0.39‡	0.35‡	0.23†	0.10	0.29†
PVFs/PVFD ratio	-0.23†	-0.46§	-0.29†	-0.21†	-0.07	-0.30‡
RV-RT _m	0.27†	0.35‡	0.33‡	0.21†	0.12	0.26†

*Log transformed; † $P < 0.05$; ‡ $P < 0.02$; § $P < 0.01$.

Table 3—Effects of weight loss in obese women

	Baseline	12 months	P
BMI (kg/m ²)	37.6 ± 2.1	32.5 ± 1.5	<0.001
WHR	0.84 ± 0.07	0.78 ± 0.04	<0.001
Fasting glucose (mmol/l)	5.5 ± 0.5	5.1 ± 0.4	<0.05
Fasting insulin (μU/ml)	16.5 ± 3.2	10.8 ± 34.3	<0.03
HOMA	3.6 ± 0.4	2.2 ± 0.3	<0.05
TNF-α (pg/ml)	5.8 ± 1.5	4.0 ± 1.1	<0.01
IL-6 (pg/ml)	4.2 ± 0.9	1.6 ± 0.3	<0.01
IL-18 (pg/ml)	227.5 ± 27.4	159.4 ± 26.5	<0.01
CRP (mg/l)	3.4 ± 0.7	1.9 ± 0.2	<0.02
LVM/BSA (g/m ²)	94.1 ± 11	76.3 ± 11	<0.05
LVM/h ² (g/m ²)	63.4 ± 8	51.5 ± 6	<0.05
Fractional shortening (%)	31 ± 3	35 ± 6	NS
LVIDD (mm)	51.7 ± 5.1	48.2 ± 3.8	NS
IVS (mm)	10.9 ± 1.6	10.1 ± 1.2	NS
LVPW (mm)	10.1 ± 1.3	9.8 ± 1.4	NS
Mitral deceleration (ms)	156 ± 13	174 ± 12	<0.001
E/A ratio	0.9 ± 0.2	1.3 ± 0.3	<0.05
MPI	0.57 ± 0.08	0.41 ± 0.06	<0.001
PVFs/PVfd ratio	1.41 ± 0.08	1.53 ± 0.08	<0.001
RV-RT _m (ms)	42.4 ± 5	20.3 ± 6	<0.005
Ejection fraction (%)	50 ± 7	60 ± 6	<0.05

Data are group means ± SD. IVS, intraventricular septum; LVM/BSA, left ventricular mass index/body surface area; LVM/h², left ventricular mass index/height squared; LVIDD, left ventricular internal diastolic diameter; LVPW, left ventricular posterior wall.

IL-6, TNF-α, and CRP levels, a multivariate analysis was performed, in which MPI was the dependent variable and BMI, WHR, IL-6, TNF-α, and CRP levels were the independent variables. The model explained 65% of the variability in the change of MPI, with changes in IL-6, TNF-α, and CRP concentrations.

In nonobese women, anthropometric, metabolic, and echocardiographic parameters were not different from baseline after 12 months (data not shown).

CONCLUSIONS— The main findings of this study are that dyssynchrony between right and left ventricular contraction and relaxation positively correlated with indexes of adiposity, particularly visceral adiposity, and proinflammatory cytokine levels in obese women and that reduction of body weight resulted in significant improvement of the sequelae of ventricular dyssynchrony. Because any associated conditions could be ruled out through clinical investigation

and close laboratory evaluation, it is reasonable to hypothesize that in the clinical setting, any changes in cardiac function can be interpreted as a consequence of weight loss itself.

Studies have identified dyssynchrony between right and left ventricular contraction and relaxation as an independent predictor cardiac mortality in patients with heart failure (2). Obesity is associated with an increased risk of developing heart failure, irrespective of the presence of other associated risk factors, such as hypertension, hyperlipidemia, hyperinsulinemia, diabetes, elevated alcohol consumption, and smoking (4). Many of these associated factors were, by inclusion criteria, not present in our population of obese women; this seems to suggest that the morphologic and functional echocardiographic alterations are due to obesity.

The increase of MPI indicates a worse functional outcome in obese women. MPI is a Doppler index of combined systolic and diastolic function (17) derived from aortic and mitral flows and has been shown to be related to morbidity and mortality in patients with various cardiovascular disorders, including heart failure (18,19). Moreover, the diminished diastolic filling time, the prolongation of mitral regurgitation and of RV-RT_m, and the diminished effective ET also suggest that excess body fat may influence cardiac synchronization in obese women.

The present study provides evidence of an association between ventricular dyssynchrony and body weight in obese women. As for the background of this association, obesity may be responsible for an increased inflammatory process and a poor cardiac contractile function may be linked to a greater inflammatory process (20). More than 25 years ago, Lefer and Rovetto (21) reported that the sera of septic patients and experimental animals contained a “myocardial depressant factor,” the molecular nature of which has eluded definitive identification in the intervening years. During the past decade, TNF-α and IL-1β were shown to be present in the sera of septic patients and responsible for most, if not all, of the reversible cardiac depression often seen with this syndrome (22). These data are consistent with earlier reports (23) that soluble inflammatory mediators in medium conditioned by activated immunocytes altered the contractile responsiveness of beating cardiac muscle cells to β-ad-

Table 4—Relationships of reduction of anthropometric measures and reduction of proinflammatory cytokines with echocardiographic parameters after weight loss in obese women

	BMI	WHR	TNF-α	IL-6	IL-18	CRP
TNF-α*	0.20†	0.31‡	—	0.08	0.11	0.10
IL-6*	0.32‡	0.41§	0.08	—	0.22†	0.10
IL-18*	0.21†	0.45§	0.11	0.22†	—	0.12
CRP*	0.27†	0.35‡	0.10	0.10	0.12	—
HOMA	0.30‡	0.53§	0.19†	0.19†	0.24†	0.18†
Ejection fraction	-0.21†	-0.33‡	-0.18†	-0.31‡	-0.15	-0.24‡
E/A ratio	-0.19†	-0.32‡	-0.32‡	-0.32‡	-0.10	-0.22‡
MPI	0.27†	0.35‡	0.45§	0.21†	0.12	0.39‡
PVFs/PVfd ratio	-0.22†	-0.41§	-0.27‡	-0.31‡	-0.16	-0.20‡
RV-RT _m	0.21†	0.45§	0.19†	0.32‡	0.08	0.19†

*Log transformed; †P < 0.05; ‡P < 0.02; §P < 0.01.

renergic agonists, an effect that could be mimicked in this *in vitro* preparation by recombinant TNF- α or IL-1 β . Interest in these findings has been amplified by reports (24) of elevated circulating as well as intracardiac TNF- α levels in patients with heart failure. Accordingly, we found that obese women had higher circulating levels of TNF- α , IL-6, and CRP and impaired cardiac function as compared with nonobese women. Moreover, several clinical studies (9) have suggested that serum levels of TNF, IL-6, and CRP are elevated in patients with congestive heart failure regardless of the etiology of the condition. Furthermore, elevated blood levels of these inflammatory markers correlate with worsening functional class, increased hospitalization rates, and poorer survival (25). It can be speculated that the detrimental effect of obesity in cardiac function may also be due to its ability to increase circulating TNF- α , IL-6, and CRP. Interestingly enough, IL-6 and TNF- α are expressed in adipose tissue. Systemic concentrations of IL-6 increase with adiposity, and it has been suggested that ~30% of total circulating IL-6 originates from adipose tissue (7); moreover, *in vitro* release of TNF- α by adipocytes has been reported (26). Circulating concentrations of TNF- α or IL-6 have been found to be associated with BMI (27), a finding confirmed by our data. Moreover, the greater association we found between WHR and TNF- α , IL-18, and IL-6 concentrations suggests that body fat distribution may influence cytokine levels more than total fat and hence, influence cardiac function. Accordingly, the concentrations of TNF- α , IL-6, and CRP were positively related to MPI and RV-RT_m and negatively related to transmitral Doppler flow, PVF analysis, and ejection fraction. All of this seems to suggest that cytokines may be partly responsible for dyssynchrony between right and left ventricular contraction and relaxation observed in obese women, particularly those with visceral obesity.

Recent research has begun to clarify some of the intracellular signaling mechanisms that contribute to cardiac myocyte contractile dysfunction. IL-6 has been shown to rapidly suppress voltage-dependent Ca²⁺ current in adult rat ventricular myocytes (28). Consistent with these data, higher concentrations of recombinant human TNF- α have been shown (29) to result in rapid and revers-

ible declines in contractile function of isolated hamster papillary muscles and of adult guinea pig and rabbit ventricular myocytes. The effect of recombinant human TNF- α was apparent within minutes, implicating activation of the constitutively expressed nitric oxide synthase isoform in cardiac myocytes (i.e., endothelial nitric oxide synthase or inducible nitric oxide synthase) (30). Although of considerable mechanistic interest, the physiological or clinical relevance of the high concentrations of cytokines in obesity heart dysfunction remains to be determined.

The results obtained after weight loss in obese women also support a role for visceral fat as a key factor predisposing toward cardiac dysfunction, possibly through inappropriate cytokine secretion. In fact, at the same level of body weight reduction, women with the greatest degree of visceral obesity had the greatest decrease of cytokine and CRP levels and the greatest improvement of cardiac functions. Thus, the improvement of cardiac function after weight loss in obese women was more marked in those who lost more visceral fat and was strictly associated with a decrease in cytokine concentrations.

This study shows that in obese women heart contractile dysfunction is associated with increased body fat and particularly visceral fat. A likely mechanism for this association is through plasma cytokine levels, which correlated with indexes of cardiac dyssynchrony both at baseline and after sustained weight loss. Studies in cell biology, animal models, clinical research, and epidemiology have been remarkably consistent, suggesting that contractile dysfunction may be linked to an inflammatory process (9). This hypothesis has found convincing support, particularly the one linking inflammation to cardiovascular risk through changes in cardiac function (31,32). However, inflammation may be a modifiable risk factor amenable to correction by drugs (33) or lifestyle modifications (34). Because of the powerful association with obesity, weight loss may be another safe method for downregulating the inflammatory status of obese subjects, with the goal of reducing their cardiovascular risk.

References

- Xiao HB, Roy C, Fujimoto S, Gibson DG: Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. *Int J Cardiol* 53:163–170, 1996
- Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM: Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 95:2660–2667, 1997
- Bradley DJ, Bradley EA, Baughman KL, Wong KL, Goin JE, Mancini DM: Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 289:730–740, 2003
- Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS: Obesity and the risk of heart failure. *N Engl J Med* 347:305–313, 2002
- Kopelman PG: Obesity as medical problem. *Nature* 404:635–643, 2000
- Hotamisligil GS, Shargill NS, Spiegelman BM: Adipose tissue expression of tumor necrosis factor- α . *Science* 259:87–91, 1993
- Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW: Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, *in vivo*. *J Endocrinol Metab* 82:4196–4200, 1997
- Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M, D'Andrea F, Molinari AM, Giugliano D: Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 105:804–809, 2002
- Kelly RA, Smith TW: Cytokines and cardiac contractile function. *Circulation* 95:778–781, 1997
- Mann DL: Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res* 91:988–998, 2002
- Robertson RM, Smaha L: Can a Mediterranean-style diet reduce heart disease? (Editorial). *Circulation* 103:1821–1822, 2001
- Sahn DJ, DeMaria A, Kisslo J, Weyman A, The Committee on M-Mode Standardization of the American Society of Echocardiography: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 58:1072–1083, 1978
- Troy BL, Pombo J, Rackley CE: Measurement of left ventricular wall thickness and mass by echocardiography. *Circulation* 45:602–611, 1972
- De Simone G, Daniels SR, Devereux RB, Meyer RA, De Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: assess-

- ment of allometric relations and the impact of overweight. *J Am Coll Cardiol* 20: 1251–1260, 1992
15. Galderisi M, Severino S, Caso P, Cicala S, Petrocelli A, De Simone L, Mininni N, de Divitiis O: Right ventricular myocardial diastolic dysfunction in different kinds of cardiac hypertrophy: analysis by pulsed Doppler tissue imaging. *Ital Heart J* 2:912–920, 2001
 16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
 17. Poulsen SH, Jensen SE, Tei C, Seward JB, Egstrup K: Value of the Doppler index of myocardial performance in the early phase of acute myocardial infarction. *J Am Soc Echocardiogr* 13:723–730, 2000
 18. Senni M, Rodeheffer RJ, Tribouilloy CM, Evans JM, Jacobsen SJ, Bailey KR, Redfield MM: Use of echocardiography in the management of congestive heart failure in the community. *J Am Coll Cardiol* 33: 164–170, 1999
 19. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB: Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. *Am J Cardiol* 82:1071–1076, 1998
 20. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, Levy D, Wilson PW, D'Agostino RB, Framingham Heart Study: Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 107:1486–1491, 2003
 21. Lefer A, Rovetto M: Influence of a myocardial depressant factor on physiologic properties of cardiac muscle. *Proc Soc Exp Biol* 134:269–273, 1970
 22. Parrillo JE: Pathogenetic mechanism of septic shock. *N Engl J Med* 328:1471–1477, 1993
 23. Lange LG, Schreiner GF: Immune cytokines and cardiac disease. *Trends Cardiovasc Med* 2:145–151, 1992
 24. Dutka DP, Elborn JS, Delamere F, Shale DJ, Morris GK: Tumor necrosis factor-alpha in severe congestive cardiac failure. *Br Heart J* 70:141–143, 1993
 25. Kell R, Haunstetter A, Dengler TJ, Zugck C, Kubler W, Haass M: Do cytokines enable risk stratification to be improved in NYHA functional class III patients? Comparison with other potential predictors of prognosis. *Eur Heart J* 23:70–78, 2002
 26. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB: The expression of tumor necrosis factor in human adipose tissue: regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J Clin Invest* 95:2111–2119, 1995
 27. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW: C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 19:972–978, 1999
 28. Liu S, Schreier KD: G protein-mediated suppression of L-type Ca²⁺ current by interleukin-1 beta in cultured rat ventricular myocytes. *Am J Physiol* 268:C339–C349, 1995
 29. Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL: Cellular basis for the negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian heart. *J Clin Invest* 92:2303–2312, 1993
 30. Kelly RA, Balligand J-L, Smith TW: Nitric oxide and cardiac function. *Circ Res* 79: 363–380, 1996
 31. Munger MA, Johnson B, Amber IJ, Callahan KS, Gilbert EM: Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 77:723–727, 1996
 32. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL: Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies Of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 27:1201–1206, 1996
 33. Tracy RP: Is visceral adiposity the “Enemy Within”? *Arterioscler Thromb Vasc Biol* 21: 881–883, 2001
 34. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V: Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 148: 209–214, 2000