Subclinical Impairment of Left Ventricular Function in Young Obese Women: Contributions of Polycystic Ovary Disease and Insulin Resistance

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Context: Obesity and insulin resistance (IR) may produce disturbances of left ventricular (LV) function. Obese women with polycystic ovary syndrome (PCO), characterized by hormonal and metabolic abnormalities, are thought to be at particularly increased cardiovascular risk.

Objectives: We sought to determine the influence of IR on LV function in obese young women with and without PCO and without other comorbidities.

Design: This was a cross-sectional study.

Setting: The study was performed at a university hospital.

Patients: A total of 150 women aged younger than 40 yr with a body mass index (BMI) of 30 kg/m^2 or more was classified into three groups: with both PCO and IR, without PCO and with IR, and without either PCO or IR.

Main Outcome Measures: Tissue Doppler-derived myocardial velocities, strain-rate and strain, and metabolic and hormonal measurements were calculated.

Results: Subclinical impairment of LV systolic and diastolic function as indicated by lower peak strain ($P < 0.001$), peak systolic strain rate ($P < 0.001$), peak early diastolic strain rate ($P < 0.001$), and peak early diastolic velocity ($P < 0.01$) was demonstrated in both groups with IR. IR subjects with and without PCO did not differ in any LV function indices. Strain was independently associated with fasting insulin ($\beta = -0.39$; $P < 0.001$), urinary albumin excretion (UAE) ($\beta = -0.36$; $P < 0.001$), and BMI ($\beta = -0.22$; $P < 0.03$), and peak early diastolic strain rate was associated with UAE ($\beta = -0.35$; $P < 0.001$), fasting insulin ($\beta = -0.24$; $P < 0.02$), BMI ($\beta = -0.23$; $P < 0.02$), and SHBG ($\beta = 0.20$; $P < 0.04$).

Conclusions: In obese young women, fasting insulin, BMI, SHBG, and UAE are independent correlates of impaired LV performance. The contribution of PCO to LV function abnormalities is linked to IR, but not to other hormonal aberrations associated with this condition. **(*J Clin Endocrinol Metab* 93: 3748–3754, 2008)**

Obese women are at higher relative risk for heart failure than obese men (1, 2). The contribution of obesity to heart failure is multifactorial: parallel to the contributions of coexisting hypertension, diabetes mellitus, or coronary artery disease, decreased myocardial performance is at least partially attributable to metabolic effects. Weight excess and insulin resistance (IR), inherently linked to increased visceral adiposity, produce metabolic and proliferative alterations in cardiac myocytes and

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Abbreviations: BMI, Body mass index; E′, peak early diastolic mitral annular velocity; E, peak early diastolic mitral flow velocity; Em, peak early diastolic myocardial velocity; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; LV, left ventricular; OGTT, oral glucose tolerance test; PCO, polycystic ovary syndrome; Sm, peak systolic myocardial velocity; SRe, peak early diastolic strain rate; SRs, peak systolic strain rate; UAE, urinary albumin excretion.

interstitium, leading to disturbances of left ventricular (LV) function (2). The role of IR in the development of impaired cardiac function has been identified in several studies (2–6), although only a limited number of clinical studies have been performed in obesity without comorbidities.

A special subpopulation among obese females is that with polycystic ovary syndrome (PCO), in which the cardiovascular risk profile is particularly unfavorable (7, 8). PCO, characterized by chronic anovulation and hyperandrogenism, is commonly associated with hyperinsulinemia and IR, and may be accompanied by LV dysfunction (8, 9). The extent to which the hormonal and metabolic abnormalities of PCO might be synergistic in the causation of cardiac dysfunction has not been established. This issue seems particularly important because PCO is a frequent endocrine disorder in women of reproductive age, affecting up to 10% of this population (8), and because identification of the earliest asymptomatic impairment of LV performance may be important in preventing progression to overt heart failure.

Echocardiographic parameters of LV velocity and deformation may be used to detect preclinical alterations of LV function in various disease states, and are prognostically significant (10). In this study we used this technique to investigate the factors associated with LV function abnormalities in young obese females and specifically to evaluate the contribution of PCO to impaired LV performance in this population.

Patients and Methods

Patient selection

Between November 2003 and January 2006, we prospectively enrolled 150 women aged younger than 40 yr with a body mass index (BMI) of 30 kg/m^2 or more, referred to our hospitals for management of obesity, and, in a number of cases, oligo- or amenorrhea. Patients with any cardiovascular disorder (including hypertension), diabetes mellitus, thyroid and renal diseases, hypercortisolism, use of oral contraceptives or other hormonal therapy in the prior 3 months, pregnancy or breast-feeding, hyperprolactinemia, cigarette smoking, chronic alcohol consumption, or current use of any medications were excluded. Hypercortisolism was excluded on the basis of the measurement of urinary free cortisol, plasma adrenocorticotropic hormone, and circadian rhythm of cortisol secretion. Hypertension was excluded on the basis of a negative history, absence of antihypertensive treatment and normal blood pressure values ($<$140/90 mm Hg), diabetes mellitus, on the basis of normal fasting glucose and a 75-g oral glucose tolerance test (OGTT) (11), and subclinical hypothyroidism and renal impairment, on the basis of normal TSH and creatinine levels, respectively. Women were studied in the early follicular phase (2–5 d) of the menstrual cycle or after 3 months of amenorrhea. PCO was diagnosed according to the Rotterdam criteria in the presence of at least two of the following three features: oligo- or anovulation, hyperandrogenism, and polycystic ovaries (12).

Subjects were informed regarding the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the local ethics committees.

Clinical evaluation

Height, body weight, and hip and waist circumference were measured at a clinic visit after an overnight fast. Brachial blood pressure was obtained using standard sphygmomanometry with the subject in the sitting position. Measurements were repeated three times after at least 5 min of rest and then averaged.

Biochemical assays

All blood samples were drawn between 0800 and 0900 h after a 12-h fast and 30 min resting in the supine position. Serum glucose was analyzed using enzymatic assay (Dade Behring Inc., Newark, DE). Serum insulin, as well as testosterone, estradiol, LH, FSH, SHBG, and dehydroepiandrosterone sulfate were measured by chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA).

IR was estimated from the homeostasis model assessment (HOMA-IR), with values more than 2.5 considered indicative of IR (13). The OGTT was performed in each study participant, with serum glucose and insulin assessment 30, 60, 120, and 180′ thereafter. The highest value of serum insulin during the OGTT was regarded as a peak insulin level, and the sum of insulin concentrations obtained at 0–3 h was defined as the total insulin level (14). Both aforementioned OGTT-derived indices are increased in IR.

A 24-h urinary albumin excretion (UAE) was estimated by immunonephelometry (Behring Nephelometer, reagents from Dade Behring Diagnostics, Marburg, Germany) with a detection threshold of 1.8–2.3 mg/liter, and intraassay and interassay coefficients of variation of 2.2 and 2.6%, respectively.

Free androgen index, which is highly correlated with nonprotein-bound testosterone, was computed as the molar ratio of total testosterone to SHBG (15).

Conventional echocardiography

All women underwent a standard echocardiogram with harmonic two-dimensional and Doppler evaluation, using standard machines (Vivid 7 and System Five; General Electric Medical Systems, Horten, Norway). In most instances this was on the same day as the clinic review. Measurements of LV and left atrial dimensions and wall thicknesses were performed according to the recommendations of the American Society of Echocardiography (16). LV mass was derived from the modified American Society of Echocardiography cube formula and normalized for height to the power of 2.7 to obtain the LV mass index (17). A modified Simpson's biplane method was applied to calculate LV ejection fraction.

Pulsed-wave Doppler recordings of the LV inflow were obtained from the apical four-chamber view with the sample volume placed between the tips of the mitral leaflets. Peak early and late diastolic flow velocity, the ratio of peak early and late diastolic flow velocities, and deceleration time of early diastolic flow wave were evaluated.

Exercise echocardiography

Exercise two-dimensional echocardiograms were performed in women older than 35 yr old, for the exclusion of concurrent coronary artery disease. Patients underwent maximal treadmill stress, and ischemia was sought by comparison of baseline and post-stress images for the development of regional LV wall motion abnormalities.

Tissue Doppler imaging

Real-time color Doppler myocardial imaging data were acquired in the three apical views to evaluate LV longitudinal function. The image sector angle and imaging depth were adjusted to maximize frame rate. Pulse repetition frequency was set at the lowest level without aliasing. The ultrasound beam was aligned with the myocardial segment of interest to give an insonation angle less than 20°. Digital data were saved in a cine-loop format and transferred to a dedicated workstation (Echopac; General Electric Medical Systems) for off-line analysis. The sample volume was positioned in the center of each segment and tracked manually to keep a fixed mid-myocardial location throughout the heart cycle.

Myocardial velocities

Regional myocardial velocity curves were obtained from color Doppler of the basal interventricular septum to estimate peak systolic (Sm) and peak early diastolic velocity (Em). Pulsed-wave tissue Doppler recordings of the septal portion of the mitral annulus were used for the assess-

TABLE 1. Clinical characteristics of studied population

	PCO+ IR+ (n = 52)	PCO− IR+ (n = 42)	PCO− IR− (n = 54)	PCO+ IR+ *vs.* PCO− IR+	PCO+ IR+ *vs.* PCO− IR−	PCO− IR+ *vs.* PCO− IR−
Age (yr)	30.0 ± 6.2	31.1 ± 5.8	32.1 ± 5.2	NS	NS	NS
BMI (kg/m^2)	38.1 ± 9.5	38.3 ± 6.3	36.1 ± 5.5	NS	NS	NS
Waist circumference (cm)	111 ± 17	112 ± 17	109 ± 12	NS	NS	NS
Waist to hip ratio	0.92 ± 0.10	0.93 ± 0.07	0.91 ± 0.11	NS	NS	NS
Systolic blood pressure (mm Hg)	123 ± 10	124 ± 9	124 ± 8	NS	NS	NS
Diastolic blood pressure (mm Hg)	78 ± 8	78 ± 6	79 ± 7	NS	NS	NS
Heart rate (1/min)	72 ± 8	73 ± 8	73 ± 8	NS	NS	NS
Low-density lipoprotein (mmol/liter)	3.2 ± 0.8	3.4 ± 1.1	3.5 ± 0.8	NS	NS	NS
High-density lipoprotein (mmol/liter)	1.2 ± 0.2	1.2 ± 0.3	1.6 ± 0.3	NS	0.001	0.001
Triglycerides (mmol/liter)	1.8 ± 0.8	1.4 ± 0.5	1.4 ± 0.6	0.005	0.001	NS
Serum creatinine (μmol/liter)	63 ± 10	65 ± 9	65 ± 9	NS	NS	NS
Testosterone (nmol/liter)	2.9 ± 1.0	1.8 ± 0.9	1.9 ± 0.8	0.001	0.001	NS
Estradiol (pg/ml)	50.8 (46.3–65.7)	76.8 (49.9–191.0)	57.6 (37.3–124.0)	NS	NS	NS
LH (IU/liter)	6.6 (5.4–10.5)	4.5 (3.9–6.4)	4.6 (3.1–7.6)	NS	NS	NS
FSH (IU/liter)	5.9 ± 1.9	6.3 ± 2.2	6.9 ± 2.7	NS	NS	NS
DHEA-S (μmol/liter)	7.6 ± 3.7	5.8 ± 3.0	4.8 ± 2.9	NS	0.002	NS
Fasting glucose (mg/dl)	90 ± 6	91 ± 6	87 ± 8	NS	NS	NS
Glucose 120′ (mg/dl)	119 ± 29	120 ± 22	112 ± 27	NS	NS	NS
Peak insulin (mIU/liter)	143.0 (101.0–169.0)	116.5 (110.0–160.1)	57.8 (36.3–70.9)	NS	0.001	0.001
Total insulin (mIU/liter)	265.3 (164.5–363.0)	242.5 (198.1–267.5)	98.3 (67.7–133.9)	NS	0.001	0.001
HOMA-IR	4.11 ± 1.02	4.28 ± 1.32	1.64 ± 0.61	NS	0.001	0.001

DHEA-S, Dehydroepiandrosterone sulfate; NS, no significant difference.

ment of peak early diastolic mitral annular velocity (E′). The ratio of mitral inflow early diastolic velocity to the peak early diastolic annular velocity (E/E) was computed to approximate LV filling pressure.

Myocardial deformation

LV myocardial deformation curves were obtained from the apical, mid, and basal segments of each LV wall. Strain rate was assessed by measuring the spatial velocity gradient over a computation area of 12 mm. Subsequently, strain rate profiles were integrated over time to derive the natural strain curves using end diastole, defined by the R wave of the electrocardiogram. The analysis of LV deformation curves encompassed peak strain described as the greatest negative value on the strain curve, peak systolic strain rate (SRs), and peak early diastolic strain rate (SRe).

All strain, strain rate, and myocardial velocity profiles were averaged over three consecutive heart cycles. The results are expressed as the average values from all segments evaluated.

Feasibility of echocardiography

No obese female was excluded from the echocardiographic analysis because of poor imaging quality. Despite great care during acquisition, 7% of all LV segments were unsuitable for further analysis due to artifacts and signal noise.

Reproducibility of tissue Doppler measurements was estimated in 15 randomly selected subjects by two readers blinded to the patients' clinical data. The intraobserver and interobserver variations were 1.6 ± 1.2 and 1.8 ± 1.2% for strain, 0.1 ± 0.1 and 0.1 ± 0.1 sec^{-1} for SRs, 0.1 ± 0.2 sec^{-1} and 0.2 ± 0.2 sec^{-1} for SRe, and 0.2 ± 0.8 and 0.3 ± 0.7 cm/sec for myocardial velocities, respectively.

Statistical analysis

Results are presented as mean ± SD for normal and median (interquartile range) for skewed distribution. Group comparisons were performed by one-way ANOVA with Scheffé's *post hoc* test. Homogeneity of variances was assessed by the Levene test. Associations between variables were studied with Pearson's correlation coefficient and stepwise multiple regression analysis. Parameters with a P level less than 0.20 were considered in the multivariate models. Skewed variables were analyzed as log-transformed values. All calculations were accomplished with standard statistical software (STATISTICA for Windows 7 StatSoft, Inc., Tulsa, OK). $P < 0.05$ was accepted as statistically significant.

Results

Patient characteristics

The study population was divided into: 52 subjects with PCO and IR (PCO+ IR+ group, two PCO women had normal insulin sensitivity); 42 subjects without PCO and with IR (PCO− IR+ group); and 54 subjects without either PCO or IR (PCO− IR− group). The clinical data of these patients are summarized in Table 1.

Data reflecting hormones and metabolic control are listed in Table 1 and Fig. 1. All three groups showed significant differences with respect to free androgen index, which was the highest in the PCO+ IR+ and lowest in the PCO− IR− groups. The serum SHBG level was significantly higher in patients with normal insulin sensitivity as compared with the other two groups. Subjects from both groups with IR (*i.e.* PCO+ IR+ and PCO− IR+) had a significantly higher fasting, peak, and total serum insulin.

LV structure and function

The three groups did not differ regarding LV mass index, LV end-diastolic dimension, interventricular septum thickness, LV posterior wall thickness, and left atrial dimension (Table 2).

Systolic (strain and SRs) and diastolic LV function (SRe and Em) was impaired in both groups with IR as compared with PCO− IR− patients (Fig. 2). No significant differences were found among the studied groups in the conventional echocardiographic parameters. LV filling pressure (estimated by E/E′) was comparable in the three groups (Table 2).

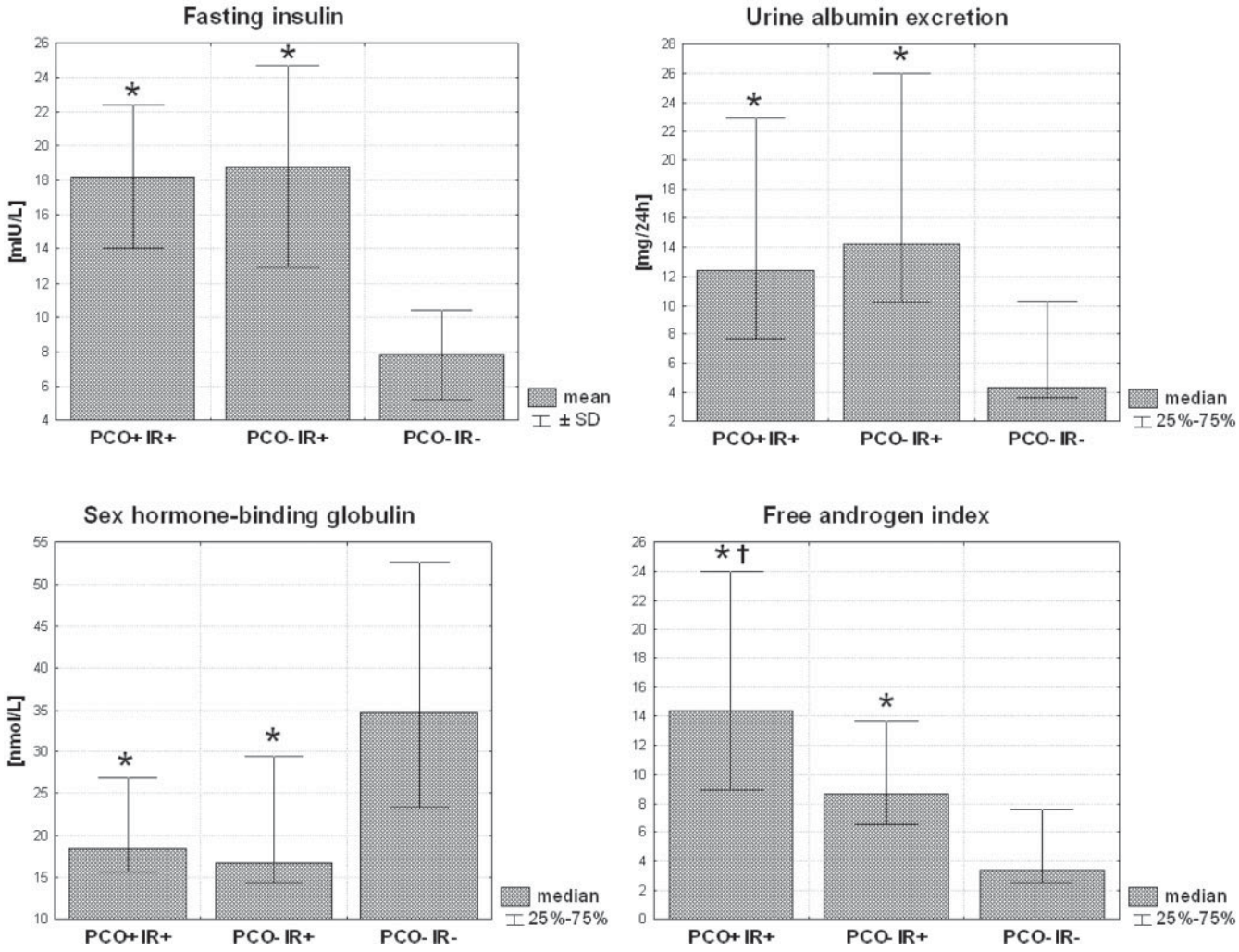

FIG. 1. Fasting insulin, urine albumin excretion, SHBG and free androgen index in the studied population. *, $P < 0.001$ *vs.* PCO− IR−; †, $P < 0.01$ *vs.* PCO− IR+.

Stepwise multiple regression models were developed to identify the independent associations of systolic and diastolic function (Tables 3 and 4). These models encompassed all factors significantly related to a dependent variable, and, additionally, waist circumference, waist to hip ratio, LV mass index, and blood pressure. The variables were put into the stepwise models in order of descending significance in the univariate analyses. Systolic function, measured by both strain (model adjusted $R^2 = 0.35$; $P < 0.0001$) and SRs (model $R^2 = 0.31$; $P < 0.0001$), was associated with fasting insulin, UAE, and BMI. Similar associations with BMI, UAE, and fasting insulin were seen with the diastolic parameters SRe (adjusted $R^2 = 0.29$; $P < 0.0001$) and Em (adjusted $R^2 = 0.25$; $P < 0.0001$).

Discussion

The main clinical findings of the present study are that fasting insulin, BMI, and UAE are among independent correlates of im-

TABLE 2. Conventional indices of cardiac morphology and function in studied population

	PCO+ IR+	PCO− IR+	PCO− IR−	PCO+ IR+ *vs.* PCO− IR+	PCO+ IR+ *vs.* PCO− IR−	PCO− IR+ *vs.* PCO− IR−
LV end-diastolic dimension (mm)	50 ± 4	50 ± 4	49 ± 5	NS	NS	NS
Interventricular septum thickness (mm)	11 ± 1	11 ± 1	10 ± 1	NS	NS	NS
LV posterior wall thickness (mm)	9 ± 1	9 ± 1	9 ± 1	NS	NS	NS
LV mass index (g/m$^{2.7}$)	46 ± 6	47 ± 10	46 ± 7	NS	NS	NS
LV ejection fraction (%)	68 ± 5	67 ± 6	68 ± 6	NS	NS	NS
Left atrial dimension (mm)	39 ± 3	39 ± 2	38 ± 3	NS	NS	NS
E/A	1.4 ± 0.4	1.4 ± 0.3	1.5 ± 0.4	NS	NS	NS
DT (msec)	204 ± 30	206 ± 31	201 ± 34	NS	NS	NS
E/E′	8.6 ± 2.4	8.9 ± 3.4	8.7 ± 1.9	NS	NS	NS

A, Peak late diastolic mitral flow velocity; DT, deceleration time of early diastolic flow wave; NS, no significant difference.

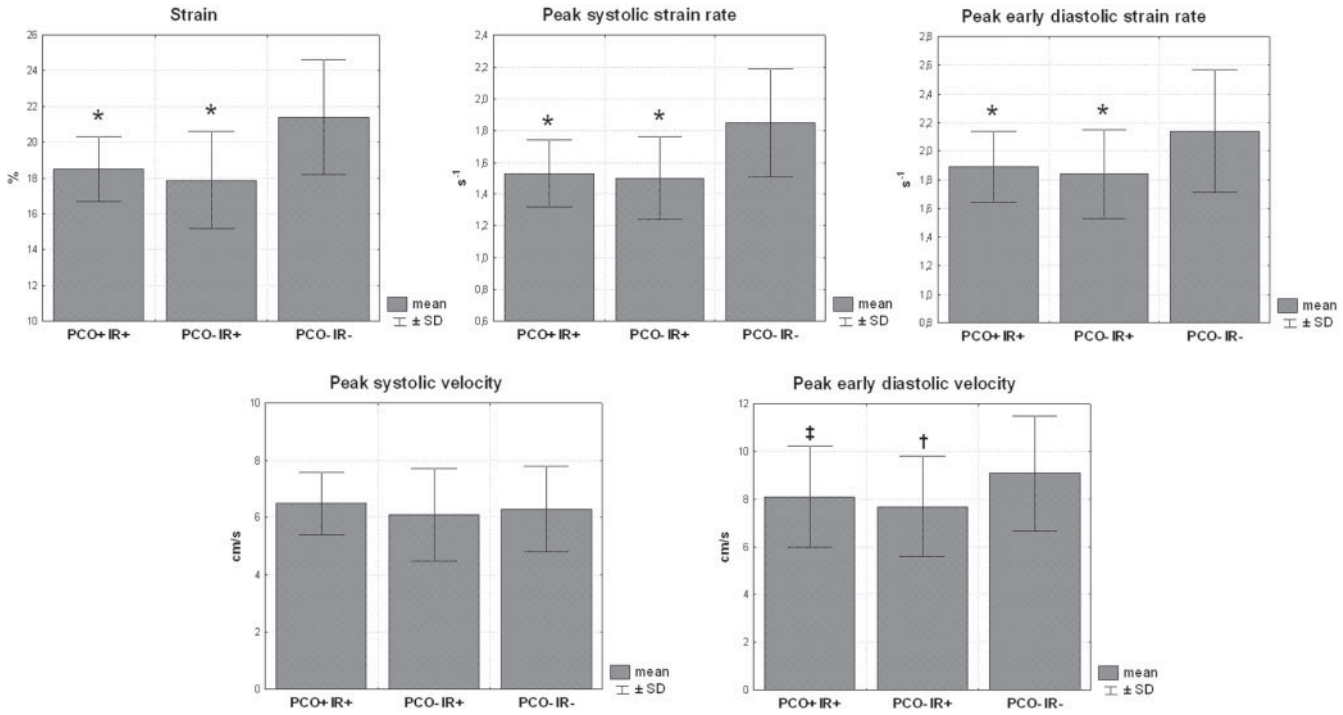

FIG. 2. Myocardial deformation parameters and myocardial velocities in the studied population. *, $P < 0.001$; †, $P < 0.01$; ‡, $P < 0.05$ *vs.* PCO− IR−.

paired LV function in young obese women, even in the pre-microalbuminuric stage, and that the contribution of the coexisting PCO to disturbances of LV function is linked to IR, rather than hormonal aberrations associated with this condition.

Weight excess and IR

Various mechanisms contribute to LV dysfunction in obesity, including lipotoxicity associated with cardiac steatosis and lipoapoptosis, alterations in fatty acid metabolism, overproduction of cardioinhibitory cytokines, up-regulation of some neurohormones (especially angiotensin II), myocardial fibrosis and chronic overload with LV dilatation and hypertrophy, and increased oxygen consumption (2, 3, 6, 18). IR may represent a relevant link between obesity and LV dysfunction. Elevated insulin levels, which are an inherent part of IR, stimulate myocyte growth and interstitial fibrosis, leading to sodium retention with subsequent blood volume increase, and activate the sympathetic nervous system, exerting deleterious effects on cardiac performance (3, 6, 19). Moreover, alterations in myocardial metabolism, including progressive increases in fatty acid turnover, resulting from inadequate insulin action, may precipitate impaired LV contractility (2).

In the present study, we found impaired LV systolic and diastolic longitudinal function in the PCO+ IR+ and PCO− IR+ groups, as compared with women with normal insulin sensitivity. The severity of LV function abnormalities was related to the magnitude of weight excess and IR. Fasting insulin was an independent correlate of both systolic and diastolic impairment, with stronger correlations than the peak and total insulin measured during the OGTT or HOMA-IR. Our findings are in agreement with previous reports showing relationships between LV systolic and diastolic dysfunction and various measures of IR (3, 6, 20). In contrast, conventional echo techniques (such as Doppler indices of mitral inflow or LV fractional shortening) show inconsistent associations with IR (21–24), perhaps due to insufficient sensitivity as well as the influence of hemodynamic load.

TABLE 3. Significant correlates of LV systolic function parameters

	SRs		Strain	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Waist circumference	$r = -0.23$; $P < 0.02$		$r = -0.27$; $P < 0.01$	
BMI	$r = -0.24$; $P < 0.01$	$\beta = -0.24$; $P < 0.01$	$r = -0.25$; $P < 0.01$	$\beta = -0.22$; $P < 0.03$
Fasting insulin	$r = -0.41$; $P < 0.001$	$\beta = -0.34$; $P < 0.001$	$r = -0.44$; $P < 0.001$	$\beta = -0.39$; $P < 0.001$
Peak insulin	$r = -0.30$; $P < 0.001$		$r = -0.28$; $P < 0.01$	
Total insulin	$r = -0.34$; $P < 0.001$		$r = -0.32$; $P < 0.001$	
HOMA-IR	$r = -0.38$; $P < 0.001$		$r = 0.41$; $P < 0.001$	
UAE	$r = -0.45$; $P < 0.001$	$\beta = -0.33$; $P < 0.001$	$r = 0.42$; $P < 0.001$	$\beta = -0.36$; $P < 0.001$
SHBG	$r = 0.38$; $P < 0.001$	$\beta = 0.21$; $P < 0.03$	$r = 0.30$; $P < 0.001$	
FAI	$r = -0.27$; $P < 0.01$		$r = -0.20$; $P < 0.04$	

FAI, Free androgen index.

TABLE 4. Significant correlates of LV diastolic function parameters

	SRe		Em	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Waist circumference	$r = -0.31$; $P < 0.001$		$r = -0.38$; $P < 0.001$	
BMI	$r = -0.31$; $P < 0.001$	$\beta = -0.23$; $P < 0.02$	$r = -0.41$; $P < 0.001$	$\beta = -0.39$; $P < 0.001$
Fasting insulin	$r = -0.40$; $P < 0.001$	$\beta = -0.24$; $P < 0.02$	$r = -0.32$; $P < 0.001$	$\beta = -0.19$; $P < 0.04$
Peak insulin	$r = -0.24$; $P < 0.01$		$r = -0.11$; $P < 0.25$	
Total insulin	$r = -0.27$; $P < 0.001$		$r = -0.09$; $P < 0.35$	
HOMA-IR	$r = -0.37$; $P < 0.001$		$r = -0.28$; $P < 0.01$	
UAE	$r = -0.40$; $P < 0.001$	$\beta = -0.35$; $P < 0.001$	$r = -0.31$; $P < 0.001$	$\beta = -0.25$; $P < 0.01$
SHBG	$r = 0.37$; $P < 0.001$	$\beta = 0.20$; $P < 0.04$	$r = -0.22$; $P < 0.03$	
FAI	$r = -0.25$; $P < 0.01$		$r = -0.09$; $P < 0.35$	

FAI, Free androgen index.

We do not believe that loading materially influenced our myocardial velocity and deformation endpoints, which are less load sensitive than conventional methods. In addition, each group had a similar degree of obesity and abdominal fat distribution, and similar loading conditions (evidenced by LV end-diastolic and left atrial dimension).

UAE

UAE is related to IR and hyperinsulinemic states (25, 26), and in our study was independently related to impaired LV systolic and diastolic function. This association was demonstrated for UAE less than 30 mg/24 h (*i.e.* below the threshold for microalbuminuria), suggesting that subtle increments in urine albumin content may be of clinical relevance, a finding concordant with the Prevention of REnal and Vascular ENdstage Disease study (25).

The mechanism linking UAE and IR is conjectural. Insulin can produce dilatation of the renal arteries with subsequent increase in intraglomerular pressure and glomerular filtration rate that may result in elevated UAE (25, 27). Nonetheless, this explanation seems inadequate because serum insulin levels were considered in our multivariate models and did not render UAE insignificant. There is a close link between IR and coexisting generalized vascular endothelial dysfunction (28), thought to be reflected by UAE. This may parallel the impairment of myocardial performance and could be a reason why UAE correlates with cardiac deformation parameters. Therefore, UAE may be a marker of the extent of systemic abnormalities, including both endothelial and myocardial dysfunction.

SHBG

There is an inverse association between SHBG and IR across various subsets of women, including those with PCO (15, 29). The lower levels of SHBG in both groups with IR are consistent with insulin exerting a direct supressive effect on SHBG (30). However, the involvement of SHBG may extend beyond IR, given that SHBG has been shown to correlate with strain rate parameters after controlling for insulin levels. SHBG might modulate LV myocardial function through its participation in the metabolism of lipoproteins (31) and in a signal transduction of sex hormones (32).

PCO

Our data suggest that a cluster of PCO-related factors potentially affecting myocardial performance, including hormonal aberrations, do not make a significant contribution to LV function impairment, in excess of that associated with IR. Prior reports on LV function in PCO provided divergent results demonstrating normal (33) or impaired cardiac performance (8, 34). In the paper by Orio *et al.* (8), LV function disturbances in women with PCO were revealed in relation to the referents with very low HOMA-IR values indicating normal insulin sensitivity. Similarly, significant differences in cardiac function parameters between groups with and without PCO, but with different IR status (PCO+ IR+ and PCO− IR−), were demonstrated also in our study. Finally, it should be emphasized that our finding cannot be simply extrapolated to older PCO groups with longer duration of the disease, or to PCO patients without excess body weight.

Androgens may have a detrimental effect on LV function in females (35, 36). However, when adjusted for other variables, the androgen excess demonstrated in the PCO+ IR+ group and to a lesser extent in the PCO− IR+ group was not a significant contributor to the impairment of LV function in our study. However, the free androgen index used in the analysis was calculated based on SHBG levels and may not correspond accurately to direct measures of free testosterone.

Limitations

This study has several limitations. First, its cross-sectional nature precludes the ability to describe causal relations, but this should not detract from the fact that functional changes appear not to be linked with hormonal aberrations. Second, we did not consider the duration of obesity as a potential determinant of LV function impairment because patient history regarding this feature is often imprecise and unreliable. Third, neurohormonal and cytokine activation, which were not measured, were likely increased in obese patients and potentially influence LV function. Fourth, although fasting and post-glucose insulin levels as well as HOMA-IR are validated surrogate markers of IR, they cannot offer the same information as the hyperinsulinemic clamp being a "gold standard" of IR assessment. Likewise, 24 h urine albumin measurements may be colored by under- or over-collection, and are less accurate than an albumin to creatinine ratio, which was not obtained in all subjects. Finally, although coronary artery disease was not excluded in all study patients, it is unlikely that this was a contributor, given the group's young age, lack of symptoms, negative family history, and negative exercise echocardiograms in older subjects.

Conclusions

Asymptomatic impairment of LV function in young women is associated with obesity and IR rather than the sex hormone disturbances associated with PCO. The recognition of myocardial dysfunction in these patients may justify the implementation of an appropriate heart failure prevention strategy, perhaps including attempts to improve insulin sensitivity.

Acknowledgments

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