Clinical research

Effects of insulin on left ventricular function during dynamic exercise in overweight and obese subjects

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Aims We designed this study in order to determine the effect of insulin on cardiac function in overweight and obese subjects during exercise.

Methods and results The cardiac function of 62 normal glucose tolerant subjects, aged 30–40 and divided into normal weight (group 1, n = 22, BMI 20–24.9 kg/m²), overweight (group 2, n = 20, BMI 25–29.9 kg/m²), and obesity (group 3, n = 20, BMI 30–35 kg/m²) was evaluated at rest and during dynamic exercise through angiocardiodynamics, when on hyperinsulinaemic euglycaemic clamp (test A) and when on normal saline infusion (test B). Left ventricular function at rest was statistically greater (P < 0.05) in both tests in overweight and obese subjects compared with normal weight controls, with no statistical difference (P = 0.057) within groups between insulin and normal saline infusion. During exercise, cardiac function improved in all the subjects in both tests. The increase was lower in overweight and obese patients, even if statistically significant only in obese vs. control subjects in both tests (P < 0.05). Insulin sensitivity showed a significant correlation (P < 0.001) with left ventricular ejection fraction (LVEF) at rest and with change in LVEF during clamp.

Conclusion Our findings suggest a metabolic pathogenesis for the impaired LV function in obesity.

Introduction

The effect of insulin on cardiac function has been well documented. The increase of circulating insulin, induced through endovenous infusion,1 mixed meal,2 or oral glucose tolerance test (OGTT),3 is followed by an increase in left ventricular ejection fraction (LVEF). Moreover, the administration of glucose–insulin–potassium solution can raise LVEF in patients with acute myocardial infarction,4 while subjects with chronic heart failure increase their cardiac output when on insulin infusion.5 On the other hand, in insulin-resistant obese humans, the OGTT-induced increase in cardiac output is impaired when compared with controls.6 Similarly, rest-LVEF is significantly lower in diabetic than in healthy subjects during insulin infusion.7 Lastly, findings show that chronic heart failure is associated with insulin resistance, and there is a significant correlation between cardiac output and insulin sensitivity.8

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In contrast, little is known about the effects of insulin during exercise. We previously showed that an increase of LVEF during submaximal work in a hyperinsulinaemic state in both normal and diabetic humans, and that the rise is significantly lower in diabetic subjects. A recent study confirmed the association between chronic heart failure and insulin resistance, and was the first to show that exercise training can improve glucose uptake in such patients.

Obesity represents an independent risk factor for congestive heart failure. A recent re-examination of 5881 participants in the Framingham Heart Study showed that there was a 5% increase in the risk of heart failure for men and 7% for women for each 1 kg/m² increase in BMI. When compared with subjects with normal BMI, obese subjects had double the risk of heart failure. These findings are indirectly confirmed by the observation that subclinical left ventricular diastolic dysfunction is present in every degree of isolated obesity, including overweight, and that it correlates with BMI. Subclinical left ventricular diastolic dysfunction may represent an early sign of the negative impact of the obesity per se on the heart.

On the other hand, various studies observed an increased systolic function at an early stage of obesity. These precocious impairments are clinically relevant, but available data offer no clear pathogenetic interpretation of the cardiovascular risk in obese subjects.

The current study was designed to examine the effect of insulin on cardiac function during exercise in lean insulin-sensitive and overweight/obese insulin-resistant humans. We recruited three groups of subjects (lean, overweight, and obese) for a better understanding of the interaction between cardiac function, insulin action, and insulin sensitivity. In other words, our aim was to clarify the direct effect of insulin and insulin resistance per se on cardiac function and eventually to find degrees of this effect.

Methods

Subjects

The study was approved by the medical ethics committee at the Second University of Naples and conducted in accordance with the Declaration of Helsinki.

All patients were recruited from the outpatient clinics dedicated to obesity, endocrinology, cardiology, and gastroenterology of the Second University of Naples over 8 months. From about 1000 consecutive patients, we selected 62 subjects according to the inclusion/exclusion criteria. After informed written consent, the 62 subjects were enrolled. Inclusion criteria were age between 30 and 40 years, BMI between 25 and 34.9 kg/m², with a history of excess fat of at least 5 years (or BMI between 25 and 34.9 kg/m² for lean controls), and normal glucose tolerance to OGTT, according to ADA criteria. Exclusion criteria were smoking, alcohol abuse, arterial hypertension (blood pressure $\geq 130/85$ mmHg), dyslipidaemia (HDL cholesterol $<1.03$ mmol/L in male and $<1.3$ mmol/L in women, triglycerides $>1.7$ mmol/L), family history of diabetes mellitus, signs, symptoms or history of cardiovascular diseases, hepatic or renal disease, anaemia, electrolyte or endocrine impairments.

All patients underwent cardiovascular screening through treadmill exercise testing and echocardiography. Subjects with ECG abnormalities at rest, and/or with down-sloping or horizontal ST segment depression during a treadmill maximal exercise electrocardiography performed according to the Bruce protocol, and/or with left ventricular segmental asynergy or hypertrophy assessed by M-mode and two-dimensional echocardiography, and/or with rest, and/or stress myocardial perfusion imaging performed after infusion of 3 mCi of $^{201}$TI suggestive of ischaemic heart disease were not enrolled.

The participants were taking no chronic drug therapy, and were engaged in similar physical activity.

The restrictive selection criteria were chosen to warrant sufficient comparability of the patients, at least for the characteristics influencing the functions we aimed to investigate.

Protocol

Subjects underwent two multiple-gated radionuclide ventriculographies, one during hyperinsulinaemic euglycaemic clamp (test A) and the other during infusion of normal saline (test B).

The studies were performed on two different occasions, 5–10 days apart, in the morning after an overnight fast of 10–12 h. Weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured and BMI was calculated as body weight divided by height squared. The waist circumference measurement was taken at the mid-point between the lower rib margin and the iliac crest. The consumption of coffee, tea, and alcohol was avoided for 12 h before and during each study. The participants were supine in a quiet room at 20°C. The left arm was utilized for blood pressure measurements, while two venous cannula in right arm veins were used, respectively, for the blood samples and the infusions, as previously described.

In test A, the clamp was started with a primed infusion of insulin (Humulin R; Eli Lilly, Basingstoke, UK) at the rate of 4 mU/kg/min for 8 min, followed by a constant infusion rate of 1 mU/kg/min. After 4 min, a variable rate 20% glucose solution was added and its infusion rate was adjusted manually to maintain the blood glucose concentration at 80 mg/dL, with a coefficient of variation of $<5\%$. K$_2$HPO$_4$ was also added to prevent hypokalaemia and hypophosphataemia. Glucose monitoring was carried out at bedside every 5 min. In test B the saline load was matched to the overall volume received during test A for each patient to avoid any difference in the preload.

After obtaining a basal blood sample, infusion was started and maintained for 120 min in both tests. Afterwards, scintigraphic acquisition at rest was made and then, exercise started without stopping infusion. The stress consisted of supine dynamic exercise on a bicycle ergometer, beginning with 25 W at 60 rpm and increasing by 25 W steps over 2 min until reaching the 75 W load. This work was maintained for 4 min for the stress scintigraphic scan.

ECG standard record and blood pressure values, calculated as the average of two measurements, were taken at basal conditions, before starting exercise, and at each step during exercise. ‘In vivo’ labelled red blood cells were used for radionuclide angiography, and the studies were carried out as previously described, with parameter evaluation at rest and at 75 W. Left ventricular end diastolic volume (LVEDV) and peak filling rate (PFR) were calculated by the Massardo et al. method.

Blood samples were taken at 0, 60, 120 min, and at the end of each work step for the determination of glucose, insulin, potassium, adrenaline, and noradrenaline.

Analytical methods

Plasma glucose was measured by the glucose oxidase method (Beckman glucose analyzer II,Fullerton, CA, USA). Plasma
insulin was assessed with a standard double antibody radioimmunoassay technique with the sensitivity of the insulin assay being <18 pmol/L (INCSTAR Corporation, Stillwater, MN, USA). Plasma adrenaline and noradrenaline were determined by high-performance liquid chromatography. Bedside plasma glucose monitoring was carried out with Accu-Chek Compact (Roche Diagnostics, Mannheim, Germany). For calculation of insulin sensitivity, a steady state condition was assumed during the second hour of the clamp. Insulin sensitivity, expressed as whole-body glucose utilization (M index, mg/min kg of body weight), was calculated from the infusion rate of exogenous glucose during the second hour of the insulin clamp period divided by the mean insulin concentration.18

Statistical analysis
Quantitative variables are expressed as mean ± SD, unless otherwise stated. Subjects were classified into three groups on the basis of the BMI: 20–24.9 kg/m² (group 1, n = 22, controls); 25–29.9 kg/m² (group 2, n = 20); 30–35 kg/m² (group 3, n = 20).

Basal comparisons between the three groups were tested with analysis of variance (ANOVA). To reduce the possibility of type I error, post hoc testing was undertaken using the Bonferroni multiple comparisons test. The sample size was calculated on change in LVEF. On the basis of a coefficient of variation /C20/2.5, a minimum of nine patients per group was necessary to detect a difference of 25%, with a power of 90%, and /α = 0.05 (two-sided), while a minimum of 17 patients per group was necessary to detect a difference of 15%, with a power of 80%, and /α = 0.05 (two-sided). Comparisons between test A and test B were made using repeated measures ANOVA. The null hypothesis was that the effect of the test (A vs. B) would be the same in the different groups. Subject was included as a random effect, body type (lean, overweight, and obese) was used as a grouping factor, while infusion solution (glucose–insulin or saline) was treated as repeated measures so that comparisons were assessed as interaction between two main effects (group and test).

Correlations were estimated through Pearson's coefficients. All tests were two-sided and a P-value <0.05 was considered statistically significant. All statistical analysis were performed using the Statistical Package Software System 8.0 for Windows (SPSS, Chicago, IL, USA).

Results
Baseline characteristics of the three groups are presented in Table 1. Except for the BMI (P < 0.001) and the waist circumference (P < 0.001), no significant difference was observed in the other parameters. In particular, no difference in left ventricular mass corrected for body surface area (LVM/BSA) was evident (P = 0.677). No significant difference was found in heart rate and systolic and diastolic blood pressure among the three groups during test A and test B, and between the two tests. None of the subjects experienced chest pain or ECG abnormalities during the exercise in either test.

Metabolic/hormonal parameters
Test A
During investigations, plasma glucose concentration was kept approximately at the normal fasting level (clamp level of 80 mg/dL, with a coefficient of variation <5%) and none of the subjects experienced hypoglycaemia (<50 mg/dL). Plasma glucose and potassium were similar among groups during the whole test duration (Figure 1) (Table 2). Plasma insulin levels were
significantly ($P < 0.01$) higher in overweight and obese patients than in control subjects at all times (Figure 2) (Table 2). M index was significantly lower ($P < 0.001$) in obese and overweight groups than in normal weight group (Table 2). Rest- and stress-adrenaline and noradrenaline concentrations were not statistically different among the three groups (Table 3).

**Test B**
No significant difference was found in serum glucose and potassium levels among groups during the whole test duration. Plasma insulin was significantly ($P < 0.001$) different in the three groups, with an increasing linear trend among the three groups (Table 2). Similar rest and stress adrenaline and noradrenaline responses were observed in the three groups (Table 3).

**Test A vs. test B**
Neither group experienced any significant difference in plasma glucose and potassium values. Similar rest- and stress-adrenaline and noradrenaline concentrations were found between the two tests (Table 3). Plasma insulin levels were significantly ($P < 0.001$) higher during test A than during test B (Table 2).

**Angioscintigraphic parameters**
Each subject showed a normal (>50%) LVEF at rest and in response to exercise, when all of them achieved 75–80% of the maximal ideal heart rate (Figure 3).

**Test A**
Rest-LVEF was significantly higher (Table 4) ($P < 0.05$) in obese and overweight subjects than in normal weight controls. Stress-LVEF was similar in the three groups, while the change in LVEF was lower in overweight and obese patients, even if significant ($P < 0.05$) only in obese subjects. Rest- and stress-LVEDV did not significantly differ among the groups. Resting and exercise-

**Test B**
Rest-LVEF was significantly higher (Table 4) ($P < 0.01$) in the obese and overweight groups when compared with controls. Stress-LVEF was not statistically different among the three groups, while the change in LVEF was significantly ($P < 0.05$) lower in obese subjects than in

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**Table 2 Metabolic parameters during clamp (test A) and saline (test B)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test A Lean</th>
<th>Test A Overweight</th>
<th>Test A Obese</th>
<th>Test B Lean</th>
<th>Test B Overweight</th>
<th>Test B Obese</th>
<th>Interaction between test and group (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG at 0 min (mg/dL)</td>
<td>85.4 ± 2.1</td>
<td>84.6 ± 2.7</td>
<td>85.5 ± 4.2</td>
<td>85.9 ± 2.9</td>
<td>84.8 ± 3.2</td>
<td>85.5 ± 4.2</td>
<td>0.607</td>
</tr>
<tr>
<td>PG at 120 min (mg/dL)</td>
<td>77.9 ± 5.4</td>
<td>78.1 ± 2.3</td>
<td>79.6 ± 6.4</td>
<td>78.4 ± 5.0</td>
<td>77.6 ± 2.8</td>
<td>80.2 ± 5.6</td>
<td>0.489</td>
</tr>
<tr>
<td>PI at 0 min (mU/mL)</td>
<td>4.6 ± 0.9</td>
<td>7.4 ± 0.7</td>
<td>9.3 ± 0.9</td>
<td>4.7 ± 0.8</td>
<td>7.4 ± 0.7</td>
<td>9.5 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PI at 120 min (mU/mL)</td>
<td>73.9 ± 3.2</td>
<td>76.7 ± 3.0</td>
<td>79.5 ± 3.0</td>
<td>4.7 ± 0.8</td>
<td>7.4 ± 0.8</td>
<td>9.4 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M (mg/min kg)</td>
<td>6.3 ± 0.3</td>
<td>4.1 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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Data are expressed as mean ± SD. PG, plasma glucose; PI, plasma insulin.
*aInteraction between test (within-subjects effect) and group (between-subjects effect).*

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Figure 2. Insulin plasma levels during test A (up) and test B (down).
controls. No significant difference was found for rest- and stress-LVEDV in the three groups. Resting and exercise-PFR were significantly \( P < 0.001 \) lower in overweight and obese subjects.

Test A vs. test B
No statistical difference \( (P = 0.734) \) was found in rest-L VEF between the two tests. Stress-L VEF was significantly \( P < 0.001 \) higher during insulin than during saline infusion. Change in L VEF was significantly \( P < 0.001 \) higher during test A than in test B. Rest- and stress-LVEDV, and rest- and stress-PFR were similar in the two tests.

Correlations

The \( M \)-value showed a negative correlation with rest-L VEF \( (r = -0.408, P = 0.001) \) (Figure 4) and a positive correlation with change in L VEF \( (r = 0.481, P < 0.001) \) (Figure 5).

As expected, the \( M \)-value correlated with BMI \( (r = 0.945, P < 0.001) \) and waist circumference \( (r = -0.850, P < 0.001) \). BMI and waist circumference were also correlated with rest-L VEF and change in L VEF (BMI: \( r = 0.353, \) P = 0.005 and \( r = -0.485, P < 0.001 \), respectively; waist circumference: \( r = 0.322, P = 0.011 \) and \( r = -0.414, P = 0.01 \), respectively). All correlations were significant at the 0.01 level (two-tailed).

Discussion

This study explored the effect of insulin on cardiac function, at rest and in response to dynamic exercise in lean, overweight, and obese subjects. The aim of our investigation was to test a possible pathogenic explanation of the cardiac impairments affecting obese patients, pointing out their metabolic characteristics.

In fact, while subclinical or clinical cardiac function abnormalities in obesity have already been known for several years, data about pathogenic mechanisms are still inconclusive. In agreement with the literature,\textsuperscript{13} we found that obese and overweight patients had an impaired diastolic function compared with healthy subjects, both at rest and during exercise, as evaluated by PFR. Moreover, insulin–glucose infusion did not modify these diastolic parameters in the groups.

Overweight and obese subjects showed higher rest-L VEF, but a lower exercise-induced change in L VEF compared with normal weight controls, even if all of them reached normal physiological post-exercise L VEF levels. These results are in agreement with previous studies, demonstrating that obese people have higher systolic ventricular function at rest,\textsuperscript{12,14} and that they showed a reduced ventricular performance during exercise.\textsuperscript{19} On the contrary, other studies showed that obesity does not influence L VEF\textsuperscript{20} or is associated with reduced L VEF.\textsuperscript{21} The discrepancy between these results suggests that left ventricular systolic function is affected late in the course of obesity, while the increased L VEF in slightly or moderately obese patients may provide an initial compensatory mechanism.\textsuperscript{12,14} Similarly, our results agree with previous studies\textsuperscript{12,14} in demonstrating a positive correlation between indices of left ventricular function at rest and indices of insulin resistance in obese subjects.
We found no difference in angiographic parameters between insulin and saline infusion at rest in normal weight subjects, overweight, or obese patients. Change in L VEF was greater when exercise was performed during insulin infusion than during saline infusion in all the groups, demonstrating that insulin can increase cardiac function. This action is reduced, however, in overweight and obese subjects. As the M index showed a significant correlation with rest-L VEF and change in L VEF, it can be hypothesized that metabolic insulin resistance is coupled to cardiac insulin resistance. The best way to measure insulin resistance is by clamp, but this is too laborious for a routine clinical setting. BMI and waist circumference can instead be simply and rapidly measured for any patient so they may be preferred in a clinical setting.

In summary, this is the first study to show that, in overweight and obese people, insulin affects neither diastolic parameters, nor ventricular systolic function at rest, while it is capable of ameliorating post-exercise L VEF, with the increase being correlated with insulin resistance. Insulin may influence cardiac function by several indirect mechanisms. To avoid hypoglycaemia we used euglycaemic hyperinsulinaemic clamp. The insulin infusion level was not high enough to determine a significant increase in plasma levels of adrenaline and noradrenaline. Vasodilatation was not significant, as demonstrated by the similar systolic and diastolic blood pressure values obtained during insulin and saline infusion. Finally, as rest- and stress-LVEDV, and rest- and stress-PFR were not statistically different between test A and test B, it can be argued that preload was

<table>
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<th>Table 4 Angioscintigraphic parameters during clamp (test A) and saline (test B)</th>
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<tr>
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<tr>
<td>R-LVEF (%)</td>
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<td>S-LVEF (%)</td>
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<tr>
<td>Change in LVEF (%)</td>
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<tr>
<td>R-LVEDV (mL)</td>
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<tr>
<td>S-LVEDV (mL)</td>
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<tr>
<td>R-PFR (LVEDV/sec)</td>
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<td>S-PFR (LVEDV/sec)</td>
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</tbody>
</table>

Data are expressed as mean ± SD. R-LVEF, rest-left ventricular ejection fraction; S-LVEF, stress-left ventricular ejection fraction; R-LVEDV, rest-left ventricular end diastolic volume; S-LVEDV, stress-left ventricular end diastolic volume; R-PFR, rest-peak filling rate; S-PFR, stress-peak filling rate.

<sup>a</sup>Interaction between test (within-subjects effect) and group (between-subjects effect).

![Figure 4](image1.png)  
**Figure 4** Correlation between M and rest-LVEF: n = 62, r = −0.408, P (two-tailed) = 0.001.

![Figure 5](image2.png)  
**Figure 5** Correlation between M and change in LVEF: n = 62, r = 0.481, P (two-tailed) < 0.001.
comparable during the two tests. Therefore, the absence of significant differences in afterload, preload, and sympathetic drive in the two tests, suggests that the increase in ejection fraction during exercise during clamp is an expression of the hormone’s direct effect on the heart.

Except for obesity, the other four parameters used for the diagnosis of the metabolic syndrome were preliminarily excluded in all the enrolled subjects, in order to minimize the interference of different metabolic parameters on the effect of hyperinsulinaemia.

According to the strict inclusion criteria, the subjects had to be affected by ‘isolated’ obesity or overweight, thus excluding other factors that could influence the impaired response to exercise during hyperinsulinaemia.

In consideration of the difficulty in recruiting this group of patients, the number of enrolled subjects is relatively large. Insulin resistance, a condition generally associated with obesity, could represent the pathogenetic link between metabolic impairment and cardiovascular morbidity in obese patients.

We already hypothesized a relationship between left ventricular function and metabolic effects of insulin. In fasting healthy subjects at rest, heart muscle takes up significant amounts of free fatty acids. Otherwise, physiological hyperinsulinaemia specifically enhances myocardial glucose, lactate, and pyruvate uptake, converting cardiac fuel reliance from fat to carbohydrate.

A similar shift of circulating substrate uptake and oxidation by the heart has been observed during atrial pacing.

Moreover, during physical exercise lactate becomes the most important source of energy for the heart. These findings suggest that hyperinsulinaemia during dynamic stress may increasingly favour myocardial carbohydrate oxidation and, consequently, improve cardiac performance in healthy subjects. On the contrary, the same relationship between heart metabolism and cardiac function could account for an impaired left ventricular function in insulin resistance conditions like obesity and overweight. Dynamic exercise performed during a hyperinsulinaemic state can be considered an ‘extreme’ test that, through the combination of two conditions favouring the switch to carbohydrate as myocardial energy source, is potentially useful to reveal a ventricular dysfunction because of an impaired heart metabolism.

In a previous study, we showed that high levels of circulating insulin in healthy humans do not modify LVEF at rest, but significantly increase it in response to a submaximal work. Interestingly, in the same conditions of hyperinsulinaemia, patients with type 2 diabetes mellitus do not increase LVEF during dynamic exercise. This difference could be justified by the insulin resistance, as suggested by the significant linear correlation between LVEF and the index of insulin sensitivity.

This relationship seems to be confirmed by this study, performed on another model of insulin resistance. Moreover, it has been found that insulin has an independent effect on lactate oxidation in the canine heart, suggesting the direct activation of pyruvate dehydrogenase.

Ferrannini et al. observed in humans that physiological hyperinsulinaemia doubles the heart’s lactate extraction rate. Therefore, a faulty pyruvate dehydrogenase may lead to deranged systolic left ventricular function during insulin resistance such as obesity.

Conclusions

Our findings originally suggest a metabolic pathogenesis for the impaired left ventricular function in obesity. This ventricular dysfunction could set the stage for heart failure. Therefore, improved left ventricular function after weight loss observed in obese subjects might be interpreted as an improved insulin effect on metabolism and cardiac function. Further investigations are necessary to confirm the relationship between insulin resistance and left ventricular dysfunction in obesity.

Acknowledgement

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References


