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**Research Article**

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# Myocardial Insulin Resistance in Patients with Syndrome X

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## Abstract

**Insulin resistance is common in patients with angina pectoris, a positive exercise electrocardiogram, and normal coronary angiograms (syndrome X). It is still not known whether insulin resistance affects the cardiac muscle itself and, if so, whether insulin resistance involves myocardial hemodynamics and energy metabolism. We investigated hemodynamics as well as metabolite exchanges across the heart and the forearm in eight patients with syndrome X and eight control subjects during a baseline period after an overnight fast and during a hyperinsulinemic–euglycemic clamp. Myocardial hemodynamics and metabolism were studied at rest, during pace stress, and in the recovery period after pacing. Neither coronary sinus blood flow nor forearm blood flow differed between the groups before and during the clamp. Whole body insulin–stimulated glucose uptake was decreased in the patients (15.6±2.1 vs. 23.1±2.0 μmol × $kg^{-1}$ × $min^{-1}$). Insulin-stimulated glucose uptake in the forearm and the cardiac muscle was equally reduced in the patients (46±5 and 48±5%). Myocardial glucose uptake correlated with total arterial delivery in the control subjects ($r = 0.63$, $P < 0.01$), but not in patients ($r = 0.22$, $P = 0.13$). Carbohydrate and lipid oxidation was similar in the two groups at rest, and changes during the clamp were not different in control subjects and patients either at rest, during pacing, or in the recovery period. Patients with syndrome X exhibit myocardial insulin resistance, but cardiac energy metabolism remains unaffected. In patients with syndrome X, insulin-stimulated glucose uptake is independent from myocardial blood flow. (*J. Clin. Invest.* 1997. 100:1919–1927.) Key words: angina pectoris • metabolism • microcirculation • skeletal muscle • cardiac muscle**

## Introduction

Insulin resistance is common among patients with angina pectoris and angiographically normal coronary arteries, an entity referred to as the cardiac syndrome X when associated with a positive exercise test (1–3). When the rate of insulin-stimulated glucose uptake is measured under euglycemic–hyperinsulinemic conditions, the majority (70–80%) of glucose is utilized by skeletal muscle (4). In patients with syndrome X, reduced glucose uptake has been found in skeletal muscle, involving both oxidative and nonoxidative pathways of glucose utilization (1). Although the mechanisms of insulin resistance in skeletal muscle are not clear, they are thought to involve a defect in membrane transport (5) or an impaired ability of insulin to promote vasodilation (6). In the heart, glucose transport is mediated via insulin-sensitive transporter proteins (GLUT-4) similar to those in skeletal muscle (7). Since myocardial blood flow is 100 times higher than skeletal muscle flow and the aorto–coronary sinus extraction fraction of substrates is low, glucose delivery may only limit glucose uptake in the heart during severe ischemia.

The nature of insulin resistance in patients with syndrome X is of particular interest because of the high frequency of systemic and coronary microvascular dysfunction (8) and because it remains uncertain whether the impaired insulin sensitivity affects cardiac muscle. Myocardial glucose extraction in patients with syndrome X is efficient at rest, but myocardial insulin resistance may explain the impaired ability to increase carbohydrate oxidation during pace stress (9).

Impaired insulin stimulated glucose uptake in the heart has been demonstrated in patients suffering from coronary artery disease with (10) or without non–insulin-dependent diabetes mellitus (11). Studies of other cardiac disorders characterized by insulin resistance such as essential hypertension have not revealed disturbances of myocardial glucose uptake (12). So far, myocardial insulin sensitivity has been studied noninvasively, using positron emission tomography (PET)[1] and 2-deoxy-2-[$^{18}$F]fluoro-D-glucose (FDG) as tracer. However, recent reports suggest that this method may underestimate myocardial glucose uptake in the presence of insulin (13, 14). In the present study, we used coronary sinus catheterization and the hyperinsulinemic–euglycemic clamp technique to establish whether patients with syndrome X display myocardial insulin resistance and, if so, to characterize the association between insulin resistance and myocardial hemodynamics and energy metabolism.

## Methods

*Subjects.* We studied eight patients with a history of typical effort angina, electrocardiographic evidence of myocardial ischemia on bicycle exercise testing (≥ 0.1 mV ST-segment depression), and angiographically smooth coronary arteries without any evidence of stenoses. Mean duration of symptoms was 31±9 mos (range 8–84 mo). All patients were otherwise healthy and none had concomitant cardiovascular or metabolic disease, or a family history of diabetes mellitus. Epicardial coronary spasm was excluded by a normal hyperventilation

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1. *Abbreviations used in this paper:* FDG, 2-deoxy-2-[$^{18}$F]fluoro-D-glucose; PET, positron emission tomography.

test (15) and a negative ergometrine test during coronary catheterization. Valvular and myocardial diseases were excluded by echocardiography and ventriculography. The echocardiographic data were also used to determine left ventricular mass as described by Reichek et al. (16). All medication except short-acting nitrates was withdrawn 14 d before the metabolic study (eight patients received long-acting nitrates, five calcium antagonists, and two β blockers). All women were postmenopausal; one received oral estrogen therapy.

The control group comprised eight subjects evaluated for atypical chest pain. All subjects had a normal physical examination, resting electrocardiogram, chest radiogram, echocardiogram, exercise stress test, hyperventilation test, and coronary and left-ventricular angiogram. All subjects were otherwise healthy with no family history of diabetes mellitus. All women were postmenopausal; none received hormone therapy.

*Procedure.* The study was approved by the local ethics committee. The cardiac metabolic study was performed during a separate admission to the hospital 2–4 wk after angiography, echocardiography, and hyperventilation test. Before the metabolic studies, plasma glucose and insulin responses to a 75-gram oral glucose load were measured. Fat-free mass was determined by bioelectric impedance (Animeter, HTS-Engineering APS, Odense, Denmark) (17). After an overnight fast, a 7-F Wilton-Webster thermodilution pacing catheter (Webster Labs, Inc., Baldwin Park, CA) was advanced from the left medial antecubital vein to a midposition of the coronary sinus for blood sampling, pacing, and flow measurements by thermodilution (36 ml saline per min for 25 s during each measurement). When comparing measurements of coronary sinus blood flow (CSBF) performed immediately after each other with measurements performed with an interval of 60 min, coefficients of variation were 9±2% and 10±3% ($P$ = 0.92) indicating that the infusion of saline per se had no influence on blood flow. An 18-gauge Venflon catheter (Viggo, Helsingborg, Sweden) was inserted retrogradely into the deep antecubital vein of the same arm for sampling of blood from the forearm muscles. The criteria for satisfactory position of the coronary sinus catheter were an oxygen saturation ≤ 35%, and for the position of the antecubital catheter ≤ 70% (actually obtained values were 67.1±2.1% [range 49.2–74.1%]). In the opposite arm, a catheter was placed antegradely into an antecubital vein for infusions. A teflon catheter for arterial blood sampling and pressure measurements was inserted into the distal aorta by way of a femoral artery. The catheters were kept patent by intermittent infusion of NaCl (154 mmol × $l^{-1}$) to which a maximum of 300 U heparin per liter was added. The small heparin dose leaves circulating levels of FFA unaffected not only between the first and the second blood sample where the initial catheter flush was introduced but also during the remaining study period despite repeated flushes (18). The electrocardiographic lead $V_5$ was continuously monitored.

Basal blood flows, pressure measurements, and blood sampling were performed in triplicate before a 1.5-h constant (0.8 mU [5.6 pmol] × $kg^{-1}$ × $min^{-1}$) infusion of insulin (Actrapid; Novo-Nordisk, Copenhagen, Denmark) was started (Fig. 1). Arterial plasma glucose was determined every 5 min during the clamp study; euglycemia (5 mmol × $l^{-1}$) was maintained by infusion of variable amounts of 20% glucose (1). Before each deep venous sample was taken, the ipsilateral forearm blood flow was determined in triplicate by venous occlusion plethysmography (19) using a mercury in silastic rubber strain gauge apparatus. The gauge was attached around the widest, most muscular segment of the forearm. Hand blood flow was interrupted by a wrist cuff inflated to 250 mmHg immediately before every blood flow determination and 1 min before every deep venous sample. The arterial inflow was determined by drawing a tangential line for the first few pulses after cuff inflation. The coefficient of variation of the three flow measurements during each stage of the protocol was 12±3%. Arterial, deep venous, and coronary sinus blood samples were drawn simultaneously.

After a 1-h clamp period, resting blood flows, pressure measurements, and blood sampling were repeated before coronary sinus pacing at a constant rate of 150 beats per minute (bpm), carried out for 10 min. To prevent pacing-induced atrioventricular block, 0.25 mg atropine was given just before the start of pacing. Pacing time to onset of chest pain and postpacing ST-segment depression were noted. Simultaneous arterial and coronary sinus blood samples were drawn and heart rate, blood pressure, and coronary sinus blood flow were determined twice during the last minute of pacing, and at 1, 3, 5, and 7 min of recovery. Forearm measurements were repeated at 7 min of recovery.

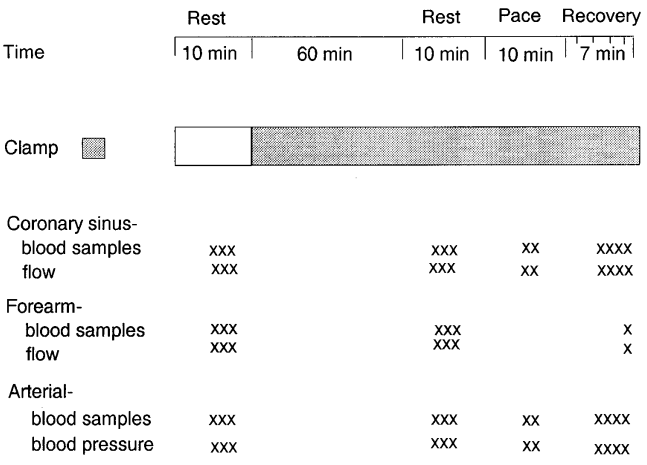


*Figure 1.* Study procedure.

*Analytical methods.* Plasma glucose was measured in duplicate immediately after sampling on a glucose analyzer (Beckman Instruments, Palo Alto, CA). The blood samples were prepared and analyzed for contents in whole blood of oxygen, total carbondioxide, hemoglobin, hematocrit, lactate, and 3-hydroxybutyrate and in plasma for free fatty acids, pyruvate, and alanine as described earlier (20, 21). In samples stored at −20°C, insulin was analyzed by ELISA using a commercial two-site immunoassay (DAKO Diagnostics Ltd., Cambridgeshire, United Kingdom). This assay system does not detect proinsulin, split(32–33)-, and des(31–32)-proinsulin, but split(65–66)- and des(64–65)-proinsulin crossreact 30 and 63%, respectively (22). The intraassay coefficient of variation was 2.0% ($n$ = 75) at a serum level of 200 pM. Serum concentrations of total cholesterol, triglyceride, and HDL cholesterol were measured with routine enzymatic methods. Serum potassium was determined with a standard method on a Kodak Ektachem 700 XR analyzer (Rochester, NY).

*Calculations and statistics.* Maximum exercise capacity was expressed as maximum oxygen uptake ($V_{O2\ max}$) determined during an incremental angina or fatigue limited exercise bicycle testing. Based on the caloric coefficient of oxygen uptake of 13.95 ml per Watt (23), maximum oxygen uptake was extrapolated from workload as:

$$V_{O2\ max}\ (ml \times min^{-1} \times kg^{-1}) = W \times 13.95/\text{body weight} + 3.5$$

where $W$ is maximum work load obtained (in Watt × $min^{-1}$) and 3.5 resting oxygen consumption in ml × $min^{-1}$ per kg (24).

The rate pressure product was determined as the systolic aortic blood pressure multiplied by heart rate. Coronary resistance was calculated from mean aortic blood pressure divided by coronary sinus blood flow. Net substrate flux across the heart was calculated as aorto–coronary sinus concentration difference multiplied by the coronary sinus blood flow for whole blood determinations and by 1-hematocrit for plasma measurement. Substrate delivery was calculated as arterial substrate concentration multiplied by the coronary sinus blood flow for whole blood determinations and by 1-hematocrit for plasma measurements. Myocardial $O_2$ consumption ($MV_{O2}$) and myocardial $CO_2$ production ($MV_{CO2}$) were calculated as the product of coronary sinus

*Table I. Clinical Characteristics of the Study Groups*

| | Controls | Syndrome X |
|---|---|---|
| Male/female | 4/4 | 2/6 |
| Smoke (yes/no) | 2/6 | 1/7 |
| Age (yr) | 51±3 | 54±2 |
| Weight (kg) | 74±4 | 71±4 |
| Body mass index (kg × $m^{-2}$) | 25.3±0.7 | 25.6±1.1 |
| Fat free mass (kg) | 52.1±4.7 | 51.3±3.5 |
| Body fat (%) | 29±4 | 28±3 |
| Waist–hip ratio | 0.87±0.01 | 0.86±0.02 |
| Hemodynamic data | | |
| Systolic blood pressure (mmHg) | 121±4 | 116±4 |
| Diastolic blood pressure (mmHg) | 75±3 | 74±2 |
| Heart rate (beats × $min^{-1}$) | 64±3 | 66±2 |
| Ejection fraction (%) | 72±4 | 75±2 |
| LVSP (mmHg) | 123±7 | 132±7 |
| LVEDP (mmHg) | 11±1 | 12±1 |
| Exercise test | | |
| Exercise duration (s) | 595±102 | 484±53 |
| $V_{O2\,max}$ (ml × $kg^{-1}$ × $min^{-1}$) | 27.7±2.7 | 27.7±1.8 |
| Rate pressure product ($10^2$ × mmHg × beats × $min^{-1}$) | 290±25 | 302±26 |
| Time to 0.1 mV ST-segment depression (s) | — | 331±57 |
| Maximal ST-segment depression (mV) | — | 0.14±0.03 |
| Serum lipids | | |
| Total cholesterol (mmol × $liter^{-1}$) | 6.1±0.3 | 5.9±0.4 |
| HDL cholesterol (mmol × $liter^{-1}$) | 1.4±0.1 | 1.4±0.2 |
| Triglycerides (mmol × $liter^{-1}$) | 1.41±0.12 | 2.02±0.41 |

Means±SE. LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure.

blood flow and the aorto–coronary sinus concentration difference. The respiratory quotient ($RQ$) was calculated as $MV_{CO2}/MV_{O2}$.

On the assumption that amino acid oxidation in the heart is negligible, net rates of carbohydrate and lipid oxidation were calculated from gas exchange measurements according to formulas derived from classical calorimetric equations (9):

$$\text{net carbohydrate oxidation } (\mu\text{mol} \times \text{min}^{-1}) = 0.57 MV_{CO2} - 0.40 MV_{O2}$$

and

$$\text{net lipid oxidation } (\mu\text{mol} \times \text{min}^{-1}) = 0.146\,(MV_{O2} - MV_{CO2})\,.$$

Myocardial energy expenditure was calculated using the caloric equivalents of glucose and fat (673 and 2,398 cal × $mmol^{-1}$, respectively) by the following formula:

$$\text{EE } (\text{Joule} \times \text{min}^{-1}) = (0.080 MV_{O2} + 0.034\, MV_{CO2}) \times 4.18.$$

All data are expressed as means±SE. Values at rest in the basal and clamp period are the means of three determinations and values during pacing are the means of two measurements. The averaged value from the individual patient are included as single values in unpaired $t$ tests to compare mean group values (1). Unpaired $t$ tests were also used to compare any other mean group values whereas Fisher's exact test was used to compare categorial values. Simultaneous comparison of more than two mean values (myocardial metabolism and hemodynamics before, during, and after pacing) was performed with ANOVA for repeated measures followed by a pairwise post hoc $t$ test when appropriate. Correlations were sought using linear regression. A $P$ value $\leq 0.05$ was considered statistically significant.

## Results

*Group characteristics.* There were no significant differences between the control group and patients with syndrome X with respect to gender, smoking habits, age, body mass index, fat free mass, fat mass, hemodynamic variables, and serum lipids (Table I). Exercise duration and $V_{O2\,max}$ were similar in the two

*Table II. Hemodynamics, Forearm Blood Flow, and Myocardial Oxygen Uptake in the Basal State and during Hyperinsulinemic–Euglycemic Clamp*

| | | | | | Recovery + insulin | | | |
|---|---|---|---|---|---|---|---|---|
| | | Rest | Rest + insulin | Pacing + insulin | 1 min | 3 min | 5 min | 7 min |
| Heart rate (beat × $min^{-1}$) | C | 70±4 | 71±4 | 149±1 | 103±7 | 101±7 | 99±7 | 95±2 |
| | SX | 67±2 | 70±2 | 148±1 | 99±5 | 93±3 | 92±2 | 90±3 |
| Mean arterial pressure (mmHg) | C | 96±4 | 98±4 | 98±4 | 99±5 | 101±5 | 104±5 | 100±3 |
| | SX | 101±4 | 99±4 | 105±5 | 106±4 | 102±3 | 103±3 | 101±3 |
| Rate-pressure-product ([beats × $min^{-1}$ × mmHg] × $10^{-2}$) | C | 99±6 | 101±6 | 197±11 | 146±10 | 145±13 | 142±11 | 135±5 |
| | SX | 99±5 | 103±5 | 217±12 | 148±7 | 137±6 | 136±6 | 134±7 |
| Coronary sinus blood flow (ml × $min^{-1}$) | C | 123±11 | 123±12 | 197±26 | 163±18 | 156±17 | 141±16 | 128±12 |
| | SX | 103±13 | 103±15 | 157±22 | 122±19 | 105±13* | 103±14 | 102±15 |
| Coronary vascular resistance (mmHg × $ml^{-1}$ × $min^{-1}$) | C | 0.85±0.12 | 0.88±0.14 | 0.55±0.06 | 0.64±0.05 | 0.70±0.08 | 0.84±0.15 | 0.88±0.15 |
| | SX | 1.09±0.15 | 1.11±0.15 | 0.77±0.11 | 0.97±0.10* | 1.08±0.13* | 1.12±0.13 | 1.17±0.18 |
| Forearm blood flow (ml × 100 $ml^{-1}$ × $min^{-1}$) | C | 1.74±0.08 | 1.74±0.15 | — | — | — | — | 1.78±0.12 |
| | SX | 1.81±0.19 | 1.98±0.22 | — | — | — | — | 1.88±0.20 |
| Myocardial oxygen uptake (μmol × $min^{-1}$) | C | 664±66 | 635±65 | 1056±104 | 788±104 | 791±108 | 700±84 | 646±65 |
| | SX | 567±75 | 535±90 | 798±98 | 635±92 | 531±59 | 534±60 | 515±69 |

Mean±SE. *$P < 0.05$ vs. corresponding value in controls. C, control; SX, syndrome X.

*Table III. Mean±SE Results of Insulin and Glucose Investigations in Patients and Controls in the Basal and the Hyperinsulinemic–Euglycemic Clamp*

| Investigation | Basal period at rest | | Euglycemic clamp period at rest | |
|---|---|---|---|---|
| | Controls | Patients | Controls | Patients |
| Circulating hormones | | | | |
| Insulin (pmol × $1^{-1}$) | 28±3 | 38±6 | 285±26 | 337±18 |
| Glucose metabolism | | | | |
| Glucose concentration (mmol × $1^{-1}$) | 5.2±0.1 | 5.3±0.2 | 5.6±0.1 | 5.5±0.1 |
| Whole body glucose uptake rate (μmol × $kg^{-1}$ × $min^{-1}$) | — | — | 23.1±2.0 | 15.6±2.1* |
| Myocardial glucose A-V differences (mmol × $1^{-1}$) | 0.04±0.05 | 0.02±0.04 | 0.50±0.07 | 0.27±0.07* |
| Forearm glucose A-V differences (mmol × $1^{-1}$) | 0.09±0.05 | 0.10±0.05 | 0.80±0.12 | 0.41±0.11* |

*$P < 0.05$ vs. controls. A-V, arteriovenous.

groups although the patients stopped because of angina pectoris, while the controls stopped because of fatigue. All patients tolerated pacing for 10 min but developed typical anginal pain after 289±182 s. Pacing induced ST-segment depression in all patients (0.15±0.05 mV). Two of the eight control subjects developed chest pain but none had significant ST-segment depressions during or after pacing and the pain was atypical for the pain of myocardial ischemia.

*Hemodynamics, coronary sinus and forearm blood flows, myocardial oxygen consumption.* Heart rate, mean arterial pressure, and rate-pressure product were similar in the control and patient groups at rest and did not change during the clamp (Table II). During recovery after pacing the heart rate remained above the resting levels in both groups. Coronary sinus blood flow tended to be lower and coronary vascular resistance tended to be higher in the syndrome X group than in the control group but significant differences were only observed in the recovery period. In all subjects pacing increased coronary sinus blood flow ($P < 0.001$) and decreased coronary vascular resistance ($P < 0.001$). The increase in blood flow and the decrease in coronary vascular resistance during pacing did not differ between the groups. Forearm blood flow was similar in the two study groups and no changes were observed during clamp in either group. $MV_{O2}$ was similar in the two groups at rest and did not change during the clamp. The increase in $MV_{O2}$ during pacing ($P < 0.001$ for both groups) did not differ between controls and patients.

*Circulating hormones.* There was no difference in fasting insulin concentrations between patients and controls. During the insulin clamp period insulin concentrations rose to similar plateaus (Table III).

*Glucose metabolism.* Fasting plasma glucose did not differ between patients and controls (Table III). Plasma glucose and insulin responses to an oral glucose load were higher in patients with syndrome X than in control subjects (Fig. 2). Arterial plasma glucose concentrations remained unchanged during clamp in both groups (Table III). Whole body glucose uptake rate was lower in the syndrome X group than in controls ($P < 0.05$). During basal conditions, aorto–coronary sinus and forearm arteriovenous concentration differences and uptakes of glucose did not differ between the study groups. During the clamp, both myocardial and forearm arteriovenous glucose differences and net uptake rates were lower in patients with syndrome X than in controls (Fig. 3). During pacing and in the recovery period, differences of the aorto–coronary sinus deficits and differences of myocardial glucose uptake between groups persisted (Fig. 3). Compared with resting values myocardial glucose uptake increased during pacing in the control group ($P < 0.001$) but not in the patient group.

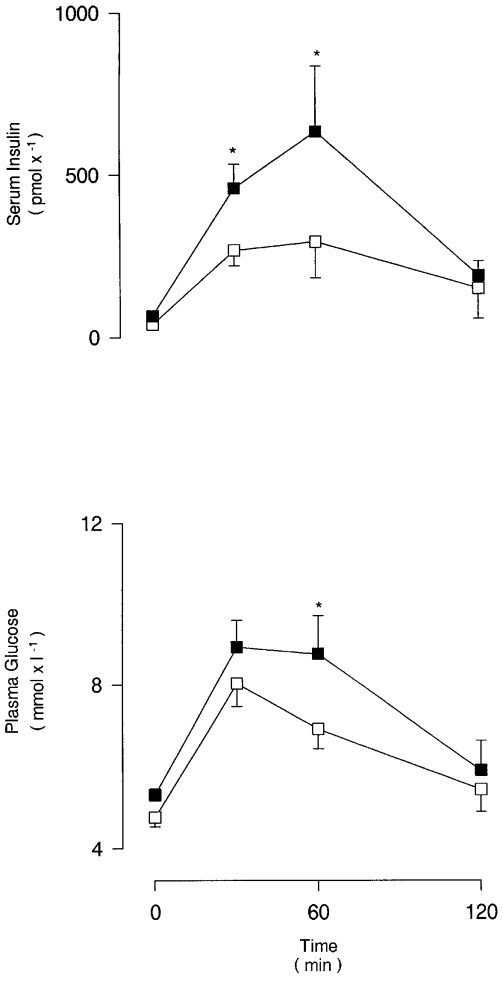


*Figure 2.* Response of plasma glucose and insulin to 75 grams of per-oral glucose in patients with syndrome X (■) and control subjects (□). *$P < 0.05$ vs. corresponding value in controls. Mean±SE.

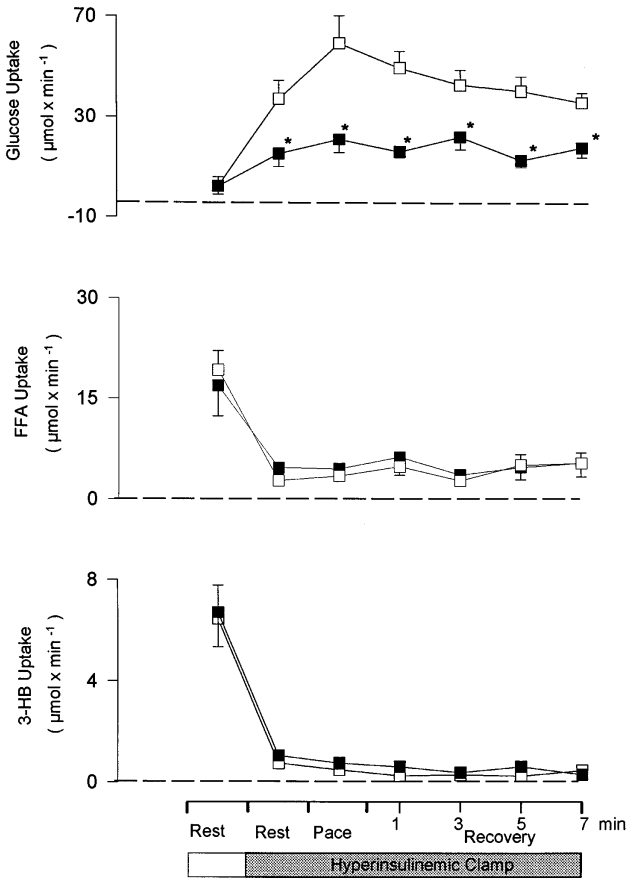


*Figure 3.* Myocardial uptake rates of glucose, free fatty acids (*FFA*), and 3-hydroxybutyrate (*3-HB*) in the basal state and during the insulin clamp period at rest, during pacing, and in the recovery period. Symbols as in Fig. 2.

*Lipid metabolism.* In the basal state syndrome X patients displayed a tendency toward increased circulating FFA levels (Table IV). This tendency was more pronounced in the case of 3-hydroxybutyrate ($P < 0.05$) but myocardial and forearm arteriovenous differences were similar in patients and controls.

During the clamp a tendency toward an impaired suppression of circulating concentrations of FFA and 3-hydroxybutyrate was observed in the patients, but differences were not statistically significant. Aorto–coronary sinus differences of FFA were suppressed to the same extent in patients and controls. Arteriovenous differences of 3-hydroxybutyrate were equally suppressed in controls and patients in the heart and in the forearm. Myocardial uptake of FFA decreased to a similar extent in patients and controls during the clamp (Fig. 3). During pacing and in the recovery period myocardial rates of FFA and 3-hydroxybutyrate uptake did not change compared with the values observed during clamp at rest (Fig. 3).

*Glycolytic products.* Basal concentrations of lactate, alanine, and pyruvate were similar in the two study groups (Table V). Neither myocardial nor forearm arteriovenous differences differed between the groups. During the clamp arterial concentrations of lactate increased in both groups. The increase of aorto–coronary sinus differences and myocardial uptake rates were of similar magnitude in patients and controls as were the decrease in forearm arteriovenous differences and release rates. Alanine concentrations were the same in both groups. No differences in myocardial and forearm arteriovenous differences and uptake rates were observed. Pyruvate concentrations did not change during the clamp; the increase in myocardial and forearm arteriovenous differences and uptake rates, respectively, were of the same magnitude in the two groups.

Myocardial lactate uptake was 61±9 mmol × $min^{-1}$ in patients and 87±12 mmol × $min^{-1}$ in controls ($P = 0.20$). No significant differences of myocardial lactate and pyruvate uptake were observed between the groups during pacing and in the recovery period. Lactate production was not observed in any of the patients during or after pacing.

*Correlates of whole body, cardiac, and skeletal muscle glucose uptake.* Significant correlations were observed between whole body glucose uptake rate and $V_{O2\,max}$ in the control group ($r = 0.72$, $P < 0.05$) but not in the patients ($r = 0.09$, $P = 0.81$). On the pooled data, myocardial and forearm glucose uptake rates correlated mutually ($r = 0.62$, $P < 0.05$) and with whole body glucose uptake (Fig. 4). Correlations between rate-pressure product and myocardial glucose uptake did not reach significant levels at rest or during pacing (data not presented).

*Correlations between myocardial substrate delivery and uptake.* During each period of the clamp, i.e., at rest, during pacing and in the recovery period, myocardial glucose uptake correlated with myocardial glucose delivery in the control group but not in the patient group (Fig. 5). In all stages of the protocol myocardial lactate delivery correlated with myocardial lactate uptake in patients as well as in controls (Fig. 4). Similar correlations were found between myocardial pyruvate delivery

*Table IV. Mean±SE Results of Lipid Investigations in Patients and Controls in the Basal and the Hyperinsulinemic–Euglycemic Clamp Period at Rest*

| | Basal period at rest | | Euglycemic clamp period at rest | |
|---|---|---|---|---|
| Investigation | Controls | Patients | Controls | Patients |
| FFA concentration (µmol × $1^{-1}$) | 997±104 | 1299±164 | 338±45 | 400±108 |
| Myocardial FFA A-V differences (µmol × $1^{-1}$) | 154±26 | 165±28 | 18±6 | 26±10 |
| Blood 3-HB (µmol × $1^{-1}$) | 173±29 | 242±46* | 18±6 | 32±16 |
| Myocardial 3-HB A-V differences (µmol × $1^{-1}$) | 87±13 | 117±21 | 10±4 | 16±3 |
| Forearm 3-HB A-V differences (µmol × $1^{-1}$) | 59±18 | 52±17 | 0±2 | 0±1 |

*$P < 0.05$ vs. controls. 3-HB, 3-hydroxybutyrate; A-V, arteriovenous.

*Table V. Mean±SE Results of Glycolytic Products in Patients and Controls in the Basal and the Hyperinsulinemic–Euglycemic Clamp Period at Rest*

| Investigation | Basal period at rest | | Euglycemic clamp period at rest | |
|---|---|---|---|---|
| | Controls | Patients | Controls | Patients |
| Lactate concentration (mol × $1^{-1}$) | 0.57±0.03 | 0.60±0.06 | 0.98±0.07 | 0.96±0.07 |
| Myocardial lactate A-V differences (mmol × $1^{-1}$) | 0.16±0.03 | 0.14±0.05 | 0.44±0.05 | 0.39±0.05 |
| Forearm lactate A-V differences (mmol × $1^{-1}$) | −0.24±0.04 | −0.21±0.06 | −0.18±0.05 | −0.07±0.04 |
| Pyruvate concentration (μmol × $1^{-1}$) | 44±2 | 50±2 | 47±2 | 52±4 |
| Myocardial pyruvate A-V differences (μmol × $1^{-1}$) | 1.01±0.74 | 1.75±0.56 | 6.10±1.24 | 6.67±2.70 |
| Forearm pyruvate A-V differences (μmol × $1^{-1}$) | −0.44±1.36 | −1.36±1.05 | 1.75±1.37 | 1.76±2.07 |
| Alanine concentration (μmol × $1^{-1}$) | 198±6 | 195±16 | 214±6 | 211±16 |
| Myocardial alanine A-V differences (μmol × $1^{-1}$) | −10±4 | −12±3 | −9±4 | −9±3 |
| Forearm alanine A-V differences (μmol × $1^{-1}$) | −75±8 | −69±12 | −54±7 | −45±7 |

A-V, arteriovenous.

and myocardial pyruvate uptake (syndrome X: $r = 0.64$, $P < 0.01$, controls: $r = 0.66$, $P < 0.01$).

*Myocardial energy metabolism.* Resting myocardial energy expenditures, respiratory quotients, net carbohydrate oxidation rates, and net lipid oxidation rates were similar in patients with syndrome X and control subjects (Fig. 6). Energy expenditure was not influenced by the clamp; respiratory quotients and net carbohydrate oxidation increased ($P < 0.01$) and net lipid oxidation decreased ($P < 0.01$) similarly in the two groups during the clamp. No differences between the groups were observed with respect to energy expenditure and net carbohydrate oxidation during pacing and the subsequent recovery period.

*Potassium exchange.* Resting serum potassium concentrations were similar in patients with syndrome X and controls and a similar decrease was observed during clamp in the two groups. Myocardial and forearm arteriovenous differences and uptake rates increased to a similar degree in the two groups

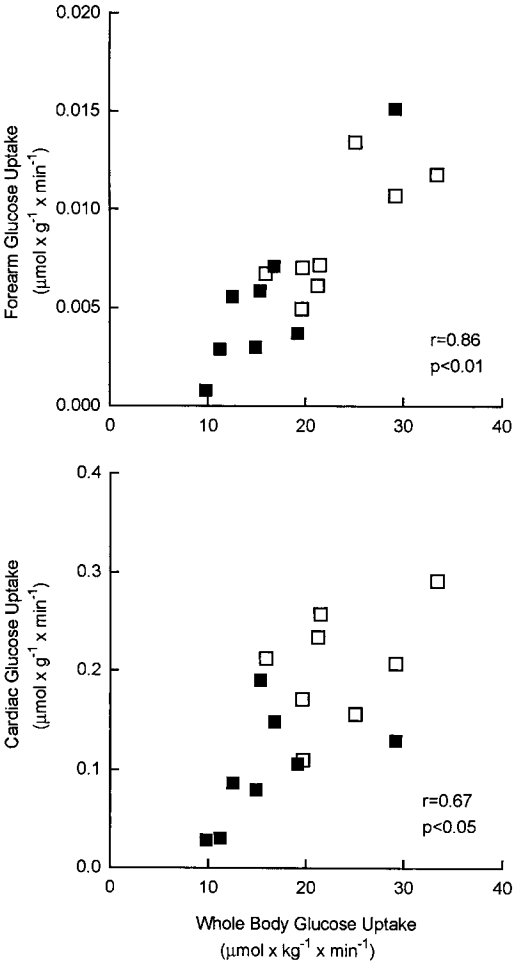


*Figure 4.* Relation between whole body glucose uptake and glucose uptake in the forearm (*upper*) and in the heart (*lower*) of patients with syndrome X (■) and control subjects (□). Myocardial uptake rate of glucose was related to myocardial mass determined by echocardiography as described in the text.

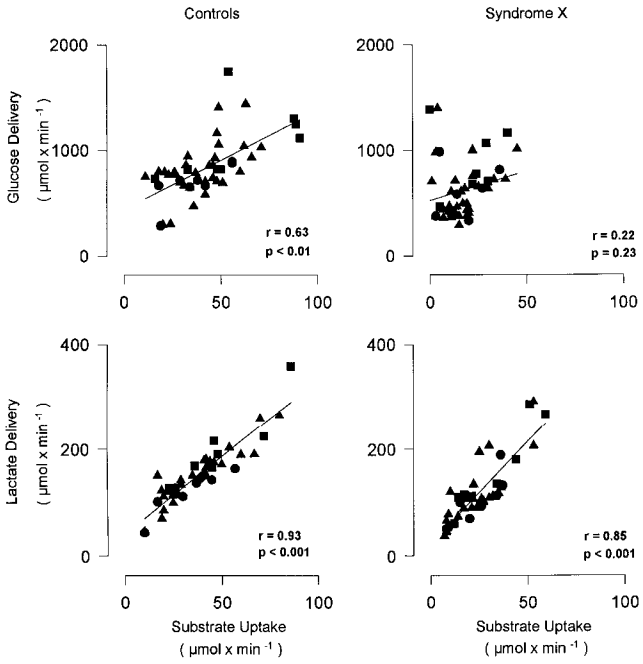


*Figure 5.* Relation between myocardial glucose (*upper*) and myocardial lactate (*lower*) delivery and uptake during clamp in controls (*left*) and patients with syndrome X (*right*). (●) At rest; (■) during pacing; and (▲) in the recovery period.

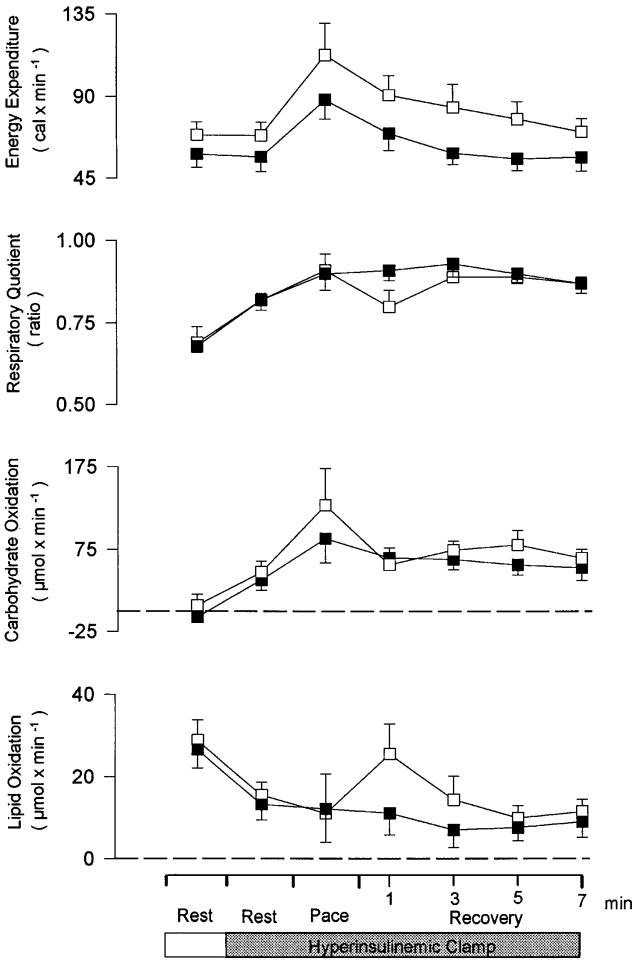


*Figure 6.* Myocardial energy expenditure, myocardial respiratory quotient, net myocardial carbohydrate oxidation, and net myocardial lipid oxidation at rest, during pacing, and in the recovery period. Symbols as in Fig. 2.

during clamp at rest (Table VI). No significant differences in myocardial potassium exchange were observed between the groups during pacing and in the recovery period.

## Discussion

The present study shows that patients with syndrome X exhibit myocardial insulin resistance. The impairment of myocardial glucose uptake is independent of blood flow, suggesting an impairment of either membrane transport or of the intracellular pathways of glucose metabolism. Despite the substantial metabolic disturbance and the tendency toward an increased coronary vascular resistance in these patients, myocardial oxidative energy metabolism remains preserved in patients with syndrome X.

We chose to use the coronary sinus technique and measurement of forearm metabolism by an invasive technique for several reasons. First, by these approaches it was possible to study myocardial and forearm exchanges of not only glucose but also of competing substrates. Secondly, myocardial oxygen and carbon dioxide exchange could be investigated. We could therefore study whether myocardial insulin resistance was present in patients with syndrome X and whether insulin resistance had any influence on vascular function and myocardial energy metabolism. Third, in contrast to PET the coronary sinus technique circumvent the problem of the disproportionate change of FDG uptake relative to glucose uptake, which has recently been discovered under different metabolic conditions in experimental animal studies (13) as well as in humans (14).

As in skeletal muscle, impairment of insulin-stimulated myocardial glucose uptake correlated with whole body glucose uptake. The coronary sinus catheterization technique does not allow quantification of glucose uptake in relation to myocardial mass. We determined left ventricular mass by echocardiography and expressed rates of myocardial glucose uptake assuming that the venous effluent of the entire left ventricular myocardium is drained into the coronary sinus. Although this approach may be suboptimal, a similar correlation has recently been demonstrated in insulin resistant patients with coronary heart disease using PET, by which myocardial mass correction is implicit (11). The results are compatible with a generalized insulin resistance of muscular tissue in syndrome X. These findings appear to be similar to the findings in patients with coronary artery disease with (10) and without non–insulin-dependent diabetes mellitus (11) but not to findings in patients with insulin-dependent diabetes mellitus (25) and essential hypertension (12), in whom skeletal muscle is insulin resistant while cardiac muscle is not.

Another important result of the present study is that physiological hyperinsulinemia with maintenance of euglycemia is not associated with significant changes in either cardiac, forearm, or systemic hemodynamics. This is in accordance with findings after a bolus injection of insulin intravenously (26) and during a hyperinsulinemic clamp technique comparable to ours (27). Impairment of insulin-mediated skeletal muscle vasodilation has been reported in insulin resistance (6, 28). The lack of increase in forearm blood flow during this moderate dose insulin clamp is consistent with previous findings demonstrating that

*Table VI. Mean±SE Results of Potassium Studies in Patients and Controls in the Basal and the Hyperinsulinemic–Euglycemic Clamp Period at Rest*

| | Basal period at rest | | Euglycemic clamp period at rest | |
|---|---|---|---|---|
| Investigation | Controls | Patients | Controls | Patients |
| Potassium concentration ($\mu mol \times 1^{-1}$) | 4.02±0.09 | 3.76±0.08 | 3.93±0.04 | 3.70±0.05 |
| Myocardial potassium A-V differences ($\mu mol \times 1^{-1}$) | −0.03±0.04 | 0.00±0.04 | −0.02±0.03 | 0.00±0.04 |
| Forearm potassium A-V differences ($\mu mol \times 1^{-1}$) | 0.16±0.04 | 0.14±0.05 | 0.22±0.07 | 0.23±0.06 |

A-V, arteriovenous.

physiological hyperinsulinemia caused moderate increases of forearm blood flow barely exceeding the methodological variation (19). Some reports indicate that not only a coronary but also a systemic vascular abnormality exist in a subset of patients with syndrome X (8). The absence of any relationship between myocardial glucose delivery and uptake in patients with syndrome X and the demonstration of reduced glucose uptake in skeletal muscle despite unchanged skeletal muscle blood flow in our study suggest that mechanisms other than impaired vascular reactivity are responsible for insulin resistance in patients with syndrome X. Such mechanisms may involve a defect located at the membrane transport level, as demonstrated in skeletal muscle from patients with diabetes mellitus (5).

We studied myocardial metabolism not only at rest but also during pacing and in the postpacing recovery period during hyperinsulinemic clamp to clarify whether insulin resistance affected energy metabolism. Patients with syndrome X developed typical angina pectoris and ST-segment depressions similar to those observed during the exercise test. The patients tended to have lower coronary sinus blood flow than controls, which could be due to differences of catheter position within the coronary sinus (29). The increment of flow during pacing was similar in the patients and the controls. The coronary flow response is analogous to the findings in several studies of patients with syndrome X (9, 30). A microvascular dysfunction may be responsible for cardiac chest pain in some patients with syndrome X (30, 31). It has been recognized, however, that these patients comprise a heterogenous group with different underlying mechanisms which are not restricted to a vascular origin (31). We found no metabolic evidence of ischemia in patients with syndrome X. Since insulin stimulates myocardial lactate uptake in normal tissue, subendocardial lactate production may be overlooked with the transmural sampling of coronary venous blood (31). The absence of an ischemic metabolic response in patients with syndrome X, when conditions such as diabetes, hypertension, and myocardial hypertrophy are excluded, agree with the results achieved in studies performed without hyperinsulinemic clamp (9, 32, 33). In addition, patients with syndrome X demonstrate no myocardial dysfunction during pace induced angina pectoris and ST-segment depression (34), generating further doubt about ischemia as a common pathophysiological mechanism in these patients. Irrespective of an established vascular disorder, patients with syndrome X are characterized by insulin resistance (1–3).

Lipids are the main fuel for the myocardium under normal conditions. A predominant utilization of lipid fuels exceeding that found in control subjects has been detected in studies using different assessment of myocardial metabolism in patients with syndrome X (9, 35). This is consistent with a state of insulin resistance. Because circulating levels of free fatty acids are elevated in this condition (2, 33), the increased uptake of lipid fuels is secondary to increased delivery (33). Intact competitive mechanisms for myocardial substrate uptake in patients with syndrome X have been demonstrated by preserved inverse relationships between arterial free fatty acid concentrations and myocardial glucose and lactate uptake (33).

Despite preserved energy efficiency, Camici et al. found in addition that myocardial energy expenditure in patients with syndrome X was impaired during pace stress due to an attenuated increment of the carbohydrate oxidation (9). In the present study, myocardial carbohydrate oxidation was not significantly different in patients and controls. The magnitude of coronary sinus blood flow is dependent on the amount of myocardium being drained into the coronary sinus and the location of the thermistor within the coronary sinus (29). It is therefore important to note that the increase of the rates of myocardial oxygen uptake and carbohydrate oxidation was quite similar in the two groups, despite a trend toward different absolute rates. This is consistent with the finding of an unchanged respiratory quotient, which is independent on flow measurements although data regarding respiratory quotient should also be interpreted with caution because its determination may be subject to inaccuracy due to variability inherent in the measurement of carbon dioxide. By means of isotopical studies of glucose metabolism we have demonstrated that the insulin resistance of skeletal muscle in patients with syndrome X involves oxidative as well as nonoxidative glucose metabolism (1). The method used in the present study does not allow an explicit calculation of oxidative glucose metabolism. However, net carbohydrate oxidation and extraction of glycolytic products were similar in controls and patients at rest as well as during pacing. Thus, the maintained carbohydrate oxidation despite reduced myocardial uptake of exogenous glucose in patients with syndrome X can only be explained by oxidation of glycogen. A preferential oxidation of glycogen compared with exogenous glucose has recently been demonstrated in the working rat heart in the basal state (36) and during increases of work load (37). The preserved total myocardial energy expenditure is in accordance with the fact that patients with syndrome X, defined by the presence of ST-segment depressions, have an excellent prognosis and a preserved left ventricular function (38).

It has been proposed that chest pain and ST-segment depressions in the absence of myocardial ischemia may be associated with disturbances of potassium flux between the extracellular space and the vascular compartment in response to a change of heart rate (39). Impaired insulin-mediated potassium uptake has been reported in obese subjects (40). There is major evidence, however, that the actions of insulin on cellular glucose and potassium uptake are independent of one another (41). In the present study patients with syndrome X and controls showed similar potassium handling in response to insulin.

We excluded patients with known insulin-resistant states. Furthermore, we carefully sought to obtain an optimal control group in terms of sex, age, body mass index, and smoking habits, all of which have been reported to affect insulin sensitivity. Because the level of physical capacity correlates well with insulin sensitivity, we chose a control group consisting of subjects with chest pain of noncardiac origin as opposed to healthy subjects. As a result, exercise capacity did not differ between the two groups although the reason for cessation was angina pectoris in the patients and fatigue in the control subjects. Of importance, the well-known correlation between physical capacity and insulin sensitivity (42) demonstrated in the controls was not found in the patients. This is in accordance with our previous findings that patients with syndrome X are insulin resistant independently of physical fitness (1) and that additional factors appears to be involved in the pathogenesis of insulin resistance (43).

In conclusion, impaired insulin-stimulated glucose uptake can be present independently of blood flow indicating that the mechanism of insulin resistance in patients with syndrome X is mainly a defect of membrane glucose transport. The regulatory mechanisms for myocardial uptake of substrates other than glucose are preserved and can account for a predominant

myocardial utilization of lipid fuels in patients with syndrome X (9, 35). However, insulin resistance does not appear to be involved in the pathogenesis of chest pain and ST-segment depression in these patients.

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