Cardiac Metabolic and Hemodynamic Effects of Insulin in Patients With Coronary Artery Disease

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To assess the effects of insulin in stable coronary artery disease (CAD), 2 U i.v. insulin was given to 9 control and 10 CAD patients during coronary sinus catheterization. Hemodynamic and metabolic data were obtained before and for 90 min after insulin injection. Insulin induced no changes in heart rate, mean aortic pressure, rate-pressure product, coronary sinus flow, or coronary resistance. Metabolic changes were similar in both groups and included *1)* 30% decrease of arterial glucose ($P < .001$) and 3-fold increase of myocardial glucose uptake ($P < .001$), *2)* 1.5- to 2.5-fold elevation of arterial lactate ($P < .001$) and myocardial lactate usage ($P < .001$), respectively, *3)* 50–70% suppression of arterial levels ($P < .001$) and myocardial uptake of free fatty acids ($P < .01$), and *4)* 10% reduction of myocardial net oxygen consumption ($P < .05$). Myocardial citrate efflux increased in the CAD patients ($P < .05$), whereas alanine release rose only in control patients ($P < .01$), suggesting that glucose enters glycogen production in the CAD patients and pyruvate production in the control patients to a high degree. Myocardial glutamate uptake remained unchanged. In conclusion, insulin sensitivity was not altered in CAD. The insulin-induced shift from myocardial free fatty acid to carbohydrate usage may be beneficial to the ischemic heart by increasing glycogen stores, saving oxygen, and inhibiting an excess free-fatty acid concentration, which may be toxic during ischemia. *Diabetes* 38:1175–80, 1989

Energy requirements during ischemia are primarily met by glucose and/or glycogen (1–4), and altered myocardial substrate usage from predominantly free fatty acids to carbohydrates has been demonstrated in patients with coronary artery disease (CAD) even when resting and asymptomatic (4–6). Insulin, glucose, and potassium have been applied clinically to enhance glycolytic energy production and thereby increase tolerance to and ameliorate damage from ischemia during exercise (7) and pacing (8), acute myocardial infarction (9,10), and aortic cross-clamping (11). Although myocardial metabolic changes during glucose, insulin, and potassium therapy have been well described (8,12), metabolic changes after insulin administered without concomitant glucose infusion are not known. Relative insulin resistance in patients with ischemic heart disease has been suggested because of increased circulating insulin responses to glucose challenge (13,14) and fasting hyperinsulinemia (15). Abnormal insulin secretory patterns have been regarded as risk factors for the development of coronary sclerosis (16) but might also be a metabolic response to the increased carbohydrate demands of the ischemic heart.

This study was undertaken to characterize the influences of insulin on myocardial lipid-carbohydrate availability and usage, cardiac oxygen consumption, and systemic and coronary hemodynamics and to evaluate whether the effects differed between CAD and control patients. An additional aim was to study a possible insulin effect on myocardial exchanges of glutamate and alanine, both increased in ischemic heart disease (6,17,18) and related to cardiac carbohydrate usage (19,20).

RESEARCH DESIGN AND METHODS

Subjects. The study included 19 nonobese patients (13 men and 6 women) with chest pain syndromes. Angiography revealed normal coronary anatomy in 9 (control) patients. All had normal resting and exercise electrocardiograms, and their chest pains were atypical and not relieved by sublingual nitroglycerin. The other 10 patients had significant CAD defined as a >50% fixed-diameter reduction of one ($n = 2$), two ($n = 6$), or three ($n = 2$) vessels. All CAD patients suffered from typical-effort angina and developed >1 mm of S-T–segment depression during stress testing. Two CAD patients were treated with metoprolol, and 8 were treated with combined diltiazim and isosorbide dinitrate. Seven of the

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CAD patients (but 0 control patients) had a history of myocardial infarction >6 mo before the study. Control and CAD patients did not differ significantly in age (51.4 ± 2.3 vs. 59.6 ± 2.7 yr), body weight (72 ± 4 vs. 74 ± 3 kg), left ventricular end–diastolic pressure (9.8 ± 1.0 vs. 14.9 ± 1.8 mmHg [$P < .10$]), or ejection fraction (64 ± 3 vs. 57 ± 5%). None of the patients had shown signs of vasospastic coronary disease during prolonged hyperventilation, and none suffered from additional heart disease, congestive heart failure, systemic hypertension, or metabolic diseases.

Procedure. All patients gave informed written consent. Long-acting antianginal medication was stopped 1 wk before the study; sublingual nitroglycerin was allowed up to 4 h before the study.

The patients were studied recumbent and without sedation after an overnight fast. Electrocardiographic lead V5 was continuously monitored. A Teflon catheter was inserted into the distal aorta through a femoral artery. A 7F Wilton-Webster thermodilution pacing catheter was advanced to a midposition of the coronary sinus via an antecubital vein. The stability of its position was repeatedly checked by fluoroscope. The catheters were kept patent by intermittent flushing with NaCl (154 mM). Arterial blood pressure was measured with a Schönander transducer. Coronary sinus blood flow was determined with thermodilution by continuous infusion of 36 ml/min (154 mM) NaCl for 25 s at each measurement (21).

After a 15-min interval for equilibration, 2 U of 100 U/ml i.v. semisynthetic human insulin (Velosulin, Nordic, Gentofte, Denmark) was given as a bolus. The dose was small to diminish hemodynamic changes secondary to a catecholamine counteraction. Simultaneous blood samples from the aorta and the coronary sinus were drawn, and coronary sinus blood flow, heart rate, and aortic pressure were determined immediately before and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, and 90 min after insulin administration.

Blood samples were collected in heparinized ice-cooled tubes. They were prepared immediately and analyzed in duplicate for oxygen saturation, hemoglobin, hematocrit, blood lactate, and plasma concentrations of glucose, free fatty acids, citrate, glutamate, and alanine as previously described (17). Plasma insulin was determined by radioimmunoassay (22).

To exclude myocardial ischemia caused by small-vessel disease, the control patients underwent coronary sinus pacing (150 beats/min for 10 min) (23). Blood samples and hemodynamic values were obtained before pacing, during the last minute of pacing, and at 1, 3, 5, and 7 min of recovery. All control patients tolerated pacing without developing chest pains or electrocardiographic S-T–segment depression. Metabolically, pacing did not decrease aortocoronary lactate differences from resting levels (0.18 ± 0.03 vs. 0.17 ± 0.02 mmol/L, NS); the increased flow even elevated net myocardial lactate uptake from 15.2 ± 2.6 to 21.6 ± 3.1 μmol/min ($P < .05$). Likewise, myocardial exchanges of citrate, glutamate, and alanine were within normal limits before, during, and after pacing (17).

Calculations and statistics. The rate-pressure product was determined as systolic aortic blood pressure multiplied by heart rate. Coronary vascular resistance was calculated from mean aortic blood pressure divided by coronary sinus blood flow. Fractional myocardial substrate extraction was calculated as aortocoronary sinus concentration difference divided by arterial concentration and multiplied by 100. Net substrate flux across the heart was calculated as aortocoronary sinus concentration difference multiplied by coronary sinus blood flow for whole-blood determinations and multiplied by 1 − hematocrit for plasma measurements.

The data are presented as means ± SE. Correlations were sought by linear regression analysis. Differences between grouped data were assessed by Student's t test. Friedman's method for randomized blocks (24) was applied for testing the nonrandom course of mean values at each sample time from 0 to 90 min after insulin administration. In the event of significant variation, the paired t test was used to determine which values were significantly different from those before insulin. Results were considered significant at $P < .05$.

RESULTS

All patients remained pain free, and none complained of hypoglycemic symptoms during the study.

Hemodynamics. Hemodynamic measurements are summarized in Fig. 1. Heart rate, arterial pressure, rate-pressure product, coronary sinus blood flow, and coronary vascular resistance were not changed by insulin. Nor did any of these variables differ significantly between control and CAD patients, although heart rate and, consequently, the rate-pressure product tended to be higher in the control patients throughout the study. One of the control patients had sinus tachycardia of 130–140 beats/min throughout the study. She denied emotional stress, but extensive examinations on the following days revealed no physical explanation of her tendency for sinus tachycardia.

Myocardial oxygen consumption. Insulin reduced aortocoronary sinus differences of oxygen by 6% (Fig. 1) and net myocardial oxygen consumption maximally by 10% from 11.0 ± 3.5 to 9.9 ± 3.7 ml/min in control patients ($P < .001$) and 12.6 ± 5.5 to 11.2 ± 4.3 ml/min in CAD patients ($P < .05$). Maximal depression occurred 25 min after injection of insulin.

METABOLIC RESULTS

Arterial concentrations and myocardial exchanges of insulin and substrates are delineated in Fig. 2.

Insulin. Basal fasting arterial levels of insulin were low and similar in control and CAD patients (10 ± 3 vs. 6 ± 1 μU/ml). Peak insulin concentrations (76 ± 10 vs. 73 ± 11 μU/ml) were measured at 5 min and returned to basal levels at 30 min after injection and were comparable in both patient groups. Mean aortocoronary sinus concentration differences of insulin at the start of the study (−0.4 ± 0.9 vs. −0.6 ± 0.6 μU/ml) did not differ from before insulin was injected; they were unrelated to arterial levels ($r = .26$ vs. $r = .21$) and were not altered consistently by insulin administration.

Glucose. Fasting arterial glucose concentrations (4.84–6.88 mM) were all within the normal range and did not differ between control and CAD patients (5.82 ± 0.19 vs. 5.58 ± 0.16 mM). Insulin progressively reduced arterial glucose levels to a minimum of 3.91 ± 0.36 mM in control patients ($P < .001$) and 3.94 ± 0.24 mM in CAD patients ($P < .001$) at 30 min. Myocardial glucose uptake was rapidly (3-fold) increased regarding aortocoronary sinus gradients and net

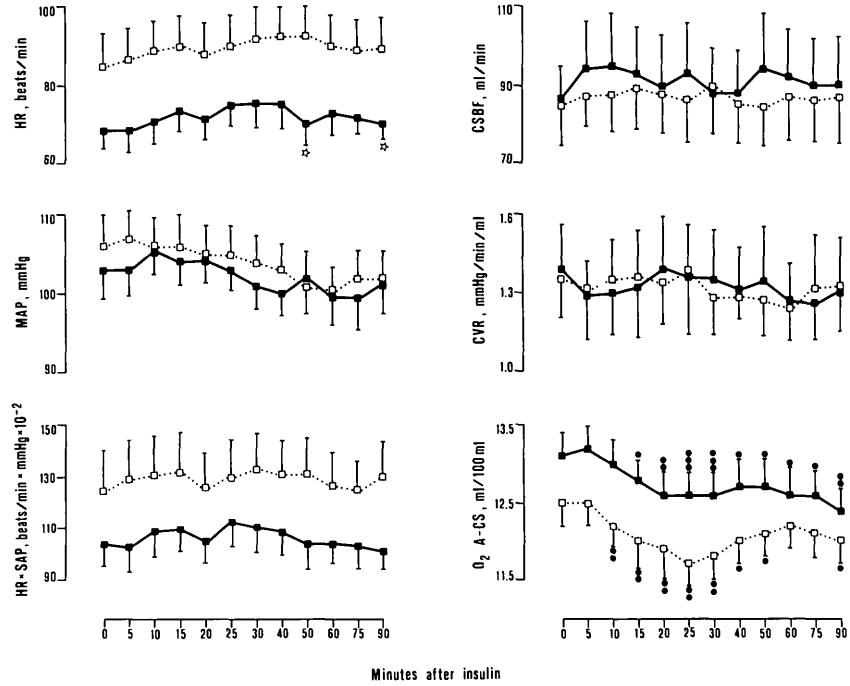

FIG. 1. Hemodynamics and myocardial oxygen uptake after 2 U i.v. insulin in control (□) and coronary artery disease (■) patients. HR, heart rate; CSBF, coronary sinus blood flow; MAP, mean arterial pressure; CVR, coronary vascular resistance; SAP, systolic arterial pressure. •P < .05, ••P < .01, •••P < .001, vs. initial values in case of nonrandom course of mean values. *P < .05 vs. respective values in controls.

fluxes in control and CAD patients. Glucose uptake returned to basal levels 40 min after insulin injection.

Lactate. With some delay, insulin enhanced arterial lactate concentrations, aortocoronary sinus lactate differences, and myocardial net lactate flux 1.5- to 2.5-fold. The alterations tended to be more pronounced in control than CAD patients but without reaching significance. Lactate aortocoronary sinus differences were linearly related to arterial concentrations before insulin (r = .72, P < .001) and regarding all samples throughout the study (r = .82, P < .001).

Free fatty acids. Arterial levels of free fatty acids were high at the start of the study, but insulin gradually halved the concentrations, with maximal depression after 20–40 min, which was comparable in both groups of patients. This change was accompanied by 60–70% suppressions of aortocoronary sinus differences and myocardial net uptake of free fatty acids. Before insulin, myocardial fractional extraction of free fatty acids was lower in CAD than control patients (22 ± 3 vs. 34 ± 2%, P < .02), but apart from that, myocardial uptake of free fatty acids was similar in both groups throughout the study.

Citrate. Arterial citrate levels gradually fell by 7% during the study in control and CAD patients. In CAD patients, myocardial release of citrate increased rapidly after insulin administration but returned to basal levels after 25 min. The same pattern tended to be present, although insignificantly, in control patients.

Glutamate. Arterial glutamate concentrations remained virtually unchanged after insulin despite significant nonrandom courses. Net myocardial glutamate uptake rose by 15–20% during the initial 10 min after insulin, but Friedman's test failed to reveal a nonrandom course of mean values. Before insulin, glutamate aortocoronary sinus gradients were higher in CAD than control patients (P < .05), and their net uptakes of glutamate tended to remain elevated throughout the study.

Alanine. Toward the end of the study, there was a subtle, although significant, decrease in arterial alanine concentrations, which were constantly lower in CAD than control patients. At basal state, myocardial release of alanine was higher in CAD than control patients (P < .05) and tended to remain so after insulin. Net alanine release showed a nonrandom course in both groups of patients. In the control group, but not in the CAD group, alanine release increased immediately after insulin, whereas it tended to decrease in both groups during the late phase of the study.

DISCUSSION

This study revealed in control and CAD patients similar effects of insulin including *1*) a prompt shift in myocardial substrate availability and usage from free fatty acids to carbohydrates, with evidence of glycogen storage, and *2*) a decrease in cardiac oxygen consumption despite unaltered systemic and coronary hemodynamics but *3*) only inconsistent changes of myocardial uptake of glutamate. Most of the effects had subsided by the end of the study. Limitations of the study include the relatively small number of patients and the fact that the control patients were not unequivocally healthy. Despite symptoms, however, they showed no angiographic, electrocardiographic, or metabolic signs of ischemic heart disease.

Fasting is known to be associated with low circulating insulin concentrations (25) as found in control and CAD patients, which was consistent with several other studies (13,14) but contrasted with a single report of fasting hyperinsulinism in CAD (15). Despite 10-fold increases of arterial levels after insulin, even peak values remained inside the normal physiological range seen in the fed state (26) or after glucose challenges (13,14). At no sampling did arterial levels differ between the two patient groups, suggesting the same peripheral handling of insulin. In agreement with earlier reports, we were unable to demonstrate extraction of insulin across the heart in patients while fasting or after insulin (26,27).

The well-known acceleration of glucose transport by in-

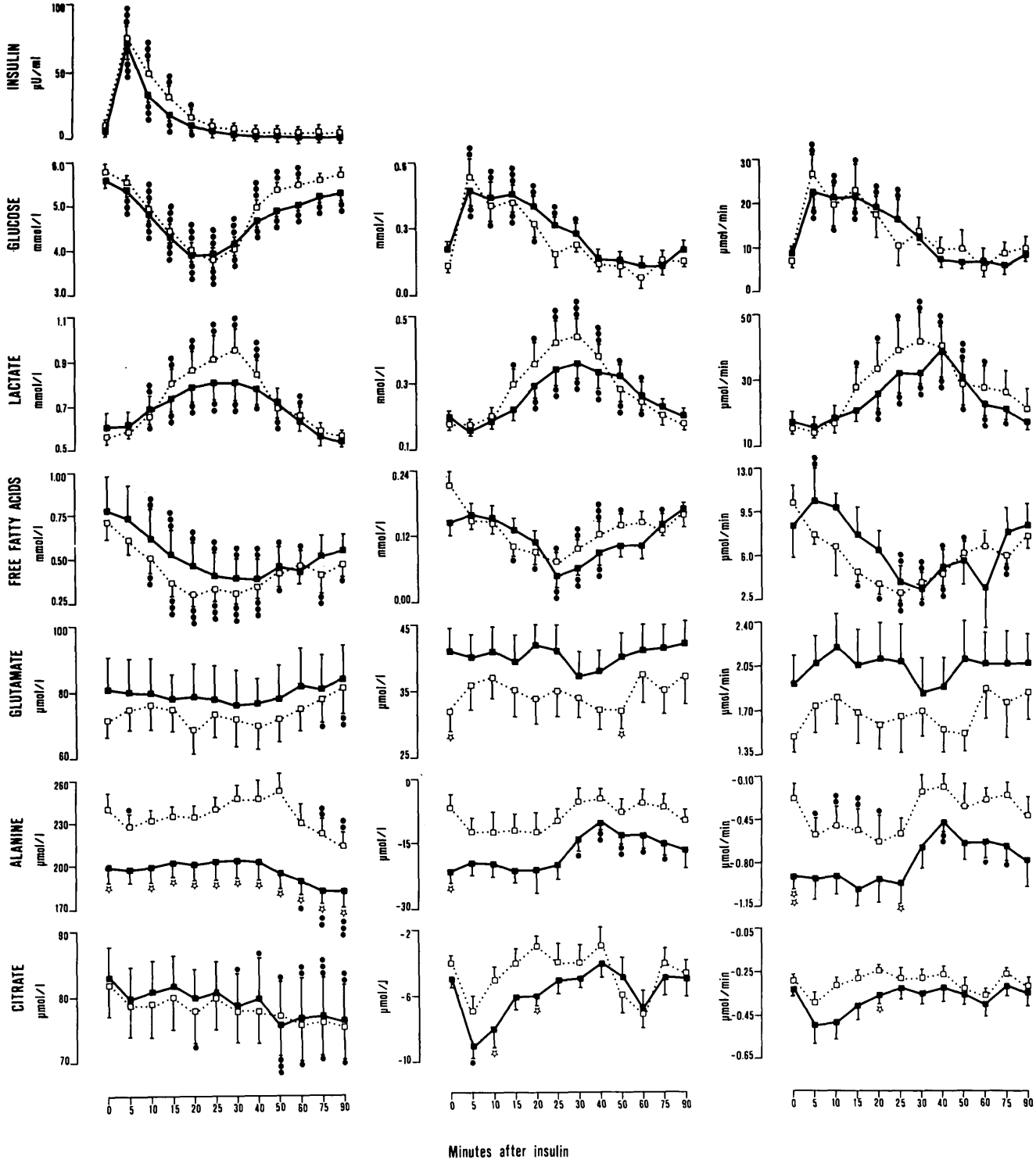

FIG. 2. Arterial concentrations, aortocoronary sinus concentration differences, and myocardial net fluxes of substrates after 2 U i.v. insulin in control (□) and coronary artery disease (■) patients. $^{\bullet}P < .05$, $^{\bullet\bullet}P < .01$, $^{\bullet\bullet\bullet}P < .001$, vs. initial values in case of nonrandom course of mean values. $^{\star}P < .05$ vs. respective values in control patients.

sulin in the whole body and in the heart (1,3,28) was reflected by rapid decreases of arterial glucose concentration and increases of myocardial glucose uptake, respectively. The glucose disposal rates did not differ between control and CAD patients, indicating similar insulin sensitivity. Earlier suggestions of increased insulin resistance in CAD have been based on relative glucose intolerance and hyperinsulinism (13–16), whereas the actual effect of insulin on glucose uptake in CAD has not been reported to our knowledge.

Once inside the cell, glucose may either be stored as glycogen or undergo oxidation, depending largely on the activity of the glycolytic key enzyme phosphofructokinase (1,3). This enzyme is strongly inhibited by high cytosolic

citrate concentrations (3), which is reflected by myocardial release of citrate (29). Consequently, the rapid elevation of citrate efflux after insulin in the CAD patients suggests that glucose was directed initially into glycogen rather than glycolysis. Because of repetitive glycogen depletion during ischemia (2,6), CAD hearts may possess a high glycogen-building ability. Citrate changes were less evident and were insignificant in the control patients, perhaps indicating a different intracellular fate for glucose. This is supported by an early rise of cardiac alanine output in the control patients, presumably reflecting increased glycolytic pyruvate production (17,20). Glycogen synthesis and restriction of phosphofructokinase seem most pronounced when insulin is administered in the presence of free fatty acids or acetate (30,31) and are less pronounced when glucose is the sole or main substrate (32,33). In this study, arterial free fatty acids were initially very high, which is characteristic with fasting. Insulin progressively lowered arterial free fatty acids by 50%. Free–fatty acid oxidation is the main source of citrate (3,29). Because of the reduced substrate availability, myocardial uptake of free fatty acids was gradually suppressed. Citrate efflux fell concomitantly. This indirectly indicates a delayed activation of glycolysis, which may further be stimulated by insulin because of production of fructose 2,6-biphosphate, a strong activator of phosphofructokinase (31). Accelerated peripheral glycolysis was indicated by augmentation of arterial lactate concentrations (33), which secondarily increased myocardial lactate uptake.

Glutamate aortocoronary sinus differences have been found to be greater in CAD than control patients (6,17,19) as confirmed in this study. The increased glutamate uptake is localized to ischemic areas (18), and perfusion with glutamate has been shown to improve myocardial recovery after transient ischemia (34,35). This has stimulated interest in the intermediary glutamate metabolism, which at several points is linked to the carbohydrate metabolism. The malate-aspartate shuttle, which is responsible for moving glycolytically produced NADH across the mitochondrial membrane, is dependent on glutamate (36,37). Via transamination with pyruvate, glutamate may be converted to and released from the cell as alanine (17,20). In humans, myocardial uptake of glutamate was found related to uptake of glucose and lactate (6,19). Consequently, insulin should be expected to elevate myocardial glutamate consumption. However, this study demonstrates that insulin does not influence myocardial glutamate uptake despite inducing pronounced alterations in glucose and lactate usage.

The change in myocardial substrate preference from free fatty acids to glucose and lactate was associated with a 10% decrease in myocardial oxygen consumption. Because the ATP/oxygen ratio is higher for free fatty acids than for carbohydrates, a switch from oxidizing only lipids to exclusive glucose oxidation would diminish oxygen consumption by 13% (38). There is reason to believe that this reduction in myocardial oxygen consumption represents a metabolic oxygen-saving effect of insulin, because myocardial oxygen demand when determined as the rate-pressure product remained unchanged. No estimates were made of myocardial contractility, another major determinant of myocardial oxygen requirement (39); it can be argued that insulin might reduce myocardial oxygen uptake by depressing contractility. Such an argument seems unreasonable because of numerous studies reporting that insulin produces a positive inotropic effect (but without changing coronary flow) in various species and cardiac preparations (40).

Clinical implications. Preventive application of a small dose of insulin before planned ischemia (e.g., aortic cross-clamping or coronary balloon inflation) may enhance ischemic tolerance. Of greatest importance is probably enlargement of myocardial glycogen depots, which are the sole energy source when coronary flow is nil as during aortic cross-clamping (11,41). In cases of less severe ischemia, the oxygen-saving effect of the altered myocardial substrate preference may improve the myocardial oxygen demand-to-supply balance. Finally, the reduction of arterial free fatty acids may be beneficial to the ischemic heart because of diminished intracellular accumulation of toxic intermediates (42,43).

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