Comparison of local and systemic effects of insulin on myocardial glucose extraction in ischemic heart disease

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McNulty, Patrick H. Comparison of local and systemic effects of insulin on myocardial glucose extraction in ischemic heart disease. Am. J. Physiol. Heart Circ. Physiol. 278: H741–H747, 2000.—Physiological increases in circulating insulin level significantly increase myocardial glucose uptake in vivo. To what extent this represents a direct insulin action on the heart or results indirectly from reduction in circulating concentrations of free fatty acids (FFA) is uncertain. To examine this, we measured myocardial glucose, lactate, and FFA extraction in 10 fasting men (ages 49–76 yr) with stable coronary artery disease during sequential intracoronary (10 mU/min, coronary plasma insulin = 140 ± 20 µU/ml) and intravenous (100 mU/min, systemic plasma insulin = 168 ± 26 µU/ml) insulin infusion. Basally, hearts extracted 2 ± 2% of arterial glucose and extracted 27 ± 6% of FFA. Coronary insulin infusion increased glucose extraction to 5 ± 3% (P < 0.01 vs. basal) without changing plasma FFA or heart FFA extraction. Conversion to intravenous infusion lowered plasma FFA by ~50% and heart FFA extraction by ~75%, increasing heart glucose extraction still further to 8 ± 3% (P < 0.01 vs. intracoronary). This suggests the increase in myocardial glucose extraction observed in response to an increment in systemic insulin concentration is mediated equally by a reduction in circulating FFA and by direct insulin action on the heart itself. Coronary insulin infusion increased myocardial lactate extraction as well (from 20 ± 10% to 29 ± 9%, P < 0.05), suggesting the local action may include stimulation of a metabolic step distal to glucose transport and glycolysis.

correlation in vivo between myocardial glucose uptake and circulating concentrations of free fatty acids (FFA), the oxidation of which inhibits the rate-limiting enzymes in glycolysis and glucose oxidation, suppressing glucose uptake by end-product inhibition of hexokinase (11, 24, 30). A number of investigators (5, 13, 14, 16, 26, 27) have subsequently confirmed the operation of the Randle principle for the case of the human heart. Thus in fasting subjects, plasma FFA levels are high, and the heart utilizes only small amounts of glucose; insulin secretion or administration inhibits peripheral lipolysis, reduces FFA levels, and increases heart glucose uptake to a degree directly proportional to the magnitude of reduction in FFA (14, 16, 27).

Inferential evidence suggests insulin should also stimulate heart glucose extraction via direct, locally mediated effects on the myocardium. Cardiomyocytes express abundant insulin receptors. Receptor binding initiates translocation of glucose transporters to the sarcolemma and may activate hexokinase, pyruvate dehydrogenase, and glycogen synthase, all of which would be predicted to increase net glucose disposal. Perfusing isolated hearts with high concentrations of insulin and glucose in vitro does in fact increase their glucose uptake and metabolism (2, 24). However, the degree to which such direct actions contribute to the stimulation of myocardial glucose extraction observed during systemic hyperinsulinemia in vivo is unclear, particularly in humans who exhibit a significant degree of generalized muscle insulin resistance. Indeed, recent studies of adult human subjects using positron emission tomography with fluorodeoxy-[18F]glucose to indirectly estimate myocardial glucose uptake suggest that the entire insulin effect can be accounted for by reduction in circulating FFA levels (12).

Knowing whether local or systemic insulin actions are the dominant influence on myocardial glucose extraction may be clinically important. Techniques currently in development aim to achieve therapeutic upregulation of heart glucose utilization by engineered overexpression of components of the myocardial insulin-responsive system, delivered as transgenes or gene products (15). Such strategies presume that the biological effects of systemic hyperinsulinemia are predominantly mediated by direct insulin actions on the myocardium, but formal proof of this is lacking. In this study, we combined local coronary infusion and arterial coronary sinus catheterization techniques to directly com-

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pare the relative contributions of local versus systemic insulin effects on myocardial glucose metabolism in vivo.

METHODS

Subjects. Ten men aged 61 ± 4 yr (range 49–76 yr) were enrolled from the population of patients referred to the Connecticut Department of Veterans Affairs Medical Center for elective coronary angiography to evaluate chest pain. Subjects were sedentary and mildly obese (body mass index = 27.7 ± 1.3 kg/m²). Six subjects carried a diagnosis of hypertension. Medications included nitroglycerin in seven patients, β-adrenergic blockers in six, and calcium channel blockers in five. Because the study design required instrumentation of the left main coronary artery, it was elected to perform the study in patients already undergoing coronary angiography for a clinical indication rather than normal control subjects. This resulted in the selection of a group of subjects all of whom had significant coronary artery disease. Precautions were therefore taken to ensure that arterial-venous balance measurements were made across only structurally and functionally normal regions of myocardium and excluding myocardial ischemia. Accordingly, subjects were excluded if they had reduced left ventricular function, evidence of previous myocardial infarction, or angina pectoris within 24 h preceding the study. It should also be noted that no subject showed clinical, hemodynamic, or electrocardiographic evidence of myocardial ischemia during the research study. Subjects with diabetes mellitus were also excluded.

Experimental protocol. The study protocol was approved by the Human Studies Committee of the Connecticut Veterans Affairs Medical Center and subjects gave written informed consent. The protocol is illustrated in Fig. 1. Subjects fasted 12–16 h and received 5,000 U iv heparin sodium to prevent thrombosis. Percutaneous femoral arterial and coronary sinus catheterization were performed as previously described (16, 17). The coronary sinus was cannulated with a size 5-Fr end-hole sampling catheter placed under fluoroscopic guidance from either the femoral or internal jugular vein. The catheter was placed sufficiently proximal (near the junction with the great cardiac vein) to avoid admixture of right atrial blood during sampling.

Thirty minutes after heparin administration, paired samples of arterial and coronary venous blood were obtained in quadruplicate over a 10-min period and immediately chilled in heparinized tubes on ice for measurement of glucose, lactate, FFA, and insulin concentrations. Basal heart rate, blood pressure, and the surface electrocardiogram were recorded.

A size 5-Fr coronary angiography catheter (J L-4 catheter; United States Catheters, Billerica, MA) was then advanced through the femoral arterial sheath into the left main coronary artery, and a 40 mU/ml solution of regular human insulin (Humulin, Eli Lilly) in saline was infused continuously into the left coronary circulation at a rate of 0.25 ml/min (10 mU/min) for 70 min. This insulin dose was calculated to raise coronary plasma insulin concentration from the fasting level to the upper physiological range without increasing systemic plasma levels. Because left coronary blood flow averages ~100 ml/min in humans (16) intracoronary infusion at 0.25 ml/min would not be expected to appreciably dilute coronary arterial plasma substrate concentrations. Blood sampling was repeated during the last 10 min of intracoronary infusion.

The insulin infusate was then switched to a peripheral intravenous line and administered as a primed (200 mU min⁻¹ 10 min⁻¹) continuous (100 mU/min) intravenous insulin infusion for 70 min. The 70-min infusion times were chosen as the best compromise between steady-state insulin effect (see Fig. 2) and patient tolerability. Arterial blood glucose was measured at intervals and was prevented from falling with a variable-rate infusion of 20% dextrose. Final quadruplicate paired arterial and coronary venous blood samples were
obtained during the last 10 min of intravenous infusion. Small samples of arterial and venous blood were also obtained at intervals throughout the intracoronary and intravenous infusion to define the time course of insulin action. After completion of all measurements, selective coronary and left ventricular angiography were performed using standard techniques.

Analytic methods. Glucose and lactate concentrations were measured immediately in whole blood using an automated glucose/lactate analyzer (Statplus 2000, Yellow Springs Instruments) calibrated to external standards and having a between-measures variance of 1.0%. FFA concentrations were measured on chloroform-heptane extracts of plasma using a microfluorometric modification of the Dole method (18). Plasma insulin concentration was measured with a double-antibody RIA kit (New England Nuclear). Because glucose and lactate concentrations measured in frozen plasma did not differ significantly from those measured in freshly obtained whole blood, plasma measurements are reported throughout this study.

Calculations. Cardiac arterial-venous balance (in mmol/l) for glucose, lactate, and FFA under each of the three conditions was calculated by subtracting the coronary venous concentration from the arterial plasma concentration. This arterial-venous concentration difference was divided by the arterial concentration and multiplied by 100 to yield a percent myocardial extraction for each substrate.

Data analysis. Results from measurements made on quadruplicate pairs of plasma were averaged to yield one value for each of the three study conditions. Comparisons between conditions were made by paired t-tests with a correction for one repeated measurement. Data are expressed as means ± SD. Differences were considered significant at a P value of <0.05.

Table 1. Plasma substrate concentrations and myocardial uptake

<table>
<thead>
<tr>
<th>Subject</th>
<th>Insulin Condition</th>
<th>Glucose</th>
<th>Lactate</th>
<th>FFA</th>
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<td>[Art], mmol/l</td>
<td>Balance, mmol/l</td>
<td>Extraction, %</td>
<td>[Art], mmol/l</td>
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Arterial plasma concentration ([Art], mmol/l), myocardial arterial-coronary venous concentration balance (Balance, mmol/l), and percent extraction from arterial plasma for glucose, lactate, and free fatty acids (FFA) in the basal fasting state and during coronary and systemic hyperinsulinemia. Individual data are shown for each of 10 subjects.

RESULTS

Hemodynamic and angiographic data. Basal systolic and diastolic blood pressure averaged 128 ± 16 and 85 ± 8 mmHg, and heart rate averaged 64 ± 5 beats/min; these were not affected by intracoronary or intravenous insulin infusion. Angiography demonstrated that the left main coronary and its left anterior descending and circumflex branches were patent and constituted the primary left ventricular blood supply in all subjects. Obstructive atherosclerosis (>50% luminal narrowing) was present in at least one of the three major coronary branches in all subjects, but left ventricular contractile function was preserved with left ventricular ejection fraction averaging 52 ± 4%.

Plasma insulin and substrate concentrations. Individual metabolic data are listed in Table 1. In the basal, overnight-fasted state, arterial plasma insulin concentration averaged 14 ± 4 µU/ml. Intracoronary insulin infusion succeeded in raising coronary venous insulin concentration to 140 ± 20 µU/ml without appreciably increasing systemic arterial levels (16 ± 4 µU/ml). Intravenous infusion produced a similar degree of
generalized hyperinsulinemia, with both systemic arterial and coronary venous plasma insulin concentrations averaging 168 ± 26 µU/ml.

In the fasted state, arterial plasma glucose, lactate, and FFA concentrations averaged 5.6 ± 0.6, 0.7 ± 0.2, and 1.3 ± 0.4 mmol/l, respectively. During intracoronary infusion, there was no significant reduction in arterial glucose (5.3 ± 0.7 mmol/l) or FFA (1.3 ± 0.5 mmol/l) concentration and no increase in arterial lactate concentration (0.6 ± 0.6 mmol/l), all indicating the absence of a systemic insulin metabolic effect.

Intravenous insulin infusion reduced arterial FFA concentration by 50% to 0.7 ± 0.2 mmol/l (P < 0.01 vs. both basal and intracoronary), whereas arterial glucose was maintained slightly above the basal level (~6.1 mmol/l) by dextrose infusion. Only small quantities (1.5 ± 0.8 mg·kg⁻¹·min⁻¹) of dextrose were required to prevent a fall in arterial glucose concentration during insulin infusion, indicating some degree of whole body insulin resistance in this population (16, 17). Arterial lactate level rose in every subject during intravenous infusion, reaching 0.9 ± 0.2 mmol/l (P < 0.05 vs. both basal and intracoronary).

Myocardial substrate extraction. Substrate extraction data are summarized in Fig. 3. In the basal, fasted state, the arterial glucose concentration exceeded that of coronary venous plasma in each patient, indicating consistent net myocardial extraction of glucose. However, the magnitude of the glucose arterial-venous difference was small, averaging 0.12 ± 0.11 mmol/l (2.4 ± 2.1% extraction from arterial plasma). In contrast, FFA were the preferred myocardial substrate, with 0.34 ± 0.13 mmol/l (27 ± 6%) extraction from arterial plasma.

Interval measurements of arterial-coronary venous glucose and FFA balance during the serial insulin infusions are shown in Fig. 2. As illustrated, arterial-venous glucose balance began to widen ~40 min into intracoronary infusion and had stabilized at a new level by ~50 min. At 60–70 min, myocardial arterial-venous balance had widened in every subject to 0.27 ± 0.14 mmol/l (5.2 ± 2.9% extraction). This occurred in the absence of any significant change in arterial concentration, myocardial arterial-venous balance (0.36 ± 0.13 mmol/l), or fractional extraction (28 ± 8%) of FFA.

Systemic insulin infusion reduced both arterial FFA concentration and myocardial FFA extraction (to 14 ± 4%) resulting in a 75% reduction in FFA arterial-venous balance to 0.09 ± 0.04 mmol/l (P < 0.05 vs. both basal and intracoronary). Coincident with this, glucose arterial-venous balance rose still further, reaching a new plateau at 0.51 ± 0.19 mmol/l (7.6 ± 3.1% extraction from arterial plasma, P < 0.05 vs. both basal and intracoronary). During systemic hyperinsulinemia, arterial plasma FFA concentration correlated positively with myocardial FFA uptake (r = 0.87, P < 0.01) and negatively with myocardial glucose uptake (r = −0.65, P < 0.05). These relationships are illustrated in Fig. 4.

In the case of lactate, in the basal state its fractional extraction from arterial plasma was higher (20 ± 10%) than that of glucose, and its net arterial-venous balance averaged 0.15 ± 0.10 mmol/l. Local coronary hyperinsulinemia increased lactate fractional extraction to 29 ± 9% (P = 0.07 vs. basal) and increased arterial-venous balance to 0.19 ± 0.07 mmol/l (P = 0.06 vs. basal). Conversion to systemic hyperinsulinemia increased arterial lactate concentration to 0.9 ± 0.2 mmol/l and percent extraction from arterial plasma to
39 ± 9% (P < 0.05 vs. intracoronary), increasing the net arterial-venous balance to 0.36 ± 0.16 mmol/l (P < 0.05 vs. intracoronary).

Relative significance of local versus systemic insulin effects. If the effect of systemic hyperinsulinemia is expressed as the fractional increase from the fasting state in percent cardiac glucose extraction during intravenous insulin infusion

\[
\left(\%\text{Ext}_\text{veninf}\right) - \left(\%\text{Ext}_\text{basal}\right) / \left(\%\text{Ext}_\text{basal}\right)
\]

(where \% Ext coronary inf is percent coronary infusion extraction) is seen to be a 117% increase. Thus it could reasonably be concluded that during systemic hyperinsulinemia in vivo, the portion of the observed increment in myocardial glucose extraction, which is attributable to direct local insulin action would have been 117%/217% or ~54% of the total effect, with the remaining ~46%, by inference, attributable to reduction in circulating concentrations of FFA and perhaps other substrates. For the case of lactate, the corresponding calculation shows that 45%/95% or ~47% of the insulin effect could be attributed to direct local action on the heart.

DISCUSSION

The results of this study confirm previous observations by McNulty and co-workers (16, 17) and others (5, 12, 27) that systemic physiological hyperinsulinemia increases myocardial glucose extraction approximately fourfold in middle-aged human subjects and that the magnitude of this effect correlates inversely with the insulin-induced reduction in arterial plasma FFA level. The novel finding is that insulin appears to act both by lowering plasma FFA and by a direct action or actions mediated within the heart itself. The relative influences of these two mechanisms appear to be approximately equal, with each accounting for about one-half of the total insulin effect. This represents evidence that insulin exerts quantitatively significant local metabolic actions on the myocardium of intact organisms in vivo.

The current results are observational in nature and do not identify the specific mechanism responsible for the local insulin effect. Nevertheless, in the context of our current understanding of insulin action, several possibilities could be considered. First, administration of insulin for 60 min would be expected to increase cardiomyocyte glucose transport capacity by inducing translocation of insulin-sensitive glucose transporters to the sarcolemma (23) and increasing hexokinase activity (21). Because glucose transport is generally considered rate limiting for muscle glucose utilization in the fasting state, this would most likely represent the primary mechanism of local insulin action. In this regard, our results could perhaps be considered an index of the relative control strengths for myocardial glucose utilization of the “push” effect of stimulating glucose transport versus the “pull” effect of relieving FFA-mediated downstream glycolytic and oxidative glucose metabolism. Second, local hyperinsulinemia could also stimulate one or more downstream enzymatic steps in glucose metabolism, and here our observations regarding lactate balance may be relevant. Each subject in this study exhibited net myocardial lactate extraction in the fasting state, and systemic insulin administration increased the circulating lactate concentration, its arterial-coronary venous balance, and its fractional extraction by the heart, in agreement with previous findings in canines (28) and humans (5, 13, 26, 27). This observation had previously been interpreted as simply reflecting classic substrate competition, i.e., systemic hyperinsulinemia lowers circulat-
ing FFA concentration while increasing lactate concentration by stimulating glycolysis in skeletal muscles. The finding that the lactate arterial-venous balance increased in response to local coronary insulin administration, in the absence of significant change in circulating substrate levels, would be consistent with the stimulation of glucose flux not merely into glycogen synthesis (which would have left the lactate arterial-venous balance unchanged) or through glycolysis (which would have shifted it toward net lactate production) but all the way through pyruvate dehydrogenase, the rate-limiting step for glucose, and lactate entry into mitochondrial oxidation. Third, insulin might act at the tissue level to suppress the utilization of endogenous myocardial substrates. Cardiomyocytes contain endogenous pools of glycogen and triglycerides, which are thought to undergo continuous turnover (8, 9). Whereas little is known about the regulation of these processes in vivo, insulin inactivates muscle glycogen phosphorylase and hormone-sensitive lipase as well as inhibiting transport of long-chain fatty acids into mitochondria (22), all of which should reduce the contribution of glycogen and endogenous lipid to oxidative carbon flux and favor the use of exogenous glucose as an alternative.

In its dual response to hyperinsulinemia, the myocardium would appear to be qualitatively similar to skeletal muscle. For example, Gelfand and Barrett (6) observed that forearm glucose uptake increased fourfold during local brachial artery insulin infusion compared with the sevenfold increase noted by Consoli et al. (3) during systemic hyperinsulinemia of the same magnitude. Similarly, Kelley et al. (10) reported a threefold increase in leg glucose uptake during systemic hyperinsulinemia when plasma FFA were clamped at their basal level but noted a sevenfold increase if they were allowed to fall. Whereas the current data are the first to directly compare local and systemic insulin actions on heart metabolism in any species, Barrett et al. (1) in studies of mongrel dogs correspondingly observed that myocardial glucose uptake increased twofold when insulin was infused intravenously with FFA levels clamped versus fourfold when they were permitted to fall. Our results do, however, demonstrate a dissimilarity between cardiac and skeletal muscle with respect to lactate metabolism. Whereas we observed an increase in net myocardial lactate consumption during local coronary hyperinsulinemia, human forearm muscle is in contrast a net lactate producer in the fasting state and responds to hyperinsulinemia by increasing its glycolytic lactate production to a greater degree than its oxidative consumption, with the result that forearm arterial-venous balance becomes even more negative (3). This difference may reflect the inherently greater oxidative capacity of cardiac muscle.

The techniques of local coronary infusion and arterial-coronary sinus catheterization used in these experiments are uniquely suited to the nondestructive study of myocardial metabolism in human subjects. Nevertheless, the study has limitations. A general difficulty of study design is that for obvious reasons it was not possible to randomize the sequence of the two insulin infusion protocols, because leading with the intravenous infusion would also increase local coronary plasma insulin levels and produce prolonged reduction in circulating FFA. This raises the theoretical possibility that the additional increment in glucose extraction attributed to systemic hyperinsulinemia may reflect in part a "priming" effect of the preceding local infusion. As a precaution against this, arterial-coronary venous balance measurements were not made until 60–70 min into each infusion or ~20 min beyond the point at which serial measurements demonstrated a stable plateau insulin effect (Fig. 2). It is also theoretically possible that the increase in glucose extraction during coronary insulin infusion was accompanied by a decreased uptake of an alternative substrate not measured in the study. A further limitation concerns the measurement of lactate arterial-venous balance. Because the myocardium both consumes and releases lactate simultaneously (27), the widening of lactate arterial-venous balance observed during intracoronary insulin infusion could theoretically reflect suppression of lactate release rather than direct insulin stimulation of lactate oxidation. Thus the hypothesis that local hyperinsulinemia directly stimulates myocardial lactate disposal will need confirmation by additional studies of lactate radiotracer kinetics. Because only one level of hyperinsulinemia was examined, whether the local insulin effect has a threshold or dose-response characteristics, will require further study. Finally, the study did not examine the metabolic fate of glucose imported into the heart in the two hyperinsulinemic states, nor whether they are identical.

In summary, the increase in myocardial glucose uptake observed to follow an increment in the circulating insulin concentration in vivo appears to be mediated equally by glucose-FFA competition and direct, local insulin action on the heart. Insulin exerts quantitatively important direct metabolic actions on the myocardium even in subjects relatively resistant to its effects on whole body glucose disposal, and these may include stimulating the energetically important process of oxidative glucose metabolism.

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