Effect of Non–Insulin-Dependent Diabetes Mellitus on Myocardial Insulin Responsiveness in Patients With Ischemic Heart Disease

Dinesh Jagasia, MA; Jennifer M. Whiting, BS; John Concato, MD; Steven Pfau, MD; Patrick H. McNulty, MD

Background—Patients with non–insulin-dependent diabetes mellitus (NIDDM) exhibit poor clinical outcomes from myocardial ischemia. This may reflect an impairment in their cardiac insulin-response system.

Methods and Results—We used AV balance and intracoronary infusion techniques to compare the intrinsic cardiac responsiveness to insulin in 26 coronary disease patients with (n=13) and without (n=13) NIDDM. During fasting, NIDDM hearts demonstrated lower fractional extraction of glucose from arterial plasma than controls (1.0±0.5% versus 2.1±0.5%, P<0.05) despite higher circulating insulin levels (26±5 versus 13±4 μIU/mL, P<0.05). This was compensated for by higher circulating glucose levels, so that net cardiac glucose uptake in the 2 groups was equivalent (5.2±1.1 versus 5.3±1.1 μmol·min). Intracoronary insulin infusion produced an ≈3-fold increase in fractional extraction and net uptake of glucose across the heart in both groups (to 3.7±0.4% and 18.3±3.5 μmol·min in NIDDM and to 5.4±0.7% and 17.7±4.3 μmol·min in controls) accompanied by an ≈30% increase in net lactate uptake, suggesting preserved insulin action on both glucose uptake and glucose oxidation in the NIDDM heart. In nondiabetics, insulin consistently increased coronary blood flow, but this effect was absent in NIDDM.

Conclusions—In contrast to their peripheral tissues and coronary vasculature, the myocardium of patients with NIDDM expresses a competent insulin-response system with respect to glucose metabolism. This suggests that insulin resistance is mediated at the level of individual organs and that different mechanisms are involved in muscle and vascular tissue.

Key Words: diabetes mellitus • myocardium • insulin • arteries

Patients with non–insulin-dependent diabetes mellitus (NIDDM) experience disproportionate morbidity and mortality from ischemic heart disease.1 The observation that NIDDM specifically increases the incidence of congestive heart failure2 and death3 after an index myocardial infarction implies that this adverse risk may reflect a primary impairment in myocardial ischemic tolerance. Considerable evidence now suggests that the myocardium adapts to ischemia in part by increasing its uptake and energetic metabolism of glucose via recruitment of specific elements of the intrinsic myocardial insulin-response system.4–5 This raises the question of whether the development of NIDDM in patients with ischemic heart disease is associated with impaired expression and/or function of this system.

Most previous attempts to address this question have used the technique of [18F]fluorodeoxyglucose PET to indirectly estimate the myocardial glucose uptake response to systemic insulin administration. These studies have yielded mixed results.6–9 More important, systemic insulin administration stimulates myocardial glucose uptake mainly indirectly by suppressing lipolysis in adipocytes and lowering the plasma fatty acid concentration, which removes fatty acid inhibition of heart glucose uptake and oxidation.10 This does not allow direct assessment of the interaction of insulin with the insulin-response system of the heart itself. To circumvent these limitations, in the present study we combined local intracoronary insulin infusion with direct measurement of arterial-coronary sinus glucose balance to compare the intrinsic myocardial responsiveness to insulin in ischemic heart disease patients with and without NIDDM.

Methods

Subjects
Twenty-six male subjects were enrolled from the population referred for evaluation of chest pain. Subject characteristics are listed in Table 1. Thirteen had NIDDM (duration, 6±4 years; range, 1 to 18 years), and 13 were nondiabetic control subjects. Subjects were excluded if they had reduced left ventricular ejection fraction (<45%), previous myocardial infarction, or chest pain within 24 hours preceding study. All subjects were taking β-adrenergic blockers and aspirin. Hypoglycemic medications (glyburide in 10 subjects and insulin in 3) were withdrawn ≥48 hours before study.
TABLE 1. Characteristics of Control and NIDDM Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NIDDM</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>13</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±6</td>
<td>62±6</td>
<td>...</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±6</td>
<td>83±6</td>
<td>...</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±2</td>
<td>28±2</td>
<td>19–23</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>13±4*</td>
<td>26±5*</td>
<td>5–12</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.3±0.7</td>
<td>8.9±1.1*</td>
<td>4.5–5.5</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0.6±0.2</td>
<td>0.8±0.3</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>FFA, mmol/L</td>
<td>1.2±0.3</td>
<td>1.3±0.3</td>
<td>0.4–1.2</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>5.3±1.0</td>
<td>8.0±1.2*</td>
<td>3.5–5.8</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>53±5</td>
<td>57±5</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HbA₁c, hemoglobin A₁c; and LVEF, left ventricular ejection fraction.

Data Analysis

Results from quadruplicate sets of plasma samples were averaged to yield 1 value for each measured variable under basal and insulin-infused conditions for each subject. All data are expressed as mean±SD. Within each group, comparisons between the 2 sampling times were made by paired t tests. Comparisons between the 2 groups at each sampling time were made by 2-tailed unpaired t tests. A sample size of 11 patients per group provides 80% power to detect a 15% difference in glucose AV balance between NIDDM and control subjects, assuming an SD of 16 and 35 µmol · L for measurement of glucose and lactate AV balances, respectively, and using a 5% two-tailed significance level.

Results

Heart and Coronary Artery Size

In the basal state, NIDDM subjects had higher arterial plasma concentrations of glucose (8.9±1.1 versus 5.3±0.7 µmol · mL, P<0.01) and insulin (26±5 versus 13±4 µU · mL, P<0.05) and higher hemoglobin A₁c levels (8.0±1.2 versus 5.3±1.0%, P<0.05) than nondiabetic control subjects (Table 1). Plasma lactate levels were marginally higher in NIDDM patients (0.8±0.3 versus 0.6±0.2 µmol · mL, P=0.10), whereas FFA levels were uniformly high in both groups (1.2±0.3 versus 1.3±0.3 µmol · mL, P=NS), consistent with the fasting state and heparin administration. Intracoronary insulin infusion succeeded in raising the coronary venous plasma insulin concentration to slightly above the physiological range in both groups (142±14 versus 156±20 µU · mL for control subjects versus NIDDM patients, P=NS) without substantially increasing the systemic arterial insulin level (Figure 1). Arterial plasma glucose, lactate, and FFA concentrations were not affected by insulin infusion in either group (Table 2), confirming the lack of any systemic metabolic insulin effect during intracoronary infusion.

Coronary Sinus Blood Flow and Myocardial Oxygen Consumption

Intracoronary insulin infusion increased coronary sinus blood flow in each of 6 nondiabetic subjects by an average of ∼20%
Basal myocardial blood flow was measured. Consistent with the arterial-coronary sinus balance data, intracoronary insulin infusion increased net myocardial glucose uptake \( \approx 3 \)-fold and lactate uptake \( \approx 40\% \) in both control subjects and NIDDM patients, and there were no differences in the magnitude of insulin-stimulated glucose or lactate uptake between the groups \((P > 0.20\text{ for all comparisons})\).

### Discussion

In this study, we used direct techniques to measure the response of the arterial-coronary sinus glucose balance to an increment in local intracoronary insulin concentration. Because this balance is quantitatively determined by the operation of a number of insulin-responsive metabolic processes within the heart, we reasoned that this measurement should provide an assay of the functional integrity of this integrated insulin-response system. We observed that raising local coronary insulin concentration from a fasting to a slightly supraphysiological level increased myocardial glucose uptake equivalently in ischemic heart disease patients with and without NIDDM. This suggests that in such patients, the development of NIDDM does not impair the intrinsic insulin-response capacity of the heart with respect to glucose consumption.

In the fasting state, our NIDDM patients differed from nondiabetic control subjects in exhibiting hyperglycemia and hyperinsulinemia. These traits are known to indicate resistance to the insulin stimulation of glucose uptake by skeletal muscles, the major target tissue for insulin action.\(^\text{13}\) Correspondingly, we observed that fasting heart glucose uptake in NIDDM patients was merely equivalent to that of control subjects despite higher fasting glucose and insulin levels. This suggests that both skeletal and cardiac muscles of NIDDM patients are insulin resistant during fasting relative to those of nondiabetic control subjects. Because transmem-
brane transport is generally considered to be rate limiting for muscle glucose consumption during fasting, this further implies a fasting impairment in myocardial glucose transport in NIDDM, as has been described for skeletal muscles.14

The observation that NIDDM subjects and control subjects nevertheless exhibited a quantitatively similar glucose-uptake response to local insulin administration can perhaps be explained in the context of our present understanding of muscle glucose metabolism. Insulin stimulates muscle glucose uptake primarily by effecting translocation of the GLUT4 transporter from an intracellular compartment to the sarcolemma.15 Although a variety of defects in intracellular glucose metabolism have been described in individuals or families with NIDDM,13 studies measuring the rate of muscle glucose-6-phosphate accumulation during insulin stimulation have established that the insulin resistance of NIDDM primarily involves an impairment in muscle glucose transport/phosphorylation.16 After its transmembrane transport, the major metabolic fate of glucose imported into both human heart17 and skeletal muscles18 is storage in the form of glycogen. Insulin stimulation of glycogen synthesis in skeletal muscle is also specifically impaired in NIDDM,19 and this impairment accounts quantitatively for almost all the reduction in net glucose consumption in NIDDM muscles.20 Because even healthy prediabetic offspring of NIDDM patients exhibit impaired insulin stimulation of skeletal muscle glucose transport and glycogen synthesis,21 it has been suggested that the disease involves genetically transmitted defects in muscle glucose transporter and glycogen synthase expression.13 How can this be reconciled with the present finding that in NIDDM patients exhibiting insulin resistance of peripheral tissues, cardiac muscle nevertheless appears to remain as insulin responsive as in nondiabetic subjects? The answer may lie in the markedly different contractile work histories of cardiac versus skeletal muscles. In limb muscles of insulin-resistant subjects, contractile exercise increases the capacity for both glucose transport23 and glycogen synthesis.24 In contrast, reducing cardiac workload downregulates myocardial GLUT4 expression25 and produces marked resistance to stimulation of glycogen synthesis by even supraphysiological doses of insulin.26 Thus, the preserved insulin response of the NIDDM heart, relative to other tissues of the body, may reflect the protective effect of repetitive, high-frequency contractile work on glucose transporter and glycogen synthase expression and function.

Obtaining a maximum energy yield from imported glucose requires glycolytic conversion to pyruvate and subsequent mitochondrial oxidation. Although we did not directly measure myocardial glucose oxidation in this study, the finding that local hyperinsulinemia increased net myocardial uptake of lactate and glucose would be consistent with stimulation of glucose carbon flux through pyruvate dehydrogenase, the rate-limiting step for lactate and pyruvate entry into the citric acid cycle. Augmenting myocardial pyruvate dehydrogenase flux has been demonstrated to improve the functional recovery from ischemia in the isolated heart.27 The observation that insulin widened the arterial-coronary sinus lactate balance by an equivalent amount in control subjects and NIDDM patients suggests that the capacity for this important response may also be preserved in the NIDDM heart.
Although hyperinsulinemia in the midphysiological range (50 to 60 µU/mL) appears to be without effect on coronary blood flow in humans,²⁸ we previously observed that raising the systemic insulin level to ≈200 µU/mL increases it by ≈20%,¹¹ The similar response to local hyperinsulinemia in the present study, unaccompanied by any change in myocardial oxygen demand or consumption, suggests a direct, local insulin action on coronary arterial tone. It is well established that insulin exerts an endothelium-dependent, nitric oxide–mediated vasodilatory action in skeletal muscle.²⁹ In that tissue, the magnitude of the effect tracks the magnitude of the effect of insulin on tissue glucose uptake and thus is progressively blunted by the development of insulin resistance and NIDDM.³⁰ Although fewer data are available concerning the heart, a similar loss of vasodilator response to intracoronary insulin infusion has been reported to accompany the development of whole-body insulin resistance in canines.³¹ On the basis of observations in skeletal muscles, a number of explanations could be considered for the impaired blood flow response observed in NIDDM patients, including a primary defect in coronary endothelial function, more extensive atherosclerosis, or simply their prevailing hyperglycemia.³² The present observations do not allow these to be distinguished and furthermore involve only a small number of subjects. Nevertheless, they suggest that at least in the heart, the insulin responsiveness of vascular tissue and muscle may be mediated independently.

The study has several limitations. NIDDM patients were studied at plasma glucose concentrations ≈70% higher than nondiabetic control subjects. This might be predicted to increase the absolute magnitude of their heart glucose uptake by mass action, even in the face of diminished intrinsic insulin responsiveness. Nevertheless, studies of the whole-body response to insulin in NIDDM demonstrate that even hyperglycemic insulin infusion produces less than one half the fractional increase in whole-body glucose uptake produced by euglycemic insulin infusion in nondiabetic subjects.³³ In the case of tissues of the whole body, this difference is attributable to both a rightward shift in the insulin dose-response curve and decreased maximal insulin response.³³ The present results demonstrating proportionally equal insulin stimulation of myocardial glucose uptake in control subjects and NIDDM patients suggest that these changes in insulin sensitivity and response capacity are not demonstrable in the heart. Because the study design required fasting and heparin administration, our observations were necessarily made at relatively high circulating FFA levels, which would tend to suppress absolute myocardial glucose uptake.¹⁰ Further studies are needed to determine whether the glucose-uptake response of the NIDDM heart remains equivalent to that of the nondiabetic heart at higher glucose utilization rates. Finally, although we did not directly measure whole-body insulin sensitivity in these subjects, our previous observations¹¹ suggest that even in the absence of NIDDM, ischemic heart disease patients exhibit some degree of whole-body insulin resistance relative to age-matched healthy subjects.²⁸ Because the study did not include control subjects without heart disease, we cannot distinguish whether the myocardial insulin-response characteristics of our NIDDM and nondiabetic groups would have been equivalent to those of healthy subjects or instead simply impaired to an equivalent degree.

In summary, in patients with ischemic heart disease, the development of NIDDM appears to impair the effects of insulin on coronary tone but not on myocardial glucose consumption. Ischemic heart disease patients both with and without NIDDM express equally responsive cardiac metabolic insulin-response systems, which should be equivalent targets for insulin-based metabolic therapy.

### Acknowledgments

This work was supported by a merit review grant from the Department of Veterans Affairs and the General Clinical Research Center of Yale-New Haven Hospital. We thank the staff of the Connecticut VA Healthcare System cardiac catheterization laboratory for help in the performance of these studies.

### References


Effect of Non–Insulin-Dependent Diabetes Mellitus on Myocardial Insulin Responsiveness in Patients With Ischemic Heart Disease
Dinesh Jagasia, Jennifer M. Whiting, John Concato, Steven Pfau and Patrick H. McNulty

_Circulation_. 2001;103:1734-1739
doi: 10.1161/01.CIR.103.13.1734

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/13/1734

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/