Ineffectiveness of Glucose, Potassium, and Insulin Infusion During Pacing Stress in Chronic Ischemic Heart Disease

By Michael Lesch, M.D., Louis E. Teichholz, M.D., J. Stuart Soeldner, M.D., and Richard Gorlin, M.D.

SUMMARY

Eight patients with coronary artery disease and positive exercise electrocardiograms undergoing cardiac catheterization were subjected to periods of atrial pacing-induced tachycardia at identical rates, before and during a glucose, potassium, and insulin (GKI) infusion. Steady state elevation of glucose and insulin was obtained prior to repeating the atrial pacing test in the GKI state. With each patient serving as his own control, five developed augmented clinical signs of acute ischemia during the paced GKI state, two no change, and one subjective improvement. Left ventricular end-diastolic pressure (LVEDP) was elevated in all patients (1–8 mm Hg) at rest during GKI infusion as compared to the rest control state. LVEDP during pacing was greater during the GKI paced state as compared to the control paced state in three of the eight patients whereas after pacing LVEDP was higher in four of eight patients during GKI. ST-segment depression was less during pacing in the GKI as compared to control state in four patients. A decrease in ST-segment depression was noted in two patients after pacing in the GKI state as compared to this measure after pacing in the control state. Augmented myocardial glucose uptake was demonstrated in the paced GKI state but lactate analysis failed to demonstrate a stoichiometric relationship between enhanced glucose uptake and lactate production.

It is concluded that tolerance to ischemia is not extended and in the majority of cases may be adversely affected by GKI.

Additional Indexing Words:

Left ventricular end-diastolic pressure

Myocardial lactate extraction

THE THERAPEUTIC BENEFIT from glucose-potassium-insulin (GKI) in numerous cardiovascular disease states was first postulated in 1960.1 The theoretical basis for this proposal was the supposition that an intracellular potassium deficit in the heart was a feature common to many cardiac disorders.

Initial studies, limited to the investigation of the effectiveness of GKI in acute coronary ligation in the dog and acute myocardial infarction in humans, suggested GKI to be of benefit in both situations.2-5 Subsequent studies in large randomized patient populations with acute myocardial infarction have not substantiated the initial clinical impression of effectiveness.6,7 Retrospective analysis of these negative studies has led some to postulate that acute myocardial infarction is a sufficiently complex event that appropriate evaluation of GKI therapy is not feasible.8

Previous clinical trials have primarily evaluated the ability of GKI therapy to protect an infarct population from the development of arrhythmias. Data of a more basic nature obtained with experimental cardiac preparations have demonstrated that glucose alone, or in combination with insulin and potassium, is capable of ameliorating the deleterious effects of an acutely imposed low oxygen state on various aspects of cardiac function.8 One postulated mechanism for the protective effect of glucose is an enhancement of anaerobic energy production during an oxygen deficit due to an associated increase in the rate of glycolytic metabolism.8

The present study was designed to directly test whether tolerance to an ischemic stress could be increased in humans with coronary artery disease if
glycolytic substrate and insulin were present in excess and thus were not limiting. The ability of patients to withstand the ischemic stress of pacing-induced tachycardia during a control and a glucose-insulin state was evaluated. If GKI is beneficial in humans with coronary artery disease during ischemic stress, increased tolerance of the heart to the stress of pacing should be demonstrable during an infusion of glucose and insulin that significantly elevates the concentration of these moieties in the blood. Moreover, if the biochemical basis for this effect is an enhancement of anaerobic energy production, increased myocardial glucose utilization and/or lactate production should be simultaneously demonstrable.

Methods

Patient Selection

Eight patients with severe angina pectoris and a positive Master's Two-Step Exercise Test who were to undergo diagnostic catheterization and angiography constituted the study group. All had normal fasting blood sugar levels, and none was receiving digitalis glycosides. Informed consent was obtained from all.

Study Protocol

Studies were performed following an overnight fast. The study protocol was initiated prior to diagnostic catheterization and angiography in three of the eight subjects. Clinical evaluation suggested the remaining five subjects might not tolerate both diagnostic catheterization and a metabolic study. These five patients were therefore studied following the completion of their diagnostic evaluation. In these cases the study protocol was performed after the patients had been allowed to remain quiet in a basal state following diagnostic catheterization and angiography. Catheters were placed in the left ventricle, a brachial artery, the coronary sinus, and a central vein and were flushed periodically with heparinized saline only. Total heparin dosage over the study period did not exceed 20 mg. Solutions containing glucose were not used until the study protocol was initiated. Pacing was obtained via the coronary sinus catheter which was maintained in a fixed position during the study as determined by fluoroscopy.

Left ventricular end-diastolic pressure (LVEDP), ST-segment depression (measured in the lead where ST-segment depression was greatest during the precatheterization Master's Test) and paired transmyocardial arteriovenous (A-V) glucose, lactate, insulin, and potassium differences were measured at rest. Coronary sinus pacing was initiated and the pacing rate increased in increments of 10 beats/min until angina pectoris or atroventricular block occurred, or a rate of 160 beats/min was obtained. Pacing was continued for 3 min once a pacing end point had been reached, and LVEDP, ST-segment depression, and paired transmyocardial glucose, lactate, insulin, and potassium differences were again measured while the paced rate was maintained for an additional 60-90 sec. A continuous high gain left ventricular pressure and ECG were recorded during and immediately following the pacing state. LVEDP and ST-segment depression were measured during the final 60 sec of pacing and in the first five beats following cessation of pacing.

The "control" phase of the protocol was terminated with the cessation of pacing. The subject was then allowed to rest for 15-30 min to permit a return to the basal state. Previous studies 10 indicate a basal state is attained and LVEDP returns to prepping levels within 1-2 min unless angina persists after pacing is terminated. Angina subsided immediately with cessation of pacing in all subjects who developed this end point during the control paced state. Heart rate and mean arterial pressure were nearly identical in the resting control and resting GKI state (table 1) in all patients except 6. These data provide additional evidence that a basal state had been obtained at the time of the GKI pacing studies. Although fasting blood sugars were normal in all subjects on the day prior to catheterization, the control glucose levels at zero time immediately preceding GKI infusion were elevated in all. Since no glucose-containing solution was administered prior to GKI infusion, these values presumably represent a form of stress reaction. However, by this criterion, the degree of stress present during the control state and immediately before initiation of the GKI infusion must have been identical since blood sugar levels in the control state were identical in each patient to that obtained immediately prior to initiation of GKI (table 1).

The GKI state was initiated by injecting a 50 cc bolus containing 25 g glucose and 10 units crystalline zinc insulin (CZI) into the central venous catheter over 5 min. Immediately following the bolus injection 150 ml of solution containing 75 cc glucose, 9 units CZI and 30 mEq potassium chloride were infused at a constant rate over a 60 min period. The glucose content of venous blood was measured prior to initiation of GKI and 5, 20, 35, and 50 min after the infusion had been started. LVEDP, ST-segment depression, and transmyocardial A-V glucose, lactate, insulin and potassium differences were measured with the patient in the resting state 40 min after initiation of the constant infusion. Pacing was reinstated and the rate increased in increments of 10 beats/min until a rate identical to the last reached in the control state was achieved. The paced rate was maintained for 3 min and the same measurements taken in the

<table>
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<th>Blood glucose</th>
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</table>

Heart rate and mean arterial pressure in the resting state are listed for each patient. These values were measured immediately before initiation of pacing in the control or GKI state. Blood glucose values obtained in the control state and immediately prior to initiation of GKI are listed.

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paced control state were repeated in the paced GKI state.

Biochemical, Hemodynamic, and Angiographic Techniques
LVEDP was measured with standard procedure and equipment as previously described in this laboratory. Coronary angiography was performed by either the Sones or Judkins technique and left ventriculograms were obtained utilizing retrograde catheterization of the ventricle. The technique for lactate determinations in this laboratory and the definition of lactate extraction or production have been described. Plasma glucose was determined by a microglucose method adapted for the Technicon Auto-Analyzer using the ferricyanide method. The coefficient of variation of this method is 1.3%. Each sample was divided into nine aliquots which were analyzed separately. Serum immunoreactive insulin levels were measured as previously described. Serum potassium was determined with atomic absorption spectrometry.

Results

Clinical Data
Table 2 contains basic clinical data describing the subjects studied. All were male, between the ages of 28 and 63 years, with severe coronary artery disease and varying degrees of abnormality of ventricular wall motion. In addition, interpretation of the resting ECG, and a symbol for identification in all subsequent figures are provided.

Alteration by GKI of Threshold for Clinical Signs Induced by Pacing Tachycardia

The clinical response and the maximum paced rate tolerated during the control state are depicted in the left-hand side of figure 1. The response of each patient to this pacing rate during GKI is shown on the right-hand side of the figure. The responses to pacing in patients 1 and 2 were identical in control and GKI states. In the former atrioventricular conduction block developed at a rate of 150 beats/min without angina in both states, whereas in the latter a rate of 160 beats/min was tolerated for five minutes in both states. Patient 3 was the only subject to exhibit a salutary clinical response to GKI. In the control state a pacing rate of 120 beats/min induced angina pectoris, whereas the same rate was tolerated without angina during GKI.

Tolerance to pacing was diminished during GKI in the remaining five patients. The range of decreased tolerance included: a subjective response of more

<table>
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<td><strong>Clinical Data</strong></td>
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<td>7 (◇)</td>
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<td>8 (◆)</td>
</tr>
</tbody>
</table>

**Percentage figures indicate the degree of obstruction in the coronary artery noted.**

Abbreviations: RCA = right coronary artery; LM = left main coronary artery; LCFM = left circumflex marginal artery; LAD = left anterior descending artery; DMI = diaphragmatic myocardial infarction; ASMI = antero-septal myocardial infarction.
GKI IN ISCHEMIC HEART DISEASE

The clinical response of eight patients with coronary artery disease to the stress of pacing-induced tachycardia in the control state (see Methods) is presented on the left. The clinical response to an identical pacing stress following infusion of glucose, potassium and insulin (GKI state) is presented on the right. Patient *5* (*6*) developed spontaneous angina after 20 min of GKI infusion. See table 2 for patient number corresponding to symbol used. VPB = ventricular premature beat.

Severe angina at a given pacing rate during GKI (patient *4*); angina at three minutes of pacing at a rate of 135 beats/min in both states but development of pulsus alternans with angina during GKI (patient *6*); atrioventricular block without angina at a paced rate of 115 beats/min in the control state, with atrioventricular block, angina, and ventricular premature contractions at this same rate during GKI (patient *7*); angina at four minutes of pacing at a rate of 155 beats/min in the control state, and after only two minutes of pacing at this same rate during GKI induction of angina, rapid atrial fibrillation, and complete circulatory collapse requiring immediate cardioversion (patient *5*); and angina at a paced rate of 125 beats/min during the control state but the development of severe spontaneous angina following 20 minutes of GKI infusion at a resting heart rate of 85 beats/min (patient *8*). Mean arterial pressures were similar in the control pacing as compared to the GKI pacing state in all patients except *6* (table 3) indicating the product of heart rate \( \times \) mean blood pressure obtained during pacing was similar in the GKI and control state.

Alterations of LVEDP During Pacing Stress with GKI

LVEDP recorded at rest, during the terminal phase of a pacing stress, i.e., immediately prior to the termination of pacing at the time of maximum clinical response, and in the five beats immediately following cessation of pacing in control and GKI states are separately recorded for each patient in the eight panels of figure 2. LVEDP decreased during pacing in the control state in patients *1* and *7*. GKI did not affect the response of patient *7* to pacing whereas in patient *1* LVEDP rose during pacing in the GKI state. The remaining patients exhibited varying degrees of elevation of LVEDP during pacing in the control state, and this pattern was not significantly altered by GKI. Resting LVEDP in the GKI state was higher by 1–8 mm Hg in all patients as compared to the control state, and rose proportionately higher with pacing during GKI in patients *3* and *4*. In patients *2*, *5*, and *6*, resting LVEDP was higher in the GKI state as compared to the control rest state, whereas LVEDP during pacing was identical in both states.

Alteration of ST-segment Depression

Figure 3 illustrates the degree of ST-segment depression in control and GKI states measured simultaneously with LVEDP in the terminal portion of the pacing stress and in the first five beats following

<table>
<thead>
<tr>
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<th>GKI paced state</th>
</tr>
</thead>
<tbody>
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<tr>
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<tr>
<td>#8</td>
<td>85</td>
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</tr>
</tbody>
</table>

Mean arterial pressure during pacing in the control and GKI state for each patient is listed.

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Table 3

Mean Arterial Pressure During Pacing

Figure 2

LVEDP recorded at rest, during the terminal phase of a pacing stress, and in the first 5 beats immediately following cessation of pacing in control and GKI states are recorded for each patient in the study.
cessation of pacing. In subject 6, ST-segment depression was 1.5 mm less in the GKI state both during and immediately after pacing. Three patients had 0.5 mm less ST-segment depression during pacing in the GKI state, as compared to the control, but this salutary effect persisted into the postpace period in only one patient. GKI had no effect on the resting ECG.

Glucose-Insulin Relationships

Central venous plasma glucose measured prior to GKI and at 5, 20, 35, and 50 min following initiation of the 60 min infusion are presented in figure 4. In all subjects plasma glucose levels were significantly elevated five minutes after initiation of the infusion and did not further increase during the infusion. In seven of the eight subjects the infusion resulted in an elevation of plasma glucose levels to the range of 330-410 mg/100 ml. In patient 5, a plasma glucose of 700 mg/100 ml was produced by GKI.

Serum insulin levels in arterial blood in control and GKI states are illustrated in figure 5. In all subjects except 5, a twenty to one hundred fold increase in serum insulin level was observed during GKI. Insulin levels obtained in the rest and paced GKI state were identical in any single patient indicating steady state conditions for insulin were met during the GKI infusion. Analysis of arterial — coronary sinus insulin data revealed no consistent pattern in either the control or GKI state (data not presented).

Arterial — coronary sinus plasma glucose levels at rest and during maximum pacing for control and GKI states are presented in table 4. The transmyocardial arterio — venous glucose difference in the control as compared to the GKI rest state was more positive (or less negative) during GKI for all patients except 4 and 6. Similarly, data for the control as compared to the GKI paced state was more positive (or less negative) during GKI for the six subjects on whom complete studies were obtained. Data for patients 5 and 8 in the paced GKI state are unavailable since the clinical deterioration of these patients precluded a complete

Figure 3

ST-segment depression (mm) measured during peak pacing and in the first 5 beats immediately following cessation of pacing in control and GKI states are recorded for each patient in the study. Abbreviations: SAP = spontaneous angina pectoris; AF = atrial fibrillation. Symbols for patient identification as in table 2.

Figure 4

Central venous plasma glucose (mg/100 ml) plotted as a function of time. Zero minute refers to a determination immediately prior to initiation of GKI infusion. Symbols for patient identification as in table 2.

Figure 5

Serum immuno reactive insulin (u units/ml) is plotted in control and GKI states for all patients. Symbols for patient identification as in table 2.
study. The mean arterio-venous glucose difference was 18 mg/100 ml more positive in the GKI rest as compared to the control rest state. Although suggestive of an enhancement of myocardial glucose uptake during GKI, the data were scattered and the increase not statistically significant. In contrast, the mean arterio-venous glucose difference in the GKI paced state was 10 mg/100 ml more positive than in the control paced state. These data were uniform and the difference is significant at the \( P < 0.005 \) level.

Effects of GKI on Myocardial Lactate Metabolism

Arterial lactate levels obtained at rest and following 3 min of pacing in control and GKI states are presented in table 5. The data for transmyocardial lactate determinations are presented in table 6. Lactate levels rose two-three fold in response to GKI in all subjects except patient 5. Lactate levels obtained in the rest and paced GKI state were nearly identical in any single patient indicating steady state conditions for lactate were met during GKI infusion. Lactate extraction was positive at rest in both control and GKI states and was numerically lower during pacing as compared to resting values in the control state for all patients. Lower extraction was noted in the paced GKI as compared to the rest GKI state in all instances except for patient 4. Three subjects produced lactate during pacing in the control state but only one of these demonstrated lactate production during pacing in the GKI state.

Effects of GKI on Potassium Metabolism

GKI altered neither the absolute serum potassium level nor the transmyocardial arterio-venous values observed in resting and paced states when compared to control values.

Discussion

In contrast to detailed studies in experimental preparations,8 investigation of the role of GKI in human cardiac disease has not been directed toward the simultaneous evaluation of effectiveness and definition of mechanism in specific disease states. Frequently GKI has been administered to patients with terminal cardiac disease of diverse etiology and therapeutic response is reported without consideration to the underlying pathology.17 Initial attempts to systematically evaluate GKI in human cardiac disease have been made relative to only two hypotheses: a) that GKI can prevent ventricular arrhythmias and arrhythmic deaths in acute myocardial infarction and b) that decreased insulin reserve is characteristic of, and related to chronic or acute congestive heart failure.

### Table 4

Transmyocardial Arterial – Coronary Sinus Glucose (mg/100 ml plasma)

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<thead>
<tr>
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<th>Paced state</th>
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*Net Change* refers to the algebraic differences in arterial – coronary sinus glucose values in the GKI as compared to the control state.

Each value represents an arterial – coronary sinus glucose value in a given state. Individual arterial and coronary sinus glucose values used to calculate the arterial – coronary sinus difference were obtained by averaging nine separate determinations from a given sample as described in methods.

### Table 5

Arterial Lactate (mM/L)

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</table>

Arterial lactates obtained in the rest and paced states during control and GKI periods. All values represent the average of duplicate determinations performed on a single sample aliquot.
Following reports by Sodi-Pallares that GKI causes a more rapid normalization of injury currents and possibly decreases the incidence of arrhythmias during acute myocardial infarction, several controlled clinical trials attempted to evaluate the role of GKI in preventing death due to arrhythmia in acute ischemic disease. Whereas early studies suggested GKI was capable of reducing mortality from arrhythmias, subsequent studies found no difference in mortality rate or incidence of arrhythmia between control and treated groups. Although these negative studies did not follow exactly the formulae for GKI administration as originally proposed by Sodi-Pallares, there is at present no evidence to support the contention that GKI therapy can significantly affect either mortality rate or incidence of arrhythmia in acute myocardial infarction.

Taylor et al. have described decreased insulin secretion following intravenous tolbutamide as characteristic of patients with congestive heart failure and/or cardiogenic shock and have correlated the severity of the cardiac dysfunction with the degree to which insulin secretion is depressed. Other observations, however, are not consistent with the contention that the congestive failure of chronic ischemic heart disease is either causally related to hypoinsulinemia or correctable by insulin therapy.

The present study was designed to determine whether cardiac tolerance to a controlled and reversible ischemic stress could be improved if blood glucose and insulin levels were raised such that the supply of glycolytic substrate to the myocardial glucose transport system could not be limiting in human subjects with chronic ischemic heart disease. In order to obtain conditions amenable to controlled observation, pacing-induced tachycardia was utilized as the ischemic stress in a coronary disease population without congestive heart failure. Furthermore, by using transmyocardial arterio-venous sampling an attempt was made to directly test the hypothesis that GKI infusion could increase myocardial glucose uptake, and presumably, anaerobic energy production during ischemia.

For the conclusions of the present study to be valid, it must be demonstrated that pacing tachycardia is a reproducible ischemic stress which can be repetitively utilized to test cardiac function in patients with coronary artery disease and that each patient had returned to a basal state prior to the initiation of the pacing tolerance test in the GKI state. Ideally, the GKI state would have been investigated prior to the control state in half of the subjects, but such a protocol is not feasible if the metabolic state of the patient in the "control" state is to be controlled.

Since heart rate, mean arterial pressure, and blood glucose were not significantly different prior to pacing in both the control and GKI state (table 1), it would appear that a basal state had been reattained. Previous observations have demonstrated pacing-induced tachycardia to be a reproducible ischemic stress in patients with coronary disease. Over the short term the pacing rate at which angina occurs in a given patient does not vary and changes in pacing threshold have been used to evaluate the effects of various interventions on cardiac function in patients with ischemic heart disease. Any intervention which increases the anginal threshold to pacing can be considered to have rendered the heart more resistant to ischemia whereas the opposite holds for interventions which decrease the anginal threshold.
tolerance to pacing tachycardia was not significantly increased during GKI infusion in the present study despite significant steady state elevations of blood glucose and insulin. Only one patient benefited “clinically” as demonstrated by an increased clinical tolerance to pacing. As noted above, calculation of the blood pressure × heart rate product would not have altered the conclusions drawn from analysis of the clinical data.

Cardiac function in general did not improve and had possibly deteriorated during the GKI state. LVEDP in the rest control state was normal in patients 1, 2, 5, and 7 and elevated above 12 mm Hg in patients 3, 4, 6, and 8. In all instances LVEDP in the rest GKI state was greater than that of the rest control state (range 1–8 mm Hg). Two patients in the present series exhibited a normal decrease in LVEDP during pacing in the control state (1, 7). This response was not altered in patient 7 during GKI whereas an abnormal response, indicated by a sustained elevation of LVEDP during pacing, was noted during GKI in patient 1.

LVEDP during pacing was not substantially different in the control paced as compared to the control rest state in patients 2, 3, and 5 but rose significantly in the control paced state in patients 4 and 6. LVEDP during pacing in the GKI state was lower than the corresponding value in the control state in patient 7. In all other instances LVEDP during pacing in the GKI state was equal to or greater than that recorded in the control paced state. LVEDP in the postpace control state was abnormally elevated in six patients (1, 3, 4, 6, 7, 8). In all instances the postpace LVEDP during GKI was equal to or greater than that recorded in the postpace control state.

Although a variable but definite elevation of LVEDP at rest occurred during the GKI state, this cannot be attributed solely to hypervolemia because the volume of the infusion was roughly equivalent to the amount of blood removed for biochemical analysis during the course of study. A decrease in anginal threshold to pacing and increase of LVEDP has been reported following acute volume expansion in coronary patients and a similar phenomenon might be responsible for the results of the present study. This seems unlikely, however, since it was necessary to infuse an average of 398 ml of dextran solution over 13.3 min in order to obtain these results. In the present study a total volume of 200 ml was infused over 60 min, an equal volume of blood was simultaneously withdrawn for biochemical analysis and the infusate did not contain a high molecular weight plasma expander. Thus, the volume of the infusate per se cannot be implicated. Whether the increase in serum osmolarity caused by an elevation of blood glucose to 300–500 mg% can cause a sufficient expansion of the circulating blood volume so as to alter cardiac function is difficult to assess. If, however, this effect is responsible for the differences in LVEDP in the GKI and control state, the argument of the present study is strengthened, i.e., acutely raising the blood sugar to 300–500 mg% in patients with coronary artery disease may have deleterious rather than beneficial effects on cardiac function. It is unlikely that the observed effect was due to hyperosmolarity per se because hyperosmolarity due to mannitol infusion actually can protect ventricular function from ischemic insult.

ST-segment depression was decreased by 0.5 mm in three patients and by 1.5 mm in one patient during pacing in the GKI as compared to control states. In the immediate postpacing period, ST-segment depression was decreased during the GKI state, albeit to a lesser degree when compared to values obtained during maximum pacing. Although ST-segment depression was not uniformly improved by GKI, the data suggest the infusion may have decreased electrocardiographic evidence of ischemia. The fact that opposite conclusions regarding the efficacy of GKI may be drawn from analysis of the ECG vs clinical or hemodynamic data reinforces the observation that ST-segment abnormalities, although associated with ischemia, are nonspecific and represent only one aspect of the ischemic response.

Blood glucose, insulin, and lactate levels obtained during the GKI state indicate that steady state conditions for all metabolites were achieved during the GKI infusion. Results obtained cannot be attributed to rapid alterations in blood levels of these metabolites.

The data presented in table 2 demonstrate a consistent pattern of induced directional change in transmyocardial glucose values in response to GKI, although actual glucose uptake was not noted in all instances. A change in the arteriovenous difference of a metabolite across an organ in two states cannot be equated with uptake or release of the metabolite unless absolute blood flow to the organ is known in both states and steady state conditions of blood flow are present at the time observations are made. The complexity of the present study precluded measurements of coronary flow. However, certain considerations suggest flow rates were identical in the GKI and control states which were compared and steady state had been achieved. A 15 minute rest period followed the control paced state prior to the initiation of GKI, and resting observations in the GKI state were obtained after 40 minutes of infusion. Thus, observations in the GKI rest state were made after a 55 minute interval.
during which time the patient was lying quietly and blood pressure and heart rate did not change. Steady state conditions for all metabolites had been reached by 40 minutes of infusion. In order to create identical paced states during control and GKI periods, observations were obtained at identical paced rates and after an identical duration of pacing at the threshold rate in both situations. Moreover, since angina pectoris was present in a majority of patients in both control and GKI paced states, coronary flow was presumably comparable and maximal for any given patient during the pacing stress. GKI could conceivably alter coronary flow owing to the primary vasodilator effects of the pari passu rise in plasma lactate.\textsuperscript{31} This effect could mask augmented glucose uptake by slightly increasing coronary flow.

The large negative transmural glucose differences recorded in many of the patients in the control rest and control paced state presently defy explanation since the heart does not "produce" glucose. Previous studies in humans\textsuperscript{29} and animals\textsuperscript{3} have not reported similar values. In contrast to previous studies, however, the present data were obtained exclusively from patients with severe chronic ischemic heart disease. The possibility that abnormal patterns of carbohydrate metabolism are characteristic of the chronically ischemic heart cannot be ruled out.

Enhanced anaerobic energy production in the heart during the GKI paced state would be strongly suggested if the more positive arterio–venous glucose differences were associated with increased tolerance to pacing stress and increased production of lactate by the myocardium. Although patient \textsuperscript{7} demonstrated less lactate extraction during the GKI paced state, lactate extraction in the control state was not converted to lactate production during GKI in any subject. Samples for lactate analysis were drawn at the instant that rapid atrial fibrillation and circulatory collapse developed in patient \textsuperscript{5}. A marked increase in lactate production was noted in this state as compared to the paced control state. However, the dire clinical situation precluded glucose analysis and the instability of the patient's cardiovascular status make any comparisons between paced control and paced GKI states invalid. In patient \textsuperscript{6}, lactate production in the control paced state was converted to lactate extraction in the GKI state despite a more positive arterio–venous glucose difference of +4 mg/100 ml and deterioration of cardiac function as evidenced by the appearance of pulsus alternans.

Consequently the present data agree with previous studies of ischemic human and dog hearts wherein a stoichiometric relation between enhanced glucose uptake and increased lactate release could not be demonstrated, i.e., 2 moles lactate released per mole glucose uptake.\textsuperscript{32} Possible explanations for this discrepancy have been discussed elsewhere\textsuperscript{32} and include a) heterogeneity of tissue ischemia and the inability of coronary sinus sampling techniques to discern local metabolic alterations on a background of unchanged substrate relations, b) continued utilization of endogenous glycogen stores by ischemic tissue, c) complex nonuniform transmembrane kinetics for glucose influx and lactate efflux independent of their metabolic stoichiometry and d) induction of relative or partial ischemia, permitting hypoxic cells to continue glucose oxidation.

Metabolic data notwithstanding, the clinical observations from the present study indicate that neither the anginal threshold to pacing nor alterations in left ventricular dynamics induced by pacing are improved if blood glucose and insulin are significantly elevated. In contrast, the data suggest that GKI may adversely affect these parameters and that abnormalities of left ventricular function may be noted in the resting state if blood glucose levels are elevated only threefold.

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Ineffectiveness of Glucose, Potassium, and Insulin Infusion During Pacing Stress in Chronic Ischemic Heart Disease

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