Effects of Low and High Glucose in a Glucose-Insulin-Potassium Infusion on Hemodynamics and Exercise Tolerance in Patients with Angina Pectoris

UDHO THADANI, M.B.B.S., MIGUEL A. CHIONG, M.D., PH.D., AND JOHN O. PARKER, M.D.

SUMMARY. The effects of infusion of normal saline (NS) and glucose-insulin-potassium (GIK) with either low or high G concentrations on hemodynamics and exercise tolerance were studied in patients with angina pectoris. Studies were performed at rest and during exercise, twice before and once after one of the infusions. Eleven patients (low-G GIK group) received 150 ml of GIK solution that contained 15 g G, 8 U I, and 12 mEq KCl; 10 patients received 150 ml NS; and seven patients (high-G GIK group) received 1.5 g/kg of G orally followed by a 100 ml infusion that contained 0.5 g/kg G, 1.5 U/kg I, and 10 mEq KCl.

Before infusion, left ventricular end-diastolic pressure (LVEDP) was higher during the first exercise period (Ex1) than during the second exercise period (Ex2), but the exercise time to angina did not change significantly. After NS, exercise time to angina, hemodynamics and G levels were similar to the preinfusion Ex2 values.

After low-G GIK infusion, G levels increased from 99 to 140 mg/dl (p < 0.01), but the exercise time to angina did not change significantly from the preinfusion Ex2 values. Only two of the 11 patients exercised for a longer period of time and had less ST-segment depression. However, LVEDP during exercise after low-G GIK infusion was lower compared with the preinfusion Ex2 values (18 vs. 23 mm Hg, p < 0.02).

After high-G GIK infusion, G levels increased from 109 to 331 mg/dl (p < 0.01), but exercise tolerance decreased from a mean preinfusion (Ex2) value of 159 to 74 seconds (p < 0.01) after this infusion.

These studies show that while low-G GIK had variable effects on exercise tolerance and reduced LVEDP during exercise-induced angina, high-G GIK had detrimental effects. Therefore, increasing substrate (G) availability had no beneficial effects on supine exercise tolerance in patients with angina pectoris.

GLUCOSE-INSULIN-POTASSIUM (GIK) reduces myocardial ischemia and the extent of myocardial damage after acute coronary artery occlusion in animal experiments.1-7 However, infusion of GIK after acute myocardial infarction has been reported to have variable effects in man, producing either beneficial,8-18 deleterious or no effects19-26 on mortality. Similarly, GIK infusions have produced variable effects on pacing- and exercise-induced angina.27-31 GIK with a low glucose concentration has been reported to reduce myocardial ischemia during pacing and to prolong treadmill exercise tolerance in some patients with coronary artery disease.28, 30, 31 GIK with a high glucose concentration has produced detrimental effects during pacing and decreased tolerance to treadmill exercise in patients with coronary artery disease.27, 29 The present investigation was designed to study the effects of GIK with either low or high glucose concentrations on hemodynamics at rest and during exercise, and on exercise tolerance in the supine position in patients with angina pectoris due to coronary artery disease.

Methods

The study was performed in 28 patients with exertional angina who were referred for assessment of coronary artery disease (table 1). All were in sinus rhythm and had stable angina pectoris that could be readily induced during treadmill exercise. The duration of the anginal syndrome ranged from 4-48 months (average 14 months).

Twelve of the 28 patients had had a previous myocardial infarction at least 6 months before the study. No patient had diabetes mellitus, cardiac arrhythmias, cardiomegaly or heart failure, and no patient was taking digitalis or diuretic agents. Sixteen of the 28 patients had previously received propranolol and isosorbide dinitrate but none had taken these medications for at least 4 days before the investigation. Informed consent was obtained from all patients.

Patients were studied in the morning after an overnight fast and received no premedication. Under local anesthesia, the brachial artery and a vein were isolated in the right antecubital fossa. A #8 Courand catheter was passed into the right side of the heart and advanced to the main pulmonary artery. A #8 Sones catheter was inserted into the left ventricle from the right brachial artery, and the left brachial artery was cannulated with a Teflon needle using the Seldinger technique.

Two separate protocols were used to study the effects of GIK containing either low or high glucose concentration in different groups of patients.

Low-glucose GIK Protocol

This part of the study was double blind in design and placebo controlled. Patients were allocated randomly to either normal saline (10 patients) or GIK (11 patients) groups (table 1).
A rest period of 15 minutes followed the instrumentation. The heart rate, ECG and intravascular and intracardiac pressures were recorded at rest over a 10-minute period with the feet on the bicycle ergometer pedals, the axle of which was 30 cm above the table level. Cardiac output was measured in duplicate during the final 3 minutes of the rest period with the dye-dilution technique using indocyanine green. Exercise was then begun at a work load of 200 kpm/min, which was increased every 3 minutes until the onset of angina. When angina developed, the work load was kept constant. During exercise, measurements were made at 1-minute intervals and at the onset of pain. Immediately after the onset of angina, the cardiac output was measured in duplicate, after which the pressures were recorded and exercise was discontinued. Subsequently, the pressures were recorded at 1, 3 and 5 minutes during recovery.

After a 15-minute recovery period, the reproducibility of both the hemodynamic parameters at rest and during exercise and the exercise duration to angina were evaluated by repeating the study as described above.

After another 15-minute recovery period, the infusion of either 150 ml of normal saline or 150 ml of GIK containing 15 g glucose, 8 IU insulin, and 12 mEq KCl was infused in the main pulmonary artery over a 45-minute period. GIK solution was prepared by mixing 20 units of crystalline insulin and 40 mEq of KCl in 500 ml of 10% glucose in water as

<table>
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<th>Angiographic findings</th>
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Low-glucose GIK Group (11 Patients)

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<th>Angiographic findings</th>
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High-glucose GIK Group (Seven Patients)

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<th>Angiographic findings</th>
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<td>41</td>
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<td>RCA 4</td>
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Abbreviations: RCA = right coronary artery; LCA = left coronary artery; LAD = left anterior descending coronary artery; LCx = left circumflex artery; Coll = collateral circulation; LV = left ventricular; 0 = normal coronary arteries; 1 = < 50% decrease in diameter; 2 = 50–75% decrease in diameter; 3 = 75–100% decrease in diameter; 4 = complete occlusion.

GIK IN ANGINA PECTORIS/Thadani et al.
recommended originally by Sodi-Pallares and used in
two previous studies from our laboratory. 28, 30
Immediately after the completion of infusion,
measurements were repeated at rest and during exer-
cise.

High-glucose GIK Protocol

This part of the study was open and was designed
after completion of the low-glucose GIK study. A
separate group of seven patients was studied (table 1).
Control measurements at rest and during exercise and
the reproducibility of the clinical and hemodynamic events were assessed in the same
manner as discussed under the low-glucose GIK
protocol. However, after a 15-minute recovery after the second exercise period, patients were given 1.5
g/kg glucose orally in a flavored solution, followed 10
minutes later by the i.v. infusion of a 100-ml solution
containing 0.5 g/kg glucose, 1.5 IU/kg insulin, and 10
mEq KCl over a 5-minute period. A 50% glucose solu-
tion in water was used to prepare this GIK solution.
Immediately after completion of this infusion, measurements were repeated at rest and during exercise-induced angina.

During both studies, 5 ml of venous blood were
collected at rest and during the final minute of exercise
during the two preinfusion control studies and during the postinfusion studies for determination of glucose,
lactate and potassium. Blood was collected in EDTA
tubes, spun in a centrifuge at 3000 rpm at 3°C within
15 minutes of sampling, and the plasma was stored at
−30°C. Chemical analysis of glucose and lactate were
carried out using automated techniques with an ABA
100 analyzer. Lactate was determined with the Calbiochem Rapid Lactate Stat Pack, which has a coefficient of variation (CV) of 0.89% for n = 30.
Glucose was analyzed with an enzymatic colorimeter method using glucose oxidase (CV 1.8% for n = 29).
In addition, 10 ml of venous blood was collected in heparanized tubes at rest before and after the infusion to
determine serum osmolality.

Pressures were recorded with P23Db Statham
strain gauges, from a zero reference level 5 cm below
the level of the angle of Louis. Pressures were
measured over two respiratory cycles and the mean
pressures were obtained electronically. Recordings
were made on a photographic recorder normally
operating at 25 mm/sec, but to determine left ven-
tricular end-diastolic pressure, a high sensitivity was
used at a paper speed of 100 mm/sec. The criterion for
an ischemic electrocardiographic response was a flat or
downward-sloping depression of the ST segment of
at least 1 mm (0.1 mV), persisting for 0.08 second or
longer. ST segments were averaged over 10 beats during
both rest and exercise.

Left ventricular stroke work index (g·m/m²) was
calculated using the formula
LVSWI = SI (BAm − LVEDP) × 13.6/1000, where SI = stroke
index (ml/beat/m²), BAm = brachial arterial mean
pressure (mm Hg) and LVEDP = left ventricular end-
diastolic pressure (mm Hg). The product of heart rate
and brachial artery systolic pressure (BASP) (rate-
pressure product) was expressed in mm Hg/
min × 10².

After the hemodynamic studies were completed,
selective cinecoronary angiography and left ven-
triculography were carried out in all patients. Paired
and unpaired t tests were used for statistical analysis.

Results

All patients had evidence of severe, obstructive, luminal narrowing (> 75% cross-sectional area) of one or more coronary arteries (table 1). Patients who received normal saline infusion and those who received either low-glucose GIK or high-glucose GIK were comparable in regard to the severity of coronary artery disease and the appearances of the resting left ventriculograms (table 1).

Low-glucose GIK Study

Normal Saline Infusion Group (10 Patients)

The hemodynamic studies were completed without
untoward incidents. The group values for the
hemodynamic and biochemical parameters at rest and
during exercise before and after the infusion are shown in
table 2.

Preinfusion Studies. Comparison of the first two
resting periods (R₁ and R₂), which were separated by
the first exercise period (Ex₁), showed significantly
lower values (p < 0.02) during R₂ for BASP
(145 ± 19 vs 139 ± 21 mm Hg, mean ± SD),
pulmonary arterial mean pressure (PAMP) (21 ± 4 vs
18 ± 5 mm Hg), and LVEDP (19 ± 5 vs 14 ± 5 mm
Hg). Individual data showed that the LVEDP was
lower during R₂ than R₁ in nine of the 10 patients (fig.
1).

All patients had angina during the two preinfusion exercise periods. The average exercise time to angina
during the first (Ex₁) and second exercise (Ex₂) periods
was similar. Individual and group values for the ex-
ercise time to angina are shown in figure 2. Comparison
of hemodynamics during Ex₁ and Ex₂ at the onset of
angina showed significantly lower values (p < 0.05)
during Ex₂ for PAMP (37 ± 9 vs 27 ± 8 mm Hg) and
LVEDP (29 ± 9 vs 24 ± 9 mm Hg) (fig. 3). Individual
data showed that LVEDP values at the onset of
angina during Ex₂ were lower in eight and higher in
two patients when compared with the levels during Ex₁
(fig. 3). The group values for ST depression were
similar during Ex₁ and Ex₂ (fig. 4).

Glucose values at rest were normal in all patients
and did not change significantly during exercise. The
group values during R₁ and R₂ and Ex₁ and Ex₂ were
similar (fig. 5). Lactate values were higher during Ex₂
than during R₁ (14.3 ± 6.7 vs 27.7 ± 11.7 mg/dl,
p < 0.02), but were similar during Ex₁ and Ex₂.

Because some of the hemodynamic measurements
were not reproducible during the two exercise periods
and because the initial period of exercise modified the
subsequent resting hemodynamics, the postinfusion
values at rest (R₂) and during exercise (Ex₂) have been
compared with the corresponding values during the second control preinfusion study (R2 and Ex2).

Postinfusion Studies. After normal saline, the values at rest (R3) and during exercise (Ex3) for heart rate, BAS, diastolic and mean pressures, PAMP, LVEDP (figs. 1 and 3), cardiac index (CI), SI and LVSWI were similar to the corresponding values obtained at R2 and Ex2. All patients had angina during exercise after the normal saline infusion, and the group values for the exercise time to angina were similar to those during Ex3 (169 ± 87 vs 176 ± 73 seconds) (fig. 2). Similarly, ST-segment depression (fig. 4) and the double product at the onset of angina were similar before and after the infusion (table 2).

Glucose levels did not change during normal saline infusion or during exercise after the completion of the infusion (fig. 5). Serum osmolality before and after the infusion was similar before and after the infusion (291 ± 6 vs 288 ± 5 mOsm).

Low-glucose GIK Group (11 Patients)

The hemodynamic studies were completed without untoward incidents. However, two patients developed mild symptoms and signs of hypoglycemia 30 minutes after the final exercise period and required intravenous glucose. The group values for the various hemodynamic and biochemical data at rest and during exercise before and after the GI infusion are shown in table 2.

Preinfusion Studies. Comparison of the first two resting periods (R1 and R2), which were separated by the first exercise period (Ex1), showed significantly lower values (p < 0.05) during R2 for LVEDP (17 ± 5 vs 13 ± 5 mm Hg) (fig. 1). Individual data showed that LVEDP during R2 was lower in 10 patients and higher in one patient compared with the values during R1.

All patients had angina during the two preinfusion exercise periods. The average values for the exercise time to angina during Ex1 and Ex2 were similar. Individual and group values for the exercise time to angina are shown in figure 2. Comparison of hemodynamics during Ex1 and Ex2 at the onset of angina showed significantly lower values (p < 0.05) during Ex2 for BAMP (117 ± 6 vs 113 ± 8 mm Hg) and LVEDP (28 ± 6 vs 23 ± 8 mm Hg). At the onset of angina during Ex2, LVEDP levels were lower in eight and higher in three patients compared with the values during Ex1 (fig. 3). Group values for ST segments were similar at the onset of angina during Ex1 and during Ex2 (fig. 4).

Glucose levels were normal in all patients at rest (fig. 5) and did not change significantly during exercise.

Postinfusion Studies. Infusion of low-glucose GIK did not alter the resting hemodynamics, but the glucose levels at rest (R3) after the infusion were significantly higher than those before (R2) the infusion (140 ± 11 vs 99 ± 9 mg/dl, p < 0.01) (fig. 5). After GIK infusion, all patients experienced angina during exercise (Ex3) and the average exercise time to angina did not change significantly compared with the values obtained during Ex2 (231 ± 197 vs 154 ± 57 seconds). The apparent increase in average exercise time to angina was due to a marked improvement in exercise tolerance in two patients after the GIK infusion (fig. 2). These two patients also showed a reduction in ST-segment depression during exercise after the GIK infusion (fig. 4). Of the remaining nine patients, exercise duration to angina increased by 30 seconds or more in three, decreased in three and did not change in the remaining three patients (fig. 2). The average ST-segment depression at the onset of angina was similar during Ex3 and Ex2 (fig. 4). Comparison of hemodynamic data during exercise before and after the GIK infusion showed lower values for LVEDP (23 ± 8 vs 18 ± 7 mm Hg, p < 0.02), and higher values for RPP (195 ± 20 vs 178 ± 17 mm Hg/min × 10², p < 0.02) after the GIK infusion. Individual data showed that LVEDP at the onset of angina during exercise was lower after GIK infusion in all 11 patients than during the preinfusion exercise period (Ex2) (fig. 3).

After GIK infusion, glucose levels decreased during exercise from 140 ± 11 to 109 ± 19 mg/dl (p < 0.001), but the glucose levels during exercise were still higher than the corresponding values during exercise before the infusion, 109 ± 19 vs 99 ± 9 mg/dl (p < 0.05). Serum plasma osmolality did not change significantly after the infusion compared with the preinfusion values (293 ± 3 vs 293 ± 5 mOsm).

High-glucose GIK Study

High-glucose GIK Group (Seven Patients)

Hemodynamic studies were completed without untoward incidents, but five patients developed symptoms of hypoglycemia requiring intravenous glucose within 15 minutes to 1 hour after the final exercise period. The group values for the hemodynamic and biochemical data at rest and during exercise-induced angina before and after the infusion are shown in table 2.

Preinfusion Studies. Comparison of R1 and R2, which were separated by Ex1, showed significantly higher values for heart rate (70 ± 15 vs 75 ± 14 beats/min, p < 0.05) during R2, but the other hemodynamic findings were similar during the two rest periods. During R2, LVEDP values were lower in five, unchanged in one and higher in the remaining patient compared with the values during R1 (fig. 1).

All patients had angina during the two exercise periods before the GIK infusion. The time to onset of angina during Ex1 and Ex2 were similar. At the onset of angina, the values for ST-segment depression (fig. 4) and the hemodynamic parameter were similar during Ex1 and Ex2.

Glucose levels at rest (R1) were normal in all but one patient and the values did not change significantly during exercise. The group values for glucose were similar during R1 and R2 (fig. 5) and Ex1 and Ex2.

Postinfusion Studies. After the GIK infusion, the heart rate was higher than the preinfusion R2 values.
Table 2. Summary of Clinical, Hemodynamic and Metabolic Data

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<td>4 Ex4</td>
<td>176 ± 73</td>
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<td>5 R3</td>
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<td>6 Ex4</td>
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Effects of normal saline infusion (10 patients)

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Effects of low-glucose GIK infusion (11 patients)

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<tr>
<td>1 R4</td>
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<td>135 ± 7</td>
</tr>
<tr>
<td>2 Ex1</td>
<td>231 ± 197</td>
<td>116 ± 10</td>
<td>169 ± 10†</td>
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</table>

Effects of high-glucose GIK infusion (seven patients)

*p values are for differences between 1 and 3, 2 and 4, 3 and 5, and 4 and 6.

Abbreviations: HR = heart rate; BAS = brachial artery systolic pressure; BAD = brachial artery diastolic pressure; BAM = brachial artery mean pressure; PAM = pulmonary artery mean pressure; LVED = left ventricular end-diastolic pressure; CI = cardiac index; SI = stroke index; LVSWI = left ventricular stroke work index; SBP = systolic blood pressure; R = rest; Ex = exercise.

(89 ± 18 vs 75 ± 14 beats/min, p < 0.02). None of the patients had resting angina after the GIK infusion or developed abnormalities in the resting ECG, but all patients experienced angina during exercise. The group values for the exercise time to angina decreased significantly after the GIK infusion compared with the pre-GIK Ex2 values (74 ± 30 vs 159 ± 90 sec, p < 0.01). Reduced exercise tolerance occurred in six patients; no change occurred in the remaining patient (fig. 2). The average ST-segment depression at the onset of angina was similar before and after the infusion (fig. 4). Hemodynamics did not change during exercise-induced angina before and after the GIK infusion (table 2).

After GIK, glucose levels at rest increased significantly from the pre-GIK R3 values (331 ± 42 vs 109 ± 27 mg/dl, p < 0.01) (fig. 5). During exercise after the GIK infusion, glucose levels were reduced compared with the resting post-GIK infusion values (280 ± 50 vs 331 ± 42 mg/dl, p < 0.01), but the values of glucose during exercise were still higher than the corresponding values during exercise (Ex4) before the infusion (280 ± 50 vs 104 ± 6 mg/dl, p < 0.01). Serum osmolality did not change significantly after the infusion compared with the preinfusion values (292 ± 4 vs 290 ± 5 mOsm).

Our results show that an exercise period modified the subsequent resting hemodynamics in all the three
### Table 2. (Continued)

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<th>CI (l/min/m²)</th>
<th>SI (ml/beat/m²)</th>
<th>LVSWI (g-m/beat/m²)</th>
<th>HR × SBP (mm Hg/min × 10⁻¹)</th>
<th>Glucose (mg/dl)</th>
<th>Potassium (mEq/l)</th>
<th>Lactate (mg/dl)</th>
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<td>3.89 ± 0.67</td>
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<td>53 ± 10</td>
<td>58 ± 13</td>
<td>103 ± 20</td>
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<td>6.40 ± 1.04</td>
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<td>42.2 ± 23.4</td>
</tr>
<tr>
<td>3.96 ± 0.80</td>
<td>54 ± 9</td>
<td>62 ± 12</td>
<td>102 ± 18</td>
<td>100 ± 11</td>
<td>—</td>
<td>18.2 ± 9.0†</td>
</tr>
<tr>
<td>6.26 ± 1.35</td>
<td>51 ± 11</td>
<td>59 ± 12</td>
<td>194 ± 29</td>
<td>98 ± 11</td>
<td>—</td>
<td>35.0 ± 19.9†</td>
</tr>
<tr>
<td>Effects of low-glucose GIK infusion (11 patients)</td>
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<tr>
<td>3.73 ± 0.86</td>
<td>51 ± 10</td>
<td>55 ± 14</td>
<td>103 ± 11</td>
<td>97 ± 9</td>
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<tr>
<td>5.45 ± 1.22</td>
<td>50 ± 11</td>
<td>62 ± 15</td>
<td>182 ± 17</td>
<td>99 ± 8</td>
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<td>25.2 ± 13.9</td>
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<tr>
<td>3.89 ± 0.87</td>
<td>51 ± 11</td>
<td>58 ± 16</td>
<td>103 ± 6</td>
<td>99 ± 9</td>
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<td>18.7 ± 11.8</td>
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<tr>
<td>5.79 ± 1.21</td>
<td>52 ± 10</td>
<td>64 ± 18</td>
<td>178 ± 17</td>
<td>99 ± 9</td>
<td>—</td>
<td>25.1 ± 12.8</td>
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<tr>
<td>3.87 ± 0.85</td>
<td>49 ± 11</td>
<td>58 ± 17</td>
<td>107 ± 8</td>
<td>140 ± 11†</td>
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<td>17.2 ± 6.5</td>
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<tr>
<td>6.20 ± 1.42</td>
<td>53 ± 11</td>
<td>71 ± 23*</td>
<td>195 ± 20†</td>
<td>109 ± 19*</td>
<td>—</td>
<td>24.0 ± 10.5</td>
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<tr>
<td>Effects on high-glucose GIK infusion (seven patients)</td>
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<tr>
<td>4.04 ± 0.98</td>
<td>58 ± 13</td>
<td>65 ± 23</td>
<td>101 ± 30</td>
<td>107 ± 25</td>
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<td>5.30 ± 1.64</td>
<td>51 ± 11</td>
<td>64 ± 21</td>
<td>170 ± 38</td>
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<td>24.3 ± 9.2</td>
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<tr>
<td>3.95 ± 0.96</td>
<td>52 ± 8</td>
<td>60 ± 9</td>
<td>102 ± 22</td>
<td>109 ± 27</td>
<td>3.7 ± 1.1</td>
<td>15.6 ± 3.4*</td>
</tr>
<tr>
<td>5.31 ± 1.56</td>
<td>50 ± 10</td>
<td>58 ± 17</td>
<td>172 ± 35</td>
<td>104 ± 6</td>
<td>3.6 ± 0.8</td>
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<td>5.46 ± 1.00</td>
<td>60 ± 6</td>
<td>65 ± 6</td>
<td>127 ± 26†</td>
<td>331 ± 42†</td>
<td>3.3 ± 0.9</td>
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<td>51 ± 11</td>
<td>65 ± 21</td>
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<td>280 ± 50†</td>
<td>3.2 ± 1.0</td>
<td>25.4 ± 7.1</td>
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Groups of patients and that LVEDP and PAMP were consistently lower during Ex₃ than during Ex₁ in the preinfusion control studies. Infusion of normal saline did not alter exercise tolerance and had no effect on hemodynamic parameters either at rest or during exercise. Infusion of low-glucose GIK lowered LVEDP during exercise-induced angina but increased exercise tolerance in only two of the 11 patients, while infusion of high-glucose GIK caused a deterioration in exercise tolerance in six of the seven patients.

**Discussion**

The results have shown that while low-glucose GIK had variable effects on the patients studied, high-glucose GIK had detrimental effects on exercise tolerance. Before these results can be put into proper perspective, it is necessary to examine the methods used in the present study.

All patients had stable angina due to obstructive disease of one or more coronary arteries and none suffered from diabetes mellitus or were taking medications at the time of the investigation. Such strict criteria for patient selection are necessary to evaluate the effects of therapeutic interventions in a complex syndrome such as angina pectoris.

A recent study revealed that the hemodynamic alterations during pacing- or exercise-induced angina are not always reproducible. This was taken into consideration in the design of the present study. Furthermore, the effects of normal saline infusion were evaluated in a comparable group of patients to those who received the GIK infusion. We believe that such an experimental design is necessary to assess the effects of therapeutic interventions.

Numerous animal studies have shown that both glucose and GIK reduce histologic and biochemical evidence of myocardial ischemia and necrosis. However, studies in man with GIK after acute myocardial infarction have produced conflicting results. It has been argued that the diverse reported effects of GIK infusion in man may be related to the...
Figure 1. Individual (closed circles) and mean ± SEM (open circles) values for left ventricular end-diastolic pressure (LVEDP) at rest. Mean LVEDP was significantly lower during R2 after a period of initial exercise in comparison to the preexercise resting (R1) values in the normal saline infusion group (p < 0.02) and the low-glucose (G) GIK group (p < 0.05). After any of the infusions, the resting values (R3) were not significantly different from the preinfusion R2 values.

Figure 2. Individual (closed circles) and mean ± SEM (open circles) values for exercise time to angina. There was no difference between the first (Ex1) and second (Ex2) exercise periods. No change in this variable occurred during exercise (Ex3) after either the normal saline or low-glucose GIK infusion, but exercise tolerance deteriorated significantly (p < 0.01) in the high-glucose GIK group. In the latter group, exercise tolerance deteriorated in six of the seven patients, while in the low-glucose GIK group, variable effects on exercise tolerance occurred.
different composition of the infusion and modes of administration. The basis for the discrepancy between the results in animals and in man has been discussed in detail.

Because GIK can consistently reduce the effects of acute myocardial ischemia in experimental animals, various workers have administered this combination in man during pacing and exercise-induced myocardial ischemia, but with variable results. Lesch and colleagues were the first to report the effects of GIK during pacing in man. They found that GIK infusion was associated with deleterious effects on the angina threshold and left ventricular filling pressure despite reductions in postpacing ST-segment depression in five of eight patients. These workers used a GIK solution that contained 30% glucose. In another study, using a GIK solution with 10% glucose, tolerance to pacing improved and electrocardiographic and metabolic evidence of myocardial ischemia diminished. Furthermore, eight of the 10 patients had less severe angina during the GIK infusion. However, in view of a recent report regarding the importance of documenting the reproducibility of the clinical and hemodynamic parameters during pacing-induced angina when the effects of a therapeutic intervention are being evaluated, the conclusions of these two studies are open to criticism.

In a recent placebo-controlled, double-blind study, Kostis et al. found that a GIK infusion containing 30% glucose reduced treadmill exercise tolerance and produced detrimental effects on the ECG in nine patients with coronary artery disease. However, when 10% of glucose in the GIK mixture was used in another placebo-controlled, double-blind study, no deleterious effects on the ECG were observed and seven of the 14 patients exercised longer on the treadmill and achieved higher double product at angina after GIK infusion. These patients also showed less ST-segment depression after GIK. However, in the other seven patients, exercise tolerance after the GIK infusion deteriorated in three, was unchanged in two and increased by less than 50 seconds in two patients compared with the post-saline infusion values.

In the present study, normal saline infusion did not alter either the hemodynamics or exercise tolerance to angina, whereas infusion of GIK containing 10% glucose prolonged exercise duration to angina in only two of the 11 patients (fig. 2). The group values for exercise time to angina before and after the infusion...
were not statistically significant (154 ± 57 vs 231 ± 197 seconds). Despite lack in improvement in exercise tolerance after low-glucose GIK, the values of LVEDP at the onset of angina were significantly lower compared with the preinfusion exercise values. The reduction in LVEDP induced by GIK may have caused an improvement in subendocardial perfusion that could account for the increase in exercise tolerance in the two patients.

The improvement in upright exercise tolerance in several patients in a previous study using the same GIK mixture may be due to a great reduction in LVEDP in the upright than in the supine position. This presumption is supported by a recent report in

**Figure 4.** Individual (closed circles) and mean ± SEM (open circles) values for ST-segment depression at the onset of angina. The mean values during the two exercise periods (Ex₁ and Ex₂) before the infusion and during the exercise period (Ex₃) after the infusion were similar in any given group.

**Figure 5.** Individual (closed circles) and mean ± SEM (open circles) values for plasma glucose concentrations before the infusion during the two rest periods (R₁ and R₂) were similar in all three groups. The mean values did not change after normal saline infusion, but increased significantly at rest (R₃) after low-glucose GIK (p < 0.01) and high-glucose GIK infusion (p < 0.01).
which LVEDP at the onset of angina was significantly lower during upright than during supine exercise. In contrast to the variable effects of GIK containing 10% glucose, the infusion of GIK containing 50% glucose decreased exercise tolerance in six of the seven patients studied. These findings are consistent with reports in which a high-glucose GIK mixture was infused. In the present study, after an infusion of GIK with 50% dextrose, resting heart rate and LVEDP increased, in contrast to either normal saline or GIK infusion containing 10% glucose. The effects of high-glucose GIK mixture on LVEDP at rest and during exercise are in conflict with a previous report by Majid and colleagues, who used a similar mixture and showed a reduction in the LVEDP both at rest and during exercise in patients with heart failure. However, the reproducibility of hemodynamic findings during exercise was not documented and no placebo group was reported. Their data should be interpreted with caution in view of the findings of the present study where, without any intervention, the LVEDP during EX was consistently lower than during EX in all three groups of patients.

The consistent reduction in exercise tolerance and pacing threshold to angina after high-glucose GIK infusion is probably caused by an increase in circulating blood volume after infusion of 30–50% dextrose, with resultant increase in left ventricular volume. This is suggested by the higher LVEDP in this group (fig. 1). The fact that increasing plasma volume by dextran infusion reduces tolerance to pacing-induced angina supports this theory.

The results of the present study clearly show that an increase in substrate availability had no beneficial effect in the majority of the patients with stable angina pectoris caused by obstructive coronary artery disease. GIK containing 50% glucose had a detrimental effect in six of the seven patients, while the GIK mixture containing 10% glucose produced variable effects on exercise tolerance, with only two patients showing a significant improvement in exercise tolerance. The difference between the present results and our previous report, in which seven of the 14 patients improved significantly, may be explained by the effect of posture, as mentioned earlier in this discussion. However, in the present state of knowledge, neither the hemodynamic profile nor the angiographic findings were helpful in predicting whether a given patient would benefit from this therapy.

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References

1. Hearse DJ, Chain EB: The role of glucose in the survival and "recovery" of the anoxic and isolated perfused rat heart.


27. Lesch M, Teichholz LE, Soeldner JS, Gorlin R: Ineffectiveness

28. Lech M, Teichholz LE, Soeldner JS, Gorlin R: Ineffectiveness

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Treadmill Score Quantifies Electrocardiographic Response to Exercise and Improves Test Accuracy and Reproducibility

Milton Hollenberg, M.D., W. Roger Budge, M.D., Judith A. Wisneski, M.D., and Edward W. Gertz, M.D.

SUMMARY We have developed a sensitive, accurate and highly reproducible treadmill exercise score (TES) that grades the ST-segment ("ischemic") response to exercise. Instead of using a single value for peak ST depression, our method integrates all ST-amplitude and slope changes that occur during the test, from onset of exercise to the end of recovery. By reflecting not only the depth of ST depression but the manner and time course by which ST changes develop and resolve, TES incorporates data that correlate with severity of coronary artery disease. Exercise ECGs of 70 patients who also had coronary arteriography were analyzed, as well as exercise records of 46 healthy volunteers. Sensitivity, specificity, predictive accuracy and correct classification rate were 85% (50 of 59), 98% (56 of 57), 98% (50 of 51) and 91% (30 of 33), respectively. Use of TES for qualitative interpretation increased sensitivity 10-15% compared with conventional criteria. TES distinguished the group of patients with three-vessel or left main coronary artery disease from those with two-vessel (p < 0.002) or one-vessel disease (p < 0.01). These differed from patients with no vessel disease (p < 0.05). TES also varied linearly when compared with angiographically determined coronary scores (p < 0.001, r = 0.71, see = 24.2). Thus, the use of TES greatly improves our ability to diagnose and quantify serially the extent of coronary artery disease and improves the accuracy of statistical statements relating to the probability of disease.

QUALITATIVE CLASSIFICATION of test results, i.e., as either positive or negative for induced myocardial ischemia, slowly has given way to the realization that the exercise response has quantitative features that reflect the extent and severity of cardiac disease and that yield prognostic information.1,2 In the past decade several groups have begun using computer technology in an attempt to improve accuracy and to quantify stress electrocardiography. The computer not only improves signal quality and reduces the large interobserver variation in interpretation,3 but also allows use of different types of ST measurements in a variety of diagnostic algorithms that otherwise would be impossible.4 Several groups5-7 are measuring the degree of depression to improve diagnostic sensitivity and specificity.

Using such microcomputer-assisted signal processing and analysis we have extended the above approaches and have devised a new, quantitative treadmill exercise score that grades the electrocardiographic response to exercise. Based on the continuous recording and calculation of the J-point deviation and ST slope of two simultaneous leads whose signals have
Effects of low and high glucose in a glucose-insulin-potassium infusion on hemodynamics and exercise tolerance in patients with angina pectoris.

U Thadani, M A Chiong and J O Parker

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