Glucose Intolerance in Nonischemic Cardiac Disease

Role of Cardiac Output and Adrenergic Function

By Philip O. Ettinger, M.D., Henry A. Olzewurkel, Barry Dzindzio, M.D., Virender Sethi, M.D., and Timothy J. Regan, M.D.

SUMMARY
To investigate hemodynamic and neurohumoral factors as a basis for glucose intolerance in cardiac patients without ischemic heart disease, intravenous glucose tolerance tests were performed on 70 patients aged 14 to 69 years. The mean glucose fractional disappearance rate (G_k) for 41 patients less than age 50 was 1.19 ± 0.07% fall in glucose/min, while in 19 normal subjects, it was 1.60 ± 0.14, P < 0.01. The decreased G_k was independent of age and lipid levels, and was directly related to a reduced plasma concentration of immunoreactive insulin. The glucose response to tolbutamide of 40 patients was similarly reduced and correlated with G_k.

Since enhanced adrenergic stimulation may be present in cardiac patients with resultant reduction of insulin secretion, the effects of alpha- and beta-adrenergic blockade were examined in two groups of cardiac patients. G_k was unchanged after administration of phenoxybenzamine and propranolol. Since a reduced cardiac output correlated with diminished G_k, the influence of sustained improvement after corrective cardiac surgery was evaluated in 13 patients. Postsurgical increments of resting cardiac output were usually associated with lower fasting insulin levels, enhanced clearance of administered glucose, and a more rapid rise of plasma insulin to higher peak levels, followed by a relatively rapid decline. Enhanced insulin response to tolbutamide after surgery in seven of these patients was also demonstrated. It is suggested that chronically reduced levels of cardiac output can result in reduced insulin secretion and in glucose intolerance and that these may be reversed with improved cardiac function.

Additional Indexing Words:
Adrenergic blockade  Cardiac output  Cardiac surgery  Glucose clearance
Insulin secretion  Phenoxybenzamine  Propranolol  Tolbutamide

While acute and chronic abnormalities in glucose tolerance are frequent in patients with coronary heart disease,1-9 we observed that patients with nonischemic cardiac disease also exhibit glucose intolerance.10 The rate of glucose removal from the circulation was reduced, with a reduced rate of rise of plasma insulin as well as diminished peak concentrations. Cardiac outputs were usually reduced in the patients we studied, so that a circulatory basis for the metabolic abnormality could exist. Alternately, since norepinephrine reduces glucose tolerance and insulin secretion in normal subjects,10 a neurohumoral mechanism for glucose intolerance in cardiovascular disease was suggested. Patients with ischemic11 and nonischemic12,13 heart disease frequently have evidence of enhanced adrenergic activity.

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To evaluate the role of reduced cardiac function in the production of delayed glucose clearance (Gk) in this study of cardiac subjects, glucose and tolbutamide tolerances have been related to cardiac indices. Since a sustained improvement in cardiac function might enhance glucose disposal, a group of patients undergoing corrective cardiac surgery was tested before and after operation with glucose and tolbutamide. The patterns of insulin response and Gk were compared to the change in cardiac output produced by the surgical intervention. The possible role of the adrenergic system in effecting such glucose intolerance has been evaluated in patients before and after alpha- and beta-adrenergic blockade.

Methods
All patients were screened to exclude those who were obese, hypertensive, or who had a history of diabetes in self, siblings, or parents. The 70 selected for study varied in age from 14 to 69 years; 56 were male and 14 were female. Fifteen had cardiomyopathy, 53 had valvular heart disease, and one each had constrictive pericarditis and idiopathic hypertrophic subaortic stenosis. None had clinical evidence of ischemic cardiovascular disease. Since electrolyte status can affect glucose metabolism,14 the patients studied were nononatremic and normokalemic. Some had received diuretics for varying periods; these were discontinued at least 3 days prior to testing, and glucose tolerance was unrelated to diuretic status. Hematocrit, serum bilirubin, serum albumin, and serum transaminase were normal in all. Because of the nature of patients referred for cardiac catheterization, most were in New York Heart Association functional class III, although some were in class II and a few were in class IV. While the class IV patients (six) were limited to rest in bed, the remainder were ambulatory in varying degrees. All received 1-g sodium diets and were compensated at the time of testing; most of them were taking digitals. All received 300 g of carbohydrate daily for 72 hours before study. Subjects with cardiomyopathy had been hospitalized 6 weeks prior to testing. The initial glucose and tolbutamide tolerance studies were performed within 10 days of diagnostic cardiac catheterization. While every patient underwent glucose tolerance testing, tolbutamide, adrenergic blockade, and preoperative and postoperative studies involved different but overlapping fractions of the entire group.

Our intravenous glucose tolerance test (IVGTT) has been described previously.10 After an overnight fast, without smoking, a percutaneous indwelling venous catheter was placed in a forearm vein and attached to a stopcock to allow a saline drip or blood sampling. After a fasting sample was drawn in disodium ethylenediamine tetraacetate, glucose was infused over 60 to 90 seconds in a dosage of 1 g/kg.7,10,15 This dose was shown by Moorhouse and associates15 to allow clear separation of normal and diabetic subjects. Blood samples were drawn at 2, 4, 6, 10, 20, 30, 40, 50, 60, and 120 min. These were iced, centrifuged, and the plasma was frozen for subsequent analysis of glucose,16 immunoreactive insulin,17 free fatty acid,18,19 and triglyceride.20

The analysis for serum insulin was performed by radioimmunoassay using the double-antibody technique of Hales and Randle.17* The membrane filter discs were immersed in 4.5% bovine albumin in 0.04 m phosphate buffer at pH 7.4 overnight, since it was found that this pretreatment reduced the nonspecific binding of free insulin to a negligible level.

The standards were prepared from analyzed human insulin.† Calculations of insulin concentrations were as recommended by Hales and Randle,17 where the radioactivity ratio of zero insulin level (C0) to known insulin level (Ci) is plotted against standard insulin concentrations. This resulting linear function allows computer reduction of the data. When a C0/C1 slope greater than four was encountered, the preincubation step was omitted to avoid an increased sensitivity which would shorten the range of insulin concentrations that could be reliably analyzed. Each day a quality control sample, prepared from a large pool of serum stored frozen in individual tubes, was analyzed as a continuing check on the integrity of the reagents and procedure. Statistical analysis of the data from two pools with arithmetic mean values of 67 and 118 μU of insulin/ml showed standard errors of the mean of 1.19 and 1.71 μU/ml, respectively. When the quality control value differed by 15% or more from the updated mean value of the control pool, all serum sample analyses were rejected.

Tolbutamide sodium21,22 in a dose of 1 g/70 kg23,24 was administered intravenously to 40 cardiac patients immediately after collection of the 120-min sample of the IVGTT, which was considered the control level in determining the response to this agent. The mean 120-min value for glucose was 95 ± 3 mg/100 ml, as compared with a mean fasting level of 100 ± 3 mg/100 ml. This difference was significant (paired t-test),

†Generously provided by Dr. Mary A. Root, Eli Lilly and Co.

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but the 120-min values were close and felt to be realistic base lines for the measurement of tolbutamide response. Specimens were drawn at 2, 4, 6, 10, 20, 30, and 40 min after tolbutamide was given and were analyzed as before.

To evaluate the role of alpha-adrenergic stimulation, phenoxybenzamine, 1.0 mg/kg/day, was administered orally in divided doses for 48 to 72 hours to produce alpha-adrenergic blockade after a control IVGTT in five patients. A second identical IVGTT was performed at the end of the period.

To study the effect of beta-adrenergic blockade, 0.10 to 0.15 mg/kg of propranolol, diluted in 50 ml of normal saline, was infused intravenously into six patients over a 20-min period immediately following collection of the 120-min sample of the control IVGTT, while the electrocardiogram was monitored. On completion of this infusion, a baseline blood sample was drawn, and an identical dose of glucose was given to begin a second IVGTT, which was terminated after 60 min.

Thirteen patients with reduced or borderline values of Gk, including 12 with valvular heart disease and one with constrictive pericarditis, had IVGTT at the time of catheterization and again 2 to 8 months following reparative surgery. Seven had tolbutamide testing on both occasions as well. The same diet and drug regimens were followed, but the dose of glucose was adjusted in some instances because of minor changes in weight. Postoperatively, cardiac output was measured in the basal state after injection of indocyanine green (Cardio-Green) into a peripheral vein with brachial artery sampling. Preoperative measurements of cardiac output were made during cardiac catheterization. No differences have been noted in cardiac outputs calculated from the different injection and sampling sites in our laboratory. Bassingthwaighte, Edwards, and Wood25 noted a small (2.5%) but significant difference in the area of dye curves recorded from the central and peripheral circulation, resulting in a minor underestimation of cardiac output when calculated from curves recorded at a peripheral sampling site. The glucose tolerance was expressed as the slope constant of a single exponential function determined from a straight line of best fit between 10 and 40 min which related glucose values versus time on semilogarithmic paper.26 The slope constant was derived from considerations of exponential decay, and the expression Gk is the calculated slope constant multiplied by 100 to convert to a whole number:

$$G_k = \frac{0.693 \times 100}{t_{1/2}}$$

Gk thus indicates instantaneous per cent fall of blood glucose per minute. A Gk greater than 1.1 was considered normal, while a Gk of less than 0.9 was considered indicative of diabetes, and Gk between 0.9 and 1.1, borderline.6, 10, 15 Tolbutamide response was measured as the percentage fall of plasma glucose from control at each time interval sampled.23, 24

Statistical analyses were performed by computer. Regression lines were derived by least-square polynomial analysis. Comparison of the means of different groups was made by nonpaired t-testing (Student's t-test). When the same group was evaluated after drugs or surgery, means were compared by paired t-tests of values before and after intervention.

Since changes in plasma glucose and insulin after infusion of glucose represent increments above fasting levels, Seltzer and co-workers27 suggested that the increments in insulin (ΔI) and glucose (ΔG) may be more representative of the status of carbohydrate metabolism than are the absolute concentrations of these substances. Accordingly, we have evaluated the ΔI/ΔG ratio, termed the "insulinogenic index."

The early insulin response has been considered an index of the adequacy of response to glycemic stimulus.28 Consequently, for surgical patients, the plasma insulin at 2 min after administration of glucose was correlated with cardiac output changes produced by surgery. Additionally, the area under the insulin curve in the first 10 min was calculated mathematically as the "10-min insulin area" and expressed in microunit minutes per milliliter for glucose and for tolbutamide.

Results

Glucose Tolerance Tests

The data for 70 patients, including data on 28 that have been previously reported, are summarized in figure 1. The mean Gk of 41 patients less than 50 years of age was 1.19 ± 0.07 (SE) % fall in glucose/min whereas that of 19 normal subjects was 1.69 ± 0.14 (SE), P < 0.01. A decade-by-decade analysis revealed slight but insignificant reductions in Gk with each decade.

Tolbutamide Tolerance Tests

Forty patients were tested with tolbutamide. Plasma insulin peaked within 2 to 6 min and then gradually declined. Plasma glucose declined gradually to reach lowest values between 20 and 40 min after administration. In accordance with others,28, 24 analysis of the percentage fall of glucose at 20 and 30 min

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Alpha-Adrenergic Blockade

Significantly lower blockade responses. In cardiovascular disease by Gk persons. The effect of orthostatic hypotension. The mean Gk was noted with increasing age. In the two right-hand bars, the Gk of 41 patients below age 50 is compared with that of 19 normal persons.

from the control level provided the most satisfactory separation of diabetic and normal responses. In figure 2, the percentage of control plasma glucose at 20 and 30 min after administration of tolbutamide is shown as a function of Gk in each patient. A significant correlation between glucose and tolbutamide tolerance is evident, although there is a fair degree of scatter. Similar correlations have been reported in normal subjects and in those with ischemic cardiovascular disease. Tolbutamide responses are not age related; this is in contrast to the decline in normal tolbutamide tolerance with increasing age.

Alpha-Adrenergic Blockade

Alpha-adrenergic blockade failed to increase Gk in the five patients studied (table 1). The effect of phenoxybenzamine was to lower systolic and diastolic blood pressure 10 to 15 mm Hg; patients complained of lassitude and orthostatic hypotension. The mean Gk before blockade (1.00 ± 0.10 se) was unchanged after blockade (0.99 ± 0.10 se), as were plasma glucose, immunoreactive insulin, and insulin/glucose ratios.

Beta-Adrenergic Blockade

Infusion of propranolol into six patients also failed to increase Gk (table 2). In all patients mean heart rate decreased (from 83 ± 5 se to 73 ± 5 se, P < 0.05), but the mean Gk before propranolol (1.04 ± 0.12 se) was unchanged after propranolol (0.98 ± 0.08 se). No patient complained of any side effects of the medication, but only 0.10 mg/kg was given to one patient with severe mitral stenosis and slow atrial fibrillation because of marked slowing of the ventricular rate. Plasma glucose levels were unchanged, but the immunoreactive insulin response to glucose was depressed. The result was significantly lower insulin/glucose ratios throughout the second glucose tolerance test. Although sequential oral glucose tolerance testing improves glucose tolerance (Staub-Traugott effect), it is not clear that intravenous testing results in similar events. In two recent studies of this phenomenon, the second tests were begun before plasma glucose returned to fasting values, resulting in higher peak glucose during the second test.

Figure 1

AGE GROUPS (YEARS)

Figure 2

Tolbutamide response as a function of Gk in non-ischemic cardiac disease. While some scatter is apparent, the correlations are significant. Per cent of control plasma glucose 20 and 30 min after tolbutamide, 1 g/70 kg, are shown. At 20 min, n = 40, r = 0.392. P < 0.02; at 30 min, n = 39, r = 0.347, P < 0.05.
ACQUIRED GLUCOSE INTOLERANCE

Table 1

Plasma Glucose, Immunoreactive Insulin, and Insulin-to-Glucose Ratios in Five Patients Before and After Oral Administration of Phenoxybenzamine, 1 mg/kg/day for 3 Days*

<table>
<thead>
<tr>
<th>Interval after administration of glucose</th>
<th>Glucose (mg/100 ml)</th>
<th>Insulin (μU/ml)</th>
<th>Insulin/glucose ratio (μU/ml/mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
<td>2 min</td>
<td>4 min</td>
</tr>
<tr>
<td>Before</td>
<td>103</td>
<td>278</td>
<td>237</td>
</tr>
<tr>
<td>( \pm 2 )</td>
<td>( \pm 21 )</td>
<td>( \pm 9 )</td>
<td>( \pm 9 )</td>
</tr>
<tr>
<td>After</td>
<td>99</td>
<td>276</td>
<td>222</td>
</tr>
<tr>
<td>( \pm 3 )</td>
<td>( \pm 34 )</td>
<td>( \pm 11 )</td>
<td>( \pm 12 )</td>
</tr>
<tr>
<td>Before</td>
<td>15</td>
<td>57</td>
<td>120</td>
</tr>
<tr>
<td>( \pm 3 )</td>
<td>( \pm 28 )</td>
<td>( \pm 30 )</td>
<td>( \pm 25 )</td>
</tr>
<tr>
<td>After</td>
<td>13</td>
<td>70</td>
<td>125</td>
</tr>
<tr>
<td>( \pm 2 )</td>
<td>( \pm 26 )</td>
<td>( \pm 35 )</td>
<td>( \pm 31 )</td>
</tr>
</tbody>
</table>

*All values are means \( \pm \) standard error of the mean (SEM). No significant changes are noted.
†Values for \( G_k \) in this and other tables are in % fall in glucose/min.

our present study, 2½ hours always elapsed between the two tests, to assure return of glucose, insulin, and free fatty acids to fasting base lines. Three patients had sequential IVGTT in this fashion without drugs and showed no change of \( G_k \).

Relation of \( G_k \) and Tolbutamide Response to Cardiac Index

The relation between \( G_k \) and basal cardiac index (CI) is shown in figure 3. While a considerable scatter is present, those patients with the greatest reduction of cardiac index demonstrated, in general, the greatest degree of reduction of \( G_k \). The correlation is significant \( (P < 0.05) \), and those patients with normal basal indices usually had normal \( G_k \). A normal individual would be expected to fall within the shaded area, with \( G_k > 1.1 \) and cardiac index \( > 2.5 \) liters/min/m².

The correlation of tolbutamide response at 20 and 30 min with cardiac index is seen in figure 4. The correlations here are more significant than those with \( G_k \) and cardiac index.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3**

\( G_k \) as a function of cardiac index in nonischemic cardiac disease. Despite scatter, the correlation is weakly significant \( (n = 58, \ r = 0.265, \ P < 0.05) \). Values for normal persons would fall within the shaded areas.

**Fasting Plasma Triglycerides**

Fasting plasma triglycerides were measured in 32 patients and were normal in all, averaging 94 ± 7 mg/100 ml.

*Circulation, Volume XLIII, June 1971*
<table>
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<tr>
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<th>Before and after propranolol</th>
<th>Fasting</th>
<th>2 min</th>
<th>4 min</th>
<th>6 min</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>40 min</th>
<th>50 min</th>
<th>60 min</th>
<th>120 min</th>
<th>Gk</th>
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<tr>
<td><strong>Glucose (mg/100 ml)</strong></td>
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<tr>
<td>Before</td>
<td>87</td>
<td>222</td>
<td>201</td>
<td>193</td>
<td>180</td>
<td>158</td>
<td>143</td>
<td>134</td>
<td>121</td>
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<tr>
<td>±5</td>
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<td>±7</td>
<td>±6</td>
<td>±5</td>
<td>±4</td>
<td>±5</td>
<td>±6</td>
<td>±7</td>
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<td>±0.12</td>
<td>±0.08</td>
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<tr>
<td>After†</td>
<td>79</td>
<td>235</td>
<td>248</td>
<td>213</td>
<td>192</td>
<td>170</td>
<td>156</td>
<td>143</td>
<td>130</td>
<td>121†</td>
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<tr>
<td>±6</td>
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<td>±14</td>
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<td><strong>Insulin (µU/ml)</strong></td>
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<td>28</td>
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<td>After</td>
<td>18</td>
<td>44</td>
<td>73</td>
<td>57‡</td>
<td>38‡</td>
<td>28</td>
<td>25</td>
<td>23</td>
<td>19</td>
<td>24</td>
<td>—</td>
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<tr>
<td><strong>Insulin/glucose ratio (µU/ml/mg/100 ml)</strong></td>
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</tr>
<tr>
<td>Before</td>
<td>0.24</td>
<td>0.27</td>
<td>0.55</td>
<td>0.51</td>
<td>0.33</td>
<td>0.22</td>
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<td>After</td>
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<td>0.26</td>
<td>0.35‡</td>
<td>0.28‡</td>
<td>0.20‡</td>
<td>0.17‡</td>
<td>0.16</td>
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<td>±0.03</td>
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</table>

*All values are means ± SEM. Insulin responsiveness and insulin-to-glucose ratios are significantly reduced. Gk is unchanged.
†The post-propranolol GTT was followed to 60 min only.
‡P < 0.05.
Table 3

Effect of Cardiac Surgery Upon Cardiac Index and Glucose Fractional Disappearance Rate

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age &amp; sex</th>
<th>Preoperative</th>
<th>Postoperative*</th>
<th>Clinical improvement</th>
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<tr>
<td></td>
<td></td>
<td>FBS (mg/100 ml)</td>
<td>Gk</td>
<td>CI (liters/min)</td>
</tr>
<tr>
<td>1. (D.H.)</td>
<td>34M</td>
<td>90</td>
<td>1.15</td>
<td>1.2</td>
</tr>
<tr>
<td>2. (A.H.)</td>
<td>37F</td>
<td>96</td>
<td>0.86</td>
<td>1.8</td>
</tr>
<tr>
<td>3. (H.H.)</td>
<td>42M</td>
<td>110</td>
<td>0.67</td>
<td>1.8</td>
</tr>
<tr>
<td>4. (N.K.)</td>
<td>42M</td>
<td>104</td>
<td>0.76</td>
<td>†</td>
</tr>
<tr>
<td>5. (W.L.)</td>
<td>31M</td>
<td>85</td>
<td>0.60</td>
<td>1.3</td>
</tr>
<tr>
<td>6. (A.M.)</td>
<td>28M</td>
<td>97</td>
<td>1.01</td>
<td>1.9</td>
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<tr>
<td>7. (E.M.)</td>
<td>38M</td>
<td>115</td>
<td>0.91</td>
<td>1.8</td>
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<tr>
<td>8. (J.D.)</td>
<td>43M</td>
<td>105</td>
<td>1.21</td>
<td>2.9</td>
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<tr>
<td>Mean</td>
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<td>100</td>
<td>0.90</td>
<td>1.8</td>
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<td>± SE</td>
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<td>0.08</td>
<td>0.2</td>
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<tr>
<td>P</td>
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Patients > 50 yr of age

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<tr>
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<th></th>
<th>FBS (mg/100 ml)</th>
<th>Gk</th>
<th>CI (liters/min)</th>
<th>FBS (mg/100 ml)</th>
<th>Gk</th>
<th>CI (liters/min)</th>
<th>Diagnosis and surgery</th>
<th>Clinical improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. (J.A.)</td>
<td>58M</td>
<td>70</td>
<td>0.70</td>
<td>1.2</td>
<td>100</td>
<td>0.51</td>
<td>1.7</td>
<td>RHD, AR; valve replacement</td>
<td>Good</td>
</tr>
<tr>
<td>10. (S.G.)</td>
<td>52M</td>
<td>85</td>
<td>1.24</td>
<td>1.5</td>
<td>97</td>
<td>0.64</td>
<td>1.3</td>
<td>RHD, AS, AR, MS, MR; mitral valvulotomy</td>
<td>None</td>
</tr>
<tr>
<td>11. (H.MeC.)</td>
<td>50M</td>
<td>95</td>
<td>0.68</td>
<td>1.9</td>
<td>95</td>
<td>0.79</td>
<td>1.6</td>
<td>RHD, MS; open valvulotomy</td>
<td>Fair</td>
</tr>
<tr>
<td>12. (R.T.)</td>
<td>53M</td>
<td>81</td>
<td>1.06</td>
<td>2.2</td>
<td>84</td>
<td>0.88</td>
<td>2.6</td>
<td>RHD, AS; valve replacement</td>
<td>Good</td>
</tr>
<tr>
<td>13. (P.P.)</td>
<td>64M</td>
<td>100</td>
<td>0.97</td>
<td>2.0</td>
<td>105</td>
<td>0.99</td>
<td>3.2</td>
<td>Calcific AS; valve replacement</td>
<td>Good</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>86</td>
<td>0.93</td>
<td>1.8</td>
<td>96</td>
<td>0.76</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>± SE</td>
<td></td>
<td>5</td>
<td>0.11</td>
<td>0.18</td>
<td>3</td>
<td>0.08</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>FBS (mg/100 ml)</th>
<th>Gk</th>
<th>CI (liters/min)</th>
<th>FBS (mg/100 ml)</th>
<th>Gk</th>
<th>CI (liters/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95</td>
<td>0.91</td>
<td>1.8</td>
<td>97</td>
<td>0.94</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>± SE</td>
<td>3</td>
<td>0.06</td>
<td>0.1</td>
<td>5</td>
<td>0.10</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*While cardiac index increased significantly, fasting blood sugar (FBS) and Gk failed to improve.
†Not measured.
Abbreviations: RHD = rheumatic heart disease; MS = mitral stenosis; MR = mitral regurgitation; AS = aortic stenosis; AR = aortic regurgitation; NS = not significant.
Glucose Tolerance Before and After Cardiac Surgery

The 13 patients studied did not have a significant change in weight following surgery, and all were maintained on digitalis. Most demonstrated increases in resting cardiac index postoperatively, and the mean increase was significant (table 3). While the mean $G_k$ failed to improve, analysis revealed that those patients who did improve $G_k$ were as a rule in the under-50 age group, and no patient who improved metabolically failed to show clinical improvement.

Patient 7 (E.M.) was the only young patient without clinical improvement, and he demonstrated a further decline in $G_k$. Patient 11 (H.McC.), in whom cardiac output and $G_k$ were not improved, nevertheless showed a more normal pattern of insulin secretion. Patient 1 (D.H.) had excellent clinical improvement and increases in $G_k$ and cardiac index as well. Figure 5 demonstrates the changes in $G_k$ and cardiac index in these patients. In general, in those less than age 50, $G_k$ and cardiac index improved or declined concomitantly, but this relationship was not as consistent in the older group. Five of the patients had a third IVGTT 1 to 2 years after operation; hemodynamic improvements again paralleled metabolic changes.
### Table 4

**Plasma Glucose, Immunoreactive Insulin, and Insulin-to-Glucose Ratios in 13 Patients Before and After Cardiac Surgical Repair**

<table>
<thead>
<tr>
<th>Values before and after operation</th>
<th>Interval after administration of glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 min</td>
</tr>
<tr>
<td>Glucose (mg/100 ml)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>±3</td>
</tr>
<tr>
<td>After</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>±5</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>±5</td>
</tr>
<tr>
<td>After</td>
<td>22†</td>
</tr>
<tr>
<td></td>
<td>±3</td>
</tr>
<tr>
<td>Insulin/glucose ratio (− μU/ml/mg/100 ml)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>±0.05</td>
</tr>
<tr>
<td>After</td>
<td>0.24‡</td>
</tr>
<tr>
<td></td>
<td>±0.04</td>
</tr>
</tbody>
</table>

*All values are means ± SEM. Insulin and insulin-to-glucose ratios are lower at rest and rise more rapidly to higher peak values after operation.
†P < 0.02.
‡P < 0.05.
Changes in insulin and insulin-to-glucose ratios (Δ insulin, Δ insulin/Δ glucose) from fasting levels in surgical patients. Insulin responsiveness improved postoperatively with a more rapid rise to an earlier and higher peak, followed by a more rapid decline to basal levels.

Table 4 shows the plasma levels of glucose and insulin, and insulin/glucose ratios in the patients before and after operation. Fasting glucose values were not different. Immunoreactive insulin levels were significantly lower in the fasting state after operation, and after glucose infusion the insulin levels rose more rapidly to a higher peak than before operation and declined more rapidly as well. The postoperative fasting insulin/glucose ratios were significantly lower. After glucose infusion the insulin/glucose ratios rose abruptly to an earlier and higher peak than before operation and declined to a significantly lower level by 20 min.

The magnitudes of the rises in insulin (Δ insulin) and insulin/glucose ratios (Δ insulin/Δ glucose) are demonstrated in figure 6. The more rapid rise to higher peak values after surgery suggests that sustained improvement of cardiovascular function resulted in a return toward a more normal insulin response.

In figure 7 are seen the changes in cardiac index in 11 of these surgical patients compared with their insulin responses at 2 min after glucose injection. The 2-min insulin response is better in almost every instance in the higher index state. The mean insulin increase, comparing the lower and higher index state for each patient whether before or after surgery, is highly significant (P < 0.02). The 2-min insulin value is an indication of the rapidity of response to the glucose stimulus.
The 4-min insulin values, while higher postoperatively, were not significantly so, because many of the postoperative patients peaked at 2 min and were already declining. Preoperative insulin responses were slower, tending to peak at 4 or 6 min. As a result, the 10-min insulin area after operation, 968 ± 145 μU-min/ml, was not significantly higher than the one before operation, 826 ± 78 μU-min/ml, although it differed in a direction compatible with improved function.

**Tolbutamide Tolerance Before and After Cardiac Surgery**

Seven of the 13 surgical patients had tolbutamide tests before and after surgery. Four of these patients were under 50 years of age, and three were over 50. Plasma glucose fell from a similar base line (table 5). Although the mean postoperative glucose levels were slightly higher, the differences were not significant. Insulin responses, however, were substantially improved postoperatively; they were similar to the postoperative response to glucose, with a more rapid rise at 2 min to a higher peak. The area under the first 10 min of the insulin curve was 438 ± 27 μU-min/ml preoperatively and 704 ± 99 μU-min/ml postoperatively, a significant increase (P < 0.05).

The metabolic and hemodynamic improvement seen after cardiac surgery is illustrated best by patient 1 (D.H.), a 35-year-old man in whom cardiac index, Gk, and insulin responses to glucose and tolbutamide had increased 1½ years after replacement of his mitral valve. Peak insulin responses occurred progressively earlier, with higher peak levels. Glucose fall after tolbutamide has not yet improved, however.

**Discussion**

The glucose intolerance demonstrated acutely and chronically after myocardial infarction and in ischemic heart disease without infarction has been interpreted as evidence that diabetes mellitus antedated and contributed to this cardiovascular disease. However, the high frequency of glucose intolerance in nonischemic cardiac disease suggests that the carbohydrate abnormality after infarction, may, in many instances, be an acquired phenomenon. Thus, the persistent glucose intolerance in many patients long after infarction and in a large percentage of symptomatic subjects with valvular disease or cardiomyopathy suggests a common mechanism which may have a hemodynamic or neurohumoral basis.
Glucose intolerance in acute infarction is a complex phenomenon, in which acute hemodynamic abnormalities may be associated with acute stress reactions. Although our patients had well compensated cardiac disease and no clinical evidence of stress, it is possible that high levels of corticosteroids or growth hormone were present. Corticosteroid metabolites were not measured. The abnormality produced by excess of these hormones, however, is associated with elevated levels of insulin during glucose tolerance testing.33, 34

Glucose intolerance in nonischemic cardiovascular disease appears related to a reduced rate of appearance of insulin in peripheral blood in response to acute hyperglycemia.10 While a few patients demonstrate a supernormal insulin response with some insulin resistance, the large majority show reduced response. Several other features of the IVGTT in these patients were investigated. While the mean fasting level was significantly greater than in normal controls, the individual free fatty acid (FFA) levels did not have predictive value in terms of Gk. The level of fasting blood sugar (FBS) was significantly correlated with Gk. However, because of considerable overlap with the normal range, its predictive value for Gk was not good unless FBS was elevated, as in classical diabetes mellitus. After glucose injection, FFA fell rapidly to levels similar to those seen in normal subjects and gradually returned toward fasting levels after 2 hours.

Difficulties in the evaluation of glucose intolerance in cardiac disease are evident. Chronic heart failure with anorexia may lead to protein malnutrition and inadequate carbohydrate preparation. In addition, malabsorption,35-39 hepatic congestion,39 administration of thiazide,40, 41 and electrolyte imbalance41 are some of the factors that may slow the rate of glucose disposal. To control these variables, stringent selection of patients excluded subjects with liver disease, cachexia, hypertension, obesity, or diabetes from our series. Circulatory congestion was eliminated by rest in bed, salt restriction, and digitalis. When thiazides were used, administration of the drug was interrupted at least 72 hours prior to study and most such patients had not received thiazides for 1 week or more. Impairment of hepatic function undetected by the tests employed is unlikely to explain the abnormal glucose tolerance since the glucose intolerance of liver disease is associated with hyperinsulinism.42, 43 All patients with cardiomyopathy were treated in the hospital with vitamin supplements including folic acid, for at least 6 weeks prior to examination. Plasma sodium, potassium, albumin, bilirubin, and transaminase were normal in every patient. Rest in bed itself can cause glucose intolerance with hyperinsulinism.44 Although limited in exercise tolerance in varying degree, most of these patients were ambulatory, and hyperinsulinism was not the usual state.

Although tolbutamide-induced stimulation of insulin secretion45-49 appears to be accompanied by extrapancreatic effects,50 the blood glucose response appears to have a general correlation with Gk in diabetes mellitus,29 that is largely attributable to the drug's action on the pancreas. In the cardiac patients receiving tolbutamide, the significantly smaller decline of blood glucose than in the normal subject is consistent with the view that reduced secretion of insulin is the basis for the glucose intolerance observed. Since cardiac index had a significant relationship to Gk and the glucose response to tolbutamide, a circulatory factor such as pancreatic blood flow may be postulated as a correlate of the reduced response to glucose. Acute changes of blood glucose and systemic blood flow have been shown to affect pancreatic blood flow and insulin secretion rate in intact dogs.51, 52 but the effect of chronically reduced cardiac output on insulin production has not been tested experimentally. While extrapolation of peripheral venous insulin concentrations to the rate of pancreatic secretion of insulin is speculative because of the unknown effect of the liver on secreted insulin before it reaches the peripheral circulation, there is evidence that a high correlation exists between the

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ACQUIRED GLUCOSE INTOLERANCE

Peripheral insulin concentration and pancreatic output in an anesthetized dog preparation\(^{51, 52}\) and in man.\(^{53}\)

Postsurgical increments of resting cardiac output were usually associated with lower fasting insulin levels, a more rapid rise of plasma insulin to higher peak levels, and a more rapid decline to near control levels. This therapeutic response supports the view that glucose intolerance was acquired. The failure to normalize these parameters completely may be due to irreversible injury of a segment of the beta cell population or incomplete restoration of cardiac status to normal.

The enhanced adrenergic activity of heart failure, if present in these patients, did not appear to have a major effect on the production of the observed glucose intolerance, as judged by studies of adrenergic blockade. This intolerance was presumably not related to irreversible beta cell injury, since pancreatic endocrine function improved after successful surgery. Thus, an enhanced sympathomimetic activity in chronic heart failure may not produce the suppression of insulin secretion that is seen during acute administration of catecholamines.\(^{54, 55}\) The reduction of insulin output during the propranolol-IVGTT may be explained on the basis of suppression of the normal beta-adrenergic stimulus affecting insulin release.\(^{56}\) Alternatively, it is possible that a reduction of cardiac output after propranolol was responsible for the decline in insulin secretion, although cardiac output was not measured.

The influence of acquired glucose intolerance on the course of cardiac disease is unknown and its evaluation would require a relatively large number of patients. The group of subjects under the age of 50 are of particular interest, since they are presumed to have had their cardiac disease for a shorter period, and reversal of the metabolic abnormality was more common in this group. They are also less influenced by age-related reduction in glucose tolerance. Elevation of cardiac output after surgery in this group was usually associated with an improved glucose tolerance and insulin output.

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References


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Correction
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Pulmonary Arterial Banding in Babies with Large Ventricular Septal Defects
Glucose Intolerance in Nonischemic Cardiac Disease: Role of Cardiac Output and Adrenergic Function

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