Cardiovascular function and survival during severe systemic hypoxaemia: influence of glucose-potassium-insulin solution and of beta-blockade

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AUTHORS' SYNOPSIS Anaesthetized dogs were ventilated with 3.6% O₂ after having been given infusions of isotonic saline or glucose-potassium-insulin (GKI) solution. Initial tachycardia and hypertension were superseded by progressive circulatory failure and death in all dogs. In the absence of beta-adrenergic blockade, no significant differences in haemodynamic responses or survival times occurred in the animals that received the two solutions. Propranolol, itself, increased the survival time in both groups. In addition, after pretreatment with propranolol, which prevented a rise in blood glucose after the onset of hypoxia, dogs that received GKI survived significantly longer than those with persistently low blood glucose levels.

In the absence of oxygen the heart derives energy from anaerobic glycolysis. Theoretically, elevated levels of blood glucose might be expected to increase anaerobic energy production and thus to extend the duration of cardiac function for a few minutes during total anoxia. In partially hypoxic tissue, enhanced glycolysis might provide just enough extra adenosine triphosphate (ATP) to prevent cellular necrosis.

This concept provides the basis for what has been termed the 'glucose hypothesis' (Opie, 1970b), which suggests that a rational therapy for myocardial infarction would be intravenous infusions of large amounts of glucose or solutions containing glucose, potassium, and insulin (GKI). Beneficial effects of such therapy might be mediated not only by an increase in glycolytic capability, but also by a reduction in serum free-fatty acids, which may be potentially toxic (Oliver, Kurien, and Greenwood, 1968; Henderson, Craig, Gorlin, and Sonnenblick, 1970; Henderson, Most, Farmley, Gorlin, and Sonnenblick, 1970; Opie, 1970a; Kurien, Yates, and Oliver, 1971); by an enhanced entry of potassium into myocardial cells (Sodi-Pallares, Bisteni, Medrano, de Micheli, Ponce de León, Calva, Fishleder, Testelli, and Miller, 1966); or by an elevation of circulating insulin, which may be depressed in patients with cardiac failure and which may itself exert beneficial effects on the heart (Dykes, Saxton, and Taylor, 1969; Hiatt, Sheinkopf, and Warner, 1971; Taylor and Majid, 1971).

The use of GKI has usually been advocated in the context of cardiac ischaemia, but its theoretical benefits should be equally applicable to inadequate myocardial oxygenation secondary to systemic hypoxaemia. However, studies of experimental animals have failed to give a clear indication of the potential value of high glucose levels in hypoxic conditions. There is no doubt that myocardial function is preserved better if glucose is present than if it is totally absent, when cardiac tissue is made anoxic in vitro.
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(Winbury, 1956; Weissler, Kruger, Baba, Scarpelli, Leighton, and Gallimore, 1968; Whiting, Penpargkul, and Scheuer, 1969). It has never been established, however, whether a high concentration of glucose, itself, offers greater benefits than a normal level in intact animals. Hypoxia induces an increase in the uptake and utilization of glucose even if blood levels are constant (Opie, 1968-69), and any additional augmentation of glycolysis by a modest rise in glucose to a level that could be maintained for long periods clinically might be negligible.

The present experiments were designed to test in a simple and direct way whether GKI solution has any ability in vivo to influence cardiovascular function and to alter the duration of survival during severe oxygen deficiency. In addition, tests were made to evaluate the influence of beta-adrenergic blockade with propranolol on the response to hypoxia and on the effectiveness of GKI.

Methods

Thirty-five mongrel dogs weighing 13–20 kg were studied after having been starved for 15–21 hr before the experiments. Each dog received 200 mg sodium thiopental intravenously as a temporary anaesthetic, followed by 100 mg/kg intravenous chloralose, which sufficed for the duration of the experiment. The animals were ventilated artificially with 100% O2 by an automatic Harvard respirator. A femoral artery was cannulated for measurement of blood pressure with a Statham P23Db strain gauge transducer and for withdrawal of blood samples. A femoral venous cannula was inserted for infusion of fluids. Arterial pressure, heart rate, and the electrocardiogram were recorded continuously. At 2 to 4 min intervals arterial samples were obtained and pH, PO2, and PCO2 were determined on an Instrumentation Laboratories analyser, model 313. Ventilatory rate and depth were adjusted to achieve a stable pH value between 7·36 and 7·42. In addition to blood gas determinations, samples were taken periodically for measurement of haematocrit, blood glucose (glucose oxidase technique), plasma Na+ and K+ (flame photometry), serum osmolality (freezing point determination with a Precision System Osmette), and serum free fatty acids (modified technique of Trout, Estes, and Friedberg, 1960).

After stabilization of blood gas levels for 15 min, one of two solutions was infused intravenously over a 7 to 8 min period: 14 control dogs received 25 ml/kg 0·9% NaCl (154 m-mole/l.), and 14 experimental animals received an identical volume of GKI solution (268 m-mole glucose + 20 m-mole KCl + 10 U regular insulin/l. H2O). The osmolality of the solutions was approximately 308 mOsm/kg H2O. Six additional control dogs received no infusions.

Ten minutes after the infusion, the inspired gas was changed from 100% O2 to a mixture containing 3·6% O2 + 96·4% Nz. In half the animals this was preceded by a slow (5 min) intravenous injection of propranolol (1 mg/kg). Death was defined as an inability to sustain the arterial pressure at a level greater than 15 mm Hg, coupled with an absence of regular ventricular contractions. In some dogs this was the result of ventricular asystole or, rarely, fibrillation; in others it coincided with the development of a slow (<15/ min) idioventricular rhythm which proceeded to asystole shortly thereafter. Occasionally, the transition from sinus rhythm with normal atrioventricular conduction and with aortic pressure ≤ 30 mm Hg to a slow idioventricular rhythm with aortic pressure <15 occurred over a period of 1–2 min rather than being abrupt. In those instances precise definition of the end-point of the experiment to within a few seconds was difficult. The point of ‘death’ was determined only to the nearest minute, therefore, and that degree of exactness sufficed satisfactorily for the purposes of the study.

Results

The response to hypoxia was qualitatively similar in all dogs. A few minutes after ventilation on low oxygen was begun, a rise in heart rate and blood pressure occurred. This was followed by a progressive decline in arterial pressure. As the pressure gradually dropped to shock levels the heart rate declined as well, and ultimately the arterial pressure fell toward zero and a slow idioventricular rhythm, ventricular fibrillation, or asystole ensued. In no dog was death caused by ventricular arrhythmias at a time when blood pressure was still being maintained at greater than 30 mm Hg.

Although the haemodynamic response to hypoxia was directionally similar in all dogs, the magnitude of the changes varied widely. The maximal heart rate and arterial pressure recorded in each dog were not influenced by GKI, but they were altered by pretreatment with propranolol. The mean maximal heart rate in beta-blocked animals was $211 \pm 6·3$ (SEM) beats/
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FIGURE. Duration of survival of hypoxaemic dogs pretreated with various agents. Each bar represents one dog. GKI = pretreatment with glucose - potassium - insulin solution. Saline = pretreatment with 0-9% NaCl. Beta-blockade = pretreatment with 1-0 mg/kg propranolol.

min and the maximal pressure averaged 299 ± 5-7/174 ± 3-8 mm Hg. In contrast, dogs without beta-blockade had maximal rates of 152 ± 6-5 and pressures of 240 ± 7-6/166 ± 5-7 (P < 0-001 for both sets of values).

Even though they never led to ventricular fibrillation, multiple premature ventricular contractions during hypoxia did occur in several dogs. Pretreatment with GKI conferred no protection against these arrhythmias. Five of seven dogs that were given the solution in the absence of propranolol had multiple premature contractions vs three of seven animals that received saline and one of three that received no infusion; after propranolol two of seven GKI-treated dogs developed premature contractions vs three of seven in the saline group and none of three in the group that received no infusion. The reduction in the incidence of hypoxic arrhythmias in the dogs that had received propranolol was not significant statistically.

The total survival times for dogs pretreated with GKI or saline, with or without propranolol, are illustrated in the Figure. Mean values for each group are given in the Table. As is apparent from the Figure, major differences were present between the various groups. To test for interactions and independent effects of the two factors that varied among the groups (saline vs GKI; beta-blockade vs no beta-blockade), the results were evaluated by analysis of variance with factorial arrangement of treatment (Steel and Torrie, 1960). The dogs that received GKI survived significantly longer than saline-treated dogs (40-7 vs 27-7 min, P < 0-01), and those that received propranolol survived longer than those without beta-blockade (44-4 vs 24-1 min, P < 0-001). The interaction of the two beneficial factors was of marginal significance (0-05 < P < 0-10). Analysis of the simple effects of GKI revealed that there was a significant difference between GKI and saline only in beta-blocked animals (P < 0-05), and not in those that did not receive propranolol (P > 0-50).

Values for most blood constituents were similar in all groups of dogs (Table). Mean serum osmolality remained at between 303 and 308 mOsm/kg H2O with all infusions, before and after hypoxia. During hypoxic ventilation arterial pO2 fell to 15-20 mm Hg. Initially, pH rose to alkalotic levels, as CO2 production fell with blockade of the oxidative processes and expiration of pre-formed CO2 continued; after 5 min the alkalosis was gradually superseded by progressive lactic acidosis. Changes in pO2 and pH were the same in all groups.

Small differences in Na+, K+, haematocrit, and free fatty acid values were present in some
### TABLE

**Blood composition and survival times in dogs pretreated with infusions of glucose-potassium-insulin (GKI), saline or no infusion, in presence and absence of propranolol**

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>(pO_2) (mm Hg)</th>
<th>Haematocrit (%)</th>
<th>Na(^+) (m-equiv/L)</th>
<th>K(^+) (m-equiv/L)</th>
<th>FFA (u-mole/100 ml)</th>
<th>Glucose (mg/100 ml)</th>
<th>5 min after hypoxia</th>
<th>15 min after hypoxia</th>
<th>Duration of survival (min)</th>
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<tr>
<td><strong>Without propranolol</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GKI</td>
<td>7.38</td>
<td>&gt; 500</td>
<td>41</td>
<td>140</td>
<td>4.0</td>
<td>325</td>
<td>205</td>
<td>7.42</td>
<td>15</td>
<td>145</td>
</tr>
<tr>
<td>(7 dogs)</td>
<td>± 0.005</td>
<td></td>
<td>± 1.1</td>
<td>± 1.9</td>
<td>± 0.19</td>
<td>± 5.0</td>
<td>± 40.1</td>
<td>± 0.005</td>
<td>± 0.017</td>
<td>± 0.6</td>
</tr>
<tr>
<td>Saline</td>
<td>7.39</td>
<td>&gt; 500</td>
<td>42</td>
<td>145</td>
<td>3.8</td>
<td>420</td>
<td>71</td>
<td>7.43</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>(7 dogs)</td>
<td>± 0.010</td>
<td></td>
<td>± 2.5</td>
<td>± 2.5</td>
<td>± 0.19</td>
<td>± 91.2</td>
<td>± 4.1</td>
<td>± 0.013</td>
<td>± 0.024</td>
<td>± 1.1</td>
</tr>
<tr>
<td>No infusion</td>
<td>7.38</td>
<td>&gt; 500</td>
<td>45</td>
<td>143</td>
<td>4.3</td>
<td>450</td>
<td>75</td>
<td>7.43</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>(3 dogs)</td>
<td>± 0.012</td>
<td></td>
<td>± 2.5</td>
<td>± 1.9</td>
<td>± 0.23</td>
<td>± 50.0</td>
<td>± 5.7</td>
<td>± 0.006</td>
<td>± 0.023</td>
<td>± 0.6</td>
</tr>
<tr>
<td><strong>With propranolol</strong></td>
<td></td>
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<tr>
<td>GKI</td>
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<td>&gt; 500</td>
<td>40</td>
<td>138</td>
<td>4.5</td>
<td>310</td>
<td>180</td>
<td>7.43</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>(7 dogs)</td>
<td>± 0.007</td>
<td></td>
<td>± 1.5</td>
<td>± 2.6</td>
<td>± 0.28</td>
<td>± 71.2</td>
<td>± 17.6</td>
<td>± 0.020</td>
<td>± 0.022</td>
<td>± 0.9</td>
</tr>
<tr>
<td>Saline</td>
<td>7.39</td>
<td>&gt; 500</td>
<td>40</td>
<td>146</td>
<td>4.0</td>
<td>366</td>
<td>50</td>
<td>7.43</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>(7 dogs)</td>
<td>± 0.008</td>
<td></td>
<td>± 1.3</td>
<td>± 0.18</td>
<td>± 4.2</td>
<td>± 0.014</td>
<td>± 1.2</td>
<td>± 0.018</td>
<td>± 1.1</td>
<td>± 8.1</td>
</tr>
<tr>
<td>No infusion</td>
<td>7.38</td>
<td>&gt; 500</td>
<td>45</td>
<td>145</td>
<td>4.4</td>
<td>425</td>
<td>54</td>
<td>7.43</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>(3 dogs)</td>
<td>± 0.006</td>
<td></td>
<td>± 2.3</td>
<td>± 2.0</td>
<td>± 1.7</td>
<td>± 0.000</td>
<td>± 0.6</td>
<td>± 0.006</td>
<td>± 1.2</td>
<td>± 1.0</td>
</tr>
</tbody>
</table>

*The means ± 1 standard error of the means are shown for each group. Differences in survival and in glucose concentrations before and after hypoxia are discussed in the text.*
dogs (Table), but the major difference among the various groups was in blood glucose concentration. Before hypoxia, blood glucose was high in all GKI-treated animals and low in all controls. This pattern did not persist, however: glucose concentrations in the control dogs that did not receive propranolol rose significantly after the onset of hypoxia, and by 15 min they had reached levels that equaled the values observed in GKI-treated dogs (Table). Thus, under the conditions of these experiments, differences in glucose levels were maintained only in dogs with beta-blockade; in unblocked animals with normal catecholamine responses, hyperglycaemia quickly supervened, whatever infusion the dogs had received.

Dogs that received no infusion before hypoxia responded like saline-treated animals, both in the presence and absence of propranolol (Table).

**Discussion**

In theory, it should be possible to preserve cardiac function during hypoxia to some extent by slowing the net depletion of ATP from the heart. This could be accomplished by reducing the demand for ATP utilization or by increasing its synthesis.

Heart rate, tension development, and the inotropic state of the heart are important determinants of energy utilization, and all these factors are reduced by beta-adrenergic blockade (Braunwald, 1969). Accordingly, it seems likely that the beneficial effect of propranolol was due in large part to a reduction of ATP utilization.

Increased anaerobic glycolysis in the presence of raised levels of glucose might be expected to increase ATP production, but practical benefits of high glucose in maintaining circulatory function under controlled hypoxic conditions in vivo have not previously been demonstrated conclusively. The present study suggests that under some conditions intact animals with hyperglycaemia are, in fact, better able to withstand the stress of hypoxia than those that have low glucose levels.

The beneficial effect of treatment with GKI was apparent only in dogs pretreated with propranolol. It is not certain how propranolol might 'unmask' GKI's beneficial action, but it seems likely that the reason may relate in part to the response of the blood glucose concentration to catecholamines. An early response to severe hypoxia is an outpouring of catecholamines from the adrenal medulla and sympathetic nerve endings (Kontos and Lower, 1969), and such an effect can induce hyperglycaemia (Himms-Hagen, 1967). Under the special condition of these experiments all dogs that had not been given propranolol had high circulating levels of glucose within a few minutes after the onset of hypoxia, no matter what solution they had received previously. Only when the hyperglycaemia reaction was avoided by blockade of beta-receptors did differences in glucose concentration persist throughout the experiment. When that occurred, survival was significantly longer in the group pretreated with GKI.

Intense beta-receptor stimulation also promotes the uptake of potassium by the heart (Sarnoff, Gilmore, McDonald, Daggett, Weisfeldt, and Mansfield, 1966; Regan, Moschos, Oldewurtel, Weisse, and Askan, 1967), the release of insulin from the pancreas (Ashmore, 1970), and the production and myocardial uptake of free-fatty acids (Himms-Hagen, 1967; Regan et al., 1967). Accordingly, if the beneficial effects of GKI could be mediated not only by glucose but also by actions of K⁺, insulin, or reduced fatty acid levels (Sodi-Pallares et al., 1966; Allison, Chamberlain, and Hinton, 1969; Gupta, Young, Jewitt, Harton, and Opie, 1969; Taylor and Majid, 1971), intense adrenergic stimulation might serve to mask still more any potential differences between dogs receiving the various infusions.

The cardiovascular effect of GKI has been difficult to interpret in some previous studies in which glucose has been infused as a hypertonic solution (Austen, Greenberg, and Picunini, 1965; Burke, Askan, Moschos, Oldewurtel, and Regan, 1969), inasmuch as cardiovascular function is known to be altered by a sudden increase in serum osmolality, independent of the type of agent given (Wildenthal, Mierzwik, and Mitchell, 1969). Accordingly, isotonic solutions were used in the present experiments, and serum osmolality did not vary. Thus, the beneficial effects of GKI observed in this study were not due to hyperosmolality or to a non-specific
increase in extracellular volume, as has been thought to be the case with its actions in reducing the incidence of arrhythmias after experimentally-induced cardiac ischaemia (Burke et al., 1969).

The question remains whether GKI may be of practical benefit clinically. Although the present data do constitute direct evidence in vivo that GKI in a dosage that produces a moderate rise of glucose may provide significant protection against systemic hypoxia in some circumstances, such findings are not necessarily relevant in clinical conditions. In this regard, it should be pointed out that the marked hyperglycaemic response that occurred in the 'normal' control dogs is not usually present in hypoxaemic patients, in whom hypoxia usually develops more slowly and rarely causes such an overwhelming sympathoadrenal response. Therefore, conditions in the beta-blocked dogs may in some ways be more akin to clinical hypoxia. Nevertheless, the question of whether cardiovascular depression could temporarily be reversed or myocardial death averted by giving GKI in amounts sufficient to elevate blood glucose in severely hypoxic patients can be answered only by appropriate clinical trials.

Finally, it should be emphasized that conditions prevalent during systemic hypoxaemia are in many ways quite different from those that accompany myocardial ischaemia. Thus, although a final common denominator in both conditions is myocardial hypoxia, it is impossible to extrapolate results from one condition directly to the other.

The authors wish to thank Mr. Eugene Berry and Mr. M. J. King for technical assistance and Mrs. Joan Reich for help in statistical analysis of the data. The work was supported by grants from the USPHS National Heart and Lung Institute and the Southeast Texas Health Foundation. Dr. Wildenthal holds a USPHS Research Career Development Award.

References


