Effects of Glucose Infusion on Dog
Myocardial Metabolism

By BLANCHE REBAR, M.S., AKIRA OMACHI, PH.D., AND JOHN REBAR, JR., PH.D.

Infusion of glucose to the whole animal results in increased myocardial content of phosphocreatine, glycogen and potassium. Metabolic alterations induced by coronary ligation were not modified by glucose infusion.

Our knowledge of the role of glucose in the metabolism of the heart in the whole animal appears to be restricted to its extraction from circulating blood and its effect on glycogen elevation, despite extensive studies in isolated tissue and organ preparations. In this study the myocardial content of high energy phosphate compounds, estimated as acid-labile phosphate, was examined following infusion of glucose to the whole dog. In addition, the concentrations of inorganic phosphate, glycogen, lactate, potassium and sodium were determined. The possibility that glucose infusion may have a salutary effect on the metabolism of the coronary-occluded heart was also investigated.

Methods

Mongrel dogs, weighing 10 to 20 Kg., were anesthetized with 25 mg./Kg. of sodium pentobarbital (Nembutal) administered intraperitoneally. Twenty per cent glucose was administered into the femoral vein at the rate of 8 ml./Kg./hr. In some experiments, 125 units of insulin were added to each 100 ml. of glucose solution. After 4 hours, the heart was removed quickly and plunged immediately into a dry ice-ether freezing mixture. Tissue samples were obtained from the left ventricular apex and from the right ventricle.

In a second group of animals, the descending branch of the left coronary artery was ligated approximately 2 to 3 cm. from the border of the left atrial appendix, which usually produced a darkened area of about 1/4 inches in diameter in the region of the apex. Before the artery ligation, a tracheal cannula was inserted and artificial respiration with room air applied at the time of the opening of the chest. The chest was opened by a midline incision and a pericardial erable was constructed. At the time of ligation 20 per cent glucose or 0.9 per cent NaCl solution was administered into the femoral vein at the rate of 8 ml./Kg./hr. The exposed surface was covered with gauze moistened with saline. The chest was roughly approximated with hemostats and the animal maintained in this condition with continued artificial respiration for 4 hours. Following removal and freezing of the entire heart, tissue samples were removed from the region of the left ventricular apex which appeared relatively dark to the eye following artery ligation and also from the base of the left ventricle, an area not directly affected by the artery ligation.

The analytical procedures were identical to those described previously. Inorganic phosphate (IP) was precipitated with calcium from a neutralized trichloroacetic acid extract, phosphocreatine (PC) was hydrolyzed with molybdic acid at room temperature for 30 min., and the labile phosphate of adenosine polyphosphate (APP) was hydrolyzed by heating at 100 C. in 1 N HCl for 5 min. Inorganic phosphate was determined by the method of Fiske and SubbaRow and the concentrations of PC and APP were determined by difference. Lactic acid was analyzed by the Barker and Summerson procedure and glycogen by the Good, Kramer and Somogyi method. Potassium and sodium were analyzed in solutions diluted from a nitric acid digest with a Perkin-Elmer model 52 flame photometer, using lithium as an internal standard.

Results

Effects of Glucose Infusion on Normal Hearts. The finding of chief interest is the higher content of phosphocreatine in hearts of intact dogs given glucose infusion for 4 hours compared to control, noninfused hearts (table 1). In the left ventricle, this was associated with no significant alteration in IP and APP concentrations. The presence of insulin in addition to glucose did not further modify
TABLE 1.—Content of Chemical Constituents in Normal Dog Hearts* Infused with Glucose or with Glucose-Insulin

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Left Ventricle</th>
<th>Right Ventricle</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glucose</td>
</tr>
<tr>
<td>Inorganic phosphate (mg. % P)</td>
<td>25.9±1.1 (8)†</td>
<td>21.2±1.0§ (11)</td>
</tr>
<tr>
<td>Phosphocreatine (mg. % P)</td>
<td>9.1±0.4 (8)</td>
<td>9.7±0.9 (8)</td>
</tr>
<tr>
<td>Adenosine polyphosphate (mg. % P)</td>
<td>31.3±0.9 (8)</td>
<td>31.6±1.0 (8)</td>
</tr>
<tr>
<td>Glycogen (mg. %)</td>
<td>619±40 (10)</td>
<td>1204±52§ (12)</td>
</tr>
<tr>
<td>K (mEq./Kg.)</td>
<td>65.1±1.0 (10)</td>
<td>84.5±2.5§ (9)</td>
</tr>
<tr>
<td>Na (mEq./Kg.)</td>
<td>33.6±1.0 (10)</td>
<td>34.3±2.2§ (9)</td>
</tr>
</tbody>
</table>

*Blood sugar in glucose and glucose-insulin infused dogs was 391±23 and 341±35 mg %, respectively. Figures in parentheses indicate number of animals from which mean and standard error of mean were calculated. †p<0.01. §p<0.02.

left ventricular phosphate concentrations. PC content in nonschismic areas of coronary-ligated hearts was also higher when these hearts were infused with glucose rather than with saline (table 2). In these experiments, IP was significantly lower in the presence of glucose.

In right ventricles of intact dogs given glucose, PC concentration was also higher and IP concentration lower than in right ventricles of control, noninfused dogs. With insulin and glucose, a significant decrease in APP was observed. As noted previously,3,4 metabolic differences of a quantitative nature appear to exist between left and right ventricles.

Potassium and glycogen concentrations were affected in a qualitatively similar manner in these experiments. Both K and glycogen were higher in glucose-infused than in control hearts. With insulin and glucose, left ventricular K (p < 0.02) and glycogen (p < 0.01) were lower than with glucose alone. In contrast, there was no significant difference in right ventricular K or glycogen between animals given glucose or glucose-insulin. Although the effects of glucose on glycogen content are known5 and that of insulin on glycogen content observed before in the isolated heart,6 the corresponding results on K content have not been previously reported as far as we are aware.

Effects of Coronary Ligation. Following ligation of the descendens artery, mean arterial blood pressure did not decline below 100 mm. Hg over a period of 4 hours in 14 dogs. Tissue samples were obtained from these animals for chemical analysis. In 2 other animals, blood pressure dropped below 100 mm. Hg and in 3 others ventricular fibrillation occurred. The incidence of fibrillation is lower than that reported by Cherbakoff et al.6 which may be related primarily to the lower site of ligation on the descendens artery.

The mean concentrations of various constituents examined in saline-infused, coronary-ligated left ventricles were significantly different from mean values in nonschismic regions of the same heart with the exception of IP and Na (table 2). The affected areas were as markedly altered in hearts given glucose as in hearts given saline. Concentration differences between affected areas of saline-
GLUCOSE INFUSION AND MYOCARDIAL METABOLISM

TABLE 2.—Content of Chemical Constituents in Coronary-Ligated Dog Hearts Infused with Saline or Glucose

<table>
<thead>
<tr>
<th></th>
<th>Inorganic phosphate (mg. % P)</th>
<th>Phosphocreatine (mg. % P)</th>
<th>Adenosine polyphosphate (mg. % P)</th>
<th>Glycogen (mg. %)</th>
<th>Lactate (mg. %)</th>
<th>K (mEq./Kg.)</th>
<th>Na (mEq./Kg.)</th>
</tr>
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<tbody>
<tr>
<td>Saline infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Control area</td>
<td>33.9±1.6 (5)*</td>
<td>13.1±2.0 (5)</td>
<td>33.7±3.0 (5)</td>
<td>784±19 (7)</td>
<td>20.0±1.2 (7)</td>
<td>89.6±3.2 (7)</td>
<td>46.0±2.0 (7)</td>
</tr>
<tr>
<td>Ischemic area</td>
<td>37.9±2.0 (5)</td>
<td>5.1±0.5f (5)</td>
<td>16.8±3.2f (5)</td>
<td>532±27f (7)</td>
<td>30.6±1.2f (7)</td>
<td>67.0±4.7f (7)</td>
<td>50.5±1.2f (7)</td>
</tr>
<tr>
<td>Glucose infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control area</td>
<td>23.9±2.1 (5)</td>
<td>22.7±1.4 (5)</td>
<td>39.6±1.8 (5)</td>
<td>818±64 (7)</td>
<td>36.4±3.1 (6)</td>
<td>87.6±4.2 (7)</td>
<td>39.9±3.7f (7)</td>
</tr>
<tr>
<td>Ischemic area</td>
<td>38.7±2.7f (5)</td>
<td>5.4±0.9f (5)</td>
<td>13.9±4.2f (5)</td>
<td>398±46f (7)</td>
<td>55.1±10.1 (6)</td>
<td>72.6±4.6f (7)</td>
<td>45.5±2.7f (7)</td>
</tr>
<tr>
<td>Difference between saline- and glucose-infused hearts</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control area</td>
<td>-10.0f</td>
<td>+9.6f</td>
<td>+5.9f</td>
<td>+34</td>
<td>+16.4f</td>
<td>-2.0</td>
<td>-6.1f</td>
</tr>
<tr>
<td>Ischemic area</td>
<td>+0.8</td>
<td>+0.3</td>
<td>-2.7</td>
<td>-134</td>
<td>+24.5f</td>
<td>+5.6</td>
<td>-5.0</td>
</tr>
</tbody>
</table>

*Figures in parentheses indicate number of animals from which mean and standard error of mean were calculated.

fP<0.01.

§P<0.02.

and glucose-infused hearts were not statistically significant indicating that glucose administration did not have a salutary effect on the metabolism of coronary-occluded tissues in these experiments.

Our results on the effects of coronary ligation are similar to previous findings. Four minutes after ligation, PC is decreased with no change in APP although in cat hearts a decline in the latter has been reported 2 min. after occlusion.8 Our results show that 4 hours after ligation, PC and APP are both decreased. Glycogen decrease has been noted before9 as have K decrease10 and lactate increase.11 Although Na accumulation during anoxia is a well known observation,12 the increase in Na content was not statistically significant. In temporary occlusion of 45 min. followed by a 4 to 5 hour recovery period, increased Na, Cl and water have been found without change in K or in glycogen.13

It may be noted that the concentrations in the nonischemic base of coronary-occluded, saline-infused left ventricles (table 2) are generally greater by 30 to 40 per cent than the corresponding concentrations in the apex of intact, noninfused hearts (table 1). The possibility that a nonspecific dehydration of tissues might have occurred was not supported by measurement of water content in 6 additional experiments, 4 with and 2 without occlusion. The higher Na content suggests that increase in extracellular space may in part account for these results.

**DISCUSSION**

The higher phosphocreatine content in hearts of normal animals infused with glucose indicates that increased synthesis of high energy phosphate compounds occurs in the presence of added glucose. Thus, in addition to increased storage as glycogen,2 increased degradation of glucose by way of the Embden-Meyerhof and tricarboxylic acid cycles appears to take place since the reactions in these cycles are coupled with the synthesis of high energy phosphate. The increased lactate content in nonischemic tissues of coronary-ligated hearts also points to an increased turnover of glucose in the Embden-Meyerhof cycle. These results provide added
support for the view that glucose is an important substrate for cardiac metabolism in vivo.

The effects of coronary ligation, which essentially confirmed previous findings, may be explained on the basis of lowered oxygen supply. Since a small amount of collateral circulation appears to be present following acute ligation, it seemed possible that glucose administration might reverse to some extent the metabolic changes following coronary occlusion. The alterations observed as a result of glucose addition to normal hearts, which were in sharp contrast to the effects of ligation, indicated that this effect might be possible. The results have shown, however, that no detectable improvement in metabolism occurred.

Our results do not rule out the potential value of glucose administration in reducing the incidence of fibrillation since this effect may be due mainly to the lowering of serum K. In addition, our data suggest that glucose infusion might be of some value in aiding recovery from temporary or partial occlusion.

Summary

Infusion of glucose to whole dogs increases left ventricular PC, glycogen, and K with no change in IP, APP and Na concentrations. In non-ischemic areas of coronary-ligated hearts, PC and lactate increased and IP decreased in the presence of glucose. Ligation of the descending branch of the left coronary artery resulted in decreased content of PC, APP, glycogen and K with an increase in lactate. Infusion of glucose caused no significant reversal of these effects.

Acknowledgment

The late Dr. A. G. Mulder was responsible for initiating this study.

Summary in Interlingua

Le infusion de glucosa in canes intacte augmentava le concentrationes sinistro-ventriculare de phosphocreatina, glycogeno, e kalium, sin ulle alteration de phosphato inorganic, adenosinopolyphosphato, e natrium. In areas non-ischemic de cordes a ligation coronari, phosphocreatina e lactato se augmentava e phosphato inorganic se reduciva in le presentia de glucosa. Le ligation del branca descendente del arteria sinistro-coronari resultava in reducile contentos de phosphocreatina, adenosinopolyphosphato, glycogeno, e kalium, con augmento de lactato. Le infusion de glucosa causava nulle significative reversion de ista effectos.

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