EFFECTS OF GLUCOSE-INSULIN-POTASSIUM INFUSION
ON MYOCARDIAL INFARCTION AND MYOCARDIAL BLOOD FLOW
FOLLOWING EXPERIMENTAL CORONARY ARTERY OCCLUSION

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To determine the therapeutic effects of glucose-insulin-potassium (GIK) solution, 5 control dogs and 5 GIK-treated dogs were investigated 24 hours after coronary artery occlusion by use of myocardial creatine phosphokinase (CK) activity and myocardial thallium-201 uptake. There was no significant difference in myocardial blood flow estimated by thallium-201 uptake between the control and the GIK group, but myocardial CK activity in the ischemic zone of GIK-treated animals was significantly higher than that of the control group. This suggests that administration of GIK solution is effective in protecting myocardial tissue in the central ischemic area and that this protecting action of GIK seems to be independent of myocardial blood flow.

GLUCOSE-insulin-potassium (GIK) infusion was introduced by Sodi-Pallares et al1 as a means of normalizing the electrocardiographic signs of myocardial infarction. The clinical efficacy of this therapy, however, remained controversial2–19. Although animal studies20–25 have suggested that GIK infusion might exert a beneficial influence on the effects of coronary artery occlusion by decreasing the extent of myocardial damage and infarct size, yet relatively little data26,27 are available on the effects of GIK infusion on myocardial damage and blood flow and many more experimental details are required to clarify the mechanism.

This study was undertaken to investigate the effects of GIK on acute ischemic damage of the myocardium and on myocardial blood flow measured by radionuclide technique.

MATERIALS AND METHODS

Animals and Preparation

Ten mongrel dogs of either sex, weighing 10 to 15 kg were anesthetized by a single intravenous injection of sodium pentobarbital (30 mg/kg of body weight) with respiration maintained by Harvard respirator. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. The left anterior descending artery was dissected and ligated just distal to the first diagonal branch. The chest was then closed in layers with an indwelling drainage tube and the dog was allowed to breathe on its own. In 5 control dogs normal saline solution was infused intravenously at a rate of 1.5 ml/kg per hour and in the other GIK group of 5 dogs a solution with a concentration of 300 g of glucose, 40 mEq of

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potassium ion and 50 units of regular insulin per liter was given at a rate of 1.5 ml/kg per hour started 15 minutes after coronary artery ligation for the following 24 hours. Animals were sedated by intermittently administered pentobarbital during this period and electrocardiogram was continuously monitored. Twenty-four hours after ligation of the coronary artery approximately 0.1 mCi of thallium-201 chloride was injected intravenously. Five minutes after thallium-201 administration a large dose of sodium pentobarbital was given. The chest was reopened and the heart excised. Transmural specimens were obtained for the analysis of myocardial creatine phosphokinase (CK) concentration and the measurement of radio-activity of thallium-201. Specimen sites chosen were located in the central area supplied by the occluded artery, in a zone of the left ventricle remote from the occluded artery which presumably was adequately perfused, and in a marginal zone which was defined as a border area adjacent to a clearly visible infarct area. Three or 4 specimens were obtained from each zone and were rapidly frozen to avoid chemical degradation.

Measurement of Radioactivity

The specimens were weighed and then placed in a well counter. Thallium-201 activity was counted with a window of 50–100 kev and the counts per minutes were corrected for background activity and for weight of the specimen. Subsequently, in each dog the counts of each specimen were divided by average counts of all specimens which were taken in zones of the adequately perfused myocardium. The radioactivity percentage thus obtained was considered to represent relative myocardial blood flow compared to that in normal zones.

Biochemical Procedures

Myocardial specimens were homogenized with buffer solution and centrifuged at 16000 × g for 10 minutes at 4°C, according to the method of Kjekshus and Sobel.28 CK activity of the supernatant was assayed spectrophotometrically by Union Carbide Centrifichem system according to modified Oliver method.29–31 CK activity of each tissue specimen was corrected for weight and divided by average CK activity of all specimens taken in normally perfused zones in each dog. The percentage activity of CK was considered to represent the degree of myocardial viability.

RESULTS

Myocardial uptake of thallium-201 administered 24 hours after coronary artery occlusion in normal, marginal and infarcting zones defined by anatomical relationship to the occluded coronary artery as described previously was 100 ± 14% (n = 16), 56 ± 35% (n = 7) and 23 ± 21% (n = 16), respectively in the control group; 100 ± 15% (n = 19), 63 ± 40% (n = 11) and 17 ± 10% (n = 19), respectively in the GIK group (Fig. 1).
There was no significant difference between the two groups in any of the zones.

Myocardial CK activity 24 hours following coronary artery ligation in the control group was 100 ± 20% (n = 16) in the normal zone, 53 ± 35% (n = 7) in the marginal zone and 18 ± 22% (n = 16) in the infarcting zone. In the GIK group CK activity was 100 ± 25% (n = 19), 68 ± 21% (n = 11) and 41 ± 22% (n = 19), respectively (Fig. 2). There was no significant difference of myocardial CK activity in the normal or marginal zone between the control group and the GIK group, but there was a significant difference of CK activity in the infarcting zone between the control and the GIK group (p < 0.002 by the nonpaired t-test).

Scatter diagram comparing percent activities of myocardial CK against percent uptake of thallium-201 in each of the control and the GIK group are shown in Fig. 3. The correlation coefficient was 0.82, with a regression equation of $Y = 4.46 + 0.82X$ (39 measurement sets) in the control group, and $r = 0.67$, with a regression equation of $Y = 35.16 + 0.57X$ (49 measurement sets) in the GIK group. The less the myocardial thallium-201 uptake was, the greater the difference of myocardial CK activity between the GIK group and the control group.

**DISCUSSION**

GIK infusion has produced variable effects on pacing- and exercise-induced angina according to glucose concentration of infusate but most beneficial effects were obtained when given with concentration of 300 g glucose, 80 mEq of potassium ion and 50 units of regular insulin per liter at a rate of 1.5 or more ml/kg per hour. In the present study potassium concentration was decreased to 40 mEq per liter to avoid hypokalemia as indicated in the previous report.

Previous studies have demonstrated a close linear relationship between the myocardial distribution of thallium-201 and the distribution of myocardial blood flow after acute coronary artery occlusion. This relationship appears to be maintained under variable conditions in both the ischemic and nonischemic regions, but Schwartz et al. and Pohost et al. have described early redistribution of thallium-201 activity to the ischemic region after restoration of blood flow. Therefore, when myocardial blood flow is assessed by thallium-201 activity, it is necessary to measure the activity within 10 minutes after thallium-201 injection. In the present study the animals were sacrificed 5 minutes after injection of thallium-201.

The accurate assessment of cellular damage following myocardial infarction is difficult, but it has been shown that the reduction in myocardial CK activity is a quantitative indicator of the extent of cell death 24 hours after coronary artery occlusion. The experiments described in this communication were undertaken to determine the degree of myocardial cell injury, judged by CK depletion in full-wall thickness specimens of the left ventricle.

Interest in GIK has been renewed by the study of Maroko et al. demonstrating a reduction of infarct size in a canine myocardial model. Theoretical benefits of GIK solution have been extensively reviewed and include antiarrhy-
thmic action, reduction of myocardial infarction size and augmentation of myocardial contractility. Proposed mechanisms of action of GIK are ill defined and may include increase in glycolytic flux, restoration of myocardial intracellular potassium, reduction of plasma free fatty acids, increase in serum osmolality, decrease in lysosomal activity and perhaps enhanced ratio of adenosine triphosphate production. A direct effect of insulin cannot be excluded.

With infusion of GIK, arterial-coronary sinus difference for oxygen fell in dogs with developing myocardial infarction and similar decrease in oxygen extraction was reported in patients with stable coronary artery disease. This phenomenon was attributed to reduction of myocardial oxygen demand due to decreased free fatty acids. Other experimental data demonstrate no alteration of myocardial blood flow with GIK infusion, while recent clinical observations in patients with stable ischemic heart disease suggest an increase of coronary blood flow during GIK infusion, and increased serum osmolality was considered a possible mechanism. According to our present data there is no evidence to suggest that coronary blood flow was altered in either the marginal or the infarcting zone.

In the marginal zone, GIK infusion showed no significant difference in CK activity when compared with the control group. In the infarct zone, however, GIK infusion reduced the loss of CK from the myocardium by about 23%, while there was no significant difference in thallium-201 uptake. The size of the infarct itself was not measured in this study, but the data suggest that GIK infusion plays a role in protecting the myocardium from necrosis and that this action of GIK appears to be mediated by a metabolic process not directly related to myocardial blood flow.

Reservations in applying the above therapeutic findings in dogs with coronary artery ligation include 1) the infusion was started 15 minutes after the onset of coronary artery occlusion, whereas medical care may be delayed for some hours, 2) sudden coronary artery ligation in the previously healthy dogs may not be valid in patients with diffuse coronary disease, and 3) a more substantial collateral circulation appears to obtain in dogs than in humans, which is important since the GIK infusate presumably reaches the infarcting myocardium through these collateral channels.

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