The Effect of Hypoglycemia on Myocardial Ischemic Injury During Acute Experimental Coronary Artery Occlusion

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SUMMARY
To determine the effect of hypoglycemia on myocardial ischemic injury following coronary artery occlusion epicardial electrograms were recorded 15 minutes after two 20-minute coronary artery occlusions in seven anesthetized dogs. The first occlusion was a control (blood glucose 85 ± 5 (sd) mg%). Before the second occlusion hypoglycemia was induced (blood glucose 40 ± 5 mg%) by the intravenous administration of insulin (2 units/kg). The average ST-segment elevation in leads during control was 3.5 ± 1.0 mV which rose to 6.1 ± 1.4 mV during the second occlusion (P < 0.05). The number of sites showing ST-segment elevation exceeding 2 mV increased from 7.6 ± 1.6 during control to 10.6 ± 1.4 (P < 0.05) during the occlusion with hypoglycemia. In other dogs, a coronary artery was occluded for 24 hours. Epicardial ST-segment elevations were compared to creatine phosphokinase (CPK) activity and histological appearance from the same sites. CPK activity in sites with normal ST segments (0–2 mV) was 33.1 ± 6.0 IU/mg protein. Six additional dogs received insulin following the 15 minute epicardial map and blood sugar was maintained at a level of 46 ± 6 mg% for the 24 hours. These dogs showed more myocardial necrosis than predicted by the ST-segment elevation prior to insulin administration. Forty-six percent of sites, which in control dogs would have been expected to have normal CPK and histological appearance, showed depressed CPK activity and histological evidence of early myocardial necrosis. Thus, hypoglycemia increases myocardial damage, as reflected by enzymatic and histological analyses.

Additional Indexing Words:
Myocardial necrosis  Epicardial electrocardiography  ST-segment elevation
Creatine phosphokinase  Diabetes mellitus  Myocardial infarction

There has been considerable interest in possible deleterious effects on the heart of hypoglycemia in patients with coronary artery disease. Since the association of ischemic heart disease and diabetes mellitus requiring treatment with insulin is common, it is of practical importance to clarify the effects of hypoglycemia in the presence of myocardial ischemia. In addition, the role of glucose availability in the survival of ischemic myocardium has assumed new importance since recent work suggests that an augmented glucose supply may increase the viability of ischemic cardiac tissue. Considering the clinical importance of the size of myocardial infarcts following coronary occlusion, and the fact that large increases in the extent of myocardial necrosis have been demonstrated to occur after coronary occlusion if myocardial energy balance is altered in an unfavorable direction, the present investigation was designed to examine the effect of insulin-induced hypoglycemia on the extent and severity of myocardial ischemic injury and necrosis after acute coronary occlusion.

Methods
Two experimental protocols were utilized.

Protocol A
In 22 dogs the extent and magnitude of acute myocardial ischemic injury following coronary artery occlusion was analyzed during normoglycemia and hypoglycemia. Dogs weighing between 22 and 28 kg were anesthetized with sodium thiamylal and their respiration maintained with a Harvard respirator. The heart was exposed through the left fifth intercostal space and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) or its apical branch was dissected free from adjacent tissue and occluded intermittently for 20 min using a Schwartz intracranial arterial clamp. As previously described, epicardial electrograms were obtained from 10 to 14 sites on the anterior surface of the left ventricle distributed in areas supplied by the occluded artery as well as in distant, presumably adequately perfused areas. The clamp was then released and flow permitted for 60 min. In 15 dogs there was no intervention prior to the second occlusion; in seven dogs the second occlusion was carried out 15 min after

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the intravenous administration of 2 units/kg crystalline zinc insulin. In two of these seven dogs 1 mg/kg propranolol was given intravenously prior to the first occlusion. Epicardial electrograms were recorded prior to each occlusion and at 5 min intervals while the occlusion was maintained. The changes in acute myocardial ischemic injury were analyzed using the average ST-segment elevation in all sites (ST) and the number of sites showing ST-segment elevation exceeding 2 mV (NST).

Any site which exhibited a QRS duration exceeding 0.065 sec on any single tracing (from an average normal of 0.040 sec), and therefore showing secondary changes in ST-segment height, was excluded from analysis for the entire experiment. The paired t-test was used to determine the statistical significance of differences between ST and NST in the consecutive occlusions. In all dogs aortic pressure was measured through a catheter inserted via the left carotid artery by a Statham P23Db pressure transducer.

Protocol B

The effect of hypoglycemia on the extent of myocardial infarction was studied in 21 dogs, using histological and enzymatic methods. The surgical procedure was identical to the one used in Protocol A. However, in these dogs, the coronary artery occlusion was maintained for 24 hours. Epicardial maps were recorded 15, 30, and 45 min following coronary occlusion. The dogs' chests were then closed, they were extubated and allowed to recover for 24 hours. Arterial pressure and electrocardiogram (lead aVF) were constantly monitored. Twenty-four hours after coronary ligation the dogs were again anesthetized, their chests re-opened, the hearts excised and immediately washed in cold saline. Transmural myocardial specimens were obtained from the same sites at which electrograms had been recorded 24 hours earlier. These specimens were analyzed for CPK activity as previously described and for histological appearance following Bouin's fixation and hematoxylin and eosin staining. Blood glucose and potassium were estimated as previously described. Insulin does not influence the CPK assay system or in itself alter myocardial CPK activity in experiments with incubated tissue slices.

Fifteen of the 21 animals served as controls, i.e., no insulin was administered. In the remaining six animals, 2 units/kg insulin was administered intravenously 17 min following occlusion and a blood glucose level of 46 ± 6 mg% was maintained for 24 hours with additional doses of insulin administered whenever the glucose level exceeded 50 mg%. The data were analyzed by comparing ST-segment elevation at each site 15 min following occlusion with myocardial CPK activity and histological appearance 24 hours later, as described previously.

Results

1. The Influence of Hypoglycemia on ST-segment Elevation

In 15 dogs two consecutive 20-minute occlusions without any drug administration were performed (Protocol A). Average ST-segment elevation (ST) and the number of sites showing ST-segment elevation over 2 mV (NST) were similar during the two occlusions: 4.5 ± 0.8 (SEM) and 4.2 ± 0.9 mV, and 5.5 ± 1.0 and 5.5 ± 1.0 sites 15 min following each occlusion. Insulin-induced hypoglycemia did not alter the ST segments remote from the myocardium supplied by the occluded vessel, indicating the absence of nonspecific effects. In the five dogs in which the first (control) occlusion was carried out without pretreatment with propranolol and with the

![Figure 1](Image)

**Figure 1**

Example of an experiment showing increased ST-segment elevation during hypoglycemia. Right panel: The diagram depicts the anterior surface of the heart showing location of the arbitrarily selected sites. The striped area represents the area of sites with abnormal ST segments 15 min after occlusion alone. The starred area shows the substantially greater area of ST-segment abnormality 15 min after the second occlusion which was carried out during hypoglycemia. Left panel: Time course of average ST-segment elevation (ST). Triangles denote data from occlusion alone, circles show increased ST-segment elevation during second occlusion in the same dog after insulin treatment.
level of glucose at 85 ± 5 mg%, the ST was 3.5 ± 1.0 mV and NST was 7.6 ± 1.6 fifteen minutes following occlusion. Prior to the second occlusion 2 units/kg insulin was administered and blood sugar fell to an average of 40 ± 5 mg% 15 min following occlusion. ST increased to 6.1 ± 1.4 mV (P < 0.05) and NST to 10.6 ± 1.4 sites (P < 0.05), (figs. 1, 2). Heart rate was 149 ± 13 and 131 ± 6 beats/min (NS), mean arterial pressure 113 ± 12 and 104 ± 6 mm Hg (NS) and serum potassium 4.2 ± 0.3 and 3.4 ± 0.2 mEq/L (P < 0.05) measured 15 min after the control and post-insulin occlusions, respectively. In two additional dogs, pretreated with propranolol, ST increased from 1.4 and 1.9 mV to 3.4 and 9.3 mV, respectively, and NST increased from 2 and 6 to 8 and 9 sites, respectively, following the second occlusion, showing an increase similar to that observed in the nonpropranolol treated group.

In dogs in which the coronary artery occlusion was maintained (Protocol B), ST-segment elevation increased from the level found 15 min following occlusion just prior to insulin administration, to that observed 30 and 45 min following occlusion. Thus, ST increased from 0.6 ± 0.3 to 1.5 ± 0.3 mV (P < 0.01) after 30 min and to 2.7 ± 0.6 mV (P < 0.01) after 45 min (fig. 2). NST increased from 1.4 ± 0.7 to 3.5 ± 0.8 (P < 0.05) after 30 min and to 6.0 ± 1.2 (P < 0.05) after 45 min (fig. 2). This shows that hypoglycemia significantly increases the extent and severity of myocardial ischemic injury whether it is induced before or after coronary artery occlusion.

II. The Effect of Insulin-induced Hypoglycemia on Myocardial Necrosis Studied by Histologic and Enzymatic Methods

In the control group (occlusion alone), sites with normal ST-segment elevation (0–2 mV) showed normal CPK activity 24 hours later, i.e., 33.1 ± 6.0 IU/mg protein (N = 49). Sites with ST-segment elevation of 3 and 4 mV 15 min following occlusion showed depressed CPK activity, i.e., 16.3 ± 4.0 IU/mg protein (N = 37). In the insulin-treated dogs, 46% of sites with no ST-segment elevation (0–2 mV) before insulin administration showed ST-segment elevation exceeding 2 mV 15 and 30 min later. These sites, when biopsied 24 hours later, showed CPK depression: 19.1 ± 6.0 IU/mg protein (N = 14), while sites which exhibited no ST-segment elevation either before or after insulin administration (sites remote from the occluded artery) showed CPK activities averaging 36.5 ± 10.0 IU/mg protein (N = 14), a value similar to that observed in the control group, indicating that insulin by itself did not change CPK activity (figs. 3, 4).

On histologic examination, in the control group, 47 of 49 (96%) sites without ST-segment elevation (0–2 mV) were normal, whereas 36 of 37 (98%) sites with ST-segment elevation exceeding 2 mV 15 min after occlusion showed early signs of myocardial infarction 24 hours later, such as a deeper eosinophilic appearance of the cytoplasm, karyolysis, karyorrhexis, polymorphonuclear cell infiltration and disruption of the cell membrane. In contrast, in the experimental group, all 14 sites showing no ST-segment elevation (0–2 mV) before insulin administration, but exhibiting ST-segment elevation following insulin treatment, showed signs of necrosis, whereas all 14 sites which continued to show no ST-segment elevation even after insulin administration (sites remote from the occluded area) exhibited normal histologic appearance. Therefore, when evaluated both by histological appearance and by myocardial CPK activity,
hypoglycemia caused an increase in the extent of necrosis following coronary artery occlusion.

Discussion

Since the earliest use of insulin in the treatment of diabetes mellitus the possibility of deleterious cardiac effects of insulin-induced hypoglycemia was recognized and many instances of exacerbation of ischemic heart disease associated with insulin therapy have been reported. Several authors have specifically noted an association between insulin-induced hypoglycemia and acute myocardial infarction. However, since the diabetic population is predisposed to both of these complications, i.e., hypoglycemia and acute myocardial infarction, a causal relationship between hypoglycemia and myocardial infarction or exacerbation of angina pectoris is difficult to establish.

Theoretically, hypoglycemia could exert a deleterious effect on the ischemic heart in several ways. Evidence is accumulating that in the presence of coronary obstruction, survival of myocardial tissue and symptoms of angina pectoris depend on the balance between energy supply and demand. The severely ischemic myocardium is dependent on anaerobic pathways for its energy production and is uniquely dependent on carbohydrate substrates.
HYPOGLYCEMIA AND MYOCARDIAL ISCHEMIA

Under these conditions, hypoglycemia could limit substrate availability and consequently energy supply to the ischemic myocardium. Another possible mechanism by which hypoglycemia could increase myocardial damage would be through an increase in energy requirements, again unfavorably altering the balance between energy supply and demand. This is possible since hypoglycemia is known to provoke a sympathoadrenal discharge which could increase heart rate, the inotropic state of the myocardium and ventricular afterload. These variables are important determinants of myocardial ischemic injury and necrosis.

The present investigation showed that hypoglycemia produced a significant increase in the extent and magnitude of myocardial ischemic injury following coronary artery occlusion when insulin was administered either before or shortly after occlusion. Moreover, it showed a hypoglycemia-provoked extension of myocardial necrosis demonstrated by histological appearance and myocardial CPK activity depression 24 hours after occlusion.

The finding that the hypoglycemia-induced increase in the severity and extent of ischemic injury was not prevented by propranolol suggests that in these experiments it was not due primarily to a beta-adrenergic mediated sympathoadrenal response to hypoglycemia. In addition, in these dogs, already subject to significant sympathetic stimulation by barbiturate anesthesia, heart rate and blood pressure were not significantly altered by insulin, further arguing against the possibility that the observed effect was mediated by the autonomic nervous system. Thus, it appears that this deleterious action of insulin-induced hypoglycemia on the ischemic heart was due to a metabolic effect, perhaps limitation of substrate for anaerobic metabolism. This does not deny the possibility that when an adrenergic discharge is added, ischemic injury may increase even further.

It is conceivable that one or more of insulin’s metabolic effects other than hypoglycemia could contribute to the observed deleterious actions during myocardial ischemia. However, each of insulin’s other major metabolic effects might be expected to limit, rather than increase, myocardial ischemic damage. For instance, circulating free fatty acids (FFA) have been implicated in arrhythmogenesis and increased myocardial ischemic damage. Although insulin may increase FFA by an indirect, catecholamine-mediated effect, the direct effect of insulin would be to favor FFA incorporation into triglycerides. Indeed, in experiments using methods similar to those of the present study, inhibition of lipolysis with β-pyridyl carbino1 decreased signs of myocardial ischemic injury, and exerted a protective effect against deleterious action of isoproterenol. Likewise insulin’s activation of glycogen synthetase would be expected to protect against oxygen lack, as does experimental increase of myocardial glycogen stores induced by reserpine. Finally, although insulin’s anabolic effect might protect the ischemic myocardium, preliminary reports suggest that in spite of stimulating chain initiation, insulin does not significantly increase protein synthesis in experimental myocardial ischemia.

Some authors have concluded that hypoglycemia should not exert a direct metabolic adverse effect on the heart since this organ does not depend solely on carbohydrate substrates. This argument does not apply, however, to the ischemic heart, which as noted is quite dependent on carbohydrate substrates.

Insulin-induced hypoglycemia may be associated with alterations in the electrocardiogram, particularly the ST segment and T waves and in the cardiac rhythm, presumably due in part to shifts of potassium into the cells. In these experiments, no ST segment changes occurred with induced hypoglycemia in sites remote from the occlusion. Furthermore, in the presence of coronary occlusion, hypoglycemia caused an increase of ST-segment elevation, and the effect expected from hypokalemia would have been ST-segment depression. In addition, the deleterious effects of hypoglycemia, as reflected in tissue CPK and histologic appearance, were independent of any possible nonspecific electrocardiographic effects since the electrocardiographic measurements with which these markers of tissue damage were compared were made before the administration of the insulin.

Extrapolation of data obtained from experimental animals is always fraught with hazard, and the anesthetized, otherwise healthy dogs used in this study obviously differ from patients with atherosclerosis and diabetes mellitus. However, the principle that insulin-induced hypoglycemia may exert a deleterious effect on the ischemic heart may well apply to such patients. Many agents other than insulin may provoke hypoglycemia, and although this study only examined insulin, the results may be more general. For example, propranolol, a medication frequently employed in ischemic heart disease, may induce hypoglycemia, and thus has been associated with acute myocardial infarction.

Although the numerous case reports of associated hypoglycemia and exacerbation of the clinical manifestation of coronary disease do not necessarily establish a causal relationship, epidemiologic data show that insulin-treated diabetic patients have a much higher incidence of cardiac failure when compared to others with the same age, blood pressure,
weight, serum cholesterol and symptomatic coronary disease. This finding has been interpreted as evidence that such patients are subject to a cardiomyopathy. Unexplained cardiac failure was not observed in patients treated by diet or oral hypoglycemic agents alone, suggesting that it was related to the therapy employed (although criteria for choice of therapy are not mentioned in this study). The present experiments raise the possibility that insulin, perhaps through its hypoglycemic action, may contribute to cardiac injury by causing multiple microinfarctions in diabetic patients with coronary disease and could lead to impaired cardiac function. We do not wish to imply that tight control of blood sugar in diabetic patients is contraindicated. However, the results of this study do suggest that in the context of acute coronary occlusion, insulin-induced hypoglycemia may increase the extent and severity of consequent cardiac damage. Therefore, special care should be exercised to avoid hypoglycemia during insulin therapy of diabetic patients with acute myocardial infarction.

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