Hyperglycemia during Cardiopulmonary Bypass

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With the increasing frequency of bypass grafting with cardiopulmonary bypass for occlusive disease of the coronary arteries, an increasing number of patients with diabetes mellitus and coronary atherosclerosis are undergoing operation. A year ago two diabetic patients developed severe hyperglycemia during cardiopulmonary bypass for coronary bypass grafts and subsequently developed fatal hyperosmotic hyperglycemic non-ketotic coma. The correct diagnosis was belatedly made in both patients. Until this time the pump oxygenator had been routinely primed with 12.5 Gm. of 50 per cent glucose because of reports that glucose increased the tolerance of the myocardium to anoxia.[1-5,7,8,10,11] A prospective study of glucose metabolism was accordingly initiated in 20 patients undergoing cardiopulmonary bypass. The findings are described in this report.

Methods

Four diabetic and 16 non-diabetic patients (ages 43–69) were studied. Adult patients were selected at random from the daily operating schedule, studying one patient daily with Class III or Class IV (NYHA) heart disease until a total of 20 had been evaluated.

The four diabetic patients (Group I) were well controlled with daily administration of insulin. In the non-diabetic cases (Group II) preoperative fasting blood sugars or 2 hour post-prandial blood sugars were normal. Twelve of the 20 patients had aorto-coronary bypass procedures, seven had prosthetic valve replacement, and one had removal of a large left atrial thrombus developing after a previous mitral valve replacement.

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Anesthesia was induced with thiopental and succinylcholine and subsequently maintained with halothane. Perfusion was at a flow rate of 2.25 L/sq M body surface, temperature 30 to 34° C, using a Pemco roller pump and a Bentley disposable bubble oxygenator. The patients were heparinized with 300 units of heparin/Kg. of body weight. The pump oxygenator was primed with 2000 ml. Ringer's lactate solution and 1000 to 1500 ml. citrated blood. The pH of the citrated blood was adjusted to 7.4 with THAM (tromethamine). In addition, 0.6 Gm. of calcium chloride were given for each 500 ml. of citrated blood, and 1.0 Gm. magnesium sulfate and 10 mEq. of potassium chloride were added. No dextrose was given.

Blood samples were obtained from the patient and the pump oxygenator immediately before bypass, 30 minutes after bypass had begun, and at hourly intervals thereafter. These were analyzed for glucose, sodium, potassium, and osmolality.

Blood glucose levels were measured by the ferrous cyanide autoanalyzer method; osmolality with the Fisk osmometer; sodium and potassium with the flame photometer. Urine samples were collected at the same time as the blood samples were drawn and measured for glucose and acetone. Regular insulin, U-40, was given during operation to the four diabetic patients in Group I and to six of the 16 non-diabetic patients in Group II.

Results

The data from the four diabetic patients in Group I are summarized in Table 1. Blood glucose levels varied between 275 and 520 mg./100 ml. Two to 4+ glycosuria was present, and acetone was present in the urine in one patient. Fifty to 475 units of U-40 regular in-

TABLE 1. *Glucose Levels and Regular Insulin (U-40) Administration during Cardiopulmonary Bypass in Four Diabetic Patients*

Patient	Operation	Bypass Time (Hr-Min)	Blood Glucose (mg./100 ml.)	Urine Sugar/Volume in cc.	Insulin (Units)
1	A-C Bypass#	3′ 3″	350–385	3+ /1130	55
2	A-C Bypass	2′ 36″	250–305	3+ /1500	50
3	A-C Bypass	4′ 11″	420–520	4+A/ 630	475
4	A-C Bypass	2′ 5″	220–275	2+ / 950	50

KEY: +A = Acetone # = Aorto-coronary bypass

sulin were given to these four patients during bypass, but in only one did a decrease in blood glucose concentration occur, a 40 mg./100 ml. decrease after 275 units of insulin had been given. Serum sodium concentrations decreased below 131 mEq./L in two of the four patients in this group despite normal sodium concentrations before the operation in both the patient and the pump oxygenator.

In the 16 patients in Group II, blood glucose levels ranged between 180 and 385 mg./100 ml. (Table 2). Ten of the 16 patients developed 1+ to 4+ glycosuria. Twenty to 120 units of U-40 regular insulin were given to six of the 16 patients during bypass. The blood glucose concentration decreased 35 mg./100 ml. in one patient after 10 units of insulin but did not change after administration of a second dose of 30 units. Administration of insulin to the other five patients did not produce any significant change in glucose concentration.

Nine of the patients were hyponatremic preoperatively (122 to 131 mEq./100 ml.) and six of these developed glycosuria during bypass. In addition, two patients with normal preoperative serum sodium concentrations developed hyponatremia and glycosuria during bypass (Table 3). Four of the 16 patients in Group II died in the first 8 days following operation from causes unrelated to hyperglycemia. There were no neurologic injuries.

TABLE 2. *Glucose Levels and Regular U-40 Administration during Cardiopulmonary Bypass in Sixteen Non-diabetic Patients*

Patient	Operation	Bypass Time (Hr-Min)	Blood Glucose (mg./100 ml.)	Urine Sugar/Volume in cc	Insulin (Units)
1	A-C Bypass#	3′30″	285–325	3+/520	40
2	A-C Bypass	4′18″	255–350	4+/1820	60
3	A-C Bypass	3′32″	240–270	1+/490	0
4*	A-C Bypass LV Aneurysm	8′24″	255–300	−/1160	0
5	Double valve	2′28″	275–300	3+/365	20
6	Mitral valve	2′14″	350–380	Tr/175	0
7*	Triple valve	4′19″	200–210	0/300	0
8	A-C Bypass	1′51″	325–345	4+/590	0
9*	Atrial Thrombectomy	2′33″	260–280	0/180	0
10	A-C Bypass	2′ 0″	285–345	1+/270	0
11	Aortic valve	2′ 8″	225–255	2+/915	0
12	Aortic valve	2′35″	180–190	0/180	0
13	Aortic valve	1′54″	360–385	4+A/380	50
14	A-C Bypass LV Aneurysm Mitral valve	4′10″	250–310	4+A/660	120
15	A-C Bypass	4′14″	260–305	4+/1525	90
16*	Double valve	4′16″	260–285	Tr/1565	0

Key: * = Expired +A = Acetone # = Aorto-Coronary Bypass

TABLE 3. *Preoperative Serum Sodium and Glycosuria during Cardiopulmonary Bypass in Non-diabetic Patients (Group II)*

Normal Preoperative Serum Sodium		Preoperative Hyponatremia (122-131 mEq/100 ml.)		Total Patients
7 Patients		9 Patients		16
Negative urine sugars	Glycosuria	Negative urine sugars	Glycosuria	
5	2	3	6	16

In both groups of patients, osmolality values did not rise above 313 mOsm/Kg. of water. This is well below the reported average value of 353 mOsm/Kg. of water found in hyperosmolar hyperglycemic coma.[6]

Within 6 hours after bypass, the blood glucose concentration in both groups of patients decreased to the preoperative levels. Only the diabetic patients required insulin in the postoperative period.

Discussion

The uniform finding in all patients studied, both diabetic and non-diabetic, was the development of hyperglycemia during bypass which was almost totally resistant to the administration of insulin. However, the hyperglycemia promptly subsided within 6 hours after perfusion. These data did not indicate the mechanism for the development of hyperosmotic hyperglycemic non-ketotic coma in the two diabetic patients operated upon earlier. Possibly the addition of glucose to the pump oxygenator may have produced a more severe hyperglycemia in these patients. A greater awareness of the possibility of the development of this complication similarly may have prevented its development in the postoperative course.

The cause of the hyperglycemia, and its resistance to insulin, is uncertain. Tentative explanations have been suggested in other reports, but these are primarily speculative. Measurement of insulin levels during cardiopulmonary bypass with hypothermia has found an inhibition of the normal secretion of insulin in response to infusion of glucose.[7,12] This may represent a hypothermic depression of the response of pancreatic acini to hyperglycemia. The simple process of oxygenation of blood during cardiopulmonary bypass is also associated with a decrease in plasma insulin levels.[5] This may result from changes in composition of plasma proteins,

particularly alterations in sulfhydryl group bonding at the blood gas interface.[2]

Data from these studies and reports by others[5,7] indicate that the utilization of insulin is altered during cardiopulmonary bypass, as there is a decreased response to exogenous insulin. Hyponatremia, either from preoperative sodium restriction or hemodilution, may be partly responsible for the decreased sensitivity to insulin, as sodium is required for intracellular transport of glucose, normally initiated by insulin.[1] In this regard it was noteworthy that 10 of 14 of the patients studied with hyponatremia below 131 mEq./L had glycosuria during bypass. Other factors which may inhibit the secretion of insulin include suppression of insulin reactivity with a low cardiac output, and inhibition of insulin reactivity by catecholamines secreted during cardiopulmonary bypass.[9,10]

The frequent occurrence of hyperglycemia during cardiopulmonary bypass indicates that the addition of glucose to the pump oxygenator may be superfluous. Although not demonstrated in these studies, the possibility exists in diabetic patients that such additions of glucose may actually be harmful. The insidious development of fatal hyperosmotic hyperglycemic nonketotic coma in two patients following cardiopulmonary bypass indicates the need for more cautious evaluation of even mildly diabetic patients following operation. It seems probable that instances of fatal neurologic injury from hyperosmotic coma in the past have been erroneously diagnosed as being due to other causes, such as air embolism or vascular occlusion.

Summary

Two fatal cases of neurologic injury with hyperosmotic hyperglycemic non-ketotic coma in mildly diabetic patients following cardiopulmonary bypass prompted a study of insulin and glucose metabolism in 20 patients undergoing cardiopulmonary bypass for different lesions. Four diabetic and 16 non-diabetic patients were studied. Some degree of hyperglycemia developed in almost all patients studied during bypass. In the diabetic patients the blood glucose levels ranged from 275 to 520 mg./100 ml., while the glucose levels in the 16 non-diabetic patients ranged from 180 to 385 mg./100 ml. The hyperglycemia was almost totally resistant to administration of regular insulin during bypass, up to 475 units. However, following bypass the hyperglycemia subsided within about 6 hours. No adverse complications were detected. The cause of the hyperglycemia and its resistance to exogenous insulin is uncertain. Serum osmolality values remained below 313 mOsm/Kg. There was some glycosuria and mild hyponatremia.

Although the mechanism of hyperosmotic coma was not detected in these studies, the uniform occurrence of hyperglycemia during cardiopulmonary bypass indicates that further addition of glucose during perfusion is superfluous and may possibly be harmful.

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