Blood Sugar and Insulin Response of Humans in Shock

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CONTROL of blood glucose is accomplished through a complex interaction of a number of substances. This complexity is greatly enhanced in "the rude unhinging of life" associated with shock and injury. Blood sugar and insulin are intimately related under normal conditions with one of nature's best examples of a servo-control system. Conflicting reports from animal experiments of the effects of shock on the interaction of these two substances have raised doubts as to how man might react. Various authors have observed insulin levels to rise with blood sugar in dogs.[5, 14, 15] Moss,[17] however, found insulin to be depressed in shock in primates while blood sugar rose as expected. Until now, blood sugar and simultaneous insulin levels in humans suffering from traumatic, hemorrhagic shock have not been reported. The following data was collected as a part of the shock research program of the United States Navy at the Naval Station Hospital, DaNang, Republic of Viet Nam. It was hoped that the answers to several questions might be obtained. 1. How quickly after injury in man does hyperglycemia occur? 2. How high does the blood sugar go in man in response to shock? 3. How long does the hyperglycemia of shock persist? 4. Is the degree of hyperglycemia related to the severity of shock and injury? 5. Is the degree of hyperglycemia of any prognostic value? 6. What is the insulin response in humans in shock, which direction does it go, how long is it altered?

Materials and Methods

Three groups of patients were studied. Group I consisted of eight normal hospital corpsmen. Blood samples were drawn in the morning after an overnight fast and in the evening at least 4 hours after the noon meal. Group II was composed of 17 combat Marines from whom blood samples were obtained in the fasting state immediately before and after a combat patrol. Group III consisted of 14 severely wounded Marines admitted to the hospital in severe shock from hemorrhage and trauma. None of these men had received any previous treatment. There were no known diabetics in any of the patients studied.

Blood glucose determinations were done using the Hultman method.[11] Samples for serum insulin were frozen at −20° C. and shipped to the United States in dry ice via military evacuation aircraft. Immuno Reactive Insulin (IRI) was measured in du-

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plicate by the radioimmunoassay method as described by Hales and Randle.[9] In the Group III patients arterial lactate levels were measured by the enzymatic method.[10] Blood gas determinations were performed on arterial blood with an Instrumentation Laboratories Model 127 blood gas analyzer. Group III patients had blood glucose and insulin measurements upon admission before any treatment and at 30-minute intervals for 5 hours and then twice daily until the end of 4 days or death. The 14 injured were resuscitated with 0.9% sodium chloride and whole blood. Two of this group never responded to resuscitation and were retrospectively considered to be in irreversible shock. Their findings will be discussed separately. Seven of the 14 patients had one or more extremities blown off at the time of admission (Table 1).

The mean time from injury until admission was 62 minutes. Resuscitation and preoperative evaluation time averaged 1½ hours and the average time of operation was 2¼ hours.

The method of patient management was not altered from that routinely employed for all casualties. As soon as possible after arrival, three large bore (14 gauge) intravenous catheters were inserted. Blood samples were drawn and typed and crossmatched. The urinary bladder was catheterized. Electrolyte solution was given until whole blood was prepared and then whole blood and electrolyte solution until clinical stability was achieved. Necessary x-rays were obtained and required surgery was accomplished. Following operation, the patients were sent to the Intensive Care Unit. A member of the research team was in constant attendance from the time of admission until discharge from the research unit (4 days) or death of the patient.

TABLE 1

Wounds	No.
Amputations	7 (11 limbs)
Fractures	4
Abdominal	2
Vascular	1
Total	14

Results

Blood Sugar

Blood sugar levels in the controls were within normal range for the method used. The wounded patients were uniformly hyperglycemic with a mean admission blood sugar of 242.9 mg./100 ml. We are unable to positively determine the time required after injury and shock for hyperglycemia to develop. Seven of the 14 patients were admitted to the hospital within 30 minutes of wounding and their mean blood sugar was 215 mg./100 ml. Clearly hyperglycemia occurs quickly after shock and injury. The highest admission blood sugar in these patients was 420 mg./100 ml. One of the two men in irreversible shock was admitted with a blood sugar of 370 which by the end of 120 minutes had reached 622 mg./100 ml. This is the highest endogenously generated blood sugar we have observed in man.

As can be seen in Figure 1, the blood sugar elevation persists for the total 5-hour observation period. There was a decline in the average for 180 minutes and then a leveling off for the next 2 hours. Normal levels had been reached in all patients by the end of 24 hours and usually by

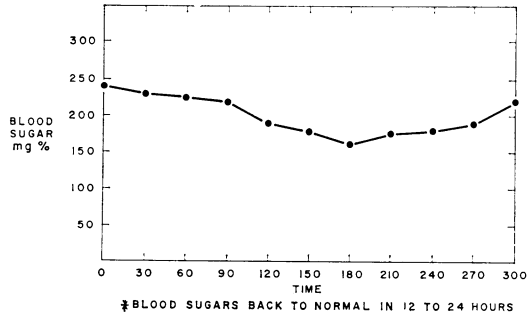

FIG. 1. Blood sugar levels fall gradually over a 5-hour period. In all surviving patients blood sugar returned to normal within 12 to 24 hours and remained normal.

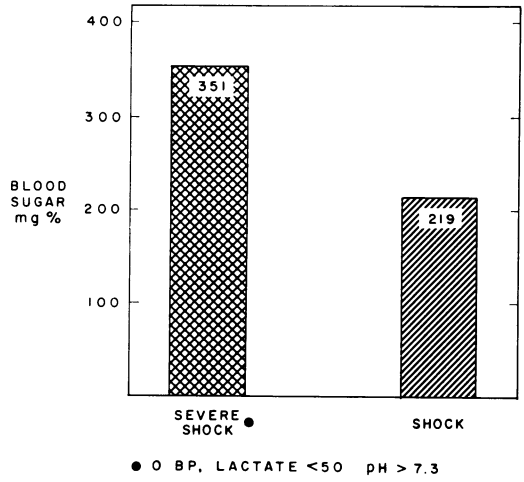

FIG. 2. The blood sugar in those patients in severe shock were considerably higher than those in less severe shock. Blood pressure of 0 mm. Hg, arterial lactate of 50 mg./100 ml. or more and pH of 7.3 or less were the criteria for severe shock.

the end 12 hours postoperatively. The two patients in irreversible shock responded differently. In both, the blood sugar rose after admission. It was still rising at the time of death in one, 150 minutes after admission; in the other, it rose sharply from 370 mg./100 ml. to 622 mg./100 ml. in 2 hours but fell precipitously to 25.2 mg./100 ml. just prior to death 12 hours after admission.

There appears to be a relationship between the severity of the shock and the magnitude of hyperglycemia. It is difficult to quantitate the severity of shock in man. Using the criteria of arterial lactate, arterial pH and systolic blood pressure the following can be seen (Fig. 2). The mean admission arterial lactate was 41.6 mg./100 ml. (twice normal). Four patients (including the two in irreversible shock) had levels over 50 mg./100 ml. and in those, the mean blood sugar was 351.5 mg./100 ml. compared to 219.4 mg./100 ml. in those with lactate levels below 50 mg./100 ml. These same four subjects were the only ones with admission arterial pH levels 7.3 or below. These same four patients plus one additional were the only five admitted with no detectable blood pressure. From these comparisons, it appears that there is a definite relationship between the severity of shock and the magnitude of the hyperglycemic response.

The insulin levels in the patients in shock at the time of admission were quite similar to those in men before and after combat patrol. As resuscitation proceeded, plasma insulin rose reaching a peak at 150 minutes (Fig. 3). Student's T test analysis show the rise in insulin at 150 minutes to be significant at the $p > 0.05$ level. Likewise, the fall in blood sugar from admission to 150 minutes is significant at the 0.05 level.

When considering the data in light of events in the patient's course after admission the following can be seen. The mean maximum insulin levels were 34.9 uu./ml. At the time of peak insulin, the mean blood sugar was 190.7 well below the average maximum blood sugar. In the 12 patients (excluding the two in irreversible shock) it occurred during operation in 11 and at the time of admission in the other. The serum insulin level drawn within 5 to 20 minutes after induction averaged 18.9. The peak serum insulin occurred near induction in only one of the 11 and toward the middle or end of operation in the other 10. Recalling that hyperglycemia on admission for those patients in most severe shock was considerably more severe, insulin levels on this group were examined separately. The average admission insulin for those admitted without blood pressure was 24.8 compared to 14.2 for those with a detectable blood pressure.

Serum insulin levels in the two patients in irreversible shock were interesting and different from each other as well as the other patients. In one (Fig. 4), insulin on admission was 51 uu./ml., fell in 90 minutes to 6.7 then rose sharply to 195 (the highest recorded for any patient). Over the next several hours, insulin fell to 9.0 just prior to death. In the other patient, the in-

sulin curve was flat but at levels well below average.

Discussion

Hyperglycemia was noted to be associated with shock by Claude Bernard nearly 100 years ago.[4] Watts[21] showed blood epinephrine levels to rise in dogs in shock. Porte[18] demonstrated that epinephrine caused elevation of blood sugar in man but the hyperglycemia did not result in an insulin response. He further found that the insulin response to Tolbutamide was lessened by the administration of epinephrine. There have been excellent reviews of the carbohydrate metabolic changes in shock.[6, 12] The magnitude of the rise in blood sugar with shock seems related to liver glycogen levels and in part the integrity of the adrenal cortex.[7, 19] It was observed that as liver glycogen was depleted, blood sugar levels fell. The role of the adrenal cortex has been difficult to assess. Selye[19] in 1941 showed that hyperglycemia did not occur in shocked adrenalectomized animals. The administration of cortical extract permitted the hyperglycemia but the amount of steroid required did not produce hyperglycemia in the absence of shock. More recently, Egdahl[14] and coworkers compared animals after adrenal

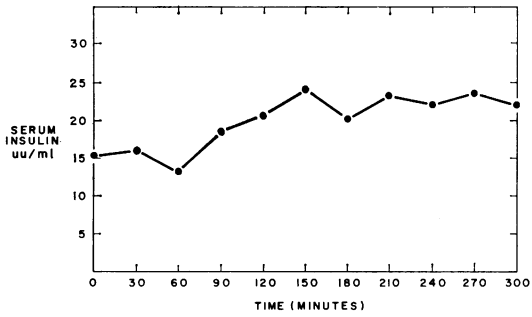

FIG. 3. Immuno reactive insulin rose gradually as blood sugar fell. The insulin rise at 150 minutes is statistically greater than that on admission $p > 0.05$.

cortical suppression with a group which had been adrenalectomized. It was found that the animals with cortical suppression became hyperglycemic in shock but the adrenalectomized ones did not. The obvious conclusion is that adrenal medulla, but not cortex, is responsible for the blood sugar elevation in shock.

It is clear from our data that severe hyperglycemia occurs in man in response to shock and trauma. As resuscitation progresses, the blood sugar gradually returns toward normal but remains well above normal for as long as 5 hours. It also appears that the magnitude of the hyperglycemia is related to the severity of shock. This is in agreement with observations of Allison[1]

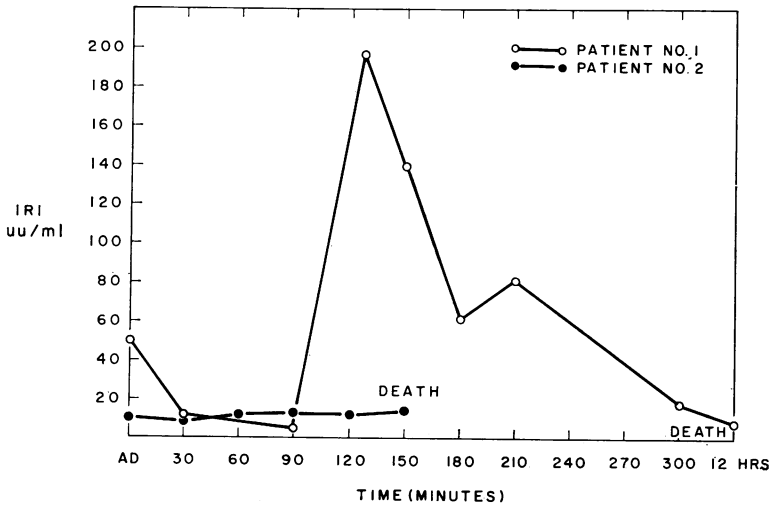

FIG. 4. The insulin curves in the two patients in irreversible shock are different from the other patients. In No. 1, an insulin response of some magnitude occurred while in the other there was no rise over base line.

who studied blood glucose after myocardial infarction in man and found hyperglycemia to be greater in the presence of cardiogenic shock than when shock was not present.

The question of the prognostic value of blood sugar levels in shock in man is unanswered by these studies but there are some clues. The two patients who never responded to resuscitation had blood sugar patterns different from any other patient. They were also the only two who died within the 4-day study period. Of interest is that blood sugar levels in both remained elevated or rose while in other patients blood sugar fell. In one patient hypoglycemia, described in terminal shock in animals, was evident immediately prior to death.[8] It seems possible that blood sugar determinations may have an important role in following severely ill patients and more studies in this regard are indicated.

While there is general agreement concerning the blood sugar response to shock, the effect on insulin levels is less clear. Epinephrine and elevated blood sugar are both extremely potent in their effect on serum insulin. Porte *et al.*[18] showed that infusions of epinephrine in normal man incited severe hyperglycemia well suppressing insulin response. While the levels of blood sugar achieved were well below those in our patients, they were of sufficient magnitude to have stimulated insulin secretion had not the epinephrine been present. Likewise in studying cardiogenic shock in man, Allison[1] found that serum insulin levels were depressed. Mendelbaum[13] and Morgan studied response of insulin to a glucose load in patients after extracorporeal circulation and found the response impaired. McCormick *et al.*[15] found serum insulin to be elevated in dogs in shock unless they were adrenalectomized and thought the insulin rise was related to the hyperglycemia. Bauer *et al.*[3] also studying dogs, found insulin to rise with blood sugar in severe shock and both to gradually decline as the animals began to deteriorate. If at this point glucose was given, insulin levels rose. Moss[17] found in sub-human primates insulin levels did not rise with hyperglycemia in shocked animals.

The only patient in whom we observed serum insulin rise was one of the two in irreversible shock whose blood sugar rose to 622 mg./100 ml. From our studies, man does not manifest rise in serum insulin in response to the hyperglycemia of traumatic hemorrhagic shock. It is likely that the suppressive effects of catecholamines on pancreatic islets overwhelms the stimulating effect of blood sugar elevation. It is unlikely that impaired pancreatic blood flow during shock is of great significance. As these patients were resuscitated their impaired circulation was corrected as evidenced by clinical observation (blood pressure, urine output, etc.) and laboratory studies (lactate pH). For some time after circulation had been restored blood glucose remained adequately high to incite an insulin response and yet none was seen.

The application of this information toward improvement in the management of the severely injured awaits further study. McCormick *et al.*[14] suggested that manipulation of intermediary metabolism in shock might prove beneficial. Moffat[16] found that administration of glucose of benefit in hypovolemic shock. Bauer *et al.*[2] suggested that decline in plasma catecholamines in shock might be of benefit in improving utilization of exogenous glucose. Allison[1] has studied insulin and glucose in severely burned humans. He suggests that there may be considerable improvement in cell membrane function with this regimen. There is ample evidence to support further investigation of the role of glucose and insulin in the management of the critically ill.

Conclusions

1. Humans in traumatic hypovolemic shock develop severe hyperglycemia within minutes.

2. The magnitude of the hyperglycemia is related to the severity of the shock.

3. The blood sugar falls gradually but is still high after 5 hours.

4. There appears to be a relationship between the pattern of decline in blood sugar and survival.

5. Serum insulin in man is unresponsive to the hyperglycemia of shock.

6. The serum insulin suppression does not resolve after resuscitation has been accomplished.

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Discussion

Dr. George H. A. Clowes, Jr. (Boston): Dr. McNamara demonstrated his point that the infused blood probably contains material which plugs the pulmonary capillary circuit to increase its resistance. Recently, we have obtained both clinical and experimental evidence concerning the significance of his findings.

Patients in the postshock state (slide) undergo a period in which the cardiac output is up and the oxygen tension of arterial blood is down. This patient suffered a gunshot wound in the pelvis. The bleeding period was prolonged and he required almost 44 units of blood. When his blood volume was finally restored, the cardiac output was actually twice the resting normal value. At the same time the pulmonary pressure rose to a proportionately greater value. Experimental evidence suggests that left atrial pressure does not increase, giving some evidence of right heart failure.

Although Dr. McNamara demonstrated part of the story, this is not all of it. In dogs one can block this increase of pulmonary resistance by the use of "trasylol" in large doses. Unfortunately, this is not permissible in the clinical setting at the moment. This finding is significant, because the