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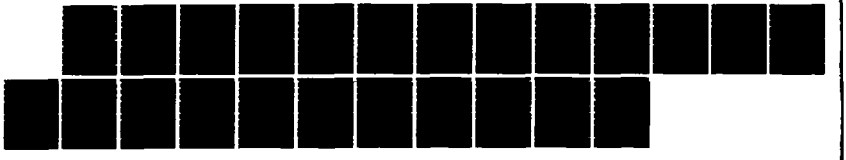

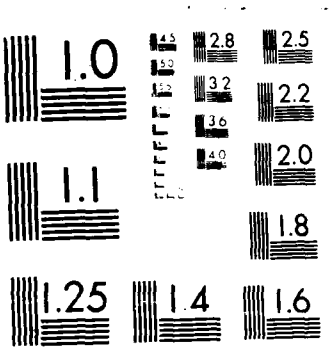

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ENDOCRINE AND PULMONARY RESPONSE TO HEMORRHAGIC SHOCK (U)

ANNUAL PROGRESS REPORT

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Control and pancreatectomized-adrenalectomized rhesus monkeys were shown to exhibit comparable urinary nitrogen excretion rates and to have similar levels of metabolic dysfunction in isolated skeletal muscles. Nutritional support with 50 percent dextrose with sufficient insulin to prevent hyperglycemia profoundly altered the metabolism of subsequently isolated skeletal muscle and prevented the induction of a nitrogen catabolic state by hemorrhagic shock.

20. Abstract

Subclassifications of acute respiratory failure based on pathophysiologic alterations are described. In animal work, changes following the infusion of oleic acid may be distinguished from E. coli. In humans, the lung changes following aneurysm surgery are different from those seen with sepsis.

The metabolic functions of the lungs have been examined and found to be causative in inducing cardiac depression with high levels of PEEP.

Part I.

Control and pancreatectomized-adrenalectomized rhesus monkeys were shown to exhibit comparable urinary nitrogen excretion rates and to have similar levels of metabolic dysfunction in isolated skeletal samples. Nutritional support with 50 percent dextrose with sufficient insulin to prevent hyperglycemia profoundly altered the metabolism of subsequently isolated skeletal muscle and prevented the induction of a nitrogen catabolic state by hemorrhagic shock.

KEY WORDS: ADRENAL HORMONES - SKELETAL MUSCLE - METABOLISM - PANCREATIC HORMONES - NITROGEN BALANCE - HEMORRHAGIC SHOCK - GLUCOSE AND AMINO ACID UTILIZATION

Part II.

Subclassifications of acute respiratory failure based on pathophysiologic alterations are described. In animal work, changes following the infusion of oleic acid may be distinguished from E. coli. In humans, the lung changes following aneurysm surgery are different from those seen with sepsis.

The metabolic functions of the lungs have been examined and found to be causative in inducing cardiac depression with high levels of PEEP.

KEY WORDS: PLATELET - WHITE BLOOD CELL - PULMONARY ENDOTHELIUM - CARDIAC FAILURE - POSITIVE END EXPIRATORY PRESSURE

CONTENTS

PART I.

ENDOCRINE AND METABOLIC RESPONSES TO SHOCK

1. Adrenal and Pancreatic Hormones and the Metabolic Response to Shock in Nutritionally Undisturbed Animals Compared to Nutritionally Supported Groups

The metabolic and endocrine response to major injury can induce a series of deleterious effects which play an important role in the prognosis of severely ill patients. Reversal of these aspects of the response by providing the required metabolic substrates and the means for their adequate utilization may promote a more rapid recovery. Management of the catabolic response to injury will best be obtained following identification of the controlling mechanisms and triggering signals involved in this sequence of events.

During the current project year our laboratory has studied the role of the adrenals and the pancreas in the metabolic response to hemorrhagic shock. Hemorrhage evokes a marked secretion of the adrenal hormones which have metabolic effects similar to those observed after shock (please see attached manuscript for discussion), and appeared to be likely contributors to the generation of the observed changes. Similarly insulin and glucagon, with their profound effects on protein and carbohydrate are considered contributors to the shock induced imbalances of blucose and amino acid utilization.

In order to abolish the influence of nutritional changes after shock, a replacement program was introduced. Each animal received

80 cal/kg/day (normal for a monkey) as intravenously administered 50% dextrose plus freamine and electrolytes. Insulin was infused in an amount adequate for the maintenance of blood sugar levels below 200 mg per 100 ml. This regimen was begun a week prior to shock and continued during and after shock.

Although many of the biochemical alterations induced by hemorrhagic shock occurred in approximately the same degree in both intact and adrenalectomized-pancreatectomized monkeys, the probable effects of nutritional support obscured the significance of the metabolic responses in the two groups.

One parameter, shock induced muscle insulin resistance was not significantly altered by either the nutritional support or the absence of induced adrenal and pancreatic hormone levels. The response of isolated skeletal muscle to insulin is shown in the table. Although the streptozotociun treated and pancreatectomized groups are not strictly comparable (this comparison was not the intended goal of this study), it can be seen that in both groups the tissue becomes unresponsive to insulin after shock. The pre-shock sensitivity to insulin appears to be depressed in the nutrition-supplemented animal, but since these experiments were done at separate times this assertion cannot be validly made at this writing.

Leucine oxidation to CO_2 by isolated skeletal muscle (see table) was the same in intact sham-op and endocrine operated groups, although the increase was only of marginal significance in the nutritionally supported groups in which the post-shock increase in leucine oxidation appeared to be suppressed.

Leucine incorporation into protein responded to shock in a diametrically opposed manner in the ad libitum fed versus the nutritionally supported group (see table). In the control and adrenalectomized animals consuming food ad libitum, shock reduced leucine incorportation into protein to about one-third control values, while in both groups of monkeys receiving intravenous nutrition, shock increased leucine incorporation into protein. Nutritional support appeared to slightly reduce the preshock leucine incorporation rate.

The animals receiving nutritional support were studied to determine nitrogen balance. Measurements corresponded with the reduced post-shock leucine oxidation and increased incorporation into protein, in that shock did not evoke a nitrogen catabolic response. The lack of a nitrogen losing phase after shock may have been partially the result of post-shock fluid retention, but certainly the large catabolic response usually observed after major trauma did not occur.

Determination of the significance of these findings will require further study, but it is possible that high glucose availability (or the high levels of insulin necessary to cover the glucose) may have prevented or modified the normal catabolic stimuli after shock. Further experiments will be necessary to better define the effects of shock on metabolism and the ability of nutritional influences to modify the usual response, as well as to determine the role of hormones in controlling these changes.

Studies were preformed with rabbits to determine the ability of 50% glucose with insulin and potassium to prolong survival after shock. Positive results were obtained and an abstract describing this

TABLE

	Ad Libitum Fed		Nutritionally Supported	
	Intact	Adrenalectomized Streptozotocin diabetic	Intact	Adrenalectomize Pancreatectomiz
	(8)[2]	(7)[2]	(8)[2]	(8)[2]
		Glucose Oxidation (CPM/hr/mg)		
PRESHOCK				
Baseline	20 ± 13.6	21.4 ± 2.8	21.6 ± 3.1	4.5 ± 2.8
With Insulin[1]	90 ± 12.6	96.4 ± 3.5	36.5 ± 3.6	38.7 ± 3.5
24 HR POSTSHOCK Baseline	24.3 ± 1.4	26.1 ± 2.4	21.1 ± 1.6	15.8 ± 2.8
With Insulin[1]	28.9 ± 2.6	20.7 ± 1.1	21.1 ± 1.6	21.4 ± 3.1
		Leucine Oxidation to CO_2 (CPM/mg/hr)		
PRESHOCK	12.0 ± 1.3	12.7 ± 2.3	8.4 ± 1.1	12.6 ± 3.2
24 HR POSTSHOCK	22.6 ± 3.2	26.0 ± 1.9	9.7 ± 0.9	13.4 ± 2.1
		Leucine Incorporation Into Protein (CPM/mg/hr)		
PRESHOCK	24.1 ± 2.6	21.9 ± 3.1	13.5 ± 1.8	8.0 ± 2.1
24 HR POSTSHOCK	8.3 ± 1.6	7.9 ± 1.1	17.0 ± 2.7	23.3 ± 3.6

1 Insulin added to the incubation medium (24 MU/ML)
2 Number of animals

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PART II

PULMONARY RESPONSE TO SHOCK

1. Platelet and White Blood Cell Entrapment in the Lungs

a) Oleic Acid and E. coli Induced Respiratory Failure

The role played by platelets in inducing acute respiratory failure (ARF) is debated. Most reports which relate lung damage to platelet entrapment refer to experiments where platelet aggregates exist. This study examines the interactions of normal stored autologous platelets with the lungs of animals pretreated with oleic acid or E. coli. Platelet entrapment was accessed by indicator dilution methods (1) and the amount of entrapment related to lung function and pathologic changes observed at postmortem.

The intravenous injection of oleic acid or E. coli resulted in a significant deterioration in lung function. The physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) rose from 10.5% $\pm$ 7.3 SD* to 28.3% $\pm$ 6.5 after oleic acid ($p < .001$) and to 25.2% $\pm$ 16.3 after E. coli ($p < .01$). The physiologic deadspace (V_D/V_T) rose from 39.9% $\pm$ 10.8 to 52.8% $\pm$ 6.7 after E. coli ($p < .01$). There was no significant change after oleic acid. Compliance (C_L) fell from 39.6 ml·cm H_2O^{-1} $\pm$ 6.8 to 27.8 $\pm$ 6.0 after oleic acid ($p < .001$), while pulmonary vascular resistance (PVR) rose from 0.284 mm Hg·sec·ml^{-1} $\pm$ .096 to 0.639 $\pm$ .192 ($p < .001$). E. coli was without effect on C_L or PVR.

Platelet entrapment rose from baseline values of 7.8% 8.0 to 17% $\pm$ 10.5 after oleic acid ($p < .02$) and to 24.6% $\pm$ 11.7 after E. coli ($p < .001$). The increased platelet entrapment could

* SD is standard deviation

only be correlated with the increase in PVR following E. coli ($r = 0.93$, $p < .02$).

Pathologic examination showed severe hemorrhagic edema following oleic acid. Surprisingly few abnormalities were observed after E. coli, pointing out the frequent disparity between pulmonary function and pathology. Further, although both groups of animals had similar shunts ($\dot{Q}_S/\dot{Q}_T$) the remaining pulmonary function studies were dissimilar.

We conclude from these observations that ARF may properly be categorized into subclassifications based on pathology and functional abnormalities. Secondly, that platelet entrapment is not related to aggregate formation, that it may occur with normal platelets and that histologic abnormalities of the endothelium are not required to produce platelet sticking. Finally, platelets are not the agents which cause lung damage.

b) Platelet and White Blood Cell Interactions in the Lungs of Septic Patients and in Patients Underoing Aneurysm Surgery

A group of 23 septic patients and 10 patients undergoing abdominal aortic aneurysm surgery were studied. Platelet, white cell counts and differentials were performed in mixed venous and arterial blood samples. At the same time pulmonary function was measured.

In sepsis the entrapment of platelets and WBCs across the lungs was significant ($p < .001$). The entrapment of WBCs was directly

correlated with the entrapment of platelets ($r = 0.56$, $p < .001$). This was not true following aneurysm surgery where the deterioration in lung function ($\dot{Q}_S/\dot{Q}_T$) was similar to that observed in sepsis. In sepsis there were strong correlations between $\dot{Q}_S/\dot{Q}_T$ and both platelet entrapment ($r = 0.50$, $p < .001$) and white cell entrapment ($r = 0.52$, $p < .001$). In contrast the aneurysm patients demonstrated no significant correlation between these variables. Finally differential counts in septic patients showed significant decline in WBC count across the lung and also showed that polymorphonuclear leukocytes were selectively filtered out ($p < .05$).

We conclude that physiologic shunting need not be related to platelet and white cell entrapment. It is likely that damaged endothelium (metabolically derranged) causes both phenomena, ie., platelet and WBC entrapment and abnormalities in pulmonary function.

2. Acute Pulmonary Insufficiency Following Abdominal Aortic Aneurysm Repair

The development of acute respiratory failure (ARF) following shock and massive fluid infusions was studied by comparing 16 patients undergoing elective aneurysm repair (E) with 13 patients operated on for aneurysm rupture (R). Patients in the R group uniformly suffered pre and intraoperative hypotension. They also received more blood (R: 12.3 $\pm$ 4.5; E: 4.9 $\pm$ 1.7 units; $p < .01$) and crystalloid fluids (R: 4.5 $\pm$ 1.9; E: 1.0 $\pm$ 0.9 L; $p < .05$) intraoperatively than did the E group. Physiological shunt

($\dot{Q}_S/\dot{Q}_T$; F_IO_2 = 0.5) and functional residual capacity (FRC, by helium dilution) were measured serially in each patient. During the first 12 hours there was a nonsignificant fall in $\dot{Q}_S/\dot{Q}_T$ (R: 11.5 ± 5.0; E: 9.9 ± 5.4%) and rise in FRC (R: 109 ± 10; E: 100 ± 13% predicted) compared to preoperative studies ($\dot{Q}_S/\dot{Q}_T$: 14.1 ± 5.5%; FRC: 160 ± 52% predicted). At 24 and 36 hours both groups showed similar and significant ($p < .01$) increases in $\dot{Q}_S/\dot{Q}_T$ (24 hrs., R: 20.5 ± 9.2, E: 18.2 ± 7.5%; 36 hrs., R: 26.2 ± 10.4, E: 30.3 ± 9.2%) and decreases in FRC (24 hrs., R: 69 ± 24, E: 87 ± 29% predicted; 36 hrs., R: 66 ± 25, E: 75 ± 26% predicted). There was no difference between the two groups in their pulmonary response to surgery during the first 48 hours. All patients underwent fluid restriction and diuresis; 6 patients (21%, 4R, 2 E) were not improved. This group had severe associated medical problems, e.g. 4 had sepsis.

Moderate pulmonary insufficiency developed in all patients, 24 hours following aneurysm repair and was not related to hypotension, declamping or massive blood or fluid infusions. Respiratory failure persisting beyond 48 hours was associated with other complications and was not itself a cause of death.

3. Biventricular Cardiac Failure As A Result of Positive End Expiratory Pressure

a) Closed Chested Study

Positive end expiratory pressure (PEEP) will often depress the

cardiac output (CO). Nine mongrel dogs were studied to examine the nature of this depression. The animals were anesthetized and pulmonary arterial, peripheral arterial, inferior vena caval, left atrial, and pleural catheters were inserted; the animals were then placed on sequential increments then decrements of PEEP.

At 0 cm H_2O PEEP the mean cardiac index was 108 ml/min·Kg. This fell to 82.1 ml/min·Kg at 16 cm H_2O PEEP ($p < .05$). Net central venous (CVP), left atrial (LAP), pulmonary arterial (PAP), and pulmonary artery wedge (PAWP) pressures were obtained by subtracting the intrapleural pressures from the measured intravascular pressures. The mean net CVP rose from 5.2 mm Hg at 0 cm H_2O PEEP to 8.4 mm Hg at 16 cm H_2O PEEP ($p < .01$), mean net PAWP rose from 6.7 mm Hg to 9.5 mm Hg ($p < .02$) while the mean net LAP rose from 6.75 to 7.28 ($p < 0.1$).

Intracavitary electrocardiograms failed to show evidence of subendocardial ischemia. Mean net PAP rose from 6.7 to 9.5 mm Hg ($p < .02$) while mean arterial pressure fell from 117 to 91 mm Hg ($p < .01$).

The data indicate that PEEP did not lead to lowered CO because of decreases in venous return or simple right ventricular failure. Biventricular failure, not simple right ventricular failure, is the principal mechanism whereby CI is reduced by PEEP.

b) Open Chested Study

Preliminary results in three animals whose entire chest wall was

excised provide supporting evidence of biventricular failure with PEEP. The open chests negate pressure effects on venous return or myocardial mechanics. Under these conditions 15 cm PEEP led to decreases in cardiac output and increases in left atrial, pulmonary arterial and central venous pressure - evidence for biventricular failure.

In order to resolve the question of ventricular interdependence (where sudden pulmonary hypertension leads to a shifting of the interventricular septum and left ventricular failure) the pulmonary artery was banded. In the one animal where this was done, and pulmonary pressure raised to at least that produced by 15 cm PEEP, there was no decline in cardiac output.

These studies are only in their initial phases and will be completed within six months.

4. The Importance of Humoral Factors in Depressing Left Ventricular Function During PEEP

Four pairs of dogs have undergone cross-circulation from femoral artery to femoral vein using matched roller pumps. When one of the 2 animals (donor) was placed on 15 cm PEEP the cardiac output of the other animal (recipient) was depressed. The pulmonary arterial wedge pressure of the recipient was maintained constant throughout the experiment. After PEEP was removed from the donor, the recipients cardiac output returned to baseline levels. These observations have been consistent in all 4 pairs of dogs during

multiple applications of PEEP.

Although these experiments are not yet concluded, the data strongly suggests that a humoral factor is being transmitted to the recipient animal. This factor appears to produce a decline in cardiac output by decreasing left ventricular contractility. This is indicated by a reduction in flow at the same preload. The one series of Starling curves constructed in a recipient animal also indicated in decrease in contractility. When the donor was on 15 cm PEEP the Starling curve of the recipient was shifted downward and to the right (a negative inotropic effect).

5. Evidence of Abnormal Coronary Perfusion Following PEEP

The experimental design requires the measure of myocardial oxygen consumption on and off PEEP and secondly relating oxygen consumption to left ventricular stroke work.

Only one experiment has been done to date because of the difficulty in working out a satisfactory technique for measuring coronary blood flow (see below). The result of this experiment demonstrated that PEEP led to a decrease in coronary blood flow, a decrease in A-V oxygen content difference and therefore a marked fall in oxygen consumption. Coronary sinus PO_2 rose to 40 mm Hg. These results suggest an abnormal distribution of coronary blood flow induced by PEEP.

The technique eventually perfected to measure coronary flow was a modification of Morawitz's old method where a cannula is used to provide a direct volumetric measure of flow. Only minor

problems have been encountered in 15 consecutive dogs in which this method has been applied. The exteriorized coronary sinus blood is warmed and returned to the animal with a roller pump.

The other technique to measure coronary flow which we have temporarily abandoned is a varient of the nitrous oxide method. The tracer we have used is a thermal one. Iced D_5/W is injected at a constant rate into the pulmonary artery and temperature is sampled both in the aorta and coronary sinus until a new temperature equilibrium is established. Coronary blood flow (CBF) in ml/min·100 g tissue may be calculated from the formula

$$CBF = \frac{(T_S - T_E) \cdot 100}{\int_0^\infty (T_{CS}\ T_A)\ dt}$$

where T is temperature in the coronary sinus (CS) and aorta (A) at the start (S) and end (E) of the iced infusion. Our problems with this new technique are (1) the prolonged time (8-10 minutes) before equilibration (2) the large volume of infusate necessary (30-40 ml/min) and most important (3) the lack of precision of the measurement.

6. Advances in Methodology

a) Smoothe muscle bioassay system. All instrumentation has been assembled. Changes in isometric tension has been measured of various types of smoothe muscle (rat stomach strip, colon; rabbit

aorta, chick rectum, guinea pig gallbladder, cat jejunum). The system provides heating to 37° C and oxygenation of the perfusate. A few more in-vitro experiments are required to evaluate the effects of various antagonists eg. α and β blockers, as well as blockers of serotonin and histamine.

b) A microprocessor system has been developed for the storage and calculation of indicator dilution data. This small inexpensive system provides us with final calculations of in-vivo indicator curves in minutes.

c) Doppler measurements of cardiac output (CO). This non-invasive system has been applied to the measurement of CO in 21 patients. Velocities are measured in the aortic root and combined with a measure of aortic diameter (standard echo measurement) to derive flow. In one patient who had a prosthetic aortic valve, flow was twice that measured by thermodilution. Excluding this patient the correlation of doppler measured flow (CO_D) with thermodilution flow (CO_{TD}) is $r = 0.89$. The regression equation is $CO_D = 0.84\ CO_{TD} + 0.08$, where flow is expressed in L/min.

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