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CARDIO-PULMONARY RESPONSE TO SHOCK

ANNUAL PROGRESS REPORT

August 1978

(1 February 1978 to 31 August 1978)

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-78-C-8026

Harvard Medical School  
Boston, Massachusetts 02115

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3. Investigator: Herbert B. Hechtman, M.D.  
4. Number of Pages: 11  
5. Date: August 31, 1978  
6. Contract Number: DAMD17-78-C-8026  
7. Supported by: U.S. Army Medical Research &  
Development Command, Department  
of the Army, Washington, DC 20314

Pressure breathing and particularly PEEP were found to alter pulmonary metabolic activities. In animals treated with PEEP: there was release of a humoral agent which decreased contractility; plasminogen activator normally cleared by the lungs during spontaneous breathing was now secreted; there was a decreased ability to clear barbiturates and lactate; a selective red cell acidosis was induced (during lactate infusion); and systemic blood flow was redistributed. Metabolism was severely altered when a lung lobe was isolated and perfused from a support dog. A variety of negative inotropic agents were released which led to death of the support animal. These cardiac muscle studies were assisted by the development of a new, isolated papillary muscle chamber.

KEY WORDS: END-EXPIRATORY PRESSURE - CONTRACTILITY - PLASMINOGEN ACTIVATOR -  
FLOW DISTRIBUTION - LACTATE - VASOACTIVITY - PAPILLARY MUSCLE - LUNG METABOLISM

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM	
1. REPORT NUMBER DAMD17-78-C-8026	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER	
4. TITLE (and Subtitle)  CARDIO-PULMONARY RESPONSE TO SHOCK		5. TYPE OF REPORT & PERIOD COVERED Annual Progress Report Feb. 1, 1978 - Aug. 31, 1978	
		6. PERFORMING ORG. REPORT NUMBER	
7. AUTHOR(s)  Herbert B. Hechtman, M.D.		8. CONTRACT OR GRANT NUMBER(s)  DAMD17-78-C-8026 <sup>tw</sup>	
9. PERFORMING ORGANIZATION NAME AND ADDRESS  Harvard Medical School 25 Shattuck Street Boston, Mass. 02115		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS  62772A, 3S762772A814 00.053	
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Medical Research and Development Command Fort Detrick, Frederick, Maryland 21701		12. REPORT DATE August 31, 1978	
		13. NUMBER OF PAGES 18	
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report)  Unclassified	
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	
16. DISTRIBUTION STATEMENT (of this Report)  Approved for public release; distribution unlimited.			
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)			
18. SUPPLEMENTARY NOTES			
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) END-EXPIRATORY PRESSURE - CONTRACTILITY - PLASMINOGEN ACTIVATOR - FLOW DISTRIBUTION - LACTATE - VASOACTIVITY - PAPILLARY MUSCLE - LUNG METABOLISM			
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Pressure breathing and particularly PEEP were found to alter pulmonary metabolic activities. In animals treated with PEEP: there was release of a humoral agent which decreased contractility; plasminogen activator normally cleared by the lungs during spontaneous breathing was now secreted; there was a decreased ability to clear barbiturates and lactate; a selective red cell acidosis was induced (during lactate infusion); and systemic blood flow was redistributed. Metabolism was severely altered when a lung lobe (continued) <span style="float: right;">↓</span>			

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1. Metabolic Consequences of Pressure Breathing

a) Release of negative inotropic agent(s)

Removal of chest wall (1):

A series of experiments were conducted in dogs who had undergone complete chest wall resections. This preparation assured the maintenance of a constant pleural pressure. Mechanical effects of PEEP on the veins of the chest and on the coronary circulation were removed.

Eight dogs on mechanical ventilation underwent complete chest wall excision so that pleural pressure was always atmospheric. Central venous, pulmonary and systemic arterial and left atrial catheters were placed. Application of 15 cm of PEEP caused a significant drop in thermodilution measured CO from a mean of 3.03 to 2.06 L/min ( $p < .01$ ) and mean systemic arterial pressure (MAP) from 105 to 69 mm Hg ( $p < .001$ ). Concurrently, there was a rise in mean central venous pressure (CVP) from 5.5 to 8.3 mm Hg ( $p < .01$ ) and mean left atrial pressure (LAP) from 6.3 to 8.0 mm Hg ( $p < .03$ ). Tightening of a pulmonary artery choker to reproduce the elevated PAP observed with 15 cm of PEEP, from a mean of 18.0 to 24.4 mm Hg ( $p < .001$ ), failed to cause a drop in CO. There was also no significant change in CVP, LAP or MAP.

The data indicate that PEEP may depress the CO independent of intra-thoracic pressure. This drop in CO is accompanied by a rise in both right and left ventricular filling pressures, the criteria for biventricular failure. Furthermore, CO does not drop when right ventricular afterload is increased to a level equal to that at which PEEP caused a fall in CO. The results are consistent with the action of a neural and/or humoral agent on cardiac function. The results do not support previous concepts concerning the mechanisms of the hemodynamic abnormalities induced with PEEP.



Despite the fact that the same amount of PEEP (15 cm H<sub>2</sub>O) was applied to the no chest dogs that had previously been applied to a closed chest group, the depression in CO and increase in filling pressures were significantly greater in the no chest group. This led us to theorize that the PEEP effect was primarily related to lung stretch and not to applied pressure. The absence of the restraining effect of the chest wall led to markedly greater resting lung volumes in the no chest group.

#### Cross Circulation (2)

Since the lungs are known to be metabolically active organs, we postulated that pulmonary stretch caused the release of a humoral agent that led to cardiac failure. In the next set of experiments (now completed), strong support was given to this concept.

To examine the hypothesis that the biventricular failure induced by PEEP could be humorally mediated, we studied a group of 16 dogs (eight pairs) using a cross circulation preparation where 300 ml blood was exchanged per minute. One member of each pair was arbitrarily designated as donor and the other as recipient. The recipient's PAWP was maintained constant throughout the experiment by the infusion of fluid. When the donor's end expiratory pressure was increased from 0 to 15 cm H<sub>2</sub>O, the recipient's cardiac index fell from 95.2 ml/min·Kg to 74.1 ml/min·Kg ( $p < .01$ ) and returned towards baseline levels with the removal of PEEP. These data confirm the hypothesis that PEEP induces cardiac depression which is mediated in part by humoral factors.

The degree of decrease in CO in the animal treated with PEEP was significantly correlated with the decrease in CO in the untreated animal. These results indicate the release of a humoral agent whose cardiac effects could be both qualitatively and quantitatively transferred through the circulatory system.

### Isolated Hearts (3)

Experiments were conducted in a group of 33 temperature controlled, isolated, paced, canine hearts undergoing coronary perfusion from a support dog, at a fixed rate of 1.3 ml/min-g tissue. A left ventricular balloon was used to construct Starling curves during each period that a new variable was applied to the support dog. Application of 15 cm H<sub>2</sub>O PEEP led to a fall in peak systolic pressure (PSP) within 2 to 3 minutes in the isolated heart. This occurred at each of five diastolic pressures (DP) tested within the range 7.1 to 19.4 mm Hg ( $p < .01$ ). Thus, at a DP of 19.4 mm Hg, PSP fell from 132 to 112 mm Hg after PEEP was applied ( $p < .01$ ). Bleeding the support dog while on 0 cm H<sub>2</sub>O PEEP (ZEEP) to reduce cardiac output (CO) to levels observed on PEEP led to an adrenergic response. PSP increased relative to the PSP observed during ZEEP ( $p < .01$ ). PEEP plus blood infusions to restore CO of the support dog to baseline levels, led to myocardial depression ( $p < .01$ ). Finally, 15 cm H<sub>2</sub>O PEEP was applied while pleural and airway pressures were equal. This condition was achieved by coupling the expiratory port to bilateral thoracostomy tubes. The functional residual capacity was held constant. The isolated heart was not depressed ( $p < .01$ ). Levels of PGF<sub>2</sub> $\alpha$  and its metabolite 15-keto-13,14-dihydro-PGF<sub>2</sub> $\alpha$ , measured by radioimmunoassay in arterial, pulmonary arterial and coronary sinus blood were unchanged during PEEP. Indomethacin blockade lowered PGs but did not abolish the PEEP effect. Results indicate that lung stretch produced by PEEP causes the release of a humoral agent which decreases left ventricular contractility.

### b) Pressure Breathing and Altered Fibrinolytic Activity (4)

Mechanically ventilated, anesthetized patients undergoing surgery show increased peripheral venous fibrinolytic activity (FA). This study

examines the role played by pressure breathing in stimulating the fibrinolytic system. Ten anesthetized dogs were intubated. Euglobulin lysis times, expressed as FA units were obtained from femoral (a), pulmonary artery (p), infra (i) and supra (s) renal vena caval blood. During spontaneous breathing FA activity increased across the peripheral circulation from  $FA_a = 3.2 \pm 0.6$  units (mean  $\pm$  standard deviation) to  $FA_i = 4.5 \pm 0.9$  ( $p < .01$ ) and further increased after admixture with renal blood,  $FA_s = 7.9 \pm 0.6$  ( $p < .001$ ). Hepatic clearance reduced  $FA_p$  to  $5.3 \pm 1.1$ , but this level remained higher than  $FA_a$  ( $p < .01$ ) indicating loss of FA in the lungs. Positive inspiratory pressure, ZEEP<sub>1</sub> (rate 12, tidal volume 15 ml/kg) increased  $FA_a$  to  $5.8 \pm 0.9$  a value now higher than  $FA_p$  ( $p < .05$ ). After application of end expiratory pressure, (15 cm H<sub>2</sub>O PEEP)  $FA_a$  rose to  $8.5 \pm 1.0$ , higher than ZEEP<sub>1</sub> ( $p < .001$ ).  $FA_a$  returned to ZEEP<sub>1</sub> levels with removal of PEEP. During the study,  $FA_i$  increased with  $FA_a$  ( $r = .67$ ,  $p < .05$ ) while  $FA_p$  and  $FA_s$  remained constant. This indicates a reciprocal relationship between renal and pulmonary FA function. Lung biopsy showed a 13.3% fall in saline extractable plasminogen activator during ZEEP ( $p < .05$ ) and a 37.9% fall after PEEP ( $p < .001$ ). Fibrinogen, plasminogen and fibrin degradation products were unchanged. These results indicate that the lungs normally extract and perhaps store plasminogen activator, secreted in large part by the kidneys. Pressure breathing, particularly PEEP, causes the release of activator from the lungs with an increase in arterial and peripheral venous FA activity.

c) Pressure Breathing and Systemic Organ Function

Barbiturate metabolism is thought to occur primarily in the liver. A series of 8 animals received a constant infusion of pentobarbital. Blood barbiturate levels were measured after 30 minutes of 0 or 15 cm H<sub>2</sub>O

positive end expiratory pressure. Barbiturate was significantly higher during PEEP ( $p < .01$ ), rising in all animals from a mean of 15.2 to 17.3  $\mu\text{g/ml}$ . There was no evidence that this small but significant rise in barbiturate, induced myocardial depression since independent assays using an isolated papillary muscle showed depression in contractility to occur at levels in excess of 100  $\mu\text{g/ml}$ .

Lactate clearance (5) by the body was also studied using a similar protocol. Normally PEEP does not lead to a lactic acid acidosis during saline infusions. However, infusion of Ringers lactate led to a rise in lactate from 16.2 to 20.4  $\mu\text{M/g Hb}$  during PEEP ( $p < .01$ ), and a fall in base excess from -2.5 to -7.8 meq/L ( $p < .01$ ). These changes reverted to normal when PEEP was removed.

In addition to these abnormalities of lactate clearance associated with PEEP, we observed that lactate infusions during PEEP led to a selective red cell acidosis (5). Intracellular red cell pH fell from 7.21 to 7.10 ( $p < .001$ ) while plasma pH fell slightly and nonsignificantly from 7.45 to 7.42. This resulted in a widening of the normal pH difference between the exterior and interior of the cells from .24 (during 0 cm H<sub>2</sub>O PEEP) to .32 pH units ( $p < .001$ ). All changes returned to baseline with removal of PEEP and were not observed during saline infusions. The mechanisms for these metabolic changes are unknown but the observations may be pertinent to patients who receive lactate infusions.

Citrate clearance may also be abnormal with PEEP and may have important clinical consequences regarding ionized  $\text{Ca}^{++}$  levels during blood transfusions. In preliminary experiments ( $n = 2$ ) the infusion of 1 ml/kg CPD solution over 10 minutes to dogs (equivalent to 1 "dog" unit of blood) led to a reduction of  $\text{Ca}^{++}$  from 2.4 to 2.1 meq/L (0 cm H<sub>2</sub>O PEEP). During PEEP,  $\text{Ca}^{++}$  fell to 1.9 meq/L. Recovery of  $\text{Ca}^{++}$  levels was prolonged during PEEP.

Systemic flow redistribution (6) during PEEP was measured to test the hypothesis that end expiratory pressure redistributes flow and may be directly responsible for systemic organ dysfunction.

Eight anesthetized dogs were studied during (1) 0 cm H<sub>2</sub>O PEEP (Z<sub>1</sub>), (2) 15 cm H<sub>2</sub>O PEEP (P), (3) Z<sub>2</sub> and (4) bleeding (B) to reduce the CO to the same level as P. At each of the 4 periods a different, 15  $\mu$  radiolabelled microsphere was injected into the left atrium. Another 4 dogs were used to verify that each type of microsphere had the same flow distribution. CO fell from 3.1 L/min to 1.9 during P ( $p < .01$ ) and to 2.0 during B ( $p < .01$ ). Mean arterial pressure (MAP) declined from 102 mm Hg to 83 ( $p < .01$ ) and 86 ( $p < .01$ ) respectively. Left atrial pressure (LAP) rose from 5.0 mm Hg to 7.9 during P ( $p < .01$ ) and fell during B to 2.7. CO and its distribution was the same during Z<sub>1</sub> and Z<sub>2</sub>. P caused selective reductions in hepatic (52%), adrenal (25%) and bronchial (24%) blood flows ( $p < .01$ ). In contrast, total flow to these organs during B was the same as Z. Total renal flow was unchanged by P or B but the cortical/medullary flow ratio increased during P from 24 to 49 ( $p < .01$ ) and was unchanged by B. P induced a decrease in fundal mucosal flow compared with Z ( $p < .01$ ). Total coronary flow fell from 100 ml/min to 64 during both P and B ( $p < .01$ ). P led to a selective fall in subendocardial flow (67 ml/min·100 g) compared with B (82.5,  $p < .01$ ) as well as in the subendocardial/subepicardial flow ratio (1.069 vs 1.112,  $p < .05$ ).

It is likely that the higher left ventricular filling pressure (LAP) during P compared with B compressed the endocardium and induced relative ischemia. Similarly the high airway pressure during P may have impeded bronchial mucosal flow. The causes and consequences of the other P induced variations in flow are speculative.

d) Lung Isolation

Ten studies were done to examine the cardiac and hemodynamic consequences of PEEP when applied to an isolated left lower lobe (LLL) perfused by a support animal which in addition perfused an isolated heart. Perfusion flow to both the isolated heart and LLL was fixed at 217 ml/min. The system was temperature controlled. The LLL was ventilated with 50% O<sub>2</sub> and 5% CO<sub>2</sub> at a tidal volume of 120 ml and rate of 10.

Application of 15 cm H<sub>2</sub>O PEEP to the lobe led to a rise in mean pulmonary arterial pressure (MPAP) from  $10.1 \pm 3.3$  mm Hg (mean  $\pm$  standard deviation) to  $15.1 \pm 4.2$  mm Hg ( $p < .01$ ). Pulmonary venous PO<sub>2</sub> increased from  $145 \pm 45$  mm Hg to  $165 \pm 48$  mm Hg ( $p < .001$ ). The PCO<sub>2</sub> and pH were stable. Within minutes, the support dog in 9 experiments showed a fall in mean arterial pressure (MAP) from  $110 \pm 14$  mm Hg to  $95 \pm 26$  mm Hg and a fall in cardiac output (CO) from  $4.04 \pm 2.06$  L/min to  $3.48 \pm 2.24$  L/min ( $p < .01$ ). The pulmonary arterial wedge pressure (PAWP), CVP and MPAP were unchanged. In the 10th experiment the support dog became extremely hypotensive and died, despite massive fluid infusions. Starling type performance curves were constructed in the isolated heart by inflating a left ventricular balloon. During PEEP peak systolic pressure (PSP) decreased at balloon volumes ranging between 30 to 50 ml ( $p < .05$  to  $p < .01$ ). Coronary perfusion pressure was unchanged. After the removal of PEEP support dog hemodynamics and PSP of the isolated heart returned to baseline. In 4 experiments the support dog was excluded from the perfusion circuit. PEEP did not affect PSP under these conditions. Flagrant pulmonary edema was observed in 5 experiments: the lobe was involved in 2 and the support animal in 3. In an additional 3 animals prostaglandin E was measured by radioimmune assay in pulmonary arterial and arterial blood. PEEP did not alter lung catabolism of this agent.

The results demonstrate that PEEP will alter pulmonary metabolism of an isolated perfused lung which will directly or indirectly decrease cardiac contractility and lead to systemic hypotension.

Preliminary data in other studies of an isolated LLL, perfused by a support dog (n = 5) indicate that similar hemodynamic events occur. In addition as soon as the LLL is placed in the perfusion circuit there is a 10 fold increase in plasminogen activator activity in blood coming from the support animal. We believe that an agent(s) from the LLL circulates to the support animal and stimulates the release of proteolytic activity. Measurements taken across the LLL show that the isolated lung clears plasminogen activator. Further, control studies in over 50 isolated, support dog perfused canine hearts indicate that organ perfusion, without a lung in the circuit, will not stimulate these events.

## 2. Measurement Techniques

Refinements of the isolated papillary muscle preparation have been made to allow assays of contractility to be made in plasma. Usually, oxygenation of plasma with a sintered disc leads to foaming and mechanical distortions of the test muscle. We have substituted a diffusion membrane which provides a  $PO_2$  of 400 to 450 mm Hg and allows the volume of test plasma to be reduced to 4.5 ml.

This system with a rat papillary muscle was used to test contractility of plasma obtained during 0 cm  $H_2O$  PEEP and 15 cm  $H_2O$  PEEP in 7 dogs. Peak developed tension was reduced by PEEP from 1.08 to .89 g ( $p < .01$ ). PEEP plasma stored for over 3 hours at room temperature still had a negative inotropic effect. Further refinements routinely permit the muscle at baseline to generate 4 g developed tension.

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