



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

12

AD _____

AD-A150 943

CARDIO-PULMONARY RESPONSE TO SHOCK

ANNUAL AND FINAL REPORT

Herbert B. Hechtman, M.D.

September 30, 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-78-C-8026

Harvard University
Holyoke Center, Room #458
1350 Massachusetts Ave.
Cambridge, Massachusetts 02138

DTIC
SELECTED
FEB 2 1985
S E D

DOD DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

DTIC FILE COPY

85: 02 12 118

AD _____

CARDIO-PULMONARY RESPONSE TO SHOCK

ANNUAL AND FINAL REPORT

Herbert B. Hechtman, M.D.

September 30, 1983

Supported by

**U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012**

Contract No. DAMD17-78-C-8026

**Harvard University
Holyoke Center, Room #458
1350 Massachusetts Ave.
Cambridge, Massachusetts 02138**

DOD DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

**The findings in this report are not to be construed as an
official Department of the Army position unless so
designated by other authorized documents.**

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A150943	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Cardio-Pulmonary Response to Shock		5. TYPE OF REPORT & PERIOD COVERED Annual (1 Oct. 82 - 30 May 83) Final (1 Feb 78 - 30 May 83)
7. AUTHOR(s) Herbert B. Hechtman, M.D.		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS Harvard University Holyoke Center, Room #458 1350 Massachusetts Ave. Cambridge, MA 02138		8. CONTRACT OR GRANT NUMBER(s) DAMD17-78-C-8026
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Medical Research and Development Command Fort Detrick, Frederick, Maryland 21701-5012		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62772A. 3S162772A874.AA.132
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		12. REPORT DATE 30 September 1983
		13. NUMBER OF PAGES 15
		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) PROSTACYCLIN - THROMBOXANE - CARDIOPULMONARY FUNCTION - INFLAMMATION - MICROVASCULAR PERMEABILITY - PRESSURE BREATHING - EMBOLISM - ACID ASPIRATION		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Entire ABSTRACT on following page.		

ABSTRACT

The general objectives of this laboratory have been to study cardio-pulmonary abnormalities associated with shock and trauma, with a focus on the intermediary role of lung and circulating blood cell metabolism. Pressure breathing, pulmonary embolism and acid aspiration, by altering arachidonic acid metabolism were found to depress cardiac contractility and alter the distribution of systemic blood flow. The roles of prostacyclin (PGI₂) and thromboxane (Tx) A₂ in these settings were quantitated by radioimmunoassay and use of selective antagonists. These same prostanoids, along with platelet serotonin, also moderated changes in pulmonary function, particularly physiologic shunt, physiologic dead space and pulmonary vascular resistance. The secondary consequence of injury, the recruitment of an inflammatory reaction, was found to be a significant determinant of increased microvascular permeability both in acid injury of the lungs and heat injury to the skin. In both instances, neutrophil accumulations and permeability edema could be attenuated by inhibition of Tx synthesis. These data indicate that the prostanoids exert direct and indirect actions in moderating cardiopulmonary function following injury.

Accession For	
NTIS GRA&I	<input checked="" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification	
By	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A-1	

DTIC
COPY
INSPECTED
4

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

Studies for the past five years have been focused on cardiopulmonary abnormalities associated with shock, hemorrhage and trauma.

Pressure breathing and particularly positive end-expiratory pressure (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.

Pressure breathing and particularly PEEP was also found to induce the pulmonary production of prostaglandins (PG). These PG regulate cardiac contractility and the release of plasmin mediated fibrinolytic activity. A high molecular weight protein has been tentatively identified as the circulating negative inotropic agent whose production is stimulated by PG synthesis during PEEP.

The large amount of prostacyclin (PGI_2) secreted by the lungs in response to surgery may protect against microaggregate entrapment and damage of the lungs. PGI_2 infusion was effective therapy for experimental pulmonary embolism.

Investigations continued into the relationship of pulmonary PG production and systemic organ function. Our study preparations were of pulmonary embolism and/or PEEP which we believe to be analogous to the microembolism and hyperventilation of severe injury. Both embolism and PEEP led to the production of thromboxanes (Tx) as well as decrease in cardiac contractility. The latter event could be prevented with Tx antagonists. Tx caused the elaboration of a high molecular weight protein fraction which suppressed myocardial Ca^{++} -ATPase and reduced activity of Krebs cycle enzymes in cardiac mitochondria.

During acute thrombocytopenia, serotonin (5-HT) infusion was found to protect against petechiae. Antagonists to 5-HT promoted petechiae. Endogenous or exogenously infused PGI_2 caused a reduction in plasma and increase in platelet 5-HT. Endothelial 5-HT transport was blocked. These findings may underly the ability of PGI_2 to enhance permeability.

Prostacyclin was found to regulate the production of plasminogen activator. This may be one of the mechanisms related to the dramatic effectiveness of PGI_2 in reversing the cardiopulmonary abnormalities of pulmonary embolism and in reversing lethal endotoxemia. However, PGI_2 was without benefit in treating acid aspiration, whereas blocking the proaggregatory prostanoid, TxA_2 , effectively reversed the

pulmonary edema and the gas exchange abnormalities. Under other circumstances PGI_2 may be hazardous such as during organ perfusion. These studies indicate that PG are important mediators of critical illness, although their actions may not be predictable.

Our major hypothesis that platelet and white blood cell (WBC) secretions modify cardiopulmonary function has undergone further scrutiny. Particular attention has been paid to the role of arachidonic acid derivatives. Several common events have been found which stimulate the production of Tx such as exposure of blood to foreign surfaces, PEEP ventilation and pulmonary embolism. The release of TxA_2 was associated with the formation of a circulating substance which caused a decrease in contractility and abnormalities in myocardial ATPase. Prostacyclin has been found to be produced in large quantity following surgical trauma. Under these circumstances, endogenous PGI_2 increased cardiac output and dilated the systemic vasculature. An infusion of PGI_2 in an experimental setting of severe cardiac depression induced by endotoxemia led to rapid improvement of cardiac function. Unfortunately, PGI_2 also had adverse effects and paradoxically stimulates the production of TxA_2 in settings where blood is exposed to artificial surfaces.

Several experimental preparations have been used to study permeability edema. TxA_2 is centrally involved in the edema of acid aspiration, complement activation and burns. Leukotrienes (LT) are also of importance in the biochemical sequence which leads to capillary damage. We have also evaluated the vasoactive agent 5-HT as a potential culprit in the induction of respiratory failure without pulmonary edema. It was found that platelet entrapment in the lungs with 5-HT release can account for the increase in pulmonary vascular resistance, bronchoconstriction and hypoxia noted in acute respiratory failure prior to edema formation.

Edema following burn injury was due to WBC invasion and secretion of permeability factors related to arachidonic acid metabolism. This study was designed to test the ability of TxA_2 synthetase inhibitors and a LT receptor antagonist to modify burn edema. Four standard 2 cm^2 burns (100°C for 2 s) were produced on the backs of 400 g to 450 g rats at intervals of $\frac{1}{2}$ h to 1 h. Evans blue dye (5 mg IV) was injected $\frac{1}{2}$ h prior to sacrifice, at which time the burns were 3 h, 2 h, 1 h and $\frac{1}{2}$ h old. In controls ($n = 9$) water content of unburnt skin was $67.6 \pm 0.4\%$ ($x \pm \text{SE}$). This rose to $73.2 \pm 0.9\%$ $\frac{1}{2}$ h after burning; $71.7 \pm 0.9\%$ after 1 h; $71.9 \pm 0.8\%$ after 2 h; and $77.7 \pm 0.6\%$ after 3 h. Imidazole (25 mg/kg IV bolus) ($n = 8$) given $1\frac{1}{2}$ h and $\frac{1}{2}$ h after the "3 h" and "2 h" burns without effect; however, compared to untreated controls it did reduce blue dye accumulation and edema in the subsequent burns, inflicted $\frac{1}{2}$ h and 1 h after drug administration ($p < 0.05$). Another Tx inhibitor, a pyridine derivative, (OKY 1555, 2 mg/kg IV bolus) ($n = 11$) was given at the same time as imidazole. It not only prevented edema formation in the skin burned 1 h after the

drug was administered ($66.4 \pm 1.4\%$, $p < 0.05$), but compared to untreated controls reduced edema to $71.0 \pm 0.5\%$ and $68.9 \pm 0.7\%$ in the skin burned 1 h and $\frac{1}{2}$ h before drug therapy ($p < 0.05$). All burns showed reduced bluing. The LT antagonist (FPL 55712, 1.5 mg/kg IV bolus) ($n = 5$) compared to untreated controls reduced edema and bluing of the skin burned 1 h before therapy ($72.8 \pm 0.9\%$, $p < 0.05$) and prevented edema of skin burned after therapy ($69.6 \pm 1.4\%$, $p < 0.05$). These results indicate that TxA_2 inhibition can both prevent and treat burn permeability edema, an event mediated at least in part by LT.

Pulmonary arterial vasoconstriction mediated by platelet 5-HT was believed to be an important determinant of the increase in mean pulmonary arterial pressure (MPAP) after embolization. Using $^{99\text{m}}$ technetium-macro-aggregated albumin (Tc-MAA) perfusion lung scans, we examined the effects of ketanserin, a specific 5-HT receptor inhibitor on the cross-sectional area of the pulmonary vascular bed after experimental embolism. Five mongrel dogs were injected with 0.75 g/kg autologous clot. After 30 min MPAP had risen from 17 ± 2 mm to 43 ± 4 mm Hg ($x \pm \text{SE}$). Multiple perfusion defects were noted on the initial low dose (600 uCi) Tc-MAA scan. Ketanserin, 0.15 mg/kg IV bolus, led to a fall after 30 min in MPAP to 27 ± 7 mm Hg ($p < 0.05$) and resolution of perfusion defects on a second high dose (12 uCi) Tc-MAA scan. There was no change in cardiac output. Computer subtraction of the high and low dose scans showed an increase of $12.0 \pm 5.1\%$ ($p < 0.02$) in perfusing lung areas after ketanserin, but not in untreated controls, reflecting vascular recruitment. Calculation of the expected increase in pulmonary vasculature cross-sectional area to explain the fall in MPAP according to Poiseuille's Law showed an increase of 21%; hence, the change in pulmonary vascular resistance mediated by 5-HT inhibition by both vascular recruitment and distention.

Acid aspiration leads to the pulmonary entrapment of platelets and WBC. We speculate that Tx produced by these cells leads to lung permeability and diminished cardiac performance. Twelve dogs were aspirated with 0.1 N HCl, 3 ml/kg. Within 30 min in untreated controls ($n = 6$); cardiac index (CI) decreased from 121 ml/min.kg to 104 ml/min.kg ($p < 0.05$); mean arterial pressure (MAP) fell from 142 mm Hg to 120 mm Hg ($p < 0.05$); PaO_2 fell from 91 mm Hg to 73 mm Hg ($p < 0.05$); while TxB_2 levels increased from 70 pg/ml to 130 pg/ml ($p < 0.05$). ²At 1 h, plasma was used to bathe a rat papillary muscle, and in comparison to pre-aspiration plasma led to a 10% decline in developed tension (Tpd) ($p < 0.05$). Transpulmonary WBC sequestration occurred after 2 h, while at 2.5 h edema fluid was noted in the endotracheal tube. Treated dogs ($n = 6$) received an infusion of the imidazole derivative ketoconazole 1 h after aspiration (2.5 mg/kg bolus followed by 10 mg/kg.h for 2 h). After 30 min of treatment: CI rose from 106 ml/min.kg to 143 ml/min.kg ($p < 0.05$); MAP rose from 128 mm Hg to 137 mm Hg ($p < 0.05$); PaO_2

rose and remained 20 mm Hg higher than controls ($p < 0.05$); TxB_2 fell from 130 pg/ml to 70 pg/ml ($p < 0.05$). At 2.5 h after aspiration plasma from treated animals in comparison to untreated controls led to a 8% higher Tpd ($p < 0.05$). Sequestration of WBC was not observed. After 4 h, 24 ml endotracheal edema fluid was collected in contrast to 127 ml in controls ($p < 0.05$). The importance of WBC Tx synthesis in the induction of permeability was tested by stimulating isolated WBC with the calcium ionophore A23187 in the presence or absence of 10^{-6} M ketoconazole. Ketoconazole reduced the number of leakage sites in the hamster cheek pouch from 196/cm² noted in controls to 28/cm² ($p < 0.05$). These data demonstrate that Tx directly or indirectly lead to cardiac depression and WBC mediated permeability.

PUBLICATIONS

1. Manny J, Patten MT, Liebman PR, Hechtman HB. The association of lung distention, PEEP and biventricular failure. *Ann Surg.* 187;151-159, 1978.
2. Liebman PR, Patten MT, Hechtman HB. A method for direct coronary sinus flow measurement and blood sampling in the dog. *Ann Thorac Surg.* 25;155-157, 1978.
3. Liebman PR, Patten MT, Manny J, Benfield J, Hechtman HB. Hepatic-portal venous gas in adults: etiology; pathophysiology and clinical significance. *Ann Surg.* 187;55-61, 1978.
4. Patten MT, Liebman PR, Manny J, Shepro D, Hechtman HB. Humorally mediated alterations in cardiac performance as a consequence of positive end-expiratory pressure. *Surgery* 84;201-205, 1978.
5. D'Amore PA, Hechtman HB, Shepro D. Ornithine decarboxylase activity in cultured endothelial cells stimulated by serum, thrombin and serotonin. *Thromb Haem.* 39;496-503, 1978.
6. Liebman PR, Philips E, Patten MT, Dennis RC, Manny J, Weisel RD, Hechtman HB. Diagnostic value of portable chest x-rays in pulmonary edema. *Am J Surg.* 135;604-606, 1978.
7. Hechtman HB, Lonergan EA, Staunton HPB, Dennis RC, Shepro D. Pulmonary entrapment of platelets during acute respiratory failure. *Surgery.* 83;277-283, 1978.
8. Liebman PR, Patten MT, Manny J, Shepro D, Hechtman HB. The mechanism of depressed cardiac output on positive end-expiratory pressure (PEEP). *Surgery.* 83;594-598, 1978.
9. Manny J, Grindlinger GA, Mathe AA, Hechtman HB. Positive end-expiratory pressure, lung stretch, and decreased myocardial contractility. *Surgery* 84;127-133, 1978.
10. Hechtman HB, Manny J, Grindlinger GA, Shepro D, Valeri CR. Rapid increase in in-vitro P_{50} during PEEP. *Federation Proceedings.* 37;647, 1978.
11. Manny J, Justice R, Hechtman HB. Maldistribution of blood flow during PEEP. *Surgical Forum* 29;203-205, 1978.
12. Manny J, Justice RE, Hechtman HB. Subendocardial flow determined by diastolic pressure. *Federation Proceedings.* 37;647, 1978.
13. Hechtman HB, Shepro D. Lung metabolism and systemic organ function. *Circulatory Shock.* 9;457-467, 1982.
14. Manny, J, Justice R, Hechtman HB. Abnormalities in organ blood flow and its distribution during positive end-expiratory pressure. *Surgery* 85:425-432, 1979.
15. Grindlinger GA, Manny J, Justice RE, Dunham B, Shepro D, Hechtman HB. Presence of negative inotropic agents in canine plasma during PEEP. *Circ. Res.* 45;460-467, 1979.

16. McLoughlin GA, Manny J, Grindlinger GA, Hechtman HB. Pressure breathing and altered fibrinolytic activity. *Ann Thorac Surg.* 29;156-165, 1980.
17. McLoughlin GA, Manny J, Grindlinger GA, Hechtman HB. Induction of fibrinolytic activity by pressure breathing. *Surgical Forum.* 29;201-203, 1978.
18. Shepro D, Schleef R, Hechtman HB. Plasminogen activator activity by cultured bovine aortic endothelial cells. *Life Sciences.* 26;415-422, 1980.
19. Sweetman HE, Shepro D, Hechtman HB. Inhibition of thrombocytopenic petechiae by exogenous serotonin administration. *Hemostasis.* 10;65-78, 1981.
20. Shepro D, Robinson A, Hechtman HB. Serotonin clearance by capillaries isolated from epididymal fat. *Biblitcha Anat.* 18;108-110, 1979.
21. Grindlinger GA, Vegas AM, Manny J, Hechtman HB. Prostaglandin mediated decreases in contractility during PEEP. *Surgical Forum* 30;163-164, 1979.
22. Vegas AM, McLoughlin GA, Grindlinger GA, Hechtman HB. The control of pulmonary fibrinolytic activity by prostaglandins. *Surgical Forum.* 30;180-181, 1979.
23. Hechtman HB, Utsunomiya T, Krausz MM, Valeri CR, Shepro D. Treatment of pulmonary embolism with prostacyclin (PGI₂). Society of University Surgeons, Houston, TX; February 7-9, 1980.
24. Justice RE, Grindlinger GA, Shepro D, Hechtman HB. A new papillary muscle chamber to test small plasma volumes. *Microvascular Res.* 18;120-123, 1979.
25. Hechtman HB, Vegas AM, Grindlinger GA. Importance of oxygen transport in clinical medicine. *Critical Care Med.* 7;419-423, 1979.
26. Dunham BM, Grindlinger GA, Utsunomiya T, Krausz MM, Hechtman HB, Shepro D. Role of prostaglandins in positive end-expiratory pressure induced negative inotropism. *Am J Physiol.* 241; H783-H788, 1981.
27. Grindlinger GA, Vegas AM, Levine L, Shepro D, Hechtman HB. Prostaglandin mediation of unstable hemodynamics during lung perfusion. *Federation Proceedings* 39;367, 1980.
28. Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Induction of myocardial damage with nitroprusside. *J Surg Res* 31;195-200, 1981.
29. Shepro D, Hechtman HB. Endothelial cells in homeostasis: Pulmonary microvasculature as a model. *American Physiological Society Symposium on the Metabolism of Endothelial Cells.* Dallas, TX, 1980.
30. Shepro D, Hechtman HB. Saturable carrier mediated and non-facilitative diffusion of serotonin by intimal and microvessel endothelium in-vitro. *Symposium on Biology of Vascular Endothelial Cells,* Cold-Spring Harbor, NY; May 6-11, 1980.
31. Shepro D, Sweetman HE, Hechtman HB. Experimental thrombocytopenia and capillary ultrastructure. *Blood.* 56;937-941, 1980.

32. Robinson-White A, Peterson S, Hechtman HB, Shepro D. Serotonin uptake by isolated adipose capillary endothelium. *J Pharmacol Exp Therap.* 216;125-128, 1981.
33. Shepro D, Carson MP, Hechtman HB. Modes of serotonin transport by intimal and capillary endothelial cells. Microcirculatory Society, La Jolla, CA; 1980.
34. Shepro D, Hechtman HB. Pericytic venule permeability regulation by platelet serotonin. Microcirculatory Society Annual Meeting, Atlanta, GA; April 11-12, 1981.
35. Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Prostacyclin control of plasma and platelet 5-hydroxytryptamine in normal and embolized animals. *Am J Physiol.* 241;H766-H771, 1981.
36. Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Prostacyclin control of plasma and platelet 5HT in normal and embolized dogs. *Federation Proceedings* 40:774, 1981.
37. Utsunomiya T, Krausz MM, Shepro D, Valeri CR, Hechtman HB. Treatment of pulmonary embolism with prostacyclin (PGI₂). *Surgery.* 88;25-30, 1980.
38. Utsunomiya T, Krausz MM, Valeri CR, Levine L, Shepro D, Hechtman HB. Treatment of pulmonary embolism with positive end-expiratory pressure and prostaglandin E₁. *Surg Gynecol Obstet.* 153;161-168, 1981.
39. Krausz MM, Utsunomiya T, Dunham B, Shepro D, Hechtman HB. Thromboxane response to prostacyclin (PGI₂) and aspirin treatment in lethal endotoxemia. *Federation Proceedings.* 40;619, 1981.
40. Koshal A, Krausz MM, Utsunomiya T, Hechtman HB, Collins J Jr, Cohn LH. Preservation of platelets and their function in prolonged cardiopulmonary bypass using prostacyclin (PGI₂). *Proceedings of the annual meeting of the American Heart Association. Circulation.* 64:(Suppl II) 44-48, 1981.
41. Krausz MM, Utsunomiya T, Shepro D, Hechtman HB. Adverse effects of prostacyclin (PGI₂) on the isolated perfused lung. *Federation Proceedings.* 39;965, 1980.
42. Shepro D, Li S, Hechtman HB. Plasminogen activator activity of isolated cardiac muscle microvessel endothelial cells. *Thromb Res.* 18;609-616, 1980.
43. Utsunomiya T, Krausz MM, Shepro D, Valeri CR, Hechtman HB. Cardiopulmonary effects of prostacyclin (PGI₂) on the isolated perfused lung. *Federation Proceedings* 39;965, 1980.
44. Shepro D, Hechtman HB. Loss of microvascular integrity with fluoxetine, a serotonin antagonist. *Federation Proceedings* 40;619, 1981.
45. Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Positive end-expiratory pressure effect on myocardial ATPase activity. *Proceedings of the annual meeting of the American Heart Association. Circulation* 64:(Suppl II), 1980.

46. Krausz MM, Utsunomiya T, Feuerstein G, Wolfe JHN, Shepro D, Hechtman HB. Prostacyclin (PGI₂) reversal of lethal endotoxemia in dogs. *J Clin Invest.* 67;1118-1125, 1981.
47. Krausz MM, Utsunomiya T, Feuerstein G, Shepro D, Hechtman HB. Reversal of lethal endotoxemia with prostacyclin (PGI₂). *Surgical Forum* 31;37, 1980.
48. Koshal A, Krausz MM, Utsunomiya T, Hechtman HB, Collins J Jr, Cohn LH. Preservation of platelets and their function in prolonged cardiopulmonary bypass using prostacyclin. *Circulation. (Suppl II)*;44-48, 1981.
49. Justice RE, Krausz MM, Valeri CR, Shepro D, Hechtman HB. A miniaturized chamber for the measure of oxygen consumption. *J Appl Physiol. (Respirat Environ Exercise Physiol)* 52;488-490, 1982.
50. Justice RE, Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. A miniaturized chamber for the measure of oxygen consumption. *Federation Proceedings.* 40;477, 1981.
51. Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Treatment of aspiration pneumonia with ibuprofen and prostacyclin (PGI₂). *Surgery* 90;170-176, 1981.
52. Hechtman HB, Utsunomiya T, Krausz MM, Shepro D. Treatment of aspiration pneumonia with ibuprofen and prostacyclin (PGI₂). *Society of University Surgeons, Hershey, PA; February 12-14, 1981.*
53. Krausz MM, Justice RE, Utsunomiya T, Hechtman HB. A cooling system for prostaglandin infusions. *Ann Biomed Eng.* 9;257-262, 1981.
54. Grindlinger GA, Utsunomiya T, Vegas A, Levine L, Shepro D, Hechtman HB. Prostaglandin mediation of unstable hemodynamics during lung perfusion. *Surgery.* 92;52-60, 1982.
55. Utsunomiya T, Krausz MM, Dunham B, Shepro D, Hechtman HB. Depression of myocardial ATPase activity by plasma obtained during positive end-expiratory pressure. *Surgery* 91;322-328, 1982.
56. Utsunomiya T, Krausz MM, Dunham B, Shepro D, Hechtman HB. Circulating negative inotropic agent(s) following pulmonary embolism. *Surgery.* 91;402-408, 1982.
57. Utsunomiya T, Krausz MM, Levine L, Shepro D, Hechtman HB. Thromboxane mediation of cardiopulmonary effects of embolism. *J Clin Invest.* 70;361-368, 1982.
58. Utsunomiya T, Krausz MM, Kobayashi M, Shepro D, Hechtman HB. Myocardial protection by prostacyclin after lethal endotoxemia. *Surgery.* 92;101-108, 1982.
59. Hechtman HB, Krausz MM, Utsunomiya T, Levine L, Shepro D. Cardiovascular function following surgical stimulation and pulmonary prostacyclin synthesis. *Thrombosis and Hemostasis* 46;264, 1981.
60. Aznavoorian S, Utsunomiya T, Krausz MM, Cohn LH, Shepro D, Hechtman HB. Prostacyclin inhibits 5-hydroxytryptamine release but stimulates thromboxane synthesis during cardiopulmonary bypass. *Prostaglandins* 25;557-570, 1983.

61. Aznavoorian SA, Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Prostacyclin stimulation of thromboxanes during cardiopulmonary bypass. Federation Proceedings 41:1118, 1982.
62. Krausz MM, Utsunomiya T, Levine L, Dunham B, Shepro D, Hechtman HB. Adverse effects of prostacyclin used to perfuse isolated lung lobes. Am J Physiol. 242;H745-H750, 1982.
63. Utsunomiya T, Krausz MM, Dunham B, Valeri CR, Levine L, Shepro D, Hechtman HB. Modification of the inflammatory response to aspiration with ibuprofen. Am J Physiol. 243;H903-H910, 1982.
64. Shepro D, Utsunomiya T, Krausz MM, Hechtman HB. Effect of ibuprofen combined with prostacyclin in platelet and leukocyte counts following acid aspiration injury. Thrombosis and Haemostasis 46; 442, 1981.
65. Dunham B, Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Modification of the inflammatory response to aspiration with ibuprofen. Federation Proceedings 41:1503, 1982.
66. Hechtman HB, Huval WV, Mathieson MA, Stemp LI, Valeri CR, Shepro D. Therapy of acid aspiration by inhibition of thromboxane (Tx) synthetase. Microcirculation: Clinical and Experimental 1:242, 1982.
67. Krausz MM, Utsunomiya T, Dunham B, Valeri CR, Shepro D, Hechtman HB. Inhibition of permeability edema with imidazole. Surgery. 92;299-308, 1982.
68. Krausz MM, Utsunomiya T, Dunham B, Valeri CR, Shepro D, Hechtman HB. Inhibition of permeability edema with imidazole. Society of University Surgeons, 43rd Annual Meeting; New York, NY; Feb. 11-13, 1982.
69. Teoh KHT, Mathieson MA, Huval WV, Stemp LI, Valeri CR, Shepro D, Hechtman HB. Granulocyte mediation of burn edema. Surgical Forum 33:65, 1982.
70. Shepro D, Hechtman HB. Capillary fragility induced by psychotropic serotonergic drugs. Thrombosis and Haemostasis 46;8, 1981.
71. Huval WV, Mathieson MA, Stemp LI, Dunham BM, Jones AG, Shepro D, Hechtman HB. Therapeutic benefits of 5-hydroxytryptamine inhibition following pulmonary embolism. Ann Surg. 197:220-225, 1983.
72. Huval WV, Stemp LI, Mathieson MA, Dunham BM, Shepro D, Hechtman HB. Therapeutic benefits of 5HT inhibition following pulmonary embolism. Surgical Forum 33:262, 1982.
73. Justice RE, Krausz MM, Aznavoorian SA, Hechtman HB. Jet ventilation permits oxygenation during endotracheal suctioning. Proceedings: Annual Meeting of the Association of the Advancement of Medical Instrumentation.
74. Hechtman HB, Utsunomiya T, Vegas Am, Grindlinger GA, McLoughlin GA, Krausz MM, Shepro D. Prostaglandin mediation of pulmonary fibrinolytic activity. In:

- Tissue Hormones In The Acutely Ill. (R. McConn, ed); Raven Press, New York, 243-251, 1982.
75. Huval WV, Dunham BM, Lelcuk S, Valeri CR, Shepro D, Hechtman HB. Thromboxane mediation of cardiovascular dysfunction following aspiration. *Surgery*. 94:259-266, 1983.
 76. Huval WV, Dunham BM, Mathieson MA, Lelcuk S, Valeri CR, Shepro D, Hechtman HB. Thromboxane (Tx) mediation of cardiovascular dysfunction following aspiration. Society of University Surgeons, 44th Annual Meeting; Oklahoma City, OK; February 8-12, 1983.
 77. Hechtman HB, Utsunomiya T, Krausz MM, Shepro D. The management of cardiorespiratory problems in surgical patients. In: *Advances in Surgery*. Vol. 15, Maclean LD, ed. Chicago; Year Book Medical Publishers, 1981; pp 123-156.
 78. Hechtman HB, Huval WV, Mathieson MA, Stemp L, Valeri CR, Shepro D. Prostaglandin and thromboxane mediation of cardiopulmonary failure. Hechtman HB (ed), *Surg Clin NA* 63:263-283, 1983.
 79. Hechtman HB, Huval WV, Lelcuk S. The use of serotonin antagonists in treatment of pulmonary embolus. *Resident And Staff Physician* 29:64-78, 1983.
 80. Stemp LI, Huval WV, Mathieson MA, Jones AG, Hechtman HB. Pulmonary vasodilatation by serotonin (5HT) inhibition after pulmonary embolism. *Federation Proceedings* 42(3):650, 1983.
 81. Mathieson MA, Teoh KHT, Huval WV, Valeri CR, Shepro D, Hechtman HB. Arachidonic acid metabolites mediate burn edema. *To: J Trauma* 11/04/82. (Accepted pending author modifications-03/30/83)
 82. Lelcuk S, Huval WV, Shepro D, Hechtman HB. Role of serotonin in experimental aspiration. *Federation Proceedings* 42(4):797, 1983.
 83. Dunham BM, Hechtman HB, Valeri CR, Shepro D. Inhibition of vascular permeability induced by A23187 stimulated human polymorphonuclear leukocytes (PMN). *Federation Proceedings* 42(3):695, 1983.
 84. Dunham BM, Hechtman HB, Valeri CR, Shepro D. Alterations of vascular permeability induced by human neutrophils (PMN) or platelets (PT). *Microvascular Research* 25:232, 1983.

PERSONNEL RECEIVING CONTRACT SUPPORT

<u>NAME</u>	<u>POSITION</u>	<u>% EFFORT</u>	<u>TIME PERIOD</u>
Herbert Hechtman, MD	Principal Investigator	25%	02/78 - 06/83
Richard Justice	Associate in Surgery	60%	02/78 - 12/82
Gene Grindlinger, MD	Research Fellow/Surgery	50%	02/78 - 06/78
Armando Vegas, MD	Research Fellow/Surgery	50%	02/78 - 06/78
Takayoshi Utsunomiya, MD	Research Fellow/Surgery	50%	02/78 - 06/80
Michael Krausz, MD	Research Fellow/Surgery	50%	07/80 - 06/82
William Huval, MD	Research Fellow/Surgery	50%	07/81 - 06/83
Shlomo Lelcuk, MD	Research Fellow/Surgery	50%	07/82 - 06/83

DISTRIBUTION LIST

4 copies **Commander**
Letterman Army Institute of
Research (LAIR), Bldg. 1110
ATTN: SGRD-ULZ-RC
Presidio of San Francisco, CA 94129-6815

4 copies **Commander**
US Army Medical Research and Development Command
ATTN: SGRD-RMS
Fort Detrick, Frederick, Maryland 21701-5012

12 copies **Defense Technical Information Center (DTIC)**
ATTN: DTIC-DDAC
Cameron Station
Alexandria, VA 22304-6145

1 copy **Dean**
School of Medicine
Uniformed Services University of the
Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799

1 copy **Commandant**
Academy of Health Sciences, US Army
ATTN: AHS-CDM
Fort Sam Houston, TX 78234-6100

END

FILMED

4-85

DTIC