AD_____

Contract Number DAMD17- 97-C-7034

TITLE: Extracorporeal Life Support in Military Casualties

PRINCIPAL INVESTIGATOR: Robert H. Bartlett, M.D.

CONTRACTING ORGANIZATION: University of Michican Medical Center
Ann Arbor, Michigan 48109-1274

REPORT DATE: January 1999

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 1999	Final (31 Dec 96 - 01 Oct 98)

4. TITLE AND SUBTITLE
Extracorporeal Life Support in Military Casualties

5. FUNDING NUMBERS
DAMD17- 97-C-7034

6. AUTHOR(S)
Robert H. Barlett, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Michigan Medical Center
Ann Arbor, Michigan 48109-1274

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

The purpose of this contract is to develop a portable extracorporeal life support (ECLS) device and a vascular access system. Part of this project includes the development of a non-thrombogenic surface to allow ECLS with minimal or no system anti-coagulation, During the second year of the contract the prototype device was completed by the subcontractor, animal models were refined, and the non-thrombogenic NO releasing surace was further tested.

14. SUBJECT TERMS
Extracorporeal life support, heart-lung machine, vascular access, non-thrombogenic surface, total automation

15. NUMBER OF PAGES
26

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

NA Where copyrighted material is quoted, permission has been obtained to use such material.

NA Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

NA For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

NA In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

NA In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

NA In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Robert W Barcomb 1/30/99

PI - Signature Date

TABLE OF CONTENTS

Annual Report for Contract DAMD 17-97-C-7034
Extracorporeal Life Support in Military Casualties

INTRODUCTION

Extracorporeal life support (ECLS) is the term used for prolonged use of a modified heart-lung machine to sustain life during severe respiratory or circulatory failure. ECLS is widely used for the treatment of children and adults with severe respiratory failure. In addition ECLS is the only mechanical life support system to sustain systemic perfusion during profound circulatory shock. The purpose of this contract is to develop a portable ECLS system which could be used in a far forward military setting.

The requirements for ECLS in this military setting include portable size, automated operation with servoregulation based on physiologic measurements, built in safety features, automatic priming and volume resuscitation, low energy requirement, and minimal or no systemic anticoagulation. Another goal of this project is to develop a quick and simple vascular access system which could be used in the field to achieve ECLS without thoracotomy.

Our research group has studied both basic and clinical application of ECLS for the past 30 years. A non-occlusive peristaltic blood pump developed in our laboratory is ideally suited for automation, safety, and portability applications for military ECLS. Based on this pump and based on our laboratory background in surface thrombogenicity evaluation we were awarded this contract to further develop ECLS for military applications.

As discussed in our original contract proposal, our laboratory has a long history of research on development of ECLS, and has been conducting research on the general topics related to this contract supported by grants from the National Institutes of Health and other sources. Our clinical experience with ECLS, while not supported at all by this contract, has important bearing on further development of ECLS therefore it is discussed in this progress report. All of our laboratory experience, and subcontract activities at MC3 related to this project are summarized in this annual report.

Although the contract start date was January 1, 1997, the expenditure of significant funds from this contract did not begin for a few months while University contract and MC3 subcontract administrative details were being arranged. Because of this we asked Fort Detrick sponsors to change the year 2 and year 3 awards dates to May 1998 and May 1999, with the contract to be completed by May 2000. This request was approved. The first annual report was submitted January 27, 1998, and the current report covers December 31, 1997 to December 30, 1998. In November, 1998 we were officially notified that this contract would not continue beyond December 1, 1998, so **this report is both the annual report and the final scientific report.**

Methods And Results

Work on this project was carried out simultaneously in five specific areas: Further development of the pump and pumping systems, development of the small portable ECLS system under subcontract at MC3, development of an anti-platelet non-thrombogenic surface, clinical experience relevant to this contract, and vascular access devices.

Non-Occlusive Peristaltic Pump and Pumping Technology

The unique pump upon which this system is based was developed at Michigan Critical Care Consultants, Inc. (MC3) and tested in our laboratories. University of Michigan holds the patent on this pump which is licensed to MC3 and sub-licensed to Avecor, Inc. of Minneapolis, Minnesota. During the first contract year the Avecor version of this pump was approved by the FDA for use in cardiac surgery. This approval is related to this contract only in that it indicates that the FDA approved the pump, the pumping chamber, and the electronics for general use, insuring that potential commercial development in multiple production of the portable ECLS device will be possible. The pump was tested in our laboratories throughout the first year in a series of animal experiments which demonstrated that total support of gas exchange is possible using a tidal flow single catheter system in adult-sized animals. This is the first time that total respiratory support with tidal flow has been reported. This demonstrates the applicability of the portable ECLS system using different modes of vascular access for different specific applications. The reference describing this work is listed below. In related experiments a modified ECLS system was used to achieve precise temperature control over a wide range of temperatures in experimental animals. This is particularly important to the military application because hypothermia is a common problem in military casualties, and the ability to warm the subject and maintain precise temperature by perfusion control will be important for ultimate application of the ECLS system. A modified ECLS circuit was also evaluated using a series of hemofilters to clear toxic molecules from the blood in treatment of induced liver failure in animals. Although not addressed in our original contract proposal, the ability to include blood processing for the treatment of fluid overload, renal failure, and multiple organ failure, combined with general cardiopulmonary life support will be a major advantage of this technology. Preliminary reports of this work were included in the first annual report.

During the second year, the pump was tested with a smaller, lighter motor for the portable system. There were two reports of leaks in clinical application at the sealed edge of the pumping chamber. Because of this we evaluated a single piece extruded pumping chamber. There were no leaks during one month of testing at high pressure. Although we can begin animal testing with the sealed chamber, the ultimate application of this device will include a solid extruded or die-cast pumping chamber.

Development of a Portable Automatic ECLS System

This development is subcontracted to MC3. All of the components for the small portable system were acquired and assembled in the first year. The motor of the pump is smaller than that used for the Avecor cardiac surgery version of the pump. The microprocessor program for automated pump control has been further refined by Dr. Scott Merz of MC3. The development of an automated suction system to allow venous drainage which does not depend on gravity is crucial to the further development of this device. The controlled suction is achieved by encasing the pump chamber in a solid sealed chamber and applying vacuum to the sealed chamber as described in the contract proposal.

During the second year, the portable device was designed using CAD-CAM three dimensional imaging. The components were assembled based on this plan. The final device was assembled and bench tested. The CAD-CAM design and the photographs of the final device are included in the appendix. We were about to begin large animal testing of the device when we were notified that the contract would not be continued. The portable device is designed to be used with any small membrane oxygenator. During the second year, under the

MC3 contract, a variety of small oxygenators were tested using microporous, hollow fiber technology. The best of these devices were also tested in animals in our laboratory, perfused by the right ventricle. These oxygenators will ultimately be used as implantable prosthetic lungs and that research is not covered by this contract. However, testing these devices is crucial for development of the portable ECLS system. In addition to the microporous devices, a solid silicone rubber membrane for oxygenators was developed and tested at MC3 which could ultimately be used in this portable system. During the second year of this contract, hemolysis testing by Dr. Sean Chambers in our laboratory. These studies showed that negative pressure applied to flowing blood does not cause hemolysis in the absence of a blood gas interface. This information was crucial to the development of the portable ECLS system because active suction is applied to the venous drainage. Therefore at the conclusion of this contract the portable ECLS device has been designed, assembled, tested, and is ready for animal trials, following the schedule in the original statement of work.

The rapid vascular access system is also under development at MC3. Prototype devices using guide wire access followed by balloon dilatation were studied and compared to sequential solid dilators as a means of gaining major vascular access. During the second year, inflatable balloons of various sizes and shapes were fabricated at MC3. The catheter designed to go over the guidewire and inflate the balloon was contracted out by MC3. At the end of the contract, MC3 was ready to fabricate devices for animal testing.

Non-Thrombogenic Surfaces

Major progress has resulted from the development and evaluation of plastic surfaces which release nitric oxide gas. Nitric oxide gas elaborated from the normal human endothelium inhibits platelet adhesion to endothelial cells. We have taken advantage of this principle in developing a plastic surface which releases nitric oxide. During in-vitro testing using rabbit platelets radio-labeled with ^{111}Indium we have demonstrated that platelet adhesion is remarkably reduced when this compound is incorporated as a plastic coating. We have evaluated this coating in our four-hour ex-vivo rabbit extracorporeal circulation model. This is a very unforgiving model of non-thrombogenic surfaces. Heparin coated surfaces have only minimal favorable effect in this rabbit test model. In our initial testing with nitric oxide releasing surfaces the ex-vivo loops stay patent and platelet count is maintained near normal levels during four hours of extracorporeal circulation. This finding is unprecedented in our laboratory. This indicates that the use of nitric oxide releasing plastics will be a major advance in ECLS, particularly in military applications where hemorrhage and injury make anticoagulation contraindicated. The initial results of these studies were presented at American Society of Artificial Internal Organs (ASAIO) in May 1997. The abstract describing those studies was included in the first annual report.

During the second year of the contract, reports describing the rabbit animal model with labeled platelets, and the success with the nitric oxide releasing surface were submitted for publication and accepted. During this year we evaluated the possibility that the DMHD-NO compound was released from the poly vinyl chloride (PVC) plastic surface intact, rather than leeching out pure nitric oxide. The DMHD molecule may have undesirable side effects and it appeared that some of this molecule leeched into the flowing blood from the plastic. For this reason, Dr. Meyerhoff developed and evaluated several other compounds which released nitric oxide leaving the carrier molecule in the plastic surface. These other molecules are being tested in Dr. Meyerhoff's laboratory under separate NIH support. We plan to incorporate the study of these molecules into the rabbit thrombogenicity model. During the second contract

year, a phosphoryl choline coating and a non-thrombogenic coating based on heparin manufactured by Avecor were tested in the rabbit model. The performance of these materials was similar to previous studies with heparinized surfaces, and not satisfactory for further study of non-thrombogenic surfaces to be used without systemic anticoagulation. Therefore the nitric oxide releasing surface continues to be the most promising material. During the current contract year, Dr. Annich developed an in-vitro test system for non-thrombogenic surfaces based on coating of glass and polypropylene tubes with test compound, then incubation with radio labeled platelets for two hours. This test system correlates very well with the rabbit thrombogenicity model but is much simpler and less expensive. The nitric oxide releasing surface inhibited platelet adherence in this in-vitro test system. In the future this in-vitro system will be used to screen non-thrombogenic materials prior to proceeding to the complex and expensive rabbit and sheep models. During the last contract year, we evaluated a device called a "Clot Signature Analyzer" from the Xylum Corporation. Preliminary reports indicate that this device allowed in-vitro measurement of platelet function at the bedside. Currently there is no test system to measure platelet function without subjecting the blood to centrifugation and dilution (which in itself affects platelet function). Such a device would be extremely useful for the laboratory and clinical evaluation of extracorporeal circulation. Our testing of this device showed wide variability in measurement results, but refinements in the methodology may solve that problem. Further testing of in-vitro platelet function measurements will continue with other support after the end of this contract.

Clinical ECLS

Although no human studies are supported by this contract, our on-going clinical experience is relevant to the military applications of ECLS. Two of our clinical projects have direct application on this project: venoarterial support for cardiogenic and hemorrhagic shock, and evaluation of the route of vascular access for respiratory support. Our experience with extracorporeal life support as part of cardiopulmonary resuscitation for hemorrhagic and cardiogenic shock continued under the direction of Dr. John Younger. Venoarterial access and VA perfusion resulted in approximately 40% survival rate. This is one of the major military applications of ECLS, particularly in far forward positions. This experience demonstrates that the technique is not only feasible but the results of these early trials are encouraging.

During the last two years we evaluated methods of venting the left atrium and left ventricle during venoarterial support in which total cardiac arrest has occurred. In this circumstance bronchial and thebesian venous flow fills the left side of the heart, even during total cardiopulmonary bypass. This results in left ventricular over distention, pulmonary hypertension, and pulmonary edema. This may occur under combat conditions. We have developed a simple method to vent the left side of the heart and prevent this over distention by transvenous atrial septostomy. This is currently done in the cardiac catheterization lab but we are developing the methodology to do this guided by echocardiography only. This makes the application of ECLS in total cardiac arrest feasible, even in the absence of radiographic equipment.

We have also evaluated two modes of vascular access for respiratory support: right atrium drainage with femoral vein return, and femoral vein drainage with right atrium return. Although our standard clinical practice for several years has been to drain from the right atrium, we have determined that femoral (inferior vena cava) drainage with internal jugular to right atrial return achieves the same level of total respiratory support at lower blood flow rates, therefore it is a preferable mode of access. Studies were conducted in patients using catheters placed via

both routes, comparing the two modes of access. The tidal flow system described above will be preferable to the dual catheter system once it is developed for clinical use. However for the foreseeable future the route of venous access will be very important for any application of ECLS in respiratory failure.

We have continued to gain clinical experience with percutaneously placed large access catheters for both respiratory and cardiac support. Clinically we are using commercially available sequential solid dilators. As noted above a simpler, quicker balloon dilation system developed under this contract is currently in the prototype stage at MC3.

We reported our results with the first 100 adult patients with respiratory failure supported with ECLS. This work was reported to the American Surgical Association by Dr. Kolla. This report demonstrates that the use of ECLS for respiratory failure in adults is becoming a standard approach in civilian practice. A review of 141 patients with ARDS referred for ECMO was published by Dr. Rich.

CONCLUSIONS

The purpose of this contract is to develop a portable extracorporeal life support (ECLS) device and a vascular access system. Part of this development includes the development of a non-thrombogenic surface to allow ECLS machine with minimal or no systemic anticoagulation. During the first year of the contract the components for the prototype device were assembled, the non-occlusive peristaltic pump was tested in detail, and a non-thrombogenic nitric oxide releasing surface was developed and tested in our rabbit model. During the second year of the contract, the portable ECLS machine was assembled and bench tested by the subcontractor. New membrane lung prototypes were tested in the sheep model. Improved methods of thrombogenicity testing were developed in the laboratory and non-thrombogenic coatings were tested in the rabbit model. This research contract was prematurely terminated in November, 1998, but at the time the contract was concluded we were ready to begin large animal testing of the completed prototype.

REFERENCES

First Year:

Kolla S, Crotti S, Lee A, Gargulinski MJ, Lewandowski T, Bach D, Hirschl RH, Bartlett RH: Total respiratory support with tidal flow extracorporeal circulation in adult sheep. ASAIO J. 43:M811-M816, 1997.

Kolla S, Awad SA, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH: Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226:544-566, 1997.

Nitric Oxide-Releasing Coating Decreases Platelet Consumption in a Rabbit Model of ECC: GM Annich, S. Merz, J. Meinhardt, B. Ashton, B. Chung, RB Hirschl, RH Bartlett. (Abstract presented at the American Society of Artificial Internal Organs annual meeting May, 1997.)

Systemic Hyperthermia Induced by Venoarterial Perfusion for Cancer Therapy: O. Soldes, S. Award, P. Rich, W. Lynch, J. Younger, R. Hirschl, R. Bartlett. (Abstract submitted for presentation at the American Society of Artificial Internal Organs annual meeting April, 1998.)

Evaluation of an Extracorporeal Liver Assist Device Utilizing Selective Hemodiafiltration in an Animal Model of Hepatic Failure: S. Awad, O. Soldes, S. Sawada, P. Rich, M. Gargulinski, S.

Mahler, R. Hirschl, R. Bartlett. (Abstract submitted for presentation at the American Society of Artificial Internal Organs annual meeting April, 1998.)

Outcome Following Extracorporeal Resuscitation: J. Younger, R. Schreiner, R. Hirschl, R. Chapman, R. Bartlett. (Presented at the European Extracorporeal Support Organization Annual Scientific Meeting Oxford, England, August 1997.)

Second Year:
Rich PB, Awad SS, Kolla S, Annich G, Schreiner RJ, Hirschl RB and Bartlett RH: Approach to the Treatment of Severe Adult Respiratory Failure. Journal of Critical Care 13:26-36, 1998.

Rich, PB, Younger J, Soldes OS, Awad SS, Bartlett RH: The Use of Extracorporeal Life Support for Adult Patients with Respiratory Failure and Sepsis. ASAIO Journal (In Press 1998).

Chambers S, Bartlett RH, Ceccio S: Spherical Bubble Dynamics: A Model to Predict Red Blood Cell Damage by Hydrodynamic Cavitation. Proceedings of the Third International Symposium on Cavitation, April 1998, Grenoble, France (In Press).

APPENDICES
First Year:
Evaluation of an Extracorporeal Liver Assist Device Utilizing Selective Hemodiafiltration in an Animal Model of Hepatic Failure: S. Awad, O. Soldes, S. Sawada, P. Rich, M. Gargulinski, S. Mahler, R. Hirschl, R. Bartlett.

Outcome Following Extracorporeal Resuscitation: J. Younger, R. Schreiner, R. Hirschl, R. Chapman, R. Bartlett.

Systemic Hyperthermia Induced by Venoarterial Perfusion for Cancer Therapy: O. Soldes, S. Award, P. Rich, W. Lynch, J. Younger, R. Hirschl, R. Bartlett.

Nitric Oxide-Releasing Coating Decreases Platelet Consumption in a Rabbit Model of ECC: GM Annich, S. Merz, J. Meinhardt, B. Ashton, B. Chung, RB Hirschl, RH Bartlett.

Kolla S, Awad SA, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH: Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226:544-566, 1997.

Kolla S, Crotti S, Lee A, Gargulinski MJ, Lewandowski T, Bach D, Hirschl RH, Bartlett RH: Total respiratory support with tidal flow extracorporeal circulation in adult sheep. ASAIO J. 43:M811-M816, 1997.

Second Year:

Rich PB, Awad SS, Kolla S, Annich G, Schreiner RJ, Hirschl RB and Bartlett RH: Approach to the Treatment of Severe Adult Respiratory Failure. Journal of Critical Care 13:26-36, 1998.

Summary from MC3 with diagrams and photographs of the portable ECLS system.

Michigan Critical Care Consultants, Inc.
245 Jackson Industrial Drive, Suite J, Ann Arbor, MI 48103
Phone: (734) 995-9089 Fax: (734) 995-0840

Brigadier General John S. Parker, M.D.
Commanding General
US Army Research & Materiel Command
Fort Detrick, MD 21702-5012
RE: Combat Casualty Care Contract #DAMD 1797C7034

10/24/98

Dear General Parker,

We recently received notice from the University of Michigan that funding for the contract referenced above was suspended, which in turn terminated a sub-contract between the University of Michigan and Michigan Critical Care Consultants (MC3) for the development of the equipment necessary for military casualty extracorporeal support. MC3 is a small company devoted to the development of specialized equipment used for cardiorespiratory applications. We have been successful developing equipment for this purpose, for the most part, under federal grants awarded by the National Institutes of Health SBIR program, and more recently under this sub-contract arrangement with the University of Michigan. A safer blood pump that was developed at MC3 is currently FDA approved and used routinely by many hospitals all over the world for heart-lung bypass operations. Other products that we are currently involved in developing include an implantable artificial lung, a nitric oxide releasing blood compatible surface, a highly efficient gas transfer membrane, and a digital controller for extracorporeal circulation. These technologies, which are at various stages of development, can be integrated into a single device which would be appropriately used in the emergency support of military casualties. This is why MC3 is an ideal contractor for the development of the equipment proposed in the contract. We truly believe that this equipment would be useful in situations where emergency support must be quickly and readily provided. We envisioned a system that is portable and could be easily transported in a helicopter or an ambulance to the location of the casualty, and could be completely set up and placed in operation by a single paramedic by means of automatic control and simplified percutaneous access to blood vessels.

Our first prototype (See enclosed early digital rendition and actual prototype photo) has demonstrated that it is feasible to package a totally self contained extracorporeal support system in a portable package within the proposed specifications. We now further realize that this package can be made significantly smaller and lighter in an effort to ease its portability, an endeavor planned for the second iteration prototype. This system, as proposed, will be able to provide ambulatory extracorporeal support for up to 4

hours, which would allow for transporting critically ill patients to medical units where the patients can be treated, or the system's battery and gas can be recharged.

We believe that MC3 is uniquely positioned to develop this system because of key technologies proprietary to MC3, or in an advanced stage of development here. We also believe that the system as proposed would have widespread application in non-military emergency situations that could benefit the public at large.

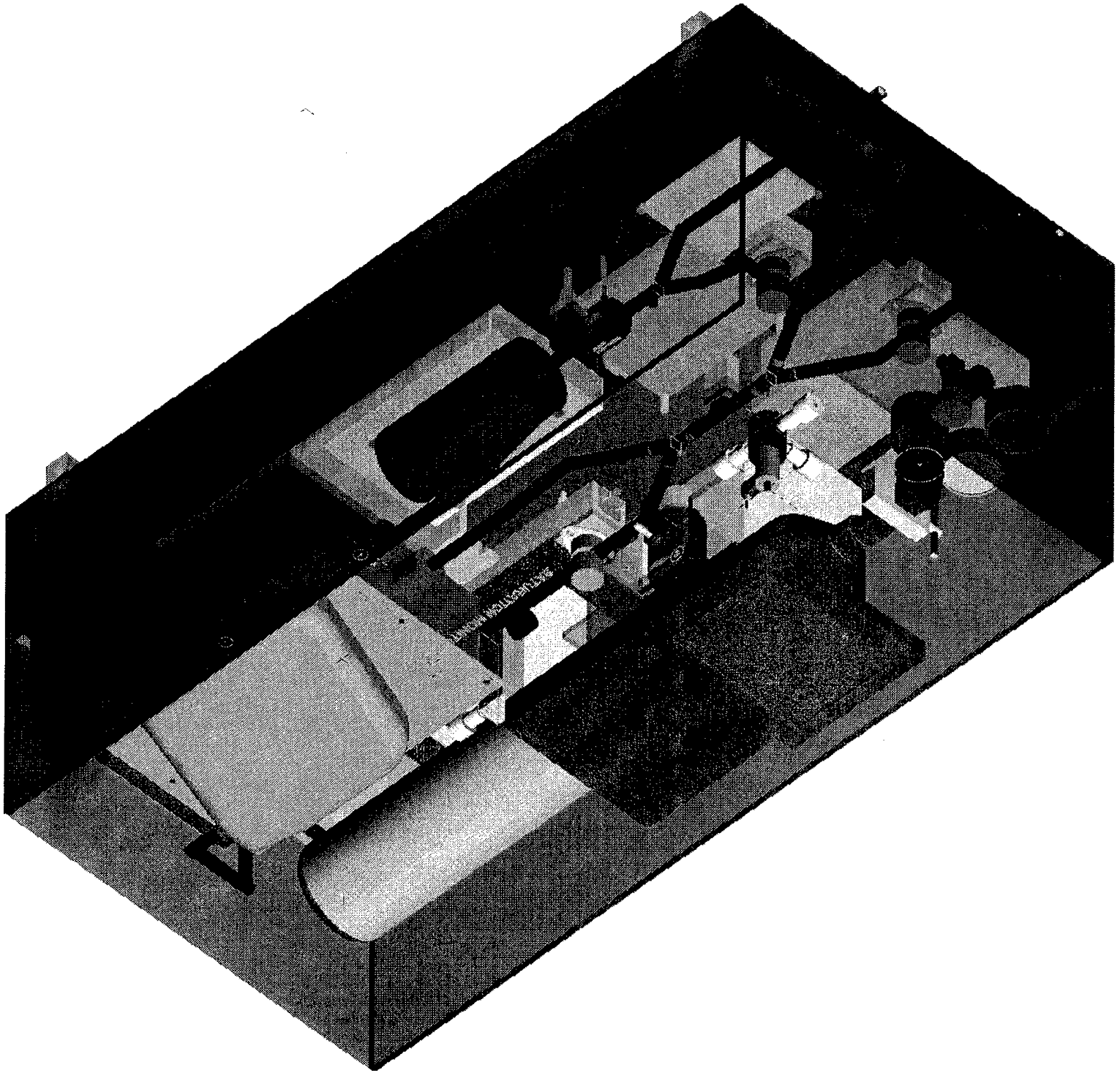
After 17 months of our sub-contract with the University of Michigan, we have accomplished our goals of completing a first prototype of the integrated system which is currently ready for laboratory testing. We are currently awaiting the molding dies for the balloon access catheter which will allow us to very quickly prototype and test these catheters. We're also currently in the midst of improving the pump system such that it is unaffected by body forces found during transportation, thus making this pump uniquely and safely suited for this application.

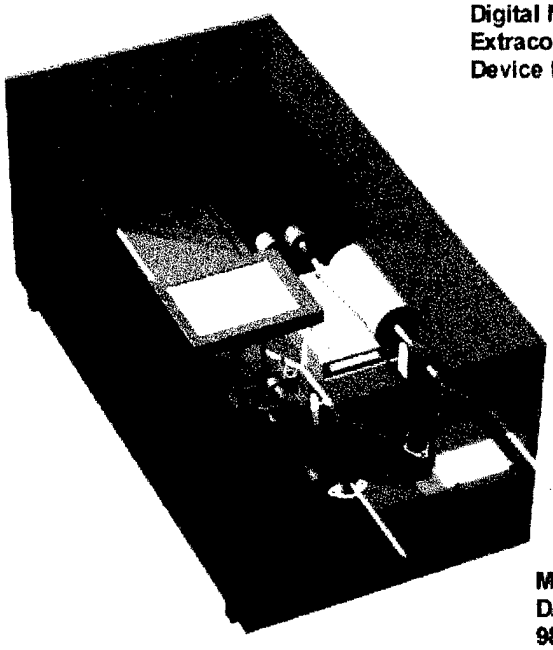
A suspension or termination at this stage would have a significant impact on the development of a product that would be of significant use to the military as well as to civilian applications. Furthermore, this would also impact our company's ability to financially support key personnel involved in this project. We respectfully appeal to your knowledge in this field to support continuing funding for this project. We would also like to invite you to visit our modest facilities to see first hand how we have been developing this and other beneficial products.

Please feel free to call me at (734) 995-9089 if you have any questions or wish to discuss specific aspects of the project.

Sincerely,

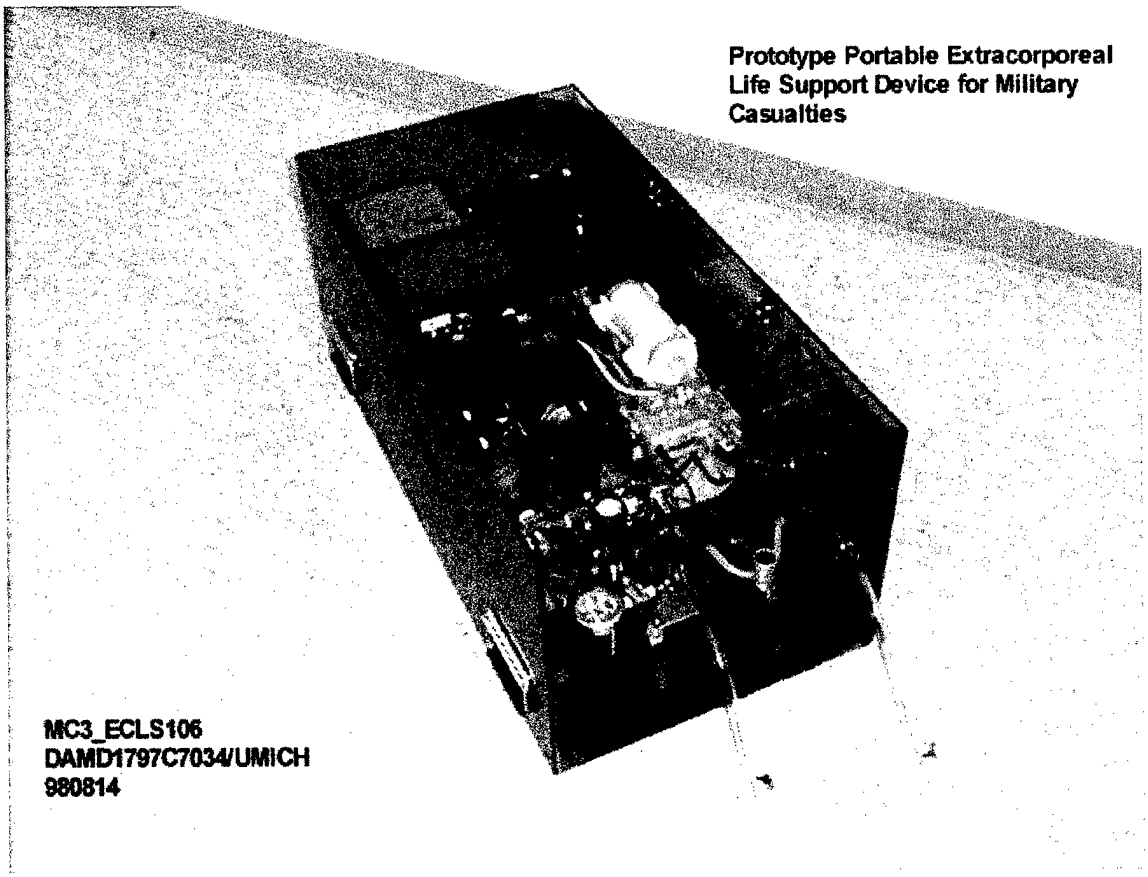
Patrick Montoya, Ph.D.
President





Digital Model of the Portable Extracorporeal Life Support Device for Military Casualties

MC3_ECLS101
DAMD1797C7034/UMICH
980520



Prototype Portable Extracorporeal Life Support Device for Military Casualties

MC3_ECLS106
DAMD1797C7034/UMICH
980814

An Approach to the Treatment of Severe Adult Respiratory Failure

Preston B. Rich, Samir S. Awad, Srinivas Kolla, Gail Annich, Robert J. Schreiner, Ronald B. Hirschl, and Robert H. Bartlett

Objectives: **The purpose of this article is to evaluate outcome in adult patients with severe respiratory failure managed with an approach using (1) limitation of end inspiratory pressure, (2) inverse ratio ventilation, (3) titration of PEEP by Svo_2, (4) intermittent prone positioning, (5) limitation of Fio_2, (6) diuresis, (7) transfusion, and (8) extracorporeal life support (ECLS) if patients failed to respond.**

Patients and Methods: **This study was designed as a retrospective review in the intensive care unit of a tertiary referral hospital. One-hundred forty-one consecutive patients with hypoxic (n = 135) or hypercarbic (n = 6) respiratory failure referred for consideration of ECLS between 1990 and 1996. Overall, initial Pao_2/Fio_2 (P/F) ratio was 75 ± 5 (median = 66).**

Results: **Lung recovery occurred in 67% of patients and 62% survived. Forty-one patients improved without ECLS (83% survived); 100 did not and were supported with ECLS (54% survived). Survival was greater in patients cannulated within 12 hours of arrival (59%) compared with those cannulated after 12 hours (40%, $P < .05$). Multiple logistic regression identified age, duration of mechanical ventilation before transfer, four or more dysfunctional organs, and the requirement for ECLS as independent predictors of mortality.**

Conclusions: **An approach that emphasizes lung protection and early implementation of extracorporeal life support is associated with high rates of survival in patients with severe respiratory failure.**

RESPIRATORY FAILURE is a significant source of morbidity and mortality, affecting approximately 150,000 people per year in the United States.[1-11] Although inciting events may be diverse, injury to the alveolar-capillary membrane with obliteration of the gas-alveolar interface appears to be a final common pathway.[12] Progressive hypoxemia and hypercapnia eventually mandate endotracheal intubation and mechanical ventilation. Traditionally, this has consisted of delivering supplemental oxygen and fixed gas tidal volumes with adjustments in Fio_2 and minute ventilation to maintain normocapnia and arterial oxygenation. As lung compliance worsens, the inspiratory pressures required to deliver these fixed volumes increase.[13] Substantial evidence has accumulated that alveolar overdistention caused by high inspiratory pressures can contribute to or even cause lung injury.[14-20]

Treatment of the adult respiratory distress syndrome (ARDS) is continuously evolving.[21,22] The use of pressure-limited mechanical ventilation has been advocated to avoid overdistension by limiting pressure and allowing tidal volume to be variable.[23,24] Inverse-ratio ventilation (IRV) and positive end-expiratory pressure (PEEP) may provide alveolar recruitment while preventing the cyclical collapse and re-expansion of surfactant deficient lung units.[19,24-27] Despite these approaches, many patients fail to respond, ultimately dying with respiratory and other organ failure. However, combining these potentially less injurious ventilator techniques with extracorporeal support of the failing lung may reduce the extent of ventilator-induced lung injury, provide improved gas exchange and perfusion, and maximize recovery from reversible lung disease.[23,28-32]

We reserve extracorporeal life support (ECLS) for those patients who deteriorate *despite and after* implementation of these treatments. Based on our initial experience with neonatal extracorporeal membrane oxygenation (ECMO)[33,34] and encouraged by the European experience with extracorporeal CO_2 removal ($ECCO_2R$),[28] we initiated a clinical management strategy in 1990, which incorporated techniques of lung protection, maximization of oxygen delivery, and ultimately ECLS, to care for the adult patient with severe respiratory failure. We have previously described patients managed with ECLS,[35-39] and now present our experience with all patients referred for the consideration of extracorporeal support during this time period. This study was undertaken to examine the survival and characteris-

From the Department of Surgery, University of Michigan Medical Center, Ann Arbor, MI.

Received September 8, 1997. Accepted October 23, 1997.

Funded in part by National Institutes of Health RO1 grant HD15434.

Address reprint requests to Robert H. Bartlett, MD, University of Michigan Medical Center, 1500 E. Medical Center Dr, 2918 Taubman Center Box 0331, Ann Arbor, MI 48109-0331.

0883-9441/98/1301-0006$8.00/0

tics of a cohort of patients treated with this approach.

PATIENTS AND METHODS

The hospital records of 141 patients with severe respiratory failure referred to the University of Michigan Hospital for ECLS between the years 1990 and 1996 were retrospectively reviewed. All patients were referred from other intensive care units after 0.5 to 25 days of treatment. The referring intensivists considered these patients to have ARDS, which was unresponsive to vigorous therapeutic efforts.

Our criteria for considering ECLS were a transpulmonary shunt greater than 30% [corresponding to a P/F ratio < 100 on Fio_2 1.0 or an alveolar-arterial oxygen gradient (A-aDO_2) > 550], and compliance less than 0.5 mL/cm H_20/kg. Initially, contraindications to ECLS included: mechanical ventilation > 5 days, age > 60 years, irreversible or incurable disease, an immunocompromised state, poor predicted neurologic outcome, or the presence of septic shock. As our experience progressed, age > 60 years, > 5 days of mechanical ventilation, and septic shock became relative contraindications, and some patients were accepted outside of these initial limits. These selection criteria were chosen in an attempt to identify patients with a high predicted mortality and the potential for lung recovery and survival. The measures of hypoxia (shunt > 30%) generally correspond to the 1975 to 1979 National Institutes of Health ECMO trial entry criteria.[40] Measurements were made after the implementation of treatment, and therefore represent the highest arterial oxygenation obtained after intervention.

Blood gas values at the time of transfer to our institution were used to calculate P/F ratios. The number of ventilated days (total and before initiation of the protocol), days in the intensive care unit, and total number of hospitalized days were tabulated. For those patients who received ECLS, the number of ventilated days before ECLS, the number of hours on bypass, and the method of cannulation were recorded.

The development of concurrent organ dysfunction (at any time during the hospital course and not limited to the time of transfer) was defined as follows. These definitions were arbitrarily selected to define our patient population and were established in 1985 for use in our ICU.

1. *Renal insufficiency:* creatinine > 3.0 mg/dL for 24 hours or the need for renal replacement therapy (RRTx).
2. *Hepatic insufficiency:* SGOT and SGPT > 120 IU and/or total serum bilirubin > 2.4 mg/dL for 48 hours. Because of the need for ECLS-associated transfusion and its subsequent contribution to hyperbilirubinemia, serum bilirubin > 5.0 defined hepatic insufficiency in ECLS patients.
3. *Cardiac insufficiency:* cardiac index < 2.0 L/min/m^2 or any inotropic support ≥ 5.0 μg/kg/min.
4. *Central nervous system (CNS) dysfunction:* traumatic brain injury, CT evidence of intracranial hemorrhage, documented seizure activity, or coma not attributable to sedation or paralytics.
5. *Sepsis:* Because of artificial normalization of physiological parameters and altered immunoregulatory functions imposed by the conduct of ECLS, documentation of sepsis by standard systemic inflammatory response syndrome (SIRS) criteria was not possible and the presence of positive blood cultures was used as a gauge for sepsis, realizing that this may unavoidably lack sensitivity.

Survival was defined as discharge from the hospital, and respiratory recovery as discontinuation of mechanical ventilation, regardless of survival.

Consent for ECLS and its related procedures was obtained for candidates at the time of transfer.

Patient Management

Maximizing systemic oxygen delivery in relation to oxygen requirement was the mainstay of management.[41] Fio_2, PEEP, PCIRV, hematocrit, cardiac output, sedation, and paralytics were titrated based on this concept. All patients received an Oximetrix pulmonary artery catheter (Abbott Laboratories, Chicago, IL), allowing continuous attention to the oxygen delivery:consumption ratio (DO_2/VO_2). Inotropes were administered to maintain cardiac index ≥ 3 L/m^2/min and blood was transfused to maintain hematocrit > 40%. After maximizing DO_2, if DO_2/VO_2 remained less than approximately 4:1 as determined by SvO_2, sedatives and/or paralytics were administered to decrease VO_2. This goal was based on our own laboratory studies[42-44] and did not change during the study period.[45] Airways were assessed and cleaned by fiberoptic bronchoscopy when required. Early enteral nutrition was formulated to meet or surpass by 10% to 15% the resting energy expenditure (REE) as measured by indirect calorimetry. When unable to enterically provide full support, the parenteral route was used.

In all patients, end-inspiratory plateau pressure (EIP) was kept below 40 cm H_2O with time-cycled pressure-limited mechanical ventilators using inspiratory:expiratory ratios of 1 to 3:1 (pressure-controlled inverse ratio ventilation, PCIRV). This technique often resulted in hypercarbia. As has been previously demonstrated,[30,31,46,47] in the absence of concomitant metabolic acidosis, head trauma, or cardiac ischemia, this was well tolerated and we allowed $Paco_2$ to rise as high as 80 mm Hg and arterial pH to decrease as low as 7.0 without administering buffering solutions. Over a range of 3 to 20 cm H_2O, PEEP was titrated at least daily to levels which maximized Svo_2. Fio_2 was decreased from 1.0 as tolerated to maintain SaO_2 > 85%.

In most patients, prone positioning resulted in improved oxygenation, permitting the decrease of Fio_2 to 0.6 or less. If patients improved with repositioning, this was repeated every 6 to 8 hours. Diuresis to dry weight was aggressively pursued. If diuretics were unsuccessful, continuous veno-venous hemofiltration (CVVH) or slow continuous ultrafiltration (SCUF) were used.

The decision to institute ECLS was based on initial physiological status and response to the treatment regimen described previously. ECLS was used immediately for patients who could not be transported from the referral institution because of either hemodynamic instability or inability to oxygenate on the transport ventilator. Such patients were placed on ECLS in the referral hospital and transported on bypass. Otherwise, all patients were managed with the techniques described above. ECLS was subsequently used for patients who failed to improve (Fio_2 1.0, P/F < 100, shunt > 30%, hemodynamic instability) on this regimen. Additionally, six patients with hypercarbic respiratory failure secondary to airway occlusion or status asthmaticus were supported with ECLS.

After initiating ECLS, Fio_2 was reduced to 0.5 or less, and EIP limited to 35 cm H_2O. Respiratory rate was decreased to 6 breaths per minute and I:E ratio was maintained at 2 to 4:1. All other aspects of patient care, including prone positioning, were

used during ECLS. Detailed description of ECLS management is reported elsewhere.[35-39]

Statistical Methods

The SAS (SAS Institute, Cary, NC) statistical analysis software was used to analyze data and derive statistical relationships. Dichotomous variables were examined via chi-square analysis. Student's *t* tests were applied to continuous variables. Stepwise multiple logistic regression modeling identified significant factors predictive of mortality. Significance was interpreted as $P < .05$. Data are presented as mean ± SEM.

RESULTS

Between 1990 and 1996, we managed 141 ECLS candidates between the ages of 18 and 63 (35 ± 1) years. Seventy-five patients (53%) were female. Patient distribution is represented in Figure 1. Seventy-five patients were placed on ECLS either in the referral hospital before transfer, or within 12 hours of arrival ("early ECLS" patients). Sixty-six patients were initially managed with non-ECLS strategies; 25 of these did not improve and were placed on ECLS 12 or more hours after arrival ("late ECLS" patients). This resulted in a total of 100 patients treated with ECLS.[39] Forty-one patients improved and were managed without ECLS for the duration of their treatment ("non-ECLS" patients). These 41 patients are characterized in Table 1. There was no significant difference in age or sex between any of the treatment groups.

The initial P/F ratio for 135 patients treated for hypoxic respiratory failure was 67 ± 3 (median = 66; range, 32 to 226). Initial P/F ratio for 6 patients with hypercarbic respiratory failure was 266 ± 66 (median = 250; range, 51 to 480; $Paco_2$ = 89 ± 32 mm Hg). All patients with hypercarbic respiratory failure were treated with ECLS. In the hypoxemic group, both the initial P/F ratio and Pao_2 were higher in non-ECLS patients compared with the ECLS group [P/F: ECLS = 56 ± 2 (median = 54; range, 32 to 128), non-ECLS = 92 ± 6 (median = 77; range, 52 to 226), $P < .001$; Pao_2: ECLs = 55 ± 2 (median = 53; range, 32 to 128), non-ECLS = 82 ± 5 (median = 66; range, 49 to 226), $P < .05$]. In the non-ECLS group, P/F ratio increased in all patients after treatment such that all P/F ratios were greater than 100 and no patient remained an ECLS candidate. No difference in oxygenation measurements was observed between the early and late ECLS patients.

Durations of ventilation, ICU days, and total hospitalization for all patients are listed in Table 2. There were no significant differences in these durations between the various treatment groups.

ECLS patients remained on bypass a mean of 270 ± 25 hours (median = 175; range, 14 to 1,246). There was no difference in time on ECLS between the early and late groups (early hours = 257 ± 28, late = 307 ± 53). Sixty-five patients were placed on veno-venous (VV) bypass, 12 on veno-arterial (VA) bypass, and 23 underwent at least one conversion from VV to VA.

Primary diagnoses are listed in Table 3. A greater percentage of patients in the non-ECLS group carried a diagnosis of ARDS ($P < .002$). There were more viral pneumonias in the ECLS group ($P < .003$). Sample size in the remaining groups was too small for further comparison. By logistic

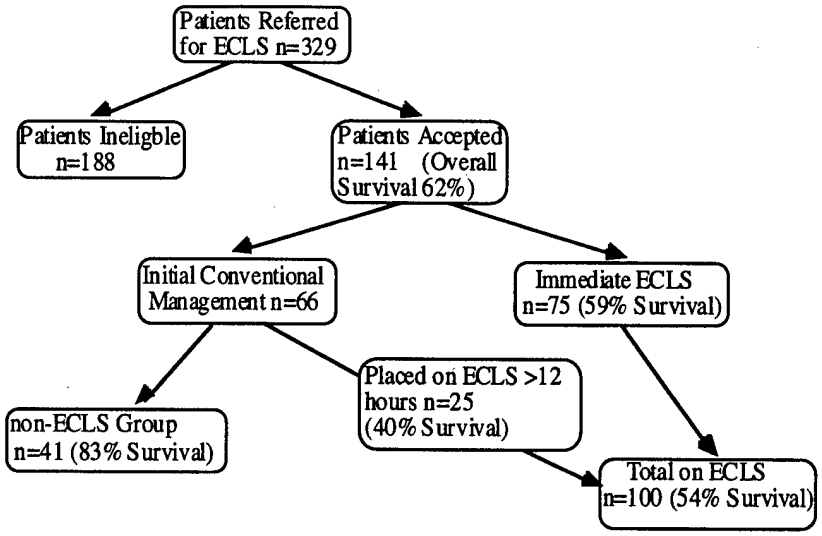


Fig 1. University of Michigan respiratory failure experience 1990 to 1996. Includes all patients referred for the consideration of ECLS.

Table 1. Characteristics of the 41 Patients Who Improved and Did Not Meet Criteria for ECLS*

Patient No.	Age	Sex	Diagnosis	Related Diagnoses	Pao_2	P/F Ratio	Respiratory Recovery	Survival	Cause of Death
1	22	F	ARDS	Wegener's, pancreatitis	54	68	Y	Y	
2	30	M	Viral	Varicella	77	77	Y	Y	
3	23	M	ARDS	Trauma	70	70	Y	Y	
4	49	F	ARDS	Postop, TAH	226	226†	Y	Y	
5	53	M	Bact	Staphylococcus, BPF, empyema	110	110	Y	Y	
6	37	M	ARDS	Pancreatitis	68	68	Y	Y	
7	21	M	ARDS	Postop, trauma	148	148†	Y	Y	
8	32	M	ARDS	Postop, trauma, ruptured aorta	76	127	Y	Y	
9	18	F	ARDS	Postop, trauma	64	64	Y	Y	
10	52	M	ARDS	Postop, SBO	59	59	Y	Y	
11	31	F	ARDS	Postpartum HELLP	65	68	N	N	MSOF/DIC
12	48	F	ARDS	Postop, splenectomy	134	134†	Y	Y	
13	31	F	ARDS	Placental abruption	82	82	Y	Y	
14	39	F	ARDS	Postop, trauma	97	97	Y	Y	
15	33	F	ARDS	Postop, CBD injury S/P lap chole	54	54	Y	Y	
16	31	M	ARDS	Postop, SB resection, pancreatitis	68	68	N	N	MSOF/Sepsis/DKA
17	38	M	Bact	Legionella	75	75	Y	Y	
18	41	M	ARDS	Trauma	77	77	N	N	MSOF
19	19	M	ARDS	Postop, trauma	67	67	Y	Y	
20	48	F	ARDS	Postop, TAH, ventral hernia	92	153†	Y	Y	
21	50	F	Asp	Acetaminophen overdose	52	52	Y	Y	
22	32	M	ARDS	Postop, trauma	88	88	Y	Y	
23	53	F	ARDS	Postop, laminectomy, pancreatitis	64	85	Y	Y	
24	33	F	Bact	Pneumococcus	114	114	N	N	Sepsis
25	29	F	Bact	Pneumococcus	58	58	Y	Y	
26	25	F	ARDS	Postop, trauma, ruptured aorta	53	53	Y	Y	
27	33	F	ARDS	Postop, CBD injury	70	70	Y	Y	
28	40	F	ARDS	Cardiac depression, dehydration	67	134†	Y	Y	
29	60	M	Bact	Pseudomonas	138	197†	Y	N	MSOF/UGI bleed
30	42	F	ARDS	Postop, left tubo-ovarian abscess	68	136†	Y	Y	
31	57	M	ARDS	Postop, ruptured AAA	68	68	Y	Y	
32	8	F	ARDS	Septic abortion	49	70	Y	Y	
33	18	F	ARDS	Asthma	58	83	Y	Y	
34	34	M	ARDS	Trauma	65	65	Y	Y	
35	50	M	Bact	Pneumococcus	78	78	N	N	Sepsis
36	18	M	ARDS	Postop, trauma	92	92	Y	Y	
37	32	F	Viral		68	68	Y	Y	
38	35	M	Bact	Community acquired	62	62	Y	Y	
39	57	M	ARDS	Trauma, submersion	93	93	N	N	Respiratory failure
40	41	M	Asp		123	123	Y	Y	
41	28	M	ARDS	Trauma	65	93	Y	Y	

*A comprehensive description of all patients treated with ECLS can be found in a previous publication.[39]
†Between the initial consultation and eventual transfer, 7 patients improved to P/F ratios >130.

regression, diagnosis was not predictive of survival (Table 4).

The presence, type, and survival related to individual organ dysfunction are listed in Table 5. More patients in the ECLS group suffered from renal insufficiency ($P = .027$) and required renal replacement therapy ($P = .011$) when compared with the non-ECLS group. There was no difference in the frequency of positive blood cultures, CNS, cardiac, or hepatic insufficiency between the ECLS and non-ECLS groups. The mean number of organ systems meeting criteria for insufficiency was 2 ± 1 in both the ECLS and non-ECLS groups. Modifying the definition of hepatic insufficiency in the ECLS patients did not alter this.

Sixty-seven percent of patients had a respiratory recovery. Overall survival was 62%. Survival was 83% in the non-ECLS group and 54% in the ECLS group ($P = .001$). Survival was greater in the early ECLS group (59%) compared with the late ECLS group (40%, $P < .04$). Six of the seven deaths in the non-ECLS group were non-respiratory (Table

Table 2. Duration of Ventilation Before Transfer, Total Duration of Ventilation, University of Michigan ICU Stay, and University of Michigan Hospitalization by Treatment Group

Duration	All Patients Days (range)	Non-ECLS	ECLS	Early	Late
Pre-transfer/ECLS*	3 ± 1 (0-25)	3 ± 1 (0-25)	4 ± 0 (0-12)	3 ± 0 (0-12)	5 ± 1 (0.5-11)
Total ventilation†	25 ± 2 (1-116)	24 ± 3 (1-91)	25 ± 2 (2-116)	24 ± 2 (2-85)	29 ± 5 (8-116)
ICU (U of M)	24 ± 2 (1-111)	23 ± 3 (1-76)	24 ± 2 (21-111)	24 ± 2 (1-94)	26 ± 5 (1-111)
Hospital (U of M)	34 ± 3 (1-202)	31 ± 4 (1-146)	36 ± 4 (1-202)	35 ± 4 (1-202)	39 ± 7 (4-147)

No statistical difference between groups was demonstrated for any specific duration.

*Includes the total number of days either before transfer for the non-ECLS patients or before ECLS for those who received extracorporeal support.

†Includes the entire duration of mechanical ventilation, both before and after transfer.

1). One patient, a victim of drowning, died shortly after admission to the hospital while evaluation for ECLS was ongoing. Of the seven patients, five had improved but remained on a ventilator, and one died many days after weaning from mechanical ventilation after recovering fully from respiratory failure. A detailed description of the cause of death in those patients treated with ECLS is reviewed elsewhere.[39]

To assess the contribution of initial respiratory failure severity to survival, patients were grouped by P/F ratio. Survival was statistically different only in the 41 patients with initial P/F ratios less than 50 ($P < .003$). Survival of these patients was 32%, and all were placed on ECLS. Survival of the 94 other hypoxic patients with initial P/F ratios > 50 was 73%.

A decline in survival was observed with increasing numbers of dysfunctional organs (Fig 2). When examined by multiple logistic regression, only insufficiency in four or more organs was predictive of mortality (using both definitions for hepatic failure). Only one patient sustained insufficiency in all five organs, and this was a survivor. Individually, renal failure ($P < .001$), the need for renal replacement therapy ($P < .001$), and cardiac failure ($P < .05$) were associated with decreased survival, although when applied as a group to multiple logistic regression, significance was lost. There was no difference in survival when the presence of positive blood cultures, hepatic insufficiency, or CNS insufficiency were compared.

When the significant univariate predictors of mortality were applied as a group to multiple logistic regression analysis, the need for ECLS, advanced age, four or more insufficient organs, and the duration of mechanical ventilation before transfer remained as significant predictors of mortality (Tables 6 and 7, Fig 2 through 4).

Table 3. Primary Diagnoses

Diagnosis	Non-ECLS n	ECLS n	Total n (%)	*P* Value*
ARDS†	30	43	73 (52%)	0.003
Bacterial pneumonia	7	25	32 (23%)	NS
Viral pneumonia	2	21	23 (16%)	0.019
Airway obstruction	—	6	6 (04%)	‡
Aspiration	2	2	4 (03%)	‡
Other	—	3	3 (02%)	‡
Total	41	100	141	

*When ECLS and non-ECLS are compared by Chi-square analysis.

†Includes all respiratory failure not attributable to other categories ("secondary ARDS").

‡Groups too small to characterize.

DISCUSSION

Since Ashbaugh et al[2] first reported mortality in 12 patients with refractory respiratory failure in 1967, evidence has implicated our therapy of this syndrome as potentially promoting rather than reducing lung dysfunction.[17] The traditional view of ARDS as a diffuse and homogeneous condition is changing.[48,49] Although standard anteroposterior chest films may suggest diffuse bilateral air space disease, CT scans reveal very inhomogeneous dependent lung consolidation with relative preservation of anterior segments. Specific compliances of these segments reveal normal pressure-volume

Table 4. Survival by Diagnosis

Diagnosis	Non-ECLS	ECLS	Overall
ARDS	26/30 (87%)	22/43 (51%)	48/73 (66%)
Bacterial pneumonia	4/7 (57%)	12/25 (48%)	16/32 (50%)
Viral pneumonia	2/2 (100%)	13/21 (62%)	15/23 (65%)
Airway obstruction	—	5/6 (75%)	5/6 (83%)
Aspiration	2/2 (100%)	1/2 (50%)	3/4 (75%)
Other	—	1/3 (33%)	1/3 (33%)
Total	34/41 (41%)	54/100 (54%)	88/141 (62%)

Diagnosis, overall or within either the ECLS or non-ECLS groups, was not predictive of survival by logistic regression.

Table 5. Organ Insufficiency

Organ	Non-ECLS Number (%)	ECLS Number (%)	Total Number (%)	% Survival*
Respiratory	All	All	All	62
Renal	11/41 (27%)	47/100 (47%)	58/141 (41%)	41
Renal replacement	8/41 (20%)	42/100 (42%)	50/141 (35%)	40
Hepatic	17/41 (41%)	41/100 (41%)	58/141 (41%)	53
$Hepatic_{ECLS}$†	N/A	4/100 (4%)	45/141 (32%)	67
Cardiac	9/41 (22%)	23/100 (23%)	32/141 (23%)	47
CNS	8/41 (20%)	13/100 (13%)	21/141 (15%)	52

The percentage of patients in each treatment group with insufficiency of a particular organ, and the survival rate related to dysfunction of that specific organ is listed.

*By multiple logistic regression, the presence of individual organ insufficiency was not predictive of survival.

†Calculated using the modified criteria for hepatic insufficiency in ECLS patients.

relationships, suggesting that the failing lung is small, rather than stiff.[48-53] Administering standard gas tidal volumes to injured lungs may result in overdistention of these relatively normal anterior units. This so-called "volutrauma" could result in insult to the alveolar-capillary membrane with subsequent accumulation of intraalevolar fibrin, fluid, and inflammatory exudate within these remaining healthy regions.[54]

There is a growing body of evidence which validates this concept of ventilator-induced lung

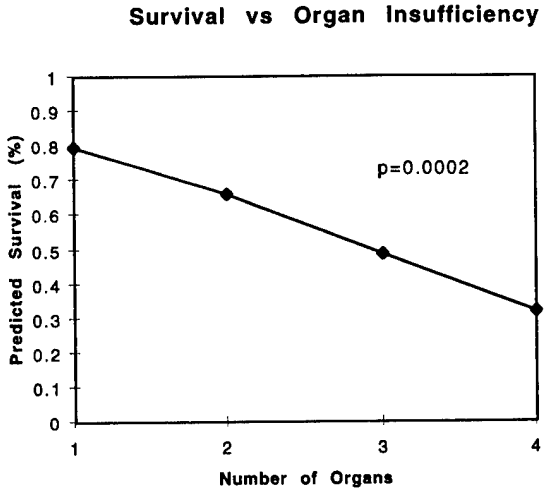


Fig 2. Survival by number of insufficient organs using univariate logistic regression. A significant stepwise decrement in survival was observed with an increasing number of dysfunctional organs, although only the presence of four or more insufficient organs predicted mortality by multiple regression ($P \leq .002$). Calculated using the univariate regression equation: $1/1+-[(2.0629-0.7030(\geq 4 \text{ more organs})]$

Table 6. Individual Predictors of Mortality When Presence Is Compared Between Survivors and Nonsurvivors by Chi-Square Analysis

Significant Variable	*P* Value
Age	.023
Need for ECLS	.001
Initial Pao_2	.003
P/F ratio	.018
Pre-protocol vent days	.009
Number of insufficient organs	.001

These variables were associated with decreased survival when the mean values of survivors were compared with nonsurvivors using chi-square analysis.

injury,[14-18] and targeted techniques have been designed in an effort to reduce it. Pressure-controlled ventilation has been proposed to avoid alveolar overdistention whereas extracorporeal support may provide both rest and gas exchange for the failing lung. It has been suggested that inverse-ratio ventilation, PEEP, and prone positioning promote recruitment of susceptible alveoli while avoiding cyclical collapse and re-expansion of surfactant-deficient lung units with low closing pressures, thereby further reducing lung injury.[13,19,50,51,55,56]

We have incorporated these concepts in a physiological lung protective strategy. We call this "physiologic" because the goals of treatment are to assure physiologically normal hematocrit (>40%), fluid balance (dry weight), nutrition, and oxygen delivery:consumption ratio (>4:1, $Svo_2 > 75\%$); we call this "lung protective" because our goal is to limit Fio_2 and prevent overdistention by limiting inflation pressure while recruiting alveoli by position rather than pressure.

Evaluation of this approach requires a prospective clinical study to allow comparison with other methods of management. To prepare for such a study, we can compare our results to others reported in the literature, but identification of matching patient cohorts is challenging. Our patients were selected for a reasonable chance of recovery if

Table 7. Predictors of Mortality by Logistic Regression Modeling

Variable	*P* Value	Odds Ratio
Age	.0105	0.958
Number of ventilated days before protocol	.0196	0.857
Need for ECLS	.0006	0.150
Four or greater insufficient organs	.0022	0.123

These variables remained significant after controlling for covariance by stepwise multiple logistic regression modeling.

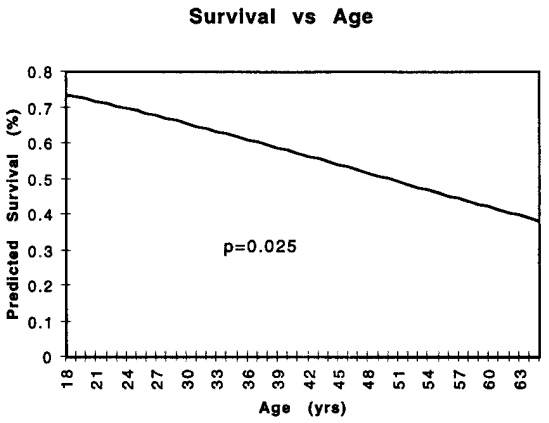


Fig 3. Survival by age using univariate logistic regression modeling. Significance remained with multivariate regression ($P = .025$). Calculated using the univariate regression equation: $1/1+e^{-[1.6075-00321(age)]}$

they survived their acute respiratory failure; patients with an age > 60 years, a prolonged course of mechanical ventilation, and incurable disease were excluded, but these types of patients can be found in other reports. All of our hypoxemic patients had the syndrome of ARDS and a diversity of primary diseases; some reports of ARDS exclude pneumonia, autoimmune disease, or pulmonary hemorrhage. Our patients were selected to have a high mortality risk based on low P/F ratio *despite and after* intervention. Most reports of severe ARDS characterize the severity of disease based on worst case P/F ratio *before* optimal treatment. Additionally, half of our patients immediately met ECLS criteria and were placed on ECLS before initiating our strategies. There are few reports in the

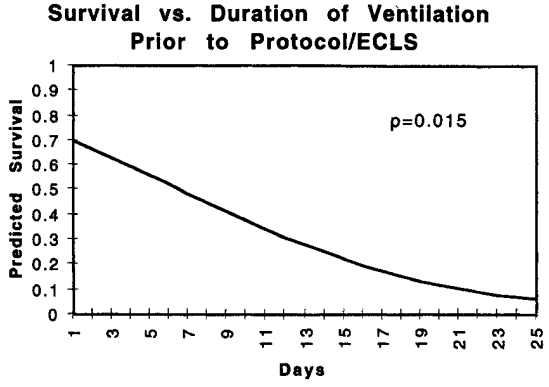


Fig 4. Survival by number of pretransfer ventilated days using univariate logistic regression. Significance remained with multivariate regression ($P = .015$). Calculated using the univariate regression equation: $1/1+e^{-[0.9895-0.1497(\#\ pre\text{-}vent\ days)]}$

literature comparable to this group. Given these limitations, it is still worthwhile to compare our result of an overall 62% survival to series utilizing other types of management.

A very similar protocol including ECLS has been followed in three centers. Lewandowski et al[5] from Rudolph Virchow Hospital in Berlin reported 124 patients referred for ECLS between 1989 and 1995.[57] Of these patients, 4 had contraindications to ECMO (none survived), 69 improved with their ventilator management protocol (96% survival), and 51 did not and were subsequently treated with ECLS (57% survival). The overall survival in this series was 77%. Guinard et al[58] from Hopital Universitaire Lariboisiere in Paris recently reported 36 patients referred for ECLS. Nineteen of these patients improved with optimal ventilator management (79% survival), and 17 did not (12% survival). Of the latter group, $ECCO_2R$ was used for 8 patients with 2 survivors. The overall survival in this series was 52%. Manert et al[59] from Munich used a very similar protocol, with the addition of low-dose steroids, to treat 66 patients with severe respiratory failure. Thirty-seven patients improved with optimal ventilator management and 2 had contraindications to ECLS (for 39 total patients in the conventional non-ECLS group, 77% survival); 23 did not improve, and 21 of these were treated with ECLS (17 survivors, 81% survival). Eleven patients met "fast entry criteria" for ECMO (100% survival) and 10 "slow entry criteria" (60% survival). The overall survival for this series was 78%.

Other centers reporting survival results with *ECLS only* include Pesenti et al[60] (87 cases, 46% survival), Lennartz[61] (182 cases, 58% survival), Brunet et al[62] (23 cases, 50% survival), Peek and Firmin[63] (50 cases, 66% survival), Bindslev et al[64] (14 cases, 43% survival), and Macha et al[65] (33 cases, 39% survival). In all these reports, severe ARDS was identified by some version of the entry criteria originally designed for the NIH sponsored multicenter ECMO trial in 1975 to 1979, wherein the mortality for both the ECMO and control groups was 90%.[40] What is the mortality for a similar group of patients today?

Two randomized prospective studies of ECLS have been performed in the past and neither demonstrated benefit attributable to this technique. In 1979, a multicenter NIH sponsored trial examining ECLS in severe respiratory failure was conducted.[40] In that study, the conduct of ECLS was

very different from that currently used at our institution. In addition to frequent bleeding complications resulting from excessive anticoagulation, mechanical ventilation was not reduced during bypass, eliminating any anticoagulation, mechanical ventilation was not reduced during bypass, eliminating any theoretical benefit provided by lung rest. Between 1991 and 1993, Morris et al[29] conducted a trial of protocol-driven ventilation versus PCIRV and $ECCO_2R$ in 40 patients with ARDS. Survival was 42% in the control group and 33% in the $ECCO_2R$ group, for an overall survival of 38%. No difference in the two groups was identified. In that study[29] (and in the study of Guinard et al[58]), $ECCO_2R$ was used with low blood flow for CO_2 removal, relying on the native lung for oxygenation. In our experience, almost all patients require major oxygenation support with high blood flow in addition to CO_2 clearance.[39] For these reasons, we believe that the current conduct of ECLS, and therefore our results, cannot be compared with these previous trials.

A more representative report of worldwide experience with acute respiratory failure is found in the report by Vasilyev et al.[66] That study, designed as background for the intravenous oxygenator (IVOX) clinical trials, described the severity and outcome for respiratory failure in 1,426 patients in 25 centers in North America and Europe. Overall survival was 56%. However, a subset of patients with severe respiratory failure (defined as a P/F ratio < 100, and a Murray lung injury score > 3.5) had a survival of 18%. Krafft et al,[11] in a meta-analysis of outcome in respiratory failure, identified 101 reports of outcome in 3,264 patients with respiratory failure. Mean P/F ratio was 118 (worst value), and treatment included varied strategies including ECLS. Mean survival rate for all series was 47%.[11]

Excellent results in severe respiratory failure have been reported by Hickling et al,[30,31] who described 74% and 84% survivals in two groups of patients with severe respiratory failure treated with a protocol including pressure limitation and permissive hypercapnia. These patients were characterized by the worst case blood gases during the first 24 hours of treatment. Amato et al[19] reported an overall survival of 57% in 28 patients with ARDS. In this series, a survival of 67% using low PIP (<40 cm H_2O) and high PEEP (above the lower inflection point of the pressure-volume curve), was not statistically different from a 46% survival using conventional ventilation, although improved lung function and earlier weaning were noted in the experimental group.

We believe that almost all of the 75 patients placed on ECLS within 12 hours of transfer would have died, because all went through a phase of minimal native gas exchange. Despite this, 59% survived to discharge. Of the 66 patients treated with the full physiological and lung protective strategy, 41 improved to the point where ECLS criteria were no longer met. Eighty-three percent (34 of 41) of these patients ultimately survived, and 6 of the 7 deaths in that group were due to nonrespiratory causes. Of the 25 patients who eventually met ECLS criteria and were subsequently treated with ECLS, 40% recovered and survived. We have previously reported that prolonged time on the ventilator before ECLS is associated with poor outcome,[67] and these patients may have fared better had they proceeded to ECLS directly on referral.

The number of ventilated and ICU days were not different between those patients who improved on the initial protocol and those who required ECLS, suggesting that the requirement for ECLS may be a marker for disease severity, but does not in itself impart or predict a longer duration of acute illness. Those patients who survived, and therefore demonstrated reversible lung disease, appeared to require a finite duration of supported ventilation and intensive care regardless of the need for ECLS.

In accordance with other published data, the development of multiple system organ dysfunction (MSOF) in our series was a strong predictor of mortality.[5,8,66,68] The presence of respiratory failure in isolation was associated with a survival of 83%. A stepwise decrement in survival was observed as the number of dysfunctional organs increased, although only severe organ dysfunction (4 or more) was predictive of mortality by regression modeling.

Accurate characterization of this patient population is challenging. Readily available validated scoring systems designed to describe and qualify illness severity are difficult to apply to the ECLS population. Many of the physiological variables measured by the APACHE II system are altered by the conduct of ECLS and may result in misleading calculations.[69] Our definition of sepsis is necessarily altered for similar reasons, such that only those patients with positive blood cultures were catego-

rized as having sepsis. This may account for the failure of our study to support previous series which identified sepsis as a strong predictor of mortality.[5,8,9] Our definition of organ failure differs from other published reports in some aspects,[4,5,9,28,30] and this may again make generalization to other cohorts difficult.

In conclusion, severe respiratory failure regardless of cause carries a significant risk of mortality. In our experience, a strategy that emphasizes lung inflation, potentially minimizes barotrauma, and limits exposure to high levels of Fio_2, is associated with high rates of survival. We believe that when conventional methods of ventilation fail to provide adequate support at low airway pressures and Fio_2 levels, the early implementation of ECLS may provide pulmonary protection, and should be used as an adjunctive mode of respiratory support. Advanced age, the duration of mechanical ventilation, multiple organ dysfunction, and severe gas exchange abnormalities manifested by the need for ECLS all predict increased mortality. Based on comparison of this series to others reported in the literature, and in the face of a modified approach to the conduct of ECLS, the stage is set for a prospective comparative study involving many centers, testing this physiological lung protective approach against other methods of management.

ACKNOWLEDGMENTS

Many individuals from the University of Michigan Medical Center have contributed to the care of these challenging patients. The authors thank the dedicated staff of the Surgical Intensive Care Unit, the Survival Flight transport team, the medical records department, and the members of the Metabolic Laboratory/Critical Care Diagnostic Service for their unyielding support. Particular thanks go to the very capable and caring members of the University of Michigan ECLS team.

REFERENCES

1. Bernard GR, Artigas A, Brigham KL, et al: The american-european consensus conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818-824, 1994

2. Ashbaugh D, Bigelow D, Petty T, et al: Acute respiratory distress in adults. Lancet 2:319-323, 1967

3. Fowler A, Hamman R, Good J, et al: Adult respiratory distress syndrome: Risk with common predispositions. Ann Intern Med 98:593-597, 1983

4. Bell RC, Coalson J, Smith J, et al: Multiple system organ failure and infection in adult respiratory distress syndrome. Ann Intern Med 99:293-298, 1983

5. Suchyta MR, Clemmer TP, Orme JF, et al: Increased survival of ARDS patients with severe hypoxemia (ECMO criteria). Chest 99:951-955, 1991

6. Bartlett RH, Morris AH, Fairley HB, et al: A prospective study of acute hypoxic respiratory failure. Chest 89:684-689, 1986

7. Milberg JA, Davis DR, Steinberg KP, et al: Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. JAMA 273:306-309, 1995

8. Sloane PJ, Gee MH, Gottlieb JE, et al: A multicenter registry of patients with acute respiratory distress syndrome. Am Rev Respir Dis 146:419-426, 1992

9. Doyle RL, Szaflarski N, Modin GW, et al: Identification of patients with acute lung injury: Predictors of mortality. Am J Respir Crit Care Med 152:1818-1824, 1995

10. Stauffer JL, Fayter NA, Graves B, et al: Survival following mechanical ventilation for acute respiratory failure in adult men. Chest 104:1222-1229, 1993

11. Krafft P, Fridrich P, Pernerstorfer T, et al: The acute respiratory distress syndrome: Definitions, severity and clinical outcome. Intensive Care Med 22:519-529, 1996

12. Mathay MA: The adult respiratory distress syndrome: New insights into diagnosis, pathophysiology, and treatment. West J Med 150:187-194, 1989

13. Gattinoni L, Pesenti A, Caspani M, et al: The role of static lung compliance in the management of severe ARDS unresponsive to conventional treatment. Intensive Care Med 10:121-126, 1984

Dreyfuss D, Basset G, Soler P, et al: Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 137:1159-1164, 1985

15. Parker JC, Townsley MI, Rippe B, et al: Increased microvascular permeability in dog lungs due to high peak airway pressures. J Appl Physiol 57:1809-1816, 1984

16. Lachmann B, Jonson B, Lindroth M, et al: Modes of artificial ventilation in severe respiratory distress syndrome: Lung function and morphology in rabbits after wash-out of alveolar surfactant. Crit Care Med 10:724-732, 1982

Kolobow T, Gattinoni L, Moretti MP, et al: Mechanical ventilation at high airway pressures: Is it safe? Int J Artif Organs 7:315-316, 1984

18. Kolobow T, Moretti M, Fumagalli R, et al: Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. Am Rev Respir Dis 135:312-315, 1987

19. Amato MBP, Barbas CSV, Medeiros DM, et al: Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 152:1835-1846, 1995

20. Greenfield LJ, Ebert PA, Benson DW: Effect of positive pressure ventilation on surface tension properties of lung extracts. Anesthesiology 25:312-316, 1964

21. Kolobow T: Acute respiratory failure: on how to injure healthy lungs (and prevent sick lungs from recovering) Trans Am Soc Artif Intern Organs 34:31-34, 1988

22. Hickling K: Ventilatory management of ARDS: Can it affect outcome? Intensive Care Med 16:219-226, 1990

23. Parker J, Hernandez LA, Peevy KJ: Mechanisms of ventilator-induced lung injury. Crit Care Med 21:131-141, 1993

24. Lain DC, DiBenedetto R, Morris S, et al: Pressure control inverse ratio ventilation as a method to reduce peak inspiratory pressure and provide adequate ventilation and oxygenation. Chest 95:1081-1088, 1989

25. DiRusso SM, Nelson LD, Safcsak K, et al: Survival in patients with severe respiratory distress syndrome treated with high-level positive end-expiratory pressure. Crit Care Med 23:1485-1496, 1995

26. Pesenti A, Marcolin R, Prato P, et al: Mean airway pressure vs. positive end-expiratory pressure during mechanical ventilation. Crit Care Med 13:34-37, 1985

27. Marcy T, Marini J: Inverse ratio ventilation in ARDS: Rationale and implementation. Chest 100:494-504, 1991

28. Gattinoni L, Pesenti A, Mascheroni D, et al: Low frequency positive pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 256:881-886, 1986

29. Morris AH, Wallace CJ, Menlove RL, et al: Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 149:295-305, 1994

30. Hickling KG, Walsh J, Henderson S, et al: Low mortality rate in adult respiratory distress syndrome using low-volume pressure-limited ventilation with permissive hypercapnia: A prospective study. Crit Care Med 22:10:1568-1578, 1994

31. Hickling KG, Henderson SJ, Jackson R: Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372-377, 1990

32. Rappaport SH, Shpiner R, Yoshihar G, et al: Randomized, prospective trial of pressure-limited versus volume-controlled ventilation in severe respiratory failure. Crit Care Med 22:22-32, 1994

33. Shanley CJ, Hirschl RB, Schumaker RE, et al: Extracorporeal life support for neonatal respiratory failure: A 20-year experience. Ann Surg 220:269-282, 1994

34. Moler FW, Custer JR, Bartlett RH, et al: Extracorporeal life support for pediatric respiratory failure. Crit Care Med 20:1112-1118, 1992

35. Anderson HL, Delius RE, Sinard JM, et al: Early experience with adult ECMO in the modern era. Ann Thorac Surg 53:553-563, 1992

36. Anderson H III, Steimle C, Shapiro M, et al: Extracorporeal life support for adult cardiorespiratory failure. Surgery 114:161-172, 1993

37. Shapiro MB, Kleaveland AC, Bartlett RH: Extracorporeal life support for status asthmaticus. Chest 103:1651-1654, 1993

38. Pranikoff T, Hirschl RB, Steimle CN, et al: Efficacy of extracorporeal life support in the setting of adult cardiorespiratory failure. ASAIO J 40:M339-M343, 1994

39. Kolla S, Awad S, Rich P, et al: Extracorporeal life support for 100 adult patients with severe respiratory failure. Presented at the 117th annual meeting of the American Surgical Association, April 17-19, 1997, Quebec City, Quebec, Canada. Ann Surg 226:544-566, 1997

40. Zapol WM, Snider MT, Hill JD, et al: Extracorporeal membrane oxygenation in severe acute respiratory failure. JAMA 242:2193-2196, 1979

41. Bartlett RH: Critical Care Physiology. Boston, Little Brown, 1995

42. Hirschl RB, Heiss KF, Cilley RE, et al: Oxygen kinetics in experimental sepsis. Surgery 112:37-44, 1992

43. Cilley RE, Scharenberg AM, Bongiorno PF, et al: Low oxygen delivery produced by anemia, hypoxia, and low cardiac output. J Surg Res 51:425-433, 1991

44. Sinard JM, Hultquist K, Bartlett RH: Effects of moderate hypothermia on O2 consumption at various O2 deliveries in a sheep model. J Appl Physiol 72:2428-2434, 1992

45. Bartlett RH, Anderson HL: Multiorgan failure, in Zelenock G, et al (eds): Clinical Ischemic Syndromes: Mechanisms and Consequences of Tissue Injury. St. Louis, Mosby 1989, pp 565-572

46. Thorens JB, Jolliet P, Ritz M, et al: Effects of permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. Intensive Care Med 22:182-191, 1996

47. Bidani A, Tzouanakis AE, Cardenas VJ, et al: Permissive hypercapnia in acute respiratory failure. JAMA 272:957-962, 1994

48. Pelosi P, D'Andrea L, Vitale G, et al: Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med 149:8-13, 1994

49. Gattinoni L, Pesenti A, Avali R, et al: Pressure-volume curve of total respiratory system in acute respiratory failure. Am Rev Respir Dis 136:730-736, 1987

50. Gattinoni L, Pelosi P, Vitale G, et al: Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. Anesthesiology 74:15-23, 1991

51. Gattinoni L, Pelosi P, Crotti S, et al: Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807-1814, 1995

52. Gattinoni L, D'Andrea L, Pelosi P, et al: Regional effects and mechanisms of positive end-expiratory pressure in early adult respiratory distress syndrome. JAMA 269:2122-2127, 1993

53. Gattinoni L, Pesenti A, Bombino M, et al: Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 69:824-832, 1988

54. Tsuno K, Miura K, Takeya M, et al: Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis 143:1115-1120, 1991

55. Sandhar BK, Niblett DJ, Ariras EP, et al: Effects of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. Intensive Care Med 14:538-546, 1988

56. McCulloch PR, Forkert PG, Froese AB: Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. Am Rev Respir Dis 137:1185-1192, 1988

57. Lewandowski K, Lewandowski M, Pappert D, et al: Outcome and follow-up of adults following extracorporeal life support, in Zwischenberger J, Bartlett RH (eds.): ECMO: Extracorporeal Cardiopulmonary Support in Critical Care. Extracorporeal Life Support Organization, Ann Arbor, MI, 1995

58. Guinard N, Beloucif S, Gatecel C, et al: Interest of a therapeutic optimization strategy in severe ARDS. Chest 111: 1000-1007, 1997

59. Manert W, Haller M, Briegel J, et al: Venovenous extracorporeal membrane oxygenation (ECMO) with a heparin-lock bypass system: An effective addition in the treatment of acute respiratory failure. Anaesthetist 45:437-448, 1996

60. Pesenti A, Gattinoni L, Bombino M: Longterm extracorporeal support: 20 years of progress. Intensive Crit Care Dig 12:15-18, 1993

61. Lennartz H: Extracorporeal lung assist in ARDS: history and state of the art. Acta Anaesthesiol Scand Suppl 109:114-116, 1996

62. Brunet F, Belghith M, Mira J, et al: Extracorporeal carbon dioxide removal and low-frequency positive-pressure ventilation: Improvement in arterial oxygenation with reduction of risk of pulmonary barotrauma in patients with adult respiratory distress syndrome. Chest 104:889-898, 1993

63. Peek GJ, Firmin RK: Extracorporeal membrane oxygenation, a favourable outcome? Br J Anaesth 78:235-236, 1997

64. Bindslev L, Bohm C, Jolin A: Extracorporeal carbon dioxide removal performed with surface-heparinized equipment in patients with ARDS. Acta Anaesthesiol Scand Suppl 95:125-130, 1991

65. Macha M, Griffith B, Kennan R: ECMO support for adult patients with acute respiratory failure. ASAIO J 42:M841-M844, 1996

66. Vasilyev S, Schaap RN, Mortensen JD: Hospital survival rates of patients with acute respiratory failure in modern respiratory intensive care units. Chest 107:1083-1088, 1995

67. Pranikoff T, Hirschl RB, Steimle CN, et al: Mortality is directly related to the duration of mechanical ventilation before the initiation of extracorporeal support for severe respiratory failure. Crit Care Med 25:28-32, 1997

68. Bone R, Balk R, Slotman G, et al: Adult respiratory distress syndrome: Sequence and importance of development of multiple organ failure. Chest 101:320-326, 1992

69. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: a severity of disease classification system. Crit Care Med 13:818-829, 1985