Randomized Clinical Trial of Pressure-controlled Inverse Ratio Ventilation and Extracorporeal CO_2 Removal for Adult Respiratory Distress Syndrome

ALAN H. MORRIS, C. JANE WALLACE, RONALD L. MENLOVE†, TERRY P. CLEMMER, JAMES F. ORME, JR., LINDELL K. WEAVER, NATHAN C. DEAN, FRANK THOMAS, THOMAS D. EAST, NATHAN L. PACE, MARY R. SUCHYTA, EDUARDO BECK, MICHELA BOMBINO, DEAN F. SITTIG, STEPHAN BÖHM, BARBARA HOFFMANN, HAYO BECKS, SAMUEL BUTLER, JAMES PEARL, and BRAD RASMUSSON

Pulmonary and Critical Care Division, Department of Medicine, and the Statistical Data Center, LDS Hospital, and the Pulmonary and Critical Care Division and the Division of Cardiology, Department of Medicine, the Division of Epidemiology and Biostatistics, Department of Family and Preventative Medicine, and the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah

The impact of a new therapy that includes pressure-controlled inverse ratio ventilation followed by extracorporeal CO_2 removal on the survival of patients with severe ARDS was evaluated in a randomized controlled clinical trial. Computerized protocols generated around-the-clock instructions for management of arterial oxygenation to assure equivalent intensity of care for patients randomized to the new therapy limb and those randomized to the control, mechanical ventilation limb. We randomized 40 patients with severe ARDS who met the ECMO entry criteria. The main outcome measure was survival at 30 days after randomization. Survival was not significantly different in the 19 mechanical ventilation (42%) and 21 new therapy (extracorporeal) (33%) patients ($p = 0.8$). All deaths occurred within 30 days of randomization. Overall patient survival was 38% (15 of 40) and was about four times that expected from historical data ($p = 0.0002$). Extracorporeal treatment group survival was not significantly different from other published survival rates after extracorporeal CO_2 removal. Mechanical ventilation patient group survival was significantly higher than the 12% derived from published data ($p = 0.0001$). Protocols controlled care 86% of the time. Average Pa_{O_2} was 59 mm Hg in both treatment groups. Intensity of care required to maintain arterial oxygenation was similar in both groups (2.6 and 2.6 PEEP changes/day; 4.3 and 5.0 FI_{O_2} changes/day). We conclude that there was no significant difference in survival between the mechanical ventilation and the extracorporeal CO_2 removal groups. We do not recommend extracorporeal support as a therapy for ARDS. Extracorporeal support for ARDS should be restricted to controlled clinical trials. **Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK, Dean NC, Thomas F, East TD, Pace NL, Suchyta MR, Beck E, Bombino M, Sittig DF, Böhm S, Hoffmann B, Becks H, Butler S, Pearl J, Rasmusson B. 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 1994; 149:295–305.**

(Received in original form January 25, 1993 and in revised from September 24, 1993)

Supported by Grant No. HL36787 from the National Institutes of Health, by the Deseret Foundation, the Respiratory Distress Syndrome Foundation and by LDS Hospital/IHC, Inc.

Correspondence and requests for reprints should be addressed to Alan H. Morris M.D., Pulmonary Division, LDS Hospital, Salt Lake City, UT 84143.

† Deceased.

Current addresses: Eduardo Beck and Michela Bombino, Instituto di Anestesia e Rianimazione, Università di Milano, Milan, Italy; Dean F. Sittig, Center for Biomedical Informatics, Vanderbilt University, Nashville, TN; Stephan Böhm and Barbara Hoffmann, Institut für Physiologie, Medizinische Fakultät, Rheinisch-Westfälische Techniche Hochschule, Aachen, Germany.

See NAPS document No. 05073 for 10 pages of supplementary material. This is not a multiarticle document. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, N.Y. 10163-3513. Remit in advance, in U.S. funds only. $7.75 for photocopies or $4 for microfiche. There is a $15.00 invoicing charge on all orders filled before payment. Outside U.S. and parts of Canada add postage of $4.50 for the first 20 pages and $1.00 for each 10 pages of material thereafter, or $1.75 for the first microfiche and 50¢ for each fiche thereafter.

Am J Respir Crit Care Med Vol 149. pp 295–305, 1994

Patients with ARDS (1–5) have a high mortality rate (6–12), although those who survive generally resume productive lives (see table 1 for definitions). Pulmonary function abnormalities are detectable in patients who have had ARDS, but survivors generally have no serious pulmonary limitations (13–18). The ARDS mortality of > 60% has remained stable during the past 15 to 20 yr (6–12, 19). This is disappointing considering the many technical advances that have occurred in ICU care.

ARDS therapy is usually only supportive, with mechanical ventilation playing a central role. Animal study results (20–23) have suggested that application of high Ppeak levels needed to deliver commonly used tidal volumes (10 to 12 ml/kg) (24) may damage the ARDS lung (25). This damage is expected because of the nonuniformity of the lung injury. ARDS patients may sustain an overexpansion of the remaining small fraction of compliant lung still capable of gas exchange. Conventional ventilator therapy may thus superimpose an iatrogenic lung injury upon the ARDS lung (25–27). The reduction in Ppeak permitted by PCIRV or by LFPPV-$ECCO_2R$ may eliminate potentially harmful regional lung overdis-

TABLE 1

ABBREVIATIONS, DEFINITIONS, AND UNITS

ACT	Activated clotting time (Hemochron®)	s
APTT	Activated partial thromboplastin time	s
ARDS	Acute (adult) respiratory distress syndrome	
AT III	Antithrombin III	%
BWp	Predicted average body weight (68) (R^2 = 0.997): BWp (men) = 24.881H² + 0.0957A − 3.508, BWp (women) = 19.347H² + 0.1885A − 2.2575, where BWp = kg; H = height (m); A = age (yr)	kg
$C(a-\bar{v})O_2$	Arteriovenous content difference for O_2	ml O_2/dl
CI	Cardiac index	L/min/m²
CPAP	Continuous positive airway pressure	cm H_2O
CPPV	Continuous positive-pressure ventilation	
CTH	Total thoracic compliance	ml/cm H_2O
ECMO	Extracorporeal membrane oxygenation	
FFP	Fresh frozen plasma	
F_{IO_2}	Fraction of inspired oxygen	
$FMLO_2$	Fraction of membrane lung oxygen	
HELP	Health evaluation through logical processing (hospital information computer system)	
Hb	Hemoglobin	g/dl
ICU	Intensive care unit	
LFPPV-$ECCO_2R$	Low-frequency positive-pressure ventilation–extracorporeal carbon dioxide removal	
Pmean	Mean airway pressure	cm H_2O
Ppeak	Peak airway pressure	cm H_2O
PCIRV	Pressure-controlled inverse ratio ventilation	
PCIRVb	PCIRV before LFPPV-$ECCO_2R$	
PCIRVa	PCIRV after LFPPV-$ECCO_2R$	
PEEP	Positive end-expiratory pressure	cm H_2O
PRBC	Packed red blood cells	
P_{aO_2}	Arterial oxygen partial pressure	mm Hg
P_{aCO_2}	Arterial carbon dioxide partial pressure	mm Hg
P_{AO_2}	Alveolar oxygen partial pressure = $F_{IO_2}(P_B - 47) - P_{aCO_2}[F_{IO_2} + (1 - F_{IO_2})/R)]$, where R, respiratory quotient = 0.8, P_B = barometric pressure	mm Hg
$P(a/A)O_2$	P_{aO_2}/P_{AO_2}	
pHa	Arterial pH	
Pw	Pulmonary artery wedge (occlusion) pressure	mm Hg
$\dot{Q}t$	Thermodilution cardiac output	L/min
$\dot{Q}s/\dot{Q}t$	Right-to-left shunt fraction	
S_{aO_2}	Arterial oxygen saturation	
SEM	Standard error of the mean	
V_T	Tidal volume	ml
V_T/kg	Tidal volume/kilogram body weight	ml/kg
$\dot{V}_E$	Minute ventilation	L/min
VR	Ventilatory rate	Breaths/min
$\dot{V}O_2$	Oxygen consumption	ml STPD/min

tension and achieve beneficial changes in ARDS patients (28). This hypothesis is compatible with, although not proven by, the high survival of European patients with severe ARDS (77% after PCIRV followed by LFPPV-$ECCO_2R$ [29]; 49% after LFPPV-$ECCO_2R$ alone [26]). These survival rates are not easily compared with the 9% survival of the 1974 to 1977 clinical trial of ECMO in the United States (10, 30). This is in part because of the uncontrolled nature of reported LFPPV-$ECCO_2R$ studies (31).

We performed a randomized clinical trial to compare this new therapy (PCIRV followed by LFPPV-$ECCO_2R$) (29) with control therapy (CPPV) in severe ARDS patients. Survival was the primary outcome measure. We analyzed hospital costs, physiologic data, length of hospital stay, and blood product consumption as secondary outcome measures.

METHODS

Patient referrals were actively solicited from within the LDS Hospital and from other medical centers. All patients at the LDS Hospital were screened for ARDS. ARDS was defined by the presence of all the following: $P(a/A)O_2 <$

TABLE 2

ECMO ENTRY CRITERIA (10, 30) P_{aO_2} < 50 mm Hg (REPEATED THREE TIMES)*

Entry Type	Testing Time (h)	PEEP F_{IO_2}	PEEP (cm H_2O)	$\dot{Q}s/\dot{Q}T$	P_{aCO_2} (mm Hg)	ICU (h)
Rapid	2	1.00	> 5	—	30–45	—
Slow	12	> 0.60	> 5	> 0.3	30–45	> 48

* ECMO exclusions:

1. Contraindication to anticoagulation (for example, gastrointestinal bleeding, recent cerebrovascular accident, or chronic bleeding disorder).
2. Pw > 25 mm Hg (superceded by our screening criterion that Pw ⩽ 15 mm Hg).
3. Mechanical ventilation > 21 days.
4. Severe chronic systemic disease or another clinical condition that, in itself, greatly limits survival; for example,
   a. Irreversible central nervous system disease
   b. Severe chronic pulmonary disease (FEV_1 < 1 L, FEV_1/FVC < 0.3 of predicted, chronic P_{aCO_2} > 45 mm Hg, chest x-ray evidence of overinflation or interstitial infiltration, or previous hospitalization for chronic respiratory insufficiency)
   c. Total-body surface burns > 40%
   d. Rapidly fatal malignancy
   e. Chronic left ventricular failure
   f. Chronic renal failure (we required serum creatininine ⩾ 2 mg/dl or chronic dialysis therapy)
   g. Chronic liver failure (we required total serum bilirubin ⩾ 2 mg/dl)

0.2, bilateral chest radiographic infiltrates, CTH < 50 ml/cm H_2O, and Pw ⩽ 15 mm Hg (or no clinical evidence of heart failure) (8, 18).

Severe ARDS patients who met ECMO entry and exclusion criteria were considered candidates for the clinical trial (table 2) (10, 30). We excluded patients < 12 and > 65 yr of age and those who had already undergone mechanical ventilation (ARDS duration) for > 21 days (10, 30). We added to the original ECMO exclusions the following two categories: immunosuppressed patients and patients with a positive human immunodeficiency virus test. Hypercapnea (an original ECMO exclusion criterion) was not an exclusion criterion because of the current clinical acceptance of permissive hypercapnea (32). The families of these patients provided written and oral informed consent. The clinical trial was approved by the LDS Hospital Human Research Committee.

Illness severity at the time of randomization was assessed by the APACHE II scoring system (33), by a sepsis severity scoring system (34), and by the LDS Hospital scoring system that produced a quantitative severity score and a sum of the number of failing organs (18).

A clinical trial (randomized, controlled, and noncrossover) was carried out in the Shock Trauma/Intermountain Respiratory ICU at the LDS Hospital (28). Patients were stratified by age (⩽ 40 and > 40 yr) and by the presence or absence of trauma. Blinded randomization with blocking was used, and patients were assigned to receive either control therapy or the new therapy described in 1984 (29). We used explicit protocols to ensure uniformity of care, with equal frequency of monitoring, consistent decision-making logic for the management of arterial oxygenation, and common Pa_{O_2} end points for all randomized ARDS patients from the time of randomization to extubation or death, regardless of the therapy limb (28, 35–37). The protocols reduced FI_{O_2} and PEEP to the minimum levels necessary to maintain Pa_{O_2} either between 55 and 60 mm Hg when barotrauma was present or between 60 and 68 mm Hg in the absence of barotrauma. The nominal maximum therapy was FI_{O_2} = 1.0 and PEEP = 25 cm H_2O. The protocols included formalized trials to test patient response to increases in PEEP to an absolute maximum of 35 cm H_2O when hypoxemia was unrelenting. Therapy was increased rapidly and vigorously but decreased slowly and conservatively (increases in FI_{O_2} and PEEP that followed decreased Pa_{O_2} were more rapid and larger than decreases in FI_{O_2} and PEEP that followed increased Pa_{O_2}). The sequence of increases and decreases in therapy as Pa_{O_2} changed and crossed a threshold of 55 or 60 mm Hg is listed with thresholds for FI_{O_2} and PEEP in table 3.

General patient care was not rigidly controlled, but the following general rules were observed. Detailed variable values that reflect patient care are listed in the supplemental tables in NAPS document No. 05073. Patients were always sedated and usually paralyzed before randomization. Sedation was usually achieved with midazolam plus morphine sulfate (for analgesia). Fentanyl citrate, diazepam, and sufentanyl citrate were also administered. Paralysis was usually achieved with vecuronium, but pancuronium and metocurine iodide were also used. The first 2 randomized patients were supported with the Ohmeda CPU 1 ventilator; the other 38 patients were supported with the Siemens 900C Servo® ventilator (equipment donated by the manufacturers is listed in the ACKNOWLEDGMENT). Blood pressure and $\dot{Q}t$ were supported, when necessary, with intravenous fluid administration, cardiotonic agents (usually dopamine or dobutamine), and afterload reduction (usually with Na nitroprusside). The matching of $\dot{Q}t$ to $\dot{V}O_2$ was assessed with the $C(a\text{-}\bar{v})O_2$, the target for which was 4 ml O_2/dl blood (38, 39). Urine flow was maintained at ⩾ 25 ml/h. The lowest tolerated Pw was maintained. Nutrition was regulated with a computerized protocol that provided a balanced caloric substrate (40). The Harris-Benedict equation was used to compute basal energy expenditure (BEE) (41). Total caloric intake goal was 1.7 BEE parenterally or 1.5 BEE enterally. Lipid provided 30% of total calories, and protein was administered at 1 g/kg body weight.

Physiologic measurements, as part of routine clinical care, were made with standard techniques. The term PEEP indicates the PEEP setting (extrinsic PEEP) for all patients except those supported with PCIRV. During PCIRV, PEEP represents intrinsic PEEP (end-expiratory alveolar pressure) (35). All derived physiologic variables were calculated by previously established computer programs as part of the routine clinical application of the HELP hospital information system (42, 43).

TABLE 3

PROTOCOL THERAPY CHANGE SEQUENCE*

Therapy Change Sequence‡	Thresholds: Baratrauma† Yes	No
Improvement (Pa_{O_2} above a threshold)		
1. ↓ FI_{O_2} to	0.7	0.5
2. ↓ PEEP (Δ = 1) to	15	15
3. ↓ FI_{O_2} to	0.4	0.4
4. PEEP (Δ = 1) to	5	5
5. ↓ FI_{O_2} (if Pa_{O_2} > 90) to	0.3	0.3
Deterioration (Pa_{O_2} below a threshold)		
1. ↑ FI_{O_2} to	0.8	0.6
2. ↑ PEEP (Δ = 2) to	20	20§
3. ↑ FI_{O_2} to	1.0	1.0
4. ↑ PEEP (Δ = 2) to	25	25§

* General principles governing the sequence of FI_{O_2} and PEEP changes for management of arterial oxygenation.

† Barotrauma was present if 1 or 2 was present: (1) thoracostomy tube or (2) any of the following radiographic findings: subcutaneous air, pneumothorax, pneumomediastinum, or pneumoperitoneum.

‡ Δ = increments of change in PEEP (cm H_2O).

§ Δ = 5 if Ppeak < 50.

PCIRV and LFPPV-$ECCO_2R$

Through collaboration with the group in Milan, we attempted to duplicate the technique used in Milan for the 1984 report (29). We constructed an extracorporeal system with a parallel and series configuration of the two 3.5 m^2 Sci-Med membrane lungs for gas and blood flow, respectively (26). If PCIRV support failed, LFPPV-$ECCO_2R$ was initiated. Failure of PCIRV was based either on failure to maintain Pa_{O_2} or on failure to maintain pHa (35). Between April 1986 and Feburary 1987, we prepared our LFPPV-$ECCO_2R$ team for the randomized clinical trial. We supported seven sheep with LFPPV-$ECCO_2R$ for a total of 271 h. Two humans with severe ARDS who met ECMO criteria were supported with LFPPV-$ECCO_2R$ for a total of 193 h (one survived) before we launched the clinical trial and began patient randomization.

Arterial oxygenation was achieved primarily through the patient's natural lung. We used a variant of apneic oxygenation, with a continuous tracheal flow of 100% O_2 (~ 1.5 L/min) saturated with H_2O at 37° C. The target Ppeak was 35 cm H_2O (upper limit 45 cm H_2O) for the first 10 LFPPV-$ECCO_2R$ patients (26, 29). Thereafter, we used a minimum V_T of 4 ± 0.5 ml/kg BWp rather than a Ppeak limit. We abandoned use of the Ppeak limit because of difficulty in maintaining a V_T > 100 ml in some patients after several days of extracorporeal support. After the first 10 patients, we were advised to insist upon a minimum V_T of about 250 ml (A. Pesenti, personal communication). (Of 6 survivors receiving LFPPV-$ECCO_2R$, 3 were maintained with the Ppeak limit and 3 with the minimum V_T after we abandoned the Ppeak limit.)

To maintain anticoagulation during LFPPV-$ECCO_2R$, porcine heparin was administered intravenously. We monitored anticoagulation with bedside ACT (Hemochron® Model 400, CA510 test tubes; International Technidyne Corp., 23 Nevsky St., Edison, NJ 08820) and with APTT. ACT was maintained between 180 and 210 s (10, 26, 29, 30, 44). APPT was maintained between 55 and 80 s (1.8 to 2.5 × control) (L. Uziel, personal communication) (45). After our first 11 LFPPV-$ECCO_2R$ patients, we maintained ATIII levels > 70% of normal by adjusting the intravenous infusion of FFP (L. Uziel, personal communication). LFPPV-$ECCO_2R$ was discontinued because of excessive hemorrhage if any of the following were present:

1. Blood product replacement > 12 L/day for 1 day
2. Blood product replacement > 6 L/day for 2 days
3. Uncontrollable thoracostomy tube blood loss > 200 ml/h for > 3 h.

Blood products included packed red cells, FFP, albumin, and plasmanate.

Costs and Charges

Costs and charges for clinical care are routinely computed in the HELP hospital information system for all chargeable items and for all nonphysi-

cian personnel time on the basis of industrial engineering time studies (46). Clinical costs and charges reported here include only compensation for all clinical nonphysician personnel and all clinical resources consumed during the course of usual hospital care. They do not include expenses incurred by research staff members or by the senior clinical physician who was in the hospital 24 h per day (on call for extracorporeal emergencies) for the first 2 to 3 yr of the clinical trial. They do not include expenses for extracorporeal equipment or extracorporeal disposable supplies (including membrane lungs, tubing, and filters). New therapy patient clinical costs and charges are therefore an underestimate.

Statistical Methods

Life table analysis was used to compare survival in the two treatment groups. The end point of this analysis was the time until death occurred. Patients were censored (death time unknown) upon hospital discharge. Descriptive actuarial indices of survival (e.g., proportion surviving at 30 days ± the standard error of proportion) were obtained from Kaplan-Meier curves (47). The log-rank statistic was used to compare the two survival distributions (48). In sample size calculations, a large survival effect was required because of the potential long-term dangers associated with the invasive and complicated LFPPV-ECCO$_2$R procedure. A change in survival rate from the 9% predicted for the control group to the 40% for the group receiving new therapy was chosen as a clinically important effect of the new therapy (one likely to lead to widespread adoption of the new therapy throughout the medical community). This fourfold increase in survival (9 to 40%) is half the eightfold increase in survival reported by researchers in Milan (9 to 77%) after support with PCIRV followed by LFPPV-ECCO$_2$R (29). We determined that a sample size of 60 patients (30 per group) was necessary to detect the survival difference between 9 and 40% at α = 0.05 (two-sided) and power = 0.80 (49, 50).

Two interim analyses were obtained after 20 and after 40 patients. This allowed early termination of the clinical trial if there were (*1*) demonstration that the two therapies showed different survival times early in the trial or (2) a 0.10 or less probability of finding a different survival between the two therapies when the result of the interim analysis was projected to a total enrollment of 60 randomized patients. The "group sequential" design (51) required that a significant difference be found at p = 0.001 for 20 patients, at p = 0.015 for 40 patients, and at p = 0.047 for 60 patients. The advantages of the group sequential design included an overall and final test α level of approximately 0.05, a final test power of approximately the same value as that for a single test design, and the possibility of early termination if the treatment effect was large (51, 52). A β projection (53) was used to estimate the probability of obtaining a significant difference in survival with 60 patients. This was conditional upon the result obtained at the interim analyses with 20 and 40 patients. In addition, proportional survival comparisons were made by chi-square (χ^2) analysis.

Patient characteristics at the time of randomization and secondary results from the trial are presented as mean ± SEM or % with exploratory significance test p values. For the patient characteristics at randomization, this was done as a confirmatory test of the randomization by exploring for chance uneven distribution of patients to the two therapy groups. When the data were categorical and resulted in a two-by-two contingency table, the χ^2, corrected for continuity, or Mantel-Haenszel (M-H) tests were used. Fisher's exact test was used for two-by-two contingency tables for expected frequency in any cell < 5 and total sample size < 30. When data were categorical and resulted in more than two values in any dimension, the χ^2 analysis and categorical analysis of variance (54) were used. When data were interval or could be ranked, the Mann-Whitney (M-W) test was used. For summary data (mean, standard deviation, and SEM) from previously published studies, analysis of variance was used.

A comparison with the previously published survival of ARDS patients meeting ECMO criteria (10–12, 19) was made by χ^2 analysis. We used the criteria employed in the 1974 to 1977 ECMO clinical trial for assigning death to "respiratory" and "nonrespiratory" causes (55). Unless otherwise specified, all data are presented as mean ± SEM. For clarity, the applied statistical test precedes each p value. SPSS and BMDP statistical programs were used.

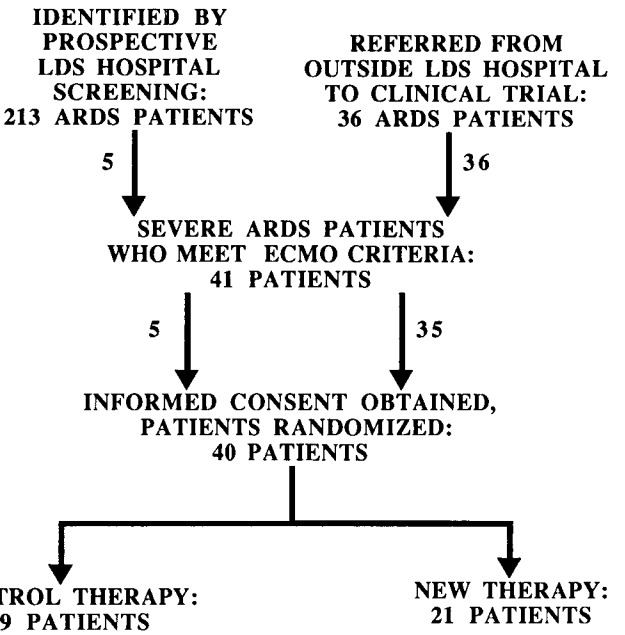

Figure 1. Flow of ARDS patients, including patients identified by prospective screening, those referred to the LDS Hospital for consideration in the clinical trial, those who met ECMO criteria, and those who were randomized.

TABLE 4

CLINICAL TRIAL PATIENT DEMOGRAPHICS AND ILLNESS SEVERITY AND DURATION, MEAN ± SEM OR RATIO*

	Age (*yr*)	Sex	Weight (*kg*)†	Height (*cm*)	AP.II	ECMO‡	CT	Baro-trauma§	Sepsis‖	Event to Randomization (*days*¶) Since Onset	Give O_2	Intubate	ARDS
All 40 randomized patients	35 ± 2.3	23F 17M	74.9 ± 3.2	167 ± 1.8	18 ± 0.7	27R 13S	1 ± 0.21	27/40	9/40	20.6 ± 3.4	9.5 ± 1.0	7.7 ± 0.9	7.6 ± 0.8
19 Control therapy group patients	38 ± 3.3	10F 9M	81.8 ± 5.1	169 ± 2.7	17 ± 0.9	13R 6S	0.8 ± 0.28	11/19	5/19	14.2 ± 2.9	7.9 ± 1.3	6.8 ± 1.3	6.4 ± 1.3
21 New therapy group patients	33 ± 3.1	13F 8M	68.7 ± 3.5	165 ± 2.3	18 ± 1.1	14R 7S	1.3 ± 0.29	16/21	4/21	26.4 ± 5.7	10.9 ± 1.5	8.6 ± 1.2	8.6 ± 1.1
p Values for group differences**	0.21	0.55††	0.09	0.51	0.33	0.91††	0.99	0.22††	0.58††	0.07	0.21	0.25	0.11

Definition of abbreviations: AP.II = APACHE II score (33) at LDS Hospital ICU admission; R = rapid; S = slow; CT = number of thoracostomy tubes.

* All data were obtained at randomization unless specified. All summary data are the mean ± SEM or ratio.

† Entry ECMO blood gas criteria (table 2).

‖ Sepsis by Montgomery's definition (7).

¶ Days from event to randomization: event is initial illness onset time, initial oxygen administration time, initial intubation time, or time that ARDS criteria (see Methods) were first satisfied.

§ Barotrauma was present if 1 or 2 was present: (*1*) thorascostomy tube or (*2*) any of the following chest radiographic findings: subcutaneous air, pneumothorax, pneumomediastinum, or pneumoperitoneum.

** All p values are Mann-Whitney tests, except as noted.

†† Chi square tests.

TABLE 5

CLINICAL TRIAL PHYSIOLOGIC CHARACTERISTICS AT RANDOMIZATION, MEAN ± SEM*

Pa_{O_2}	FI_{O_2}	Pa_{O_2}/FI_{O_2}	PEEP	CTH	CI	$\dot{Q}s/\dot{Q}T$	pHa	Pa_{CO_2}	Ppeak	VT/kg	VR	$\dot{V}E$	Hb	Sa_{O_2} (%)
All 40 randomized patients														
57 ± 2	0.9 ± 0.02	63.2 ± 2.8	16 ± 0.8	20 ± 2	3.9 ± 0.2	0.47 ± 0.01	7.38 ± 0.01	49 ± 2	56 ± 2	9.5 ± 0.4	27 ± 1	15.6 ± 0.8	12.5 ± 0.4	83 ± 1
19 Control therapy group patients														
58 ± 3	0.9 ± 0.02	63.8 ± 3.8	16 ± 1	22 ± 3	3.9 ± 0.2	0.44 ± 0.02	7.40 ± 0.02	48 ± 4	56 ± 2	10.2 ± 0.6	26 ± 2	16.2 ± 1.2	12.6 ± 0.6	84 ± 1
21 New therapy group patients														
56 ± 3	0.9 ± 0.02	62.6 ± 4.2	17 ± 1	18 ± 2	4.0 ± 0.2	0.50 ± 0.02	7.36 ± 0.02	50 ± 3	55 ± 3	8.9 ± 0.6	28 ± 1	15.0 ± 1.1	12.4 ± 0.4	81 ± 2
p Values for group differences														
0.99	0.88	0.80	0.97	0.63	0.96	0.10	0.14	0.19	0.29	0.21	0.30	0.34	0.94	0.35

* All p values are Mann-Whitney tests. All blood gas, hemodynamic, and ventilation data were obtained within 4.9 ± 1.1 h of randomization. All other data were obtained at randomization. See table 1 for definitions and units.

RESULTS

Among the 249 patients with ARDS we identified, 41 met ECMO entry criteria. All but 1 of the 41 families consented to participate. A total of 40 patients were enrolled in the clinical trial and were randomized from August 25, 1987 to April 24, 1991 (figure 1). Of these 40 randomized patients 5 were originally admitted at the LDS Hospital and 35 were transferred there from other hospitals (6 from Salt Lake City hospitals, 6 from Utah hospitals outside Salt Lake City, and 23 by air from out-of-state hospitals). The mean ± SEM and (range) one-way statute air miles of patient transport was 347 ± 112 (0 to 2,029) for all 19 control patients and 314 ± 70 (0 to 1,433) for all 21 new therapy patients.

Of the 40 randomized patients, 27 met the rapid ECMO entry criteria and 13 met the slow ECMO entry criteria (table 2) (10, 30). Pulmonary artery occlusion pressures were measured in all patients. A total of 19 patients were randomized to the control group and 21 to the group that received new therapy. Of the 21 patients who received new therapy 19 were supported with LFPPV-$ECCO_2R$ (1 died before LFPPV-$ECCO_2R$ could be initiated, and 1 improved and survived after PCIRV). The differences between demographic and physiologic characteristics of the two patient groups at the time of randomization were not statistically significant (tables 4 and 5). Both patient groups had equivalent illness severity at the time of randomization (tables 5 and 6).

The presumptive cause of ARDS for our randomized trial patients, for those of the 1974 to 1977 ECMO clinical trial (10, 30), and for those in the 1980 to 1986 Milan study are listed in table 7 (26, 29). There were significant differences in the causes of ARDS among the three different groups (χ^2, $p < 0.001$). Bacterial or viral pneumonia appeared to lead to ARDS in at least 60% of our patients (some of the 6 patients with ARDS of unknown cause may also have had pneumonia). There is no significant difference between our distribution of ARDS causes and that of the 1974 to 1977 ECMO clinical trial (10) (χ^2, $p > 0.76$). Our 40 patients were therefore combined with the 90 patients in the 1974 to 1977 ECMO clinical trial to produce a pooled U.S. data base. The distribution of ARDS causes in the pooled U.S. data was significantly different from the distribution of Milan (χ^2, $p = 0.0001$), with a higher incidence of trauma and a lower incidence of pneumonia in Milan. The average duration of LFPPV-$ECCO_2R$ in our 19 LFPPV-$ECCO_2R$ patients (table 8) is comparable to that reported by the Milanese group (26, 29).

Outcome

The clinical trial was concluded after 40 patients had completed their care, despite our original design based on 60 randomized patients. All deaths occurred within 30 days of randomization (figure 2). The first interim analysis (life table) was carried out after 20 patients were enrolled in the trial. It revealed that more control patients survived at 30 days (42 ± 18%) than patients receiving the new therapy (23 ± 14%), with log-rank $p = 0.11$. Since this probability was greater than the $p = 0.001$ required for early termination and β projection resulted in $p = 0.34$ of obtaining a significant difference between groups with 60 randomized patients, the clinical trial was continued. The second interim analysis (life table) was carried out after 40 patients were enrolled in the trial. It revealed a smaller difference in survival between the control therapy group (39 ± 12%) and the new therapy group (30 ± 10%), with log-rank $p = 0.47$ at 30 days. The probability was greater than the $p = 0.015$ required for early termination. However, since the β projection of the likelihood that a significant difference in survival would be observed at 60 patients was only $p = 0.10$, the trial was stopped with the conclusion that the difference between new and traditional therapies was too small for a significant survival difference to be demonstrated with 60 randomized patients.

Simple rates and proportions, although not as powerful as the preceding life table analysis, led to the same conclusion. Survival rates in control therapy (42%) and new therapy (33%) patient groups were not significantly different (χ^2, $p = 0.8$). Of the 40 pa-

TABLE 6

ILLNESS SEVERITY AT THE TIME OF RANDOMIZATION, MEAN ± SEM

Therapy Group	APACHE II (33)	Sepsis Severity Score (34)	LDS Hospital Organ Failure Score (18)	LDS Hospital Organ Failure Count (18)*
Control	17.2 ± 0.9	31.6 ± 3.6	6.3 ± 0.7	1.5 ± 0.1
New therapy	17.9 ± 1.1	31.4 ± 3.5	5.8 ± 0.8	1.4 ± 0.1

* LDS hospital organ failure count includes lung failure.

TABLE 7

ETIOLOGY OF ARDS EXPRESSED IN THE FOUR CATEGORIES USED IN THE 1974 TO 1977 ECMO CLINICAL TRIAL

Source	Pneumonia	Trauma	Emboli	Other
Current trial	24	3	2	11
ECMO trial (10, 30)	59	6	7	18
Milan (26, 29)	27	20	4	8

From references 10 and 30.

TABLE 8

CLINICAL TRIAL OUTCOME DATA, MEAN ± SEM OR RATIO*

	Survived/ Died	Study Days	Hospital Days	ICU Days	CPPV Days	PCIRVb Days	$ECCO_2R$ Days	PCIRVa Days	CPAP Days
19 Control therapy group patients	8S/11D	27.1 ± 5.7	28.8 ± 5.7	24.2 ± 4.4	19.3 ± 3.7				2.0 ± 0.9
21 New therapy group patients	7S/14D	23.6 ± 4.8	26.9 ± 4.9	23.8 ± 4.0	4.46 ± 2.2	2.4 ± 0.6	8.7 ± 1.7	3.7 ± 1.6	0.9 ± 0.4
p Values for therapy group differences	0.56†	0.57	0.79	0.92	0.0001				0.50
All 40 randomized patients	15S/25D	25.3 ± 3.6	27.8 ± 3.7	24.0 ± 2.9	11.5 ± 2.4				1.5 ± 0.5

* All p values are Mann-Whitney tests, except as noted. Days for ventilation modes are computed from the time of randomization to death or extubation. Mortality outcome: survived (S) or died (D). Study days are days from randomization to death or hospital discharge. Hospital days are days from LDS Hospital admission to death or hospital discharge; ICU days are days from LDS Hospital ICU admission to death or ICU discharge. See table 1 for other definitions.

† Chi-square test.

tients, 15 (38%) ultimately survived (8 of 19 control patients and 7 of 21 new therapy patients) (table 8). The 8 survivors in the control group recovered after support with CPPV and CPAP. One of the survivors in the new therapy group recovered after support with PCIRV and CPAP only; the other 6 survivors in the new therapy group recovered after support with PCIRV, LFPPV-$ECCO_2R$, CPPV, and CPAP.

There were no statistically significant differences in total hospital length of stay (hospital days), ICU length of stay (ICU days), or clinical trial time (study days) between the control patient group and the new patient group (M-W, $p > 0.56$) (table 8).

Data from control therapy patients during CPPV support were compared with data from new therapy patients during all new therapy mechanical ventilation support modes grouped together (PCIRVb plus LFPPV-$ECCO_2R$ plus PCIRVa plus CPPV) (see supplemental tables in NAPS document No. 05073 for a complete report of physiologic variables). The mean ± SEM (number of measurements) Pa_{O_2} was 59.3 ± 0.3 mm Hg (2,062) versus 58.6 ± 0.3 mm Hg (3,568) and the pHa was 7.36 ± < 0.01 (2,062) versus 7.39 ± < 0.01 (3,568) for patients in the control and new therapy groups, respectively. There are no clinically important differences in blood gas mean values between the therapy groups, whether we use all the data, use the individual patients as the unit of analysis, or use only the data from the first few days of the therapy.

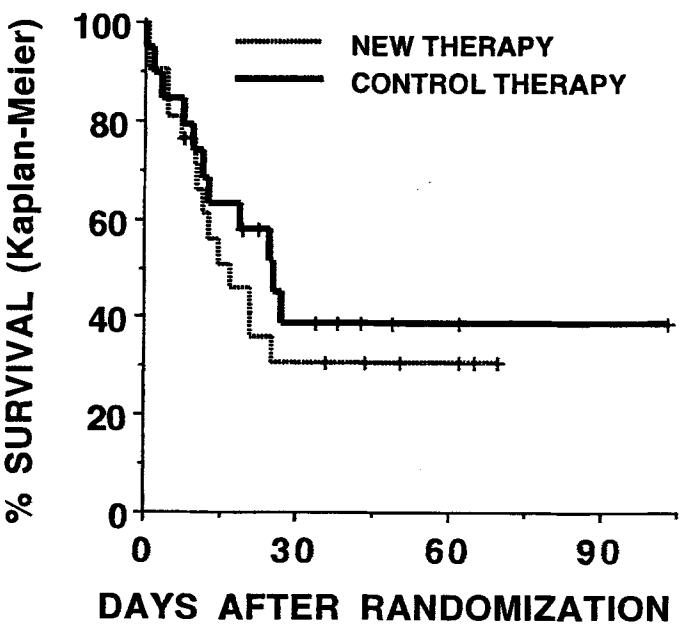

Figure 2. Kaplan-Meier survival curves for the 19 control (traditional) therapy (*solid line*) and the 21 new therapy patients (*dotted line*). Small vertical bars superimposed on curves indicate censored patients. p = 0.47.

The duration of LFPPV-$ECCO_2R$ in the 6 survivors (10.9 ± 3.5 days) was not statistically significantly different from that of the 13 patients who died (9.0 ± 2.1 days) (M-W, $p > 0.79$). The 19 LFPPV-$ECCO_2R$ patients were supported extracorporeally for 55 ± 7% of their total mechanical ventilation time. Extracorporeal blood flow was 2.38 ± 0.01 L/min (3,064). The 21 patients receiving new therapy spent 8.7 ± 1.7 days supported by LFPPV-$ECCO_2R$ (19 patients), 6.1 ± 1.8 days supported by PCIRV (21 patients), and 4.5 ± 2.2 days supported by CPPV (21 patients) (table 8). Costs and charges were greater for the new therapy group patients (table 9).

Three to 6 h after initiating LFPPV-$ECCO_2R$, the Ppeak was 45.4 ± 1.7 cm H_2O (mean ± SEM, with number of observations in parentheses) for the 19 new therapy patients supported extracorporeally (35.8 ± 0.5 cm H_2O for the first 10 patients) (table 10). The desired low Ppeak goal was maintained for the first day of LFPPV-$ECCO_2R$ since Ppeak was only 41.2 cm H_2O 24 to 27 h after initiating LFPPV-$ECCO_2R$ in the first 10 LFPPV-$ECCO_2R$ patients (table 10). During the entire LFPPV-$ECCO_2R$ period Ppeak was 54.1 ± 0.2 cm H_2O (2,865). VR was reduced to 3 to 5/min in all patients during LFPPV-$ECCO_2R$ initiation and was kept at 3.3 ± 0.1/min during the first 3 to 6 h of LFPPV-$ECCO_2R$, in all patients. For all 21 patients receiving new therapy, Ppeak during all mechanical ventilation support modes grouped together (PCIRVb plus LFPPV-$ECCO_2R$ plus PCIRVa plus CPPV) was 49.5 ± 0.2 (6,331). For the 19 control patients, Ppeak during the entire CPPV period was 57.8 + 0.2 cm H_2O (4,868) (see supplemental tables in NAPS document No. 050703 for details).

Major complications (other than organ failure) were divided into four groups: central nervous system (CNS; 3 control and 2 new therapy); cardiac, peripheral vascular, and other (13 control and 7 new therapy); non-CNS hemorrhage (0 control and 21 new therapy); and $ECCO_2R$ circuit clotting (4 new therapy) (table 11). There were 16 major complications (other than organ failure) in the control group and 34 in the new therapy patient group. There was no statistically significant difference between the two therapy groups with regard to total complications ($p = 0.12$). There was a statistically significant increase in non-CNS hemorrhage in the new therapy group ($p = 0.00$) and a suggestive but not statistically significant increase in peripheral vascular complications in the control therapy group ($p = 0.09$). Cardiac complications, CNS complications, and other complications were not statistically significantly

TABLE 9

CLINICAL TRIAL COSTS AND CHARGES FROM LDS HOSPITAL ADMISSION TO DEATH OR DISCHARGE IN THOUSANDS OF DOLLARS (PHYSICIAN COST AND CHARGES EXCLUDED), MEAN ± SEM

		Daily Costs (K$)			Total Costs (K$)			Charges (K$)	
	N	Fixed	Variable	Contract Adjusted	Fixed	Variable	Contract Adjusted	Daily	Total
Control	19	1.59 ± 0.09	1.69 ± 0.12	4.11 ± 0.27	38.3 ± 5.4	39.4 ± 5.6	97.2 ± 13.6	4.48 ± 0.35	103.9 ± 15.3
Live	8	1.18 ± 0.06*	1.15 ± 0.04*	2.92 ± 0.12*	53.8 ± 8.5*	53.3 ± 9.8*	133.8 ± 22.9*	3.04 ± 0.13*	142.2 ± 27.2*
Die	11	1.89 ± 0.08	2.08 ± 0.11	4.97 ± 0.23	27.0 ± 4.7	29.4 ± 5.0	70.5 ± 12.1	5.53 ± 0.34	76.1 ± 12.9
New	21	2.25 ± 0.24	2.44 ± 0.27	5.87 ± 0.63	46.3 ± 6.4	50.3 ± 7.1	120.8 ± 16.7	6.59 ± 0.64	138.2 ± 19.3
Live	7	1.33 ± 0.08†	1.40 ± 0.08†§	3.42 ± 0.19†§	71.3 ± 12.4†	76.6 ± 13.6†	185.0 ± 32.0†	3.79 ± 0.25†	207.5 ± 37.0†
Die	14	2.71 ± 0.3*	2.96 ± 0.32*	7.09 ± 0.76*	33.7 ± 4.9	37.1 ± 5.7	88.6 ± 13.2	7.99 ± 0.70	103.6 ± 16.4

Definition of abbreviations: K$ = thousands of dollars; N = number of patients.
* Significantly different from control patients who died.
† Significantly different from new therapy patients who died.
§ Significantly different from control patients who lived (Mann-Whitney $p < 0.01$).

TABLE 10

VENTILATORY SUPPORT DATA AT 3–6 H AND 24–27 H AFTER INITIATING LFPPV-$ECCO_2R$*

	All 19 Patients, 3–6 h						First 10 Patients				Last 9 Patients			
	All		Live		Die		3–6 h		24–27 h		3–6 h		24–27 h	
	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM
Ppeak	54	45.4 ± 1.7	18	48.1 ± 3.2	36	44.0 ± 2.1	28	35.8 ± 0.5	21	41.2 ± 1.7	26	55.7 ± 2.2	22	52.8 ± 1.7
PEEP	67	24.2 ± 0.6	28	21.7 ± 1.2	39	26.0 ± 0.6	39	22.4 ± 0.9	25	21.2 ± 1.3	28	26.7 ± 0.7	25	25.4 ± 0.7
Pmean	64	24.9 ± 0.6	27	22.7 ± 0.4	37	26.5 ± 0.6	38	22.8 ± 0.7	18	23.9 ± 1.4	26	28.0 ± 0.7	22	26.3 ± 0.8
Vt/kg BWp	50	3.0 ± 0.3	14	3.4 ± 0.5	36	2.9 ± 0.3	24	2.9 ± 0.4	18	3.9 ± 0.7	26	3.2 ± 0.3	21	2.9 ± 0.3
CTH	40	11.0 ± 1.2	11	8.4 ± 1.4	29	12.0 ± 1.5	19	14.6 ± 2.2	14	10.0 ± 0.7	21	7.8 ± 0.5	18	8.8 ± 1.0
VR	57	3.3 ± 0.1	18	3.1 ± 0.1	39	3.4 ± 0.1	30	3.0 ± 0.1	17	3.6 ± 0.6	27	3.6 ± 0.2	24	3.2 ± 0.1

Definition of abbreviation: N = number of measurements.
* For all LFPPV-$ECCO_2R$ patients, for those who lived and those who died, and for the first 10 and last 9 LFPPV-$ECCO_2R$ patients.

different ($p > 0.65$). The 21 instances of non-CNS hemorrhages in the new therapy group occurred only in patients who received heparin for extracorporeal support. We discontinued LFPPV-$ECCO_2R$ in 7 of the 19 LFPPV-$ECCO_2R$ patients because of hemorrhage (5 of the 7 patients survived). The 5 survivors had improving lung function and had sustained uneventful extracorporeal support for as long as 3 wk before the hemorrhage forced discontinuation of LFPPV-$ECCO_2R$.

TABLE 11

MAJOR COMPLICATIONS*

	Patients	
Category	Control Therapy	New Therapy
Cardiac		
Cardiac dysrhythmia arrest	2	2
Cardiac tamponade		1
Central nervous system		
Intracranial hemorrhage	1	1
Cerebral arterial gas embolism	1	
Cerebral hypoxia depression	1	1
Peripheral vascular		
Extremity ischemia	2	
Arterial embolism	1	
Venous thrombosis	2	1
Vasculitis	2	
Dermatitis		1
Hypertension	1	
Neuromuscular (weakness)	3	2
Hemorrhage (non-CNS)		
Intrapulmonic		4
PRBC transfusion > 0.8 L/day		10
Requiring $ECCO_2R$ discontinuation		7
$ECCO_2R$ circuit clotting		4

* Major complications for control therapy and new therapy patient groups. Number of patients with the indicated complication (not number of episodes).

Using the criteria employed in the 1974 to 1977 ECMO clinical trial for assigning death to "respiratory" and "nonrespiratory" causes (55), 4 of 25 (16%) of our patients who died had a nonrespiratory and 21 of 25 (84%) had a respiratory cause of death. This is not statistically significantly different from the results in the 1974 to 1977 ECMO clinical trial (5 nonrespiratory and 77 respiratory deaths) (55) ($p > 0.25$).

Blood product requirements were higher in the new therapy group than in the control group patients (table 12).

The number of changes per day in FIO_2 and PEEP were similar in the two therapy groups (table 13).

Since survival of our control therapy patients was so much higher than previously experienced, we compared demographic and physiologic characteristics of all current study patients with those of the patients randomized in the 1974 to 1977 ECMO clinical trial (30) (table 14).

DISCUSSION

Of the 249 identified patients with ARDS, 16% (41) had severe ARDS and met the ECMO criteria. This rate of severe ARDS (satisfying ECMO criteria) among patients with less severe hypoxic respiratory failure (ARDS) is within the reported range. The ECMO trial of 1974 to 1977 reported 36 ARDS patients per year, between 12 and 65 yr of age, meeting ECMO criteria (10) in the nine collaborating hospitals. The same nine hospitals encountered 450 other patients per year between 12 and 65 yr of age, with only moderate hypoxic respiratory failure (requiring intubation, posi-

TABLE 12

BLOOD PRODUCT REQUIREMENTS, MEAN ± SEM*

	N	Red Cells	FFP	Platelets	Albumin	Plasmanate
Daily, L/ICU day						
Control	19	0.20 ± 0.04	0.11 ± 0.04	0.06 ± 0.03	0.01 ± 0.01	< 0.00 ± < 0.00
Live	8	0.10 ± 0.02†	0.12 ± 0.08	0.06 ± 0.05	0.02 ± 0.02	0.00
Die	11	0.27 ± 0.06	0.10 ± 0.04	0.05 ± 0.03	0.01 ± 0.01	0.00
New	21	1.76 ± 0.63	1.63 ± 0.49	0.42 ± 0.13	0.03 ± 0.02	0.06 ± 0.03
Live	7	2.70 ± 1.90‡	2.09 ± 1.11‡	0.25 ± 0.21	< 0.00 ± < 0.00	0.04 ± 0.04
Die	14	1.29 ± 0.17†	1.41 ± 0.51†	5.06 ± 1.63†	0.05 ± 0.03†	0.07 ± 0.04
Total, L/ICU stay						
Control	19	3.53 ± 0.79	1.51 ± 0.53	0.70 ± 0.29	0.63 ± 0.53	0.05 ± 0.04
Live	8	3.34 ± 0.78	2.39 ± 1.01	0.81 ± 0.58	1.26 ± 1.25	0.13 ± 0.08
Die	11	3.66 ± 1.28	0.87 ± 0.51	0.62 ± 0.31	0.17 ± 0.16	0.00
New	21	11.15 ± 2.29	12.85 ± 3.11	2.85 ± 0.92	0.11 ± 0.03	0.25 ± 0.10
Live	7	15.75 ± 5.75‡	17.62 ± 5.54‡	1.27 ± 0.70	0.09 ± 0.06	0.18 ± 0.12
Die	4	8.84 ± 1.79†	10.47 ± 3.74†	3.64 ± 1.31†	0.13 ± 0.04	0.28 ± 0.14

Definition of abbreviations: red cells = packed red blood cells; FFP = fresh frozen plasma; N = number of patients.

* Significance tests: Mann-Whitney, $p < 0.05$.

† Significantly different from control patients who died.

‡ Significantly different from control patients who lived.

TABLE 13

THERAPY CHANGES PER DAY, MEAN ± SEM FOR PERIOD FROM RANDOMIZATION TO DEATH OR EXTUBATION

	No. Patients	Patient-days	FIO_2 ↑ Mean ± SEM	N	FIO_2 ↓ Mean ± SEM	N	PEEP↑ Mean ± SEM	N	PEEP ↓ Mean ± SEM	N	$FMLO_2$ ↑* Mean ± SEM	N	$FMLO_2$ ↓ Mean ± SEM	N
Control	19	441	2.3 ± 0.1	1,026	2.6 ± 0.1	1,151	1.0 ± 0.1	453	1.5 ± 0.1	669				
Live	8	291	2.2 ± 0.1	652	2.5 ± 0.1	732	0.9 ± 0.1	257	1.7 ± 0.1§‖	483				
Die	11	150	2.5 ± 0.2†	374	2.8 ± 0.2‡	419	1.3 ± 0.2	196	1.2 ± 0.1‖	186				
New	21	538	2.0 ± 0.1	1,047	2.4 ± 0.1	1,258	1.1 ± 0.1	605	1.4 ± 0.1	772	2.5 ± 0.2	466	3.2 ± 0.2	584
Live	7	339	2.1 ± 0.1	708	2.5 ± 0.1	830	0.9 ± 0.1	316	1.4 ± 0.1§¶	475	4.0 ± 0.3	262	4.9 ± 0.3	321
Die	14	199	1.7 ± 0.1†	339	2.2 ± 0.2‡	428	1.5 ± 0.1	289	1.5 ± 0.2¶	297	1.7 ± 0.2	204	2.2 ± 0.4	263

Definition of abbreviation: N = total number of therapy changes.

* All symbol pairs indicate significant differences (Mann-Whitney, $p < 0.05$).

TABLE 14

COMPARISON BETWEEN PATIENTS RANDOMIZED IN THE 1974 TO 1977 EMCO AND CURRENT CLINICAL TRIALS*

	1974–1977 Mean ± SEM or Ratio	N	Current Trial Mean ± SEM or Ratio	N	p
N, patients		90		40	
Age, yr	35.4 ± 1.5	90	35.0 ± 2.3	40	0.86
Male/female	35/54	89	17/23	40	0.73
Weight, kg	66.4 ± 1.7	88	74.9 ± 2.5	40	0.029†
Rapid/slow	44/45	89	27/13	40	0.056
ARDS, days	8.2 ± 0.5	90	7.5 ± 0.8	40	0.46
Pump, days	5.4 ± 0.8	47	7.9 ± 1.2	19	0.38
Study, days	10.6 ± 1.7	90	25.7 ± 2.5	40	< 0.001†
Died/survived	82/8	90	25/15	40	< 0.001†
Data when arterial blood samples satisfied ECMO criteria					
FIO_2	0.83 ± 0.01	90	0.87 ± 0.03	40	0.16
PaO_2, mm Hg	42.3 ± 0.5	90	44.0 ± 0.6	40	0.046†
SaO_2, %	75.9 ± 0.9	82	75.6 ± 1.3	40	0.81
$\dot{Q}s/\dot{Q}T$	0.43 ± 0.01	48	0.50 ± 0.01	31	0.001†
$\dot{Q}t$, L/min	6.08 ± 0.26	50	7.00 ± 0.35	30	0.037†
PEEP, cm H_2O	9.1 ± 0.5	84	11.7 ± 0.8	40	0.005†
V_T, ml	892 ± 26	89	616 ± 26	40	< 0.001†

Definition of abbreviations: N = number of patients for whom data were available; rapid/slow = ECMO blood gas entry criteria (see table 2); ARDS = time from ARDS onset to randomization; study = time from randomization until death or extubation; pump = time on extracorporeal support.

* Comparison of demographic and physiologic data for current clinical trial patients with those of the 1974 to 1977 ECMO clinical trial (10, 30).

† Statistically significant.

tive pressure ventilation, and ≥50% O_2 breathing for ≥24 h) (56). Only 7% of the 486 patients with at least moderate hypoxic lung failure (36 + 450) had severe ARDS and met the ECMO criteria. In contrast, Zapol and colleagues reported that 49% of 302 patients with at least moderate hypoxic respiratory failure met ECMO criteria (12). In addition, among 227 patients without respiratory failure but at risk for developing ARDS, 11 developed moderate hypoxic respiratory failure and 18 developed severe ARDS and met ECMO criteria. Of these 29 patients at risk who developed respiratory failure (11 + 18), 62% (18 of 29) developed severe ARDS and met ECMO criteria (12). Although the definition of moderate respiratory failure in these publications is not the same as our definition of ARDS, it defines a seriously ill population with reported mortality rates of 64% (56) and 55% (12). This seriously ill population includes many patients with ARDS and provides evidence of the expected range (7 to 62%) for ARDS patients meeting ECMO criteria among patients with moderate hypoxic respiratory failure. We enrolled 40 of the 41 eligible ARDS patients meeting ECMO criteria. Our 40 clinical trial patients, therefore, are likely representative of the eligible ARDS patients meeting ECMO criteria in our hospital. Transportation of these severely ill patients by air over long distances has been demonstrated to be safe and to be without significant impact on patient blood gas values (57).

During preparation for this clinical trial, we concluded from published reports (26, 29) that there was about a 0.5 prior probability that LFPPV-$ECCO_2R$ was a superior therapy for ARDS. We ex-

pected a survival of 9% in the control CPPV patient group (10, 11). Whether our unexpected overall 40 patient survival of 38% is the result of patient selection, therapeutic or clinical environment changes, the use of detailed protocols for respiratory care, or other factors is not known. Our protocols for management of mechanical ventilation and for management of LFPPV-$ECCO_2R$ reflect the clinical care style in Milan. Despite our attempts to duplicate the care applied in Milan (26, 29) through multiple visits to Milan and through collaboration with Milanese coworkers in Salt Lake City, there remain many differences in our two clinical environments. The difference in distribution of ARDS etiology (table 7) is one that could be important. Trauma was a more frequent cause in the Milanese studies. Some have suggested that trauma as an ARDS etiology may be followed by higher survival (59). It is the existence of such differences that makes interpretation of clinical outcomes difficult (60). The inclusion of concurrent control subjects and the control of medical care process (for example, through the use of computerized protocols) in clinical investigation are important responses to this problem.

We stopped the clinical trial after enrolling only 40 patients. This followed our second interim analysis β projection. This indicated that we would be unlikely to demonstrate a significant difference in survival between the two therapy groups with the originally projected enrollment of 60 patients. *Post hoc* power calculations were performed for $\alpha = 0.05$ and power = 0.8 (50). For one-sided α we would need to enroll 300 patients in each therapy group and for two-sided α we would need to enroll 400 patients in each therapy group to reach statistical significance. Interestingly, the small survival difference we observed favored the control therapy. The contribution of our limited experience with LFPPV-$ECCO_2R$ is difficult to assess. One of our first 2 patients supported with LFPPV-$ECCO_2R$ survived (before the clinical trial began). In addition, we observed the same survival in the first 10 and last 9 LFPPV-$ECCO_2R$ patients in the clinical trial. We therefore saw no evidence of increasing survival as we gained experience with LFPPV-$ECCO_2R$.

The Milan group initially reported a 77% survival of severe ARDS patients after support with PCIRV, followed if necessary by LFPPV-$ECCO_2R$. Half of these survivors recovered after PCIRV alone, without ever receiving LFPPV-$ECCO_2R$ (29). Subsequent reports from Milan and other centers did not include PCIRV in the therapy program. Only 1 of our 21 new therapy patients recovered after PCIRV, without LFPPV-$ECCO_2R$; 1 new therapy patient died before LFPPV-$ECCO_2R$ could be initiated. The remaining 19 new therapy patients were supported with LFPPV-$ECCO_2R$. The survival of these 19 patients after LFPPV-$ECCO_2R$ is consistent with the survivals reported from several European centers. LFPPV-$ECCO_2R$ support of ARDS patients meeting ECMO criteria has been followed by survival rates of 49% (21 of 43) (26), 50% (38 of 76) (61), and 43% (15 of 35; personal communication, Brunet, Cochin-Port Royal Hospital, University of Paris) (69). The 32% survival for our 19 LFPPV-$ECCO_2R$ patients is statistically indistinguishable from the 43 to 50% survival data from other centers (M-H, $p = 0.5$). We randomized all patients who met entry criteria, despite the gravity of their clinical state (1 new therapy patient died rapidly before we could initiate LFPPV-$ECCO_2R$, and 2 patients died within 1 day after initiating LFPPV-$ECCO_2R$). We observed the "intention-to-treat" principle in our evaluation of this new therapy in the clinical trial (62). In contrast, we expect that a more selective LFPPV-$ECCO_2R$ application policy would be used by clinical centers providing LFPPV-$ECCO_2R$ as an established therapy.

The 42% survival of our 19 control patients is an unexpected increase (our ARDS patients meeting ECMO criteria experienced a 0 to 9% survival from 1974 to 1985) (10 , 11). The 12.8% combined published survival rate for ARDS patients who meet ECMO criteria and receive only mechanical ventilation support (10–12) is significantly different from our current control group survival of 42% (8 of 19) (χ^2, $p = 0.0001$). It does not seem to be explained by the etiology of ARDS. The distribution of etiologies of the patients in the current clinical trial is similar to that of the patients in the ECMO clinical trial of 1974 to 1977 (table 7). This unexpected increase in control patient survival emphasizes the importance and necessity of concurrently controlled, randomized clinical trials with precise patient selection. It underscores the limitations both of historical control subjects (10) and of concurrent control subjects from other institutions (12).

An uneven distribution of patients at the time of randomization is a potential explanation for this unexpectedly high survival in the control group. New therapy patients were randomized later than control patients (table 4). However, these differences and those in demographic and physiologic variables at the time of randomization were not statistically significant (tables 3 and 4). The severity of illness, assessed by several scoring systems and an organ failure count, was almost identical in both therapy groups. The equivalent patient transportation distances were further evidence that the randomization appropriately distributed patients between the two therapy groups. We recognize that statistical analyses are easier to interpret than the clinical significance of the observed therapy group differences. Nevertheless, these data strongly support the conclusion that the randomization process distributed patients uniformly between the control and the new therapy groups.

Our patients appear to have died a "respiratory" death (pulmonary gas-exchange failure) as frequently as the patients in the 1974 to 1977 ECMO clinical trial. This observation, coupled with the similarity of etiologies of ARDS (table 7) and of physiologic variables at the time Pa_{O_2} satisfied ECMO entry criteria (table 14), lead to the conclusion that our 40 randomized patient population is comparable to the 90 randomized patient population of the 1974 to 1977 ECMO clinical trial.

Nonuniformity of patient care following randomization was likely reduced by the protocol control of care. The two patient groups were subjected to equivalent intensity of therapy. The similar numbers of changes in $F_{I_{O_2}}$ and PEEP in the two therapy groups indicates that the computerized protocol control of mechanical ventilation achieved the goal of controlling and making uniform the intensity of care (for maintenance of Pa_{O_2}) of all patients in the randomized clinical trial.

The average duration of LFPPV-$ECCO_2R$ in our 19 LFPPV-$ECCO_2R$ patients (table 8) is comparable to that reported by the Milanese group (26, 29). Since the goal of LFPPV-$ECCO_2R$ is to allow "lung rest," it is crucial that the technique lead to a reduction in Ppeak and VR. The mean Ppeak was 45.4 cm H_2O for the 19 new therapy patients supported extracorporeally (35.8 cm H_2O for the first 10 patients) 3 to 6 h after initiating LFPPV-$ECCO_2R$, (table 10) , and the overall mean Ppeak, from randomization to death or extubation, for all modes of mechanical ventilation considered together was 49.5 cm H_2O in new therapy patients. These are 12.1 and 8.3 cm H_2O lower than the Ppeak of 57.8 cm H_2O in control patients during mechanical ventilation with CPPV (see supplemental tables in NAPS document No. 05073 for details). Our inability to maintain Ppeak below 45 cm H_2O in the group receiving new therapy appears primarily due to the overall mean Ppeak (54.1 cm H_2O) required to maintain a minimum V_T of about 250 ml (3.5 to 4.5 ml/kg BWp) during the entire LFPPV-$ECCO_2R$

period, when the mean CTH was 8.2 ml/cm H_2O (the lowest observed during the clinical trial). There was a significant reduction in overall VR and $\dot{V}E$ during LFPPV-ECCO$_2$R. Regarding lung rest, these low levels of VR (3.9/min) and $\dot{V}E$ (0.9 L/min) seem likely to be clinically significant.

In contrast to the experience in Milan (26) and in Paris (Brunet, personal communication) (69), we did not observe dramatic increases in Pa_{O_2} within a few hours after LFPPV-ECCO$_2$R initiation, even though the Ppeak was reduced to an average of 35.8 cm H_2O 3 to 5 h following the initiation of LFPPV-ECCO$_2$R in our first 10 patients.

For all patients, the arterial oxygenation protocols consistently reduced FI_{O_2} and PEEP to the lowest values necessary to maintain the common Pa_{O_2} end point of 59 mm Hg. This goal of minimal therapy was based upon concern for barotrauma as a result of overinflation and upon concern for O_2 toxicity. We recognize that this is only one of many possible therapeutic strategies. The common Pa_{O_2} end point for arterial oxygenation protocols enhances the interpretability of our results since it eliminates the difficult problem of comparing two groups of patients maintained at different Pa_{O_2} end points. For example, interpretation of the impact of a new mechanical ventilation mode would be made more difficult by allowing the control group to have a Pa_{O_2} of 68 mm Hg and the test group a Pa_{O_2} of 134 mm Hg. Driving all patients to the same end point by different therapy methods allows explicit testing of the methods without interference from nonuniform end points.

The complications (table 11) raise clear concerns and an interesting observation. The new therapy patients clearly suffered more non-CNS hemorrhage and had a greater blood replacement requirement (table 11). However, the anticoagulation that likely predisposed these patients to these complications may have provided some protection against peripheral vascular complications, which were more common in the control therapy group.

Bleeding remains the major complication of LFPPV-ECCO$_2$R (63, 64), with transfusion requirements of 1.4 to 1.8 L/day in experienced hands (26, 65). Blood product consumption was higher in our LFPPV-ECCO$_2$R patients. It exceeded the transfusion requirements currently reported from experienced LFPPV-ECCO$_2$R centers (66). Perhaps this reflects our inexperience with the technique. Nevertheless, our survival is similar to that reported from more experienced centers. In addition, we made a major effort to apply the principles and technique developed by Gattinoni, Pesenti, Kolobow, and others in their innovative application in Milan. It is noteworthy that our experience during the 1974 to 1977 collaborative ECMO clinical trial was the same as that of our more experienced colleagues (we had one of the four survivors in the ECMO group).

The hospital costs for a new therapy patient ($120,800) exceeded those for a control therapy patient ($97,200) by $23,600 (table 9). Recent estimates of ARDS incidence suggest that 12,500 ARDS per year could be expected in the United States (67). Should these patients be supported with LFPPV-ECCO$_2$R, this would produce a cost increase of $295,000,000 per year compared with the cost of treatment with mechanical ventilation alone.

In summary, we failed to find a statistically significant difference in survival between control and extracorporeal treatment patient groups. We therefore do not recommend LFPPV-ECCO$_2$R as a therapy for ARDS. In our opinion, LFPPV-ECCO$_2$R for ARDS patients should be restricted to controlled clinical trials.

Acknowledgment. We are grateful to Drs. Roberta M. Golding, Waldemar G. Johanson, Jr., and Robert M. Rogers for their foresight and support during the preparatory phase of this clinical trial. We thank Marlene Egger, Ph.D. for statistical and experimental design advice during study preparation. For protocol field testing and administrative support, we thank Polly Bailey, R.N., Scott Crowley, R.N., Layne Gordon, R.R.T., (Registered Respiratory Therapist), Jeff Holverson, R.R.T., Roger Lewis, R.R.T., Steve Gordon, R.R.T., Rosalie Warnock, R.R.T., Emily Shifrar, R.R.T., Larry Meyers, R.R.T., Terianne Davis, R.R.T., Lori Carpenter, R.R.T., Ted Tarr, R.R.T., Max Eskelson, R.R.T., Marge Budd, R.N., M.S., Judy Blaufuss, R.N., M.S., Pamela Cipriano, R.N., M.S., Vicki Spuhler, R.N., M.S., Loren Greenway, R.R.T., (Director, Respiratory Therapy), the nursing staff of the Shock Trauma/Intermountain Respiratory ICU, and the nursing, respiratory therapy, and administrative staff of the LDS Hospital. We thank Ronald Veitch, C.C.P. for initial guidance and Lewis Ershler, M.S. for technical support with the development and operation of the extracorporeal system and Susan Henderson, B.A., Debra Carlson, B.A., and Robert Crapo, M.D. for protocol performance data analysis, Susan Horn, Ph.D. for statistical consultation and assistance with data analysis, and Drs. Robert Crapo, C. Gregory Elliot, Fabrice Brunet, George Thomsen, and Susan Horn for critically reviewing the manuscript. We thank the referring physicians in the United States and Canada for their trust and support and Drs. Robert Bartlett, Theodore Kolobow, Luciano Gattinoni, Antonio Pesenti, and their colleagues for their advice and support. We gratefully acknowledge the donation of the following equipment: Venous Return Catheters (Research Medical, Inc., 1847 West 2300 South, Salt Lake City, UT 84119); Centrimed System 1 centrifugal pump (Centrimed, 651 16th Ave. South, Hopkins, MN 55343); Biomedicus Model 540 Series Bio-Console® centrifugal pump (Biomedicus, 9600 West 76th St., Eden Prairie, MN 55344); COBE precision blood (roller) pump (COBE Laboratories, Inc., 1185 Oak Street, Lakewood, CO 80215); silicone rubber tubing (Fluorocarbon-Flo-Med, 555 Weddell Ave., Sunnyvale, CA 94089; Sil-Med Corp., Snug Harbor Station, Doxbury, MA 02332); membrane lungs and brackets (SciMed Life Systems, Inc., 13000 County Road 6, Minneapolis, MN 55441); O_2 humidifiers (Mauna Loa Lava Pak®, Mauna Loa Medical, Inc., 3305 Springmountain Rd. #60, Las Vegas, NV 89102); 900C Servo® ventilators (Siemens Medical Systems, Inc., 10 Constitution Avenue, Piscataway, NJ 08855); Ohmeda CPU-1 ventilators (Ohmeda, 9065 Guilford Road, Columbia, MD 21046-1801); Sechrist 3500HL Hi/Lo® flow air oxygen mixers (Sechrist Industries, Medical Products Division, 2820 Gretta Lane, Anaheim, CA 92806); and Accuflow classic flowmeters (Timeter Instrument Corporation, 2501 Oregon Pike, Lancaster, PA 17601).

References

1. Ashbaugh D, Bigelow D, Petty T, Levine B. Acute respiratory distress in adults. Lancet 1967; 2:319–23.
2. NHLI. Respiratory diseases: task force report on problems, research approaches, needs. Washington, DC: U.S. Government Printing Office, 1972; DHEW Publication No. (NIH) 73–432.
3. Pontoppidan H, Wilson R, Rie M, Schneider R. Respiratory intensive care. Anesthesiology 1977; 47:96–116.
4. Rinaldo J, Rogers R. Adult respiratory distress syndrome—changing concepts of lung injury and repair. N Engl J Med 1982; 306:900–9.
5. Fowler A, Hamman R, Good J, Kim N, Benson B, Baird B, Eberle D, Petty T, Hyers T. Adult respiratory distress syndrome: risk with common predispositions. Ann Intern Med 1983; 98:593–7.
6. Bell RC, Coalson J, Smith J, Johanson W. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:293–8.
7. Montgomery AB, Stager M, Carrico C, Hudson L. Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132(3):485–8.
8. Fowler A, Hamman R, Zerbe G, Benson K, Hyers T. Adult respiratory distress syndrome: prognosis after onset. Am Rev Respir Dis 1985; 132(3): 472–8.
9. Artigas A. Adult respiratory distress syndrome: changing concepts of clinical evolution and recovery. In: Vincent J, ed. Update in intensive care and emergency medicine, vol. 5, Update 1988. Berlin: Springer Verlag, 1988; 97–114.
10. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce ECII, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG. Extracorporeal membrane oxygenation in severe acute respiratory failure. JAMA 1979; 242:2193–6.
11. Rollins R, Morris A, Mortensen C, Cipriano P. Arterial hypoxemia in 1985 predicts a mortality identical to that in 1975. Clin Res 1986; 34:79A.
12. Zapol WM, Frikker MJ, Pontoppidan H, Wilson RS, Lynch KE. The adult respiratory distress syndrome at Massachusetts General Hospital, etiology progression and survival rates, 1978–1988. In: Zapol W, Lemair F, eds. Adult respiratory distress syndrome. New York: Dekker, 1991; 367–80.
13. Klein J, van Haeringen J, Sluiter H, Holloway R, Peset R. Pulmonary function after recovery from the adult respiratory distress syndrome. Chest 1976; 63:350–5.
14. Lakshminarayan S, Stanford R, Petty T. Prognosis after recovery from adult respiratory distress syndrome. Am Rev Respir Dis 1976; 113:7–16.
15. Douglas M, Downs J. Pulmonary function following severe acute respira-

tory failure and high levels of positive end-expiratory pressure. Chest 1977; 71:18–23.
16. Yahav J, Lieberman P, Molho M. Pulmonary function following the adult respiratory distress syndrome. Chest 1978; 74:247–50.
17. Elliott C, Morris A, Cengiz M. Pulmonary function and exercise gas exchange in survivors of adult respiratory distress syndrome. Am Rev Respir Dis 1981; 123:492–5.
18. Suchyta MR, Clemmer TP, Orme JF, Morris AH, Elliott CG. Increased survival of ARDS patients with severe hypoxemia (ECMO criteria). Chest 1991; 99:951–5.
19. Kolobow T. An update on adult extracorporeal membrane oxygenation-extracorporeal CO_2 removal. Trans Am Soc Artif Intern Organs 1988; 34:1004–5.
20. Nash G, Bowen J, Lanlinais P. "Respirator lung": a misnomer. Arch Pathol 1971; 21:234–40.
21. Greenfield L, Ebert P, Benson D. Effect of positive pressure ventilation on surface tension properties of lung extracts. Anesthesiology 1964; 25:312–6.
22. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985; 132:880–4.
23. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Am Rev Respir Dis 1988; 137:1159–64.
24. Snyder J. The development of supported ventilation: a critical summary. In: Snyder J, Pinsky M, eds. Oxygen transport in the critically ill. Chicago: Year Book Medical Publishers, 1987; 283–94.
25. Pesenti A, Gattinoni L, Kolobow T, Damia G. Extracorporeal circulation in adult respiratory failure. Trans Am Soc Artif Intern Organs 1988; 34:43–7.
26. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, Iapichino G, Romangnoli G, Uziel L, Agostoni A, Kolobow T, Damia G. Low frequency positive pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986; 256:881–6.
27. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total curve of total respiratory system in acute respiratory failure. Am Rev Respir Dis 1987; 136:730–6.
28. Morris AH, Menlove RL, Rollins RJ, Wallace CJ, Beck E. A controlled clinical trial of a new 3-step therapy that includes extracorporeal CO_2 removal for ARDS. Trans Am Soc Artif Intern Organs 1988; 34(1):48–53.
29. Gattinoni L, Pesenti A, Caspani M, Pelizzola A, Mascheroni D, Marcolin R, Iapichino G, Langer M, Agostoni A, Kolobow T, Melrose D, Damia G. The role of total static lung compliance in the management of severe ARDS unresponsive to conventional treatment. Intensive Care Med 1984; 10:121–6.
30. NHLBI. Extracorporeal support for respiratory insufficiency: a collaborative study in response to RFP-NHLI-73-20; appendices 1 and 2. Bethesda: U.S. Department of Health, Education and Welfare; National Institutes of Health, 1979; 247–64.
31. Bone R. Extracorporeal membrane oxygenation for acute respiratory failure (editorial). JAMA 1986; 256:910.
32. Hickling K. Low volume ventilation with permissive hypercapnia in the adult respiratory distress syndrome. Clin Intensive Care 1992; 3:67–78.
33. Knaus W, Draper E, Wagner D, Zimmerman J. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818–29.
34. Stevens L. Gauging the severity of surgical sepsis. Arch Surg 1983; 118:1190–2.
35. East TD, Böhm SH, Wallace CJ, Clemmer TP, Weaver LK, Orme JF Jr, Morris AH. A successful computerized protocol for clinical management of pressure control inverse ratio ventilation in ARDS patients. Chest 1992; 101:697–710.
36. East T, Morris A, Wallace C, Clemmer T, Orme J Jr, Weaver L, Henderson S, Sittig D. A strategy for development of computerized critical care decision support systems. Int J Clin Monit Comput 1992; 8:263–9.
37. Henderson S, Crapo R, Wallace C, East T, Morris A, Gardner R. Performance of computerized protocols for the management of arterial oxygenation in an intensive care unit. Int J Clin Monit Comput 1992; 8:271–80.
38. Morris AH. Acute respiratory failure: therapeutic strategies. In: Parillo JE, ed. Current therapy in critical care medicine. BC Decker, Toronto, 1986; 142–8.
39. Morris AH, Crapo R. Buffer equlibria in specialized tissues lungs. In: Geibisch DSaG, ed. The regulation of acid-base balance. New York: Raven Press, 1989; 123–37.
40. Larsen KG, Clemmer TP, Nicholson L, Conti MT, Peterson H. Computer support in monitoring of nutritional therapy. Nutr Support Serv 1983; 3:7.
41. Harris, B. A biometric study of basal metabolism in man. Publication No. 279. Washington, DC: Carnegie Institution of Washington, 1919.
42. Pryor TA, Warner HR, Gardner RM, Clayton PD, Haug PJ. The HELP system development tools. In: Orthner H, Blum B, eds. Implementing health care information systems. New York: Springer-Verlag, 1989; 365–83.
43. Kuperman GJ, Garder RM, Pryor TA. HELP: a dynamic hospital information system. New York: Springer-Verlag, 1991.
44. Uziel L, Cugno M, Cacciabue E, Columbo A, Stabilini R, Mascheroni D, Agostoni A. Evaluation of tests for heparin control during long-term extracorporeal circulation. Int J Artif Organs 1986; 9:111–6.
45. Uziel L, Cugno M, Fabrizi I, Pesenti A, Gattinoni L, Agostoni A. Pathophysiology and management of coagulation during long-term extracorporeal respiratory assistance. Int J Artif Organ 1990; 3:1280–7.
46. Killpack A, Budd M, Chapman R, Ranzenberger J, Johnson D, Pryor T. Automated patient acuity in critical care units from nursing documentation. Proceedings 8th Annual Symposium on Computer Applications in Medical Care. Washington, DC: IEEE Computer Society Press, Los Alamitos, CA, 1984; 709–11.
47. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. Am Stat Assoc 1958; 53:457–81.
48. Kalbfleish J, Prentice R. The statistical analysis of failure time data. New York: John Wiley and Sons, 1980.
49. Lachin JM. Introduction to sample size determinations and power analysis for clinical trials. Controlled Clin Trials 1981; 2:93–113.
50. Cohen J. Statistical power analysis for the behavioral sciences, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
51. O'Brian PC, Flemming TR. A multiple-testing procedure for clinical trials. Biometrics 1979; 35:549–56.
52. Pocock J. Interim analyses for randomized clinical trials the group sequential approach. Biometrics 1982; 38:153–62.
53. Lan K, Wittes J. The beta-value: a tool for monitoring data. Biometrics 1988; 44:579–85.
54. Light R, Margolin B. An analysis of variance for categorical data. Stat Assoc 1971; 66:534–44.
55. NHLBI. Extracorporeal support for respiratory insufficiency: a collaborative study in response to RFP-NHLI-73-20, Appendices 9 and 10. Bethesda: U.S. Department of Health, Education and Welfare, National Institutes of Health, 1979; 305–70.
56. Bartlett RH, Morris AH, Fairley HB, Hirsch R, O'Connor N, Pontoppidan H. A prospective study of acute hypoxic respiratory failure. Chest 1986; 89:684–9.
57. Harless KW, Morris AH, Cengiz M, Hold R, Schmidt CD. Civilian ground and air transport of adults with acute respiratory failure. JAMA 1978; 240:361–5.
58. Gattinoni L, Pesenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, Scarani F, Marcolin R, Capelletti G. Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imag 1986; 1(3):25–30.
59. Artigas A, Carlet J, Le Gall J, Chastang C, Blanch L, Fernandez R. Clinical presentation, prognostic factors, and outcome of ARDS in the European collaborative study (1985–1987): a preliminary report. In: Zapol W, Lemaire F, eds. Adult respiratory distress syndrome. New York: Dekker, 1991; 37–63.
60. Hickling KG. Extracorporeal CO_2 removal in severe adult respiratory distress syndrome. Anaesth Intensive Care 1986; 14:46–53.
61. Wagner P, Knoch M, Sangmeister C, Muller E, Lennartz H. Extracorporeal gas exchange in adult respiratory distress syndrome: associated morbidity and its surgical treatment. Br J Surg 1990; 77:1395–8.
62. Hulley S, Cummings S. Designing clinical research. Baltimore: Williams and Wilkins, 1988.
63. Eagan T, Duffin J, Glynn M, Todd T, DeMajo W, Murphy E, Fox L, Cooper J. Ten-year experience with extracorporeal membrane oxygenation for severe respiratory failure. Chest 1988; 94(4):681–7.
64. Pesenti A, Gattinoni L, Cugno M. Problems in long-term veno-venous bypass. In: Gille J, ed. Neonatal and adult respiratory failure. Paris: Editions Scientifiques Elsevier, 1989; 173–7.
65. Pesenti A, Kolobow T, Gattinoni L. Extracorporeal respiratory support in the adult. Trans Am Soc Artif Intern Organs 1988; 34:1006–8.
66. Anderson HI, Steimle C, Shapiro M, Delius R, Chapman R, Hirschl R, Bartlett R. Extracorporeal life support (ECLS) for adult cardiorespiratory failure. Surgery 1993; 114:161–72.
67. Thomsen G, Morris A, Danino D, Ellsworth J, Wallace C. Incidence of the adult respiratory distress syndrome in Utah. Am Rev Respir Dis 1993; 147(4, Part 2):A347.
68. Build 1979. Build Study. Society of Actuaries and Association of Life Insurance Medical Directories of America, 475 Martingale Road, Schaumburg, IL 60173–2226, 1980; 25–42.
69. Brunet F, Belgith M, Mira J, Lanore J, Vaxelaire J, Dall'ava Santucci J, Dhainaut J. Extracorporeal carbon dioxide removal and low-frequency positive-pressure ventilation. Chest 1993; 104:889–98.