

Low-Frequency Positive Pressure Ventilation with Extracorporeal Carbon Dioxide Removal (LFPPV-ECCO₂R): An Experimental Study

L. GATTINONI, MD*
T. KOLOBOW, MD†
T. TOMLINSON, BS‡
G. IAPICHINO, MD*
M. SAMAJA, PhD§
D. WHITE, MD§
J. PIERCE, DVM†
Bethesda, Maryland||

We describe a new form of mechanical pulmonary ventilation, low-frequency positive pressure ventilation with extracorporeal CO₂ removal (LFPPV-ECCO₂R). In a series of animal studies the rate of mechanical ventilation was 0.66, 1, 2, and 4 min⁻¹ at a tidal volume of 3, 10, and 15 ml kg⁻¹. We were able to maintain normal blood gases and normal lung volumes and lung mechanics even at the lowest ventila-

tor rate with tidal volumes of 10 or 15 ml kg⁻¹. Each experiment lasted 7 hours. Our data suggest a possible new dimension in the management of a difficult patient on mechanical pulmonary ventilation.

Key Words—VENTILATION, extracorporeal CO₂ removal and.

SINCE the introduction of intermittent positive pressure breathing (IPPB) in respiratory treatment some twenty years ago, many forms of mechanical ventilation (MV) have been described: continuous positive pressure breathing (CPPB),¹ high-frequency positive pressure ventilation (LFPPV),² and intermittent mandatory ventilation (IMV).³

Mechanical ventilation is frequently a life-saving procedure. But depending on the underlying pulmonary disease, 35%,⁴ 50%,⁵ or 95%⁶ of patients treated with MV ultimately die, either of the underlying disease process or of complications of pulmonary therapy with MV. There is a question as to whether MV offers the proper environment for the healing of the lungs, and whether

*Assistant Professor in Anesthesia. Present address: Institute of Anesthesiology, University of Milan, Via F. Sforza 35, 20122, Milano, Italy

†Senior Investigator

‡Biologist

§Staff Associate

||National Institutes of Health, National Heart, Lung, and Blood Institute, Laboratory of Technical Development, Building 10, Room 5D-20, Bethesda, Maryland 20014

Address reprint requests to Dr. Kolobow.

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it may contribute to the ultimate demise of the patient, since both pulmonary^{7,8} and systemic^{9,10} complications have been attributed to positive pressure breathing.

The ultimate goal of MV is not merely to prolong life, but to provide an optimum environment for healing of the lungs. Unfortunately, it is not easy to show what constitutes an optimum environment. In pneumonia involving a single lobe, consolidation of the involved lobe with no ventilation is considered the optimal milieu for lung healing. It is not known what constitutes the optimum milieu for lung healing when the lungs are diffusely diseased.

Recently, IMV has been used not only in weaning of the patient from a ventilator, but also in treatment of acute respiratory failure.¹¹ It has been suggested that mechanical ventilation at a rate of 1 to 2/min coupled with spontaneous breathing results in less barotrauma¹² and has less effect on circulatory hemodynamics.¹³ This low rate of mechanical ventilation is not possible when CO₂ elimination by spontaneous respiration is impaired. Whether IMV at this low rate provides a better environment for lung healing remains unproven.

It has been recently shown that spontaneous ventilation for CO₂ removal can be substantially decreased or can stop completely if part or all of the metabolic CO₂ produced is removed by an artificial lung.¹⁴ This suggests the possibility of controlling all forms of MV at will and still maintaining adequate alveolar ventilation. In this report we describe a new form of mechanical ventilation, low-frequency positive pressure ventilation with extracorporeal CO₂ removal (LFPPV-ECCO₂R). The total respiratory rate in these experiments was as low as 1 breath every 90 seconds. In studies in healthy paralyzed animals, LFPPV-ECCO₂R maintains normal lung volumes, normal lung mechanics, and normal blood gases.

MATERIALS AND METHODS

Five tracheostomized lambs weighing between 12 and 16 kg were anesthetized with pentobarbital, paralyzed with d-tubocurarine, and mechanically ventilated with a Harvard ventilator. The ventilator was modified to give a constant inspiratory-expiratory time ratio of 1:1.5. A small Teflon® catheter (ID 1 mm) was placed through the tracheostomy tube, advanced to the level of the carina, and then connected to a source

of O₂. Intratracheal pressures were recorded by a Statham pressure transducer. Total ventilation was continuously monitored with a recording bell spirometer. Positive end-expiratory pressure (PEEP), when used, was obtained by placing an appropriate weight on the top of the bell. Mixed expired gases, partial pressures were measured by a Medical Mass Spectrometer.* Pulmonary gas was aspirated at the end of each study period (ie, every 30 minutes) at a constant rate of 8 ml · sec⁻¹ for 20 seconds, and the composition of the gas as it emerged from the tracheal inlet was measured by a Medical Mass Spectrometer. The sampled gases were assumed to be "alveolar" when the PCO₂ plateau equaled arterial PCO₂ (±1.5 torr). The functional residual capacity (FRC) was measured by the helium dilution technic and expressed at BTPS. The total static compliance was computed from the tracheal pressure reading after 100 ml of air were injected. Both FRC and total lung compliance were measured at atmospheric pressure. Lycra® polyurethane catheters (ID 3.5 mm) were placed in the subclavian artery and in the external jugular vein, and blood was pumped from the artery through an extracorporeal carbon dioxide membrane lung (CDML), surface area 1.6 m², and into the vein. The CDML was designed for optimum CO₂ removal.¹⁵

The extracorporeal circuit was primed with heparinized lactated Ringer's solution (8 units/ml). Extracorporeal blood flow ranged between 500 and 800 ml min⁻¹. Continuous heparinization was maintained at 100 μ kg⁻¹ hr⁻¹. Oxygen saturation of arterial hemoglobin was monitored by an on-line oximeter.¹⁶ The membrane lung was ventilated with humidified room air (37 C) at a flow between 3500 and 4000 ml min⁻¹. The gas compartment of the CDML was kept at 200 to 250 mm Hg below the atmospheric pressure. Total CO₂ removed by the CDML was computed from the gas flow and the CO₂ concentration of effluent gas, measured by an infrared CO₂ analyzer, † and expressed at STPD.

The experimental setup is shown in fig 1. Arterial blood samples were obtained before and after the CDML, and the mixed venous blood samples were obtained through a 5 French Swan-Ganz catheter positioned in

*Medical Mass Spectrometer—MM-8, Scientific Research Instrument Corporation, Baltimore, Maryland

†Beckman, Model 315A

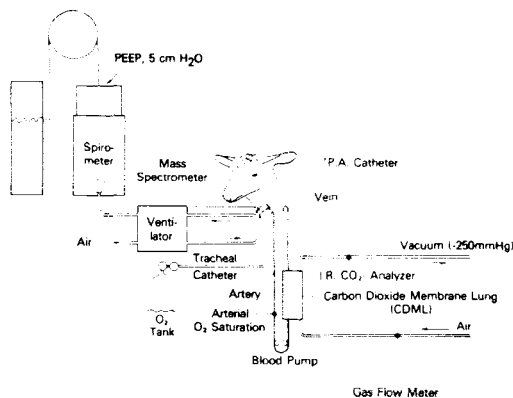


Fig 1. Experimental setup

the pulmonary artery. Blood P_{O_2} , P_{CO_2} , and pH were immediately measured by a Radiometer Blood Gas Analyzer.* Oxygen saturation of hemoglobin was measured by an A.O. Oximeter† calibrated for sheep blood. Total hemoglobin was measured by Drabkin's method. Using standard formulas, from these data we computed O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), venous admixture fraction (QVA/QT), and cardiac output (CO).

EXPERIMENTAL PROCEDURE

The lambs initially were mechanically ventilated with room air for 30 minutes at 10 ml kg^{-1} tidal volume and at a respiratory rate of 16 min^{-1} . The expiration was passive to the atmosphere (baseline conditions). There was no extracorporeal CO_2 removal at this time (zero gas flow through the CDML). At the end of 30 minutes, a complete set of measurements was taken.

The animals were then started on apneic oxygenation, and CO_2 was removed by the extracorporeal CDML for a period of 30 minutes in the following manner: The mechanical ventilator was stopped and 100% O_2 was supplied to the natural lung through a Teflon® catheter to maintain the lungs inflated at 5 cm H_2O pressure. We then began CO_2 removal by starting the gas flow to the CDML. At the end of 30 minutes a new set of measurements was taken.

Following this, the animals were ventilated at 5 cm H_2O PEEP with room air at 0.66, 1, 2, or 4 breaths min^{-1} . Measurements were taken at tidal volumes (TV) of 3, 10, or 15 ml kg^{-1} at these 4 frequencies after 30

minutes. During all 12 LFPPV periods, the CO_2 was continuously removed by the CDML and 100% O_2 was continuously supplied at 190 ml min^{-1} through the Teflon® cannula. The complete study lasted 7 hours. At the end of the experiments the animals were electively sacrificed.

RESULTS

The CO_2 transfer of the CDML has been previously described, and was consistent with our previous findings.¹⁵ The amount of CO_2 removed was always sufficient to clear the CO_2 production, even during periods of apnea (table 1). The O_2 consumption during the control periods in this series of lambs averaged $5.09 \text{ ml kg}^{-1} \pm 0.59$. We did not observe any significant changes in acid-base balance. Table 2 shows the effects of LFPPV-ECCO₂R on alveolar gases, arterial and mixed venous blood gases, arterial and mixed venous pH, and arterial and mixed venous blood O_2 content difference. The low-frequency positive pressure ventilation appears to be meaningful from the ventilatory point of view only at TV-15. The P_{aCO_2} at TV-15 is significantly lower than at TV-3 and at TV-10, and decreases with increasing respiratory frequency (fig 2). However, even though without respiratory meaning, different TV ventilation appears to affect lung mechanics and the shunt fraction (table 3). The FRC was a function of the TV and was independent of respiratory frequency (fig 3). Total static compliance correlated with the FRC ($r = 0.96$, $p < 0.001$; not shown).

DISCUSSION

These studies were performed at a RR heretofore not possible, and yet we were

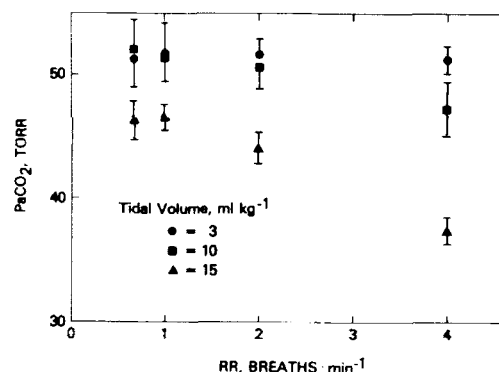


FIG 2. Arterial P_{CO_2} as a function of respiratory rate, at different tidal volumes (mean values ± 1 SE)

*Mod. PHM 27, Copenhagen, Denmark

†A. O. Oximeter, Model 10800, Buffalo, New York

TABLE 1
Performance of the CDML at Different Tidal Volumes and
Respiratory Rates
(Mean Values \pm 1 SD)

RR breaths \cdot min ⁻¹	Apnea		TV-3		TV-10		TV-15					
	0	0.66	1	2	1	2	1	2				
Pco ₂ after CDML (mm Hg)	31.16 \pm 1.28	32.8 \pm 3.70	33.1 \pm 3.36	33.2 \pm 2.92	32.7 \pm 2.38	32.1 \pm 3.36	30.1 \pm 3.95	28.4 \pm 5.40	31.8 \pm 2.97	34.3 \pm 5.69	26.6 \pm 2.88	27.8 \pm 0.81
pH after CDML	7.48 \pm 0.073	7.486 \pm 0.088	7.498 \pm 0.081	7.476 \pm 0.091	7.476 \pm 0.083	7.472 \pm 0.073	7.496 \pm 0.077	7.500 \pm 0.065	7.504 \pm 0.071	7.524 \pm 0.085	7.538 \pm 0.0739	7.520 \pm 0.063
CO ₂ transfer (ml min ⁻¹)	80.7 \pm 16	80.14 \pm 13.84	81.14 \pm 12.57	82.92 \pm 17.7	82.90 \pm 14.9	80.26 \pm 14.7	79.24 \pm 13.2	74.5 \pm 12.03	76.68 \pm 13.32	72.14 \pm 12.11	68.44 \pm 12.7	63.9 \pm 13.6
			81.77 \pm 13.7				78.58 \pm 12.3			70.29 \pm 12.7		

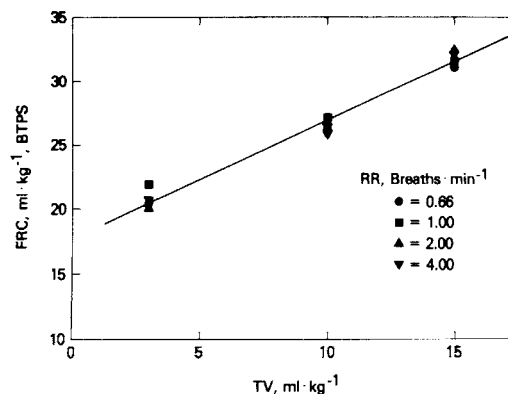


FIG 3. Functional residual capacity as a function of tidal volumes, at different respiratory rates (mean values)

able to maintain normal blood gases at RR less than 1/min. The extracorporeal CO₂ removal is the key element; all metabolically produced CO₂ can be removed by the CDML at a relatively low extracorporeal blood flow of 500 to 1000 ml min⁻¹.¹⁵ The technical complexity of extracorporeal CO₂ removal lies between hemodialysis (except that it must be used continuously) and extracorporeal blood gas exchange as used during cardiopulmonary bypass. No doubt LFPPV-ECCO₂R can be performed equally well with venovenous or venoarterial pumping.

A second key point is the continuous supply of 100% O₂ delivered directly into the trachea in an amount at least equal to the O₂ consumption. During LFPPV-ECCO₂R, the minute ventilation is greatly reduced and results in "alveolar hypoventilation." However, this is a unique form of hypoventilation characterized by a normal PACO₂. In classical terms hypoventilation implies hypercapnea, but in the LFPPV-ECCO₂R the PACO₂ is kept normal as the required amount of CO₂ is removed by the CDML. However, rather than raising FIO₂ to prevent alveolar hypoxia, we continuously administered 100% O₂ at 190 ml min⁻¹ directly into the trachea at a rate substantially in excess of V̇O₂. This insured that the O₂ consumed was continuously replaced, molecule for molecule, and alveolar PAO₂ remained unchanged; any excess of O₂ supplied was vented out through the endotracheal tube into the spirometer. It is important that 100% O₂, rather than air, be fed directly into the trachea; as O₂ is consumed, 100% O₂ must be replaced, rather than air which contains mostly nitrogen. By supplying all the O₂ consumed (and remov-

TABLE 2
Alveolar P_{O₂}, Arterial and Mixed Venous P_{O₂} and P_{CO₂}, and pH:
Arterial-Mixed Venous O₂ Differences at Different Respiratory Rates
and Tidal Volumes
(Mean Values ± 1 SD)

	Control		Apnea		TV-3		TV-10		TV-15		
	16	0	1	2	4	1	2	4	1	2	4
RR breaths · min ⁻¹			0.66		0.66		0.66		0.66		0.66
PA O ₂	98	135	247	232	308	332	109	157	174	197	166
torr	±11	±19	±108	±71.8	±102	±70	±19	±45	±35	±40	±38
			286 ± 89		166 ± 57						133 ± 35
PaO ₂	72.6	63.6	76.6	76.0	74.0	90.2	72.7	78.3	89.4	115.4	99.2
torr	±26	±7.7	±10.2	±9.9	±9.5	±19.6	±10.0	±4.3	±10.6	±27.7	±30.0
			79.2 ± 13.6		90.4 ± 22.8						79.2 ± 13.6
PaCO ₂	43.5	50.6	51.4	51.8	51.6	51.2	52.7	51.4	50.5	47.1	37.5
torr	±3.1	±6	±4.9	±6.0	±2.5	±2.5	±5.9	±5.2	±4.0	±4.6	±2.6
			51.4 ± 3.9		49.7 ± 5.7						44.0 ± 4.62
pHa	7.330	7.261	7.328	7.336	7.326	7.328	4.304	7.318	7.350	7.346	7.486
	±0.83	±0.83	±0.067	±0.059	±0.070	±0.060	±0.047	±0.062	±0.065	±0.033	±0.127
			7.329 ± 0.059		7.330 ± 0.053						7.410 ± 0.085
PvO ₂	45.6	49	50.2	50.3	47.6	52.5	52.7	54.5	51.5	55.4	48.2
torr	±10.2	±9.8	±8.4	±7.5	±5.9	±8.5	±8.8	±7.7	±7.8	±12	±10.9
			50.1 ± 7.24		54.0 ± 8.7						47.5 ± 8.7
PvCO ₂	46.6	49.2	49.2	49.3	48.4	46.9	46.9	47.3	46.5	44.8	39.1
torr	±4.68	±5.02	±5.72	±3.52	±1.81	±3.09	±7.66	±7.07	±7.64	±4.54	±4.85
			48.45 ± 3.6		47.05 ± 6.56						41.9 ± 4.57
pHv	7.296	7.27	7.346	7.358	7.364	7.338	7.318	7.325	7.352	7.370	7.456
	±0.89	±0.092	±0.073	±0.066	±0.085	±0.063	±0.046	±0.088	±0.076	±0.054	±0.089
			7.351 ± 0.067		7.342 ± 0.064						7.418 ± 0.073
Δ(a-v) O ₂	2.446	2.12	1.87	2.29	2.14	2.18	1.32	1.61	1.78	1.76	2.43
ml %	±1.25	±0.59	±0.24	±0.28	±0.94	±0.41	±0.72	±0.81	±0.73	±0.30	±0.91
			2.14 ± 0.559		1.67 ± 0.61						2.34 ± 0.077

TABLE 3
Peak Pressure, Total Static Compliance, Functional Residual Capacity, and
Venous Admixture at Different Respiratory Rates and Tidal Volumes
(Mean Values \pm 1 SD)

	Control		TV-3				TV-10				TV-15			
	16	0	1	2	4	1	2	4	1	2	4	1	2	4
RR breaths \cdot min ⁻¹			0.66			0.66			0.66			0.66		
Peak pressure (cm H ₂ O)	15.5 \pm 4.7		8.3 \pm 1.5	8.65 \pm 3.1	9.3 \pm 2.4	9.2 \pm 2.2	22.9 \pm 2.6	23.9 \pm 0.9	27.0 \pm 3.8	25.1 \pm 3.7	33.6 \pm 3.1	31.4 \pm 3.7	36.6 \pm 3.4	28.9 \pm 3.4
			8.68 \pm 2.22				24.7 \pm 3.13				31.3 \pm 3.6			
Total static compliance (ml \cdot cm H ₂ O ⁻¹)	10.8 \pm 2.62	8.8 \pm 2.10	7.9 \pm 4.0	8.6 \pm 3.3	6.4 \pm 3.6	7.6 \pm 4.1	9.7 \pm 2.6	10.0 \pm 1.4	10.0 \pm 2.8	10.7 \pm 2.9	11.6 \pm 4.9	12.6 \pm 4.3	12.3 \pm 4.6	13.0 \pm 4.4
			7.61 \pm 3.56				10.16 \pm 2.20				12.34 \pm 4.16			
FRC (ml kg ⁻¹ BTPS)	32.7 \pm 8.9	25.6 \pm 6.1	20.3 \pm 3.3	22.2 \pm 7.3	20.9 \pm 1.88	20.7 \pm 1.06	26.4 \pm 2.6	27.4 \pm 2.2	27.1 \pm 3.4	25.7 \pm 2.2	31.1 \pm 5.3	31.6 \pm 5.2	32.9 \pm 6.9	32.7 \pm 6.4
			20.8 \pm 3.63				26.67 \pm 2.52				32.03 \pm 5.25			
\dot{Q}_{VA}/\dot{Q}_R	0.268 \pm 0.18	0.30 \pm 0.17	0.37 \pm 0.11	0.34 \pm 0.07	0.38 \pm 0.12	0.36 \pm 0.11	0.22 \pm 0.20	0.21 \pm 0.09	0.21 \pm 0.11	0.19 \pm 0.11	0.24 \pm 0.11	0.21 \pm 0.14	0.11 \pm 0.11	0.14 \pm 0.11
			0.357 \pm 0.10				0.22 \pm 0.11				0.16 \pm 0.11			

ing all CO₂ produced), it becomes possible to maintain prolonged apnea. We have shown this during our control studies, as well as in our earlier study,¹⁷ where apnea was maintained for 24 hours with normal blood gases and full recovery.

We found a consistent respiratory effect for CO₂ removal through the natural lungs only at TV-15 ventilation, which increased with the respiratory rate.

While the PaCO₂ was steady during the LFPPV-ECCO₂R, our results showed a great variability of PAO₂ among the study periods. It has been established that during normal breathing with room air, the composition of alveolar gas becomes mainly a function of alveolar ventilation. During apnea, the gas composition in the natural lungs was totally controlled by the CDML; we previously showed that this control is through PN₂ in the CDML (ie, the PN₂ in the CDML is equal to the PaN₂ and PAN₂).¹⁷ TV-3 ventilation appears to be mainly a "dead-space" ventilation; in 3 out of 5 sheep the expired PCO₂ was zero. The relatively high PAO₂ found at TV-3 (mean, 280 torr) reflects nitrogen washout by the excess O₂ entering the trachea through the Teflon catheter, with only dead-space ventilation.

However, during the TV-10 and TV-15 ventilation, the lower PAO₂ is due to the supply of some nitrogen when ventilating with room air.

We would like to point out the paradoxical finding of higher Pco₂ and lower pH in arterial blood compared to pulmonary arterial blood. This is due to the acidification of blood by oxygenation of hemoglobin. The CO₂ content of the pulmonary arterial blood virtually equals the arterial CO₂ content, since little or no CO₂ is removed by the natural lungs. At constant total CO₂ in the blood, lowering pH by hemoglobin oxygenation results in raising Pco₂.

While low-frequency positive pressure breathing alone has little or no respiratory meaning, the mechanical inflation of the lungs has great effect on the lung volumes and compliances. This effect is not related to the frequency, but to tidal volume (fig 3). During apnea FRC fell to about 80% of control values, and during the subsequent TV-3 ventilation it was approximately 60% of control. With TV-10 and TV-15 ventilation, at all RR, lung volume and compliance returned to control values.

The mechanism responsible for the change in FRC, ie, alveolar collapse, is not clear. The effects of anesthesia and paralysis on FRC¹⁸ and on diaphragmatic mechanics¹⁹ have been well documented in man. Preliminary studies in our laboratory immediately after anesthesia and paralysis followed by apneic oxygenation in a plethysmograph showed a sudden small change in FRC, followed by a steady continuous decrease with time. A fall in FRC did not occur with LFPPV-ECCO₂R at TV-10 and TV-15. Intermittent sighing during IPPB in man also is known to prevent a decrease in FRC.²⁰ A rise in FRC resulted in a decrease in venous admixture, but no linear relationship could be demonstrated.

We have not explored the long-term effects of LFPPV-ECCO₂R. However, preliminary experiments of LFPPV-ECCO₂R for 24 hours confirm our present results.

The main function of mechanical inflation of the lungs in this study was to maintain lung volumes rather than to provide for CO₂ and O₂ exchange; this was successful in TV-10 and TV-15 ventilation, but not successful at TV-3 ventilation. The RR of 1 breath every 90 seconds was the lowest setting of the ventilator; however, it might be possible to lower the RR to once every 2 or 5 minutes and still maintain the basal FRC. This is suggested from our earlier studies when the FRC returned to normal after 5 minutes of manual ventilation following 24 hours of apnea.¹⁷ These findings could become useful in the understanding and management of patients on MV.

As described here, LFPPV-ECCO₂R was used for controlled ventilation in paralyzed animals. No doubt the CDML can also be used in conjunction with IMV to permit low-frequency positive pressure ventilation in spontaneously breathing patients, including those in whom IMV at a low frequency may be desirable but not now possible because of inability of spontaneous respiration to adequately remove CO₂.

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PULMONARY FUNCTION AFTER TRANSFUSION

Ventilatory volumes, blood gases, and other aspects of pulmonary function were measured before and after intraoperative transfusion in 16 patients who had undergone operation under general anesthesia. One group of 8 patients was transfused with an average of 1275 ml of stored blood passed through a standard nylon-mesh filter (SF group). Another group of 8 patients was transfused with an average of 1375 ml of stored blood passed through a dacron-wool filter (DWF group).

Since respiration was depressed slightly by preanesthetic sedation, a lowered expired minute ventilation (V_E) and tidal volume (V_T) and elevated P_{aCO_2} and respiratory dead-space ratio (V_D/V_T) were observed in both the SF and DWF groups before anesthesia and transfusion. After recovery from anesthesia, V_D/V_T remained high and F_{ECO_2} decreased in the SF group. In contrast, V_D/V_T decreased almost to normal and F_{ECO_2} remained normal in the DWF group. Physiological shunt (Q_s/Q_t) tended to decrease after anesthesia and transfusion in both groups. The ventilation-perfusion ratio increased markedly for the SF group after transfusion. The data suggest that pulmonary microembolism occurs after transfusion of stored blood with a standard nylon-mesh filter. (Takaori M, Nakajo N, Ishii T: *Changes of pulmonary function following transfusion of stored blood. Transfusion* 17:615-620, 1977)