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Laboratory Report

Control of Breathing Using an Extracorporeal Membrane Lung

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Various amounts of carbon dioxide were removed through an extracorporeal membrane lung in spontaneously breathing lambs. The decrease in alveolar ventilation was proportional to the fraction of total carbon dioxide removed by the membrane lung. When extracorporeal CO_2 removal approximated CO_2 production (V_{CO_2}), alveolar ventilation almost ceased. Pulmonary ventilation can be controlled by extracorporeal carbon dioxide removal. (Key words: Carbon dioxide, membrane lung; Surgery, extracorporeal circulation; Membrane, lung.)

PATIENTS UNDERGOING HEMODIALYSIS for renal failure experience a transient, mild hypoxemia. It has been suggested[1] that the hypoxemia is the result of carbon dioxide removal during the hemodialysis, with resultant alveolar hypoventilation. This finding suggests the possibility of controlling respiration through an extracorporeal device such as the artificial kidney or an artificial lung.

Blood carbon dioxide content in man is reduced from about 52 ml/100 ml to about 48 ml/100 ml during a single passage through the lungs. The total amount of CO_2 produced per minute, *e.g.*, 200 ml, would be removed by flowing 1 liter of blood per minute through an extracorporeal device capable of reducing blood CO_2 content from 52 to 32 ml/100 ml; half the body CO_2 production (100 ml/min) could be removed using a blood flow of 500 ml/min. The expected pulmonary hypoventilation could be compensated for by increasing the inspired oxygen concentration ($F_{I_{O_2}}$) as needed. In a patient on a mechanical ventilator, tidal volume and respiratory rate could then be substantially reduced, with resulting reductions of peak inspiratory pressure and ventilatory rate.

The present study was undertaken to determine whether removal of blood carbon dioxide by extracorporeal means could control pulmonary ventilation.

Methods and Materials

Seven lambs weighing between 10.5 and 15 kg were used. All animals were unsedated and unanesthetized. Arterial blood from the subclavian artery was pumped through a 1.6-m^2 silica-filler-free silicone rubber spiral coiled carbon dioxide membrane lung (CDML)[3,4] and was returned into the jugular vein.‡ The perfusion circuit was primed with lactated Ringer's solution containing heparin (8 U/ml), and heparin was added continuously at 100 U/kg/hr. An oximeter[4] placed before and after the CDML measured changes in oxygen saturation of blood entering and leaving the CDML. Humidified room air (37 C) was passed through the CDML. Carbon dioxide removal through CDML was computed from the gas flow and the CO_2 concentration in the effluent gas as measured by an infrared CO_2 analyzer.§

The lambs were connected through a tracheostomy tube to a closed recording spirometer system provided with a Beckman CO_2 analyzer,¶ a CO_2 absorber, a P_{O_2} meter,** and a humidifier (37 C) (fig. 1). The spirometer system was filled with room air. During some studies, the spirometer air was enriched with oxygen. Oxygen (100 per cent) was fed into the spirometer system at a flow exactly equal to the pulmonary oxygen uptake to maintain a constant volume in the spirometer and a constant $F_{I_{O_2}}$ in the spirometer system. The oxygen flow into the spirometer plus oxygen transport across the CDML, if any, equalled oxygen consumption.

Blood gases and hemoglobin were measured in samples removed from the entrance and exit of the CDML, and from the pulmonary artery with a Swan-Ganz catheter.

Each animal was connected to the extracorporeal circuit for two to three days. Experiments were performed during the day; during baseline periods, CDML gas flow was stopped.

From these data, using standard formulas, we computed cardiac output (CO), tidal volume (TV), respiratory rate (RR), total pulmonary ventilation ($\dot{V}_E$), deadspace (VD), alveolar ventilation ($\dot{V}_A$), total oxygen consumption ($\dot{V}_{O_2}$), total CO_2 production ($\dot{V}_{CO_2}$), and CDML oxygen and carbon dioxide exchange. We varied extracorporeal CO_2 removal by adjusting CDML blood flow and CDML gas flow. Blood flows ranged between 500 and 1,000

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‡ Because this device can be optimized for carbon dioxide removal, we call it a carbon dioxide membrane lung (CDML).

§ Beckman Model 315 A Infrared Analyzer.

¶ Beckman Model 160 Physiological Gas Analyzer.

** Beckman Model 777 Oxygen Analyzer.

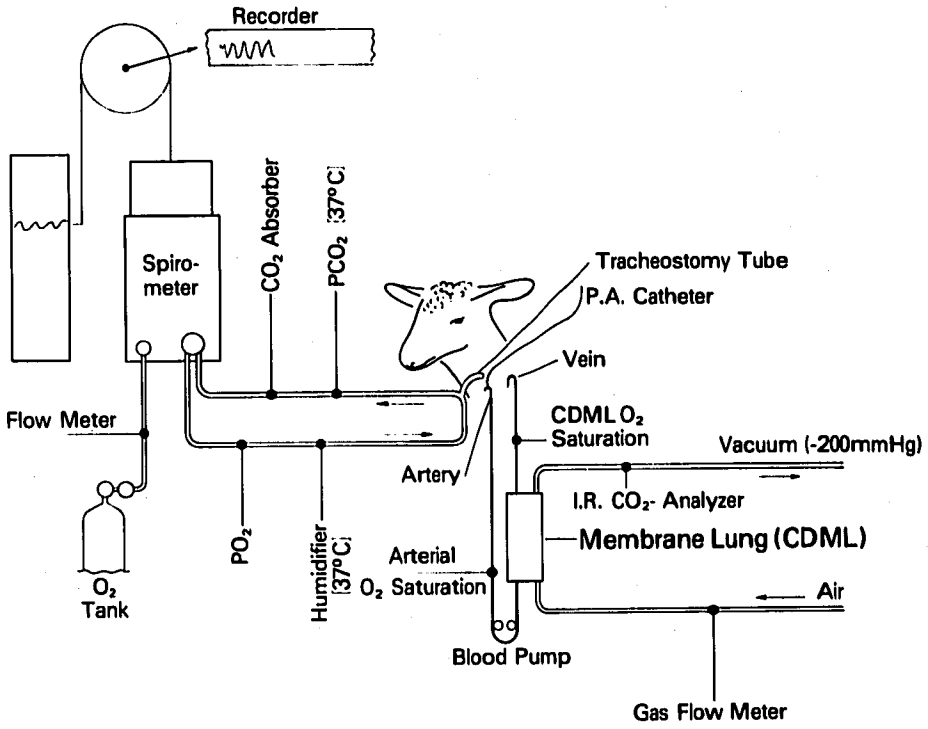

FIG. 1. The perfusion circuit.

ml/min; CDML gas flow was similarly varied between 120 and 4,500 ml/min.

We established baseline conditions without CDML gas flow. After we obtained steady values, we changed CDML gas and (if necessary) blood flows to produce the desired CO_2 removal. Blood-gas and ventilatory variables leveled off within 10 minutes of changing CDML conditions. We made a set of measurements 60 minutes after the change. Following this, we stopped extracorporeal CO_2 removal for 30 minutes and the variables returned to baseline. We then changed to new CDML conditions.

Results

Performance of the CDML was assessed during various blood flow and gas flow input conditions. Carbon dioxide removal increased linearly with exponential increase in blood flow and was dependent on Pa_{CO_2} (fig. 2). These results also demonstrate that to increase CO_2 removal under constant blood flow and input blood Pa_{CO_2} conditions the

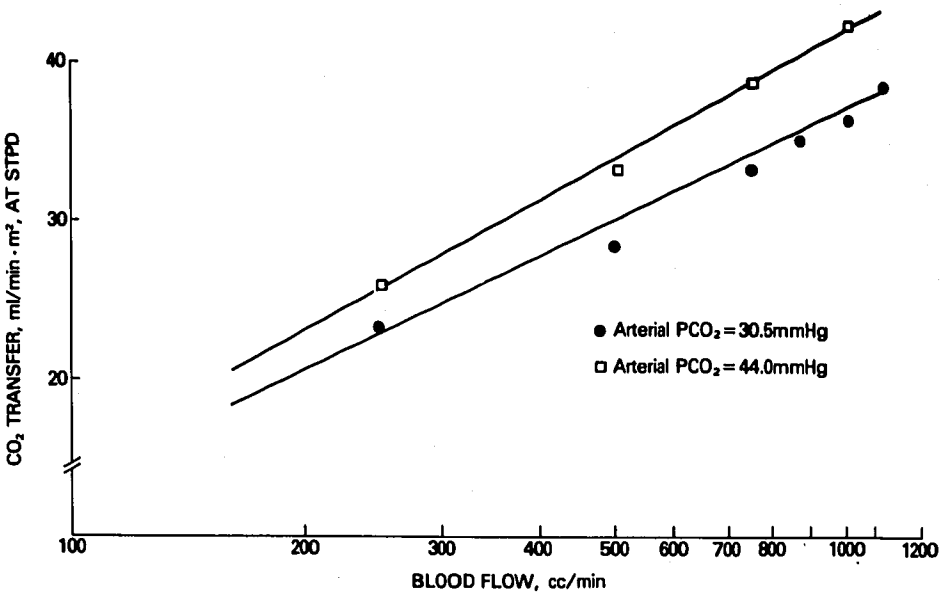

FIG. 2. Carbon dioxide exchange as a function of blood flow at different blood P_{CO_2} input levels.

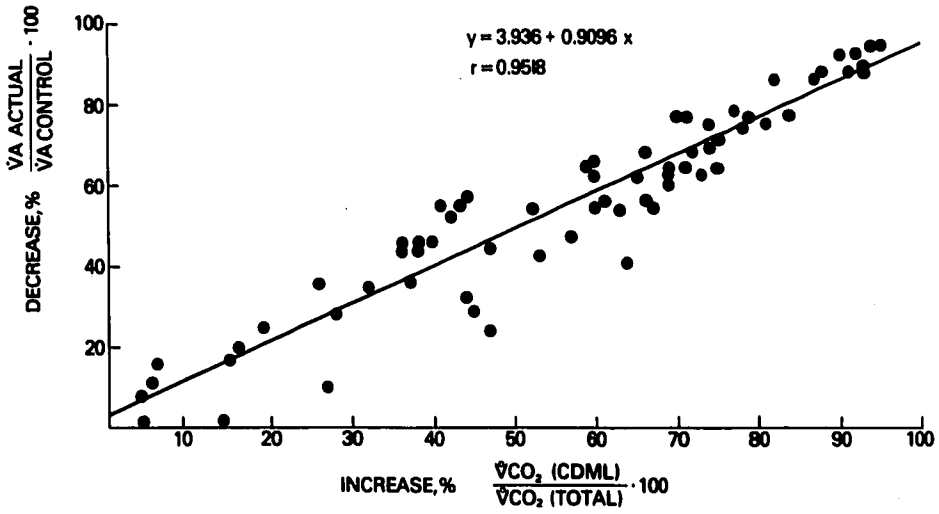

FIG. 3. Decrease in alveolar ventilation ($\dot{V}_A$) with increase in CO_2 removal through the CO_2 hemodialyzer.

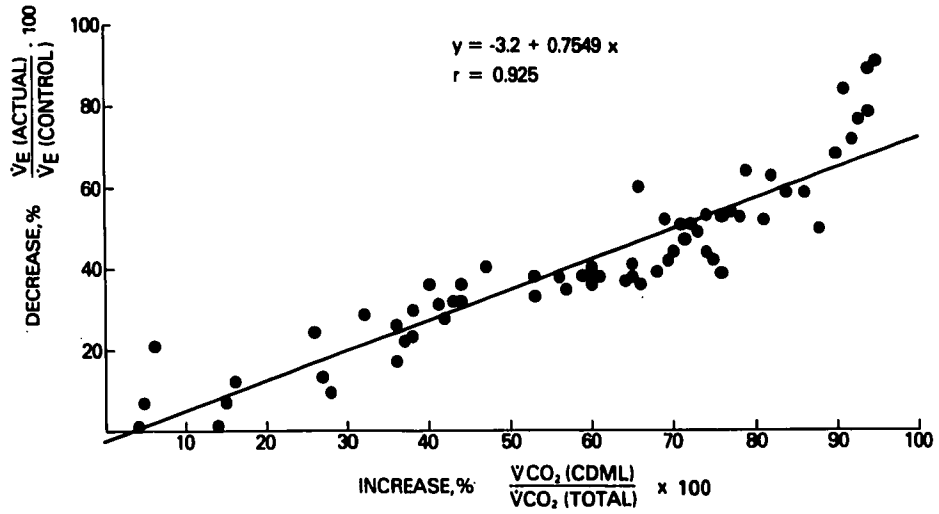

FIG. 4. Decrease in total ventilation ($\dot{V}_E$) with increase in CO_2 removal through the CO_2 hemodialyzer.

surface area of CDML must be increased. The CDML performance remained steady, and gas transfer was predictable from blood flow and Pa_{CO_2} values.

Baseline $\dot{V}_{O_2}$ in this series of lambs was 8.01 ± 2.69 ml/kg.min STPD; $\dot{V}_{CO_2}$ was 6.69 ± 2.01 ml/kg.min. After each study period $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ returned to baseline values, so there was no change between the beginning and termination of the study on a given day. The responses of $\dot{V}_E$ and $\dot{V}_A$ to CO_2 removal were highly predictable and were complete within 10 minutes. As carbon dioxide removal through the CDML increased, alveolar ventilation was reduced proportionately; when extracorporeal CO_2 removal reached 50 per cent of CO_2 production, alveolar ventilation decreased 50 per cent (fig. 3). When extracorporeal CO_2 removal neared 100 per cent of measured CO_2 production, effective alveolar ventilation virtually ceased: this always resulted in severe arterial hypoxemia, hypotension, and bradycardia, necessitating rapid elevation of Pa_{CO_2} by lowering CO_2 exchange through the CDML. However, when the animals breathed air enriched with oxygen or 100 per cent oxygen, alveolar ventilation remained sufficient to prevent arterial hypoxemia except when apnea ensued.

Total ventilation in response to increase in extracorporeal CO_2 removal decreased less than $\dot{V}_A$ due to change in physiologic deadspace (fig. 4). $\dot{V}_E$ was reduced to 50 per cent when extracorporeal CO_2 removal equalled 70 per cent of $\dot{V}_{CO_2}$. $\dot{V}_A$ decreased at first more rapidly than $\dot{V}_E$ (figs. 3 and 4). Both TV and RR decreased in response to an increase in CO_2 removal through the CDML.

Basal Pa_{CO_2} before extracorporeal carbon dioxide removal averaged 34.8 ± 5.07 mm Hg; during carbon dioxide removal it averaged 33.9 ± 6.3 mm Hg. Basal arterial blood *p*H was 7.384 ± 0.041; during carbon dioxide removal it averaged 7.386 ± 0.082.

Cardiac output averaged 239 ± 79 ml/kg.min. The P_{CO_2} difference across the CDML at a blood flow of 950 ml/min (arterial P_{CO_2} 32 ± 4 mm Hg) averaged

11.3 ± 2 mm Hg; pH rose by 0.04 ± 0.02 units. At a blood flow of 500 ml/min and an arterial blood P_{CO_2} of 59 mm Hg, the reduction in P_{CO_2} across the CDML was 38 mm Hg, and the increase in pH was 0.32 units.

All the animals survived the study protocol in good health.

Discussion

The concept of extracorporeal elimination of carbon dioxide is innovative in the context of either membrane lung or artificial kidney use, yet both artificial kidney and the membrane lung eliminate carbon dioxide efficiently; the former is usually operated at blood flows of about 250 ml/min, the latter at flows between 3 and 5 l/min.

Blood carbon dioxide elimination differs from blood oxygenation in that all carbon dioxide produced can be eliminated from less than 1 liter of blood flow per minute. This provides a tool to control pulmonary ventilation. Our observation that respiratory drive can be sharply reduced when almost all carbon dioxide is removed extracorporeally may be important in the management of patients on ventilators.

In our present studies the choice of arteriovenous perfusion rather than venovenous or venoarterial perfusion was based on simplicity of peripheral blood vessel cannulation, as the method chosen here is virtually identical to what is practiced in renal hemodialysis. In venoarterial or venovenous perfusion a large-bore venous-drainage catheter must be advanced into a large vessel such as the abdominal vena cava. Venovenous or arteriovenous extracorporeal membrane lung blood-gas exchange can accomplish both oxygen and carbon dioxide transfer, although a more complex bypass and much larger blood flow are required. The required blood flows for this procedure, 500 to 1,000 ml/min, are well within reach of some AV fistulas used in renal hemodialysis.[5]

We have used in these studies what generally might be called a membrane lung, which by definition exchanges both oxygen and carbon dioxide (unfortunately, there are still many who refer to a membrane lung as a membrane oxygenator, ignoring carbon dioxide). In these studies, arterial blood that was almost fully oxygenated passed through the membrane lung, and oxygen transfer was no more than 6 ml/min. We prefer to describe this device by its actual application: an extracorporeal carbon dioxide membrane lung (CDML). We have redesigned the spiral coiled membrane lung to allow high CO_2 transfer at low blood flow rates for this application.

It is well to recognize that artificial kidney machines now used in renal hemodialysis are also efficient carbon dioxide hemodialyzers and could be used for carbon dioxide removal with or without the use of dialysate. For control of breathing in man, these artificial kidney machines would have to be considerably scaled up, however.

It is not known at this time whether the amounts of CO_2 removed with the extremes of pH changes of blood emerging from the CDML are safe for prolonged use. Experience in artificial kidney use suggests that this is the case. Our own experience with total CO_2 removal in lambs lasting more than three days seems to confirm this.

We believe that carbon dioxide removal through the CDML may be useful in management of ventilatory problems, prime among them being uncontrollable bronchopleural fistula, and those conditions where use of an artificial ventilator is not desired or is contraindicated, or where it must be terminated. It is possible that selected patients with chronic pulmonary problems may derive temporary benefit from extracorporeal CO_2 elimination through an arteriovenous fistula, similar to what is now practiced in hemodialysis for renal insufficiency.

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