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 CO₂ removal approximated CO₂ production (V̇CO₂), 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 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 CO₂ 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 CO₂ content from 52 to 32 ml/100 ml; half the body CO₂ 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 (FIO₂) 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-m² silica-filler-free silicone rubber spiral coiled carbon dioxide membrane lung (CDML) 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 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 CO₂ concentration in the effluent gas as measured by an infrared CO₂ analyzer.

The lambs were connected through a tracheostomy tube to a closed recording spirometer system provided with a Beckman CO₂ analyzer, a CO₂ absorber, a PO₂ 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 FIO₂ 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 (V̇E), deadspace (VD), alveolar ventilation (V̇A), total oxygen consumption (V̇O₂), total CO₂ production (V̇CO₂), and CDML oxygen and carbon dioxide exchange. We varied extracorporeal CO₂ removal by adjusting CDML blood flow and CDML gas flow. Blood flows ranged between 500 and 1,000

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1 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.
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 CO₂ 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 CO₂ 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 P_{aCO₂} (fig. 2). These results also demonstrate that to increase CO₂ removal under constant blood flow and input blood P_{aCO₂} conditions the

![Fig. 2. Carbon dioxide exchange as a function of blood flow at different blood P_{aCO₂} input levels.](image)
surface area of CDML must be increased. The CDML performance remained steady, and gas transfer was predictable from blood flow and \( P_{a\text{CO}_2} \) values.

Baseline \( V_{aO_2} \) in this series of lambs was 8.01 ± 2.69 ml/kg/min STPD; \( V_{a\text{CO}_2} \) was 6.69 ± 2.01 ml/kg.min. After each study period \( V_{aO_2} \) and \( V_{a\text{CO}_2} \) returned to baseline values, so there was no change between the beginning and termination of the study on a given day. The responses of \( V_E \) and \( V_a \) to \( \text{CO}_2 \) 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 \( \text{CO}_2 \) removal reached 50 per cent of \( \text{CO}_2 \) production, alveolar ventilation decreased 50 per cent (fig. 3). When extracorporeal \( \text{CO}_2 \) removal neared 100 per cent of measured \( \text{CO}_2 \) production, effective alveolar ventilation virtually ceased: this always resulted in severe arterial hypoxemia, hypotension, and bradycardia, necessitating rapid elevation of \( P_{a\text{CO}_2} \) by lowering \( \text{CO}_2 \) 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 \( \text{CO}_2 \) removal decreased less than \( V_a \) due to change in physiologic deadspace (fig. 4). \( V_E \) was reduced to 50 per cent when extracorporeal \( \text{CO}_2 \) removal equaled 70 per cent of \( V_{a\text{CO}_2} \). \( V_a \) decreased at first more rapidly than \( V_E \) (figs. 3 and 4). Both TV and RR decreased in response to an increase in \( \text{CO}_2 \) removal through the CDML.

Basal \( P_{a\text{CO}_2} \), 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 \( pH \) was 7.384 ± 0.041; during carbon dioxide removal it averaged 7.386 ± 0.082.

Cardiac output averaged 239 ± 79 ml/kg/min. The F\(_{\text{CO}_2}\) difference across the CDML at a blood flow of 950 ml/min (arterial F\(_{\text{CO}_2}\) 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 pro-
duced 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 extracor-
porally 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 extracor-
poral carbon dioxide membrane lung (CDML).
We have redesigned the spiral coiled membrane
lung to allow high CO₂ 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 CO₂ 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 CO₂ 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 ventila-
tory problems, prime among them being uncon-
trollable bronchopleural fistula, and those condi-
tions 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 tem-
porary benefit from extracorporeal CO₂ elimination
through an arteriovenous fistula, similar to what
is now practiced in hemodialysis for renal in-
sufficiency.

References

exchange during hemodialysis, Proceedings of the Clinical
Dialysis and Transplant Forum. Volume 2. Edited by
Schreiner GE. Washington, D. C., Georgetown University
Press, 1972, pp 171–174
blood compatibility of silicone rubber free of silica
filler in the membrane lung. Trans Am Soc Artif Intern
Organs 20A: 269–276, 1974
3. Kolobow T, Bowman R L: Construction and evaluation of
an alveolar membrane artificial heart lung. Trans Am Soc
monitor for extracorporeal circulation applications. Med
Instrum 7:262–267, 1973
5. Fee HJ, Levinson J, Doud RB, et al: High output con-
gestive failure from femoral arteriovenous shunt for