Tissue Oxygen Available as a Criterion for the Effectiveness of Continuous Positive Pressure Breathing

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Summary

As little as 3–5 cm H₂O increase in proximal airway pressure applied to normal lung reduces cardiac output. It is postulated that decreased pulmonary compliance in respiratory distress syndrome (RDS) acts as a barrier thus offsetting this effect. Since cardiac output is not routinely measured, severe reduction in it could accompany regression of disease while maintaining the same airway pressure. This study was undertaken to determine whether tissue oxygen available (O_{2a}) could be used to detect changes in perfusion during continuous positive pressure breathing (CPPB). CPPB was evaluated in 10 normal rabbits (C_L = 9.5 ± 1.8 cc/g at 25 cm H₂O) and in 10 pulmonary-damaged rabbits (C_L = 5.5 ± 1.4 cc/g at 25 cm H₂O) produced by subjecting them to 100% O₂. Airway pressure was increased from 0–15 cm H₂O in 3 cm H₂O increments at 10-min intervals. O_{2a} and PaO₂ were monitored continuously. In the normal group, O_{2a} decreased at 3 cm H₂O airway pressure, reaching 22% of control at 12 cm H₂O, at which pressure PaO₂ decreased. Breathing 100% O₂ at this airway pressure increased PaO₂ to 408 mm Hg, whereas O_{2a} returned to 45% of control. In the experimental group, O_{2a} decreased at 9 cm H₂O airway

pressure, at 12 cm H₂O it was 36% of control at which pressure PaO₂ decreased slightly. Breathing 100% O₂ at this airway pressure increased PaO₂ to 316 mm Hg, and increased O_{2a} to 200% of control. These data indicate that with excessive airway pressure, muscle hypoxia may exist during systemic hyperoxemia and that a low compliance lung exerts a protective effect on O_{2a}. Since changes in cardiac output during CPPB are compliance dependent, and since O_{2a} is perfusion dependent, tissue oxygen available could provide a means of selecting optimal airway pressure during CPPB.

Speculation

This study indicates that in the presence of normal PaO₂ or every hyperoxemia, an excessive increase in airway pressure can produce a decrease in cardiac output and local oxygen supply to the tissues. The airway pressure required to produce optimal oxygenation without interference with cardiac output is lung compliance dependent. For the most efficient application of CPPB in clinical situations, measurement of physiologic variables which would reflect changes in perfusion in addition to systemic oxygenation are suggested.

INTRODUCTION

Since Gregory's report (4) on the effectiveness of CPPB for treatment of infants with Respiratory Distress Syndrome (RDS), this method has been accepted throughout the world. This method of treatment provides increased proximal airway pressure (AP) sufficient to prevent alveolar collapse at the end of expiration, while the subject breathes spontaneously. In the normal lung, as little as 3-5 cm H₂O AP may reduce cardiac output (Q) (1,8). Contrary to this, it is postulated that in RDS, decreased pulmonary compliance (C_L) acts as a barrier and minimizes this effect. Pulmonary compliance varies widely between normal subjects and those with RDS of varying severity. Therefore, a wide range of AP is required to provide optimal oxygenation without reducing Q. Since Q is not routinely measured, a reduction in Q could occur unnoticed following an excessive increase in AP. In addition, a reduction in Q could occur concomitantly with a regression of the disease, when lung compliance improves and proximal airway pressure remains unchanged.

Micro-polarographic oxygen electrodes have been used to measure the state of oxygenation of different organs, and have been accepted as a very useful research technique (2,6,7). If the micro oxygen electrode is placed in a tissue area of an active muscle, characterized by high oxygen consumption, normal A-V P_O₂ difference and no preferential blood flow, and if the oxygen consumption of the electrode does not interfere with normal cellular metabolism, then such an electrode would measure changes in tissue oxygen availability (O_{2a}) reflecting changes in both PaO₂ and perfusion.

This study was undertaken to determine whether O_{2a} could be used to detect changes in perfusion when excessive AP is applied during CPPB. In addition, the mechanisms by which perfusion is affected during excessive increase in AP are elucidated.

METHODS AND MATERIALS

Thirteen adult male New Zealand rabbits (1.8 - 2.6 kg) were divided into two groups. The control group (N) consisted of 10 animals with normal lungs and the experimental group (E) consisted of 10 animals with lungs damaged by exposure to high oxygen concentrations for 36 to 48 hours (3). Individual animals in the experimental group were placed in a chamber with adequate food and water and normobaric 100% O₂ circulating at 6 l/min. After 36 to 48 hours, the animals were removed from the chamber and exposed to room air for one to three hours before the initiation of any experimental procedure.

Animals were anesthetized with intravenous sodium pentobarbital (25 mg/kg) and placed on a heating pad (Gorman Rupp K-1) with pad temperature maintained at 39°C. A tracheostomy tube was inserted and secured. A 5F arterial catheter, containing a monopolar oxygen sensor (International Biophysics Corporation, Irvine, California - IBC) was advanced from the femoral artery to a point distal to the aortic bifurcation for monitoring of blood pressure (BP), arterial partial oxygen pressure (PaO₂), and for blood sample collection. A venous catheter was advanced from the femoral vein into the right atrium for pressure measurement (Pra) and blood sample collection. Q was determined by the Fick principle.

A balloon secured to PE 260 tubing was inserted orally to the cardiac sphincter and then withdrawn to the lower 1/3 of the esophagus for measurement of esophageal pressure (Pes). A monopolar oxygen electrode was implanted into the right triceps muscle for measurement of O_{2a}. Reference electrodes were secured to the skin and connected to the monitoring systems.

Specifics related to construction, implantation and performance of the oxygen electrode were described previously (2, 6-8). For measurement of cortical O_{2a}, oxygen sensitive electrodes were implanted in three normal rabbits. Holes were drilled in the skulls of the animals and electrodes were inserted into the parietal area of the cortex. The electrodes were soldered to external connectors which then were fixed to the skull with stainless steel screws and dental cement. Approximately 7-10 days were allowed for complete animal recovery, after which the CPPB experiment was performed.

The tracheostomy tube was connected to a pneumotachograph in a series with a CPPB system similar to the one described by Gregory (4). The system consisted of (a) a rigid wall, cylindrical 200 cc reservoir with a needle valve exhaust regulator, flowmeter, subject connector and adapters for measurement of system pressure, oxygen concentration and total system outflow, (b) exchangeable compliant 200 cc rubber bag placed in front of a rigid wall reservoir, and (c) a pressure release "pop off" system in the form of a submersible water monometer placed proximally to the rigid wall reservoir. A humidified airflow of 12 l/min. was circulated through the system.

Control values for all physiologic variables measured were obtained at this point. AP was then increased from 0.5 to 15 cm H₂O in 3 cm increments at 10 minute intervals. At 12 cm H₂O, the fraction of inspired O₂ (FIO₂) was increased from ambient to 50% and 100%. During these procedures, animals were breathing spontaneously and regulating their own respiratory rates and tidal volumes.

To verify the validity of the experimental model, static lung compliance (C_L) of the exteriorized lung and histologic evaluations were performed in six normal and six oxygen-treated animals not exposed to CPPB. Also, C_L of the exteriorized lungs was measured in all animals exposed to CPPB immediately after death. To permit comparison of lungs of different sizes, volume was expressed as ml of gas per gram of lung tissue (5).

Arterial (BP) and right atrial (Pra) pressures, respiratory rate (RR), tidal volume (V_T), minute volume (V_E), FeO₂, arterial and venous pH and partial O₂ and CO₂ pressures, saturations and contents, hematocrit, hemoglobin, oxygen consumption (VO₂), cardiac output (Q), and static lung compliance (C_L) were determined as previously described (3). Student T-test was performed to determine the statistical differences between the control and experimental groups.

RESULTS

C_L at the peak inflation pressures at 25 cm H₂O was 9.5 ± 1.8 cc/g of tissue in the control group and 5.5 ± 1.4 cc/g of tissue in the experimental group. The ratio of lung weight to body weight (gr/kg) in the control and experimental animal groups was not significantly different.

At this pressure the normal lung appeared fully inflated while the damaged lung demonstrated multiple lobulation surrounded by uninflated segments of tissue. The slope of the pressure volume curve over the entire range was reduced in the damaged lung. Histologic evaluation of damaged lungs showed pulmonary hemorrhage, atelectasis, and edema but no evidence of cellular atypia or hyaline membrane formation.

Mean Pra in the control and experimental groups was 4.2 ± 0.8 and 4.1 ± 1.2 cm H₂O respectively. Percent changes in Pra as a function of AP are shown in Fig.

1. Mean Pra in the control group increased with each increment in AP. The experimental group contrasted to this in that this increase in Pra did not occur until an AP greater than 6 cm H₂O was reached. At 6 cm H₂O the difference between the two groups was statistically significant ($t = 9.58$, $p < 0.005$). At the maximum AP of 15 cm H₂O, mean Pra for control and experimental groups was 10.0 ± 1.8 cm H₂O (240% of control) and 5.9 ± 1.8 cm H₂O (140% of control), respectively.

Q in control and experimental groups was 120 ± 17 cc/min/kg and 273 ± 43 cc/min/kg ($p < 0.001$; $t = 6.687$). Percent changes in Q as a function of AP are shown in Fig. 2. Q in the control group decreased with each increment in AP. At 9 cm H₂O it had decreased to 60%, reaching 22% of control at 15 cm H₂O AP. In the experimental group, Q remained essentially unchanged until 9 cm H₂O AP, when subsequently it decreased, and at 15 cm H₂O AP it was 57% of control.

Mean and standard deviation changes of PaO₂ and O₂ obtained at 0.5, 3, 6, 9, and 12 cm H₂O AP at an FIO₂ of 20.9%, and at an FIO₂ of 50% and 100% at 12 cm H₂O AP (which are presented in Table 1). In normal animals, PaO₂ remained unchanged with increases in AP from 0.5 to 9 cm H₂O. At 12 cm H₂O AP, it was slightly decreased to 88 mm Hg. Simultaneously, with no change in PaO₂, O_{2a} decreased with each increment in AP, reaching 22% of control at 12 cm H₂O AP. In experimental animals, PaO₂ increased at 3 and 6 cm H₂O AP, decreased to a control level of 9 cm H₂O AP, and further decreased to 39 mm Hg at 12 cm H₂O AP. In contrast to normals, O_{2a} in the experimental group initially increased, then fell below the control levels at 9 cm H₂O AP, reaching 36% of control at 12 cm H₂O AP with PaO₂ remaining almost within the control level. When 100% O₂ was administered at 12 cm H₂O AP, PaO₂ in normal animals increased to 408 mm Hg, while O_{2a} recovered only to 45% of control. However, in experimental animals 100% O₂ increased PaO₂ and O_{2a} to 295 mm Hg and 201% respectively.

Changes in BP, Pes, O_{2a}, and PaO₂ produced by increasing AP from 0.5 to 12 cm H₂O in a single animal from the normal group are shown in Fig. 3. Each increment in AP produced a simultaneous increase in Pes and a decrease in O_{2a}, reaching a maximal change at 12 cm H₂O, at which pressure PaO₂ first showed a decrease. Although mean BP did not change, Pulsus Paradoxicus occurred at 9 and 12 cm H₂O AP. Contrary to this, in an experimental animal (Fig. 4) Pes and O_{2a} changed first at an AP of 9 cm H₂O reaching maximal changes at 12 cm H₂O at which pressure PaO₂ decreased below control. BP did not change and Pulsus Paradoxicus did not occur.

Under conditions of unchanged oxygen consumption, tissue O_{2a} is primarily affected by blood oxygen content and blood flow. If supposed that during the experiment, oxygen carrying capacity remains unchanged, then oxygen content primarily will be affected by PaO₂. Therefore, the ratio of O_{2a}/PaO₂ would reflect changes in local blood flow. This ratio is shown in Fig. 5 as a function of AP. In normal animals each increment in AP produced a decrease in the ratio. In experimental animals (low lung compliance) a noticeable decrease occurred only when AP reached 12 cm H₂O.

To further verify that the decrease in muscle O_{2a} with excessive application of AP is not a local phenomenon, changes in cortical O_{2a} as a function of increase in AP were measured. In a representative single experiment performed on a normal animal (Fig. 6), each increment in AP produced a decrease in cortical O_{2a}, reaching a maximum decrease of 50% at 12 cm H₂O AP. When AP was decreased back to atmospheric, the cortical O_{2a} returned to its normal values.

O_{2a} as a function of increased AP in a single animal with different lung compliance is shown in Fig. 7. In an animal with normal lung compliance (9.0 cc/g) each increment in AP produced a decrease in O_{2a}. In an animal with mildly (7.5 cc/g) and moderately (5.0 cc/g) decreased lung compliance, an initial increase in O_{2a} at 3 and 6 cm H₂O was followed by a decrease when greater AP was applied. It should be noted that as lung compliance decreased, a maximum O_{2a} point was shifted to the right, suggesting that higher airway pressure is needed to produce optimal tissue oxygenation without interfering with tissue perfusion.

DISCUSSION

CPPB at 3-15 cm H₂O AP was evaluated in animals with normal and low lung compliance. Animals with normal compliance could not tolerate any increase in AP. This was manifested by an immediate increase in Pes and Pra and a decrease in Q and O_{2a} when as little as 3 cm H₂O was applied. Contrary to this, animals with low compliance lungs exhibited the protective "barrier effect", tolerating much higher pressures. Pes and Pra increased and Q and O_{2a} decreased at only 6-9 cm H₂O AP. Furthermore, at 12 cm H₂O AP, these changes were of less magnitude in animals with low compliance lungs. The discrepancy between the PaO₂ and O_{2a} should be specifically emphasized. In the normal group, O_{2a} decreased with each increment in AP, while PaO₂ remained relatively unchanged. In the experimental group, O_{2a} and PaO₂ showed an initial increase corresponding to the optimal AP points. Further increase in AP produced a decrease in O_{2a}, while PaO₂ remained within the control level. PaO₂ in both groups decreased only when an AP of 12 cm H₂O was reached. Administration of 100% O₂ at this pressure increased PaO₂ as high as 408 mm Hg while O_{2a} in control and experimental groups was 45% and 201% of control respectively. This exemplifies that PaO₂ can be at normal or hyperoxic levels while O_{2a} is markedly decreased, suggesting a reduction in perfusion. The reduction in perfusion was of greater magnitude in animals with normal compliance lungs. This is in agreement with the work reported by Suter et al (9) who observed that in patients with low functional residual capacity and lung compliance, maximum oxygen transport was achieved at higher levels of positive end expiratory pressure. Improvement in total lung compliance was accompanied by improvement in total oxygen transport when the "best PEEP" was obtained. This agrees with our data on tissue oxygen availability which provides the evidence that at an optimal airway pressure the highest levels of tissue oxygenation are achieved.

Our data indicate the mechanism of reduction in perfusion is by means of pressure transmission across the alveolar wall, which in turn produces an increase in Pes, followed by an increase in Pra and a decrease in pulmonary venous return, Q, and O_{2a}, and that this mechanism is compliance dependent. This suggests that for proper selection of airway pressure, measurement of variables which reflect changes in perfusion in addition to changes in systemic oxygenation is necessary.

Our data further indicate that while the appearance of Pulsus Paradoxicus occurs later than changes in Pes, Pra, and Q when excessive AP is applied, nevertheless it could be used as a warning signal. However, because changes in O_{2a} occur concurrently with changes in Pes, Pra, and Q, we stress that a reduction in O_{2a} would accurately reflect excessive AP. Since changes in Q during CPPB are compliance dependent and since O_{2a} is Q dependent, O_{2a} could provide a means of selecting optimal AP during CPPB. Therefore, we propose that in a clinical situation while continuously measuring muscle O_{2a}, a pressure sweep (Fig. 8) in the range from 0-15 cm H₂O AP should be obtained. The initial increase in O_{2a} is related to improved pulmonary performance (opening of atelectatic areas, decrease in pulmonary shunting). A succeeding decrease is related to a decrease in perfusion secondary to excessive increase in AP. The point on

the curve where the slope equals zero ($dO_{2a}/dAP = 0$), is considered the optimal airway pressure point, which produces the best transpulmonary gas exchange with the least interference with tissue perfusion.

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TABLE I

AP cm H ₂ O		.5	3	6	9	12	12	12
FiO ₂ %		20.9	20.9	20.9	20.9	20.9	50	100
PaO ₂ mm Hg	N	96 ⁺⁷	96 ⁺⁶	98 ⁺⁵	94 ⁺³	88 ⁺¹⁰	197 ⁺²³	408 ⁺³²
	E	46 ⁺⁹	56 ⁺⁹	55 ⁺¹¹	46 ⁺⁹	39 ⁺⁸	154 ⁺⁵⁵	316 ⁺⁸⁰
O ₂ a%	N	100	92 ⁺¹⁰	72 ⁺¹¹	55 ⁺¹⁰	22 ⁺¹¹	40 ⁺¹³	45 ⁺¹⁸
	E	100	107 ⁺¹²	100 ⁺²¹	78 ⁺²⁰	36 ⁺¹⁷	146 ⁺¹⁴⁴	201 ⁺¹⁹²

TABLE I. Effect of increased proximal airway pressure (AP) on PaO₂ and O₂a. N = Normal group (normal lung). E = Experimental group (oxygen damaged lung).

Fig. 1. Percent changes in right atrial pressure (Pra) as a function of increase in proximal airway pressure (AP). N = Normal group (normal lung). E = Experimental group (oxygen damaged lung).

Fig. 2. Percent changes in cardiac output $\dot{Q}$ as a function of increase in proximal airway pressure (AP). N = Normal group (normal lung). E = Experimental group (oxygen damaged lung).

Fig. 3. Changes in BP, Pes, O₂a, and PaO₂ produced by increasing proximal airway pressure (AP) in a single animal from the normal group.

Fig. 4. Changes in BP, Pes, O_{2a}, and PaO₂ produced by increasing proximal airway pressure (AP) in a single animal from the experimental group.

Fig. 5 (left). The ratio of O_{2a}/PaO₂ as a function of increase in proximal airway pressure (AP). N = Normal group (normal lung). E = Experimental group (oxygen damaged lung).

Fig. 7 (right). Percent changes in muscle O_{2a} as a function of increased proximal airway pressure (AP) in animals with different lung compliances.

Fig. 6. Changes in cortical oxygen available (O_{2a}) as a function of increase in proximal airway pressure (AP) in a single animal with normal lungs.

Fig. 8. Pressure scanning method which establishes optimal airway pressure (AP) to produce optimal tissue oxygenation. Initial increase in AP produces increase in tissue O_{2a} as a result of increase in PaO₂ due to improved lung function. Further increase in AP produces a decrease in tissue O_{2a} as a result of decreased oxygen delivery due to alveolar overdistension, resulting in a decrease in pulmonary venous return and cardiac output.