Hz has been advocated.[1,5] Most direct arterial pressure recording systems have underdamped responses, with resonances between 20 and 40 Hz. However even a small air bubble can lower the resonant frequency to 10, or even 5 Hz, and the frequencies defining the pressure pulse are typically from 3 to 5 Hz. Systolic pressure may be overestimated grossly if there are resonances below 10 Hz, so we exercised extreme care to eliminate all air bubbles from the system and checked dynamic response regularly during each measurement period. Nevertheless, we cannot exclude the possibility that the consistently low slopes observed may be due in part to an overestimation of high blood pressures and an underestimation of low blood pressures by the direct method.

In comparing the two indirect techniques, we favor the Dinamap® over the Infrasonde®. The Dinamap® gave a better measure of systolic pressure, and no worse a measure of diastolic pressure, than did the Infrasonde®. The latter also was more difficult to use; unless the microphone was placed precisely over the artery, the results were poor. The Dinamap® appears as good as a manual sphygmomanometric measurement and may be better under operating room conditions.

The residual differences between direct and indirect measures, which are nontrivial, relate to inherent limitations of both. Clinicians may have to recognize that direct and indirect "blood pressures" are inherently different measures, both related only indirectly to the physiologic phenomena of interest.

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Inability to Titrate PEEP in Patients with Acute Respiratory Failure Using End-tidal Carbon Dioxide Measurements

FRANÇOIS JARDIN, M.D.,* BRUNO GENEVRAY, M.D.,* MARTINE PAZIN, M.D.,* ANDRÉ MARGAIRAZ, M.D.*

Positive end-expiratory pressure (PEEP) increases functional residual capacity,[1] decreases venous admixture in the lungs ($\dot{Q}S/\dot{Q}T$),[2] and improves oxygenation in patients with acute respiratory failure (ARF). How much PEEP should be applied in each case has been a matter of controversy. Suter et al.[1] advocated the improvement obtained by PEEP in total compliance (CT) and used this measurement to determine the "best PEEP." Conversly, Downs et al.[3] advocated an "optimum PEEP" as producing the lowest $\dot{Q}S/\dot{Q}T$ without any consideration about lung mechanics. "Optimum PEEP" requires aggressive hemodynamic support because this high level of PEEP causes major circulatory impairment.[4] Recently, Murray et al.[5] recommended titration of PEEP by monitoring of arterial (Pa_{CO_2}) minus end-tidal carbon dioxide (Pet_{CO_2}) gradient. The Pa_{CO_2}–Pet_{CO_2} gradient can be measured by determining the P_{CO_2} in exhaled gas and in arterial blood. When some degree of alveolar dead space is present, the P_{CO_2} of end-expiratory gas will be less than that of "ideal" alveolar gas, since it is diluted with alveolar dead space gas, which is practically free of CO_2. To measure alveolar dead space, Pa_{CO_2} can be substituted for "ideal" alveolar P_{CO_2} because there is

never a measurable gradient of P_{CO_2} between alveolar gas and blood leaving the pulmonary capillaries. Moreover, since the mixed venous/arterial P_{CO_2} difference is small, no reasonable degree of venous admixture is likely to produce a serious rise in Pa_{CO_2} above the level in the end-pulmonary capillary blood. If the experimental work of Murray et al.[5] was corroborated by clinical applications, the necessity for a pulmonary artery catheter in patients requiring respiratory therapy would be reduced.

We, therefore, compared the Pa_{CO_2}–Pet_{CO_2} gradient with CT measurements to titrate PEEP, in a group of patients requiring respiratory therapy for acute respiratory failure.

MATERIALS AND METHODS

We studied 11 patients in acute respiratory failure requiring controlled ventilation with PEEP. This group consisted of four men and seven women, ranging in age from 15 to 76 years (mean: 44 years). Respiratory failure resulted from inhalation of gastric contents in four cases, bacterial pneumonia in two cases, fat embolism in one case, cardiogenic pulmonary edema in one case, acute pancreatitis in one case, and mediastinitis in one case. Seven patients recovered, and four ultimately died.

Informed consent was obtained from next of kin before the study consistent with the ethical regulations of our hospital. Hemodynamic and respiratory measurements were performed during the second or third day of controlled respiration. Patients were sedated with iv diazepam and morphine. At the time of the study, all patients were ventilated mechanically via a nasotracheal tube, using a volume-controlled ventilator (Bourns Bear One® or ATM CPU1®) delivering a constant tidal volume (11.1 ± 3.8 ml/kg) at a constant inspiratory flow rate with a respiratory frequency at 15 cycles per min and a PEEP level between 5 and 15 cmH_2O and an FI_{O_2} between 0.4 to 0.6. Average Pa_{CO_2} was 32.3 ± 4.4 mmHg (mean ± SD), and average Pa_{O_2} was 86.7 ± 38.2 mmHg. During the brief period of data recording, FI_{O_2} was increased to 0.8 because some patients with high $\dot{Q}S/\dot{Q}T$ might have become hypoxemic without PEEP, and an end-inspiratory pause of 0.8 s was preset in the respiratory cycle in order to obtain a period of no-flow for total compliance (CT) measurements.

Systemic arterial blood pressure was measured via a 20-gauge Teflon® catheter inserted percutaneously into a radial artery. Pulmonary artery and right ventricular pressures were measured via a modified triple-lumen balloon-tipped catheter in which the proximal port was located at 14 cm from the tip. Tracheal pressure was measured from a side port of the tracheal tube, and pleural pressure was measured through an esophageal balloon advanced into the esophagus down to 40 cm from the nares. All pressures were measured at end-expiration using transducers positioned at the midaxillary level, with atmospheric pressure as a zero reference level, and recorded on a photographic recorder. Vascular pressures were expressed as transmural pressures (i.e., measured minus esophageal pressure). Cardiac output was measured by the thermodilution technique, which also permitted to obtain right ventricular ejection fraction using a fast-response thermistor.[6]

Analysis of arterial and mixed venous blood gases were determined by standard electrode techniques. Pet_{CO_2} was monitored continuously with an infrared analyzer (Hewlett–Packard 47210 A Capnometer®), and the Pa_{CO_2}–Pet_{CO_2} gradient was calculated by simple subtraction. Hemoglobin and hemoglobin oxygen arterial and mixed venous saturations were measured by a Co-oximeter. From these measurements, we calculated $\dot{Q}S/\dot{Q}T$ and systemic oxygen transport using appropriate formulas.

Expired tidal volumes was measured using a disposable pneumotachograph and a Validyne MP 45-14® differential transducer connected to a Hewlett–Packard 8815 A® respiratory integrator, previously calibrated with a 500-ml syringe. CT was assessed from simultaneous recordings of expired tidal volume and airway pressure and was calculated by dividing the tidal volume by the difference between a "plateau" pressure at end-inspiratory period of no-flow and end-expiratory pressure.

Baseline hemodynamic, respiratory, and blood–gas data first were obtained at zero end-expiratory pressure (ZEEP). Using Suter's method,[1] PEEP then was applied in increments of 3 cm of water until the "best PEEP," defined as the highest level of PEEP producing the higher value of CT, was determined. All hemodynamic, respiratory, and blood–gas data then were obtained at the "best PEEP" level after 15 to 20 min stabilization. Further increments of PEEP then were applied until an approximately 20% decrease in mean systemic arterial blood pressure was observed. All measurements were repeated at this second level of PEEP after 15 to 20 min of stabilization. The increase in functional residual capacity caused by PEEP then was evaluated as the difference between the first expiratory volumes when PEEP abruptly was removed and the preceding expiratory volume.

Statistical analyses were performed using a two-way analysis of variance to compare hemodynamic, respiratory, and blood–gas data at ZEEP and at the two levels of PEEP used.

TABLE 1. Respiratory Data at the Three Levels (ZEEP, "Best PEEP," High level PEEP) of End-expiratory Pressure Studied

	ZEEP	"Best PEEP" 9.3 ± 1.6 cm H$_2$O	High Level PEEP 20.2 ± 2.4 cm H$_2$O
CT (ml/cm H$_2$O)	41.8 ± 20.5	49.5 ± 24.6*	33.5 ± 16.6*
Pa$_{O_2}$ (mmHg)	91.9 ± 41.2	101.4 ± 33.1*	125.0 ± 54.4*
P$\bar{v}_{O_2}$ (mmHg)	40.6 ± 6.5	39.8 ± 7.4	39.3 ± 6.4
$\dot{Q}S/\dot{Q}T$ (%)	34.5 ± 10.2	30.3 ± 7.7*	24.3 ± 7.9*
O$_2$ Transport (ml·min^{-1}·m^2)	539.8 ± 180.1	477 ± 157.3*	416 ± 126.3*
Pa$_{CO_2}$ (mmHg)	31.7 ± 5.3	31.6 ± 4.9	33.1 ± 6.0
Pet$_{CO_2}$ (mmHg)	24.3 ± 4.5	23.5 ± 5.2	23.9 ± 5.0
Pa$_{CO_2}$–Pet$_{CO_2}$ (mmHg)	6.8 ± 3.9	8.1 ± 5.0	9.3 ± 6.2
ΔFRC (ml)		574 ± 184*	1644 ± 559*

Δ FRC = increase in FRC produced by PEEP.
Values are mean ± SD.

* $P < 0.05$ when compared with baseline values at ZEEP.

RESULTS

Changes in respiratory function data induced by the two levels of PEEP used in the study are summarized in table 1. With the "best PEEP" (9.3 ± 1.6 cmH$_2$O), CT was improved significantly and an increase in FRC of 574 ± 184 ml was obtained. $\dot{Q}S/\dot{Q}T$ was reduced significantly and Pa$_{O_2}$ improved. Despite this improvement in arterial oxygenation, O$_2$ transport was reduced significantly. With a higher level of PEEP (20.2 ± 2.4 cmH$_2$O), FRC was increased further but CT deteriorated. Despite deterioration in lung mechanics, $\dot{Q}S/\dot{Q}T$ was reduced further and Pa$_{O_2}$ improved. No significant change was found in average Pa$_{CO_2}$ and Pet$_{CO_2}$ values, and the Pa$_{CO_2}$–Pet$_{CO_2}$ gradient was not affected significantly at any level of PEEP.

Changes in circulatory function data induced by the two levels of PEEP used in the study are summarized in table 2. With the "best PEEP," cardiac index slightly but significantly decreased. With the higher level of PEEP, the decrease in cardiac output was more pronounced. Right ventricular ejection fraction and filling pressure significantly decreased.

DISCUSSION

Acute respiratory failure is characterized by major adnormalities in ventilation–perfusion relationships. Intrapulmonary shunt resulting from perfused but not ventilated areas and alveolar dead space resulting from ventilated but not perfused areas are the ultimate results. Respiratory support with an optimum level of PEEP in this setting improves ventilation–perfusion relationships, reducing both intrapulmonary shunt and alveolar dead space.[1] Such an improvement restores lung mechanics, in part, and can be recognized clinically by the finding of an improved CT.[1,7] Moreover, because improvement in ventilation–perfusion relationships by PEEP increases

Pa$_{O_2}$, it also improves oxygen delivery so long as cardiac output is maintained.[1,8] On the opposite, when PEEP is used at an excessive level, beneficial effect on arterial oxygenation can be offset by a deleterious effect on cardiac output.[1] Moreover, an excessive level of PEEP overinflates lung areas and enlarges alveolar dead space.[1] Such an overdistension deteriorates lung mechanics and can be recognized clinically by deterioration in CT.[1,7] Thus, measurement of CT appears to be a safe mean to titrate PEEP and to determine the optimum therapeutic level for a given patient. This noninvasive measurement does not suppress the need for a pulmonary artery catheter. Even with the "best PEEP" level determined by CT measurements, cardiac output usually is depressed and hemodynamic support is required to optimize cardiac output.

Measurement of CT requires a ventilatory system that can produce an inspiratory plateau[1] or one that permits total obstruction of gas flow to reach a static

TABLE 2. Hemodynamic Data at the Three Levels (ZEEP, "Best PEEP," High Level PEEP) of End-expiratory Pressure Studied

	ZEEP	"Best PEEP" 9.3 ± 1.6 cm H$_2$O	High Level PEEP 20.2 ± 2.4 cm H$_2$O
MSAP tm (mmHg)	89.9 ± 12.6	82.3 ± 12.2	73.8 ± 14.4*
CI (ml/min/M^2)	3.9 ± 1.1	3.3 ± 0.9*	2.9 ± 0.6*
RVEDP tm (mmHg)	11.8 ± 2.5	10.5 ± 3.2	9.7 ± 2.6*
MPAP tm (mmHg)	22.1 ± 3.7	21.2 ± 3.2	21.3 ± 3.7
RVEF (%)	48 ± 16	44 ± 13*	38 ± 13*

Values are mean ± SD.
MSAP = mean systemic arterial pressure; CI = cardiac index; RVEDP = right ventricular end-diastolic pressure; MPAP = mean pulmonary artery pressure; RVEF = right ventricular ejection fraction. All pressures were expressed as transmural (tm) pressures.
* $P < 0.05$ when compared with baseline value at ZEEP.

equilibrium.[7] This is not possible in many systems used today for applying CPAP with spontaneous ventilation or with intermittent mandatory ventilation. For this reason, Murray et al.[5] recently have proposed to monitor P(a-et)CO_2 as reflecting alveolar dead-space changes with PEEP levels. In their experimental study on dogs,[5] the smallest value of P(a-et)CO_2 was reached at the optimum PEEP level, and beyond this level an enlargement in P(a-et)CO_2 was observed, with the application of an additional PEEP suggesting overdistension of lung areas.

In the present human study, we were first unable to demonstrate that "the best PEEP," defined as producing the greater improvement in lung mechanics,[1] was associated with a significant reduction in the Pa_{CO_2}–Pet_{CO_2} gradient, suggesting a reduction in alveolar dead space. In our study, however, cardiac output decreased with "best PEEP" and was not restored at baseline level. This could explain the lack of improvement in alveolar dead space at "best PEEP" level. It would probably be more convincing to measure P(a-et)CO_2 after hemodynamic support to maintain cardiac output. In fact, Matamis et al.[9] found that PEEP never reduced dead space but actually increased it, even if cardiac output was maintained.

We secondly used an excessive level of PEEP in terms of lung mechanics and hemodynamics. This level produced a decrease in CT, suggesting overinflation, and caused a decrease in cardiac output with reduced ventricular ejection fraction, suggesting right ventricular filling impairment. Moreover, some degree of right ventricular afterloading probably was added, as suggested by an unchanged pulmonary artery pressure, despite a reduced cardiac output. In this situation, an increased dead space should be expected.[10] This increase in alveolar dead space with PEEP persisted to some extent, even when cardiac output was maintained.[9] Still, we were unable to demonstrate a significant increase in the Pa_{CO_2}–Pet_{CO_2} gradient, suggesting an increase in alveolar dead space when a high level of PEEP was used.

Alveolar dead space changes with PEEP have been documented strongly by previously mentioned studies, using the multiple inert gas method,[9,10] and our results raise the question of the ability of P(a-et)CO_2 measurements to detect alveolar dead space changes in ventilated patients. In fact, many problems indicate restraining the use of Pa_{CO_2}–Pet_{CO_2} gradient in respiratory intensive care as dead space monitoring. First, the use of two different analysers (i.e., P_{CO_2} electrode for Pa_{CO_2} measurements and infrared analyzer for Pet_{CO_2} measurements) with two different sensitivities could produce imprecise measurements, so as only a large change in

dead space could be detected. Secondly, the contribution of a right-to-left shunt to alveolar arterial carbon dioxide tension difference is not negligible in patients with large shunts: a large venous admixture would increase Pa_{CO_2} above the level in the end-pulmonary capillary bed. Moreover, this contribution would change in magnitude with changes in shunt induced by PEEP. Thirdly, the use of Pet_{CO_2} as mean alveolar P_{CO_2} appears questionable in the human lung, in which uneven gas mixing and stratification by itself could result in a Pa_{CO_2}–Pet_{CO_2} gradient.[11]

In conclusion, our clinical study demonstrated that measurement of Pa_{CO_2}–Pet_{CO_2} gradient did not permit exact titration of PEEP in patients with acute respiratory failure and did not permit either to detect overinflation of the lungs caused by PEEP.

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