

Relationship of uni-lung percentage of blood flow to uni-lung percentage of carbon dioxide production in normal and unilateral injured lungs in a canine model

Kang H. Lee, Philippe Rico, Michael R. Pinsky

Abstract

It is difficult clinically to measure relative blood flow to each lung. We hypothesized that uni-lung % blood flow is linearly related to % carbon dioxide excretion (VCO_2). In a canine model of acute unilateral lung injury, we measured uni-lung flow with ultrasonic flow-probes, and uni-lung VCO_2 with two separate metabolic monitors utilizing split lung ventilation following thoracotomy. Relative flow to the lungs was altered by inflating a pulmonary artery catheter balloon in one of the lungs under conditions of nor-

mal lung function and following induction of acute lung injury. There was a significant linear relationship between % blood flow and % VCO_2 under all conditions ($R = 0.83$, $p < 0.001$, ANOVA). The slopes were identical for the injured lung and the contralateral control lung, although these slopes differed from their respective baseline values. We conclude that by measuring uni-lung % VCO_2 , one may trend changes in % flow to either lung in patients with split lung ventilation with or without unilateral lung disease.

Keywords: Acute lung injury, pulmonary blood flow, split lung ventilation.

Introduction

Total pulmonary blood flow can be estimated by thermodilution cardiac output measurements or by the Fick principle, which requires the measurement of whole body oxygen consumption (VO_2), and the arterial and mixed venous oxygen content. Using the Fick principle, and measurements of arterial and mixed venous CO_2 content, total pulmonary blood flow can also be determined [1]. This technique has been successfully applied in the measurement of total blood flow in patients following cardiac surgery [2]. However, the measurement of pulmonary blood flow to each lung separately is much more difficult [3].

Historically, the interest in determining separate blood flows to the lung derived from the attempt to describe the effects of body positioning (supine, erect, and lateral decubitus) on pulmonary blood flow distribution. Various techniques to measure pulmonary blood flow were developed. Such information is important prior to lung resection, especially pneumonectomy in order to predict postoperative pulmonary status. One of the early studies [4] employed VO_2 measurement by collecting end-expiratory gases to estimate lobar blood flow. However, there was no validation of the accuracy of this methodology. Similarly, CO_2 production from the lungs has been employed to reflect pulmonary blood flow [5] and again without separate validation of this assumption. Considering the clinical implications of these assumptions, validation of these assumptions seems warranted.

Differential lung blood flow can be quantified using a variety of techniques. Poorly soluble gases like radioactive xenon can be injected intravenously and a gamma counter is then employed to determine the distribution [6]. A more common method involves the intravenous injection of radio-labeled particles that lodge in the pulmonary micro-circulation. A lung perfusion scan is performed using a gamma counter that allows the calcula-

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tion of relative distribution of pulmonary blood flow [3]. This is a commonly used method in clinical practice, especially for the diagnosis of pulmonary embolism. However, this method employs radioactive material; it is expensive; and provides only a single snapshot of the distribution of pulmonary blood flow.

In lung transplantation, especially single lung transplants, independent lung ventilation is often employed post-operatively in the intensive care unit. This is particularly common when there is marked disparity in native and transplanted lung function, either in terms of ventilation, blood perfusion, or gas exchange efficiency. Accordingly, the ability to separate relative perfusion of each lung at the bedside may be important for determining management strategies to improve ventilation-perfusion matching. We have previously shown in 4 lung transplant recipients that split lung VCO_2 predicts uni-lung blood flow when compared to near-simultaneously measured uni-lung Xenon blood flow technique [9]. However, that study was performed only once per subject and examined uni-lung blood flow in only these 4 patients. Thus, the validity of the uni-lung VO_2 technique as lung injury varies over time and the variance of this measure have not been defined.

Thus, we attempted to validate the methodology employing split lung VCO_2 measurements by expiratory gas analysis and compared them to blood flow measurements under conditions in which no lung pathology existed, selective changes in pulmonary blood flow to one lung or the other were induced, or following induction of unilateral acute lung injury.

Materials and methods

The studies described in this report were approved by the Institutional Animal Care and Use Committee, University of Pittsburgh and were in compliance with the Animal Welfare Act and the National Research Council's Guide for the Care and Use of Laboratory Animals. Six mongrel dogs (weight $20.7 \text{ kg} \pm 1.1 \text{ kg}$) were fasted overnight prior to these studies. The animals were given morphine 4 mg/kg subcutaneously, following in 15 minutes with pentobarbital sodium (30 mg/kg i.v.). The animals' tracheas were then intubated (7F Portex). The dogs were ventilated (Harvard split lung dual-phase ventilator, Cambridge, MA) initially at FiO_2 of 0.50 with a tidal volume of 15 ml/kg and at a rate to maintain a $PaCO_2$ between 30 and 45 torr. An arterial catheter was inserted from the femoral artery to monitor arterial pressure (Pa) and sample blood. A triple lumen catheter was placed into the femoral vein for the administration of in-

travenous fluids, and continuous pentobarbital anesthesia (2 to 4 mg/kg/hr). The right external jugular vein was then exposed, and an 7.5F pulmonary artery thermodilution catheter equipped with fiberoptics to measure mixed venous oxygen saturation (SvO_2) (Abbott, Chicago, IL) was positioned in a proximal branch of the left or right main pulmonary artery for the recording of pulmonary artery pressures (Ppa), obtaining mixed venous blood samples, and transiently reducing unilateral pulmonary blood flow. A tracheotomy was then performed in the sub-cricoid position and a 13 mm double lumen endobronchial tube (Kottmier, Rusch, Germany) was placed for split lung ventilation. Separation of ventilation was confirmed later during thoracotomy by direct visualization of unilateral lung expansion without contralateral lung expansion during one lung ventilation for each lung separately.

The animals were then placed on their right side, given pancuronium (1 mg i.v.), and a thoracotomy incision was made through the 5th intercostal space. The left lung was then collapsed by placing its airway to room air after disconnecting its airway from the ventilator. The pericardium was opened and an ultrasonic flow probe (8S) (Transonic Systems Inc., Ithaca, NY) was placed around the left pulmonary artery. The main pulmonary artery was then identified and another ultrasonic flow-probe (16S) (Transonic Systems Inc., Ithaca, NY) was placed around it. Both flow-probes were packed with an agar gel mixture to optimize the flow signal and connected to a flow meter (T208 Flowmeter, Transonic Systems Inc., Ithaca, NY) for flow measurements. Both flow probes had been previously calibrated *in vitro* and found to be linear over the range of flows studied. The left lung was then re-inflated, both lungs placed on $5 \text{ cm H}_2\text{O}$ PEEP, and the chest closed. No chest tube was placed. The dogs were placed supine and allowed to stabilize for a minimum of 30 minutes, during which time hemodynamic and gas exchange variables (*vide infra*) were constant. This methodology has been previously described and validated by us in this preparation [10].

The tidal volume to each lung was adjusted to keep peak airway pressures equal and similar to the initial airway pressure levels prior to thoracotomy. The resultant summed tidal volume of the two lungs equaled the tidal volume before split lung ventilation. Respiratory rate of both ventilators was adjusted to maintain $PaCO_2 \geq 30$ torr. The respiratory rate of both ventilators was always the same and synchronized to have inflation occur simultaneously for each lung. FiO_2 was ≤ 0.50 and a PEEP of $5 \text{ cmH}_2\text{O}$ was maintained for each lung. All fluid-filled catheters were connected to low-displacement transducers (Gould Statham P-50, Gould, Cleveland, OH), and

the air-filled catheter for airway pressure were connected to a high sensitivity transducer (Bell and Howell 4-327 I, Gould). All transducers were zeroed to the midthoracic plane. Measurements were recorded on an eight-channel strip chart recorder (Gould, Cleveland, Ohio).

Expired gas from each lung was collected for the measurement of CO₂ production via two separate metabolic monitors (Deltatrac, SensorMedics, Anaheim, CA) with pediatric mixing chambers which had been previously calibrated for gas and pressure measurements as recommended by the manufacturers.

The dogs had 150 ml of blood withdrawn, heparinized (1 unit/ml) and stored. 150 ml of 0.9% NaCl solution was given as replacement. This stored blood was then reinfused as needed after blood samples were collected at the various measurement intervals to maintain the animal's hematocrit constant throughout the experiment.

Protocol

Initial measurements were performed at baseline after the period of stabilization. All measurements were performed during conditions of FiO₂ > 90%. The pulmonary arterial catheter's balloon was periodically inflated with 1 ml air, allowed to occlude, and then repeat measurements were performed followed by balloon deflation. Then 10 ml of 0.1N hydrochloric acid (HCl) was instilled into one lung via a plastic catheter after the animal was placed in the lateral decubitus position to minimize cross-damage. Further measurements were performed 1 hour (3 animals) or 4 hours (3 animals) after HCl administration. Dogs were stratified to receive HCl into either the left or right lung (2 rights and 3 lefts). One dog had 2 ml of oleic acid given through the distal end of the pulmonary artery catheter into the left pulmonary artery. 0.9% NaCl solution was infused at a fixed rate to maintain a constant left atrial pressure, and as noted above, the dogs were autotransfused after blood sampling.

Measurements

The following measurements were recorded at the 3 different time points previously noted with the pulmonary artery balloon deflated or fully inflated for 5 minutes in order to alter relative lung blood flow: blood flows for the main pulmonary artery and left pulmonary artery were recorded, with right pulmonary artery flow calculated as the difference between main pulmonary artery flow and left pulmonary artery flow, CO₂ production (VCO₂) from each lung, Pa, Ppa, and blood analysis. VCO₂ was taken over a 5 minute period of stable read-

ings, and the average was determined. Arterial and mixed venous blood samples were drawn for measurements of pO₂, pCO₂, pH, oxygen saturation, hemoglobin, and oxygen content using machines calibrated for dog blood (ABL 30 and OSM 3 hemoximeter, Radiometer, Copenhagen, Denmark).

The animals were killed at the end of the experiment with a bolus injection of saturated KCl. The lungs were examined at necropsy to confirm the macroscopic appearance of consolidation and to validate the position of all vascular catheters.

Statistical analysis

Results were presented as mean ± standard deviation. A paired t-test was employed to compare differences between 2 different groups with paired data. Linear regression was performed for comparing flow and VCO₂. Data analysis was performed using a computer software package (Microsoft Excel 5.0a). Differences corresponding to a p < 0.05 were considered significant.

Results

All dogs tolerated the experimental protocol without hypotension, apart from the initial transient decrease following acid instillation. All dogs had pink frothy edema emanating from the airways of the injured lung subsequent to HCl instillation or oleic acid injection. The pink frothy fluid in the tube was removed by suctioning as needed and measures not taken for 5 minutes post-suctioning. Furthermore, at necropsy there was dense macroscopic hemorrhagic consolidation on the side of HCl instillation or oleic acid injection, while the uninvolved lung appeared grossly normal on inspection. Hemodynamic and blood gas data (**Table 1**) demonstrated the presence of significant impairment in gas exchange in the injured lung. The inflation of the pulmonary artery balloon resulted in a significant reduction in percentage flow to the affected side at baseline conditions and after acute lung injury (baseline 25% ± 6.7%, p < 0.001; post acute lung injury 28% ± 20%, p < 0.05).

The percentage of relative flow (% uni-lung flow) to each lung was linearly related to the percentage of VCO₂ (% uni-lung VCO₂) when all the conditions were pooled (**Figure 1**). Individually for the different conditions (no lung injury with either pulmonary artery balloon deflated or inflated, and acute lung injury with either pulmonary artery balloon deflated or inflated), the linear relationships are still significant but the slopes were significantly different (**Table 2**).

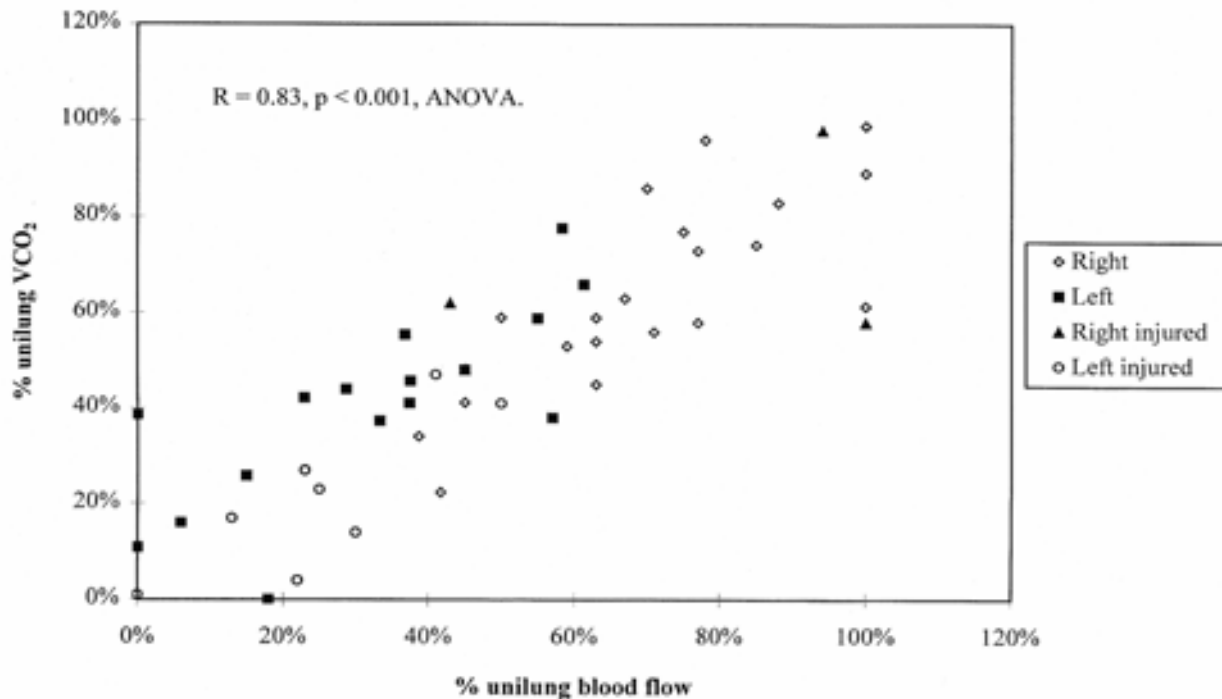


FIGURE 1. COMBINED DATA FROM ALL THE DIFFERENT LUNG CONDITIONS: NORMAL, ACUTE UNILATERAL INJURY, AND AFTER FLOW ALTERATIONS WITH THE INFLATION OF THE PULMONARY ARTERY BALLOON.

TABLE 1. HEMODYNAMIC PARAMETERS AND BLOOD GAS DATA.

| | Main pulmonary flow (l/min) | Mean arterial pressure (mmHg) | Mean pulmonary artery pressure (mmHg) | Arterial pH | Arterial pCO ₂ (torr) | Qs/Qt | PaO ₂ / FiO ₂ ratio (torr) |
|----------------|-----------------------------|-------------------------------|---------------------------------------|---------------------------|----------------------------------|---------------------------|--|
| Baseline | 1.78 ± 0.47 | 86 ± 19 | 15 ± 2 | 7.38 ± 0.045 | 35.0 ± 5.3 | 0.16 ± 0.034 | 481 ± 70 |
| Unilateral ALI | 1.43 ± 0.48 ^a | 84 ± 12 | 21 ± 6 ^b | 7.27 ± 0.090 ^a | 39.6 ± 11.4 | 0.31 ± 0.081 ^b | 236 ± 161 ^a |

ALI - acute lung injury, Qs/Qt - shunt fraction. ^ap < 0.05, ^bp < 0.005.

TABLE 2. EFFECTS OF LUNG INJURY AND ALTERATIONS IN RELATIVE LUNG PERFUSION.

| | R | Slope | 'p' value (ANOVA) |
|---------------------------------|------|-------|-------------------|
| All conditions | 0.83 | 0.69 | < 0.001 |
| Baseline | 0.75 | 0.33 | 0.005 |
| Unilateral ALI - injured side | 0.86 | 1.43 | 0.028 |
| Unilateral ALI - control side | 0.86 | 1.43 | 0.028 |
| PA balloon inflated at baseline | 0.82 | 0.59 | 0.001 |

ALI - acute lung injury, PA - pulmonary artery catheter.

Discussion

This study demonstrates that split lung VCO_2 measurements reflect individual lung blood flow over a broad range of flows in intact dogs. This linear relationship was apparent for both normal and injured lungs, although the slopes were different between normal and injured lungs. However, the slopes were similar for all animals for either their normal; or injured lungs. These differences in slope between normal and injured lungs most likely are the result of shunt flow that is unequally distributed during unilateral acute lung injury.

This bedside method may thus be a useful surrogate for lung perfusion scans in patients with independent lung ventilation for determining relative lung perfusion. Furthermore, measuring uni-lung VCO_2 has advantages over lung scans in being without radiation risks, inexpensive, relatively noninvasive, and available at the bedside on a continual basis. Although we previously showed that this

method can be readily applied in the intensive care unit, its application to patients with diseases other than acute lung injury will require further validation. This method is limited however in that it does not provide absolute flow data and gives only mean values over time. The additional analysis of oxygen concentration changes will allow one to assess changes in the respiratory quotient (RQ), and thus changes in both ventilation and perfusion [7] if FiO_2 levels were low enough to allow accurate measurements of VO_2 . Bronchoscopic directed measurements of lung segmental VCO_2 can potentially add to more specific anatomical location of perfusion abnormalities [8].

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