Validation of measurements of ventilation-to-perfusion ratio inequality in the lung from expired gas

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Prisk, G. Kim, Harold J. B. Guy, John B. West, and James W. Reed. Validation of measurements of ventilation-to-perfusion ratio inequality in the lung from expired gas. J Appl Physiol 94: 1186–1192, 2003. First published October 25, 2002; 10.1152/japplphysiol.00662.2002.—The analysis of the gas in a single expirate has long been used to estimate the degree of ventilation-perfusion (Va/Q) inequality in the lung. To further validate this estimate, we examined three measures of Va/Q inhomogeneity calculated from a single full exhalation in nine anesthetized mongrel dogs under control conditions and after exposure to aerosolized methacholine. These measurements were then compared with arterial blood gases and with measurements of Va/Q inhomogeneity obtained using the multiple inert gas elimination technique. The slope of the instantaneous respiratory exchange ratio (R slope) vs. expired volume was poorly correlated with independent measures, probably because of the curvilinear nature of the relationship due to continuing gas exchange. When R was converted to the intrabreath Va/Q (iV/Q), the best index was the slope of iV/Q vs. volume over phase III (iV/Q slope). This was strongly correlated with independent measures, especially those relating to inhomogeneity of perfusion. The correlations for iV/Q slope and R slope considerably improved when only the first half of phase III was considered. We conclude that a useful noninvasive measurement of Va/Q inhomogeneity can be derived from the intrabreath respiratory exchange ratio.

METHODS

Experimental details. The study was approved by the University of California, San Diego, Animal Subjects Committee. Nine mongrel dogs [18–24 (mean 20.6) kg body wt] were anesthetized with pentobarbital sodium (30 mg/kg iv) and paralyzed with pancuronium bromide (0.1 mg/kg iv). The level of anesthesia and relaxation was maintained by incremental administration of both drugs. A cuffed endotracheal tube (9 mm ID) was placed through a tracheostomy. Normal arterial blood gas tensions were maintained by adjusting the frequency of a Harvard mechanical ventilator set at a tidal volume of 15 ml/kg. A 7-Fr Swan-Ganz catheter was inserted via the right external jugular vein and advanced into the pulmonary artery by using direct pressure monitoring. The femoral artery was cannulated for sampling arterial blood (Fig. 1).

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Flow through the endotracheal tube was measured with a pneumotachograph (Fleisch no. 1) connected to a differential pressure transducer (Validyne MP-45). Before each study, the flowmeter was calibrated using a 1-liter precision syringe.

Gas concentrations were measured using a mass spectrometer (model MGA-1100, Perkin-Elmer) sampling from the midstream point of the proximal end of the endotracheal tube. The sample transit time was checked each day and was generally ~400 ms. This was later used to correctly align the gas concentration and flow signals before analysis. Airway pressure was measured via a Statham P23 ID transducer connected to a point 8 cm distal to the mass spectrometer sampling point. This position was selected to avoid sampling puffs of gas from the airway pressure catheter during major pressure changes.

Data were monitored on a strip-chart recorder (Gould-Brush Mark 200) and digitized at 30 Hz using a 12-bit analog-to-digital converter in a computer system.

**Methacholine administration.** We used aerosolized methacholine to induce bronchoconstriction and, thus, alter the distribution of ventilation. A 1% methacholine solution was aerosolized using a jet nebulizer (Acorn II, Marquest Medical Products) and administered via the ventilator circuit for 1 min. During this time, the respiratory rate was adjusted to maintain a normal end-tidal CO2. A short period was then allowed to obtain a new quasi-steady state, and the measurements after methacholine administration were performed. On average, postmethacholine measurements were made ~27 min after methacholine administration.

**MIGET.** MIGET was applied as described by Gale et al. (2). The inert gas solution (SF6, ethane, cyclopropane, enflurane, ether, and acetone) was prepared in 5% dextrose (2) and infused for ~20 min at ~10 ml/min before collection of the samples. The total volume of fluid infused over the course of the study (1–2 h) was ~1 liter.

Quadruplicate 15-ml samples of mixed expired gas and duplicate 6-ml samples of pulmonary and systemic arterial blood were obtained using gastight syringes under normal conditions (before the iV/Q measurements) and after the stabilization subsequent to methacholine administration (just before the iV/Q measurements). These samples were used to measure the steady-state concentrations of the six inert gases using a gas chromatograph (model 5890A, Hewlett-Packard, Wilmington, DE) (9). Va/Q distributions were calculated by using MIGET in the usual fashion. Solubilities, retentions (the ratio of arterial to mixed venous partial pressures), and excretions (the ratio of mixed expired to mixed venous partial pressure) for the inert gases were determined and corrected for body temperature, and Va/Q distributions were calculated from the inert gas data (8, 9). The second moment of the perfusion distribution exclusive of intrapulmonary shunt (SDQ) and the second moment of the ventilation distribution exclusive of dead space (SDV) were used as indicators of the degree of Va/Q inequality. Dispersion of retention (DispR), excretion (DispE), and retention minus excretion (DispR–E) were derived directly from the retention and excretion data (2). The residual sum of squares was used as an indicator of the adequacy of fit of the data to the 50-compartment model of the lung (9).

**Blood gas measurements.** Arterial samples (2 ml) were collected immediately after each inert gas sample and kept on ice until analyzed for PO2, PCO2, and pH using a blood gas analyzer (model IL-1306, Instrumentation Laboratories, Lexington, MA). Alveolar-arterial Po2 difference was determined using the ideal alveolar Po2 calculated using the alveolar gas equation and measured arterial PCO2 (Paco2) and R.

**iV/Q test maneuver.** For each test, the dogs were ventilated at a constant rate and tidal volume until stable end-tidal gas concentrations were obtained. Data were then collected for ~60 s to provide a measurement of O2 consumption and CO2 production. The technique described by Tomioka et al. (7) was used. At the end of a normal expiration, the airway was connected to a constant-pressure source of air at ~80 cmH2O pressure, and the animal was inflated to full lung volume. Inflation was via a flow restrictor limiting flow to ~0.1 l/s. On reaching maximum volume, the airway was connected to a constant-pressure source of ~80 cmH2O pressure, and the animal was inflated to full lung volume. The animal was then returned to normal ventilation.

**iV/Q analysis.** The slow vital capacity expiration was analyzed using the techniques described by Gyu et al. (3). Gas concentration data were converted on a point-by-point basis to R using the standard alveolar gas equation (3)

\[
R = \frac{P_{E_{CO2}}}{P_{E_{O2}}} = \frac{P_{E_{CO2}}}{P_{E_{O2}}} = \frac{P_{E_{CO2}}}{P_{E_{O2}}} = \frac{P_{E_{CO2}}}{P_{E_{O2}}} = \frac{P_{E_{CO2}}}{P_{E_{O2}}}
\]

where PECO2 is expired PCO2, PEO2 and PIO2 are expired and inspired PO2, and PEN2 and PIN2 are expired and inspired PN2. The data were then plotted as a function of expired volume (Fig. 2). Because a perfectly homogeneous lung produces intrabreath R curves that are curvilinear as a result of
From the plot of iV/Q as a function of expired volume (Fig. 3), we identified the onset of phase IV (airway closure) and measured the slope of the curve using linear least-squares regression as a function of expired volume (iV/Q slope). We determined the range of iV/Q (iV/Q range) by measuring the maximum differences in iV/Q over the portion of the exhalation corresponding to phase III. Thus iV/Q range included any excursions in iV/Q beyond that of slope itself caused by cardiogenic oscillations and by any deviation from the least-squares fitted line. Figure 3 illustrates these parameters. Additionally, using the intrabreath R curve (Fig. 2), we measured the slope of R as a function of expired volume (R slope) over the same lung volume range and also used this as a possible index of inhomogeneity of gas exchange, reasoning that, although the isopleths were curvilinear, an index based on this curve alone would be easier to calculate than the iV/Q-based measurements.

**RESULTS**

**Gas exchange.** During control measurements performed before methacholine administration, arterial blood gases were essentially normal, with \( P_{ACO_2} \) of 34.5 Torr and arterial \( P_{O_2} \) (\( P_{A0_2} \)) of 87 Torr (inspired \( O_2 \) fraction = 0.21 in all cases). Methacholine administration worsened gas exchange: \( P_{ACO_2} \) of 36.2 Torr and \( P_{A0_2} \) of 63 Torr (Table 1). Alveolar-arterial \( P_{O_2} \) difference increased from 23 to 40 Torr after methacholine administration.

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**Diagram Descriptions**

**Fig. 2.** Respiratory exchange ratio (R) plotted as a function of expired volume in a dog in the control state (thin trace). Dashed curves represent output from the model with ventilation-to-perfusion ratios (V/Q) differing by 20% from that of the center dashed curve. V/Q values corresponding to each model line are indicated. Thick trace, plot of intrabreath V/Q obtained by interpolating the R line on the basis of the 3 R model lines. In R and iV/Q data, cardiogenic oscillations and a terminal rise (phase IV) can be clearly seen. Note curvilinear behavior of the R isopleths, which results from continuing gas exchange. It is this curvilinear behavior that makes interpretation of the R data against volume difficult.

**Fig. 3.** Plot of iV/Q as a function of volume (data from Fig. 2). Dashed vertical lines, limits of phase III. Note abrupt rise in iV/Q at onset of phase IV. iV/Q slope as fitted between these limits is indicated by the thick line. iV/Q slope calculated over first and second halves of phase III are also shown (thin line). Solid vertical bar, iV/Q slope over phase III.

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**Continued text:**

...continuing gas exchange (4), it is difficult to separately determine the change in R caused by V/Q inequality.

For this reason, the behavior of a theoretical lung performing the same controlled vital capacity expiration was calculated. The model comprises a single, perfectly mixed compartment connected via a serial dead space to the mouth and supplied with blood of constant mixed venous concentration at a constant cardiac output (Q). Appropriate choices for residual volume, Q, lung tissue volume and ventilation, and gas exchange from the preceding period of quiet breathing are made (3). Errors made in the choice of these variables have only modest effects on the output. For example, a large (10 Torr) error in the mixed venous \( P_{CO_2} \) results in only a 5% error in the resulting variation in V/Q (3).

On the basis of these initial conditions, the mixed venous and alveolar points corresponding to that V/Q are calculated using the Kelman routines (11). The model then calculates the instantaneous R as a function of expired volume for the same volume history as the animal. To produce a family of R isopleths, the simulation is repeated varying Q (and, therefore, V/Q) from its initial estimate in 10% steps up and down. These R isopleths form a scale for V/Q, inasmuch as each individual isopleth describes the behavior of a lung, free of V/Q inequality, following the same lung volume history as the animal.

In this way, the measured R curve is transformed to an iV/Q curve by calculating the point-by-point iV/Q from linear interpolation between the family of R isopleths calculated for different V/Q values. This has the advantage of providing straight-horizontal isopleths of iV/Q vs. expired volume as opposed to the curvilinear R isopleths. Figure 2 shows a sample intrabreath R curve, the isopleths of V/Q, and the resultant iV/Q curve.

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administration. Table 1 lists the average values for the gas exchange variables and other measurements for the control period and after methacholine administration.

**Multiple inert gas variables.** Methacholine administration resulted in a significant widening of the V/A/Q distribution (Table 1), with SDQ increasing from 0.64 to 1.33 (Fig. 4). There were comparable increases in DispR, DispE, and DispR – E.  

**Expired gas variables.** Neither iV/Q range nor R slope changed significantly as a result of methacholine administration (Table 1). iV/Q slope became steeper (more negative) as a result of methacholine administration, changing from $-0.092 \pm 0.021$ to $-0.245 \pm 0.089 \; (P < 0.10; \; cf. \; Fig. \; 3 \; with \; Fig. \; 5)$.  

Because there were often significant nonlinearities in the plot of R as a function of volume and iV/Q as a function of volume, we then considered R slope and iV/Q slope over the first and second halves of phase III by dividing that portion of the exhalation into two halves and repeating the slope measurements (Fig. 5). When the breath divided into the first and second halves of phase III was considered, the effect of methacholine on iV/Q slope was much greater over the first than over the second half of the breath. Over the first half of phase III, iV/Q slope significantly steepened from $-0.020 \pm 0.025$ to $-0.379 \pm 0.108 \; (P < 0.05)$; over the second half of the breath, iV/Q slope changed from $-0.149 \pm 0.034$ to $-0.122 \pm 0.076$ (not significant). In contrast, R slope over the first half of the exhalation became considerably steeper after methacholine administration ($-0.014 \pm 0.017$ vs. $-0.190 \pm 0.033; \; P < 0.05$), but R slope over the second half of the breath was considerably flatter after exposure to methacholine

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**Table 1. Gas exchange, inert gases, and iV/Q**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Control (n = 9)</th>
<th>Postmethacholine (n = 9)</th>
</tr>
</thead>
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<tr>
<td>PAO2, Torr</td>
<td>86.9 ± 2.7</td>
<td>62.8 ± 3.4*</td>
</tr>
<tr>
<td>AADQ, Torr</td>
<td>23.3 ± 2.5</td>
<td>39.6 ± 2.5*</td>
</tr>
<tr>
<td>PacO2, Torr</td>
<td>34.5 ± 0.7</td>
<td>36.2 ± 1.0</td>
</tr>
<tr>
<td>SDQ</td>
<td>0.64 ± 0.07</td>
<td>1.33 ± 0.14*</td>
</tr>
<tr>
<td>SDV</td>
<td>1.10 ± 0.15</td>
<td>0.83 ± 0.07*</td>
</tr>
<tr>
<td>DispR</td>
<td>4.12 ± 0.56</td>
<td>11.81 ± 1.60*</td>
</tr>
<tr>
<td>DispE</td>
<td>5.50 ± 0.99</td>
<td>8.01 ± 1.00*</td>
</tr>
<tr>
<td>DispR – E</td>
<td>8.60 ± 1.32</td>
<td>17.28 ± 2.16*</td>
</tr>
</tbody>
</table>

- Values are means ± SE. PAO2 and PacO2, arterial PO2 and PO2; AADQ, alveolar-arterial PO2 difference; SDQ and SDV, log standard deviations of perfusion (Q) and ventilation (V) distributions; DispR, DispE, and DispR – E, dispersion of retention, excretion, and reten-
  - **Fig. 4. Sample distributions of ventilation (V) and perfusion (Q) as a function of V/A/Q before (A) and after (B) methacholine administration. Data were obtained using the multiple inert gas elimination technique (MIGET). Methacholine administration resulted in a significant widening of distribution of perfusion. Presence of ventilation at high V/A/Q is commonly seen with mechanical ventilation.**
MEASURING V\textsubscript{A}/Q INEQUALITY FROM EXPIRED GAS

**DISCUSSION**

\(i \dot{V} / Q\) slope. The correlations between \(i \dot{V} / Q\) slope and independent measures of \(V_{A}/Q\) inhomogeneity before and after methacholine administration (Table 2) suggest that \(i \dot{V} / Q\) slope provides a useful index of gas exchange disruption. In particular, in this circumstance, it appears that the administration of aerosolized methacholine resulted in different behavior of the lung when the gas expired from the lung in the first half of the breath was compared with the gas expired from the lung in the second half of the breath. When we considered \(i \dot{V} / Q\) slope calculated from only the first half of the exhalation, we obtained better correlations with independent measures of \(V_{A}/Q\) inhomogeneity (Table 2). Although calculation of \(i \dot{V} / Q\) slope is somewhat complex, \(i \dot{V} / Q\) slope has the advantage of being a completely noninvasive measurement and relatively simple to perform experimentally.

Necessary assumptions in the calculation of \(i \dot{V} / Q\) are the concentrations of \(O_2\) and \(CO_2\) in the mixed venous blood entering the lungs. We used an estimate of these based on \(O_2\) consumption, \(CO_2\) production, and assumed \(Q\) (the Fick principle). West et al. (10) showed that although the value of \(i \dot{V} / Q\) corresponding to a particular value of \(R\) is sensitive to the composition of the mixed venous blood, the fractional change in calculated \(i \dot{V} / Q\) is very insensitive. Errors in \(O_2\) and \(CO_2\) concentration in opposite directions (such as those arising from an error in metabolic rate or \(Q\)) result in very small errors in \(i \dot{V} / Q\). A 10% error of this nature results in changes in \(i \dot{V} / Q\) of <1%, which, when coupled with the previous observations of West et al., shows that conversion from \(R\) to \(i \dot{V} / Q\) is robust.

**Effect of methacholine.** We used methacholine to induce bronchoconstriction and, presumably, uneven ventilation, thus disrupting gas exchange. We wished to induce gas exchange lesions of varying intensity to test the usefulness of the change in \(i \dot{V} / Q\) slope over a range of gas exchange defect severity. \(P_{A}O_2\) was be-

**Fig. 5.** Plot of \(i \dot{V} / Q\) as a function of volume (thick trace) and intra-breath \(R\) (thin trace) in the same dog used in Figs. 2 and 3 after exposure to methacholine. Note significantly different behavior between the first and second half of phase III for \(i \dot{V} / Q\) that is not apparent in \(R\). Lines for calculated phase III slopes and range are shown only for \(i \dot{V} / Q\) for reasons of clarity; format as in Fig. 3.

**Fig. 6.** Indexes of \(V_{A}/Q\) inequality and gas exchange before (open bars) and after (solid bars) methacholine administration. \(P_{A}O_2\), arterial \(P_{A}O_2\); \(AaDO_2\), alveolar-arterial \(P_{A}O_2\) difference; \(SDO_2\), log SD of perfusion (multiplied by 100 for display purposes); \(i \dot{V} / Q\) slope, slope of \(i \dot{V} / Q\) plot vs. volume over phase III (multiplied by \(-1.000\) for display purposes); 1st and 2nd \(i \dot{V} / Q\) slope over first and second halves of phase III; \(R\) slope, \(R\) plot vs. volume over phase III (multiplied by \(-1.000\) for display purposes); 1st and 2nd \(R\) slope over first and second halves of phase III. \(* P < 0.05; (+) P < 0.10\) compared with control.

blood gases and with the indexes of MIGET associated with pulmonary perfusion, \(DispR\) and \(SDQ\).

Not surprisingly, \(i \dot{V} / Q\) slope over the first half of the breath correlates strongly with \(i \dot{V} / Q\) slope over the entire breath \((r^2 = 0.85, P < 0.05)\). However, \(i \dot{V} / Q\) slope over the first half of the breath is much less strongly correlated with \(i \dot{V} / Q\) slope over the second half of the breath \((r^2 = 0.28)\), supporting the observation of significant nonlinearities in \(i \dot{V} / Q\) slope. The change in \(i \dot{V} / Q\) slope over the first half of phase III was the most strongly correlated with all other variables measured in these dogs, showing significant correlations with all measures of \(V_{A}/Q\) inhomogeneity, with the exception of \(SDV\). Correlations with \(i \dot{V} / Q\) slope over the second half of the breath were much weaker (Table 2).

Similarly, \(R\) slope over the first half of phase III was strongly correlated with other measures of gas exchange. In general, \(R\) slope over the first half of the breath correlated with the same variables as did \(i \dot{V} / Q\) slope over the first half of the breath, and the correlations were of similar strength (Table 2). As was the case with \(i \dot{V} / Q\) slope, \(R\) slope over the second half of the breath was poorly correlated with other measures of gas exchange.

**Fig. 6.** Indexes of \(V_{A}/Q\) inequality and gas exchange before (open bars) and after (solid bars) methacholine administration. \(P_{A}O_2\), arterial \(P_{A}O_2\); \(AaDO_2\), alveolar-arterial \(P_{A}O_2\) difference; \(SDQ\), log SD of perfusion (multiplied by 100 for display purposes); \(i \dot{V} / Q\) slope, slope of \(i \dot{V} / Q\) plot vs. volume over phase III (multiplied by \(-1.000\) for display purposes); 1st and 2nd \(i \dot{V} / Q\) slope over first and second halves of phase III; \(R\) slope, \(R\) plot vs. volume over phase III (multiplied by \(-1.000\) for display purposes); 1st and 2nd \(R\) slope over first and second halves of phase III. \(* P < 0.05; (+) P < 0.10\) compared with control.
between 93 and 44 Torr (between 93 and 69 Torr for control condition and between 83 and 44 Torr after methacholine), which shows that we were successful in inducing a range of severity of the gas exchange defect between different animals. Similarly, calculated alveolar-arterial \( P_{\text{O}_2} \) difference rose from 23 to 40 Torr after methacholine administration. That \( iV/Q \) slope (and especially \( iV/Q \) slope over the first half of the exhalation) correlates well with the change in \( P_{\text{AO}_2} \) and with alveolar-arterial \( P_{\text{O}_2} \) difference (Table 2) is a good indication that the measurement is a useful noninvasive means by which to determine the severity of a gas exchange defect. The change in the distribution of \( V_{\text{A}}/Q \) distributions from MIGET (Fig. 4) is similar to that reported in previous studies. In particular, an increase in the inhomogeneity of ventilation resulting from bronchoconstriction in dogs results in a widening of the distribution of perfusion (an increase in \( SD_{Q} \)) through the appearance of a low \( V_{\text{A}}/Q \) mode (6).

**Intrabreath changes in \( V_{\text{A}}/Q \)**. There were significant differences in \( iV/Q \) slope measured over the first and second halves of phase III of the vital capacity expiration, in particular, in those tests after methacholine administration (Table 1). Although it might be tempting to compare the first and second halves of the breath, such a comparison is almost certainly invalid when attempting to compare the data before and after methacholine administration. Although after methacholine administration the portion of the lung that empties first exhibits a greater degree of \( V_{\text{A}}/Q \) inhomogeneity than does the portion that empties last, there is no means to determine whether these correspond to the same lung regions measured before methacholine administration.

To investigate the degree of \( V_{\text{A}}/Q \) inequality in the entire lung, it is important to consider data only from phase III. The onset of phase IV represents the point at which airway closure occurs somewhere in the lung. Thus, after that point, exhaled gas is a reflection of only those regions still contributing to the exhalate. However, it is not generally possible to determine which lung regions close, especially in abnormal lungs, such as those exposed to methacholine. Although the \( iV/Q \) data from phase IV may provide insight into other aspects of \( V_{\text{A}}/Q \) inhomogeneity, they are likely not useful in comparing \( iV/Q \) with whole lung measures such as MIGET.

It is important to recognize that the model used to generate the \( R \) isopleths, from which \( iV/Q \) is calculated, is not intended to represent an actual lung. Rather, it is used to provide a series of reference lines describing how a perfect lung, following the same lung volume history as the test lung, would behave. The data from the test lung are then interpreted using this scale “as if” the test lung were a collection of such perfect lungs following the same volume history. Although the gas arising from a particular lung unit with a given \( V_{\text{A}}/Q \) may well have significant phase III slopes of \( O_{2} \) and \( CO_{2} \), there is no corresponding effect on the phase III slope for \( R \) (and, hence, for \( iV/Q \)). This is because, on the \( O_{2}-CO_{2} \) diagram, the value of \( R \) is the slope of the line joining the inspired point and the alveolar point. Thus any factor that contributes to variable mixtures from these sources produces no change in \( R \) (the obvious example being the lack of effect of dead space admixture, which has a big effect on the \( O_{2} \) and \( CO_{2} \) trace, especially in the first half of expiration). Thus, with changes in \( R \) (and \( iV/Q \)), we are measuring the effects of different lung regions with different \( V_{\text{A}}/Q \) ratios emptying at different points in the breath. The causes of such differences in emptying cannot be inferred from these measurements. However, it is clear from these data, and from those of West et al. (10) and Guy et al. (3), that the patterns that result are strikingly different between normal and abnormal lungs.

**Using \( R \) slope instead of \( iV/Q \) slope**. We also attempted to determine whether the slope of the \( R \) plot vs. expired volume (\( R \) slope) could be used instead of the computationally more demanding \( iV/Q \) plot. As the data in Table 2 illustrate, there were virtually no significant correlations between \( R \) slope and the independent measures of \( V_{\text{A}}/Q \) inhomogeneity, nor did \( R \) slope change as a result of methacholine administration (Table 1). We were not entirely surprised by this finding. As Fig. 2 illustrates, even a perfectly mixed lung (the model lines in Fig. 2) produces curvilinear \( R \) plots. Attempting to measure a slope from a curvilinear plot such as that shown in Fig. 2 introduces consider-

### Table 2. Significant correlation coefficients

<table>
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<th></th>
<th>( iV/Q ) Slope</th>
<th>( iV/Q ) Range</th>
<th>( Pa_{\text{O}_2} )</th>
<th>( AaDO_{2} )</th>
<th>( SD_{Q} )</th>
<th>( SD_{D} )</th>
<th>( S_{\text{DispR}} )</th>
<th>( S_{\text{DispDE}} )</th>
<th>( S_{\text{DispR} - E} )</th>
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<td><strong>Slope</strong></td>
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<td>( 0.16 )</td>
<td>( 0.20 )</td>
<td>( 0.27 )</td>
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<td>( 0.35 )</td>
<td>( 0.26 )</td>
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<td>( NS )</td>
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<td><strong>Range</strong></td>
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<td>( 0.45 )</td>
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<td>( 0.34 )</td>
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Values are correlation coefficients (\( r^{2} \)) from linear regression between indicated variables. Only \( r^{2} \) values reaching level of statistical significance are reported. Slope 1st and slope 2nd, slopes as a function of volume over 1st and 2nd halves of phase III; NS, not significant.
able error into the resulting slope unrelated to a $\dot{V}a/Q$ defect. This is reflected in the poor correlation performance (Table 2).

$R$ slope over the first half of phase III produced correlations with independent measures of gas exchange that were almost as strong as those from $iV/Q$ slope measured over the first half of phase III. This measurement may provide a more easily calculated surrogate to $iV/Q$ slope, albeit at the expense of not having a scale that is as easily interpretable. The degree of curvilinearity (which results from continuing gas exchange as the exhalation proceeds) depends largely on lung volume and expired flow rate, with smaller lung volumes and lower flow rates exhibiting greater curvilinearity. These effects are smallest over the first half of phase III. Thus measurements of $R$ slope over the first half of phase III in adult humans in which exhalation is kept to less than $\sim 10$ s may be less prone to the curvature artifact. In that case, a stronger correlation between the independent measures of $Va/Q$ inhomogeneity and $R$ slope might result.

Other expired gas measurements of $Va/Q$ inhomogeneity. The most informative expired gas measurements of $Va/Q$ inhomogeneity in this study were $iV/Q$ slope and $R$ slope over the first half of phase III. We attempted to use the range of $iV/Q$, which also includes any contribution from cardiogenic oscillations. It might be expected that the magnitude of the cardiogenic oscillations would be an indicator of the range of $Va/Q$ inhomogeneity in the lung. If this is the case, then it might be thought that including this component in the measurement by measuring the range (as opposed to the slope, which averages out any component due to cardiogenic oscillations) would improve the noninvasive estimation of $Va/Q$ inhomogeneity. However, on the basis of the much less robust correlations in Table 2, this appears not to be the case.

In conclusion, in anesthetized dogs exposed to methacholine, measurements of $iV/Q$ slope provide a useful index of the degree of $Va/Q$ disruption in the lung. The changes in $iV/Q$ slope correlate well with more direct measurements of $Va/Q$ range obtained using MIGET and also with changes in arterial blood gas variables. The degree of correlation is improved when only gas from the first half of exhalation is considered. Because $iV/Q$ slope can readily be measured noninvasively, this may prove useful in future studies of disruption to gas exchange, especially in humans in remote environments where noninvasive techniques are often desirable.

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