

## Mechanisms of Abnormal Gas Exchange in Patients with Pneumonia

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The mechanisms of abnormal gas exchange in patients with pneumonia and the gas exchange response while breathing high inspired O<sub>2</sub> concentrations have not been clearly elucidated. To this end, we studied 23 inpatients with pneumonia and mild to severe arterial hypoxemia and/or increased alveolar - arterial O<sub>2</sub> difference. Ventilation-perfusion ( $\dot{V}_A/\dot{Q}$ ) distributions were obtained upon breathing room air (or maintenance inspired oxygen fraction) and 100% O<sub>2</sub> in random order. Subjects were divided in two groups according to whether they were spontaneously breathing (SB, n = 13) or their lungs were mechanically ventilated (MV) because of acute severe respiratory failure (n = 10). The SB patients showed only small amounts of shunt ( $7 \pm 2\%$ ) (mean  $\pm$  standard error) and moderate  $\dot{V}_A/\dot{Q}$  mismatching, characterized by the presence of a small percentage of blood flow to low  $\dot{V}_A/\dot{Q}$  units ( $\dot{V}_A/\dot{Q} < 0.1$ ) ( $4 \pm 1\%$ ). In contrast, patients whose lungs were MV had larger shunts ( $22 \pm 5\%$ ) and greater percent of perfusion to low  $\dot{V}_A/\dot{Q}$  units ( $11 \pm 5\%$ ). While breathing 100% O<sub>2</sub>, shunt remained unchanged but the dispersion of the pulmonary blood flow distribution (log SDQ) (normal range, 0.3-0.6) increased in each group (from  $1.04 \pm 0.10$  to  $1.29 \pm 0.13$  in SB and from  $1.40 \pm 0.11$  to  $1.64 \pm 0.14$  in MV;  $P < 0.05$  each), suggesting release of hypoxic pulmonary vasoconstriction. No differences between the predicted and measured arterial O<sub>2</sub> tension were elicited within each group ( $70 \pm 3$  mmHg vs.  $69 \pm 3$  mmHg in SB, and  $80 \pm 6$  mmHg vs.  $77 \pm 4$  mmHg in MV, respectively), indicating no role for additional factors (intrapulmonary O<sub>2</sub> uptake, O<sub>2</sub> diffusion limitation, or postpulmonary shunt) other than both  $\dot{V}_A/\dot{Q}$  inequality and shunt to explain the mechanism of arterial hypoxemia in these patients. (Key words: Lung, pneumonia; intrapulmonary oxygen consumption; ventilation-perfusion relationships; venous admixture. Measurement techniques: multiple inert gas elimination.)

PATIENTS WITH PNEUMONIA frequently have moderate to severe arterial hypoxemia. Different factors, namely

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increased whole-body O<sub>2</sub> uptake ( $\dot{V}_{O_2}$ ),<sup>1,2</sup> intrapulmonary shunt,<sup>3-5</sup> ventilation-perfusion ( $\dot{V}_A/\dot{Q}$ ) mismatching,<sup>3,4</sup> postpulmonary shunt (*i.e.*, increased bronchial circulation)<sup>1,\*</sup> and/or alveolar-end capillary O<sub>2</sub> diffusion limitation\*\* have been implicated as potential mechanisms of arterial O<sub>2</sub> tension (PaO<sub>2</sub>) impairment. In animal models of pneumonia, it has been observed that in the early phase of the disease, arterial hypoxemia was mainly determined by intrapulmonary shunt. Later, during recovery, the amount of shunt decreased whereas the percent of blood flow to units with low  $\dot{V}_A/\dot{Q}$  ratios increased.<sup>3,4</sup> A previous study in humans<sup>6</sup> reported  $\dot{V}_A/\dot{Q}$  distributions similar to those obtained in canine models of pneumonia,<sup>7</sup> but only patients with acute severe respiratory failure and whose lungs required mechanical ventilation (MV) were analyzed. Alternatively, increased intrapulmonary O<sub>2</sub> uptake ( $\dot{V}_{O_2p}$ )<sup>8</sup> has been recently suggested as an additional factor contributing to the decrease in PaO<sub>2</sub> in canine experimental pneumonia. Thus, the precise contribution of these mechanisms of abnormal pulmonary gas exchange in patients with pneumonia remains uncertain.

Furthermore, reports of the effects of 100% O<sub>2</sub> breathing on  $\dot{V}_A/\dot{Q}$  relationships in patients with pneumonia are conflicting. It has been formerly reported that shunt may remain unchanged or may even increase while the patient is breathing 100% O<sub>2</sub>.<sup>1,6,9-11,††</sup> Since a substantial proportion of pulmonary blood flow is diverted to low  $\dot{V}_A/\dot{Q}$  units, the development of absorption atelectasis when breathing 100% O<sub>2</sub> might be expected, such that shunt should increase in these patients.<sup>9</sup>

The multiple-inert-gas elimination technique<sup>12</sup> estimates the pulmonary  $\dot{V}_A/\dot{Q}$  distributions on the explicit assumption that no diffusion limitation for inert gases, no postpulmonary shunt, and no increased  $\dot{V}_{O_2p}$  is present, thus allowing identification as causes of hypoxemia all of the mechanisms alluded to above. However, contrary to what has been shown with more traditional techniques, the tracer nature of the method does not by itself alter gas exchange. Accordingly, we used the multiple-inert-

\*\* Alexander JK, Takezawa H, Abu-Nassar HJ, York EM: Studies on pulmonary blood flow in pneumococcal pneumonia. *Cardiovasc Res Cent Bull* 1:86-92, 1963.

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gas elimination technique to characterize the patterns of  $\dot{V}_A/\dot{Q}$  distributions in patients with both mild and severe pneumonia. A second aim of the study was to evaluate the presence of factors other than  $\dot{V}_A/\dot{Q}$  inequality and shunt (percent cardiac output to  $\dot{V}_A/\dot{Q} = 0$ ) producing hypoxemia in these patients, such as 1) increased  $\dot{V}_{O_2P}$ , 2) alveolar-end-capillary  $O_2$  diffusion limitation, and 3) postpulmonary shunt. In addition, we investigated the effects of 100%  $O_2$  breathing on the  $\dot{V}_A/\dot{Q}$  distributions in these patients.

An additional purpose of this study was the comparative analysis between inert-gas-measured shunt and venous admixture ratio ( $\dot{Q}_S/\dot{Q}_T$ ) both determined while patients were breathing maintenance  $FI_{O_2}$  and breathing 100%  $O_2$ . Since  $\dot{Q}_S/\dot{Q}_T$  is an often used variable, such a comparison might shed light on the controversies concerning its interpretation in the clinical setting.<sup>5,7,9</sup>

## Materials and Methods

### POPULATION

Twenty-three inpatients with pneumonia (12 men and 11 women) and arterial hypoxemia ( $Pa_{O_2} < 80$  mmHg, room air) and/or increased alveolar-arterial  $O_2$  difference ( $AaP_{O_2} > 20$  mmHg), ten of whom required MV of their lungs, were included. Eleven were moderate to heavy smokers (range 3–40 packs-yr [pack-yr = (number of cigarettes/20)  $\times$  years smoking]), but except for 5 MV patients, they had no previous history of respiratory disease. Subjects were studied within the first days of the disease ( $3 \pm 1$  days, range 2–5 days). Criteria for diagnosis were fever ( $>38^\circ C$ ), purulent sputum, localized rales and/or bronchial sounds on auscultation, leukocytosis, and alveolar opacities on chest radiographs. The study was approved by the Committee on Human Research of our institution, and informed consent was obtained from each patient or his or her next-of-kin after the purpose and potential risk of the investigation were explained and understood.

#### *Spontaneously Breathing Patients (n = 13)*

Pneumonia was unilobar in ten patients, whereas in the remaining three there were alveolar infiltrates in two or more lobes. The etiological agent was identified in only 3 cases: *S. pneumoniae* in two and *H. influenzae* in the other. One antibiotic was initially used in eight subjects (penicillin in three and erythromycin in five). Combinations of different antibiotics (mainly cephalosporins or erythromycin with aminoglycosides) were used in the remaining five cases. All patients survived.

#### *Patients Whose Lungs Were Mechanically Ventilated (n = 10)*

Four MV patients had a history of mild to moderate chronic obstructive lung disease and one a history of mild

bronchial asthma. Radiographic involvement was bilateral in seven cases and unilateral (lobar or bilobular) in the remaining three. The bacterial pathogen was identified in seven patients: *L. pneumophila* in three, *S. pneumoniae* in two, *E. coli* in one, and *P. aeruginosa* in one. Combined antimicrobial chemotherapy (cephalosporins and/or erythromycin with aminoglycosides) was used in all the patients. One subject died from multiple organ failure and severe acute respiratory failure (subject 14).

### HEMODYNAMIC MEASUREMENTS

The electrocardiogram was continuously monitored throughout the study. An arterial catheter (Seldicath, Plastimed, Saint Leu La Forêt, France) was inserted under local anesthesia into the radial artery of the nondominant side for blood sampling and monitoring of systemic arterial pressure. In 8 of the 10 patients whose lungs required MV (subjects 14–17 and 20–23), mixed venous blood sampling and pulmonary artery, pulmonary wedge, and right atrial pressures were recorded using a 7-Fr triple-lumen thermodilution balloon-tipped pulmonary artery catheter (Edwards Laboratories, Santa Ana, CA) placed under pressure wave monitoring. Vascular pressures were monitored using a multichannel recorder (HP 78309 A, Hewlett Packard, Waltham, MA). Calibrations were performed at the beginning and at the end of each study. The external zero reference level was placed at midchest and was checked before each measurement. Cardiac output was measured by thermodilution (bolus injection of 10 ml cold 5% dextrose) (Edwards Laboratories) in those patients with a pulmonary artery catheter, and by dye-dilution (5-mg bolus indocyanine green injected in the superior vena cava or the right atrium) (Waters Instruments, Inc., Rochester, NY) in the remaining subjects. In each patient, replicate measurements of cardiac output were done and the average of the three closest results was reported.

### RESPIRATORY GAS MEASUREMENTS

Arterial and mixed venous blood samples were obtained in duplicate and analyzed for oxygen tension ( $P_{O_2}$ ), carbon dioxide tension ( $Pa_{CO_2}$ ), and  $pH$  with standard polarographic techniques (IL 1302 Instrumentation Laboratories, Milano, Italy). Appropriate correction was made to body temperature. Hemoglobin concentration and hemoglobin  $O_2$  saturation were determined in each patient (OSM2, Radiometer, Copenhagen, Denmark). The  $AaP_{O_2}$  was calculated using the alveolar air equation:

$$AaP_{O_2} = [FI_{O_2}(PB - 47) - (PA_{CO_2}/R) + FI_{O_2}(1 - R)(PA_{CO_2}/R)] - Pa_{O_2}, \quad (1)$$

where PB is barometric pressure,  $PA_{CO_2}$  is alveolar  $P_{CO_2}$  (assuming  $PA_{CO_2} = Pa_{CO_2}$ ), and R is the respiratory ex-

change ratio. Venous admixture was calculated from the equation:

$$\dot{Q}_s/\dot{Q}_T = (Cc'_{O_2} - Ca_{O_2})/(Cc'_{O_2} - C\bar{v}_{O_2}) \quad (2)$$

where  $Cc'_{O_2}$ ,  $Ca_{O_2}$ , and  $C\bar{v}_{O_2}$  represent the  $O_2$  content of ideal, arterial, and mixed venous blood, respectively. In patients without a pulmonary artery catheter,  $C\bar{v}_{O_2}$  was derived from the Fick equation using the measured cardiac output,  $\dot{V}_{O_2}$ , and  $Ca_{O_2}$ .

From inspired (I) and mixed expired (E) gas samples, fractional concentrations ( $FI_{O_2}$ ,  $FE_{O_2}$ , and  $FE_{CO_2}$ ) were measured using either a paramagnetic  $O_2$  analyzer and an infrared capnograph (E Jaeger, Würzburg, Germany), respectively, or a mass spectrometer (Medishield, Multi-Gas Monitor MS2, Ohmeda-BOC, London, UK). Whole-body  $\dot{V}_{O_2}$  and  $CO_2$  production ( $\dot{V}_{CO_2}$ ) were calculated from these data and minute ventilation ( $\dot{V}_E$ ) measured by a calibrated Wright's spirometer. In the eight MV patients with a pulmonary artery catheter,  $\dot{V}_{O_2}$  was derived from the Fick principle using the measured cardiac output,  $Ca_{O_2}$ , and  $C\bar{v}_{O_2}$ .

#### INERT GAS ANALYSIS

The  $\dot{V}_A/\dot{Q}$  distributions were estimated using the multiple-inert-gas elimination technique.<sup>12,13</sup> Description of this technique and general features of the set-up in our laboratory have been provided elsewhere.<sup>14,15</sup> During the study, spontaneously breathing (SB) patients breathed through a low-resistance valve (Hans Rudolph, Kansas City, MO), and  $\dot{V}_E$  was measured with the above mentioned Wright's spirometer. Duplicate arterial (8 ml) and mixed expired (15 ml) samples were collected. The relative inert gas concentrations of each sample were measured by gas chromatography (HP 5880 A, Hewlett Packard), and retention (ratio of arterial to mixed venous partial pressures) and excretion (ratio of expired to mixed venous partial pressures) were calculated for each of the six inert gases. In patients without a pulmonary artery catheter, mixed venous partial pressures of the inert gases were computed by mass balance using the measured cardiac output. The  $\dot{V}_A/\dot{Q}$  distributions were estimated from the retention-solubility and excretion-solubility curves.<sup>12</sup> A predicted  $Pa_{O_2}$  was estimated from the recovered  $\dot{V}_A/\dot{Q}$  distributions.<sup>16,17</sup> The lack of a systematic difference between predicted  $Pa_{O_2}$  and measured  $Pa_{O_2}$  means that arterial hypoxemia can be fully explained by  $\dot{V}_A/\dot{Q}$  inequality and shunt.<sup>12,13</sup> Additional pulmonary factors causing hypoxemia (alveolar-end-capillary  $O_2$  diffusion limitation; postpulmonary shunt; and increased  $\dot{V}_{O_2}$ ) other than  $\dot{V}_A/\dot{Q}$  inequality and shunt may account for a lower measured  $Pa_{O_2}$  than that predicted from the  $\dot{V}_A/\dot{Q}$  distributions.<sup>16,17</sup> However, the multiple-inert-gas elimination technique does not identify which one of these three above-mentioned factors accounts for the difference

between predicted  $Pa_{O_2}$  and measured  $Pa_{O_2}$ . The duplicate samples of each set of measurements were treated separately, and the final data were the averages of the duplicates.

#### STUDY DESIGN

All SB patients were studied while semirecumbent ( $45^\circ$ ) and breathing room air (except for subject 7,  $FI_{O_2}$  0.51) and also after 30 min of breathing 100%  $O_2$  in random order. Patients in the MV group were already sedated, their tracheas intubated, and their lungs mechanically ventilated as part of their clinical management. Controlled ventilation was accomplished with a volume-cycled ventilator (Siemens/Servo 900 C, Selna, Sweden) adjusted to achieve normal  $Pa_{CO_2}$  and arterial hemoglobin  $O_2$  saturation greater than 90%. After ensuring steady-state conditions by stability of heart rate and vascular pressures while respiratory frequency and  $\dot{V}_E$  were held constant, patients were studied at maintenance  $FI_{O_2}$  ( $0.46 \pm 0.04$ , range 0.3–0.6) and, in seven of them, also after they had breathed 100%  $O_2$  for 30 min at the same ventilator settings.  $FI_{O_2}$  conditions were randomly assigned in each patient.

#### STATISTICAL ANALYSIS

All data are presented as means  $\pm$  standard error. Student's paired *t* tests were used to compare results between maintenance  $FI_{O_2}$  and 100%  $O_2$  breathing. Pearson's coefficient of correlation and linear regression analysis was used when appropriate. The statistical significance was established at  $P < 0.05$  in all cases.

#### Results

##### BASELINE CONDITIONS

##### *Spontaneously Breathing Patients* (table 1)

Twelve of 13 subjects were breathing room air. Mean calculated  $Pa_{O_2}$ , excluding patient 7 (with  $FI_{O_2}$  0.51), showed moderate hypoxemia ( $69 \pm 3$  mmHg), widened Aa $P_{O_2}$  ( $40 \pm 5$  mmHg), and increased  $\dot{Q}_s/\dot{Q}_T$ . Extrapulmonary factors influencing  $Pa_{O_2}$ , such as cardiac output and whole-body  $\dot{V}_{O_2}$ , were within the normal range, except that  $\dot{V}_E$  was slightly increased. Inert gas data showed mild to severe  $\dot{V}_A/\dot{Q}$  mismatching in all patients. Inert-gas-measured shunt (percent cardiac output to  $\dot{V}_A/\dot{Q}$  units  $< 0.005$ ) and the percent of perfusion to low  $\dot{V}_A/\dot{Q}$  units (between 0.005 and 0.1) were present in 10 patients. Two subjects (subjects 12 and 13) displayed a moderate amount of shunt alone without perfusion to low  $\dot{V}_A/\dot{Q}$  units, whereas only one subject (subject 1) showed perfusion to low  $\dot{V}_A/\dot{Q}$  units (10.7%) alone but no shunt. Inert gas shunt was always less than  $\dot{Q}_s/\dot{Q}_T$  ( $7.5 \pm 1.8\%$  vs.  $16.5 \pm 3.0\%$ , respectively). Blood flow distribution

TABLE 1. Spontaneously Breathing Patients: Conventional and Inert Gas Exchange and Systemic Hemodynamic Data

| Patient | Age (yr) | f  | $\dot{V}_E$ | HR  | SAP | $\dot{Q}_r$ | $P_{aO_2}$ | $P_{aCO_2}$ | $AaP_{O_2}$ | $\dot{V}_{O_2}$ | $\dot{Q}_s/\dot{Q}_r$ | Shunt | Low $\dot{V}_A/\dot{Q}$ | log SDQ | log SDV | Dead Space |
|---------|----------|----|-------------|-----|-----|-------------|------------|-------------|-------------|-----------------|-----------------------|-------|-------------------------|---------|---------|------------|
| 1       | 24       | 22 | 10.6        | 82  | 88  | 5.2         | 67         | 32          | 34          | 373             | 7.7                   | 0.0   | 10.7                    | 1.40    | 0.43    | 41.4       |
| 2       | 32       | 21 | 8.3         | 100 | 80  | 6.9         | 72         | 35          | 29          | 247             | 11.9                  | 6.2   | 4.7                     | 1.16    | 1.54    | 30.3       |
| 3       | 34       | 15 | 10.9        | NA  | NA  | 6.8         | 56         | 25          | 61          | 238             | 32.9                  | 22.1  | 2.8                     | 1.10    | 0.74    | 14.7       |
| 4       | 47       | 25 | 8.1         | 70  | 94  | 6.5         | 81         | 36          | 28          | 225             | 11.8                  | 1.1   | 3.1                     | 0.86    | 0.36    | 41.4       |
| 5       | 52       | 16 | 10.0        | 84  | 75  | 5.1         | 65         | 35          | 41          | 335             | 11.0                  | 5.6   | 3.9                     | 1.12    | 0.40    | 22.4       |
| 6       | 65       | 20 | 9.1         | 76  | 128 | 4.0         | 76         | 38          | 28          | 262             | 13.5                  | 4.6   | 1.4                     | 0.85    | 0.56    | 31.4       |
| 7*      | 61       | 19 | 8.0         | 72  | 100 | 6.5         | 135*       | 38          | 185*        | NA              | NA                    | 10.9  | 8.7                     | 1.41    | 0.58    | 36.1       |
| 8       | 41       | 12 | 8.7         | 75  | 90  | 4.4         | 78         | 32          | 38          | 254             | 10.6                  | 6.6   | 0.5                     | 0.57    | 0.40    | 17.5       |
| 9       | 46       | 11 | 12.2        | 77  | 110 | 7.5         | 57         | 33          | 58          | 273             | 25.8                  | 14.3  | 4.1                     | 1.27    | 0.78    | 21.5       |
| 10      | 21       | 20 | 8.3         | 74  | 68  | 6.0         | 70         | 43          | 31          | 220             | 17.2                  | 0.9   | 5.8                     | 1.22    | 0.63    | 31.8       |
| 11      | 58       | 27 | 10.7        | 95  | 103 | 5.6         | 49         | 31          | 77          | 142             | 39.2                  | 13.8  | 8.9                     | 1.51    | 0.65    | 27.9       |
| 12      | 36       | 14 | 5.2         | 100 | 84  | 7.8         | 78         | 38          | 32          | 265             | 11.1                  | 7.0   | 0.0                     | 0.42    | 0.43    | 27.1       |
| 13      | 40       | 24 | 7.8         | 78  | 85  | 6.5         | 76         | 39          | 26          | 317             | 5.8                   | 3.7   | 0.0                     | 0.59    | 0.61    | 35.3       |
| Mean    | 43       | 19 | 9.1         | 82  | 92  | 6.1         | 74         | 35          | 51          | 262             | 16.5                  | 7.5   | 4.2                     | 1.04    | 0.62    | 29.1       |
| SEM     | 4        | 1  | 0.5         | 3   | 5   | 0.3         | 6          | 1           | 12          | 17              | 3.0                   | 1.8   | 1.0                     | 0.10    | 0.09    | 2.3        |

blood flow to unventilated units; low  $\dot{V}_A/\dot{Q}$  = percentage of blood flow to units with  $\dot{V}_A/\dot{Q}$  ratios between 0.005 and 0.1; log SDQ = log standard deviation of perfusion distribution; dead space = percentage of ventilation to nonperfused units ( $\dot{V}_A/\dot{Q} > 100$ ); log SDV = log standard deviation of ventilation distribution. NA = not available.

Patients were breathing room air except patient 7\* ( $F_iO_2 = 0.51$ ).  
Age (years); f (cyc · min<sup>-1</sup>) = respiratory rate;  $\dot{V}_E$  (l · min<sup>-1</sup>) = minute ventilation; HR (beats per min) = heart rate; SAP (mmHg) = mean systemic arterial pressure;  $\dot{Q}_r$  (l · min<sup>-1</sup>) = cardiac output;  $AaP_{O_2}$  (mmHg), alveolo - arterial  $O_2$  difference;  $\dot{V}_{O_2}$  (ml · min<sup>-1</sup>) = oxygen uptake;  $\dot{Q}_s/\dot{Q}_r$  (%), venous admixture; shunt (%  $\dot{Q}_r$  to  $\dot{V}_A/\dot{Q} < 0.005$ ), percentage of

TABLE 2. Patients Whose Lungs Required Mechanical Ventilation: Conventional and Inert Gas Exchange Data and Systemic and Pulmonary Hemodynamics

| Patient | Age | $F_iO_2$ | $\dot{V}_E$ | HR  | SAP | $\dot{Q}_r$ | $P_{aO_2}$ | $P_{aCO_2}$ | $P\dot{V}_{O_2}$ | $\dot{V}_{O_2}$ | $\dot{Q}_s/\dot{Q}_r$ | Shunt | Low $\dot{V}_A/\dot{Q}$ | log SDQ | log SDV | Dead Space |
|---------|-----|----------|-------------|-----|-----|-------------|------------|-------------|------------------|-----------------|-----------------------|-------|-------------------------|---------|---------|------------|
| 14      | 43  | 0.62     | 17.0        | 96  | NA  | 10.2        | 94         | 35          | 43               | 342             | 30.2                  | 19.4  | 24.0                    | 1.89    | 0.82    | 47.8       |
| 15      | 75  | 0.51     | 9.3         | 94  | 85  | 5.2         | 85         | 36          | 47               | 175             | 31.9                  | 22.3  | 9.2                     | 1.35    | 0.66    | 47.4       |
| 16      | 68  | 0.60     | 13.4        | 82  | 85  | 5.3         | 73         | 33          | 34               | 208             | 28.7                  | 28.3  | 2.8                     | 1.31    | 0.93    | 45.3       |
| 17      | 42  | 0.57     | 17.1        | 118 | 54  | 14.4        | 79         | 39          | 48               | 282             | 44.9                  | 47.7  | 4.3                     | 1.30    | 1.17    | 42.0       |
| 18      | 63  | 0.37     | 7.1         | 84  | 107 | 7.0         | 62         | 50          | NA               | NA              | NA                    | 0.0   | 47.7                    | 1.70    | 0.91    | 30.6       |
| 19      | 43  | 0.59     | 13.0        | 80  | 107 | 10.2        | 92         | 41          | NA               | NA              | NA                    | 26.5  | 1.4                     | 1.07    | 1.08    | 32.6       |
| 20      | 23  | 0.40     | 12.9        | 98  | 96  | 9.0         | 81         | 45          | 44               | 365             | 26.1                  | 14.7  | 3.8                     | 1.15    | 0.94    | 45.4       |
| 21      | 45  | 0.41     | 13.1        | 101 | 95  | 11.5        | 61         | 63          | 43               | 301             | 49.9                  | 38.6  | 5.0                     | 1.40    | 1.01    | 30.7       |
| 22      | 55  | 0.27     | 15.9        | 102 | 75  | 10.6        | 69         | 40          | 37               | 367             | 24.1                  | 10.2  | 3.2                     | 1.12    | 0.89    | 45.4       |
| 23      | 51  | 0.26     | 15.0        | 90  | 75  | 9.2         | 75         | 30          | 38               | 345             | 18.6                  | 10.9  | 7.5                     | 1.41    | 0.63    | 38.3       |
| Mean    | 51  | 0.46     | 13.4        | 95  | 87  | 9.3         | 77         | 40          | 42               | 298             | 31.8                  | 21.9  | 10.9                    | 1.37    | 0.90    | 40.6       |
| SEM     | 5   | 0.04     | 1.0         | 4   | 6   | 0.9         | 4          | 2           | 2                | 26              | 3.7                   | 4.5   | 4.6                     | 0.08    | 0.05    | 2.2        |

$F_iO_2$  = fraction of inspired  $O_2$ ;  $P\dot{V}_{O_2}$  = mixed venous  $P_{O_2}$ . For other abbreviations and units, see table 1.

was bimodal in 10 of the 13 subjects and unimodal in the remaining 3 patients. The blood flow distribution was centered (mean  $\dot{V}_A/\dot{Q}$  ratio [mean of the perfusion distribution (first moment),  $Q$ ],  $0.89 \pm 0.09$ ) and its dispersion (log SDQ) increased (normal range for log standard deviation [SD],  $0.3-0.6$ ).<sup>18</sup> In contrast, the ventilation distribution was shifted to the right (mean  $\dot{V}_A/\dot{Q}$  ratio [mean of the ventilatory distribution (first moment),  $V$ ],  $1.60 \pm 0.14$ ) and the dispersion of the curve (log SDV) was in the upper normal limit. The ventilation distribution was unimodal in all but one patient (subject 2) who showed a moderate amount of ventilation to high  $\dot{V}_A/\dot{Q}$  units (between 10 and 100) (11.7% of alveolar ventilation). The dead space (percent ventilation to  $\dot{V}_A/\dot{Q}$  ratios  $> 100$ ) was within the normal range. If the patient breathing a high  $F_{I_{O_2}}$  (patient 7) is excluded, no differences are shown between predicted  $P_{a_{O_2}}$  from the inert gas data ( $70 \pm 3$  mmHg) and measured  $P_{a_{O_2}}$  ( $69 \pm 3$  mmHg). Identical results were obtained when the duplicates of predicted  $P_{a_{O_2}}$  ( $70 \pm 3$  and  $69 \pm 4$  mmHg) and measured  $P_{a_{O_2}}$  ( $69 \pm 3$  and  $69 \pm 3$  mmHg) were examined separately. In contrast,  $P_{a_{O_2}}$  significantly correlated with the sum of inert gas shunt plus the percentage of perfusion to low  $\dot{V}_A/\dot{Q}$  units ( $r = -0.928$ ) and with log SDQ ( $r = -0.774$ ) ( $P < 0.001$ , each).

#### Patients Whose Lungs Were Mechanically Ventilated (table 2)

The  $P_{a_{O_2}}/P_{A_{O_2}}$  ratio was markedly reduced (by  $30 \pm 3\%$ ), as expected in patients with acute severe respiratory failure whose lungs required MV. It is of note that mean pulmonary artery pressure was moderately increased ( $22.0 \pm 2.0$  mmHg) but that pulmonary vascular resistance was within the normal range ( $1.30 \pm 0.25$  mmHg  $\cdot$  l<sup>-1</sup>  $\cdot$  min<sup>-1</sup>). Despite the slightly increased whole-body  $\dot{V}_{O_2}$ , mixed venous  $P_{O_2}$  was normal. One explanation is that cardiac output increases  $O_2$  delivery (to  $1,173 \pm 87$

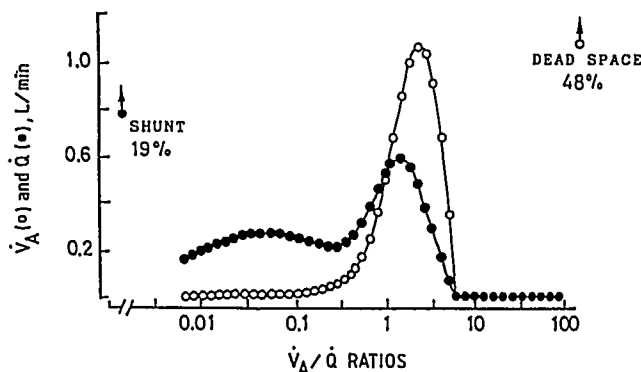


FIG. 1. Representative  $\dot{V}_A/\dot{Q}$  distributions from a patient (subject 14) with severe pneumonia whose lungs required mechanical ventilation. Increased shunt (19% of cardiac output) and perfusion to low  $\dot{V}_A/\dot{Q}$  ratios (%  $\dot{Q}_T$  to  $\dot{V}_A/\dot{Q}$  ratios between 0.005 and 0.1) were present. Dead space (%  $\dot{V}_A$  to  $\dot{V}_A/\dot{Q} > 100$ ) also was increased.

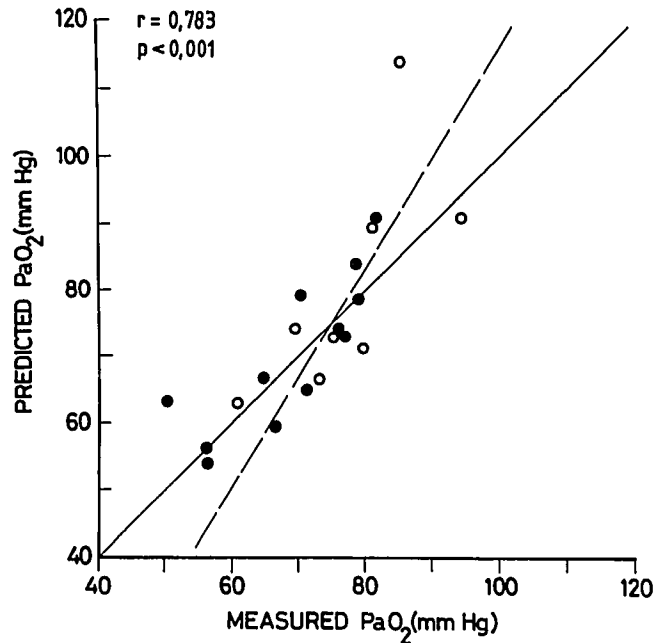


FIG. 2. Plot between predicted (abscissa) and measured (ordinate)  $P_{a_{O_2}}$ . Closed circles correspond to the patients breathing spontaneously and open circles to those whose lungs required mechanical ventilation. The solid line represents identity line, and the dashed line represents the regression line.

ml  $\cdot$  min<sup>-1</sup>) and, at a fixed capillary volume, in turn reduces the transit time in the tissue capillary.  $\dot{V}_A/\dot{Q}$ -mismatching was characterized by the presence of severe shunt and perfusion to low  $\dot{V}_A/\dot{Q}$  units. This pattern was observed in nine of the ten patients (Figure 1). Only patient 18 showed a substantial perfusion to low  $\dot{V}_A/\dot{Q}$  areas but no shunt. A bimodal pattern of the blood flow distribution was observed in half of the patients. The dispersions of both blood flow and ventilation distributions were more severely abnormal than in SB patients. Five patients (patients 16, 17, and 19-21) showed a small percentage of ventilation ( $2 \pm 1\%$ ) to high  $\dot{V}_A/\dot{Q}$  units ( $\dot{V}_A/\dot{Q}$  between 10 and 100). No differences between predicted  $P_{a_{O_2}}$  and measured  $P_{a_{O_2}}$  were shown in the eight MV patients with a pulmonary artery catheter ( $80 \pm 6$  vs.  $77 \pm 4$  mmHg, respectively) (fig. 2). Similar information was obtained when duplicate sets were analyzed separately (predicted  $P_{a_{O_2}}$   $79 \pm 6$  and  $82 \pm 6$  mmHg and measured  $P_{a_{O_2}}$   $77 \pm 4$  and  $77 \pm 4$  mmHg, respectively). Only one patient (patient 15) showed a large difference between predicted  $P_{a_{O_2}}$  (114 mmHg; duplicate sets, 117 and 110 mmHg) and measured  $P_{a_{O_2}}$  (85 mmHg; duplicate measurements, 84 and 85 mmHg). If patient 15 is excluded, the correlation coefficient between predicted  $P_{a_{O_2}}$  and measured  $P_{a_{O_2}}$  increases from  $r = 0.72$  to  $r = 0.85$ . On the other hand, the inert gas shunt was lower than the  $\dot{Q}_s/\dot{Q}_T$ , but the sum of the measured inert gas shunt plus

TABLE 3A. Effects of 100% Oxygen Breathing: Spontaneously Breathing Patients (n = 13)

| $F_{I_{O_2}}$ | f      | $\dot{V}_E$ | HR     | SAP    | $\dot{Q}_T$ | $P_{a_{O_2}}$ | $P_{a_{CO_2}}$ | $P_{a_{O_2}}$ | $P_{a_{CO_2}}$ | Aa $P_{O_2}$ | $\dot{Q}_s/\dot{Q}_T$ | Shunt     | Low $\dot{V}_A/\dot{Q}$ | Log SDQ     | Log SDV    | Dead Space |
|---------------|--------|-------------|--------|--------|-------------|---------------|----------------|---------------|----------------|--------------|-----------------------|-----------|-------------------------|-------------|------------|------------|
| 0.21*         | 19 ± 1 | 9.1 ± 0.5   | 82 ± 3 | 92 ± 5 | 6.1 ± 0.3   | 74 ± 6        | 35 ± 1         | 51 ± 12       | 298 ± 26       | 17 ± 3       | 7.4 ± 1.8             | 4.2 ± 1.0 | 1.04 ± 0.10             | 0.62 ± 0.09 | 29.1 ± 2.3 |            |
| 1.0           | 20 ± 1 | 9.5 ± 0.4   | 77 ± 3 | 95 ± 5 | 5.6 ± 0.3   | 368 ± 26      | 34 ± 1         | 298 ± 26      | <0.001         | 17 ± 2       | 9.1 ± 2.1             | 7.9 ± 2.4 | 1.29 ± 0.13             | 0.66 ± 0.08 | 25.0 ± 2.1 |            |
| P             | NS     | NS          | NS     | NS     | <0.05       | <0.001        | <0.01          | <0.001        | <0.001         | NS           | NS                    | NS        | <0.05                   | NS          | NS         |            |

For abbreviations and units, see table 1.

TABLE 3B. Effects of 100% Oxygen Breathing: Patients Whose Lungs Required Mechanical Ventilation (n = 7)

| $F_{I_{O_2}}$ | $\dot{V}_E$ | HR     | SAP     | $\dot{Q}_T$ | $P_{pw}$ | $P_{a_{O_2}}$ | $P_{a_{CO_2}}$ | $P_{\bar{V}_{O_2}}$ | $\dot{Q}_s/\dot{Q}_T$ | Shunt      | Low $\dot{V}_A/\dot{Q}$ | Log SDQ    | Log SDV     | Dead Space |
|---------------|-------------|--------|---------|-------------|----------|---------------|----------------|---------------------|-----------------------|------------|-------------------------|------------|-------------|------------|
| M             | 12.8 ± 1.4  | 93 ± 5 | 89 ± 8  | 8.8 ± 1.2   | 10 ± 2   | 81 ± 4        | 40 ± 2         | 43 ± 2              | 32.4 ± 3.3            | 22.7 ± 2.5 | 13.3 ± 6.4              | 1.40 ± 0.1 | 0.93 ± 0.06 | 41.6 ± 2.7 |
| P             | 12.4 ± 1.4  | 88 ± 6 | 87 ± 10 | 7.9 ± 1.2   | 10 ± 2   | 257 ± 24      | 42 ± 2         | 51 ± 3              | 34.7 ± 2.4            | 24.8 ± 5.2 | 15.8 ± 6.2              | 1.64 ± 0.1 | 0.86 ± 0.07 | 43.2 ± 2.1 |
|               | NS          | <0.05  | NS      | NS          | NS       | <0.001        | NS             | <0.05               | NS                    | NS         | NS                      | <0.05      | NS          | NS         |

M = maintenance  $F_{I_{O_2}}$  (0.52 ± 0.04). For other abbreviations and units, see tables 1 and 2.

the percentage of perfusion to low  $\dot{V}_A/\dot{Q}$  units was very close to the  $\dot{Q}_s/\dot{Q}_T$  (32.8 vs. 31.8%, respectively).

EFFECTS OF 100% OXYGEN BREATHING

Spontaneously Breathing Patients (table 3A)

From room air to 100%  $O_2$  breathing,  $\dot{V}_E$  did not change, and cardiac output slightly decreased. As expected,  $P_{a_{O_2}}$  increased but venous admixture ratio remained unchanged, as did inert gas shunt, whereas log SDQ slightly but significantly increased. It is of note that during 100%  $O_2$  breathing, the sum of inert gas measured shunt and the percent of perfusion to low  $\dot{V}_A/\dot{Q}$  units was similar to the venous admixture ratio.

Patients Whose Lungs Were Mechanically Ventilated (table 3B)

During 100%  $O_2$  breathing,  $\dot{V}_E$ , cardiac output, and systemic and pulmonary artery pressures remained unchanged.  $P_{a_{O_2}}$  and  $P_{\bar{V}_{O_2}}$  significantly increased, but  $\dot{Q}_s/\dot{Q}_T$  did not change. Inert gas shunt remained also unchanged, but, as happened in SB patients, there was a significant increase in log SDQ. The sum of inert gas shunt and the percent of blood flow to low  $\dot{V}_A/\dot{Q}$  units was slightly greater than the  $\dot{Q}_s/\dot{Q}_T$  though without reaching statistical significance.

Discussion

BASELINE CONDITIONS

The present study demonstrates that the most common pattern of  $\dot{V}_A/\dot{Q}$  mismatching in patients with pneumonia is a combination of both intrapulmonary shunt and increased perfusion to low  $\dot{V}_A/\dot{Q}$  units. Mild to moderate amounts of both shunt and perfusion to low  $\dot{V}_A/\dot{Q}$  units were observed in patients with moderate pneumonia (table 1) compared to those with more severe disease whose lungs required MV (table 2). Our data are thus consistent with the results formerly reported in canine experimental pneumonia and provide a paramount description of gas exchange abnormalities in patients with mild to severe pneumonia. Interestingly, Light<sup>8</sup> has suggested in a recent experimental study that an increased  $\dot{V}_{O_2}$  in the pneumonic area might be an additional factor of arterial hypoxemia in these patients. This hypothesis was based upon the systematic differences observed in a canine model of pneumonia between whole-body  $\dot{V}_{O_2}$  measured by collection of expired gases ( $\dot{V}_{O_2} \text{exp}$ ) and that calculated by the Fick principle ( $\dot{V}_{O_2} \text{Fick}$ ) (cardiac output multiplied by the difference in arterial  $O_2$  and venous  $O_2$  contents). The assumption is that  $\dot{V}_{O_2} \text{Fick}$  will not detect  $\dot{V}_{O_2} \text{p}$ , whereas  $\dot{V}_{O_2} \text{exp}$  will be systematically higher because it represents

the true whole-body  $\dot{V}_{O_2}$  including  $\dot{V}_{O_2p}$ . Light<sup>8</sup> estimated the  $\dot{V}_{O_2p}$  to be approximately 15% of whole-body  $\dot{V}_{O_2}$  in his experimental model, with the difference attributed to the cells involved in the acute inflammatory response of the lung parenchyma. It is interesting that the inert gas technique offers a singular tool to test if such a hypothetical increase in  $\dot{V}_{O_2p}$  may account for a disproportionate decrease in  $Pa_{O_2}$ . If this was the case, systematic differences between the  $Pa_{O_2}$  predicted from the  $\dot{V}_A/\dot{Q}$  distributions ( $74.2 \pm 3.8$  mmHg) and that measured from arterial blood sampling ( $72.1 \pm 3.2$  mmHg) should have been observed ( $n = 22$ ). However, there was a close agreement between predicted and measured  $Pa_{O_2}$  in both SB and MV patients. Identical results were obtained when the duplicates of predicted  $Pa_{O_2}$  and measured  $Pa_{O_2}$  were examined separately. As figure 2 indicates, individual predicted  $Pa_{O_2}$  and measured  $Pa_{O_2}$  in the two different ventilatory conditions were strongly correlated. As mentioned above, the lack of a systematic difference between predicted  $Pa_{O_2}$  from the recovered  $\dot{V}_A/\dot{Q}$  distributions and measured  $Pa_{O_2}$  excludes additional pulmonary factors (increased  $\dot{V}_{O_2p}$ , alveolar-end-capillary  $O_2$  diffusion limitation, and postpulmonary shunt) other than  $\dot{V}_A/\dot{Q}$  mismatch and shunt causing arterial hypoxemia. In the SB patients in whom the mixed venous  $O_2$  content was not measured but calculated through the Fick principle, the multiple-inert-gas elimination technique can exclude  $O_2$  diffusion limitation and postpulmonary shunt as factors causing arterial hypoxemia, but the technique may not account for an increased  $\dot{V}_{O_2p}$ . In contrast, the results from patients in whom pulmonary artery catheterization was carried out are particularly relevant to exclude an increased  $\dot{V}_{O_2p}$  because mixed venous  $P_{O_2}$  was measured directly and, in addition, because they had more extensive severe involvement of their lungs. Only one of the MV patients (patient 15) (fig. 2) showed a prominent difference between predicted  $Pa_{O_2}$  and measured  $Pa_{O_2}$  that was also observed when the duplicate sets were analyzed separately. Overall, our results are not in keeping with those reported by Light<sup>8</sup> in a canine model of pneumonia. Otherwise, the present data demonstrate that arterial hypoxemia was fully explained by the presence of both intrapulmonary shunt and  $\dot{V}_A/\dot{Q}$  mismatching.

#### EFFECTS OF 100% OXYGEN BREATHING

No changes in inert gas shunt or in  $\dot{Q}_S/\dot{Q}_T$  were observed with 100%  $O_2$  breathing, as might be expected in patients with a substantial percent of cardiac output perfusing low  $\dot{V}_A/\dot{Q}$  units who were at risk of developing reabsorption atelectasis.<sup>9</sup> It is of interest that our results are thus in accordance with those reported by Lampron and associates<sup>6</sup> using the multiple-inert-gas elimination technique in patients with severe pneumonia requiring

MV. In fact, according to our experience, only patients with status asthmaticus whose lungs required MV<sup>18</sup> have actually shown a moderate but significant increase in intrapulmonary shunt while 100%  $O_2$  breathing. Conceivably, the simultaneous decrease in cardiac output in our SB patients during 100%  $O_2$  breathing may have contributed, in part, to the lack of changes in shunt.<sup>19</sup>

However, the significant increase (worsening) in the dispersion of blood flow distribution (log SDQ) strongly suggests a release of hypoxic pulmonary vasoconstriction. This finding is consistent with the presence of a substantial hypoxic vascular response that may play a key role in protecting the lung against a further impairment of pulmonary gas exchange. Previous studies in animal preparations have documented either impaired<sup>7,20,21</sup> or preserved<sup>22</sup> hypoxic vasoconstriction.

#### RELATIONSHIPS BETWEEN INERT GAS SHUNT AND $\dot{Q}_S/\dot{Q}_T$

A characteristic finding in the present study was that, regardless of the  $FI_{O_2}$ , inert gas shunt was always less than  $\dot{Q}_S/\dot{Q}_T$  ("O<sub>2</sub> shunt"). Moreover, either at maintenance  $FI_{O_2}$  or during 100%  $O_2$  breathing, no significant differences were detected between  $\dot{Q}_S/\dot{Q}_T$  and the sum of inert gas shunt plus the percentage of perfusion to low  $\dot{V}_A/\dot{Q}$  units in each group of patients. At maintenance  $FI_{O_2}$ , this finding can be explained by the inclusion of both inert gas shunt and the percent of perfusion to low  $\dot{V}_A/\dot{Q}$  units in the measurement of  $\dot{Q}_S/\dot{Q}_T$ . By contrast, it is traditionally accepted that during 100%  $O_2$  breathing, the effect of low  $\dot{V}_A/\dot{Q}$  units on  $\dot{Q}_S/\dot{Q}_T$  is minimized or even abolished because complete denitrogenation of incompletely ventilated (low)  $\dot{V}_A/\dot{Q}$  units is assumed. Hence,  $\dot{Q}_S/\dot{Q}_T$  should decrease and approach the value of the inert gas shunt. However, the release of hypoxic vasoconstriction both in the pulmonary and in the bronchial circulations<sup>23</sup> might result in an increased blood flow distributed to low  $\dot{V}_A/\dot{Q}$  units, thus precluding the expected decrease in  $\dot{Q}_S/\dot{Q}_T$ . An alternative explanation for this discrepancy between  $\dot{Q}_S/\dot{Q}_T$  and inert gas shunt observed during 100%  $O_2$  breathing would be an increased  $\dot{V}_{O_2p}$ . Increased  $\dot{V}_{O_2p}$  would cause a lower arterial  $O_2$  content, which would raise, other things being equal,  $\dot{Q}_S/\dot{Q}_T$ . This hypothesis, however, has been previously excluded by comparing in our patients measured  $Pa_{O_2}$  and predicted  $Pa_{O_2}$  upon breathing room air. It is interesting that a similar behavior in  $\dot{Q}_S/\dot{Q}_T$  during 100%  $O_2$  breathing was shown by our group of patients with severe acute asthma in a previous study,<sup>18</sup> mentioned above. By contrast, in patients with adult respiratory distress syndrome we found that inert gas shunt and  $\dot{Q}_S/\dot{Q}_T$  were almost identical.<sup>24</sup> The latter can be explained by the small amount of perfusion to low  $\dot{V}_A/\dot{Q}$  units in this series of

patients with adult respiratory distress syndrome. However, the study by Lampron and associates<sup>6</sup> showed a decrease of venous admixture during O<sub>2</sub> breathing explained by the elimination of the low  $\dot{V}_A/\dot{Q}$  component included in the  $\dot{Q}_s/\dot{Q}_T$ .

In summary, although we are not able to provide a completely satisfactory explanation for these findings, the apparent consistency of our data strongly suggests the need for further studies to analyze the nitrogen washout over time during 100% O<sub>2</sub> breathing in order to reexamine the traditional interpretation of  $\dot{Q}_s/\dot{Q}_T$  and its concept in the clinical setting. Nevertheless, the use of inert gas technique provides a new way to exclude the presence of an increased  $\dot{V}_{O_2p}$ .

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