Effect of Respiration on Pulmonary Capillary Blood Flow in Man

By Paul Vermeire, M.D., and John Butler, M.D.

ABSTRACT
Pulmonary capillary blood flow was measured in man during slow breathing by a modification of the body plethysmograph technique for measuring N₂O uptake. In seated subjects breathing slowly, flow was significantly higher during inhalation than during exhalation. In supine subjects whose legs were raised, the difference between inhalation and exhalation was not significant. Flow was usually greater during tidal inhalation than exhalation, but there was considerable variation. The changes in flow were not directly related to intrathoracic pressures or lung volumes. The results suggest that it is the amount and pressure of the venous blood available for aspiration into the thorax that influences pulmonary capillary blood flow during the course of a respiratory cycle.

ADDITIONAL KEY WORDS
posture  venous return  right heart output  man

The first direct observation suggesting that blood flow into the thorax was influenced by respiration was made in 1826 by Batry (1) who put a glass tube in the jugular vein of a horse and saw that the blood spurted forward each time the horse inhaled. Now we can measure accurately the flow of blood in the vena cavae and the pulmonary artery by using flowmeters. Several groups (2-6) have reported that the flow in the pulmonary artery in animals increases from the start of inhalation.

No direct measurements of an increase in the output of the right side of the heart during inhalation have, to our knowledge, been made in man. The evidence that it occurs is based on the increasing interval between the Q wave of the ECG and the pulmonary component of the second sound, and the increased intensity of murmurs arising from the right side of the heart during inhalation (7). Increased oscillations in the ballistocardiogram (8) and an increased end-diastolic volume of the right ventricle have also been seen at this time (9). Recently Nakhjavan et al. (10) demonstrated a faster inflow rate of contrast material in the inferior vena cava into the thorax during inhalation in normal supine subjects.

A direct method for measuring instantaneous pulmonary capillary blood flow in man, after inhalation of nitrous oxide, was described by Lee and DuBois (11). DuBois and Marshall (12) used this method, but they did not observe a significant increase in capillary flow with tidal inhalation in five subjects—although they found a persistent increase in one subject during slow inhalations. A modification of their nitrous oxide technique simplifies the measurement of pulmonary capillary blood flow during slow breathing (13). While developing this modification, we observed increases in flow during early inhalation and decreases during exhalation in subjects in the sitting position. These variations were abolished or much reduced in the supine position. Therefore we restudied this problem to see if we could...
discover other factors that modify the effect of breathing on the pulmonary capillary blood flow in man.

Methods

Pulmonary capillary blood flow ($Q_c$) was determined by a modification (13) of the original technique of Lee and Dubois (11). The subjects (15 male, 4 female, age range 18-42 years) sat in a modified wooden body plethysmograph (Fig. 1) and took a deep breath of 80% nitrous oxide and 20% oxygen. As the nitrous oxide was absorbed into the capillaries (at a rate proportional to the blood flow), an equal volume of air flowed into the box through a flowmeter in its wall. The volume of air entering the box was obtained by integrating the signal from this flowmeter. The frequency response of the system, including recorder, was flat through 3% cps. Measurements were made again after the subject had taken a breath of air under precisely similar circumstances. Subtraction of the two records gave the uptake of nitrous oxide. We averaged the volume of $N_2O$ absorbed during two to four heart beats. The pulmonary capillary flow ($Q_c$) was obtained from the equation

$$Q_c = V_p \times f = \frac{V_{N_2O} \times 1.15}{\lambda_{N_2O} \times F_{A_{N_2O}}} \times f,$$

where $V_p$ = pulse volume perfusing pulmonary capillaries at each heart beat (ml)

$f$ = heart rate at time of measurement (beats per min)

$V_{N_2O}$ = volume of $N_2O$ absorbed during beat (ml)

$1.15$ = sum of volume correction factors (13)

$\lambda_{N_2O}$ = solubility coefficient of $N_2O$ in blood at 37°C and one standard atmosphere

$F_{A_{N_2O}}$ = fractional alveolar concentration of $N_2O$ during beat.

To correct for body size, both $V_p$ and $Q_c$ were expressed as indices: pulse volume index ($V_{pl}$) in milliliters per square meter of body surface area, and pulmonary capillary flow index ($Q_{cl}$) in liters per minute per square meter of body surface area.

Possible advantages of this technique are the following.

(1) Flow into the box is measured as the primary signal. Thus there is less noise on the record than when flow is obtained by electronically differentiating the volume (pressure) signal as in the original closed-box method.

(2) Volume (pressure) drifts during respiration due to temperature, water vapor, and alveolar pressure changes merely alter the baseline of the flow record; subtraction of the control from the $N_2O$ record eliminates these effects, provided they are identical in each period. When box pressure drifts rapidly and a closed box is used, it is difficult to select comparable air and $N_2O$ records for subtraction, although this problem has been largely overcome by breathing from bags containing saturated gas and warmed to body temperature (12).

(3) The box is open through the low resistance flowmeter so there is no error due to leakage through other small, high resistance holes. The weight of the box can be reduced since complete airtightness is unnecessary, so it is easily moved and tilted.

Measurements were made during (1) a slow exhalation for approximately 20 sec from inspiratory capacity to below functional residual capacity and (2) a slow inhalation of the same duration from residual volume to inspiratory capacity. The subject first took a breath of the $N_2O$ mixture,

\[ \text{FIGURE 1} \]  

Body plethysmograph. Air flow into the box to replace the $N_2O$ (open circles) absorbed is measured by the flowmeter (rate of box flow). The rate of inhalation from or exhalation into the bag containing $N_2O$ is measured by the other flowmeter (rate of breathing). $N_2O$ concentration at the lips is measured by the $N_2O$ analyzer.


2Fleisch flowmeter 3 ($r = 0.11$ cm H$_2$O/L/sec) from Instrumentation Associates, N. Y., N. Y.
exhaled rapidly into a bag inside the box, and then inhaled slowly from this bag (Fig. 1). The rates of inhalation and exhalation were recorded with a flowmeter at the mouth (resistance 0.25 cm H₂O/liter per sec). The pulmonary capillary blood flow was measured at the beginning (from the second to the sixth sec) and towards the end (from the twelfth to the sixteenth sec) of each breath. The lung volumes at these times were either near inspiratory capacity or functional residual capacity. Each maneuver was done twice, except in a few instances, and a mean value of the two measurements was obtained. Heart rate and rate of inhalation or exhalation were identical in the record after the breath of N₂O, and in the control record after the breath of air which was subtracted from it. The alveolar N₂O concentrations at the times the flows were measured during exhalation were obtained from the continuous record of N₂O concentration at the mouth. The N₂O analyzer pump continually sucked gas from the box. The rate of flow into the box that this caused was constant and was used as the zero level for flow recordings. The time required for the passage of the gas from alveolus to the analyzer (about 2 sec) was measured from the record as that elapsing between the start of exhalation and the appearance of the alveolar gas front. This time included the instrumental delay in detecting the mouth concentration (0.8 sec for 100% response to a sudden change in N₂O concentration at the mouth with the pump sampling at a rate of 600 ml per min). For the measurement of capillary flow during slow inhalation, the alveolar N₂O concentration was obtained by interpolating between the value at the end of the exhalation before the start of the inhalation period and that from the exhalation with which the subject concluded the maneuver.

The studies were repeated with the subject in the "supine" position after tilting the box onto its back; in this position the subject's legs were elevated.

**Results**

**Sitting**

The mean flow (average of values early and late in the maneuver) was significantly higher during inhalation than during exhalation (P < 0.02). The flow decreased significantly (−23%; P < 0.005) towards the end of inhalation (Fig. 2, Table 1). The values were lower during exhalation. The difference between flow at the start of inhalation and the start of exhalation was significant (−39%; P < 0.001).

**Supine**

In ten supine subjects the mean flow during inhalation was not significantly different (P > 0.4) from that during exhalation (Fig. 3), but there was again a significant decrease in flow between the start and the end of the inhalation (Table 2) (P < 0.001), and between the flow at the beginning of inhalation and the beginning of exhalation (P < 0.001). Studies during apnea at different lung volumes in the supine position showed that the flows (which were always higher than in the sitting position) tended to be lower at high lung volumes. This difference was not significant.

**Variations in Heart Rate and Pulse Volume with Respiration**

In the sitting position (Table 1), changes in capillary blood flow were mainly due to changes in pulse volume since there were no significant changes in heart rate. In the supine position (Table 2), the significant changes were in heart rate (sinus arrhythmia) with less marked changes in pulse volume. This difference between the sitting and supine position is seen when the pulse volume at the start of inhalation is compared with that at the start of exhalation (Fig. 4); there is a significant difference in the sitting position but not in the supine position. Thus the increase of flow with inhalation in the sitting position was mainly achieved by an increase in pulse volume.

(1) Effect of Changes of Intrathoracic Pressure in the Sitting Position

Because both intrathoracic pressure and lung volume are changing during these slow breaths, we attempted to evaluate the influence of these factors on the blood flow.

Intrathoracic pressure changes were estimated from esophageal pressure measurements during the slow breaths with an esophageal balloon using the technique described by Milic-Emili et al. (14). The capillary flow was not increased at more negative intra-
Figure 2

Records from one normal subject, sitting and supine. The control (air) tracing for each maneuver is shown below the N₂O tracing. The difference due to N₂O uptake is stippled. The ECG was used to align the events. Note the rapid N₂O uptake at the start of inhalation in the sitting but not in the supine position.

Esophageal pressures (Fig. 5). At comparable esophageal pressures it was higher during inhalation than exhalation. Two subjects exhaled and inhaled slowly against a high resistance (22 cm H₂O/liter per sec). In calculating blood flows after subtraction of the control (air) record, corrections were made for the effect of the increased or decreased alveolar pressure (assumed to be equal to the measured pressure at the mouth) on the pres-
TABLE 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pulmonary Capillary Flow Changes during Slow Inhalation and Exhalation in the Sitting Position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Inhalation</td>
</tr>
<tr>
<td></td>
<td>SA (m²)</td>
</tr>
<tr>
<td>1</td>
<td>2.18</td>
</tr>
<tr>
<td>2</td>
<td>2.04</td>
</tr>
<tr>
<td>3</td>
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<td>14</td>
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<td>15</td>
<td>1.74</td>
</tr>
<tr>
<td>Mean</td>
<td>1.74</td>
</tr>
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</table>

SA = surface area; Vpl = pulse volume index; HR = heart rate; Qcl = blood flow index.
sure of alveolar $N_2O$. The $N_2O$ analyzer was beyond the resistance and not subjected to these variations in mouth pressure. Esophageal pressures were more positive during exhal-
EFFECT OF RESPIRATION ON PULMONARY BLOOD FLOW

EFFECT OF INTRATHORACIC PRESSURE

Relation of esophageal pressure to pulmonary capillary blood flow index during slow inhalation and exhalation.

(2) Effect of Lung Volume

Pulmonary capillary blood flow was measured during apnea at about 0.5 l below inspiratory capacity and at functional residual capacity. The alveolar N\textsubscript{2}O concentration at the time of the measurements was obtained by interpolation using the values obtained after an initial short exhalation and an exhalation at the end of the apneic period.

The flow was the same when subjects in the sitting position held their breath, with the glottis open, at a high and at a low lung volume (Table 3). The flow at the beginning of inhalation was significantly higher (average, +31%; \( P < 0.001 \)) than that at the start of breath-holding at the same lung volume. Thus the marked increase in capillary flow that occurs with inhalation in the sitting position does not seem to be directly dependent on either intrathoracic pressure or lung volume.

VARIATIONS OF FLOW WITH TIDAL BREATHING

The subjects exhaled into the bag following a deep breath of the N\textsubscript{2}O mixture or air, and then they rebreathed from the bag with a sinusoidal flow pattern at a mean frequency of 12 per min and a mean tidal volume of 500 ml for 15 to 20 sec. Equal respiratory rates and equal peak inspiratory and expiratory flows during tidal breathing were

<table>
<thead>
<tr>
<th>Subject</th>
<th>( S_A ) (M\textsuperscript{2})</th>
<th>During Inhalation at functional residual capacity (FRC)</th>
<th>During breath-holding</th>
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<tr>
<td></td>
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<td>Late</td>
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<tr>
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<td>2.7</td>
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<td>4.6</td>
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<td>2.5</td>
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<tr>
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<td>1.88</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>13</td>
<td>1.84</td>
<td>2.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

**MEAN**

- Early: 4.5
- Late: 3.1
- At high lung volume: 2.4
- At low lung volume: 2.3

**Difference**

- Early: 1.4
- Late: 0.4

**Significance**

- \( P < 0.001 \)
- \( P > 0.4 \)

Circulation Research, Vol. XXII, February 1968
maintained for the N₂O and the control periods by asking the subject to follow a metronome and watch the air-flow pattern at the mouth on an oscilloscope. Alveolar N₂O concentration was interpolated from the values during each tidal exhalation. Measurement of flow was made for one or two heart beats at peak inspiratory and expiratory flows. Mean values during inhalation and during exhalation for three or four breaths were calculated for each subject.

Mean flow tended to be higher during inhalation than during exhalation with tidal breathing (Table 4). However, the results were much less clear-cut than with the slow breaths, and the difference was not statistically significant. In three of the seven subjects, capillary blood flow was actually greater during exhalation. There was a marked variability in flow from breath to breath. Many records had to be discarded because of poor matching of N₂O with air control data in heart rate or air flow rate.

**Discussion**

The N₂O plethysmographic method for measuring pulmonary capillary blood flow has been checked against other methods of measuring cardiac output (15-17) and found to yield similar values in healthy subjects. Mean values obtained in our study are consistent with normal values reported using other methods. However, since there is no other technique available for measuring moment-to-moment variations in pulmonary capillary flow in man, the changes we are reporting cannot be directly validated by any other method.

**CAUSE OF CHANGES IN PULMONARY CAPILLARY BLOOD FLOW**

At the start of inhalation when the subject was sitting, flow increased significantly, but it failed to rise in proportion to the more negative intrathoracic pressures encountered at high lung volumes. This failure of flow to rise is consistent with the concept of a vascular "waterfall" occurring where venous blood flows from higher extrathoracic to lower intrathoracic pressures, as described by Holt (18) and emphasized by Duomarco and Rimini (19). Once intrathoracic pressure has fallen below some value, partial collapse of systemic veins occurs at their point of entry into the thorax, thus preventing further increase of venous return with further decrease of intrathoracic pressure. It is important to note that the pressure difference determining venous return (driving pressure) under these circumstances is between the upstream venous pressure and the intravenous pressure where the veins enter the thorax. Increases in upstream venous pressure can still increase venous return.

In contrast, it has been shown (20) that sustained increases in intrathoracic pressure do decrease cardiac output. With cineangiography, reduction of venous return from the inferior vena cava or even reversal of flow has been observed during forced exhalation (10). Presumably the increase in intrathoracic pres-

**TABLE 4**

<table>
<thead>
<tr>
<th>Subject</th>
<th>SA (M³)</th>
<th>Seated</th>
<th>Exhalation</th>
<th>Supine</th>
<th>Exhalation</th>
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</thead>
<tbody>
<tr>
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<td>Inhalation</td>
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<td>3.5</td>
<td>3.4</td>
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<td>1</td>
<td>2.18</td>
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<td>2</td>
<td>2.04</td>
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<tr>
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<td>2.00</td>
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<tr>
<td>MEAN</td>
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<td></td>
<td>2.9</td>
<td>4.4</td>
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<td>Significance</td>
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*Circulation Research, Vol. XXII, February 1968*
EFFECT OF RESPIRATION ON PULMONARY BLOOD FLOW

sure during the rapid exhalation to residual volume, which preceded the slow inhalation in our subjects, reduced venous return. This increased the volume and pressure in the extrathoracic pool of blood available for aspiration when intrathoracic pressures fell at the start of inhalation. By contrast, no enlargement of the pool would occur during the rapid inhalation preceding the slow exhalation. However, the volume and pressure in the extrathoracic venous pool available during exhalation presumably were higher in the supine position. This position was associated with a greatly diminished difference between capillary flow in inhalation and exhalation. We suggest that the venous distension and increase in venous pressure in the extrathoracic reservoir in the supine position maintain the effective pressure gradient for venous return throughout the latter part of inhalation and the whole of exhalation. This allows the right ventricular output to remain high and relatively independent of intrathoracic pressure. In the erect posture intrathoracic suction during inhalation following exhalation becomes an important factor in overcoming gravitational impairment of venous return to the thorax.

Other possible causes for the increase of flow during slow inhalation in the upright position must be considered. An increased rate or force of right ventricular contraction may occur reflexly during inhalation. However, in the sitting position, where the changes were most marked, there was no significant alteration in heart rate during the slow maneuvers. In the lying position there was significant sinus arrhythmia, but the difference in flow between inhalation and exhalation was much less. In animal studies Hoffman et al. (4) did not find any evidence for changes in autonomic nervous tone to produce significant changes in pulmonary artery flow during inhalation.

Another possibility is that diaphragmatic contraction tends to occlude the inferior vena cava during the latter part of inhalation and early exhalation. Yet flow was the same during apnea at a high lung volume—when the diaphragm was low—as that at resting volume (functional residual capacity).

Could changes in the distribution of the inhaled N\textsubscript{2}O in relation to the blood flow through the lungs explain the difference in N\textsubscript{2}O uptake between inhalation and exhalation in the sitting position? Following 30 seconds of ventilation with 72% N\textsubscript{2}O in supine anesthetized normal subjects, Eger et al. (21) found a mean difference of 18% between end-tidal and arterial N\textsubscript{2}O concentrations. This was mainly attributed to mismatching of ventilation in relation to blood flow in different parts of the lungs. Such mismatching is likely to be greater in the sitting position (22-24). However, we feel that differences in the relation of blood flow to ventilation between inhalation and exhalation are an unlikely cause of the changes in N\textsubscript{2}O uptake because lung volumes and transpulmonary pressures were comparable during parts of each phase. Also, the differences in N\textsubscript{2}O uptake were insignificant when identical maneuvers were done in the supine position.

Although there was again a tendency toward higher mean flows during inhalation than during exhalation with tidal breathing in the sitting position (Table 4), the results were more variable. A similar variability has been found during quiet respiration in animals (4). This finding is consistent with the results obtained by DuBois and Marshall in 1957 (12). The contrast between the slow maneuvers and tidal breathing, as far as flow at the start of inhalation is concerned, was unexpected. It might be explained by a time lag between changes in vena caval flow and flow in the pulmonary capillaries. Such a time lag might obscure the relationship of any increase in flow to the inhalation at these faster respiratory rates. However, with implanted flowmeters in animals, Brecher and Hubay (3) found an increase of pulmonary artery flow within one heart beat after the increase in inferior vena caval inflow. It seems more likely that an exhalation to near residual volume, as occurred before the slow inhalation, is necessary to augment right heart output sufficiently for a consistent increase in flow to occur at the start of inhalation.

Finally, it is interesting to consider the ef-
fect of the augmentation of flow which occurs with slow inspiration on alveolar and systemic arterial gas tensions. Calculation shows that the flow changes recorded, as pointed out by DuBois and Marshall (12), would diminish the respiratory excursions of alveolar gas tensions and serve to smooth the variations in arterial gas tensions due to breathing.

Acknowledgments

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References


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