Breathing response to lung congestion with and without left heart distension

THOMAS C. LLOYD, JR.
Departments of Medicine and Physiology, Indiana University Medical Center,
Indianapolis, Indiana 46223

LLOYD, THOMAS C., JR. Breathing response to lung congestion with and without left heart distension. J. Appl. Physiol. 65(1): 131-136, 1988.—This study compared the effect of lung congestion with and without left heart (LH) distension on breathing frequency (fr) and discriminated among responses mediated by myelinated and nonmyelinated vagal afferents. Cardiopulmonary bypass perfusion of anesthetized dogs was used to isolate reflexes. The following three groups were prepared: 1) lung vessels pressurized by pumping into the main pulmonary artery (MPA); 2) lungs and fibrillating LH pressurized by pumping into MPA while draining from LH; 3) lungs congested by occluding several pulmonary veins while holding cardiac output constant. Congestion of lungs alone in groups 1 and 3 depressed fr. Congestion of lungs and distension of LH (group 2) caused transient depression of fr but a steady-state excitation. Cooling cervical vagi to 8°C prevented depression of fr by congestion in all groups. In groups 1 and 2, in which MPA pressure was higher than in group 3, congestion during vagal cooling stimulated breathing. I conclude that lung congestion may stimulate fr via C-fiber afferents, but this may be overcome by a depressor effect via myelinated afferents. Simultaneous LH distension may reflexly stimulate breathing and overcome the lung depressor reflex.

I hypothesized that depression of breathing by congestion limited to the lung vessels might be mediated by slowly adapting receptors (SAR). If so, selective blockade of myelinated vagal fibers should prevent depression and may unmask a C-fiber-mediated tachypnea. It was further postulated that the depressor effect of lung congestion would be opposed by the excitatory effect of left heart distension if both stimuli occurred simultaneously. These hypotheses were tested in pentobarbital-anesthetized dogs using surgical techniques and bypass perfusion to isolate the lungs and heart. The results were consistent with the hypotheses.

METHODS

Adult male dogs weighing from 18 to 25 kg were anesthetized with pentobarbital sodium (30 mg/kg iv), intubated with a cuffed endotracheal tube, and positioned supine. Both cervical vagus nerves were exposed for lengths of several centimeters through a midline incision, after which the skin edges were closed with a clamp to maintain body temperature around the nerves. The incision was extended caudally to theternal xiphoid process. The sternum was opened longitudinally and its edges were widely retracted. Subsequent ventilation of the lungs was provided by a piston respirator. The left subclavian artery was exposed below the aorta, making possible cannulation of a cannula that returned blood to the aorta from an external gas exchanger and perfusion pump (8) at a rate of ~100 ml/min·kg body wt−1. Heparin was given to prevent clotting. Blood flow from the dog to the external system was obtained differently in three groups of experiments.

Congestion of lung vessels in isolation was tested in the first group, and in these dogs, the right atrial appendage was cannulated to provide systemic venous blood to the external gas exchanger and pump. After establishing bypass perfusion, a cannula was passed from a purse-string opening in the right ventricular wall into the main pulmonary artery and ligated with a tie passed around the aorta and pulmonary trunk. This approach required no dissection around aorta or pulmonary trunk to place the tie, but the tie curtailed coronary blood flow and the heartbeat stopped. Ligatures previously placed around each pulmonary vein within the pericardium were tied to isolate the lung vessels. A second pump withdrew blood from the external reservoir at a flow of 400 ml/min. The outflow tube from this pump bifurcated; one...
limb was connected to the pulmonary arterial cannula and the other returned blood to the reservoir. Adjustment of a screw clamp on the reservoir return provided control of pulmonary arterial pressure. Pressure was \(-0\) cmH\(_2\)O when the clamp was open, and it was raised to \(-60\) cmH\(_2\)O for the congestion challenge, a magnitude chosen on the basis of past experience (9). The lungs were inflated to a sustained pressure of \(-5\) cmH\(_2\)O with 5% CO\(_2\) in \(O_2\) while on cardiopulmonary bypass.

Simultaneous lung vascular congestion and left heart distension were tested in the second group. Cannulations of right atrium and subclavian artery and the connections of these to the external pump and oxygenator were the same as in group 1. The main pulmonary artery was again cannulated through the right ventricle, but the cannula was ligated with a tie placed only around the pulmonary trunk. This required dissection between aorta and main pulmonary artery but left the coronary flow unimpeded. No ties were placed around pulmonary veins. Again using a second pump, blood was pumped from the oxygenator reservoir to the pulmonary artery at a rate of 500 ml/min and was returned to the reservoir from a cannula placed in the left ventricle through a purse-string opening at the apex. Ventricular fibrillation was induced electrically. Partial occlusion of the return line from the left ventricle was used to raise pressure in the lung vessels and left heart to the same general level as in group 1 (\(-60\) cmH\(_2\)O). When this occluder was open, pressure in the left heart was nominally zero and pulmonary arterial pressure was \(-10\) cmH\(_2\)O. As before, lungs were inflated to a sustained pressure of \(-5\) cmH\(_2\)O with 5% CO\(_2\) in \(O_2\).

A third approach also allowed pressure in the pulmonary vessels to be raised without distending the left heart, but it did not require as much dissection as before, and it allowed the heart to continue to beat and to perfuse the lungs. This was done by first placing a loose snare around the common trunk formed by the veins of the diaphragmatic and intermediate lobes. A 1-cm-OD cannula was then inserted into the cavity of the beating left ventricle through a stab wound at the apex. The cannula was secured with a purse-string suture. By virtue of the low resistance of the cannula and its associated tubing, left ventricular stroke volume was diverted from the aorta to the external oxygenator. Diversion was complete, as witnessed by the absence of cardiac pulsations in the systemic arterial pressure. As before, blood was returned to the left subclavian artery at flows of \(\sim 100\) ml-min\(^{-1} \cdot kg^{-1}\). This allowed the right ventricle to perfuse the lungs at a flow ultimately determined by the external pump. Once more, lungs were inflated to a sustained pressure of \(-5\) cmH\(_2\)O with 5% CO\(_2\) in \(O_2\) and gas exchange was provided extracorporeally. Tightening the venous snare diverted blood to other lobes and raised pulmonary arterial pressure. Snare occlusion caused an identical pressure to be imposed uniformly throughout the beds of the occluded lobes, but a longitudinal pressure gradient would have remained in the lobes through which flow continued. This caused more variation of pressure within the lungs than was the case in the other two groups. Right ventricular output and, therefore, left heart throughput were not expected to change when the snare was tightened unless the right ventricle failed as its load increased. A significant fall of right ventricular output would have caused progressive loss from the external reservoir, and this was not observed.

Airway pressure (Paw) was measured from a side tap on the endotracheal tube in all three groups. Pulmonary arterial pressure (Ppa) was measured in groups 1 and 2 from a catheter advanced into the artery through the wall of the tubing by which it was perfused. Ppa was acquired in group 3 by a catheter passed from the right femoral vein. Systemic arterial pressure (Psa) was measured from a catheter in the right internal thoracic artery. Breathing was monitored with an abdominal pneumograph. All pressures were acquired with transducers zeroed with respect to the midcardiac plane. Breathing frequency (fr) was continuously obtained from the pneumograph pressure by a rate computer. Data were recorded continuously at a chart speed of either 0.5 or 1.0 mm/s.

Selective blockade of the vagus nerves was achieved using thermodes cooled to 8°C (11). When not cooled, the nerves were returned to their beds and the skin edges were closed. Blockade was confirmed by the absence of a respiroinhibitory effect of lung inflation previously shown to have been present. Experiments not meeting this criterion were rejected.

The protocol for all experiments was to observe the effect of abruptly imposing the congestion stimulus for a period of 1–2 min. After recording two to four responses, the vagi were cooled and two or three more challenges were imposed. The vagi were then rewarmed and two to four more challenges were made. About 2 min were allowed between congestion challenges, and a similar period was allowed at the onset and removal of vagal cooling before challenges were again imposed. To confirm blockade and recovery using the inflation reflex, Paw was raised to \(-15\) cmH\(_2\)O for 0.5-min intervals at least once in each period before, during, and after vagal cooling.

Capsaicin was used to stimulate C fibers intermittently in groups 1 and 2 (4). In group 1, this was done by injecting a 100-μg bolus through a catheter passed into the pulmonary artery and then flushing the bolus forward by slightly raising Ppa for a few seconds. Capsaicin was washed out by alternately raising and lowering Ppa to fill and empty the vessels, which was found to remove the capsaicin effect quickly and easily. In group 2, capsaicin was given into the pulmonary arterial inflow as a 50-μg bolus.

Data analysis was undertaken to show the effect of vagal blockade and to show the differences between effects of congestion with and without left heart distension. Records from groups 1 and 2 were analyzed by obtaining fr at three different times; just before Ppa was raised, at the peak or nadir of any transient change after Ppa was raised, and during the steady-state response while Ppa was raised. The transient and steady-state responses were ultimately analyzed separately. Peaks and nadirs were not apparent in group 3, and, therefore, frequencies before, during, and after the interval of snare...
occlusion were tabulated. Differences from base-line fr were obtained in groups 1 and 2 by referring fr during congestion to the preceding base-line value. In group 3 the effect of congestion was expressed as the fr change with respect to the average of the base-line values before and after the challenge. In all groups these frequency differences were then averaged within each treatment block for each experiment to provide average values for the changes caused by congestion before, during, and after vagal cooling for each dog. Values before and after cooling were then compared by paired t test. After it was found (see RESULTS) that these did not differ within each group, the data before and after blockade were averaged for each experiment, and this value was compared with the value during vagal blockade using the paired t test. Differences between groups 1 and 2 were tested using the two-sample t test. The null hypothesis was rejected if P \leq 0.05.

RESULTS

Group 1, in which congestion was limited to the lungs, consisted of eight dogs. The average (±SD) systemic blood flow was 102 ± 2 ml·min⁻¹·kg body wt⁻¹, and the average Psa was 134 ± 17 cmH₂O. Base-line fr varied among experiments but varied much less within each experiment. Base-line fr before vagal cooling and after rewarming did not differ significantly. The average base-line fr while vagi were not cooled was 29.5 ± 21 breaths/min. Ppa, nominally zero between episodes of congestion, averaged 66 ± 7 cmH₂O during congestion intervals. Again, there was more variation among experiments than within. Frequency changes induced by congestion are given in Table 1 and an example is shown in Fig. 1. Before cooling the vagi, in all eight dogs congestion caused fr to fall to a transient nadir from which it partially recovered in seven dogs. The remaining dog recovered from the nadir to a sustained increase, which reverted to base line with decongestion. Vagal cooling did not change base-line fr significantly. The average base-line fr during block was 25.4 ± 14 breaths/min. During cold block congestion caused a transient fall in only one dog and all had sustained fr increases. After blockade the transient nadir reappeared in seven of eight dogs, but sustained responses were evenly divided among positive and negative changes. Neither the transient nor steady-state responses differed significantly when compared before and after vagal cooling, but the predominantly excitatory responses (both transient and steady state) in the presence of block differed significantly from the depressor responses that occurred without blockade.

In group 2 (9 dogs), the congestion stimulus was applied to lung vessels and left heart. Average blood flow was 108 ± 4 ml·min⁻¹·kg⁻¹, and Psa was 107 ± 13 cmH₂O. Base-line fr was not significantly different before and after vagal cold block, and fr averaged 26 ± 16 breaths/min in the absence of blockade. Ppa averaged 9 ± 3 cmH₂O in the base-line state and 57 ± 4 cmH₂O during congestion. Ppa was significantly less during congestion in group 2 than in group 1. Changes with congestion are summarized in Table 1, and an example is shown in Fig. 2. Congestion before vagal block caused transient depression of fr in eight dogs, but the sustained response was depressor in only two dogs, the rest showing stimulation of breathing. During blockade, fr was depressed in both the transient and steady states in one dog, one dog was unresponsive, and fr increased in seven dogs. Blockade did not significantly change base-line fr, and the average base-line fr during block was again 26 ± 16 breaths/min. After recovery from block, eight dogs again showed transient depression with congestion, seven dogs displayed a steady-state stimulation, and none showed a sustained depression. Again there were no significant differences in either the transient or sustained responses before and after cold block. By eliminating the transient fall, vagal blockade caused a significant difference in the transient response, but it did not

| TABLE 1. Breathing frequency changes brought about by congestion before, during, and after vagal blockade |
|---------------------------------|----------------|----------------|---------------|
|                                | Before Block   |                | After Block   |
|                                | tr             | ss             | tr            | ss             |
| Group 1                        |                |                |               |                |
| Mean ± SD                      | -17.9±11.1     | -6.6±7.9       | 5.5±12.0*     | 4.7±4.8*       |
| Median                         | -15.8          | -8.0           | 2.5           | 3.2            |
| Range                          | -30, -6.3      | -16.5, 7.3     | -12.5, 26     | 0.5, 13.5      |
| Group 2                        |                |                |               |                |
| Mean ± SD                      | -9.6±10.5      | 7.6±9.4†       | 2.1±4.7*      | 4.7±6.4        |
| Median                         | -7.0           | 7.3            | 0             | 3.4            |
| Range                          | -30, 0.7       | -4.7, 13       | -6, 9         | -4, 19         |
| Group 3                        | NA             | -8.2±7.5       | 2.2±5.7*      | NA             |
| Mean ± SD                      | NA             | -4.2           | 0.2           | NA             |
| Median                         | NA             | -21.2, -2.3    | -0.5, 15      | NA             |
| Range                          | NA             | -20.7, -0.5    | NA            | NA             |

Values in breaths/min. Group 1, lung congestion; group 2, lung congestion plus left heart distension; group 3, lung congestion by venous occlusion. tr, Transient changes; ss, steady-state changes. No transient events occurred in group 3 (see text), and those columns are not applicable (NA). * Significant change during block with respect to pooled observations before and after block. † Significant difference with respect to group 1.
increased pulmonary vascular pressure on breathing frequency (fr). Congestion imposed at 1 and removed at 4. Note transient and sustained fr falls (top trace) that changed to increases during vagal cold block (bottom trace). Br, breaths.

FIG. 1. Representative experiment from group 1 showing effect of increased pulmonary vascular pressure on breathing frequency (fr). Congestion imposed at 1 and removed at 4. Note transient and sustained fr falls (top trace) that changed to increases during vagal cold block (bottom trace). Br, breaths.

FIG. 2. Representative experiment from group 2 showing effect of increased pulmonary vascular and left heart pressure on breathing frequency (fr). Symbols as in Fig. 1. Note transient fr fall that resolved to a sustained increase (top trace). Transient depression was not present during vagal cold block (bottom trace). Br, breaths.

There were seven dogs in group 3. Average systemic blood flow and arterial pressure were 100 ± 7 ml·min⁻¹·kg⁻¹ and 129 ± 10 cmH₂O, respectively. Base-line fr averaged 39 ± 24 breaths/min when vagi were not cooled and 33 ± 19 breaths/min when cooled. This difference was not significant. Base-line Ppa averaged 17 ± 3.8 cmH₂O, but pressure rose to 33 ± 5.6 cmH₂O during venous occlusion. This stimulus was significantly less than in the other groups. Changes in fr induced by venous occlusion are shown in Table 1, and a representative response is shown in Fig. 3. In all dogs fr fell promptly to a new steady state without the transient nadir noted in the other groups. With release of the snare, fr recovered equally promptly. Vagal cooling significantly reduced the depressor effect of congestion. There was no significant difference in responses obtained before and after vagal block. Inflation during cold block stimulated breathing in six of these dogs but had no effect in one dog. Rewarming the nerves restored the respiroinhibitory response.

DISCUSSION

Congestion, when limited to the lung vessels by venous ligation, depressed breathing in group 1 of these experiments as it had done before in similar experiments (9). A sustained depressor effect also occurred when lung vessels were congested at a lower pressure by intermittent venous occlusion in group 3. Cooling the vagi to 8°C eliminated the depressor effect in both groups, and in group 1 congestion during vagal cooling stimulated breathing. Breathing was not recorded at high chart speeds in these experiments, and, as a consequence, specific changes in inspiratory and expiratory times were not obtained. Previous demonstration (9) of the depressor effect of lung congestion on breathing frequency showed it to be caused by prolongation of expiration time. Depression through prolongation of expiration time and its replacement by stimulation during 8°C vagal cooling if a sufficiently high distending pressure is used resemble the effects of lung inflation under similar experimental conditions (2, 4, 13, and present experiments). These inhibitory and excitatory effects of inflation are mediated by SAR and C-fiber endings, respectively (2, 4). This suggests, but does not prove, that the effects of congestion and inflation may be similarly mediated. The (presumed) C-fiber component was not found in my earlier study (9) because no attempt was made to selectively block the depressor effect that now appears to dominate and to be mediated by larger fibers.

When distension of the left heart was included in the congestion stimulus (group 2), the initial transient respirator depression usually gave way to a sustained stimulation even though vagi were not cooled. It has been shown (11) that distension of the isolated left heart stimulates breathing, and therefore I propose that the sustained stimulation in group 2 experiments may have been in response to a left heart reflex that was able to overcome the steady-state depressor effect of lung congestion found in group 1. Which chamber of the left heart may be responsible for this reflex is not known with certainty, but I favor a left atrial origin. The various possibilities, and evidence for them, were discussed in the earlier report (11), and no new information has been provided in the current study. Because the left heart reflex is blocked by 8°C vagal cooling (11), the residual stimulation of breathing that occurred during cooling in
group 2 could again be assigned to enhanced lung C-fiber activity.

A temperature of 8°C was chosen for vagal blockade because it is recognized to be sufficient to block transmission of nearly all activity of myelinated afferents without severely depressing conduction in nonmyelinated afferents (4, 13). Cooling the vagi did not significantly affect base-line fr in any of the three groups of experiments. One would anticipate that fr would increase on cooling vagi to 8°C because differential blockade of myelinated fibers allows background C-fiber activity to play a proportionately larger role (13). The slow, deep breathing associated with vagotomy does not occur unless the vagi are severed or totally blocked by temperatures near 0°C (13). Because the Hering-Breuer depressor reflex was eliminated by vagal cooling in the present experiments and inflation thereafter usually caused stimulation, cooling was clearly sufficient to block SAR activity and allow the C-fiber activation by large inflations (4) to be manifest. Capsaicin was used as a separate challenge to show that a C-fiber-mediated reflex would continue in the presence of vagal cooling. The absence of a sustained change in base-line fr during 8°C vagal blockade may have been because the expected change was small (13) and obscured by random variations, or it may have been because the underlying activities of the several receptor types were not the same in these experiments as in those of Pisarri et al. (13). Breathing did often change temporarily, however, with the onset or removal of vagal cooling. This was especially notable on rewarming, when fr abruptly fell and then slowly returned upward. The fall presumably was caused by return of SAR afferent conduction.

It is unlikely that rapidly adapting receptors played a role in the stimulation of breathing by either inflation or congestion during vagal cooling. These receptors should have been nearly as well blocked as the SAR (13), and in addition their rapid adaptation should have caused them to return to a quiescent state at that time in the congestion and inflation responses when breathing was stimulated.

Although it can be shown that congestion stimulates lung C-fibers (4, 14) and that C-fiber activation may simulate breathing if sufficiently intense (4), it has not been as easy to show that congestion stimulates breathing. The classic study of Churchill and Cope (3) showed that congestion of cat lung caused rapid shallow breathing, at times preceded by apnea. Aviado et al. (1) later found that congestion of dog lung caused tachypnea without antecedent apnea. Downing (5), sometimes credited with supporting the notion that congestion causes tachypnea, actually found that congestion of dog lung more often caused respiratory depression and that excitation occurred in only three of his nine successful experiments. Wead and his co-workers (15, 16) have been unable to find any effects of lung vascular congestion in dogs. The greatest amount of evidence, therefore, is against the notion that lung vascular congestion has a direct net stimulatory reflex effect on breathing in dogs when vagi conduct normally.

Congestion pressure was significantly higher in group 1 than in group 2, although this was not done deliber-