Responses to Inflation of Vagal Afferents with Endings in the Lung of Dogs


From the Departments of Physiology, Cell Biology, and Internal Medicine, and the Harry S. Moss Heart Center, University of Texas Health Science Center at Dallas, Dallas, Texas

SUMMARY. In dogs, inflating the lungs to pressures of 9 cm H2O or less reflexly increases heart rate, whereas inflating the lungs to pressures of 10-30 cm H2O reflexly decreases heart rate. The afferent fibers responsible for the cardioacceleration travel in the vagus nerves and are believed to be pulmonary stretch receptors, whereas the afferents responsible for the deceleration also travel in the vagus nerves, but are believed to be lung C-fibers. To identify the afferents responsible for these effects, we recorded the impulse activity of vagal afferents with endings in the left lung, while we slowly inflated that lung to 30-45 cm H2O. We found that 12 slowly adapting receptors fired at significantly lower inflation pressures than did 10 rapidly adapting receptors (5.8 ± 1.5 vs. 13.5 ± 2.2 cm H2O, respectively). We also found that 13 pulmonary C-fibers fired at significantly lower inflation pressures than did 10 bronchial C-fibers (16.4 ± 1.8 vs. 26.5 ± 2.9 cm H2O, respectively). We conclude that slowly adapting receptors are likely to be responsible for the cardioacceleration evoked by low levels of inflation, and that both pulmonary and bronchial C-fibers are likely to be responsible for the cardiodeceleration evoked by high levels of inflation. (Circ Res 51: 525-531, 1982)

BOTH the decrease and the increase in heart rate evoked by inflation of the lungs of open-chest dogs have been known, since the time of Anrep et al. (1936), to be reflexes whose afferent arms are contained in the vagus nerves. For the most part, two preparations have been used to study the reflex changes in heart rate evoked by lung inflation. In the first, blood flow through the heart and lungs has been bypassed and the lungs have been inflated to pressures of 25–30 cm H2O (Salisbury et al., 1959; Glick et al., 1969). In the second preparation, the left pulmonary artery has been occluded and the left lung has been unilaterally inflated to pressures of 30–40 cm H2O (Hainsworth, 1974; Angell-James and Daly, 1978; Cassidy et al., 1979; Cassidy and Johnson, 1979). These preparations have shown that when the lungs were inflated to a pressure of 9 cm H2O or less, heart rate increased, whereas, when the lungs were inflated to 30–40 cm H2O, heart rate decreased.

Slowly adapting receptors with A-fibers are stimulated by low levels of lung inflation (Miserocchi and Sant'Ambrogio, 1974) and, therefore, are likely to be the vagal afferents responsible for the reflex cardioacceleration evoked by inflating the lungs to pressures of 9 cm H2O or less (Anrep et al., 1936; Angell-James and Daly, 1978). On the other hand, pulmonary C-fibers, when stimulated chemically, reflexly evoke bradycardia and hypotension (Coleridge et al., 1965) and, therefore, are likely to be the vagal afferents responsible for the cardiac slowing evoked by inflating the lungs to 30 cm H2O. Recently, a second type of afferent vagal C-fiber with endings in the lung, the bronchial C-fiber, has been described (Coleridge and Coleridge, 1977). Bronchial C-fibers, when stimulated chemically, also reflexly slow the heart (Roberts et al., 1981; Coleridge et al., 1982); raising the possibility that these C-fibers participate in the reflex decrease in heart rate which is evoked by high levels of lung inflation. Finally, rapidly adapting receptors with A-fibers are stimulated by lung inflation (Sampson and Vidruk, 1975), but the threshold inflation pressures needed to fire these afferents have not been defined in dogs. Thus, these afferents may contribute either to the increase or decrease in heart rate which is reflexly evoked by lung inflation.

Therefore, using a preparation in which the left pulmonary artery was ligated and in which the right and left lungs were ventilated separately, we recorded the impulse activity of both afferent vagal A and C fibers with endings in the left lung, while we slowly inflated that lung to a pressure of 30 cm H2O. Our purposes were 3-fold. First, we attempted to determine whether or not the responses to inflation of lung C-fibers were consistent with the hypothesis that these afferents were responsible for causing the reflex cardiac slowing evoked by this stimulus. To accomplish this, we compared the threshold inflation pressures needed to fire pulmonary and bronchial C-fibers with those needed to evoke the reflex (Glick et al., 1969; Hainsworth, 1974; Cassidy and Johnson, 1979). Second, we attempted to show that the responses of slowly adapting receptors to low levels of lung inflation were consistent with the hypothesis that these myelinated afferents caused the reflex cardioacceleration evoked by inflating the lungs to pressures of 9 cm H2O or less (Anrep et al., 1936; Angell-
James and Daly, 1978). Third, we attempted to determine the threshold inflation pressures needed to fire rapidly adapting receptors.

Methods

General

Eighteen dogs were anesthetized with morphine sulfate (2 mg/kg, sc) followed by α-chloralose (80 mg/kg, iv). A Kottmeier endobronchial tube, which separated the right and left main bronchi, was inserted into the trachea. The chest was opened wide in the midline and the lungs were ventilated with room air by a Harvard pump, whose expiratory outlet was placed under 3–5 cm H2O. End tidal CO2 in the airway supplying the right lung was monitored continuously by a Beckman Gas Analyzer (LB-2) and was maintained at 4.5–5.0% by adjusting ventilation. The dogs were paralyzed with gallamine triethiodide (1 mg/kg, iv). The paralyzing agent was always allowed to wear off to assess the level of anesthesia. Subsequent doses of α-chloralose (10 mg/kg) were given hourly to maintain anesthesia.

Arterial blood pressure was recorded through a femoral artery cannula, which was connected to a transducer (Statham P23ID). Airway pressure in the left and right lungs were recorded from sidearms of the Kottmeier tube, both of which were connected via a stopcock to a transducer (Statham PM5ETC). Arterial blood pressure, left airway pressure, and action potentials (see below) were recorded on a direct writing electrostatic recorder (Gould ES1000).

Recording of Afferent Impulses

We recorded afferent impulse activity from the left cervical vagus nerve. We selected filaments that discharged with an obvious ventilatory rhythm and divided them until we could distinguish the impulse activity of single fibers. The conduction velocities of the fibers were measured by electrically stimulating the cervical vagus nerve with an electrode fixed in a shielded assembly. Conduction velocity was calculated by dividing the distance between stimulating and recording electrodes by the conduction time.

There are two types of pulmonary stretch receptors with myelinated vagal fibers, rapidly adapting receptors (Knowlton and Larrabee, 1946) and slowly adapting receptors (Adrian, 1933). The former were identified by their rapidly adapting response to inflating the left lung, in a stepwise manner, to 30 cm H2O. Only those receptors with conduction indices of 65% or more were classified as rapidly adapting (Sampson and Vidruk, 1975). Slowly adapting receptors were identified by their sustained response to lung inflation.

To classify unmyelinated (C) fibers with endings in the left lung, we used the methods described by Coleridge and Coleridge (1977). Therefore, pulmonary C-fibers (J-receptors) were identified by their rapid response (i.e., within 1–3 seconds) to injecting capsaicin (10 μg/kg) into the left pulmonary artery (Fig. 1, A and C). One milliliter of capsaicin solution was injected into the left pulmonary artery and was then flushed in with 5 ml of saline. These injections of capsaicin were never repeated more than 5 times in any one dog. Pulmonary C-fibers were not stimulated by injecting the same dose of this substance into the left atrium (Fig. 1B). Bronchial C-fibers were identified by their responses to left atrial injection of either capsaicin (10 μg/kg) or bradykinin (1 μg/kg; Kaufman et al., 1980). Often, bronchial C-fibers were stimulated by pulmonary arterial injection of these substances, but the latency of response of these C-fibers to left atrial injection was always 2–5 seconds shorter than the latency to pulmonary arterial injection. When recording from vagal filaments having no spontaneous activity, we gently explored the lung with a blunt probe seeking to discharge previously silent fibers. In this way, our sample of lung afferents was not biased towards only those fibers discharging spontaneously with each ventilatory cycle. We established the intrapulmonary origin of both spontaneously active and silent fibers by finding a point within the left lung from which gentle probing evoked bursts of impulses.

Experimental Protocol

Before dissecting the vagus nerve, we demonstrated that stepwise inflation of the left lung to a pressure of 30 cm H2O decreased heart rate and arterial pressure in the same dogs as those in which we recorded afferent vagal impulse activity. Following this demonstration, we isolated a vagal filament which contained a single active fiber whose ending was in the left lung. Next, we stopped the pump that was ventilating the left lung and then rapidly inflated that lung, in a stepwise manner, to 25 cm H2O, both to ensure a similar volume history for each fiber and to expand atelectatic areas. Two minutes later, still using a 95% air-5% CO2 mixture, we slowly inflated the left lung to a pressure of 30 cm H2O at a rate of approximately 1.5–2.0 cm H2O/sec. After reaching 30 cm H2O, left airway pressure was maintained at this level for 15 minutes. Left lung inflations were started from an airway pressure of 2½ cm H2O.

For fibers that were silent at left airway pressures of 2½ cm H2O, threshold was defined as the inflation pressure at which the fiber discharged its first impulse. For fibers that were spontaneously active at left airway pressures of 2½ cm H2O, threshold was defined as the inflation pressure at which the fiber increased its discharge rate over its baseline level.

In three instances, we needed to inflate the left lung to pressures of 40–45 cm H2O in order to determine the threshold of two bronchial C-fibers and one rapidly adapting receptor. We inflated the lung to these pressures only after a previous inflation to 30 cm H2O for 15 minutes failed to stimulate the three fibers.

Statistics

All values are expressed as the mean ± SEM. We used analysis of variance, followed by Dunnett post-hoc tests, to determine statistical significance (Winer, 1971).

Results

Cardiovascular Responses to Lung Hyperinflation

Before dissecting the vagus nerve, we examined the cardiovascular responses evoked by inflating the left lung in stepwise manner to 30 cm H2O in the 18 dogs used in this study. Left lung inflation decreased mean arterial pressure (from 109 ± 3 to 81 ± 6 mm Hg; \( P < 0.001 \)) and heart rate (from 165 ± 7 to 127 ± 9 beats/min; \( P < 0.001 \)), effects which began si-
multaneously 3 ± 0.3 seconds after the onset of inflation. While recording impulses from the cut peripheral ends of the vagus nerve, we found that the cardiovascular responses to hyperinflation were either absent or greatly reduced from those evoked with the nerve intact.

**Pulmonary C-Fibers**

We recorded the responses to lung inflation of 13 pulmonary C-fibers (mean conduction velocity = 1.2 ± 0.1 m/sec; range = 0.9-2.0 m/sec). All, but one, were silent while the left lung was maintained at an inflation pressure of 2½ cm H2O. Slow inflation of the lung, however, caused these C-fibers to fire at thresholds which ranged from 6-30 cm H2O (Table 1; Fig. 2A). Three of the 13 (23%) pulmonary C-fibers were firing when pressure in the left lung reached 10 cm H2O, nine (69%) were firing when pressure reached 20 cm H2O, and 13 (100%) were firing when pressure reached 30 cm H2O.

We also examined the activity of the pulmonary C-fibers during the 15-minute period in which inflation pressure in the left lung was maintained at 30 cm H2O. Six of the 13 C-fibers stopped firing within 1 minute after inflation pressure reached 30 cm H2O. However, seven continued to fire throughout the entire 15-minute period, although their discharge rates were lower than those evoked initially by slowly inflating the lung from 2½ to 30 cm H2O (Fig. 2, B and C).

**Bronchial C-Fibers**

We recorded the responses to lung inflation of 10 bronchial C-fibers (mean conduction velocity = 1.2 ± 0.1 m/sec; range = 0.9-1.8 m/sec). While the left lung was maintained at an inflation pressure of 2½ cm H2O, all of the bronchial C-fibers were either silent or fired at rates of less than 0.5 imp/sec). Slow inflation of the lung, however, increased their firing rates over baseline levels. Their thresholds ranged from 16-40 cm H2O (Table 1; Fig. 3, A and B). None of bronchial C-fibers was active at 10 cm H2O, four

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**TABLE 1**

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>Threshold (cm H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary C-fibers</td>
<td>13</td>
<td>16.4 ± 1.5</td>
</tr>
<tr>
<td>Bronchial C-fibers</td>
<td>10</td>
<td>26.5 ± 2.9</td>
</tr>
<tr>
<td>Rapidly adapting receptors</td>
<td>10</td>
<td>13.5 ± 2.2</td>
</tr>
<tr>
<td>Slowly adapting receptors</td>
<td>12</td>
<td>5.8 ± 1.5</td>
</tr>
</tbody>
</table>

All comparisons between the thresholds of any two types of afferents were statistically significant (P < 0.05) except for that between the thresholds of pulmonary C-fibers and those of rapidly adapting receptors.
FIGURE 2. Effect of unilaterally inflating the left lung on the impulse activity of a pulmonary C-fiber. A: Increasing left airway pressure from $2\frac{1}{2}$ to 30 cm H$_2$O fired the C-fiber. B: Five minutes after the left airway pressure reached 30 cm H$_2$O, the C-fiber was firing. C: Ten minutes after pressure reached 30 cm H$_2$O, the C-fiber was still firing. D: When left airway pressure was returned to $2\frac{1}{2}$ cm H$_2$O, the C-fiber stopped firing. Note that this pulmonary C-fiber is the same one as that shown in Figure 1. From above downward, time with the interval between ticks representing 1 second; action potentials; left airway pressure.

(40%) were active at 20 cm H$_2$O, and 8 (80%) were active at 30 cm H$_2$O. Furthermore, at corresponding inflation pressures, the firing rates of the bronchial C-fibers were lower than the firing rates of the pulmonary C-fibers (Fig. 4A).

Four of the 10 bronchial C-fibers stopped firing within 1 minute after inflation pressure reached 30 cm H$_2$O. Two continued to fire throughout the entire 15-minute period of lung hyperinflation, although their discharge rates were lower than those evoked initially by slowly inflating the left lung from $2\frac{1}{2}$ to 30 cm H$_2$O. Two bronchial C-fibers fired during maintained hyperinflation of the lung with an irregular discharge pattern, which consisted of periods of vigorous firing interspersed with periods of silence (Fig. 3B). The remaining two bronchial C-fibers did not fire during maintained inflation, and were found to have thresholds of 40 cm H$_2$O.

We also recorded the impulse activity of four C-fibers with endings in the left lung (range of conduction velocities = 0.9–2.3 m/sec) that were not stimulated by injection of capsaicin and bradykinin into either the pulmonary or systemic circulations. The thresholds of these four C-fibers to slow inflation of the left lung ranged from 17 to 23 cm H$_2$O. Moreover, three of the four C-fibers stopped firing with 1 minute after left lung inflation pressure reached 30 cm H$_2$O. The remaining C-fiber fired throughout the entire 15-minute period that the lung was inflated to 30 cm H$_2$O.

Pulmonary Stretch Receptors

We recorded the impulse activity of 10 rapidly adapting receptors (mean conduction velocity = 33.5 ± 4.4 m/sec; range: 16.4–48.6 m/sec) and 12 slowly adapting receptors (mean conduction velocity = 34.2 ± 2.9 m/sec; range: 15–47.5 m/sec). Slow inflation of the left lung increased the firing of both types of receptors; however, their mean thresholds and firing rates at corresponding inflation pressures were markedly different (Table 1; Fig. 4B). The threshold inflation pressures needed to fire the rapidly adapting receptors ranged from 5 to 45 cm H$_2$O, whereas the threshold pressures needed to fire the slowly adapting receptors ranged from 3 to 21 cm H$_2$O. Three (30%) of the rapidly adapting receptors were firing when left lung inflation pressure reached 10 cm H$_2$O, and nine (90%) were firing when pressure reached 20 cm H$_2$O. The remaining rapidly adapting receptor fired when pressure reached 45 cm H$_2$O. By contrast, 11 (92%) of the slowly adapting receptors were firing at 10 cm H$_2$O. The remaining slowly adapting receptor fired when inflation pressure reached 21 cm H$_2$O.

Six of the 10 rapidly adapting receptors decreased their firing rates (range: 6–30 imp/sec) as inflation pressure increased from 20 to 30 cm H$_2$O, whereas the remaining four increased their firing rates (range: 1–10 imp/sec) as pressure increased over these levels (Fig. 4B). By contrast, only one of the 12 slowly adapting receptors decreased its firing rate as inflation pressure increased from 20 to 30 cm H$_2$O.

Discussion

Using a preparation in which the left pulmonary artery was ligated and in which the right and left lungs were ventilated separately, we found that inflation of the left lung to 30 cm H$_2$O markedly decreased heart rate and arterial blood pressure, effects which were previously demonstrated by our laboratory (Cassidy et al., 1979; Cassidy and Johnson, 1979) and by Hainsworth (1974) to be reflex in origin. There are certain advantages of using such a preparation to identify the vagal afferents responsible for evoking these reflex effects. For example, the left lung does not receive any right ventricular output; moreover, it does not exchange oxygen and carbon dioxide with the pulmonary capillary blood. Therefore, the lung can be inflated slowly and held inflated over a period of time. The slow, ramplike inflation that we used to examine the relationship between left airway pressure...
and impulse activity in lung afferents was chosen because the recording life of single fiber preparations is often quite short, making repeated stepwise inflations, such as those used by Cassidy and Johnson (1979), difficult to complete. Therefore, our method of slowly inflating the lung allowed us to determine the firing rates of the lung afferents at various airway pressures. In addition, this method allowed us to determine the airway pressures at which these afferents discharged their first impulse.

Lung C-Fibers

We found that the lung inflation pressures needed to stimulate pulmonary C-fibers were significantly lower than those needed to stimulate bronchial C-fibers. In addition, for each inflation pressure that we examined, pulmonary C-fibers fired at higher frequencies than did bronchial C-fibers. Our findings confirm and extend those of Coleridge and Coleridge (1977), who, working with open-chest dogs, inflated the lungs by clamping the expiratory outlet of the ventilator. These investigators found that all of the pulmonary C-fibers tested were stimulated by inflation of the lungs to two tidal volumes above functional residual capacity, whereas less than half of the bronchial C-fibers tested were stimulated by inflation to three tidal volumes above functional residual capacity.

In our experiments, pulmonary C-fibers were stimulated by inflating the lung to pressures of 10-15 cm H₂O, whereas bronchial C-fibers were, for the most part, unaffected by this stimulus. Pulmonary C-fibers, when stimulated chemically, have been shown to reflexly decrease heart rate and arterial blood pressure (Coleridge et al., 1965), and therefore were likely to be the vagal afferents responsible for the reflex decreases in heart rate and arterial blood pressure evoked by inflating the lung to pressures of 10-15 cm H₂O (Hainsworth, 1974; Cassidy and Johnson, 1979). In addition, we found that all of the pulmonary and some of the bronchial C-fibers were stimulated when the lung was inflated to 30 cm H₂O. Thus, both types of lung C-fibers were likely to have contributed to the reflex cardiovascular effects evoked by this high inflation pressure (Cassidy et al., 1979; Hainsworth, 1974; Glick et al., 1969).

Our finding that the firing rates of both the pulmonary and bronchial C-fibers were directly proportional to the pressures used to inflate the left lung provides an electrophysiological basis for the finding by several groups of investigators (e.g., Daly et al., 1967; Lloyd, 1978; Cassidy and Johnson, 1979) that the magnitude of the reflex cardiovascular decreases to lung inflation was directly proportional to the
magnitude of the pressures used to inflate the lungs. Likewise, our finding that about half of the pulmonary C-fibers continued to fire throughout the entire period of lung hyperinflation provides a basis for the finding that maintained hyperinflation of the lungs evoked a persistent reflex decrease in arterial blood pressure (Cassidy et al., 1979), an effect which is likely to be buffered by the arterial baroreceptors (Daly et al., 1967; Ott and Shepherd, 1971).

We can only speculate as to why the inflation pressures needed to fire pulmonary C-fibers were lower than those needed to fire bronchial C-fibers. One possible explanation may be the locations of the endings within the lung of the two types of C-fibers. Paintal (1969) has suggested that pulmonary C-fiber endings are located near the alveoli, whereas Coleridge and Coleridge (1977) have shown that some bronchial C-fiber endings are located within the intrapulmonary airways. Thus, it might be expected that pulmonary C-fiber endings are situated within more compliant tissue than are bronchial C-fiber endings; hence, the former might be more susceptible to distortion at lower inflation pressures than might be the latter.

Pulmonary Stretch Receptors

In our experiments, the firing rates of the slowly adapting receptors increased steadily as left airway pressure increased from 2½ to 30 cm H2O, a finding which confirms that reported by Miserocchi and Sant’Ambrogio (1974). On the other hand, the firing rates of the rapidly adapting receptors increased as left airway pressure increased from 2½ to 20 cm H2O, but then gradually decreased as pressure increased further to 30 cm H2O (see Fig. 4B). At present, we can offer no explanation as to why the firing rates of the rapidly adapting receptors were higher at an airway pressure of 20 cm H2O than at airway pressures of either 25 or 30 cm H2O.

Because both the rapidly and slowly adapting receptors were stimulated by the lung inflation pressures that we used, it is possible that these afferents, as well as the lung C-fibers, contributed to the reflex cardiovascular depression evoked by lung inflation. However, stimulation of rapidly adapting receptors has never been demonstrated to evoke reflex cardiovascular effects (Fillenz and Widdicombe, 1972). Moreover stimulation of slowly adapting receptors is believed to increase heart rate (Anrep et al., 1936; Daly and Scott, 1958; Angell-James and Daly, 1978). For example, inflation of the lungs to a pressure of 9 cm H2O or less has been shown to reflexly increase the heart (Anrep et al., 1936), an effect attributed to the stimulation of slowly adapting receptors (Daly and Scott, 1958; Angell-James and Daly, 1978). Our data are consistent with this belief, because the slowly adapting receptors on the average, the only lung afferents stimulated by the same airway pressures as those found by Anrep et al. (1936) to reflexly increase heart rate.

On the other hand, there is evidence that the stimulation of slowly adapting receptors reflexly decreases peripheral vascular resistance, an effect which may contribute to the reflex decrease in arterial pressure evoked by lung hyperinflation. For example, Daly et al. (1967) have shown that increasing airway pressure by as little as 3 cm H2O over resting levels reflexly decreases peripheral vascular resistance, an effect which these investigators have attributed to the stimulation of slowly adapting receptors. Our findings that these receptors were the only vagal afferent endings within the lung that were stimulated by these small increases in airway pressure strongly supports the view held by Daly et al. (1967).

In conclusion, we have found that pulmonary C-fibers were stimulated by lower airway pressures than were bronchial C-fibers; moreover, the firing rates of both types of lung C-fibers were directly proportional to the pressures used to inflate the lung. These findings, therefore, raise the possibility that some pulmonary C-fibers are stimulated by lung volumes that occur during physiological or pathophysiological states, two of which may include heavy exercise and positive end-expiratory pressure ventilation. Whether or not exercise or positive end-expiratory pressure ventilation increases firing from pulmonary C-fibers or causes reflex effects remains to be determined.

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Address for reprints: Marc P. Kaufman, Ph.D., Department of Physiology, University of Texas Health Science Center at Dallas, 5333 Harry Hines Boulevard, Dallas, Texas.

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Kaufman et al. / Stimulation of Lung Afferents by Inflation

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M P Kaufman, G A Iwamoto, J H Ashton and S S Cassidy

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