Early ventilation-perfusion changes in asthma

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Regional pulmonary ventilation (\(\dot{V}\)) and perfusion (\(\dot{Q}\)) were studied nearly simultaneously in subjects just before and after the induction of asthma. Multiple focal \(V/Q\) abnormalities appeared within minutes after asthma was invoked by pollen, methacholine, and exercise. The regional ventilatory abnormalities were greater than those of perfusion although similar in distribution. Direct correlation was obtained between the severity of arterial oxygen desaturation and this regional \(V/Q\) imbalance. Asthma in its earliest stages is characterized by disturbed pulmonary function manifested by airways obstruction, hypoxemia, and hyperventilation as a result of involvement of many small areas of both the pulmonary airways and vasculature.

The mechanism responsible for the development of asthma is considered to be widespread narrowing of the bronchial passages. Confirmation has come from direct observations during bronchoscopy and bronchography, as well as inference from lung biopsy and autopsy specimens.1

After blood gas determinations were introduced, it was found that hypoxemia was present in many patients suffering from asthma.2 At first it appeared that hypoxemia was simply the result of impaired access of oxygen through the narrowed bronchi to the pulmonary capillaries. Later, scans of the lung following intravenous injection of radioactive particles demonstrated maldistribution of the pulmonary circulation (perfusion defects) in patients with asthma.3

When 34 patients in varying stages of asthma were studied with several techniques that permitted observation of both pulmonary ventilation and perfusion within minutes of each other, it was shown that ventilation and perfusion defects were present in focal areas in over 90 per cent.4 The ventilation abnormalities were more extensive than those of perfusion, and both tended to
occur in the same areas. The direct correlation of severity of symptoms with the extent of hypoxemia and ventilation-perfusion defects suggested that V/Q imbalance was responsible for the production of hypoxemia in these patients.

The present study utilized the technique which had been found to be most efficient for studying nearly simultaneous regional V/Q events. We endeavored to determine how soon after an attack of asthma ventilation and perfusion changes occur, what is the regional pattern of early V/Q changes, whether the provocative agent exerts any specific influence, and if the regional perfusion defects are primary or secondary to the ventilation abnormalities.

METHODS

Eleven patients, median age 30, range of 10 to 47 years, volunteered for the studies after the experimental details had been explained to them.

Patients were chosen who had a reasonable chance to be asymptomatic at the time of study without resort to medication and in whom asthma might be provoked by specific means. Each had a history compatible with asthma, but the chief clinical problem was seasonal pollinosis. All had strongly positive reactions by scratch tests (1:20 dilution) to a variety of grass pollens. Their chest x-rays were normal. None had required or taken antiasthma drugs within the prior month or more.

Before (and after) the induction of asthma, the following studies were performed with the patients in the supine position: (1) vital capacity (VC) and forced expiratory volume in one second (FEV1) with the use of a 6.5 L Collins spirometer; (2) peak expiratory flow rate (PEFR) expressed in liters per minute with a Wright peak flowmeter; (3) arterial PO2, PCO2, and pH; and (4) regional ventilation and perfusion studies with radionuclide (133Xe) by single breath tidal volume (Vtv), single bolus intravenous injection (Qxe), and washout (Qwo). Ventilation, perfusion, and perfusion washout scintiphotos were made in the posterior projection with an Anger type scintillation camera (Fig. 1).

When these base-line studies were completed, asthma induction was attempted on 14 occasions in 11 subjects. Three subjects inhaled a fresh extract of a grass pollen, Poa annua, in distilled water via a DeVilbiss No. 40 nebulizer, and 4 subjects received a subcutaneous injection of a fresh solution of methacholine (Mecholyl). In 3 subjects, both methods of induction were utilized on different days. In one case, naturally occurring asthma was induced in a 17-year-old boy who ran up and down several flights of stairs for 10 minutes. Asthma was considered induced when a patient experienced familiar symptoms, when wheezes were heard upon auscultation, and when expiratory airflow rates decreased at least 15 per cent from the base-line determinations. Immediately following the induction of asthma the aforementioned studies (1 to 4) were repeated.

The doses required to provoke asthma were between 100 and 200 protein nitrogen units of Poa annua pollen extract administered orally and from 2.5 to 5.0 mg. of methacholine administered subcutaneously. Because this study involved inflicting some distress in the patients, care was taken to produce minimal symptoms. In each case, by subjective and pulmonary function criteria the patients were returned to their preinduction state or better before they were dismissed from medical attention. The relief of asthma was usually accomplished by time alone and in a few by the inhalation of 125 to 250 µg of isoproterenol. Asthma was easily induced by each technique except in 2 patients who inhaled pollen. These 2 had a history of cough associated with pollinosis, but the diagnosis of asthma had not been established.

The distribution of ventilation (Vtv) was measured during breath holding of 5 mc. of 133Xe inhaled in a normal tidal volume of ambient air. When the radiation count approached background, distribution of perfusion (Qxe) was measured by injecting approximately 5

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†PHO/GAMMA, Nuclear-Chicago Corp.
mc. of radioxenon saline solution into a brachial vein, with the subject's position, lung volume, and radiation count comparable to those in the Vtv study. The perfusion scintiphoto was started 8 seconds after injection in order to allow the radiogas sufficient time to reach the alveoli into which it diffuses. The subject was then allowed to exhale the radiogas which, because of its inherent insolubility, does not re-enter the circulation. Twenty seconds after resumption of breathing of ambient air, the perfusion washout scintiphoto was started. All three studies consisted of 50,000 counts; the time required for collecting these counts was recorded.

A method to roughly quantitate the scintiphoto findings was devised. Each lung field was divided into three equal areas, and each of these six areas was graded 0 to 5 by two radiologists (E. L. S. and L. R. B.). The studies were read independently, and a mean score was obtained. Zero (0) score indicated no detectable abnormality, while a score of 15 represented the absence of function in an area equivalent to one entire lung in the Vtv and Qxe studies. Retention of gas during the Qwo is abnormal, so these studies were quantitated on the basis of presence of radioactivity in the six lung areas. Since even in the normal subject there is some slight nonhomogeneity, scintiphotos were judged abnormal only where clearly different from our extensive experience with normal subjects. The time necessary for collection of 50,000 counts is particularly useful information during the Qwo study. Areas which
Fig. 2

A and B. Abnormalities of regional ventilation compared to regional perfusion. C and D, Abnormalities of the regional differences between ventilation and perfusion compared to regional perfusion washout. The diagonal lines are points of identity. Black dots represent 6 pollen studies, and the open circles 7 methacholine challenges.

are normally perfused but inadequately ventilated will retain radioactivity longer and consequently will decrease the time for collection of 50,000 counts.

A complete study before and after asthma induction was usually performed within 60 minutes and with minimal patient discomfort. In 2 subjects, the Vtv, Qxe, and Qwo studies were repeated after the patients had returned to their asymptomatic state and expiratory airflow rates had normalized.

RESULTS

There were no significant differences prior to the induction of asthma between the pollen and methacholine groups by expiratory flow rates or blood gas measurements (Table I). It was often found that even during the preinduction phase when the subjects considered themselves asymptomatic and their pulmonary airflow rates and blood gases were near normal, small areas of decreased function were evident in both the ventilation and perfusion scintiphotos (Table I, Fig. 2, A).

As shown in Fig. 2, C, prior to the production of asthma both perfusion washout (Qwo) and the regional difference between the ventilation and perfusion scintiphotos (Vtv-Qxe) were only slightly abnormal, indicating good ventilation-
Table I. Flow rate, blood gas, and regional V/Q values in 6 subjects challenged with pollen and 7 with methacholine

<table>
<thead>
<tr>
<th>Asthma induction</th>
<th>Expiratory airflow rates* (% predicted)</th>
<th>Blood gases</th>
<th>V/Q (see text for method of quantitation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEFR</td>
<td>FEV₁</td>
<td>Pco₂ (mm. Hg)</td>
</tr>
<tr>
<td>Before allergen</td>
<td>Mean</td>
<td>90.0</td>
<td>86.6</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>9.5</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>Absolute change</td>
<td>-21.6†</td>
<td>-23.9†</td>
</tr>
<tr>
<td>Before methacholine</td>
<td>Mean</td>
<td>86.1</td>
<td>87.7</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>11.0</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Absolute change</td>
<td>-23.6†</td>
<td>-24.6†</td>
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</tbody>
</table>

Pco₂, P₂o, So₂, and B. E.: partial pressure of arterial CO₂ and O₂, arterial oxygen saturation, and base excess, respectively; V/Q: ventilation/perfusion; Ŷtv: distribution of regional ventilation (single breath, tidal volume); Žxe: distribution of perfusion (single breath, xenon bolus); Žwo: distribution of perfusion washout of perfused xenon.

*PEFR and FEV₁ corrected for body temperature and pressure, saturated.
†Significant changes at the fifth percentile level.

perfusion matching. Regional differences between ventilation and perfusion were calculated by subtracting the perfusion score from the ventilation score. Negative differences (i.e., perfusion worse than ventilation) occurred in 3 cases to a small degree; these were tabulated as zero since only low V/Q areas will appear as abnormalities on the Žwo study.

Following asthma induction, PEFR, FEV₁, arterial P₂o, and per cent oxygen saturation (So₂) decreased significantly in both groups. In each group there was a tendency, not statistically significant, for arterial Pco₂ also to drop. There were no significant changes in base excess (Table I).

In each of the 11 studies in which there was a decrease in per cent predicted FEV₁ of 20 per cent or more, regional ventilation and perfusion defects either appeared or, if already present, worsened (Table I, Fig. 2, B). Perfusion defects tended to increase in proportion to the ventilatory abnormalities, though less markedly in most cases. The changes in regional ventilation and perfusion which were observed following asthma induction, though statistically significant (Table I), were of small magnitude. On the other hand, following the onset of asthma, Žwo worsened much more than Ŷtv-Žxe (Fig. 2, D). This phenomenon is well illustrated in Fig. 3 in which typical Ŷtv, Žxe, and Žwo scintiphotos before and after pollen inhalation are shown. Following asthma induction the intravenously injected radioxenon was diffusely retained in most areas of both lungs indicating that many small areas of decreased ventilation were distributed throughout the lungs. As a consequence of this diffuse retention of radioxenon, only 57 seconds was necessary to collect 50,000 counts, whereas 402 seconds was required to collect 25,000 counts before pollen inhalation.
Fig. 3
A typical set of scintiphotos from a patient in whom asthma was pollen induced. The central clearer area represents the mediastinum. The right lung is on the right side of the photo as if the observer viewed the subject's back. Minor defects are visible in the ventilation (\(VTV\)) and perfusion (\(Qx\)) scintiphotos both before and after pollen administration, notably at the bases. The major change observed is shown on the perfusion washout films (\(Qwo\)). The pattern changes from one of background radiation to diffuse retention of radiogas in both lungs. Confirmatory evidence comes from the marked shortening of the time required to reach given levels of radioactive counts, in this case 57 seconds for 50,000 counts and 402 seconds for 25,000 counts. In the preinduction state counting was stopped at 25,000 since the rate was approaching background. Other pertinent data: 37-year-old man: before asthma, per cent predicted \(FEV_1\), 90, \(P_{O_2}\) 85 mm. Hg; after asthma, the respective values were 44 and 66.

A further indication of the value of \(Qwo\) measurements as a measure of regional ventilation-perfusion relationships can be gained from an analysis of arterial oxygen studies. A significant correlation resulted when changes in \(Qwo\) scintiphotos were compared with changes in arterial oxygen saturation. Note that as \(Qwo\) worsens, arterial oxygen saturation decreases (Fig. 4). Interestingly,
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So₂ = 0.24 Δ₀₋ₐ₀ + 0.40 ± 1.14

r = 0.72
p < 0.05

Fig. 4
Change in arterial oxygen saturation compared to change in regional perfusion washout. Note only 12 studies are plotted, since technical error resulted in loss of one oxygen determination.

So₂ seems to worsen more for a given change in Qᵦ₀ in the pollen experiments than in the methacholine experiments.

There were no significant differences in the size, number, or location of the defects between those in whom asthma was provoked by specific (allergen) and by nonspecific (methacholine) methods. When the studies were repeated in one subject of each group after asthma had been allowed to subside, it was found that their scintiphotos returned to the same state that existed prior to the production of asthma.

The subject whose asthma was provoked by exercise demonstrated smaller changes than those noted in subjects whose asthma had been induced by pollen or methacholine. Measurements were as follows: PEFR and FEV₁ before exercise 490 L per minute and 4.06 L., 30 minutes after exercise 440 and 3.44; pH, Pco₂, Po₂ before 7.43, 33.6 mm. Hg, 97 mm. Hg, and after 7.40, 31.0, and 87, respectively. The scintiphotos also demonstrated the development of focal defects in the distribution of ventilation and perfusion.

DISCUSSION

These studies again demonstrate that asthma, apparently indistinguishable from the clinical state, can be induced in susceptible individuals by either the inhalation of an extract containing a single source of pollen, in this case Poa...
annua, or the injection of a parasympathomimetic agent, methacholine. In one subject asthma was provoked by exercise alone.

These studies also demonstrated that focal ventilation and perfusion abnormalities occurred within minutes of the onset of such episodes of asthma. The severity of the regional ventilation and perfusion defects was considerably less than that which we had observed previously in cases of equal severity of naturally occurring asthma. The defects were randomly distributed, although the \( \dot{V} \) and \( \dot{Q} \) defects usually occurred in the same area, much as we had noted earlier. These regional defects were also similar in asthma provoked by pollen inhalation, methacholine injection, or, in one subject, by exercise. These abnormalities developed and disappeared as the signs and symptoms of asthma were produced and then diminished. This temporal association is additional evidence that induced asthma is a condition closely related to the natural state of asthma and that these abnormalities are part of the early pathophysiologic changes of asthma. One consequence of these regional changes was that the severity of the \( \dot{V}/\dot{Q} \) mismatching tended to correlate with the severity of signs and symptoms and arterial oxygen desaturation.

It appears that the transient and focal ventilation changes are due to narrowing of groups of more susceptible bronchi. They may be rendered more susceptible either by virtue of receiving more of the exciting agent, by containing more reaginic antibodies or cholinergic receptors, or because of shifting reactivity related to complete utilization of effector substances or local accumulation of secretions.

The reasons for the focal perfusion defects are also not settled. In only one lung area out of 156 studied did a focal perfusion defect occur without a ventilation abnormality in the same area. Since regional ventilatory changes occasionally occurred without circulatory changes and ventilatory abnormalities were usually more extensive than those of perfusion, we believe that the circulatory changes were not primary events, i.e., they did not cause the ventilatory changes. Hypoxia secondary to bronchial narrowing is a commonly cited explanation for the production of perfusion defects. We have recently found that partial clearing of the perfusion abnormalities follows the administration of oxygen, supporting only in part the hypoxic theory. Localized increases in transpulmonary pressure might also be a contributory factor. Acidosis and hypercapnia, other causes of pulmonary vasoconstriction, were not present in these studies. Additional explanations for the circulatory defects include the local release of vasoactive substances and the toxic effects of antigen-antibody complexes.

Since hypoxemia in asthma is apparently caused by an imbalance of ventilation and perfusion, our finding that ventilation and perfusion become more or less proportionately worse after asthma induction (Fig. 3, B) was unexpected. However, our system is less sensitive in the detection of areas of decreased radioisotopic concentration ("defect") surrounded by a uniform radioactive area than to the reverse situation; i.e., a radioactive area ("hot spot") is much more easily detected in a nonradioactive ("cold") field. Thus, small areas of
\( \dot{V}/Q \) imbalance will be more readily appreciated on perfusion washout scintiphotos (Qwo) in which the abnormal areas retain activity than on either ventilation or perfusion scintiphotos in which the abnormal areas have decreased activity. To test the sensitivity of our techniques we performed studies on a phantom lung model to determine the resolution capability of our system (to be reported elsewhere). We could not consistently identify a nonradioactive defect or summation of several defects until it was 5 cm. in diameter or greater. On the other hand, retention of radioxenon gas in a "lesion" in concentrations similar to that observed in the Qwo scintiphotos of our subjects easily revealed defects as small as 2 cm. in diameter. As noted in the Results section, the Qwo scintiphotos were much more abnormal after asthma was induced than the regional difference between ventilation and perfusion scintiphotos \((\dot{V}v/Qxe)\) (Fig. 2, D). This finding suggests the presence of multiple small areas of greater impaired ventilation than perfusion. Fig. 3 illustrates the greater sensitivity of the Qwo technique. Confirmation of the concept of many small areas of \( \dot{V}/Q \) imbalance is supported by Fig. 4. Note that the more abnormal the perfusion washout studies are, the greater is the evidence of hypoxemia. Change in oxygen saturation is the proper parameter to compare with change in Qwo, since each area of \( \dot{V}/Q \) imbalance represents a partial right-to-left shunt, and these shunts are linearly related to oxygen content or saturation rather than partial pressure.\(^{10}\)

It would appear a priori that the systemic administration of a chemical, in this case methacholine, would be more likely to produce a generalized effect in the lung than the inhalation of a pollen with its chance deposition in the bronchial tree. Although there was suggestion of this being true in some cases, particularly in Fig. 4, a significant difference in the \( \dot{V}/Q \) distribution between these two groups was not found.* In earlier studies with naturally occurring asthma, many patients had larger focal defects in ventilation than those in this study.\(^4\) Either the inhalation of pollen extract in the present experimental models does not exactly mimic the natural condition and/or the earliest changes are, in fact, generalized with focal defects appearing later, because of shifting reactivity, collections of mucus, etc., as outlined above. Current observations not reported here support, to some extent, the latter hypothesis.

Thus, with due consideration of the limitations imposed by the techniques involved, the following assumptions may be made from this and related studies: Asthma is characterized by selective areas of bronchial narrowing; the lung areas affected may be as small as or smaller than a few centimeters in diameter. Perfusion by capillaries serving some of the hypoventilated alveoli is diminished. This vascular response, from whatever its impetus, is a beneficial one. It tends to shunt blood away from poorly ventilated areas and thus limits the extent of arterial oxygen desaturation. Although hypoxemia appears, there is evidence of overall alveolar hyperventilation (Table I). The hypoxemia which does

*It should be noted that a uniform narrowing of all air passages will result in no change in arterial oxygen saturation if total ventilation is normal or increased. It is necessary that poorly ventilated areas coexist with well-ventilated areas for both shunt (lowered \( S_{O_2} \)) and hyperventilation (lowered \( P_{CO_2} \)) to result.
appear is a consequence of insufficiently reduced perfusion of poorly ventilated areas of the lung. As asthma progresses, hypoxemia increases. More areas of impaired ventilation occur until there is predominant hypoventilation and carbon dioxide is retained in the blood. Only when the bronchial obstruction is fully relieved do these V/Q abnormalities disappear. Patients with minimal asthma have the same random pattern of distribution of ventilation and perfusion in the lung as those with severe disease, the only difference being one of degree. These defects are changeable and transitory either over minutes, days, months, or years.\textsuperscript{4,11}

Since potentially reversible regional ventilation and perfusion defects occur in asymptomatic asthmatic patients, it is possible that some of these patients may benefit from medical therapy even during asthma-free intervals, as originally suggested by Beale and associates.\textsuperscript{2}

REFERENCES