theophylline and occasionally on steroids.

Dr. Coffey: Dr. Gee, do you find any changes in ATPase activity in relation to cytochalasin?

Dr. Gee: Yes. ATPase activity is present in macrophages but cytochalasin B did not affect this.

Dr. Coffey: I would think that more experiments are needed in this area; an effect on ATPase is still a possibility.

Dr. Reed: One of our patients was studied both on and off steroids and no difference in macroaggregated albumin (MAA) clearance was found. Poor MAA clearance was seen in several other disease states which include six subjects with chronic airway obstruction, four with questionable pulmonary emboli while on birth control pills and two renal transplant patients during an acute rejection reaction.

Dr. Clark: Clearance of Tantalum must involve coughing. Have you studied this systematically?

Dr. Nadel: We have studied the cough mechanism by examining which airways are compressed and how this affects shearing of mucus from airways.

Dr. Rogers: Regarding poor MAA clearance, can you really equate radioactivity in the lung to poor clearance, or is MAA present in bronchial mucous glands?

Dr. Reed: I agree that that is a possibility, though very unlikely since the patients received a large dose of potassium iodide to promote excretion of the radioactivity.

SESSION V: STRUCTURE AND FUNCTION

Relation between Pulmonary Arterial Pressure and Pleural Pressure during the Acute Asthmatic Attack*

Solbert Permutt, M.D.

In previous studies on subjects with acute asthmatic attacks, we were impressed with the relation between pleural pressure and pulmonary arterial pressure. I should like to review these findings and their implications.

During the asthmatic attack, there was a significant increase in pulmonary arterial pressure relative to pleural pressure, both during inspiration and expiration. The mean pulmonary arterial minus pleural pressure approximately doubled. It is not the pulmonary arterial pressure relative to atmospheric pressure, the conventional method of measurement, that is important, but rather the pulmonary arterial pressure relative to pleural pressure. The outer surface of the right ventricle is exposed to pleural pressure. Thus, from a hemodynamic standpoint, any significant increase in pulmonary arterial pressure relative to pleural pressure is pulmonary hypertension as far as the right ventricle is concerned, for the right ventricle has to produce more muscular tension to pump the blood through the lungs. We conclude, therefore, from our studies that pulmonary hypertension occurs during the acute asthmatic attack.

What is the mechanism of the development of pulmonary hypertension during the attack? Certainly hypoxia and an increased cardiac output contribute, but these changes were relatively mild in the patients we studied. One striking feature which suggests that a mechanical factor is involved was the close association between the peak negative pleural pressure achieved during inspiration and the level of the pulmonary arterial pressure relative to pleural pressure seen during expiration. In all subjects studied, there was nearly a one-to-one correspondence between the systolic pulmonary arterial pressure during expiration minus the pleural pressure during expiration to the peak negative pleural pressure reached during inspiration.

These relations are shown in detail for one subject in Figure 1. Over a period of approximately 30 minutes, with three separate inhalations of aerosolized ragweed of about one minute in duration, his vital capacity fell from about 4.5 L to a little over 1 L. During this same period, the expiratory pleural pressure rose to about 7 cm H2O while the inspiratory pleural pressure showed increasingly negative values until a pressure of approximately −30 cm H2O was reached. The changes

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in pulmonary arterial pressure relative to pleural pressure during expiration showed a near one-to-one correspondence to the changes in inspiratory pleural pressure.

We were very surprised at the changes in pleural pressure, as estimated by the pressure within an esophageal balloon, in patients in whom we induced acute asthmatic attacks. We had expected the major changes to be in expiratory pressure, but the inspiratory pleural pressure fell on the average nearly 20 cm H$_2$O, whereas the increase in expiratory pleural pressure averaged less than 4 cm H$_2$O. No subject showed an expiratory pleural pressure greater than 7 cm H$_2$O, as was present in this subject.

At first glance, it seems to make no sense that the pulmonary arterial pressure relative to pleural pressure during expiration should be so highly correlated to the degree of negativity in pleural pressure reached during inspiration. Is not this a comparison of apples and oranges? I suspect that the rise in pulmonary arterial pressure relative to pleural pressure is linked to the rise in alveolar pressure relative to pleural pressure.\(^2\)

In Figure 1, the vertical distance between the inspiratory pleural pressure line and the abscissa is close to the static transpulmonary pressure at end inspiration, so the pressure in the alveoli must have been approximately atmospheric. Thus, there was a progressive increase in the static transpulmonary pressure as the attack proceeded, and this must have been due to a large increase in the volume of the lungs at end inspiration. Since the tidal volume did not change much, there must also have been a large increase in the end-expiratory lung volume.

We do not have a measure of the pressure in the alveoli at end expiration, but it must have been about as much above the pleural pressure as the static transpulmonary pressure during inspiration, less the few cm H$_2$O due to the 752 ml smaller lung volume. Thus, the vertical distance between the inspiratory pleural pressure curve and the abscissa is probably only a little greater than it would be for the curve of the alveolar pressure relative to pleural pressure during expiration. Since the pulmonary arterial pressure is also measured relative to pleural pressure during expiration, the vertical distance between the upper two curves is close to the difference between pulmonary arterial pressure and alveolar pressure; and it can be seen that this difference remained essentially constant. Therefore, the pulmonary hypertension was probably due to the rise in alveolar pressure relative to pleural pressure. If this interpretation is correct, it is the increase in lung volume, which causes an increase in the static transpulmonary pressure, that is responsible for the pulmonary hypertension; for this is the cause of the rise in alveolar pressure relative to pleural pressure.

If this interpretation is correct, a normal subject who voluntarily breathes at a lung volume near total lung capacity will have pulmonary hypertension just as the asthmatic subject does during his attack. This has not been generally appreciated because during spontaneous respiration near total lung capacity, the pulmonary arterial pressure does not change very much in relation to atmospheric pressure. We are so used to thinking about pulmonary arterial pressures in relation to atmospheric pressure and so little in relation to pleural pressure that we overlook the obvious fact that if the pulmonary arterial pressure did not change relative to atmospheric pressure, the right ventricle must be placed under considerable strain. The only way the normal subject can breathe near total lung capacity while keeping alveolar pressure near atmospheric pressure is to keep pleural pressure at a very negative value (around $-30$ cm H$_2$O) through the use of inspiratory muscles. The right ventricle is, therefore, markedly afterloaded.

Indeed, if we could devise a valve which would stay completely closed whenever the lung volume was below a specific value near total lung capacity and was completely open whenever the lung volume was above this value, we would simulate nearly all of the symptoms and measurements.
found in a patient with a severe asthmatic attack. He would have a markedly reduced vital capacity, which would not be produced by breathing through a narrow tube of high resistance. His work of breathing would markedly increase. For instance, even if there were no change in resistance or compliance, an increase in end-expiratory lung volume of 2500 ml with constant tidal volume of 500 ml would require an 11-fold increase in the inspiratory work of breathing. He would require a greater oxygen consumption and would be exceedingly dyspneic. His cardiac output would be increased in proportion to the increased oxygen consumption. He would have significant pulmonary hypertension (relative to pleural pressure). His inspiratory resistance would be lower than expiratory resistance, which would be normal at total lung capacity, but would rise sharply toward infinity during expiration.

The pattern seen in an asthmatic attack could be largely explained if the airways between the lobar bronchi and alveoli were nearly completely closed at a low static transpulmonary pressure and lung volume, but were close to their normal dimensions when the static transpulmonary pressure was increased enough. The relations between volume, pressure, and flow have these characteristics, at least as a first approximation. Recent work of Murtagh et al. shows that exposure of bronchi of dogs to methacholine can cause complete closure of segmental airways up to distending pressures of more than 50 cm H2O. Nevertheless, once the airways are open, a high distending pressure produces essentially normal dimensions.

**Summary**

We suggest that the acute asthmatic attack can be characterized as follows. The segmental and smaller bronchi become markedly constricted with a tendency toward complete closure. The constriction can be opposed by an increase in the static transpulmonary pressure which increases the distending pressure of the bronchi. The increase in distending pressure is brought about by the patient breathing nearer his total lung capacity. If he can breathe at a high enough level, the bronchi approach their original dimensions. Even so, during forced expirations these same airways have a tendency to collapse more readily than normal bronchi as the pressure within them falls relative to the pleural pressure with increasing flow. Breathing much nearer total lung capacity is perhaps the principal cause of the early circulatory and metabolic changes: increased oxygen consumption, increased cardiac output, and pulmonary hypertension. If breathing can occur at a sufficiently high lung volume, gas exchange is unaltered; but some areas tend to remain underventilated with resulting hypoxia.

**References**


**Discussion**

Dr. Pearlman: How severe were the attacks? I assume these were done in Denver. In your patient, the PaO2 didn’t decrease much and even in mild to moderate asthmatic attacks in children we ordinarily see a significant decrease in PaO2.

Dr. Permutt: The patients had moderate obstruction before challenge as evidenced by an average FEV1/VC of 51 percent. The VC decreased on the average from 4.5 to 1.4 L. The average decrease in PaO2 for the group was 14 mm Hg.

Dr. Lyons: We have noticed that during an asthmatic attack, P pulmonale may develop on the ECG tracing. Cardiac catheterizations have demonstrated increased PA pressures. We have obtained results similar to yours. We also concluded that the increase in PA pressure was probably due to the alveolar pressure change. We also gave isoproterenol at the same time. Unfortunately, we didn’t observe a change in the PA pressure, although airway resistances did decrease.

Dr. Godfrey: Did you get pulsus paradoxicus in the arterial pressure?

Dr. Permutt: We did have an indwelling arterial needle and found huge variations of the systemic arterial pressure with respiration.

Dr. Butler: In corroborations of your speculation on the causes of the pulmonary hypertension, we have previously reported pulmonary artery and pleural pressures at high lung volumes produced by external suction chest inflation (Med Thorac 19:261, 1962). We found that the pulmonary artery pres-
Site of Airway Obstruction in Asthma*

Peter J. Macklem, M.D., P. J. Despas, M.D. and M. Leroux, M.D.

We measured maximum expiratory flow volume (MEFV) curves and pulmonary resistance (R₁) in normal subjects, asthmatics and chronic bronchitics while breathing air and while breathing an 80 percent helium-20 percent oxygen mixture. In normal subjects and some asthmatics (responders), maximal expiratory flow rates increased on He₂. Therefore, the resistance upstream from equal pressure points (Rus) in these subjects was density dependent and was principally due to turbulence and convective acceleration. In bronchitics and the other asthmatics (nonresponders) maximal expiratory flow rates did not change. Therefore, Rus in these subjects was mostly due to fully-developed laminar flow. The response to He₂ did not correlate with initial values of R₁, the initial MEFV curves or the response to bronchodilators. On subsequent retesting responders remained responders and nonresponders remained nonresponders.

In general R₁ decreased on He₂ in responders and remained unchanged in nonresponders, although there were some exceptions. If Rus and R₁ are principally due to fully developed laminar flow in nonresponders, then the major site of obstruction must be in peripheral airways where a laminar flow regimen exists. When Rus and R₁ are density dependent as in the responders, the site of obstruction must be in larger airways. We conclude that: 1) the site of obstruction varies among asthmatics; 2) measurement of the usual parameters of lung mechanics cannot detect the site when pulmonary resistance is elevated; 3) measurement of R₁ and MEFV curves breathing gas of different densities can be used to determine whether obstruction is in central or peripheral airways.

Discussion

Physician: Is there any correlation of responders to response to bronchodilators?

Dr. Macklem: No. Response to changing gas density might be a good way to pick up peripheral airway obstruction. The equal pressure point should be further upstream in these patients. Even though resistance per unit length is increased, the length is shorter so, overall, upstream resistance may not be much increased and maximum flow may not be greatly affected. However, more of the upstream resistance should be due to fully developed laminar flow so that less density dependence would be expected.

Dr. Chester: You used the term "fully developed flow." My understanding is that "fully developed flow" refers to distances over 15-20 cm. Branches of bronchi are closer together than that; therefore, is "fully developed flow" a misnomer?

Dr. Macklem: No. Fully developed laminar flow occurs a distance downstream from branch points equal to 0.26 times the Reynolds number times the radius. In the peripheral airways the Reynolds numbers and radii are small so that fully developed laminar flow exists only a short distance from branch points.

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