Bronchoconstriction in the Presence of Pulmonary Embolism

By Victor Gurewich, M.D., Duncan Thomas, M.D., Myron Stein, M.D., and Stanford Wessler, M.D.

IMPRESSIVE pathologic evidence has accumulated that suggests that recurrent showers of small pulmonary emboli are commonly undetected clinically.1–3 The eventual development of obstructive pulmonary hypertension and cor pulmonale in some cases is well known, but effective therapy of this late stage of the disease is not available. It has been reported, however, that prompt treatment can result in reversal of pulmonary hypertension.4 Unfortunately, the early detection of pulmonary emboli is difficult, especially when not associated with overt pulmonary infarction.

In the course of a recent study in dogs in which autologous venous thrombi were released to the lungs, changes in pulmonary mechanics indicative of bronchoconstriction and increased pulmonary resistance were found.5 These observations prompted an investigation of comparable measures of pulmonary function in patients whose clinical findings suggested a diagnosis of pulmonary thromboembolism. It is the purpose of this communication to document the existence of bronchoconstriction in seven patients with pulmonary embolism, and to indicate the clinical and theoretical implications of this relationship. Our observations suggest that the measurement of bronchoconstriction may be a useful aid to the early detection of pulmonary emboli.

Methods and Materials

The seven patients ranged in age from 28 to 60 years; five were women. Each patient was examined by at least one of us. Electrocardiograms, chest roentgenograms, and reports of fluoroscopic examinations of the heart and lung were available in all patients. The following pulmonary function studies were completed in all patients: vital capacity, nitrogen-meter single-breath tests,6 alveolar PCO2,7 maximal expiratory flow rate,8 1-second forced expiratory volume, and maximum breathing capacity. Pulmonary resistance9 was measured in three patients. In four of the patients, lung mechanics were measured before and after the intravenous or subcutaneous administration of heparin.10 Autopsy findings were available on the one patient who died during the course of this study.

Results

The clinical, radiologic, and electrocardiographic findings are summarized in table 1. Four features were common to all patients: exertional or paroxysmal dyspnea, anginal or pleuritic chest pain, accentuated pulmonic component of the second heart sound, and acute deep venous thrombosis of the legs. In four subjects, paroxysmal dyspnea was associated with bouts of pleuritic chest pain. In one patient, a systolic impulse was palpable over the pulmonic valve area. Expiratory wheezing was heard in one patient during an episode of paroxysmal dyspnea and chest pain. All patients had deep venous thrombosis evidenced by localized calf tenderness on posteroanterior pressure, more marked in one extremity. In addition, four patients had unilateral ankle edema, and a fifth patient had migratory superficial and deep phlebitis involving three extremities.

Roentgenograms of the chest showed right ventricular enlargement in three subjects with

*Concentrated aqueous heparin for subcutaneous injection was kindly supplied in the form of Lipo-Hepin by Riker Laboratories, Inc., Northridge, California.
### Table 1

**Summary of Clinical and Laboratory Findings**

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>28 F</td>
<td>57 F</td>
<td>60 F</td>
<td>36 F</td>
<td>41 F</td>
<td>41 M</td>
<td>48 M</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Pleuritic</td>
<td>Pleuritic &amp; anginal</td>
<td>Anginal</td>
<td>Pleuritic &amp; anginal</td>
<td>Pleuritic</td>
<td>Pleuritic</td>
<td>Pleuritic</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fever</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Audible wheezing</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Accentuated pulmonic second sound</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluoroscopy and chest x-ray</td>
<td>Normal</td>
<td>Pulmonary hypertension &amp; right ventricular hypertrophy</td>
<td>Pulmonary hypertension &amp; right ventricular hypertrophy</td>
<td>Normal</td>
<td>Normal</td>
<td>Pulmonary hypertension &amp; right ventricular hypertrophy</td>
<td>Normal</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Normal</td>
<td>Right ventricular hypertrophy</td>
<td>Right ventricular hypertrophy</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td>Normal</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
<td>Not done</td>
<td>Elevated</td>
</tr>
<tr>
<td>Pulmonary mechanics</td>
<td>Bronchoconstriction</td>
<td>Bronchoconstriction</td>
<td>Bronchoconstriction</td>
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<td>Bronchoconstriction</td>
<td>Bronchoconstriction</td>
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</tr>
<tr>
<td>Autopsy</td>
<td>Pulmonary emboli</td>
<td>Pulmonary emboli</td>
<td>Pulmonary emboli</td>
<td>Pulmonary emboli</td>
<td>Pulmonary emboli</td>
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</table>
### Table 2

**Pulmonary Function Studies Demonstrating Bronchoconstriction and the Responses to Heparin**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age &amp; sex</th>
<th>Vital capacity ml. &amp; % predicted</th>
<th>Single breath test in % N₂</th>
<th>pCO₂ mm. Hg</th>
<th>Maximal expiratory flow rate L./min.</th>
<th>Pulmonary resistance em. H₂O/L./sec.</th>
<th>1-Second forced exp. vol. ml.</th>
<th>Maximum breathing capacity L./min.</th>
<th>Arterial alveolar pCO₂ difference mm. Hg</th>
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<tr>
<td></td>
<td></td>
<td>Pred. % in ()</td>
<td></td>
<td></td>
<td>Before heparin</td>
<td>After heparin</td>
<td>Before heparin</td>
<td>After heparin</td>
<td>Pred. values in ()</td>
</tr>
<tr>
<td>Norm. val.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 F</td>
<td>2370 (78)</td>
<td>2.1</td>
<td>28</td>
<td>160</td>
<td>220*</td>
<td>190†</td>
<td>1980</td>
<td>2080†</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57 F</td>
<td>1960 (77)</td>
<td>2.6</td>
<td>26</td>
<td>160</td>
<td>3.2</td>
<td>2.2*</td>
<td>1720</td>
<td>2030†</td>
</tr>
<tr>
<td>3</td>
<td>60 F</td>
<td>1770 (73)</td>
<td>2.3</td>
<td>35</td>
<td>110</td>
<td></td>
<td></td>
<td>1370</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36 F</td>
<td>2160 (74)</td>
<td>1.3</td>
<td>37</td>
<td>70</td>
<td>220*</td>
<td>220†</td>
<td>1080</td>
<td>1740†</td>
</tr>
<tr>
<td>5</td>
<td>41 F</td>
<td>2220 (80)</td>
<td>0.5</td>
<td>34</td>
<td>150</td>
<td></td>
<td></td>
<td>1800</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>41 M</td>
<td>2730 (55)</td>
<td>0.2</td>
<td>34</td>
<td>190</td>
<td>3.8</td>
<td></td>
<td>2300</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48 M</td>
<td>2210 (57)</td>
<td>1.5</td>
<td>40</td>
<td>180</td>
<td>220*</td>
<td>4.4</td>
<td>1670</td>
<td>1710†</td>
</tr>
</tbody>
</table>

*Values obtained 5 minutes after intravenous heparin.
†Value obtained after 10 days (pt. 1) and 21 days (pt. 4) of subcutaneous heparin administered every 12 hours.
‡Value obtained after discontinuation of heparin therapy.
features characteristic of pulmonary hypertension, including dilatation of the main pulmonary and hilar arteries and decrease in size of the peripheral vessels. In one of these patients partial obstruction of one of the main pulmonary arteries was visualized by angiography.

Two patients had electrocardiographic findings consistent with the diagnosis of right ventricular hypertrophy. In no individual was there electrocardiographic evidence of acute cor pulmonale, myocardial infarction, or ischemia.

The pulmonary function studies are summarized in table 2. Evidence for bronchoconstriction was obtained in each subject, as demonstrated by diminished maximal expiratory flow rate, one-second forced expiratory volume, and maximum breathing capacity. Pulmonary resistance (patients 2, 6, and 7) and alveolar-arterial pCO₂ differences (patients 3 and 6) were found elevated when they were measured.

In four patients (patients 1, 2, 4, and 7), measurements of pulmonary function were repeated 5 minutes after an intravenous injection of 5,000 units of heparin. The subsequent bronchodilatory response, as reflected by the increased maximal expiratory flow rate or one-second forced expiratory volume in patients 1, 4, and 7, and the decreased pulmonary resistance in patients 2 and 7, are shown in table 2. Patients 1 and 4 were subsequently treated for periods of 10 and 21 days, respectively, with twice daily subcutaneous injections of 12,000 units of concentrated, aqueous heparin. During this period, both subjects remained symptomatically improved with much less shortness of breath and no recurrence of paroxysmal dyspnea or orthopnea. The clinical improvement occurred promptly and was striking in both patients. No drugs other than heparin were given. Before heparin therapy was stopped, measurement of pulmonary mechanics was repeated, and the initial improvement was found to have been maintained in patient 4 and enhanced in patient 1 (table 2). In patient 1, pulmonary studies were repeated 1 week after heparin had been discontinued; at this time, the initial low maximal expiratory flow rate and the 1-second forced expiratory volume were again observed (table 2), together with a recurrence of symptoms.

One of the patients died within 24 hours following a cesarean section. Autopsy revealed microscopic evidence of antemortem thrombi in several small pulmonary arteries. No other findings were discovered to explain the cause of death or the episodes of pleuritic and anginal pain with marked dyspnea and orthopnea. The coronary arteries were normal.

Animal Studies

In a study in dogs, bronchoconstriction was regularly produced by the release of autologous venous thrombi to the lungs. The prior administration of 5,000 units of aqueous heparin in six dogs completely prevented the bronchoconstriction. This observation is illustrated by figure 1, which represents a typical experiment.

Discussion

The significance and possible diagnostic importance of bronchoconstriction among patients with pulmonary embolism have not pre...
BRONCHOCONSTRICTION IN PULMONARY EMBOLISM

BRONCHOCONSTRICTION has previously been considered, although clinical and laboratory evidence of bronchoconstriction among such subjects has been observed. Bronchoconstriction is a nonspecific finding and may, of course, be seen among patients with allergic or intrinsic asthma, bronchitis, pulmonary fibrosis, emphysema, pneumoconiosis, left-sided heart failure, and even in normal subjects immediately after the inhalation of dust or tobacco smoke. In each patient in this study, however, these diagnoses were unlikely on the basis of the historical data and the physical and x-ray findings. Moreover, the presence of pulmonary emboli was strongly indicated on clinical grounds, and was clearly established in one patient in whom necropsy data were available. When other causes of increased lung resistance can be eliminated, the presence of bronchoconstriction raises the diagnostic possibility of pulmonary emboli. Although the causes of bronchoconstriction are many, the clinical finding of wheezing may be too readily dismissed as "intrinsic asthma," when it in fact represents recurrent episodes of pulmonary embolism. In this regard, it may be pertinent to recall the old aphorism that all that wheezes is not asthma.

In dogs, the release of autologous venous thrombi to the pulmonary arteries regularly produced changes indicative of marked bronchoconstriction and increased pulmonary resistance. Similar changes in pulmonary function indicative of bronchoconstriction have been obtained in dogs by other investigators using foreign-body emboli. Of particular interest is our finding that the intravenous injection of heparin prior to the release of thrombi completely prevented these changes in pulmonary function (fig. 1). The changes in pulmonary mechanics found in these animal experiments resembled those observed in the patients in this study. The complete inhibition of the bronchoconstriction by heparin in dogs was not seen among our patients, but the clinical observations suggest that heparin reduces the bronchoconstriction associated with pulmonary emboli in man. The site of action or the specificity of heparin in interfering with bronchoconstriction has not yet been established.

The mechanism whereby pulmonary emboli produce bronchoconstriction is unknown. Severeinghaus recently demonstrated in dogs that localized bronchoconstriction occurs secondary to decreased perfusion of alveolar capillaries. He observed, however, that ventilation with 1 or 2 percent carbon dioxide completely reversed this bronchoconstriction. In our patients, the alveolar carbon dioxide was of sufficient concentration to make it unlikely that a decrease in carbon dioxide tension was the operative mechanism. Halmagyi and Colebatch, using foreign-body emboli, have indicated that the induced bronchoconstriction is not mediated through the autonomic nervous system.

It has been suggested that pharmacologically active substances may be released at sites of thromboemboli, and lead to the excitation of specific chemoreflexes. Such agents include acetylcholine, histamine, serotonin, and the plasma kinins, all of which have bronchoconstrictor properties. The present study suggests that the bronchoconstriction occurring with pulmonary emboli may be related to the presence of a substance whose activity or release is blocked by heparin.

Infusions of serotonin, as well as fresh blood clots, produce in the dog a similar picture of pulmonary hypertension, peripheral hypotension, and hyperpnea. Heparin protects dogs against these effects possibly by preventing the release of serotonin from platelets, or by a direct antagonistic effect on serotonin. Whether heparin protects dogs against the bronchoconstrictor effects of serotonin has not, to our knowledge, been reported. Bradykinin does not produce bronchoconstriction in the dog and heparin has, moreover, been reported to enhance plasma kinin formation in vitro. Our finding that heparin blocks bronchoconstriction produced by pulmonary emboli in the dog suggests that bradykinin is not directly responsible for the observed bronchoconstriction.

It is of particular interest that the activation of the initial blood procoagulant, Hage-

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man factor (factor XII), has been shown to be an essential preliminary step for plasma kinin formation, \(^{30}\) the elaboration of intrinsic thromboplastin, \(^{31}\) the agglutination of platelets, with release of serotonin, \(^{22,\ 32}\) and, finally, for the formation of certain types of venous thrombi. \(^{33}\) The interesting possibility therefore exists that a common pathway may be responsible for both the initiation of intravascular coagulation and the production of bronchoconstriction. Whatever the mechanism may finally prove to be, the demonstration of bronchoconstriction in selected patients appears to represent an objective and sensitive, although nonspecific, index of pulmonary embolism.

**Summary**

In a group of seven patients with pulmonary embolism, evidence of bronchoconstriction was found. Heparin appeared to relieve partially the observed airway obstruction. A possible common mechanism for the initiation of intravascular coagulation and the production of bronchoconstriction was considered. When other causes can be eliminated, the detection of bronchoconstriction may serve as a useful index for the early recognition of pulmonary emboli.

**References**


21. Dawes, G. S., and Comroe, J. H., Jr.: Chemo-

Imperturbability

Imperturbability means coolness and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of great peril, immobility, impassiveness, or, to use an old and expressive word, phlegm. It is the quality which is most appreciated by the laity though often misunderstood by them; and the physician who has the misfortune to be without it, who betrays indecision and worry and who shows that he is flustered and flurried in ordinary emergencies, loses rapidly the confidence of his patients...

In a true and perfect form, imperturbability is indissolubly associated with wide experience and an intimate knowledge of the varied aspects of disease. With such advantages he is so equipped that no eventuality can disturb the mental equilibrium of the physician; the possibilities are always manifest, and the course of action clear. From its very nature this precious quality is liable to be misinterpreted, and the general accusation of hardness, so often brought against the profession, has here its foundation. Now a certain measure of insensibility is not only an advantage, but a positive necessity in the exercise of a calm judgment, and in carrying out delicate operations. Keen sensibility is doubtless a virtue of high order, when it does not interfere with steadiness of hand or coolness of nerve; but for the practitioner in his working-day world, a callousness which only thinks of the good to be effected, and goes ahead regardless of smaller considerations, is the preferable quality.—OSLER (Aequanimitas, 1889). The Quiet Art: A Doctor's Anthology. Compiled by Dr. Robert Coope. Edinburgh & London, E. & S. Livingstone Ltd., 1952, p. 205.
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