CLINICAL SIGNIFICANCE OF PULMONARY FUNCTION TESTS

Pulmonary Function after Uncomplicated Myocardial Infarction*

Charles A. Hales, M.D.** and Homayoun Kazemi, M.D.

Derangement of pulmonary function following myocardial infarction is related to the severity of hemodynamic dysfunction. Abnormalities of pulmonary function appear even in patients without clinical or radiologic evidence of congestive failure. There is a reduction in vital capacity and rates of air flow. There is evidence for dysfunction of "small airways" and diminished ventilation to dependent parts of the lung. Total lung capacity may be normal or reduced, and residual volume may be increased slightly in uncomplicated myocardial infarction. Residual volume falls with more pronounced myocardial congestion and edema. Distribution of pulmonary perfusion is altered after myocardial infarction, with a shift of perfusion away from the dependent parts of the lung (bases) towards the apices. Pulmonary gas exchange is impaired, with hypoxemia (due to both ventilation-perfusion inequality and increased shunting); and the diffusing capacity for carbon monoxide is diminished. Dead space is increased. The basic pathophysiologic mechanism responsible for abnormalities of pulmonary function is increased pulmonary water, which may be very minimal with uncomplicated myocardial infarction and stay primarily in the pulmonary interstitial space, but becomes progressively more severe with eventual alveolar flooding and marked impairment of pulmonary function.

In 1938, W. B. Bean1 noted dyspnea to be a complaint in patients with acute myocardial infarction. He observed that the vital capacity (VC) was frequently reduced and that cyanosis and an ashen color carried a grave prognosis. Since 1938, the knowledge about myocardial infarction and its effect on the lung has increased enormously. Disturbances in pulmonary function correlate with the severity of hemodynamic abnormalities following acute myocardial infarction, although some of the disturbances may persist to some degree long after hemodynamic dysfunction has disappeared.2-8 Even in uncomplicated myocardial infarction with no radiographic or clinical evidence of left ventricular failure, subtle abnormalities of pulmonary function and mild hypoxemia occur.2-8

Hemodynamic events and their effects on the lung following myocardial infarction may be divided into the following three main categories, depending on the severity of pulmonary congestion and left ventricular failure: (1) cardiogenic shock; (2) pulmonary congestion and heart failure based on clinical and radiographic evidence; and (3) no apparent evidence of heart failure or pulmonary congestion. Effects of cardiogenic shock on the lung will not be examined in this review, nor will pulmonary embolism, drug reactions, and secondary bacterial pneumonia, which may complicate myocardial infarction. Emphasis will be placed on the physiologic abnormalities of the lungs and pulmonary circulation in myocardial infarction in the absence of shock, and evidence from different sources will be compiled to indicate that the observed pulmonary dysfunction following myocardial infarction is due to increased content of water in the lungs. Abnormalities of pulmonary function because of congestive failure of varying causes have been described, and many of the changes are similar to those seen following myocardial infarction.

VENTILATORY TESTS

The reported reduction in VC in congestive heart failure correlates well with the severity of failure.9,10 Following acute myocardial infarction, the changes in VC are similar to those described in pulmonary congestion from other causes.8,12 In 78 patients hos-
pitalized at the Massachusetts General Hospital from 1968 to 1974 with acute myocardial infarction without congestive heart failure by radiographic or clinical examination, the VC in the first week after infarction was reduced, although still in the low normal range (group 1 in Table 1). In 15 patients with clinical evidence of pulmonary congestion on admission that had cleared by the time of study (group 2), the VC was slightly lower at 76.4 percent of the predicted normal value. In 12 patients who had mild congestive heart failure at the time of the study (group 3), the VC was reduced to 71.8 percent of predicted.

Serial measurements in 12 of the 78 patients with no detectable congestion (group 1) revealed a VC of 83 percent of predicted at two to four weeks after the myocardial infarction, a value which was not statistically different from the 81 percent found on admission. At examination two to six months later the VC in these patients had increased to 93 percent of predicted, demonstrating recovery with time, such as occurs in congested lungs due to other causes.

The forced expiratory volume in the first second (FEV₁) and the maximum expiratory flow rate are also reduced with pulmonary congestion, although the ratio of FEV₁ over VC expressed as a percentage (FEV₁/VC %) is usually less affected. The peak expiratory flow rate and the FEV₁/VC% were normal in 78 patients at the Massachusetts General Hospital studied in the first week following infarction in whom no evidence of pulmonary congestion was noted (Table 1); however, in 12 of these patients followed serially, there was a small rise in the peak expiratory flow rate and FEV₁/VC% with time (Fig 1). The VC in these same patients was initially more abnormal than the flow rates and likewise showed greater improvement with time (Fig 1). In 15 patients with congestion still present at the time of examination, the peak flow rate was reduced at 77.4 percent of predicted (P < 0.01), and the FEV₁/VC% was 72.7 percent (normal value, 75 percent or greater).

Table 1—Ventilatory Results in First Week after Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Data</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>78</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>VC, percent of predicted **</td>
<td>84.2</td>
<td>76.4</td>
<td>71.8</td>
</tr>
<tr>
<td>Peak flow rate, percent of predicted **</td>
<td>95.8</td>
<td>94.0</td>
<td>77.4</td>
</tr>
<tr>
<td>FEV₁/VC%</td>
<td>7.46</td>
<td>7.44</td>
<td>72.7</td>
</tr>
</tbody>
</table>

*Group 1, no congestive heart failure detectable during admission; group 2, initial evidence of congestive heart failure that cleared by time of study; and group 3, mild persistent congestive heart failure at time of study. **Normal predicted values from Kory et al.16

Dysfunction of Small Airways

Tests of abnormal function of "small airways," such as increased closing volume (CV), and frequency dependence of resistance, commonly occur following myocardial infarction, even in the absence of apparent pulmonary congestion and in patients in whom the VC and standard rates of flow are normal. The abnormalities of "small airways" detected by these tests could be due to intrinsic changes in the small airways, such as mucosal edema or muscular spasm, or could be due to changes in transmural pressure of the airways caused by peribronchial and interstitial edema. Changes in regional pulmonary compliance or alveolar collapse might also account for some of the abnormalities interpreted as dysfunction of small airways. Active bronchoconstriction is unlikely to be the cause of the abnormality, since bronchodilator drugs fail to reverse the abnormal frequency-dependent measurement of airway resistance (Raw). In the animal models of early edema, there is a peribronchial and perivascular cuff of edema causing the airways to collapse at higher than normal transpulmonary pressures, although pulmonary compliance is still normal; however, with more severe edema, pulmonary compliance decreases, resulting in decreased transpulmonary pressure, especially at the bases, where edema would be greatest and where transpulmonary pressure is lowest. Thus, although the test for CV and the frequency dependence of the measurement of Raw may well reflect abnormal function of
small airways after a myocardial infarction, especially in states of minimal edema, they can also be explained by other pulmonary changes that do not involve the airways.

Since closure of airways tends to occur in dependent pulmonary zones, ventilation to the bases in the erect patient after a myocardial infarction should decrease. Relative distribution of ventilation measured with inhaled radioactive $^{133}$Xenon in 20 patients with acute myocardial infarction at the Massachusetts General Hospital have confirmed a small, but statistically significant, reduction in ventilation at the base of the lung ($P < 0.05$) when the patient is in the erect position.

**PULMONARY VOLUMES**

The total lung capacity (TLC) is normal in mild congestion but becomes reduced as the degree of congestion worsens.$^{11}$ Data on residual volume (RV) are less consistent, with some series reporting increased, $^{18}$ normal,$^{19}$ or reduced values,$^{20}$ but regardless of the change, the ratio of RV/TLC is usually increased; however, in an individual subject the RV does seem to decrease with worsening congestion.$^{20}$ The TLC was preserved at 93 percent of predicted in 43 patients with acute uncomplicated myocardial infarctions studied at the Massachusetts General Hospital, and the RV was normal at 105 percent of predicted; however, if the RV was examined in relation to the presence or absence of abnormal closure of airways, a distinct difference was apparent. In 14 patients without congestion and with normal function of “small airways” by the test for closing capacity (CC), the RV was 90 percent of predicted. In 29 subjects with dysfunction of “small airways” (CC greater than two standard deviations above predicted), the RV was 114 percent of predicted ($P < 0.04$). Thus, the subjects with dysfunction of the small airways had a greater volume of air trapped at the end of expiration, thereby causing a high RV. This observation may explain the variety of values for RV that have been found in patients with pulmonary congestion. It may be that mild or inapparent pulmonary congestion causes either no dysfunction of small airways and, therefore, a normal RV, or such congestion may cause dysfunction of small airways with an increased volume of trapped gas and a high RV; however, with more severe congestion, the RV can be reduced.

**PULMONARY PERFUSION**

In erect man, perfusion is greatest at the pulmonary bases because of the effect of gravity; however, following acute myocardial infarction, studies of the distribution of perfusion using $^{133}$Xenon have revealed a relative shift of perfusion away from the pulmonary bases toward the apices, even in patients with no evidence of pulmonary congestion and with normal cardiac output and pulmonary wedge pressure at the time of the studies of the distribution of perfusion.$^{4,6}$ The distribution of perfusion returns towards normal by two weeks after myocardial infarction but even at six months may not have become completely normal, indicating perhaps a permanent change in regional pulmonary vascular resistance at the pulmonary base. Shifts in perfusion away from the pulmonary base have also been described in experimental myocardial infarction in animals.$^{22}$

**PULMONARY GAS EXCHANGE**

Arterial hypoxemia and an increased alveolar-arterial oxygen pressure gradient ($P(A-a)O_2$) with the patient breathing room air or 100 percent oxygen are common following myocardial infarction, as is a reduced diffusing capacity for carbon monoxide.$^{2,2,8,9,12,18,25-26}$

Arterial hypoxemia has been used to classify the severity of hemodynamic abnormalities following infarction.$^{26}$ With no evidence of pulmonary congestion at any time, the mean arterial oxygen pressure ($P_{O_2}$) was within the normal range at $89 \pm 9$ mm Hg. In serial measurements over two weeks, improvement in the $P_{O_2}$ nevertheless occurred in some patients, suggesting that mild impairment of gas exchange was initially present. In those with transient pulmonary congestion but with no congestion at the time of the study of blood gas levels, the mean $P_{O_2}$ was lower at $83 \pm 10$ mm Hg ($P < 0.05$), and it became normal over the two weeks following the myocardial infarction. In patients with moderate pulmonary congestion at the time of examination, the mean $P_{O_2}$ was at $71 \pm 8$ mm Hg and improved with clearance of the congestion. Patients with clinical pulmonary edema who were not in shock after the myocardial infarction had a mean $P_{O_2}$ of $60 \pm 7$ mm Hg.$^{28}$

Both increased venous admixture (right-to-left shunt) and ventilation/perfusion imbalance account for the arterial hypoxemia following myocardial infarction. In 21 patients with uncomplicated myocardial infarction, the $P(A-a)O_2$ was $47$ mm Hg with the patient breathing room air, of which $13$ mm Hg was due to increased shunt fraction and the rest to ventilation/perfusion imbalance. Thus, approximately one-third of the increased $P(A-a)O_2$ with the patient breathing room air is due to increased shunt, and the remaining two-thirds is due to ventilation/perfusion imbalance,$^{6}$ however,
as congestion worsens, the shunt fraction increases its relative contribution to hypoxemia.\textsuperscript{34,27-29}

The arterial carbon dioxide tension (\(\text{PaCO}_2\)) in noncongested or mildly congested patients after myocardial infarction is usually low or normal, even though the dead space may be increased, and the arterial pH is accordingly either slightly alkaline or normal.\textsuperscript{18,27,30} With more severe pulmonary congestion, the \(\text{PaCO}_2\) may still be normal or low but can be occasionally high.\textsuperscript{31} The pH fluctuates with the \(\text{PaCO}_2\) unless cardiac output is significantly reduced, at which time metabolic acidosis may appear because of hypoxia of tissues. Levels of lactate in the blood are increased in such patients.\textsuperscript{33,81,25}

**Chest X-Ray Film**

The pulmonary fields on the chest x-ray film of patients with myocardial infarction are either entirely normal or are indistinguishable from those of congestive failure due to other causes.\textsuperscript{33-35} In a general fashion the radiologic abnormalities correlate with the hemodynamic values. In early pulmonary vascular congestion (wedge pressure 18 to 19 mm Hg) a disparity in size of the pulmonary vessels of the upper and lower lobes occurs when the patient is in the upright position, with relative narrowing of the lower vessels and an increase in the relative size of the upper vessels. This finding has been seen in up to 70 percent of patients with acute myocardial infarctions but may be difficult to evaluate without a previous normal x-ray chest film for comparison.\textsuperscript{35}

With higher wedge pressures (18 to 22 mm Hg), loss of definition of vessels occurs, vessels of the outer pulmonary field become more prominent, and a perihilar haze may develop. Kerley’s B lines, which are thought to be distended septal lymphatic vessels, are found, as well as more diffuse reticular patterns.\textsuperscript{34,35}

Pulmonary capillary wedge pressure above 22 mm Hg generally becomes associated with radiographic evidence of infra-alveolar edema. This is seen first as periacinar rosettes, which are small translucencies surrounded by areas of water density perhaps representing fluid-filled alveoli. The pattern progresses to confluent opacities of water density that are variable and frequently more obvious in one lobe than another. Below a pulmonary wedge pressure of 18 mm Hg, the chest x-ray film is usually normal, although a definite lag phase of one to four days can occur between the return of the pulmonary wedge pressure to normal and clearance of the chest x-ray film.\textsuperscript{35} In reverse, it is also possible to have pulmonary wedge pressures above 19 mm Hg and yet no detectable radiographic abnormality.\textsuperscript{34,35} Therefore, although a general relationship exists between pulmonary vascular pressure and radiographic changes, the correlation in any given case is not excellent; for example, in 86 patients the admission chest x-ray film accurately predicted the patients’ wedge pressures in only 43 percent (37) of the cases, overestimating it in 33 percent (28 cases) and underestimating it in 24 percent (21 cases); however, accuracy improved to 74 percent when the pulmonary wedge pressure was 19-24 mm Hg (23 cases) and was 100 percent in 8 cases with pulmonary wedge pressures in excess of 25 mm Hg.\textsuperscript{35}

**Pathophysiologic Basis of Abnormalities**

The observed physiologic abnormalities in the lung following myocardial infarction are numerous, have a tendency to occur together, and improve together with time; they also bear a direct relationship to the severity of left ventricular dysfunction and the subsequent pulmonary congestion.

Florid pulmonary edema is at one end of the spectrum, where the increase in pulmonary water is apparent and its potential for disturbing pulmonary function obvious. At the other end of the spectrum, the presence of increased pulmonary water is inapparent by chest x-ray film or stethoscope, although measurements of pulmonary extravascular fluid may be high\textsuperscript{36} and subtle abnormalities in pulmonary function exist.\textsuperscript{2,8} Therefore, the observed abnormalities of pulmonary function after myocardial infarction can be explained by an increase in pulmonary water.

Edematous fluid initially accumulates in the interstitial space of the lung, first in the dependent parts of the lung, around the extra-alveolar vessels and their accompanying small airways.\textsuperscript{37,38} As edema progresses, the fluid begins to fill the alveoli, usually around the corners first, eventually filling or collapsing the entire alveolar space.

The accumulation of the pulmonary edema fluid after a myocardial infarction is probably initiated by an increase in pulmonary capillary and venous hydrostatic pressure secondary to increased left ventricular end-diastolic pressure. After acute myocardial infarction, pulmonary wedge pressures are high in almost all patients in the first 24 to 36 hours when the measurement has been made.\textsuperscript{9,23,29,34,39,42} Subsequently, the pressure returns to normal in uncomplicated myocardial infarction but remains elevated in more severe cases. The increased pulmonary venous pressure causes transudation of fluid into the pulmonary interstitial space, where the pressure is low,\textsuperscript{43} and then into the alveoli (Fig 2). This elevation of pressure may be
transient; however, even if the vascular pressure returns to normal, the interstitial and intra-alveolar edema can lag behind and cause abnormalities of pulmonary function.

Edema persisting in the interstitium of the dependent pulmonary zone after a myocardial infarction decreases the diameter of the extra-alveolar vessels and increases resistance to blood flow at the bases, thereby accounting for the observed shift in perfusion from the pulmonary base to the apex after myocardial infarction,4,6 a finding similar to that noted in experimental myocardial infarction in the dog22 and in man with overhydration such as occurs in renal failure or exogenous infusion of saline solution.44,45 The content of pulmonary water is increased after myocardial infarction, as measured by the double-indicator dilution technique,44 even with a normal pulmonary wedge pressure. Furthermore, the abnormalities in the pattern of pulmonary perfusion can be corrected with diuresis.4,5 Peribronchial edema causing decreased transmural pressure on small airways can account for the "closure" of small airways at higher-than-normal pulmonary volumes (increased CV),5 which occurs predominantly in the dependent part of the lung, the base, and in turn accounts for decreased basal ventilation (Fig 3).

When closure of airways occurs at a lung volume above the functional residual capacity (FRC), then alveoli distal to the collapsed airways exchange air during only part of a tidal breath. These poorly ventilated regions of lung whose relative perfusion is better preserved create regions of low ventilation/perfusion ratios, resulting in arterial hypoxemia. Thus, the occurrence of a CV above FRC would be expected to contribute to the observed hypoxemia seen following a myocardial infarction, and, indeed, such an association has been demonstrated.15 When edema is more marked the fluid becomes intra-alveolar, both filling and collapsing alveoli, resulting in increased right-to-left shunting, as evidenced by the increased P(A-a)O2 with the patient breathing 100 percent oxygen.

Early interstitial edema may also cause increased trapping of air in the lung via collapse of small airways at higher-than-normal levels, thereby creating the increased RV and decreased VC but leaving TLC unaffected. The large airways (greater than 2 mm in diameter), with their more rigid structure, are less affected by the interstitial edema, and therefore the peak flow rate and FEV1/VC% remain preserved until more pulmonary congestion occurs and Raw increases. As the magnitude of pulmonary edema increases, interstitial and intra-alveolar edema, as well as vascular engorgement, decrease pulmonary compliance, which tends to make pulmonary volumes smaller.44,45 At this point the loss of alveolar space, in addition to the fall in pulmonary compliance, can lead to a reduction in RV and TLC (Fig 4).
PERIVASCULAR
EDEMA

+ +  \( \dot{V} \) at base

PERIBRONCHIOLAR
EDEMA

+ +  \( \dot{Q} \) at base

**HYPOXEMIA**

Figure 3. Second sequential section of diagrammatic representation of sequence of events following acute myocardial infarction (MI) leading to pulmonary dysfunction. This section shows effect of perivascular and peribronchiolar edema on distribution of perfusion (\( \dot{Q} \)) and ventilation (\( \dot{V} \)). There is relative hypoperfusion of pulmonary base and shift of perfusion towards apex with patient in erect position, because of perivascular edema in dependent parts of lung. Because of reduction in transpulmonary pressure (TPP) and peribronchiolar edema, small airways tend to collapse at higher than normal pulmonary volumes, ie, increased CV. If CV becomes greater than FRC, then some airways are closed during tidal breathing. This causes areas of low ventilation, which, like perfusion, are again in dependent parts of lung; however, relative reduction in perfusion ensues, leading to areas of low V/Q ratio and hypoxemia.

Direct efforts at measuring extravascular pulmonary water are hampered by the lack of a sensitive technique in the clinical setting, but even so, studies done with the double-indicator technique

INTRAALVEOLAR EDEMA

INTERSTITIAL EDEMA

VASCULAR ENGORGEMENT

ALVEOLAR COLLAPSE

\( \downarrow \) SHUNT

( \( \uparrow A-aDo_2 \) on 100\% O\(_2\) )

"STIFF" LUNG

\( \downarrow \) COMPLIANCE

\( \downarrow VC, \downarrow RV \)

\( \uparrow \) AIRWAY RESISTANCE \( \rightarrow \) \( \downarrow \) FLOW RATES

\( \uparrow CV, \uparrow RV \)

Figure 4. Third sequential section of diagrammatic representation of sequence of events following acute myocardial infarction leading to pulmonary dysfunction. As edema worsens, there is intra-alveolar, as well as interstitial, edema and vascular engorgement. All three can cause lungs to become "stiff," with reduction in compliance, VC, and TLC. Intra-alveolar and interstitial edema can cause alveolar collapse, increasing right-to-left shunting and thus increased alveolar-arterial oxygen difference (A-aDo\(_2\)) with patient breathing 100 percent oxygen. Interstitial edema and vascular engorgement can increase Raw, leading to reduction in flow rates; and they can also cause increases in RV and CV.
(which measures only two-thirds of extravascular pulmonary water in the normal lung) do show increases in the extravascular pulmonary water after myocardial infarction. In general, extravascular pulmonary water increases as the wedge pressure rises but can be elevated even when the wedge pressure is normal; however, the technique of measuring extravascular pulmonary water becomes even less sensitive in the presence of maldistribution of perfusion, and this has been shown to occur following myocardial infarction even when the wedge pressure is normal. Thus, the inability to more consistently display an increased amount of extravascular pulmonary water after myocardial infarction in patients with a normal wedge pressure may be a technical problem due to a shift in perfusion away from the dependent lung where edema is likely to be greatest.

Hogg and associates have proposed an alternative theory to interstitial edema that may account for some of the changes in pulmonary function after myocardial infarction. In a set of experiments on dogs in which the left atrial pressure was raised, there was an increase in respiratory resistance. Below a left atrial pressure of 15 mm Hg, this increased respiratory resistance was immediately reversible when the left atrial pressure was returned to normal. Above a left atrial pressure of 15 mm Hg, respiratory resistance continued to rise but was not reversible when the left atrial pressure was lowered to normal. Hogg et al theorized that since the small airways and the small vessels run together in the narrow confines of a limiting membrane, vascular engorgement alone at left atrial pressures up to 15 mm Hg compressed the accompanying small airways and increased respiratory resistance. Above 15 mm Hg, extravasation of fluid into the interstitium occurs, and therefore the influence on respiratory resistance is no longer immediately reversible upon lowering left atrial pressure and thereby stopping the vascular engorgement. Indeed, mild elevations of pulmonary wedge pressures in patients during attacks of angina have been correlated with increases in Raw that rapidly return to normal when wedge pressure falls.

Although vascular engorgement alone could explain dysfunction of small airways after a myocardial infarction, such engorgement does not explain the decreased perfusion at the pulmonary base, since the vessels there should be more distended than usual, offer less resistance to flow, and therefore have even higher than normal flow. Furthermore, the shift in perfusion away from dependent zones of the lungs and the hypoxemia have been shown to occur even with normal wedge pressures and cardiac outputs, implying another persistent abnormality, such as increased extravascular pulmonary water.

Although a transient elevation in left ventricular diastolic pressure with an increase in pulmonary vascular hydrostatic pressure is the most plausible cause for the interstitial edema, there are other possibilities, and certainly other changes must occur to account for the persistence of edema after vascular hydrostatic pressures become normal. Catecholamines and other vasoactive substances are released at the time of infarction and may change the permeability of membranes of the pulmonary vessels. Furthermore, vascular distention alone allows proteins to escape through clefts in the pulmonary vascular endothelium. When the vascular pressure falls, the clefts become smaller, and protein is trapped in the interstitium, increasing the osmotic pressure and thus pulling fluid into the interstitial space. This phenomenon could account for the persistence of fluid in the pulmonary interstitium even though the intravascular pressures have returned to normal; however, for this assumption alone to hold true, the protein must leak into a space which the lymphatic vessels cannot drain, and such a division of pulmonary drainage has not been investigated. A decrease in intravascular colloid pressure after myocardial infarction could also produce or aggravate edema, based on Guyton and Lindsey’s observation in animals that the pulmonary arterial pressure necessary to induce pulmonary edema decreased from 24 mm Hg to 11 mm Hg when the colloid osmotic pressure was lowered to 47 percent of control.

In summary, then, increased pulmonary water of varying degrees can explain the abnormalities of pulmonary function following acute myocardial infarction. A mild increase in pulmonary water, which is often apparent on the chest x-ray film or on physical examination creates subtle abnormalities of function, invariably accompanied by some hypoxemia and detectable with sensitive tests of regional ventilation and perfusion. With more edema, pulmonary volumes and flow rates become abnormal as well until finally, in florid pulmonary edema, the lung can become overwhelmed with serious impairment of oxygen transfer and occasionally even impairment of elimination of carbon dioxide.

REFERENCES