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LUNG MECHANICS AND GAS EXCHANGE IN PULMONARY EMBOLISM

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Observations in experimental models as well as in humans have often led to disparate conclusions concerning the physiologic impact of pulmonary embolism, depending on the material embolized, the size of the particles, the temporal evolution, and the species studied. Thromboemboli, clinically the most frequent embolic event,[1] usually occlude large pulmonary arteries. The response to this occurrence is complex, involving the direct and reflex effects of vascular occlusion as well as the release of various vasoactive and bronchoactive mediators. The reaction to embolic material like fat, bone marrow, amniotic fluid, and air is more consistent with acute lung injury, pulmonary edema, and severe diffusion limitation. These materials usually cause microembolization and the mechanisms of injury are more often the consequence of neutrophil-induced damage of the pulmonary microvessels than of vascular occlusion. One should remind, however, that even large thromboemboli can eventually give rise to microembolization of vessels distal to partially occluded pulmonary arteries.

The basic disfunction of pulmonary embolism is represented by abnormalities of gas exchange. Pulmonary factors are always responsible for this disfunction, whilst non pulmonary factors, like reduced cardiac output, intracardial shunt, right ventricular failure and elevated right atrial pressure, are only occasionally involved.[2] Mechanisms of abnormal gas exchange include hypoventilation, diffusion impairment, shunt, and ventilation-perfusion ($\dot{V}A/\dot{Q}$) inequality. A decreased ventilation is not typically observed during pulmonary embolization, and complete equilibration between alveolar and end-capillary gas tensions is eventually reached in areated alveoli, unless oxygen partial pressure in mixed venous blood (PvO_2) were markedly reduced. Thus the main mechanisms responsible for abnormal blood gases following pulmonary embolism are shunt and $\dot{V}A/\dot{Q}$ inequality.

Intrapulmonary shunt during pulmonary embolism has been demonstrated both in humans and in experimental models, and in some studies[3,4] it has been reported to fully account for the hypoxemia observed in patients. Animal studies suggest that intrapulmonary shunting is the predominant cause of abnormal gas exchange during pulmonary microembolization or homologous blood clot embolization.[5,6] Although opening of arterial-venous anastomoses might be favored by hypoxia in the embolized region and/or by marked increases in pulmonary arterial pressure, this mechanism does not play a major role,[7] which is more frequently ascribed to post-embolic pulmonary edema.[8-11] Indeed less pulmonary edema, shunt formation, and hence smaller fall in arterial oxygen partial pressure (PaO_2) is seen following embolization in heparinized rather than in nonheparinized animals.[8] Heparin should in fact avoid the release of mediators or intravascular coagulation, which could lead to enhanced endothelial permeability and fluid extravasation, in association with increased pulmonary arterial pressure.[9]

Enhanced $\dot{V}A/\dot{Q}$ inequality represents the most frequent cause of abnormal gas exchange, and is present also in those instances in which shunts account for most of the concomitant hypoxemia.

The mechanisms by which $\dot{V}A/\dot{Q}$ inequality worsen blood oxygenation can be summarized as follows. Under normal conditions, the dependent lung regions are more perfused than ventilated, exhibiting a low $\dot{V}A/\dot{Q}$ ratio; relatively more oxygen is thus subtracted to the alveolar gas, so that both alveolar and arterial PO_2 are low. The opposite occurs in the upper lung regions, where both alveolar and arterial PO_2 are therefore high. Since most of the blood that leaves the lungs comes from the dependent regions, whereas differences in regional ventilation are substantially less pronounced, PaO_2 is depressed relative to mean alveolar PO_2. Moreover, the oxygen content is reduced in the blood leaving the alveoli with low $\dot{V}A/\dot{Q}$ ratios, the more so the lower this ratio, whereas, owing to the sigmoidal shape of the oxygen dissociation curve, the oxygen content increases little in the blood coming from

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alveoli with high $\dot{V}_A/\dot{Q}$ ratios. Hence hyperventilation of hypoperfused regions cannot compensate for the presence or, even worse, the augmentation of relatively hyperperfused regions, and hypoxemia ensues. It is of interest to note that while the former mechanism apply both to oxygen and carbon dioxide, the latter does not apply to carbon dioxide because the blood dissociation curve for carbon dioxide is essentially linear in the operative range of carbon dioxide partial pressures. Thus hyperventilation can eventually prevent the increase of $PaCO_2$ due to $\dot{V}_A/\dot{Q}$ inequality, but not the decrease of PaO_2.

Quite different patterns of $\dot{V}_A/\dot{Q}$ distribution can be observed during pulmonary embolism, that are largely independent of the degree of vascular obstruction; some show an increase of only low $\dot{V}_A/\dot{Q}$ units, others an increase of high $\dot{V}_A/\dot{Q}$ units, and others a broadening of the frequency distribution of $\dot{V}_A/\dot{Q}$ ratios.[12,13]

One explanation for this variety of $\dot{V}_A/\dot{Q}$ patterns, and the associated wide range of PaO_2 values, is the way in which emboli lead to redistribution of perfusion: large reductions of PaO_2 and arterial oxygen saturation are expected when cardiac output is diverted toward regions that normally receive a smaller fraction of the alveolar ventilation, whilst little changes would take place if the same diversion occurs toward highly ventilated areas, as a simple two-compartment analysis demonstrates.[12]

Both shunt and $\dot{V}_A/\dot{Q}$ distribution depend in part on lung mechanical features. Therefore changes in lung mechanics during pulmonary embolism should be taken into account in understanding the concomitant development of blood gases abnormalities.

Pulmonary embolism is frequently revealed by symptoms that are evidence of an obstructive ventilatory pattern and fairly often presents itself in the form of a bronchial asthma attack.[14] However, lung mechanics during acute thromboembolism has been poorly investigated in humans; indeed only one study has directly documented an increase of dynamic respiratory resistance.[15]

On the other hand, all reports from animal studies demonstrate that pulmonary embolization causes an increase in airway resistance, a fall in dynamic compliance, which becomes markedly frequency dependent, and a fall in static compliance.[16-18] These changes are combined with a reduction in lung volume and can be reversed with isoproterenol administration,[19] suggesting that the alterations in the dynamic and static properties of the lung are due, at least in part, to increased smooth muscle tone.

Morphological studies have shown that changes in lung mechanics are paralleled by constriction of the alveolar ducts and small airways.[19] The fall in lung volume as well as the decrease in static and dynamic compliance are therefore likely due to increased smooth muscle tone in peripheral airways and lung parenchyma. Since the morphological and, by inference, the functional changes occur in the lung segments distal to embolized vascular districts and are largely prevented by pretreatment with heparin and blockers of serotonin, they are thought to be caused by the release of vasoactive amines from platelet aggregates.[18] The increase in airway resistance suggests, however, that large airways are also involved in the response to embolization. This increase has been related to the decrease in lung volume, but vagal reflexes that enhance vagal tone can play a role, since in some instances the changes in airway resistance could be abolished by vagotomy.[18]

Finally, hypocapnia, whether due to regional pulmonary hypoperfusion or hyperventilatory response, is often indicated as an important brochoconstrictor agent,[20,21] and hence a cause of increased airway resistance.

Pulmonary edema can also contribute to the observed changes in lung mechanics. Alveolar flooding is obviously associated with a decrease in lung volume and compliance. Pulmonary edema following experimental embolism develops because of increased endothelial permeability and alteration in Starling forces. Changes in capillary permeability seem mainly due to the release of permeability-increasing substances, since edema formation is reduced in heparinized animals,[8] but additional damage from large parietal stress with increasing pulmonary capillary pressure should also be expected. Thus pulmonary edema may well extend beyond the embolized region: indeed, it has been observed also following experimental embolization of large vessels.[22,23]

On the other hand, measurements of extravascular lung water have shown that fluid accumulation, when present during pulmonary embolism, generally occurs in the interstitial space rather than the alveoli, and interstitial edema has been reported to have minimal effects on the volume-pressure curve of the lung.[24-26] Interstitial edema should have, however, more important effects on airway resistance, mainly because of mechanical uncoupling between peripheral airways and parenchyma, and partly because of compression of small airways with increasing interstitial pressure.[27]

Atelectasis represents another possible cause of decreased lung compliance, and it is often seen following experimental embolization. Substantial atelectasis, as well as reduction of lung volume, has been demonstrated radiographically in humans with pulmonary embolism.[28] Loss of surfactant occurs in non perfused or hypoperfused lungs,[29] and the increased surface tension could be responsible for alveolar and small airways collapse, as well

as for its maintenance.

Humoral mediators released from platelets coating emboli have been indicated as the main cause of atelectasis by producing loss of surfactant, beside pneumoconstriction.[3,30,31] Moreover, atelectasis might be favored by bronchiolar and pneumoconstriction due to the regional hypocapnia[20,21] that follows regional hypoperfusion.

The distribution of changes in mechanical properties within the lung is even more relevant to pulmonary gas exchange than their magnitude. Thus hypocapnic bronchoconstriction[20,21] or atelectasis in hypoperfused or non perfused regions divert ventilation to perfused lung units, and in combination with hypoxic vasoconstriction[32] of the embolized region, reduce or prevent the increase of lung units with both high and low $\dot{V}A/\dot{Q}$ ratios, besides shunting. These homeostatic mechanisms can explain the relatively rapid normalization of pulmonary gas exchange which often follows experimental embolization,[12] as well as the essentially normal PaO_2 and the only slightly increased arterial-alveolar PO_2 gradient observed in a considerable number of patients with angiographically documented pulmonary embolism.[8]

Hyperventilation increases the effectiveness of these homeostatic mechanisms, since inspired gas redistributes towards perfused lung units having low resistance and hence low time constant. The marked frequency dependence of compliance observed in animal studies is consistent with enhanced time constant inequality in embolized lungs. Ventilation is always increased in experimental animals and hyperpnea is often present in patients with acute embolism, so that hypocapnia and respiratory alkalosis are common findings. Activation of J and irritant receptors has been directly demonstrated following experimental embolization[33,34] and stimulation of these receptors is known to cause tachypnea and hyperventilation, beside reflex bradicardia, hypotension, and bronchoconstriction.

On the other hand, the effectiveness of hyperventilation in preventing the fall of PaO_2 depends in turn on PvO_2 and the magnitude of $\dot{V}A/\dot{Q}$ inequality and shunt: it is greater the lower PvO_2 and smaller the larger $\dot{V}A/\dot{Q}$ inequalities or shunts.

Changes in lung mechanical characteristics that were shown to act as homeostatic mechanisms, like bronchoconstriction, loss of surfactant and atelectasis in the embolized region, can, under certain circumstances, worsen gas exchange. Dissolution or breakdown of the initial embolus with reperfusion of atelectatic or poorly ventilated areas result in increased shunt or low $\dot{V}A/\dot{Q}$ units, and hence greater hypoxemia. Relatively rapid amelioration of hypoxemia with continuous positive pressure breathing or imposed hyperventilation observed in some patients with pulmonary thromboembolism[3,5,7] support this sequence of events.

In conclusion, pulmonary gas exchange following pulmonary embolization is influenced by numerous factors, often with contrasting effects, so that abnormalities of arterial blood gasses are non-specific and insensitive to the extent of embolization. Among those factors, changes in lung mechanical properties can play an important role.

Indeed, they help to explain the dissociation between alterations in gas exchange and extension of the embolization, which is often observed in spontaneous and experimental thromboembolism, beside contributing to the wide range of PaO_2 values and alveolo-arterial PO_2 and PCO_2 gradient that occur under these conditions.

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