A DISCUSSION OF THE HEMODYNAMICS of any circulation, and that of the pulmonary circulation in particular, must be concerned with three factors: (1) the flow through the circulation, which in the case of the lung is also the cardiac output; (2) the resistance to flow through the vascular bed, which is primarily a function of the number and diameter of resistance vessels, and to a lesser degree a function of blood viscosity; and (3) the pressure perfusing the vascular bed, which in the case of the pulmonary circulation is the pressure drop between pulmonary artery and pulmonary vein. Actually, these three quantities are interrelated, so that if two are known, the third is determined. For example, at any given cardiac output and any given diameter of pulmonary vessels (i.e., at any given resistance), the difference between pulmonary artery pressure and pulmonary vein pressure (approximately the same as left atrial pressure) is determined.

For the sake of simplicity, it is therefore possible to discuss determinants of pulmonary hemodynamics in terms of the two basic factors, namely, (1) pulmonary blood flow or cardiac output and (2) resistance or vessel diameter. From these, the behavior of pulmonary artery pressure can also be predicted.

Factors affecting pulmonary hemodynamics can be classified on this basis as follows:

I. Factors affecting flow or cardiac output:
   A. Relation between work load of heart (pressure x flow) and state of myocardium (degree of competence or failure).
      1. At any given work load, myocardial stimulation increases cardiac output.
      2. For any given state of myocardium, increased work load (right or left heart) causes decreased cardiac output.
   B. Blood gases, as they affect state of myocardium.
      1. Hypoxia: (a) Depresses myocardium directly; (b) Stimulates heart via sympatho-adrenal system.
      2. Hypercarbia: (a) Depresses myocardium directly; (b) Stimulates heart via sympatho-adrenal system; (c) Decreases effect of catecholamine hormones on heart.
   C. Blood volume; increase results in increased venous return and increased cardiac output.1

II. Factors affecting resistance or vessel diameter in lung:
   A. Factors passively affecting resistance.
      1. Distending pressures of vessels, resistance decreasing as pressure within vessel increases.8
      2. Lung volume, resistance increasing with lung volumes either smaller or larger than normal.8
      3. Distending or inflation pressure of lung, resistance increasing with distending pressure either less or greater than normal.4
      4. Blood viscosity (hematocrit).4
      5. Structural changes in vessels, causing decrease in number, diameter, or distensibility.4
   B. Factors influencing active vasomotion.
1. Hypoxia: (a) Causes vasoconstriction locally; (b) Causes minimal increased catecholamines, which cause constriction.

2. Acidosis: (a) Causes vasoconstriction locally; pH effect, rather than pCO₂; (b) Causes significant increased catecholamines which cause constriction; (c) Decreases effect of catecholamines on vessels; (d) Effect of alkalosis not clear.

This review is concerned primarily with hemodynamic responses to changes in blood gases and/or acid-base status. These humoral factors, as indicated above, affect either cardiac output or active pulmonary vasoconstriction. In turn, these determine pulmonary artery pressure and the work load of the right heart, which then "feeds back" to influence cardiac output and re-adjust the whole cycle of flow, resistance, and pressure relationships.

Hypoxia has been shown to have a depressant effect on the heart. However, it tends also to increase cardiac output by stimulating the heart via the sympatho-adrenal system, i.e., both the direct sympathetic supply to the heart and the sympathetic supply to the adrenal medulla which in turn results in increased production of catecholamines. During moderate hypoxia, the net effect in the intact animal of these two influences, one depressing the myocardium and the other stimulating it, is an increase in cardiac output.

Reports on the effects of changes in acid-base status on cardiac output are less consistent. Both respiratory acidosis and metabolic acidosis have been shown to have a direct depressant effect on the myocardium, just as hypoxia does. In addition, the effect of any given amount of adrenal medullary secretions on both the heart and blood vessels has been shown to be decreased during acidosis, indirectly depressing cardiac activity and cardiac output. However, respiratory acidosis like hypoxia also increases sympatho-adrenal activity stimulating the heart to increase its output in spite of the direct depressant effect. In the case of metabolic acidosis, sympatho-adrenal stimulation is less marked and, probably as a result, there appears to be no significant net effect on cardiac output.

The effect of respiratory and metabolic alkalosis is less clear, but they seem to have no remarkable effect on cardiac output.

The increased cardiac output during respiratory acidosis may in part be due to a vasodilating effect on the systemic circulation, resulting in more rapid run-off from the arteries to the veins, and increased venous return. This is true in the case of the kidney, for example, since it has been observed that increased renal flow during respiratory acidosis is actually of the same order of magnitude as the increase in cardiac output in comparable circumstances. Interestingly, metabolic acidosis has essentially no effect on renal resistance, possibly accounting at least in part for the failure of cardiac output to increase significantly under these conditions.

Other effects of changes in blood gases and acid-base status on pulmonary hemodynamics are those which influence pulmonary vasoconstriction. Hypoxia is one of the most potent pulmonary vasoconstrictors known. While the mechanism is not certain, it is probably a local effect (that is, not mediated by neural or endocrine factors), and may be due to accumulation of acid in hypoxic lung tissue. On the other hand, the local effect may be augmented by the increased catecholamine production observed during hypoxia since these hormones have been shown to increase pulmonary vascular resistance, although it is not likely that this is a quantitatively important factor in the pulmonary response to hypoxia.

Acid-base changes are now known to have marked effects on pulmonary vasoconstriction as well. Acidosis due to accumulation of either carbon dioxide or fixed acids (that is, either respiratory or metabolic acidosis) causes pulmonary vasoconstriction, just as hypoxia does. Acidosis, as in the case of hypoxia, appears to affect pulmonary resistance locally, since the response occurs in the isolated lung and since respiratory and metabolic acidosis
cause quantitatively comparable responses in spite of different effects on the sympatho-adrenal system. Metabolic alkalosis causes pulmonary vasodilation, but respiratory alkalosis has not been shown to have any significant effect on pulmonary hemodynamics, and it is therefore questionable whether an increase in pH per se has any significant effect.

Since acidosis causes pulmonary vasoconstriction, pulmonary artery pressure would be expected to rise if cardiac output were to increase as it does during respiratory acidosis. In metabolic acidosis, pulmonary artery pressure would also rise if output remained the same, or might be unchanged if output drops. Since the work of the right heart increases if either cardiac output or pulmonary artery pressure or both increase, it is apparent that cardiac work will increase somewhat in metabolic acidosis, but much more so in respiratory acidosis. This is of particular importance in problems associated with chronic lung disease with cor pulmonale, since this condition involves both respiratory acidosis and cardiac decompensation, so that the work load of the heart limits cardiac output. This is in contrast to the normal heart, whose output is essentially unaffected by the amount of work it must perform.

Thus, in respiratory failure both carbon dioxide retention and hypoxia increase pulmonary vasoconstriction and thereby elevate pulmonary artery pressure. Under this increased work load, does cardiac output increase as in normals who are made hypoxic and hypercarbic, or does it fail to increase, or even decrease? Do the direct depressant effects of respiratory acidosis and hypoxia on the heart also depress cardiac output and result in an abnormal circulatory response?

First, it has been shown that pulmonary artery pressure does in fact rise during exacerbations of chronic pulmonary disease accompanied by respiratory acidosis and hypoxia. Secondly, it has been shown that, on the average, cardiac output is unchanged in acute pulmonary failure associated with chronic lung disease although it tends to be chronically low between episodes of failure. While un­changed cardiac output might appear to be a normal response, it must be considered abnormal, as previously mentioned, because cardiac output increases in a normal person subjected to the same changes in blood gases. Teleologically, increased cardiac output is desirable, since increased blood flow increases tissue tensions of oxygen by increasing delivery and decreases tissue tensions of carbon dioxide by accelerating its removal. Therefore, the failure of cardiac output to rise as pulmonary disease worsens is actually inappropriate.

Since abnormalities in tensions of both oxygen and carbon dioxide can compromise the circulatory status of patients with chronic lung disease, it would be desirable to correct these tensions. This can be done, aside from correcting the basic pulmonary problem, by administering oxygen to correct hypoxia and by mechanically increasing ventilation to eliminate CO₂ retention. While these are both standard parts of the therapy of severe chronic pulmonary disease, there are possible complications of the two modes of therapy, and it is therefore desirable to estimate the average relative contributions of hypoxia and hypercarbia to increased pulmonary vasoconstriction, so the most important problem could be attacked initially and therapy individualized when necessary. There are inadequate data to make such an estimate of the relative contributions of hypoxia and hypercarbia to circulatory deterioration in cardiorespiratory failure. While a very good relationship has been shown between pCO₂ and pulmonary resistance under these conditions, this does not prove that CO₂ retention is the only or even the principal cause of increased resistance, since these same patients who have CO₂ retention also have hypoxia, and a similar relation can be demonstrated between oxygen saturation and resistance. This problem is subject to solution, but the data are not yet at hand.
Summary

1. Factors affecting pulmonary hemodynamics (cardiac output and pulmonary vascular resistance) are outlined. Among these are changes in blood gases (pO₂, pCO₂ and pH).

2. Major effects on both flow and resistance are due to decreased pO₂, increased pCO₂ and decreased pH in contrast to changes in opposite directions.

3. These blood gas changes, which are those usually observed in pulmonary disease all lead to increased pulmonary vascular resistance, direct myocardium depression, and myocardium stimulation via increased sympatho-adrenal discharge.

4. These blood gas changes in normal individuals lead to increased cardiac output in spite of direct myocardial depression and increased pulmonary resistance. In pulmonary disease with cor pulmonale, inappropriately low cardiac output is usually observed because of increased work of the heart and myocardial depression.

Resumen

1. El autor revisa los factores determinantes de la hemodinamica pulmonar entre otros los cambios gaseosos sangineos (pO₂, pCO₂ y pH).

2. La disminucin del pO₂, el aumento del pCO₂ y la reduccion del pH producen efectos intensos en el flujo y la resistencia.

3. Estos cambios gaseosos son los ordinariamente observados en las enfermedades pulmonares y resultan en aumento de la resistencia vascular pulmonar, depresion directa del miocardio y estimulo miocardico mediante el aumento de la descarga adreno-cortical.

4. La resultante es el aumento del rendimiento cardiaco apesar de la depresion miocardica y el aumento de la resistencia vascular y pulmonar. En las afecciones pulmonares con cor pulmonale el rendimiento cardiaco deficiente es la regla debido al aumento del trabajo del corazon y la depresion miocardica.

Resumé


2. Les effets principaux à la fois sur le flot sanguin et la résistance sont dus à une diminution du pO₂, une augmentation du pCO₂ et une diminution du pH en contraste avec des modifications dans les directions opposées.


ZUSAMMENFASSUNG

1. Es werdenjene Faktoren, die die pulmonalen hämodynamischen Verhältnisse betreffen (Herzminutenvolumen und pulmonaler Gefäßwiderstand) näher beleuchtet. Unter ihnen sind besonders die Veränderungen der Blutgase (pO₂, pCO₂ und pH) hervorzuheben.

2. Stärkere Wirkungen sowohl auf die Durchströmung als auch den Widerstand sind Folge eines herabgesetzten pO₂ eines erhöhten pCO₂ und eines verminderten pH im Gegensatz zu Veränderungen in umgekehrter Richtung.


Complete reference list will appear in reprints.