Oedema in cor pulmonale

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Introduction

Experimentally induced hypoxaemia in small rodents causes thickening of the right ventricular muscle, thickening of the walls of small pulmonary vessels and pulmonary hypertension. Oedema is never seen [1]. Similar changes are observed in natives living at high altitude in places such as Peru. Oedema is rare but is described when the usually active life of the compensated high-altitude native is disturbed by acute episodes of drowsiness and peripheral oedema. The condition is then called Monge's disease and, once observed, the outlook is poor [2]. Oedema is common in hypoxaemic bronchitis but rare in hypoxaemic interstitial fibrosis.

Cor pulmonale is defined according to the WHO definition (1961) as hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except where these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease. Most clinicians, however, recognize cor pulmonale only when peripheral oedema develops in association with the defined features. Its common association is chronic bronchitis and emphysema but weakness of thoracic musculature, skeletal deformity and disease of the respiratory centre contribute. Arterial blood gases show a reduced \( P_{aO_2} \), variable increase of \( P_{aco_2} \) and increased bicarbonate from compensated respiratory acidosis. Pulmonary artery pressure is very dependent upon the circumstances of measurement. Elevation is modest (approximately 30 mmHg, mean) in stable periods between early exacerbations of oedema but pressure rises steeply during acute illnesses and during exercise. Initial lability gives way to more serious permanent elevation in preterminal phases [3]. Cardiac output is usually normal or at the upper limit of the normal range, and is elevated in only the occasional patient. Clinically detectable oedema is usually confined to patients with \( P_{aO_2} \) below 8 kPa (60 mmHg), but only a small proportion (less than 10%) of bronchitic patients develop it at this pressure. \( P_{aO_2} \) falls at a variable rate but, in about one-third of patients, at a greater rate than is normally appreciated (approximately 1 kPa per year) [3]. By the time the \( P_{aO_2} \) has fallen to 5 kPa most patients will have had at least one episode of severe oedema with residual ankle swelling in convalescence. Diuretic therapy may prevent clinical detection of oedema and many acute illnesses after the first may occur with little or no oedema. Once oedema appears the outlook is grave and two-thirds of such patients will die within 5 years. The mean age in the male for the first appearance of oedema has remained at 58 years for the past two decades. Cor pulmonale is not necessarily the disease of old age that many imagine.

The deterioration in \( P_{aO_2} \) can be just as fast in fibrosing alveolitis but the appearance of oedema is less consistent and limited to the occasional patient with very low \( P_{aO_2} \) (less than 5-3 kPa: 40 mmHg). Hypercapnia is not a feature of fibrotic hypoxaemia until the preterminal phases, if then. The belief that oedema is associated with hypercapnia rather than hypoxaemia is dependent upon such observations. Hypercapnia is a feature of other causes of cor pulmonale, such as central respiratory depression, thoracic cage deformities and chronic neurological and muscle disorders.

In the acute attack, the signs of a raised jugular venous pressure, hepatomegaly and peripheral oedema, often gross, do suggest a diagnosis of congestive cardiac failure. However, a number of studies question whether the term 'failure' is correct, since cardiac output is usually normal or elevated. The question of oedema and pump failure needs closer examination.
Cardiac failure of valvular and ischaemic origin

In man, and experimentally in dogs with cardiac failure from valvular or ischaemic lesions, oedema is associated with retention of sodium and water in the extracellular compartment. Total body water (TBW), extracellular fluid (ECF), exchangeable sodium (\(\text{Na}_\text{e}\)) and body weight increase [4–7]. Increase of \(\text{Na}_\text{e}\) may be accompanied by normal or even low serum sodium concentration, depending upon whether sodium accumulates in proportion to absorbed water [4, 5]. Diuresis accompanying treatment causes loss of sodium and water but sodium loss is often less than expected from the observed water or weight loss. The excess sodium may persist in the body for many weeks after oedema has cleared [8]. Expressed as \(\text{Na}_\text{e}/\text{TBW}\) the high value could represent loss of intracellular fluid, tissue wasting or high intracellular sodium concentration [4, 5, 9]. The last-named may in part be explained by fixed sodium, particularly in tissues such as cartilage where it is osmotically inactivated but recorded as \(\text{Na}_\text{e}\) through exchange with the free pool [10]. Rather surprisingly, \(\text{Na}_\text{e}\) and exchangeable potassium (\(\text{K}_\text{e}\)) movements are not closely related [11]. \(\text{K}_\text{e}\) is usually low, particularly in oedematous patients [12]. As most potassium is intracellular, low \(\text{K}_\text{e}\) is related to events within the cell. Again low intracellular potassium concentration or loss of body tissue are possible explanations.

Cor pulmonale—is it really heart failure?

In cor pulmonale, measurements of exchangeable sodium, potassium and body weight are few. Several studies of exchangeable \(\text{Na}^+\) and \(\text{K}^+\) have pointed to differences compared with congestive cardiac failure of valvular or ischaemic origin. Aikawa & Fitz [6] in five patients showed higher \(\text{Na}_\text{e}\) after treatment and less fall with treatment. Birkenfield et al. [13] recorded opposite movements of \(\text{Na}_\text{e}\) and \(\text{K}_\text{e}\) in a few cases compared with other cardiac patients. Mader et al. [11] compared electrolyte balances of cor pulmonale and other cardiac patients and suggested greater flux of \(\text{Na}^+\) and \(\text{K}^+\) during treatment of cor pulmonale. This was partly due to excessive loss of cations from cells in the acute phase to buffer respiratory acidosis. Cox et al. [4] came to a similar conclusion. Campbell et al. [12] observed oedema without weight gain in some patients and little sodium retention. Fishman et al. [14] studied renal function in cor pulmonale and found that in hypoxia sodium excretion increased. They concluded that, unlike other types of congestive cardiac failure, sodium is not retained and hypoxia does not directly contribute to oedema in cor pulmonale.

Right ventricular muscle function

There is little doubt that progressive pulmonary hypertension is associated with clinical deterioration in cor pulmonale. The response of the right ventricle to progressive afterload has been sparsely studied. Cardiac output is normal or slightly elevated in convalescence and in acute illnesses when oedema is present [15]. The increase of cardiac output on exercise lies on the normal response curve. The severe limitation of exercise seems to be respiratory and not cardiac. Right ventricular end-diastolic volume is often increased, particularly on exercise, but this does not necessarily indicate muscle failure. When right ventricular end-diastolic pressure is related to stroke index, right ventricular function appears depressed, but right ventricular stroke work is well maintained, indicating normal right heart function (Table 1) [16, 17]. Berglund [18] studied a patient with severe oedema and polycythaemia, finding the right ventricle to respond normally to the increased demands of exercise. Thus there is little evidence for right ventricular muscle failure in cor pulmonale. The smaller right-sided muscle volume deals with high pulmonary vascular resistance by increasing fibre length (increased diastolic volume) and at the expense of some rise of end-diastolic pressure, much as Starling’s law would predict.

Left ventricle in cor pulmonale

The left ventricular wall is increased in thickness in up to 25% of patients with cor pulmonale [19].

<table>
<thead>
<tr>
<th>TABLE 1. Right ventricular function in cor pulmonale</th>
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<tr>
<td>RVEDP (mmHg)</td>
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<tr>
<td>Rest</td>
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<tr>
<td>Chronic bronchitis (never had oedema)</td>
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<tr>
<td>4.4 ± 2.5</td>
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<tr>
<td>Cor pulmonale without oedema</td>
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<tr>
<td>5.7 ± 2.5</td>
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<tr>
<td>Cor pulmonale with oedema</td>
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<td>7.6 ± 2.8</td>
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In the absence of ischaemic or valvular heart disease, this has been attributed to a direct effect of hypoxaemia on left ventricular muscle. Elevated pulmonary artery wedge pressures and elevated left ventricular end-diastolic pressure (LVEDP) are observed in a very small proportion of patients with cor pulmonale even when oedema is present [20, 21]. The changes are not related in these few patients to the level of pulmonary artery pressure. One or two studies have detected abnormalities in left ventricular function curves under stress of exercise or angiotensin infusion in cor pulmonale [17, 22].

Disorders of the right ventricle in animal experiments have been shown to have some influence on left ventricular function. Banding of the pulmonary arteries reduces contractility of both right and left ventricles. Alteration of compliance of the right ventricle from right ventricular hypertrophy alters compliance of the left ventricle. Cattle with severe pulmonary hypertension at altitude show increased LVEDP.

However, on balance, few patients have been shown to have abnormal left ventricular function [23–26]. The secondary effects of right ventricle problems have not been considered in man. The weight of evidence must be at the present time against true failure of either right or left ventricular muscle. Further studies in the oedematous phase are clearly needed.

Renal blood flow and renal hormones

In congestive cardiac failure of valvular or ischaemic disease, renal blood flow falls, and this stimulates the renin–angiotensin system. Plasma renin activity is usually raised, as is aldosterone, in both blood and urine [27, 28]. Normal levels of both renin and aldosterone have been recorded in the presence of oedema and have been shown to increase after diuretic therapy [29]. Despite some contradictions, in most studies aldosterone seemed more closely related to sodium balance than to the amount of clinically detectable oedema. Both renin and aldosterone increase during accumulation of salt and water but fall rapidly once equilibrium is reached [30].

In cor pulmonale there are few observations but most consistent is the fall in renal blood flow as oedema develops. Glomerular filtration rate is inconstantly depressed [31–33]. Renal haemodynamic changes were not closely related to arterial blood gas changes [34] but, nevertheless, hypoxaemia and possible hypercapnia would seem the most likely cause. Reduced renal blood flow stimulates release of renin. In a study by Tomaszewski et al. [35] plasma renin activity was increased in eight out of 11 patients with oedema but no elevated values were observed later in convalescence. Preliminary findings in our own laboratory suggest an elevation to four or five times normal levels of plasma renin activity and aldosterone in the first 2 days of acute oedematous cor pulmonale. Renin mediates angiotensin formation, which in turn increases aldosterone production. Increased aldosterone in the blood promotes retention of sodium and water. The increased aldosterone is achieved in part by increased secretion but also in part it seems by reduced clearance. Hypoxaemia and hepatic venous congestion may reduce catabolism of aldosterone by as much as 50% [36]. Further evidence of the involvement of aldosterone in cor pulmonale comes from the use of aldosterone antagonists, which usually promote loss of Na+ and water and secondarily improve respiratory function [37].

Hypercapnia

Cor pulmonale is almost invariably associated with hypoxaemia and hypercapnia. Hypoxaemia in association with fibrotic lung disease rarely causes oedema in the absence of hypercapnia but the distinction is not absolute. Thus we reach the intriguing situation that cor pulmonale is probably not a form of cardiac muscle failure but is associated with reduced renal blood flow of other aetiology.

The beneficial effect clinically of aldosterone antagonists in cor pulmonale suggests that aldosterone is causally implicated. Aldosterone is raised, however, in the non-hypercapnic hypoxaemia of altitude. Systemic oedema is not a feature of altitude but pulmonary oedema occurs. The coincidence of hypercapnia with increased stimulation of the renin–angiotensin–aldosterone system has not been studied. The relation of hypercapnia to renal blood flow was found to be inconstant in one study [34]. Measurements of renal haemodynamics, renal hormones (including antidiuretic hormone) and hypercapnia merit further investigation.

Increased flux of Na+ and K+ referred to above in cor pulmonale is likely to be a consequence of hypercapnia. The need to buffer extracellular respiratory acidosis with intracellular K+ as well as extracellular Na+ might explain why Campbell et al. [12] observed gross oedema in some patients in the absence of a commensurate increase of body weight. Loss of intracellular K+ and water to the extracellular space would maintain extracellular osmolality. Hypercapnia-induced redistribution of body
water, whilst being one mechanism of hypercapnic oedema, is not likely to be the sole explanation as other patients do have large increases of body weight.

**Body weight and tissue weight**

Body weight may be little changed or increased as oedema develops; it falls substantially during treatment and is regained in convalescence often to levels at least as high as when oedema was present but without deterioration of clinical state or recurrent oedema [12]. Loss of dry body weight, i.e. tissue protein, is large during therapy for oedema. The loss of weight is not simply a loss of water and always exceeds that due to the water itself. Regain of weight during convalescence occurs in the normal body proportion of water and tissue protein and presumably represents rebuilding of normal tissue [12]. In advanced disease the rebuilding process is incomplete, leading to progressive loss of overall body weight.

Draining the intracellular space seems to be associated with tissue dissolution and rise of blood urea. Loss of tissue protein is not peculiar to cor pulmonale but seems to be more severe. Suggestions that loss and regain of tissue weight must of necessity be a slow process, measured in weeks or months, is not borne out by the measurements [12], which indicate substantial changes either way can be achieved within a few days. A recent study suggests low K⁺ in cor pulmonale (which would be exacerbated by vigorous diuretic therapy) can be entirely accounted for by tissue loss and supports the important concept of large changes in dry tissue weight [38].

**Summary**

The mechanisms of oedema in cor pulmonale remain unexplained. On the basis of a small number of studies, cor pulmonale is not caused by cardiac muscle failure, at least in early oedematous phases. Progressive and persistent elevation of pulmonary vascular resistance may exceed the pumping capacity of the right ventricle in later stages. Alternative explanations for the sharp fall in renal blood flow as oedema appears should be sought. The renin–angiotensin–aldosterone system seems causally related to oedema. The curious position of hypercapnia remains an enigma. Surprisingly few studies of hypercapnia, renal blood flow and renal hormones are reported. Redistribution of body water from intracellular to the extracellular space may be in part due to the need to buffer extracellular respiratory acidosis caused by hypercapnia. It provides an explanation for one form of hypercapnic oedema. Cyclic loss and gain of tissue mass seems more evident in cor pulmonale than ischaemic or valvular heart failure.

**References**


Oedema in cor pulmonale

259


