

Water and sodium imbalance in COPD patients

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ABSTRACT: *Water and sodium imbalance in COPD patients. G. Valli, A. Fedeli, R. Antonucci, P. Paoletti, P. Palange.*

Water retention and hyponatraemia are typically observed in the final stages of Chronic Obstructive Pulmonary Disease (COPD) and the onset of edema is a poor prognostic factor. For several years the pathogenesis of edema in COPD patients was attributed to heart impairment because of pulmonary hypertension, but the evidence that cardiac output is often adequate for the metabolic demands has suggested, since 1960, that the pathogenesis of edema in these patients would be correlated with gas exchange impairment and in particular with car-

bon dioxide (CO₂) retention. The gas exchange impairment induces, in these patients several hormonal abnormalities: renin (Rn), angiotensin II (AnII), aldosterone (Ald), atrial natriuretic peptide (ANP), vasopressin (ADH) and endothelial factors are some of the factors involved. The systemic response to hypercapnia has the effect of reducing the renal blood flow and, as a result, increasing water and sodium retention with the final effect of edema and hyponatraemia. The aim of this brief review is to highlight the current knowledge on renal/hormonal abnormalities in COPD and their therapeutic implications.

Monaldi Arch Chest Dis 2004; 61: 2, 112-116.

Keywords: *Cor Pulmonale, Hypercapnia, Edema, COPD, renal vascular resistance.*

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Water retention and hyponatraemia are typically observed in the final stages of chronic obstructive pulmonary disease (COPD). In 1960, Campbell and Short [1] pointed out that, in patients with COPD, edema is almost invariably associated with gas exchange impairment and in particular with carbon dioxide (CO₂) retention. Since then solute-water retention in COPD has been considered to be the result of electrochemical imbalance (enhanced renal/tubular H⁺/Na⁺ exchange) and/or renal hemodynamic abnormalities [2]. Many patients with COPD are also unable to normally excrete a water load, and this defect that can be confirmed in the absence of overt edema, is associated with a decrease in sodium excretion and has been reported to be proportional to the severity of CO₂ retention [3]. In hypoxemic normocapnic patients with pulmonary fibrosis or lung emphysema water retention and peripheral edema are very uncommon and when they occur a transient increase in CO₂ during an exacerbation or during sleep should be ruled out.

In advanced COPD edema has been reported in a large proportion of patients but its exact incidence is not known. The onset of edema is a poor prognostic factor. Renzetti and co-workers [4] reported a four-year mortality rate of 73% in patients with "cor pulmonale", compared with 53% for the whole COPD group. More recently, Hodgking has shown a 60% of mortality up on five years in edematous COPD patients [5].

It must be clearly stated that edema formation in COPD patients is not cardiac in origin. In most

patients, even when they are frankly edematous, cardiac output is adequate for the metabolic demands, unless there is a significant co-existent cardiac disease [6, 7].

Figure 1 summarises the principal events that are supposed to induce edema in COPD patients. The aim of this brief review is to highlight the current knowledge on renal/hormonal abnormalities in COPD and their therapeutic implications.

The role of hypercapnia

During acute edematous exacerbations of COPD renal blood flow is reduced [8, 9], but increases when the clinical status improves [9]. However, in edematous COPD patients the glomerular filtration rate (GFR) is normal or only slightly reduced [8, 10] and thus the serum creatinine level remain normal until the end stage of the disease. In patients with moderate hypoxemia, mild hypercapnia, normal cardiac output, and no evidence of intrinsic renal disease, the significant reduction in effective renal blood flow (ERPF), associated with normal GFR, increases the filtration fraction (FF) and consequently induces Na⁺ retention. Recently in a group of COPD patients, Sharkey and co-workers measured, non invasively by Doppler ultrasonography, the pulsatility index (an index of renovascular resistances), showing in these patients a lack in renal vasodilatation following a protein meal (an effect known as renal functional reserve) and even an increase in vasocon-

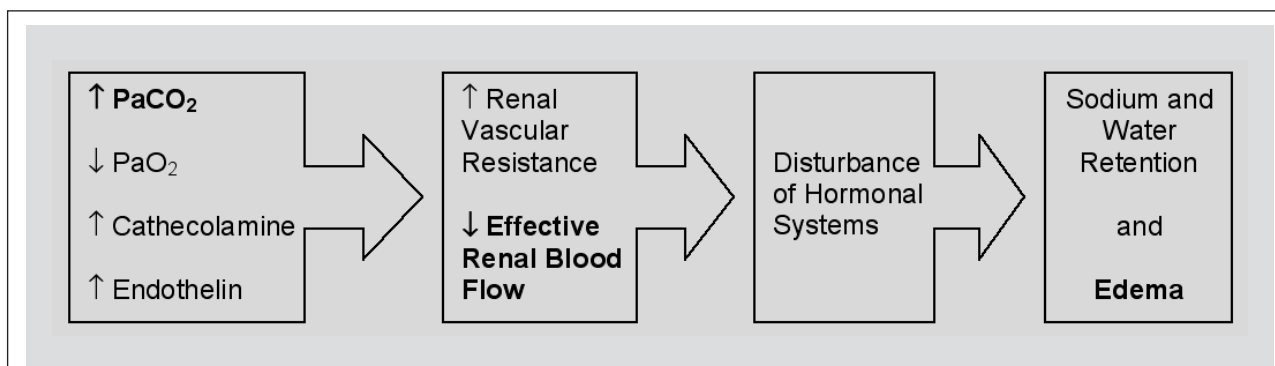


Fig. 1. - Pathogenesis of peripheral edema in COPD patients.

striction in more hypercapnic patients [11]. These findings indicate that arteriolar renal resistances are increased, perhaps because of local adrenergic discharge secondary to hypercapnia.

In the initial phase of COPD, renal perfusion is usually normal but when CO₂ retention develops, renal blood flow decreases [12-13].

Hypercapnia reduces renal blood flow by means of a direct renal vasoconstriction [14]. Moreover, hypercapnia induces an increment of noradrenalin levels, that causes a reduction in renal blood flow, through peripheral vasodilatation that inactivates baro-receptors and direct central sympathetic stimulation [15].

Role of hypoxemia

Hypoxemia alone does not seem to induce significant changes in renal hemodynamics and/or Na⁺ and water homeostasis, although oxygen administration has been shown to exert a vasodilator effect in hypoxemic normocapnic COPD patients [16]. Sharkey and co-workers [17] had recently documented that in hypoxemic COPD patients the raise in oxygen saturation from 98% to 99% reduces the renovascular resistance and, consequently, increases renal blood flow. This decrease in renovascular resistance was reversed by the addition of inhaled carbon dioxide, despite maintaining hyperoxemia. In hypercapnic patients neither short term oxygen therapy or infusion of low dose dopamine improve renal hemodynamics [18]. This suggests that the increase in CO₂ levels mainly drives the renal haemodynamic response to changes in arterial blood gases. The vast majority of studies in COPD patients showed a decrease in RBF in the presence of hypoxemia [14, 16, 18] but the mechanism whereby hypoxemia affects RBF is not fully understood. However, clinical experience suggests that correction of hypoxemia by long term oxygen therapy in hypercapnic hypoxemic COPD patients may result in significant natriuresis and improves renal function [19]. Finally, the finding that hypoxemic COPD patients are unresponsive to L-arginine, while it induces vasodilatation in normal subjects, suggests that a disturbance on NO pathway may play an important role on COPD renovascular response to hypoxia [20].

Honig and co-workers [21], in an animal study, found that changes in renal blood flow secondary

to hypoxemia are abolished by denervation of peripheral chemoreceptors and are reduced by renal denervation, while adrenalectomy does not induce changes. These findings suggest a relevant role of peripheral nervous system. In a study on a group of renal transplant subjects, kidney denervation does not totally abolish renal response to hypoxemia [22].

Role of the PRA-PA system

Disturbance of the hormonal system are common in COPD patients, especially during acute exacerbation of respiratory failure. Hypoxemia and hypercapnia induce systemic alterations that involve various organs like kidney, adrenal cortex, heart and brain with increased secretion of renin (Rn), angiotensin II (AnII), aldosterone (Ald), atrial natriuretic peptide (ANP) and vasopressin (ADH).

As a consequence of reduced renal blood flow, and as in most edematous diseases whit reduction of renal blood flow without reduction of GRF, COPD patients present a state of secondary hyperaldosteronism [8, 23, 24]. The activation of PRA-PA system occurs late in the course of the disease and concurs to worsen the ability to excrete Na⁺ and water. Patients with COPD may have levels of Rn, AnII and Ald 2-3 times higher than normal subjects, but usually lower than those observed in patients with congestive heart failure [25]. In animal studies acute hypoxia has been reported to induce an increase in PRA [26-27] whereas chronic hypoxia produced variable effects [28-29].

Hypoxemia alone does not stimulate the PRA-PA axis. Hypercapnia may play a role but the consequences of CO₂ retention on hormonal release have been examined in animal and human studies with controversial results. Experimental data demonstrated a PRA-PA axis activation during acute hypercapnia in dogs [30] and similar variation were noticed in COPD patients with acute or chronic hypercapnia [8, 9, 31]. Chabot *et al* studied a group of COPD patients, receiving mechanical ventilation, during moderate acute hypercapnia and concluded that changes in plasma hormones during acute hypercapnia are secondary to hemodynamic changes induced by acute respiratory failure and not to acute hypercapnia *per se* [32].

As a result of the stimulation of the PRA-PA axis, the activity of the angiotensin converting enzyme (ACE) is increased and high values of AnII

may be observed; despite the inhibition of ACE activity with perindopril that seems to not change sodium excretion [33].

Role of the antidiuretic hormone

The level of plasma arginin-vasopressin (ADH), the antidiuretic hormone, is inappropriately high for the level of plasma osmolarity in patients with hyponatremia [8, 31, 33]. If in normals the production of ADH is mediated by plasma osmolarity, this is not true for COPD patients where non-osmotic mechanisms should act. Although the mechanism that underlies this abnormality is not fully understood, some experimental data suggest that the increase in AnII may directly stimulate ADH [34]. Stimulation of baro-receptors in edematous patients with low circulating blood volume has also been suggested [35]. Not all patients with increased levels of ADH have hyponatraemia; in some patients Na^+ level remains normal until excessive water intake occurs.

Role of the atrial natriuretic peptide (ANP)

High circulating levels of atrial natriuretic factors were found in animal and human studies, which have shown that both hypoxia and hypercapnia stimulate the release of ANP [36, 37]. The highest atrial natriuretic factors levels have been observed in patients with marked sympatho-adrenergic activity and hypercapnic acidosis [36]; ANP has the effect to reduce the vascular tone and its increase during acute respiratory failure could be a compensatory mechanism induced by arterial gases worsening. In agreement with this observation was the finding that circulating ANP has been shown to correlate inversely with arterial PO_2 [35]. What is not completely understood is why the increment of ANP has no influence on water and sodium renal excretion. Experimental data in COPD have shown that the PRA-PA axis is not suppressed by the increase in ANP induced by exercise [38] or by the application of lower body positive pressure [25]. It is logical to assume that, in edematous COPD patients, the effects of reduced renal blood flow, GRF

and FF, induced by hypercapnia and hypoxia, are greater than those of ANP.

Role of endothelin

Recently the activation of endothelium synthesis has gained importance in the pathogenesis of vascular alteration in a group of diseases [39]. Firstly isolated in 1985 [40] as a coronary vasoconstrictor peptide produced by endothelium, endothelin-1 (ET-1) was isolated in a variety of tissues, where it acts as regulator of vasomotor tone, with a prevalent vasoconstrictor effect [41, 42]. ET-1 causes vasoconstriction activating specific receptors on muscular smooth cells and an enhancement at the contractile response to other vasoconstrictors substances [43, 44]. In addition ET-1 seems to be an inductor of mitogenesis of smooth muscle vascular cells.

ET-1 production seems to be involved in a number of diseases related to the vascular system. Patients with asthma and pulmonary hypertension have high levels of ET-1 in the lung [45, 46]. Several evidences demonstrate that endothelin causes renal vasoconstriction and increases tubular sodium and water reabsorption, probably reflecting the two principal sites of production: renal blood vessels and tubules [47]. ET-1 may contribute in fact to several vascular-related diseases of the kidney, like post-ischemic renal failure [48]. Abnormal circulating ET-1 levels have been reported in stable hypoxemic COPD patients, suggesting that ET-1 may contribute to pulmonary hypertension and vascular remodelling [49] in this syndrome. Both hypoxia and hypercapnia seem to contribute to blood ET-1 increment in COPD patients [50]. In a recent paper, Sofia and co-workers [51] have shown an increase in renal endothelin production in COPD patients, during acute exacerbation, in the absence of significant change in ET-1 circulating levels. Endothelin may contribute to a renal response to hypoxemia and hypercapnia in COPD.

Therapeutic implications

Table 1 summarises the most important therapeutic interventions in hypercapnic, edematous

Table 1. - Therapeutic interventions for "Cor-pulmonale" in COPD

Therapeutic intervention	Note
• Oxygen Supplementation	• It is the mainstay of treatment. The lowest dose (FiO_2 24%), to keep oxygen saturation > 90% should be used, in order to limit respiratory acidosis
• Bronchodilators	• The highest possible broncho-dilatation should be promoted
• Water restriction	• Usually results in stabilization and slight increase in plasma Na^+
• Corticosteroids	• The use of these drugs should be limited because induces Na^+ retention
• NIV	• May reduce arterial CO_2 . More studies are needed
• Diuretics	• To be avoided. The use of diuretics may results in metabolic alkalosis and hypoventilation
• Digitalis	• Not to be used. May expose to arrhythmias
• ACE-inhibitors	• The use of these drugs is still debated

COPD patients. In view of the above findings, it is clear that the therapeutic interventions required to control edema in COPD patients should include the reversal of hypoxemia and the improvement of gas exchange and lung mechanics, by promoting maximal bronco-dilatation. Non-invasive mechanical ventilation could improve gas exchange but its effects on renal function should be better investigated. Hyponatremia, when present, should be treated with water restriction that usually results in stabilization or slight increase in plasma sodium concentration. Therapy with diuretics should be used with caution since they result in hypocloremic metabolic alkalosis, which may lead to hypoventilation with worsening of blood gas tension and, consequently, water and sodium retention [52]. The use of digitalis should be avoided unless intrinsic heart disease with low output is documented; in the presence of severe hypoxemia, the drug may expose patients to an increase risk of arrhythmias. The effect of ACE inhibitors is not completely clear and is still debated.

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