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Review article

Chronic Obstructive Pulmonary Disease and Heart Failure

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is commonly associated with heart failure. Individuals with COPD have a 4.5-fold greater risk of developing heart failure than those without. The sensitivity and specificity of clinical judgment in the diagnosis of heart failure in patients with COPD can be enhanced by biological markers such as B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide. Correct interpretation of imaging results (mainly echocardiographic findings) and lung function tests can also help establish the co-occurrence of both conditions. There is little evidence on the management of patients with COPD and heart failure, although treatment of COPD undeniably affects the clinical course of patients with heart failure and viceversa.

Palabras clave:
Enfermedad pulmonar obstructiva crónica
Insuficiencia cardíaca
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Enfermedad pulmonar obstructiva crónica e insuficiencia cardíaca

RESUMEN

La enfermedad pulmonar obstructiva crónica (EPOC) es una enfermedad frecuentemente asociada a la insuficiencia cardíaca (IC). El riesgo de desarrollar IC en los pacientes con EPOC es 4,5 veces superior al de los sujetos sin este trastorno. Distintos marcadores biológicos, entre los que se encuentran el péptido natriurético tipo B y el fragmento N-terminal del propétpido natriurético tipo B, pueden aumentar la sensibilidad y la especificidad del propio juicio clínico a la hora de establecer el diagnóstico de IC en los pacientes con EPOC. La interpretación correcta de las técnicas de imagen (fundamentalmente el ecocardiograma) y de las pruebas de función pulmonar puede ayudar también a diagnosticar la concurrencia de ambos procesos. Existen pocas evidencias acerca del tratamiento combinado de la EPOC y la IC. Lo que es incuestionable es que el tratamiento de la EPOC puede influir en la evolución clínica de la IC, y viceversa.

Introduction

A high number of patients present both chronic obstructive pulmonary disease (COPD) and heart failure (HF)[1]; tobacco use is a common risk factor. The prevalence of COPD among individuals with HF ranges between 20% and 32% of all cases, and 10% of hospitalised HF patients have COPD.[2] Seen from the other direction, the risk of developing HF among COPD patients is 4.5 times higher than that of control individuals without that disease, after adjusting for age and other cardiovascular risk factors.[3] The high prevalence of HF in COPD patients is not surprising, particularly when we consider that these patients have a higher risk of cardiovascular morbidity and mortality which is independent from other factors, such as tobacco use. Functionally, the forced expiratory volume in 1 second (FEV_1) is as good a predictor of cardiovascular mortality as cholesterol values are.[4] Despite everything, ischaemic heart disease is the main cause of death among COPD patients, instead of heart failure.[5]

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COPD is a disease that is frequently associated with HF. Additionally, it is a short-term prognostic indicator of cardiovascular morbidity and mortality in patients who are hospitalised with this condition.[6] In this article, we review the physiopathology, the clinical aspects, the diagnosis, and treatment of patients with both conditions.

Physiopathology of COPD and Heart Failure

The relationship between COPD and cardiovascular events is not completely clear. Patients with COPD do not have a higher risk of presenting arterial hypertension or left ventricular hypertrophy. However, there is evidence suggesting that the systemic inflammation present in these patients can play an important role in the development of atherosclerosis.[7] Thus, for example, patients with severe COPD have 2.18 to 2.74 times the probability of presenting high circulating C-reactive protein (CRP) levels.[8] One hypothesis to explain the high prevalence of left ventricular systolic dysfunction in COPD patients is that the systemic inflammation accelerates coronary atherosclerosis progression, leading to the development of ischaemic heart disease. The high incidence rate of motor alterations in the left ventricular wall and left ventricular dysfunction which we observe in COPD patients could also explain the relationship between both chronic processes.[9]

Skeletal muscle alterations in patients with COPD and HF include a decrease in muscle mass size and diameter. On the fibrillar level, atrophy of type I oxidative fibres occurs, as does a relative increase in type IIa and IIb glycolytic fibres as a result of decreased oxidative enzyme activity and increased glycolytic activity, respectively.[10] Different techniques have demonstrated the presence of a reduced high-energy phosphate concentration at rest, which becomes more pronounced during exercise, in addition to a faster pH decline and slower rephosphorisation after exercise in patients with both COPD and HF.[11]

Loss of muscle mass and skeletal muscle atrophy have more serious clinical and therapeutic implications in patients with COPD and HF. Muscular atrophy contributes to muscle fatigue during exercise, which leads these patients to interrupt their exercise in spite of not exhausting their cardiac and respiratory reserves.[12] As a result, the maximum oxygen consumption is directly related to skeletal muscle mass in both processes.[13] The therapeutic interventions that improve pulmonary and left ventricular function in patients with COPD and HF respectively do not revert the muscular atrophy process, and do not, therefore, relieve functional intolerance. The mechanisms involved in muscular atrophy in both diseases are unknown, although they seem to be related with muscular disease, systemic inflammation and an increase in oxidative stress, which contributes to reducing protein synthesis and accelerating protein degradation.[14] High circulatory values of proinflammatory cytokines have been detected in patients with COPD and HF. These include 8-isoprostane, which is also found in high concentrations in the pericardial fluid of HF patients.[15]

Key Biological Markers in Patients With COPD and Heart Failure

Different studies have pointed to biological markers that are capable of offering new possibilities for studying cardiovascular disease. We might suppose that evaluating these new markers, whether in conjunction with traditional risk factors or not, could serve to offer more accurate predictions, diagnoses and prognoses for the presence or absence of events related to these two conditions. It also seems clear that COPD could also be useful as a biological marker for HF and vice versa.

Both BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal fragment of B-type natriuretic peptide) are produced from a prohormone, proBNP, which is secreted in the myocytes by an increase in atrial and ventricular filling pressure.[16] Both peptides have been fully studied in many multicentre studies such as the Breathing Not Properly Study or PRIDE study, and it was shown that they have a high negative predictive value (NPV) for excluding the diagnosis of HF in patients who call upon emergency services due to dyspnoea.[17] Thus, BNP values under 100 pg/mL or NT-proBNP values under 300 pg/mL exclude the diagnosis of HF with a NPV above 90%. Furthermore, elevated BNP and NT-proBNP levels can increase the sensitivity and specificity of clinical judgment when it comes to diagnosing HF; the phenomenon is more marked when levels are higher.

The ICON project, which included 1256 patients with acute dyspnoea, allowed us to establish various cut-off points to confirm or exclude the diagnosis of HF according to patient age. For patients younger than 50, the cut-off point was 450 pg/mL (97% sensitivity and 93% specificity); for those between 50 and 75, the value was 900 pg/mL (90% sensitivity and 82% specificity) and for those older than 75, 1800 pg/mL (85% sensitivity and 73% specificity).[18] Figure 1 shows a diagnostic approximation for HF based on the BNP and NT-proBNP values.

As for studies on COPD patients, assessing BNP and NT-proBNP has been shown to be useful for excluding the diagnosis of HF with a sensitivity and predictive values similar to those observed in previous works. In a recent study performed by Rutten et al[19] which included 405 stable patients with COPD, we observed that 20.8% of the patients were diagnosed with HF. Evaluating NT-proBNP in that study maintained a high negative predictive value for excluding the presence of HF in this patient group.

Despite the body of evidence supporting the value of BNP for diagnosing patients with dyspnoea, there are limitations in its interpretation. For example, obese patients tend to present lower BNP values than those found in subjects whose body mass index is lower than 30 kg/m^2 who consult for dyspnoea associated with HF.[20] This could be due to the fact that adipocytes have receptors that bind to and catabolise BNP, thus decreasing its level in peripheral blood.[21] Kidney failure is another process that could lead to elevated BNP levels.[22] However, we must consider that its values do not appear altered in patients with a glomerular filtration rate over 60 mL/min/m^2. In contrast, the cut-off point should be higher in elderly patients with moderate or severe kidney failure.[23] In fact, patients with glomerular filtration rates below 30 mL/min/m^2 have not been included in multicentre dyspnoea studies. Furthermore, it is not known whether this peptide would be useful in diagnosing HF in chronic renal failure patients on haemodialysis.

Some patients with dyspnoea, especially elderly patients, have been studied less and may frequently present intermediate NT-proBNP values (between 2 cut-off points), which is known as the "NT-proBNP grey zone" and does not allow for establishing or excluding the diagnosis of HF. In these cases, it is necessary to perform more complementary tests to establish the HF diagnosis precisely.

One marker that has received attention in COPD patients with or without HF is PCR, a protein that acts as an acute phase reactant in response to the stimulus induced by interleukin (IL) 6. It has a proinflammatory and proatherogenic effect on endothelial cells and favours monocytes liberating proinflammatory cytokines, such as IL-1b and the tumour necrosis factor alpha (TNFα). It seems that its proinflammatory actions are mediated, at least in part, by the activation of nuclear transcription factor kappa B (NF-$\kappa\beta$), the endothelial lesion, the production of oxygen-free radicals, and the

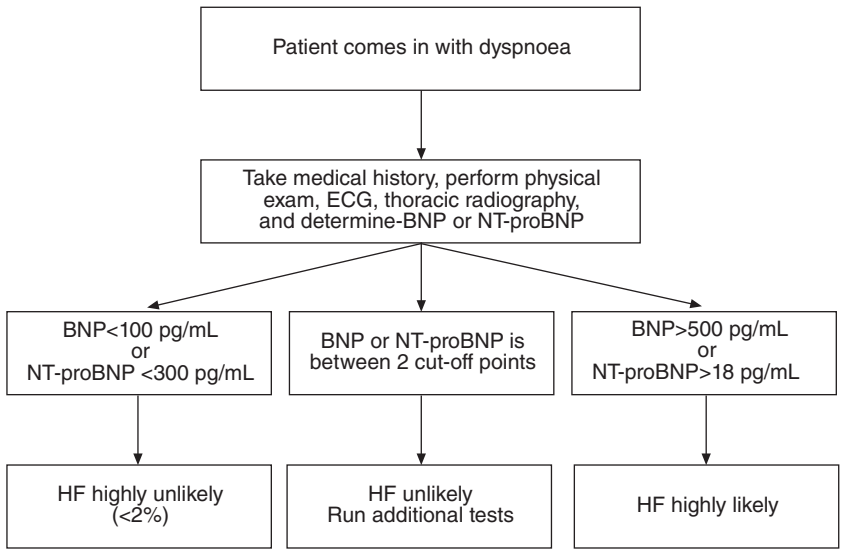

Figure 1. Approximation to a heart failure diagnosis based on BNP and NT-proBNP values. BNP: B-type natriuretic peptide; ECG: electrocardiogram; HF: heart failure; NT-proBNP: N-terminal fragment of B-type natriuretic peptide.

migration and activation of smooth muscle cells from the vascular wall.[24,25] Elevated PCR seems to be not only the main risk factor for developing cardiovascular diseases,[26,27] but it also adds a prognostic value, when applied, to that of the Framingham scale.[28] With COPD, an essentially inflammatory disease, serum values of this protein tend to be high, which can also be observed in active smokers who do not have this condition. Other biological markers that are taking on greater relevance at present are adipocines[29] which favour the development of atherosclerosis, some systemic inflammation markers such as TNFα,[30] other molecules such as IL-8 or 8-isoprostane,[31] oxidative stress markers such as superoxide dismutase (SOD),[32] and muscular enzymes, such as citrate synthase or the lactate dehydrogenase enzyme (LDH).[33]

Diagnostic Problems in Patients With COPD and Heart Failure

In patients with COPD, whether or not it is associated with HF, it is often difficult to perform differential diagnosis of the dyspnoea. The symptoms and physical signs of both diseases may coexist and they often do not correlate with the patient's haemodynamic state.[34]

The electrocardiogram, which presents a high negative predictive value for the diagnosis of systolic ventricular function when it is normal, is not a specific procedure for diagnosing HF when there are alterations, as is very frequent in patients with COPD and HF.[35] In this respect, determining BNP and/or NT-proBNP can be helpful in approximating a diagnosis for these patients when it comes to whether or not to exclude the diagnosis of HF,[36] as stated before. However, although there are studies that demonstrate the BNP's usefulness for evaluating acute dyspnoea, there is little evidence about its usefulness in patients with COPD associated with HF. Another of these parameters' important limitations is that they tend to be high in elderly patients with arterial hypertension, cor pulmonale or atrial fibrillation, which are frequently present in COPD patients.[37,38] As a result, we will need additional studies in order to understand the true role it plays in diagnosis and estimating the prognosis in this patient subgroup.

Using an echocardiogram in COPD patients can detect any left ventricular function alterations, both diastolic or systolic, that are associated with the presence of cardiovascular disease in a high percentage of cases.[39] In addition, the echocardiographic evaluation of the right ventricle, which determines the systolic pulmonary artery and interventricular septal pressures, is fundamental when it comes to assessing the presence of cor pulmonale in COPD and establishing its short-term prognosis.[40]

Although echocardiography is the test of reference for diagnosing HF, the test can be limited in those cases of obesity or COPD that have a poor echocardiographic window due to presenting pulmonary hyperinflation.[41] In these cases, evaluating the right ventricle by magnetic resonance imaging (MRI) or right catheterisation can be more objective. However, these complementary tests are expensive, invasive and require more experience and availability before their definitive use.

In the resting pulmonary function tests we can see that the obstructed airflow, the destruction of pulmonary tissue in emphysema patients and the respiratory muscle weakness in COPD patients provoke an obstructive-type respiratory defect. In turn, heart failure is accompanied by the development of a restrictive disorder, which is partly due to the heart enlargement and pulmonary venous congestion that occur in this disease.

During exercise, the dynamic hyperinflation caused by increased residual function capacity, tachypnea caused by COPD and the increase of dead space (Vd/Vt) and CO_2 consumption (VCO_2) resulting from the HF, all increase the abnormal ventilation/perfusion relationship (V/Q) caused by the respiratory conditions listed above.[42] In addition to this, a summation occurs in the drop in carbon monoxide diffusing capacity (DLCO), which is provoked by both the COPD and HF, and limits capacity during exertion.

Meanwhile, arterial gasometry allows us to detect the alterations in the gaseous exchange that occur in COPD and HF patients. During exertion, COPD provokes a decrease in O_2 arterial pressure (ApO_2) and an increase in CO_2 arterial pressure ($ApCO_2$), while the HF worsens the gaseous exchange, which favours hypoxaemia and increases or compensates for the $ApCO_2$ increase (Table 1).[43]

Therapeutic Aspects in Patients With COPD and Heart Failure

There is little scientific evidence as far as prospective studies and randomised clinical trials regarding combined treatment for patients with COPD and HF. Most of these patients come from retrospective

Table 1
Physiopathology of Respiratory Function in Patients With Chronic Obstructive Pulmonary Disorder (COPD) and Heart Failure (HF)

COPD	COPD+HF	HF
Obstructive type	Altered V/Q	Restrictive type
Tachypnea		Increased Vd/Vt
Increased RFC		Increased VCO_2
Decreased ApO_2	Gaseous interchange alteration	Decreased ApO_2
Increased $ApCO_2$		Decreased or increased $ApCO_2$
Normal or decreased DLCO	DLCO alteration	Decreased DLCO

Abbrevations: RFC, residual functional capacity; DLCO, carbon monoxide diffusing capacity; $ApCO_2$, CO_2 arterial pressure; ApO_2, O_2 arterial pressure; Vd/Vt, dead space.

studies, clinical trial subgroup analyses or meta-analyses that have other purposes than that of evaluating the effects of combined treatment for both processes. What is taken into account, however, is the fact that pharmacological treatment for COPD may have an influence on the clinical evolution of the HF patient and vice versa. We now offer a brief review of the therapeutic aspects of both.

Pharmacological Treatment for Heart Failure That Influences COPD Patient Prognosis

In recent years, one of the most controversial aspects in managing HF with systolic dysfunction has been the use of beta blockers in patients with COPD and a left ventricular ejection fraction (LVEF) below 40%. Certain studies have evaluated the risk of worsening the bronchospasm and respiratory function in COPD patients who receive those drugs.[44] However, the most recent meta-analyses show that in COPD patients with no associated asthma and no positive bronchodilation test, the use of beta blockers improves prognosis in terms of mortality and morbidity if these patients present left ventricular (LV) systolic dysfunction associated with the respiratory disease.[45] In light of the scientific evidence on this topic, a Cochrane Library review stated that COPD patients should not be excluded from treatment with beta blockers if they have a history of heart conditions including acute myocardial infarction and HF.

There is currently little evidence about blocking the renin-angiotensin-aldosterone axis in patients with COPD and HF. Some retrospective studies, like that performed by Manzini et al., show a reduced relative risk of hospitalisation (relative risk [RR=0.66, 95% confidence interval [CI], 0.51-0.85) in COPD patients treated with statins who receive combined treatment with angiotensin converter enzyme inhibitors (ACE inhibitors), and/or angiotensin II receptor blockers (ARBs).[46] In fact, in patients with an absolute contraindication for beta-blockers, associating ACE inhibitors and ARBs can be a good treatment option for increasing survival, as shown in some meta-analyses that have evaluated this topic.[47]

The use of diuretics is another important aspect that must be evaluated in these patients, as high doses of loop diuretics can produce metabolic alkalosis, which leads to the development of hypoventilation as a compensation mechanism, worsening hypercapnea in turn.[48] In addition, although no large-scale prospective studies are available, the use of high doses of diuretics in HF patients is associated with a higher risk of kidney dysfunction and morbidity/mortality.[49]

Pharmacological Treatment of COPD in the Patient With Heart Failure

β_2-adrenergic bronchodilators, whether fast-acting or slow-acting, are one of the basic pillars of pharmacological treatment for COPD patients. However, their side effects, such as tachycardia, can increase oxygen consumption in the myocardium and have a detrimental effect on the clinical evolution of HF patients, as some authors have recently demonstrated.[50] Although no randomised studies on this topic are available, some research has shown that use of fast-acting β_2-adrenergic bronchodilator agents can increase the risk of mortality in patients with a left ventricular systolic dysfunction.[51] For this reason, slow-acting bronchodilators with less of a tachycardial effect, such as tiotropium, may constitute an adequate treatment alternative for patients with both COPD and HF.[52] We must take into account the fact that tiotropium, with its anticholinergic action, does not have adverse effects for HF patients, although there is little evidence on its long-term prognosis.

On the other hand, the use of corticosteroids can increase the risk of hydrosaline retention in HF patients. There are studies that show that COPD patients who receive high doses of corticosteroids (doses of prednisone above 20 mg/day) had a higher risk of presenting an episode of decompensated heart failure than those who received these drugs in lower doses.[53] In this respect, the use of inhaled corticosteroids may be an effective alternative treatment for HF patients and several previous acute manifestations of COPD; it has a lower risk of causing side effects than oral administration of the same drugs.

Finally, euphyllins, in increasing disuse, do not seem to be a good treatment alternative for patients with COPD and HF. The main reason is that they carry a risk of arrhythmias.

Treating Pulmonary Arterial Hypertension in Patients With COPD and Heart Failure

Pulmonary arterial hypertension (PAH) is one of the survival markers for COPD, and is even more important than the pulmonary function parameters. Structural alterations are primarily due to hypoxaemia; this condition, in conjunction with the effects of tobacco use on the pulmonary endothelium, change the history of pulmonary hypertension in COPD patients[54] (Figure 2).

PAH in patients with lung diseases, particularly COPD, is variable, although in most cases it is mild to moderate. For COPD patients with mild PAH (pulmonary arterial pressure between 25 and 30 mm Hg), treatment of that complication is a topic for debate.[55] However, when PAH is moderate, its values can increase in moments when the disease is flaring up,[56] during exercise[57] or even sleep.[58] Additionally, these acute increases can contribute to the development of right heart failure, and therefore its prevention is an important part of treating PAH in these patients.

Vasodilators and antiproliferative drugs such as epoprostenol, bosentan and sildenafil have led to good results in treating idiopathic PAH. Despite this fact, its use in COPD patients is probably unjustified, except in the subgroup of patients with severe PAH (pulmonary arterial pressure above 40 mm Hg).[59] On this topic, a recent study showed that treatment with sildenafil improves exercise capacity (measured by the 6-minute walking test) and haemodynamic parameters in these patients.[60]

Another important factor in treating PAH is the use of prolonged oxygen therapy, which is logically due to the important role hypoxia plays in the development of that disease in COPD patients. Several studies have shown that its use in these patients during at least 16 hours a day provides a moderate improvement, decreasing PAH progression by stabilising or lowering pulmonary arterial pressure levels.[61,62]

In the future, it will be necessary to develop new studies that provide more data on the use of the treatment measures mentioned before. It is possible that associating pharmacological treatment with chronic oxygen therapy is the best option.

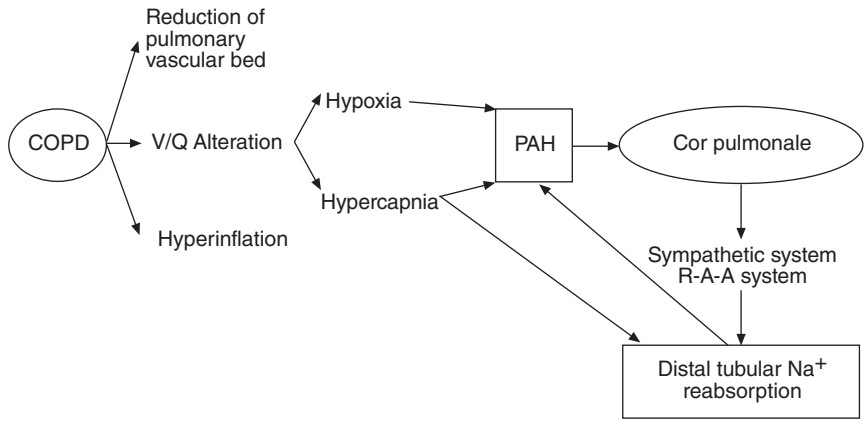

Figure 2. Physiopathology of the pulmonary arterial hypertension (PAH) and cor pulmonale in patients with chronic obstructive pulmonary disorder (COPD). V/Q alteration, change in the ventilation/perfusion ratio; R-A-A system, renin-angiotensin-aldosterone system.

Treating Right Heart Failure in COPD. Cor Pulmonale

Severe PAH can lead to developing right heart failure and give rise to systemic congestion and the inability to adapt the right ventricular output to the systemic vascular demand during exercise. Systemic congestion in COPD patients does not seem to be caused only by the mechanisms taking place in pulmonary and systemic congestion generated by left heart failure. It seems that hypercapnea is also a contributing factor; this condition increases distal tubular reabsorption of sodium and stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone axis to contribute to additional sodium reabsorption (Figure 2).[63]

Conventional measures, quitting tobacco use and administering long-term oxygen therapy in patients with COPD and PAH, seem to be ineffective for improving the right ventricular overload that is present in these patients, even when they resolve hypoxaemia and therefore improve the prognosis.[64] On the other hand, some potent systemic vasodilators, such as calcium antagonists, have been used in the past with disappointing results.[65] Therefore, the therapeutic agents used for treating primary PAH and which also have an antiproliferative action, such as bosentan or sildenafil, are beginning to be considered as a treatment for the right heart failure that appears in patients with severe COPD.

Non-invasive Mechanical Ventilation in Patients With COPD and Heart Failure

The main goal of non-invasive mechanical ventilation (NIMV) in acute COPD is to correct the hypercapnea and respiratory acidosis that result from alveolar hypoventilation, and to allow the respiratory muscles to rest. While the disease is peaking, BiPAP-type (bilevel positive airway pressure) ventilators are normally used, with an inspiratory pressure (IPAP) that increases effective alveolar ventilation and decreases muscle exertion, and an expiratory pressure (EPAP) that improves the V/Q ratio and resolves areas with pulmonary atelectasis.[66] This type of ventilator support is less effective in heart failure than in a COPD flare-up, as was shown in a recent study in which the patients had similar gasometric severity.[67]

NIMV may also be indicated for patients with COPD and chronic respiratory failure in a stable phase. The potential benefits of its use, other than resting the respiratory muscles and increasing ventilation, consists of improving the gaseous interchange alterations during sleep, increasing sleep quality, and increasing tolerance to exercise, which can mean better quality of life and better survival for the patient.[68] However, there are no available studies that demonstrate this last aspect in a conclusive way, and for that reason, it is not currently recommended as a routine treatment in these patients.

In HF, there are precedents for the successful use of CPAP (continuous positive airway pressure). This treatment method enables us to increase the residual functional capacity and decrease the right-to-left intrapulmonary shunt to increase oxygenation. It also decreases the afterload by lowering the left ventricular transmural pressure, and increases cardiac output. Most of the gaseous interchange translates to clinical improvement, which can be seen from the first hour after applying CPAP.[69]

In patients with cor pulmonale secondary to a chronic pulmonary disease like COPD, the use of BiPAP can improve the right ventricular function and decrease plasma levels of natriuretic peptides.[70] Furthermore, recent studies have concluded that administering this treatment method can play an important role for HF patients with associated muscle fatigue and hypercapnia.[71,72] Nonetheless, we need new prospective studies, with a wide range of patients, to identify the patient subgroups to which NIMV can offer increased symptomatic and functional benefits, and with them, a more pronounced effect on their quality of life and survival.

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