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Editorial

Sleep Apnea, Heart Failure and Mineralocorticoid Receptor Antagonists: A Triad to be Considered

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Abstract

Sleep apnea is a frequent breathing disorder associated to important cardiovascular diseases, mainly resistant hypertension and heart failure. In parallel the old spironolactone has showed a fantastic revival as a first class drug in the treatment of chronic heart failure, and also have been published positive results in the association of this drug with others in patients with resistant hypertension. Lately other aldosterone blockers have been approved and due to the better understanding about the mechanism of action, this pharmacologic group is now called as mineralocorticoid receptor antagonists (MRA). Thistherapeutic tool is being used not only in pure cardiovascular disorders, but also in kydney dysfunction and diabetic renal damage. This review focus on the potential benefit of MRA in patients with heart failure and sleep apnea. Severallow and médium scale studies are showing that the above beneficial effect is becoming evident. Large scale trials are strongly encouraged to demmonstrate a solid confirmation for the use of MRA in the growing incidence of the association of heart failure and sleep apnea.

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ABBREVIATIONS

SA: Sleep Apnea; HF: Heart Failure; RAAS: Renin Angiotensine Aldosterone System

INTRODUCTION

It has been clearly demonstrated that sleep apnea (SA) is frequently observed in patients with heart failure (HF) [1-3]. In general, sleep apnea consists of two types: obstructive and central sleep apnea (OSA and CSA, respectively). In patients with OSA, blood pressure is frequently elevated as a result of sympathetic nervous system and hormones overactivation. It is also important the role of exagerated negative intrathoracic pressure during obstructive apneas that may have a negative impact in cardiac output and may promote the progression of HF. The hipoxia may also produce endothelial dysfunction with its concequences in arterial blood flow [3].

Dysfunction of the hypothalamic-pituitary-adrenal axis includes the mineralocorticoid receptor which can undergo also dysfuntion related to the circadionrythm and can disrupt sleep. The hyperactivity of the axis and the receptors, may also produce negative impact in metabolic pathwasy as insuline resistance and arterial hypertension [4].These concepts have estimulate the research on mineralocorticoid recptor antagonists (MRA) in patients with HF and SA, and some guidelines and consensus have already included this pharmacoligic group as recomendation in that group of patients and also in the population with resistant hypertension [5-7]. In summary the associations of such disorders have an obvious multifactorial pathogenesis, and the search for a more effective therapeutic approach to the problem shows a growing role of MRAs on top of many other groups of drugs used in these clinical settings. The rationale for this evidence is that blocking the mineralocorticoid receptor inhibits the deleterious mechanisms that cause cardiovascular and respiratory dysfunction and potential organ damage [6,8].

MRA and outcomes in HF patients

Spironolactone appeared in the market more tan 60 years ago as a sparring potassium diuretic. And it was more than a quarter of century later that the RALES Trial showed significant benefits of the drug in survival of chronic HF patients with reduced ejection fraction [9]. After that famous trial many others studies with the same drug and with eplerenone, other compound of the MRA group, have confirmed solid benefits in the evolution of patients with different types of HF and associated problems like hypertension, diabetes, renal dysfuntion, among others [9-12] and this indication is now recommended as first line treatment in the most important recent Guidelines [13]. This is the scientific rationale for the analysis and continuos research of the relationship between SA, HF and MRA.

Pathogenic pathways

SA is the most common cause of resistant hypertension, which has been proposed to result from activation of the renin-angiotensin-aldosterone system (RAAS). SA is associated with increaseedAngiotensine II and aldosterone plasma levels, especially in hypertensive and HF patients [6,15-17]. Many neurohormones and neuromodulators have now been identified that contribute to the regulation of pharyngeal motor neuron activity and airway patency. Most of this pathophisiologic effectors and its pathways are also disturbed in the pathogenesis of HF. In particular the increase of aldosterone is considered a crutial factor in the evolution and oucomes of patients suffering HF. The hpyperactivation of RAAS prduces changes not only in the levels of aldosterone, but also in renine, angiotensine I and II, and associated systems like the sympathetic hormones, quinines and others [17,18]. In addition, these neurohormonal hyperactivation is also associated to insuline resistance, proinflammatory mechanisms, and other metabolic and enzimatic disturbances found in obesity, which play an important pathogenic role in the association of HF and SA [15,16,19].

When focusing in the relationship of aldosterone and cardiovascular dysfuntion, the high levels of the hormine have harmful effects very early in human life. It has been proved that in newborns such alteration can produce functional and even anatomical changes in the cardiac myocytes [11,20]. Definitely, this is caused by the individual's genetic profile, and it supports the current concepts about the etiopathogenia of hypertension and even of the myocardial dysfunction.In addition to the genetic influence in the production of aldosterone, the hormone contributes to the alteration of endothelial function [21], and it does so not only because of disorders in the permeability of the endothelium and reduction in the nitric oxide production, but it also increases the endothelial dysfunction generated by other particles like LDL, angiotensin, etc. [22].The contribution of these specific mechanisms to the genesis of cardiovascular dysfunction are also described in the association of HF and SA, and are the best rationale for the potentialinclusión of MRA in the treatment of patients undergoing both disorders.

Is there a room for MRA in the treatment of OSA?

Many different therapeutict tools have been tested and/or recommended for the management of SA. The list includes not only drugs and ventilatory techniques but also devices [23-26]. The assocition of HF with SA has cleary contributed to a significnat increase of the above list [27-29].

As it has been previously explained, the growing role of MRA in the treatment of chronic HF, and the frequent asociation of SA in this population, has estimulated the investigation in the benefits of this strategy. Probably the positive results observed in patients with resistant hypertension and SA, have been the strongest support to the initial research in HF [6,30-32]. Even more demmostrative, is that recent publications in the use of MRA in hypertension have already mentioned the obvious benefits of this interventions when HF is also associated to high blood pressure disorder [33]. In a a retrospective cross-sectional cohort study including 60327 hypertensive patients, within the Kaiser Permanente Southern California health system in the period between 1/1/06 - 12/31/10 , the use of MRA was clearly noted in those having higher rates of preexisting chronic kidney disease (53% vs 41%, $p<0.001$) and congestive heart failure (72% vs 34%, $p<0.001$).. Given the potential benefits of MRB in SA, the authors are currently evaluating outcomes in SA patients on MRA vs no MRA [34]. This is another evidence of the interest in this clinical and therapeutic relationship.

CONCLUSION

The incidence of SA in heart failure patients has enough evidence. It is even more important when hypertension is associated. The mechnisms to produce the breathing disorders is a combination of neurohormonal, metabolic and mechanical alterations. Among them, the hyeractivation of the RAAS plays a crutial role. Aldosterone is clearly increased and damaging. Based in this data, several studies have suggested posssitive results in patients with HF and SA. Large scale trials are encouraged to confirm if this pharmacologic intervention has a significant benefit in this population.

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