

## Aldosterone Antagonists: From Cirrhosis to Heart Failure?

**To the Editor,**

We have read with interest the article recently published in your journal by Skhiri M et al with the title: "Evidence-Based Management of Right Heart Failure: a Systematic Review of an Empiric Field." The authors carry out a wide and comprehensive review of the different pharmacological treatments that have shown clinical benefit in the treatment of right heart failure (RHF).<sup>1</sup> However, in the article the role of antialdosterone drugs in the clinical management of patients with RHF is not addressed. On the other hand, scientific evidence of the use of antialdosterone drugs in RHF is scarce. This may be one of the reasons Skhiri M et al have not included this treatment group in their review.<sup>1</sup>

Patients with RHF may present symptoms of jugular venous pressure elevation, ascites and oedema of the lower limbs. Clinically, the congestion of RHF may partially resemble, congestion with ascites due to chronic liver conditions. In this respect, there are certain aetiological and pathogenical characteristics that are common to RHF and liver cirrhosis (LC).<sup>2</sup> Both clinical situations are accompanied by a decrease of circulating arterial pressure, due to low cardiac output in the case of heart failure (HF) and decreased peripheral resistance in the case of LC.<sup>2</sup> In both HF and LC, activation of the renin-angiotensin-aldosterone axis causes vasoconstriction of the renal arteries, fluid and sodium retention and an increase in venous congestion. In this subgroup of patients with RHF and ascites, pharmacological treatment has been very little assessed in clinical trials. In patients with RHF, the use of drugs that have been shown to be

of great benefit in HF with left ventricle systolic dysfunction may be clinically difficult to tolerate. Many patients with RHF have a depletion of intravascular volume and are at risk of arterial hypotension which limits the use of drugs such as beta-blockers or angiotensin-converting enzyme inhibitors (ACEIs). On the other hand, in RHF as in LC, a certain degree of resistance to loop diuretics due to secondary hyperaldosteronism is frequently found.<sup>2</sup> In this subgroup of patients with RHF and symptoms of ascites, treatment with aldosterone inhibitors, such as spironolactone, can be useful to control volume overload, just as in LC. The main limiting factor to the use of anti-aldosterone drugs at high doses in HF is the risk of hyperpotassaemia and kidney failure that could be exacerbated by the concomitant use of other blockers of the renin-angiotensin-aldosterone axis.<sup>2</sup> In this form of RHF, antialdosterone drugs used alone or in combination with loop diuretics could be effective to maintain euvolemia without any significant increases of hyperpotassaemia.<sup>2</sup> However, we are aware that applying this practical approach to pharmacological treatment of cirrhosis to HF, although perhaps reasonable from the ethiopathogenic point of view, should have its clinical benefits confirmed by controlled randomised clinical trials performed in patients with this profile.

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been shown to improve survival. The effects of AA are believed to be mediated through neuro-hormonal modulation and not primarily through volume homeostasis. Aldosterone antagonists also improve cardiac remodeling, decreasing ventricular size and improving function.<sup>1</sup> In contrast to its proven effects in LVSD, the effects of AA in patients with left heart failure and preserved ventricular ejection fraction<sup>2</sup> or in patients with right heart failure have not been as extensively studied.<sup>3</sup>

Experimental data suggest that AA may improve endothelial function and nitric oxide release.<sup>4</sup> A pilot study in Colorado, USA, is currently investigating the role of secondary hyperaldosteronism in patients with right ventricular failure and pulmonary arterial hypertension (World Health Organization Group 1).<sup>5</sup>

One of the primary endpoints of the study will be to determine the 6-month effects of spironolactone on brain natriuretic peptide levels and hemodynamic parameters. This study will hopefully provide some insights on the role of AA in right heart failure. In patients with transposition of the great vessels and systemic right ventricles, elevation in aldosterone levels has also been noted.<sup>6</sup> More generally in congenital heart disease, it has been shown that aldosterone levels are elevated in patients with asymptomatic right ventricular dysfunction, and regardless of the type of malformation.<sup>7</sup>

At least 2 studies are investigating the effect of eplerenone or spironolactone in patients with systemic right ventricle (ClinicalTrials.gov identifier: NCT00703352, Spain) or congenital heart diseases (ClinicalTrials.gov identifier: NCT01069510, USA).

These studies will help us establish whether AA improves survival or hospitalization rates in patients with right heart failure.

At this time, a pragmatic approach adding AA to loop diuretics in patients with right heart failure and refractory volume overload appears reasonable. Whether this will be translated into better symptoms or prognosis appears unknown at this time. We have to acknowledge that, even in 2010, right heart failure remains an empirical field.

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## Response

### To the Editor,

We would like to thank Dr Méndez Bailón and his colleagues for their comments. In patients with heart failure and left ventricular systolic dysfunction (LVSD), the use of aldosterone antagonists (AA) has

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