



Aldosterone antagonism and atrial fibrillation: time for clinical assessment?

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This editorial refers to 'Spironolactone reduces fibrosis of dilated atria during heart failure *in rats with myocardial infarction*' by P. Milliez *et al.*, doi:10.1093/eurheartj/ehi478

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia. Presently available therapy for AF is suboptimal: 'rhythm control' drugs are fraught with the risk of pro-arrhythmia and other adverse effects, 'rate control' leaves the atria fibrillating and fails to reproduce physiological heart rate adaptation, and ablation procedures are expensive, complex, and incompletely effective. Over the past few years, the notion of 'upstream' therapy, targeting signalling pathways involved in the development of the substrate that supports the arrhythmia,¹ has gained increased interest, supported by experimental² and clinical³ studies which indicate that suppression of the renin-angiotensin system can prevent AF. Such therapy is particularly effective in the context of left ventricular (LV) dysfunction,⁴ perhaps because congestive heart failure (CHF) engages angiotensin-independent remodelling cascades.² A potentially important component of the renin-angiotensin system that has not been previously investigated in AF prevention is the mineralocorticoid aldosterone.

Aldosterone production is increased by activation of the renin-angiotensin system, via the action of angiotensin-II on aldosterone-producing cells. Although the primary source of aldosterone production is the renal cortex, there is also evidence for intracardiac aldosterone generation.⁵ Aldosterone has a wide range of both genomic and non-genomic actions and is a potent stimulus for cardiac fibrosis.⁵ In addition, aldosterone may produce direct electrophysiological changes.⁶ AF increases serum aldosterone concentrations, whereas restoration of sinus rhythm returns aldosterone concentrations to normal.⁷ Patients with primary hyperaldosteronism show a 12-fold greater AF risk when compared with age-, gender-, and blood pressure-matched controls.⁸ Aldosterone production is enhanced by the renin-angiotensin activation occurring in CHF, and it

would not be surprising if the resulting mineralocorticoid receptor stimulation contributed to the atrial fibrosis that is an important component of the AF substrate associated with CHF.^{1,2}

Milliez *et al.*⁸ present the results of a study assessing the effects of spironolactone, lisinopril, atenolol, or their combination on atrial arrhythmias, hemodynamics, and atrial fibrosis in rats with CHF following extensive myocardial infarction (MI). Each treatment and each treatment combination suppressed atrial ectopy in a statistically significant fashion. Only spironolactone, alone or in combination with a beta-blocker or converting enzyme inhibitor, significantly attenuated CHF-associated atrial fibrosis, an important factor in atrial tachyarrhythmia promotion.^{2,9,10}

There are a number of important novel elements presented in this report. To the best of my knowledge, this is the first description of the attenuation of CHF-induced atrial arrhythmogenic remodelling by an aldosterone antagonist. Interestingly, beneficial effects were seen when 1 month of therapy was initiated 3 months after MI, at a time when atrial remodelling was already well developed. This observation suggests that already developed CHF-related atrial fibrosis may be reversible. This concept, if confirmed, would have important potential therapeutic implications, because it is often not possible to begin treatment in man before a significant degree of atrial remodelling has already occurred. This finding contrasts with studies showing that CHF-related atrial fibrosis does not resolve upon full haemodynamic recovery 4 weeks after the cessation of ventricular tachypacing in dogs.^{9,10} The discrepancy may be due to species-related factors (dogs vs. rats) or to the fact that reversal was assessed in the context of drug therapy in the Milliez study, compared with following spontaneous haemodynamic recovery in the dog work. Further investigation is warranted to determine whether and under what conditions renin-angiotensin-aldosterone axis suppression can lead to reversal of already established CHF-related atrial fibrosis. The Milliez study is also the first, to the best of my knowledge, to assess combination therapy in the prevention of CHF-related atrial fibrosis. The authors found no advantage to two-drug combinations involving the aldosterone antagonist, converting enzyme inhibitor, and/or beta-adrenoceptor blocker.

A number of questions are raised by the data presented in the Milliez paper. Infarct size was somewhat smaller

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(by ~25%) in all of the treatment groups when compared with the control MI group. Although the differences in infarct size were not statistically significant for any group, it is possible that the control group had larger MIs by chance and that this could have contributed to some of the differences seen between control and intervention groups. P-wave durations were significantly decreased when compared with control MI in only the spironolactone-treated groups; however, the actual differences in mean P-wave duration among MI groups with and without various interventions are so small to raise questions about their functional significance.

Despite these limitations, the results of the Milliez study are intriguing. In the context of the demonstrated protection by aldosterone antagonists against other cardiac endpoints in patients with LV dysfunction,¹¹ the Milliez results point to a need for clinical trials of aldosterone antagonists in patients susceptible to AF, particularly those with CHF or important LV dysfunction. One place to start might be in the databases of already-completed randomized studies. For example, the aldosterone antagonist eplerenone has recently been studied in a randomized trial with over 3000 MI/LV dysfunction patients per group randomized to active drug or placebo.¹¹ If data on cardiac rhythm are available in this database, there may already be information available about the potential value of aldosterone antagonism for AF prevention, just as in previous studies with converting enzyme inhibitors.³ In any case, the Milliez study raises interesting and important questions for both clinical and basic investigation.

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References

1. Nattel S. Therapeutic implications of atrial fibrillation mechanisms: can mechanistic insights be used to improve AF management? *Cardiovasc Res* 2002;**54**:347–360.
2. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 2001;**104**:2608–2614.
3. Vermees E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. *Circulation* 2003;**107**:2926–2931.
4. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;**45**:1832–1839.
5. Mizuno Y, Yoshimura M, Yasue H, Sakamoto T, Ogawa H, Kugiyama K, Harada E, Nakayama M, Nakamura S, Ito T, Shimasaki Y, Saito Y, Nakao K. Aldosterone production is activated in failing ventricle in humans. *Circulation* 2001;**103**:72–77.
6. Tillmann HC, Schumacher B, Yasyev O, Junker M, Christ M, Feuring M, Wehling M. Acute effects of aldosterone on intracardiac monophasic action potentials. *Int J Cardiol* 2002;**84**:33–39.
7. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005;**45**:1243–1248.
8. Milliez P, DeAngelis N, Rucker-Martin C, Leenhardt A, Vicaut E, Robidel E, Beaufrils P, Delcayre C, Hatem SN. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. *Eur Heart J* doi:10.1093/eurheartj/ehi478.
9. Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. *Circulation* 2002;**105**:2672–2678.
10. Cha TJ, Ehrlich JR, Zhang L, Shi YF, Tardif JC, Leung TK, Nattel S. Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. *Circulation* 2004;**109**:412–418.
11. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.