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Atrial Fibrillation and ACE Inhibitors

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Earlier this year we explored a possible connection between the renin-angiotensin-aldosterone system (RAAS) and lone atrial fibrillation (*The AFIB Report*, March 2003 and Virtual Conference Room Sessions 1, 2 and 11). The idea, not supported by any medical evidence at the time, was that an afib episode would be initiated by an excess of aldosterone and terminated when this excess was eliminated through the action of natriuretic peptides released during the episode. Aldosterone is known to have many detrimental effects on the heart and some of them are associated with conditions known to promote LAF:

- Inflammation and fibrosis of the heart tissue are found in most LAF patients. Aldosterone causes inflammation and fibrosis of the heart tissue by direct action on the MC-receptors in the myocardium. This action is not accompanied by hypertension.
- Most LAF patients suffer from a systemic inflammation as expressed in abnormally high CRP (C-reactive protein) levels. Aldosterone causes inflammation.
- Atrial fibrillation is associated with an increased level of reactive oxygen species (ROS) in the heart tissue. Aldosterone causes an increased level.
- Atrial fibrillation is associated with an imbalance in the ANS. Aldosterone causes such an imbalance, primarily by increasing sympathetic activity.
- Hypokalemia (low potassium levels) is associated with an increase in PACs, which in turn are associated with an increased risk of LAF episodes. Aldosterone promotes hypokalemia.
- Hypomagnesemia (low magnesium levels) is associated with an increase in PACs, which in turn are associated with an increased risk of LAF episodes. Aldosterone promotes hypomagnesemia.

Although aldosterone production is primarily initiated by activation of the RAAS, it can also be initiated by ACTH the same hormone that stimulates the secretion of cortisol. A high potassium level or a low sodium level also causes aldosterone secretion to be increased. A magnesium deficiency causes an increase in aldosterone production and subsequent hypokalemia (potassium deficiency). An excess of calcium ions (Ca⁺⁺) can also increase aldosterone production because excess Ca⁺⁺ increases the secretion of ACTH.

An excessive production of aldosterone can also be caused by a benign tumour (adenoma) on the adrenal glands or simply by an enlargement (hyperplasia) of the adrenal glands. Hyperplasia itself has been linked to prolonged exposure to stress. Adrenal tumours are fairly common and can be genetically “ordained”.

As mentioned previously, aldosterone production is primarily initiated by the renin-angiotensin-aldosterone system. The RAAS is the body’s main system for dealing with a decrease in blood pressure that is too great to be handled by the autonomic nervous system alone. The primary purpose of the RAAS is thus to increase blood pressure by preserving (hoarding) sodium and water. The RAAS is normally activated by hypotension caused, for example, by a sudden shift from supine to standing position. The low blood pressure is first sensed by the kidneys, which proceed to secrete a small peptide called renin. Renin is transported to the liver where it helps to produce angiotensin I from a large protein called angiotensinogen. Angiotensin I, in turn, is carried by the blood to the lungs where it is converted into angiotensin II through the action of angiotensin-converting enzyme (ACE).

Angiotensin II is the most potent vasoconstrictor in the body. It causes the blood vessels to constrict and potentiates the sympathetic nervous system resulting in an increase in blood pressure. Angiotensin II also acts on the adrenal glands to produce aldosterone. Aldosterone causes sodium and water to be retained by the kidneys thus increasing the body’s fluid content and thereby the blood pressure. The action of the renin-angiotensin part of the RAAS may take seconds to minutes to kick in, but it may take days or even weeks before the full effect of aldosterone is felt.

If there is little medical evidence at the moment that aldosterone is involved in afib, is there any evidence that other parts of the RAAS may be? Indeed there is.

Researchers at the University of Leipzig in Germany recently reported that lone afibbers have significantly more receptors for angiotensin II (subtype I) in the left atrium than do people without LAF. The increase in receptors was apparent in both afibbers with mitral valve prolapse and in those without it. No increase in receptors was found in the right atrium. The researchers conclude that angiotensin II receptor subtype I may play a role in lone atrial fibrillation[1]. The presence of more receptors in afibbers would mean that the level of whatever protein is produced as a result of the angiotensin II molecule docking at its receptor would be elevated. If this protein, or perhaps aldosterone itself, is involved in promoting afib then blocking the subtype I angiotensin II receptor should result in a decrease in afib episodes.

Angiotensin II type 1 receptor (AT1R) antagonists are potent blockers of the receptors. Japanese researchers have found that candesartan (Atacand) significantly shortens afib episodes in dogs and prevents structural remodelling and fibrosis in the atrium[2]. Spanish researchers have found that the AT1R irebesartan (Avapro) allowed afibbers with persistent afib who were electrically cardioverted to stay in sinus rhythm longer after treatment with irebesartan + amiodarone than did patients medicated with amiodarone alone[3].

There is evidence that the AT1R valsartan (Diovan) can actually reduce aldosterone levels. A team of American and Italian researchers treated over 4,000 chronic heart failure patients with valsartan (160 mg twice daily) or placebo and compared plasma aldosterone levels after 24 months. The mean aldosterone level in the placebo group increased by 18.8 pg/mL, but decreased by 23.8 pg/mL in the valsartan group. Thus the mean reduction in aldosterone in the valsartan group compared with the placebo group was 29.3%. The difference between the two groups was most pronounced after just 4 months of treatment[4]. The same group of researchers later concluded that the incidence of new cases of atrial fibrillation among the heart

failure patients was significantly lower in the valsartan group than in the placebo group (5.27% versus 7.86% in 23 months of follow-up)[5].

Chinese researchers have found that the AT1R losartan (Cozaar) actually inhibits the production of aldosterone in the myocardium of rats with heart failure[6].

An alternative way of preventing the detrimental effects of angiotensin II is by inhibiting its synthesis as opposed to blocking its uptake (with AT1Rs). Angiotensin-converting enzyme inhibitors (ACE inhibitors) prevent the synthesis of angiotensin II from angiotensin I. There is now some evidence that ACE inhibitors may indeed affect afib episode frequency. Taiwanese researchers recently reported that the ACE inhibitor enalapril (Vasotec) significantly lengthens the afib-free interval following electrical cardioversion of chronic afib when given in combination with amiodarone. After 270 days 74% of the amiodarone + enalapril group was still in sinus rhythm as compared to only 57% in the amiodarone only group[7].

Danish researchers have found that the ACE inhibitor trandolapril (Mavik) decreased the risk of developing atrial fibrillation by over 50% in a group of heart disease patients (left ventricular dysfunction) who had just suffered a heart attack[8]. They point out that ACE inhibition is associated with a reduction in atrial premature beats (PACs), the forerunners of atrial fibrillation, and also tends to prevent enlargement of the left atrium.

Conclusion

Evidence is slowly accumulating to the effect that the RAAS or, perhaps more specifically, angiotensin II and aldosterone may indeed be involved in atrial fibrillation. There is now also emerging evidence that ACE inhibitors and angiotensin II receptor antagonists may act to prevent atrial fibrillation episodes most likely through a reduction in PAC frequency and prevention of structural and electrical remodelling of the atrium. Most research, so far, has involved patients with heart failure or other heart disease, so it is not clear whether the findings are applicable to lone afibbers. However, the observation by the University of Leipzig team that lone afibbers have an abnormally high level of angiotensin II type 1 receptors in the left atrium certainly lends support to the idea that the RAAS is involved in lone afib as well. If this is indeed so then ACE inhibitors or angiotensin II receptor antagonists may prove to be of some benefit in the treatment of LAF, particularly among afibbers with high blood pressure. Both types of drugs, of course, have many undesirable side effects and there are also indications that the effect of some of them, particularly the angiotensin II receptor antagonists may wear off over time[9,10].

The potential benefits of drugs that block aldosterone (mineralo corticoid) receptors rather than angiotensin II receptors should not be overlooked. Spironolactone, a potassium-sparing diuretic, is highly effective in blocking MC-receptors. By doing so, it rebalances the autonomic nervous system (increases parasympathetic activity and decreases sympathetic activity), decreases the risk of stroke, prevents hypokalemia, reduces fibrosis, improves endothelial function, and helps prevent hypertension (by blocking MC-receptors in the brain).

Spironolactone, unfortunately, has several nasty side effects, especially breast enlargement and impotence. It is therefore not likely to be a viable long-term solution for LAF prevention. However, a "cousin" of spironolactone, eplerenone, has recently been developed and shows great promise in initial trials. Eplerenone is significantly more effective than spironolactone and animal experiments have shown that it protects the heart, brain and kidneys, especially against stroke and vascular injury[11]. Eplerenone does not cause breast enlargement or impotence. Could this new drug help prevent episodes? If the hypothesis is correct, it is certainly a very real possibility, but of course only a clinical trial will tell.

In conclusion, the finding of an association between the RAAS and atrial fibrillation opens up exciting new avenues for the use of drugs, other than antiarrhythmics, in the treatment of LAF.

References

1. Boldt, A, et al. Expression of angiotensin II receptors in human left and right atrial tissue in atrial fibrillation with and without underlying mitral valve disease. *Journal of the American College of Cardiology*, Vol. 42, No. 10, November 19, 2003, pp. 1785-92
2. Kumagai, K, et al. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *Journal of the American College of Cardiology*, Vol. 41, No. 12, June 18, 2003, pp. 2197-2204
3. Madrid, AH, et al. Use of irebesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation. *Circulation*, Vol. 106, July 16, 2002, pp. 331-36
4. Cohn, JN, et al. Sustained reduction of aldosterone in response to the angiotensin receptor blocker valsartan in patients with chronic heart failure. *Circulation*, Vol. 108, September 16, 2003, pp. 1306-09
5. Maggioni, AP. Valsartan Heart Failure Trial (Val-HeFT). Presented at the ESC Congress 2003, August 30-September 3, 2003, Vienna, Austria. *Clinical Trial Update II: Heart Failure*, presentation #2457
6. Xiu, JC, et al. Effects of long-term enalapril and losartan therapy of heart failure on cardiovascular aldosterone. *J Endocrinol Invest*, Vol. 25, May 2002, pp. 463-68
7. Ueng, KC, et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. *European Heart Journal*, Vol. 24, No. 23, December 2003, pp. 2090-98
8. Pedersen, OD, et al. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation*, Vol. 100, July 27, 1999, pp. 376-80
9. Staessen, J, et al. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *Journal of Endocrinology*, Vol. 91, 1981, pp. 457-65
10. McKelvie, RS, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure. *Circulation*, Vol. 100, 1999, pp. 1056-64
11. Pitt, B, et al. New insights into the role of aldosterone in cardiorenal disease and the clinical implications. www.medscape.com/viewprogram/1004_pnt

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