Published in final edited form as:
Circulation. 2011 November 1; 124(18): e466–e468. doi:10.1161/CIRCULATIONAHA.111.067918.

Aldosterone, Mineralocorticoid Receptor Activation, and Cardiovascular Remodeling

Jane A. Leopold, MD
Brigham and Women's Hospital, 77 Avenue Louis Pasteur, NRB0630K, Boston, MA 02115, (P) 617-525-4846, (F) 617-525-4830

Jane A. Leopold: jleopold@partners.org

Large-scale clinical trials have established that mineralocorticoid receptor (MR) blockade with spironolactone or eplerenone decreases morbidity and mortality in patients with chronic severe congestive heart failure and left ventricular systolic dysfunction (EF ≤ 35); [1] with heart failure and left ventricular systolic dysfunction following an acute myocardial infarction; [2] and, in patients with chronic systolic heart failure with New York Heart Association (NYHA) class II (mild) symptoms. [3] While it was initially suggested that MR blockade with spironolactone improved outcomes, in part, by altering renal sodium and/or potassium handling, it was recognized that the mean dosage [26 mg/d) used in the Randomized Aldactone Evaluate Study (RALES) was not natriuretic, indicating that other extrarenal effects of MR antagonism were more likely to prevent adverse cardiovascular events. [1,4] Aldosterone and MR activation may also lead to dysregulation of local sodium, potassium, and water balance, promote autonomic dysfunction, impair vascular reactivity, and, importantly, increase extracellular matrix turnover and fibrosis. [5] In fact, there is now evidence to show that the hyperaldosteronism or enhanced MR activation contribute to (mal)adaptive ventricular structural and electrical remodeling by stimulating extracellular matrix deposition and turnover.

The association between aldosterone and left ventricular remodeling has been shown previously in a community-based sample. In 2,119 participants in the Framingham Offspring Study, the aldosterone-renin ratio was positively associated with both concentric (odds ratio per SD increment, 1.29; 95% confidence interval, 1.06 to 1.58) and eccentric (odds ratio per SD increment, 1.20; 95% CI, 1.05 to 1.37) left ventricular hypertrophy.[6] While this study did not measure circulating markers of extracellular matrix turnover, a follow-up study performed in the same community-based sample related elevated levels of procollagen type III aminoterminal peptide (PIIINP), a marker of matrix synthesis, or tissue inhibitor of matrix metalloproteinase-1 (TIMP1) with hazard ratios of 1.47 (95% CI, 1.11 to 1.96) or 1.72 (95% CI, 1.30 to 2.27), respectively, for mortality risk.[7] Based on these observations, it is interesting to speculate that aldosterone may influence extracellular matrix remodeling, which is associated with adverse cardiovascular events, in an otherwise healthy population.

By contrast, a series of studies performed in patients with left ventricular systolic dysfunction and heart failure clearly demonstrated the relationship between aldosterone/MR activation and extracellular matrix turnover. In a substudy from the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the MR antagonism with eplerenone resulted in a decrease in the levels of aminoterminal propeptide of collagen type I (PINP) and PIIINP after 6 months with no apparent effect on TIMP1 or type I collagen telopeptide (ICTP). Thus, it is apparent that extracellular matrix remodeling

Correspondence to: Jane A. Leopold, jleopold@partners.org.

is a dynamic process that is abrogated by MR antagonism.[8, 9] A second study of patients with NYHA class II/III heart failure and LVEF <35% randomized to eplerenone confirmed these findings. Here, after 9 months, there was a greater decrease in in PINP levels in patients treated with eplerenone as compared to control patients (−6.7 +/−2.04 vs. −2.4 +/ −1.46 units, $p<0.01$). [10]

Preclinical studies have shown that changes in extracellular matrix turnover are not solely the result of fibroblast aldosterone and MR activation and cardiomyocytes themselves do participate in extracellular matrix remodeling. Using a novel mouse model of cardiomyocyte-specific ablation of the MR, investigators examined the role of cardiomyocyte MR activation in left ventricular remodeling following myocardial infarction. One week after myocardial infarction was induced by coronary artery ligation, heart tissue isolated from control mice (with cardiomyocyte MR expression) exhibited disorganized extracellular matrix with small and fragmented collagen fibers. In contrast, mice without cardiomyocyte MR had collagen fibrils that were well organized, uniform, aligned, and sharply delineated with less extracellular matrix protein accumulation than what was observed in control mice. Similarly, ICTP levels were lower in mice with cardiomyocyte-specific ablation of the MR compared to controls (5.22 ± 0.7 ng/mL vs. 8.04 ± 0.6 ng/mL $p<0.05$).[11] Furthermore, in mouse models of heart failure with a preserved ejection fraction created by transverse aortic constriction and deoxycorticosterone infusion, MR activation was associated with increased cardiac levels of the matricellular protein osteopontin, fibrosis, and diastolic dysfunction.[12] Taken together these studies demonstrate that cardiac remodeling occurs with both systolic and diastolic dysfunction and that cardiomyocytes participate in extracellular matrix turnover.

Because MR antagonists decrease extracellular matrix deposition and fibrosis associated with ventricular remodeling in systolic or diastolic heart failure, investigators have also examined the utility of MR antagonists in cardiomyopathy characterized by early fibrosis such as occurs in Duchenne muscular dystrophy. Using a mouse model deficient for dystrophin and haploinsufficient for utrophin that has a skeletal myopathy and cardiomyopathy that mimics Duchenne muscular dystrophy, investigators found that early initiation of spironolactone and lisonopril improved myocardial function with less evidence of cardiomyocyte damage and decreased matrix metalloproteinase activity. Furthermore, *ex vivo* muscle testing of cardiac, limb, and diaphragm function demonstrated that early MR antagonism abrogated the decline in muscle function (80% of normal) as compared to (40% of normal) untreated mice.[18] While it's interesting to think that the majority of these findings may be attributed to changes in extracellular matrix turnover, it is also likely that MR antagonism influenced cell viability as well as several of the other aforementioned mechanisms to limit muscle decline.

Another consequence of aldosterone/MR activation and cardiac remodeling is electrical remodeling. The importance of this phenomenon is recognized by the prevalence of atrial and ventricular arrhythmias associated with heart failure. While it has been suggested that MR antagonism reduces the incidence of atrial fibrillation by improving atrial remodeling, this may be limited to select patient populations: epidemiological evidence from the Framingham Offspring study, failed to show that aldosterone levels predicted incident atrial fibrillation. [14] In contrast, there is evidence to confirm that aldosterone and MR activation have direct effects on cardiomyocyte Ca^{2+} handling that that may predispose to arrhythmias. Using whole-cell patch clamp methods, aldosterone (10^{-7} mol/l) for 48 h was shown to increase delayed afterdepolarizations in isolated adult rat ventricular myocytes and in cardiomyocytes isolated from mice with cardiac overexpression of human MR. This finding was attributed to MR-mediated downregulation of FK506-binding proteins, which regulate the ryanodine receptor macromolecular complex, leading to increased ryanodine receptor

activity and long-lasting and broader calcium sparks.[13] Thus one effect of MR antagonism would be to decrease prolonged cardiomyocyte Ca^{2+} sparks and potentially limit arrhythmias through this mechanism.

It should also be noted that aldosterone and MR-mediated extracellular matrix deposition and remodeling is not limited exclusively to the heart but occurs throughout the cardiovascular system. The aldosterone-renin ratio correlated well with the development of arterial stiffness in 2,000 participants in the Framingham Offspring Study. Interestingly, in this study, mean aldosterone levels were within the normal range and similar between men and women.[15] Supporting evidence to show that aldosterone and MR activation are involved in vascular remodeling is provided by a study of hypertensive patients treated with eplerenone for one year. After this time, resistance vessels isolated from a subcutaneous tissue biopsy revealed that MR antagonism decreased the collagen-to-elastin ratio to improve vessel remodeling and amerliorate vascular stiffness.[16]

Although we do not yet understand the relationship between aldosterone and heart valve remodeling, it is interesting to speculate that MR antagonism may improve extracellular matrix turnover in cardiac valves, especially in the setting of left ventricular dysfunction. For example, in a sheep model of tachycardia-induced dilated cardiomyopathy, where aldosterone levels are expected to be elevated, isolated mitral valves demonstrated valve interstitial cell activation, increased levels of the collagen and elastin turnover proteins collagen I and collagen II, lysyl oxidase, and proteoglycans.[17] These observations, therefore, lend support to the idea that valves undergo extracellular matrix remodeling similar to the myocardium.

Thus, aldosterone and MR activation regulate extracellular matrix deposition and turnover to influence myocardial structural and electrical remodeling. It is also likely that aldosterone and MR activation participate in vascular and valvular remodeling. Taken together, accumulating data suggests that the benefits of MR antagonism on extracellular matrix turnover may be extended beyond patients with congestive heart failure with systolic or diastolic dysfunction in the future; however, we await definitive evidence to support this idea.

Acknowledgments

This work was supported by NIH R01 105301

References

1. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999; 341:709–717. [PubMed: 10471456]
2. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348:1309–1321. [PubMed: 12668699]
3. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364:11–21. [PubMed: 21073363]
4. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis: Potential role of natriuretic doses of mineralocorticoid antagonist? Circ Heart Fail. 2009; 2:370–376. [PubMed: 19808361]
5. Maron BA, Leopold JA. Aldosterone receptor antagonists: Effective but often forgotten. Circulation. 2010; 121:934–939. [PubMed: 20177008]

6. Velagaleti RS, Gona P, Levy D, Aragam J, Larson MG, Tofler GH, Lieb W, Wang TJ, Benjamin EJ, Vasan RS. Relations of biomarkers representing distinct biological pathways to left ventricular geometry. Circulation. 2008; 118:2252–2258. 2255p following 2258. [PubMed: 19001021]
7. Velagaleti RS, Gona P, Sundstrom J, Larson MG, Siwik D, Colucci WS, Benjamin EJ, Vasan RS. Relations of biomarkers of extracellular matrix remodeling to incident cardiovascular events and mortality. Arterioscler Thromb Vasc Biol. 2010; 30:2283–2288. [PubMed: 20798380]
8. Iraqi W, Rossignol P, Angioi M, Fay R, Nuee J, Ketelslegers JM, Vincent J, Pitt B, Zannad F. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: Insights from the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (ephesus) study. Circulation. 2009; 119:2471–2479. [PubMed: 19398668]
9. Lopez B, Gonzalez A, Diez J. Circulating biomarkers of collagen metabolism in cardiac diseases. Circulation. 2010; 121:1645–1654. [PubMed: 20385961]
10. Udelson JE, Feldman AM, Greenberg B, Pitt B, Mukherjee R, Solomon HA, Konstam MA. Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. Circ Heart Fail. 2010; 3:347–353. [PubMed: 20299607]
11. Fraccarollo D, Berger S, Galuppo P, Kneitz S, Hein L, Schutz G, Frantz S, Ertl G, Bauersachs J. Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction. Circulation. 2011; 123:400–408. [PubMed: 21242479]
12. Mohammed SF, Ohtani T, Korinek J, Lam CS, Larsen K, Simari RD, Valencik ML, Burnett JC Jr, Redfield MM. Mineralocorticoid accelerates transition to heart failure with preserved ejection fraction via “nongenomic effects”. Circulation. 2010; 122:370–378. [PubMed: 20625113]
13. Gomez AM, Rueda A, Sainte-Marie Y, Pereira L, Zissimopoulos S, Zhu X, Schaub R, Perrier E, Perrier R, Latouche C, Richard S, Picot MC, Jaisser F, Lai FA, Valdivia HH, Benitah JP. Mineralocorticoid modulation of cardiac ryanodine receptor activity is associated with downregulation of fk506-binding proteins. Circulation. 2009; 119:2179–2187. [PubMed: 19364981]
14. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB, Tofler GH, Selhub J, Jacques PF, Wolf PA, Magnani JW, Ellinor PT, Wang TJ, Levy D, Vasan RS, Benjamin EJ. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation. 2010; 121:200–207. [PubMed: 20048208]
15. Lieb W, Larson MG, Benjamin EJ, Yin X, Tofler GH, Selhub J, Jacques PF, Wang TJ, Vita JA, Levy D, Vasan RS, Mitchell GF. Multimarker approach to evaluate correlates of vascular stiffness: The framingham heart study. Circulation. 2009; 119:37–43. [PubMed: 19103986]
16. Savoia C, Touyz RM, Amiri F, Schiffrin EL. Selective mineralocorticoid receptor blocker eplerenone reduces resistance artery stiffness in hypertensive patients. Hypertension. 2008; 51:432–439. [PubMed: 18195160]
17. Stephens EH, Timek TA, Daughters GT, Kuo JJ, Patton AM, Baggett LS, Ingels NB, Miller DC, Grande-Allen KJ. Significant changes in mitral valve leaflet matrix composition and turnover with tachycardia-induced cardiomyopathy. Circulation. 2009; 120:S112–119. [PubMed: 19752355]
18. Rafael-Fortney JA, Chimanji NS, Schill KE, Martin CD, Murray JD, Ganguly R, Stangland JE, Tran T, Xu Y, Canan BD, Mays TA, Delfin DA, Janssen PM, Raman SV. Early treatment with lisinopril and spironolactone preserves cardiac and skeletal muscle in duchenne muscular dystrophy mice. Circulation. 2011; 124:582–588. [PubMed: 21768542]