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 (ejection fraction $\leq 35\%$), heart failure and left ventricular systolic dysfunction after an acute myocardial infarction, and chronic systolic heart failure with New York Heart Association class II (mild) symptoms. Although it was initially suggested that MR blockade with spironolactone improved outcomes in part by altering renal sodium or potassium handling or both, it was recognized that the mean dosage (26 mg/d) used in the Randomized Aldactone Evaluate Study (RALES) was not natriuretic, which indicates that other extrarenal effects of MR antagonism were more likely to prevent adverse cardiovascular events. 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. In fact, there is now evidence to show that the hyperaldosteronism or enhanced MR activation contributes to (mal)adaptive ventricular structural and electric 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 2119 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, 1.06–1.58) and eccentric (odds ratio per SD increment 1.26; 95% confidence interval, 1.06–1.58) left ventricular ejection fraction ($P<0.05$). Furthermore, in mouse models of cardiac myocyte-specific ablation of the MR, investigators examined the role of cardiac myocyte MR activation in left ventricular remodeling after myocardial infarction. One week after myocardial infarction was induced by coronary artery ligation, heart tissue isolated from control mice (with cardiac myocyte 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 cardiomycocyte-specific ablation of the MR than in controls (5.22 vs. 9.08 U/mL, $P<0.05$). 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.

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 lisinopril 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) compared with untreated mice (40% of normal).13 Although it is 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 can be recognized by the prevalence of atrial and ventricular arrhythmias associated with heart failure. Although 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 Ca2+ handling that may predispose to arrhythmias. With whole-cell patch-clamp methods, exposure to aldosterone (10−7 mol/L) for 48 hours 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.15 Thus, one effect of MR antagonism would be to decrease prolonged cardiomyocyte Ca2+ sparks and potentially limit arrhythmias through this mechanism.

In addition, aldosterone and MR-mediated extracellular matrix deposition and remodeling are not limited exclusively to the heart, but occur throughout the cardiovascular system. The aldosterone-renin ratio correlated well with the development of arterial stiffness in 2000 participants in the Framingham Offspring Study. Interestingly, in this study, mean aldosterone levels were within the normal range and were similar between men and women.16 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 1 year. After that time, resistance vessels isolated from a subcutaneous tissue biopsy sample revealed that MR antagonism decreased the collagen-to-elastin ratio to improve vessel remodeling and ameliorate vascular stiffness.17

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, in which aldosterone levels are expected to be elevated, isolated mitral valves demonstrated valve interstitial cell activation and increased levels of the collagen and elastin turnover proteins collagen I and collagen II, lysyl oxidase, and proteoglycans.18 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 electric remodeling. It is also likely that aldosterone and MR activation participate in vascular and valvular remodeling. Taken together, accumulating data suggest 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.

Sources of Funding

This work was supported by funds from NIH grants HL070819 and HL105301 (to Dr Leopold).

Disclosures

None.

References

receptor ameliorates adverse remodeling after myocardial infarction. Circulation. 2011;123:400–408.


Keywords: aldosterone ■ congestive heart failure ■ left ventricular dysfunction
Aldosterone, Mineralocorticoid Receptor Activation, and Cardiovascular Remodeling
Jane A. Leopold

Circulation. 2011;124:e466-e468
doi: 10.1161/CIRCULATIONAHA.111.067918
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/124/18/e466

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/