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Eplerenone Reduces Atrial Fibrillation Burden Without Preventing Atrial Electrical Remodeling

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ABSTRACT

BACKGROUND The aldosterone inhibitor eplerenone (EPL) has been shown to reduce the incidence of atrial fibrillation (AF) in patients with systolic heart failure, but the mechanism is unknown.

OBJECTIVES This study hypothesized that by reducing atrial dilation and fibrosis in the absence of heart failure, EPL also reduces AF burden and prevents AF perpetuation.

METHODS The authors conducted a randomized controlled study in 34 sheep that were atrially tachypaced (13 ± 1 week). They compared daily oral EPL (n = 19) versus sugar pill (SP) treatment (n = 15) from the start of tachypacing. The endpoint was a continuous 7-day stretch of persistent AF (n = 29) or completion of 23 weeks tachypacing (n = 5).

RESULTS EPL significantly reduced the rate of left atrial dilation increase during AF progression. Atria from EPL-treated sheep had less smooth muscle actin protein, collagen-III expression, interstitial atrial fibrosis, and cell hypertrophy than SP-treated sheep atria did. However, EPL did not modify the AF-induced increase in the rate of dominant frequency and ion channel densities seen under SP treatment, but rather prolonged the time to persistent AF in 26% of animals. It also reduced the degree of fibrillatory conduction, AF inducibility, and AF burden.

CONCLUSIONS In the sheep model, EPL mitigates fibrosis and atrial dilation, modifies AF inducibility and AF complexity, and prolongs the transition to persistent AF in 26% of animals, but it does not prevent AF-induced electrical remodeling or AF persistence. The results highlight structural remodeling as a central upstream target to reduce AF burden, and the need to prevent electrical remodeling to avert AF perpetuation. (J Am Coll Cardiol 2017;70:2893-905) © 2017 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with an increased risk of stroke, heart failure (HF), and dementia (1-4). Nonparoxysmal AF (including persistent and permanent AF) increases the risk of thromboembolism and death, which calls for development of new upstream therapies to prevent AF progression (5). Atrial dilation, fibrosis, and electrical

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ABBREVIATIONS AND ACRONYMS

7d-PeAF = first 7-day persistent atrial fibrillation episode

11b-HSD2 = 11β-hydroxysteroid dehydrogenase type 2

12h-AF = first 12-h atrial fibrillation episode

AF = atrial fibrillation

APD = action potential duration

COLIII = collagen III

DF = dominant frequency

EPL = eplerenone

Gal = galectin

GMCT = galactomannan GM-CT-01

HF = heart failure

I_{CaL} = L-type calcium current

I_{K1} = inward rectifier potassium ion channel

LA = left atrium/atrial

MR = mineralocorticoid receptor

MRB = mineralocorticoid receptor blocker

P3NP = procollagen type III N-terminal propeptide

RA = right atrium/atrial

SMA = smooth muscle actin

SP = sugar pill

TGF = transforming growth factor

remodeling underlie the transition from paroxysmal to persistent AF (6) and contribute to AF perpetuation. Recently we demonstrated that targeting the profibrotic protein galectin (Gal)-3 using a relatively low intravenous dose of the galactomannan GM-CT-01 (GMCT) (7) reduces both structural and electrical remodeling as well as AF burden in a sheep model of persistent AF in the absence of comorbidities (8). However, Gal-3 inhibition did not restore sinus rhythm in the long term (8). Nevertheless, our study provided a solid proof of concept in support of upstream AF prevention therapy.

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Mineralocorticoid receptor blockers (MRBs) are beneficial in systolic HF (9–11). Specifically, the MRB eplerenone (EPL) has been shown to reduce new onset AF and recurrent AF in HF patients (12). Both angiotensin II and aldosterone elevations may lead to atrial fibrosis and contribute to human AF (13). Experimental results suggest that aldosterone may cause a substrate for atrial fibrosis and AF (14). Aldosterone increases the expression of 11β-hydroxysteroid dehydrogenase type 2 (11b-HSD2) leading to up-regulation of profibrotic mediators and collagen synthesis, which is prevented by MRBs (15).

Here we have investigated whether EPL prevents structural and electrophysiological remodeling, and reduces AF burden in our sheep model of persistent AF (16). In addition, we have determined whether EPL is a potentially effective upstream therapy to prevent persistent AF.

METHODS

An expanded methods section is available in the Online Appendix.

PROTOCOL FOR THE BLINDED RANDOMIZED-CONTROLLED STUDY IN SHEEP. All procedures complied with National Institutes of Health guidelines. A total of 34 male sheep (35 to 40 kg) underwent subcutaneous pacemaker implantation with a lead attached to the right atrial (RA) appendage (8,16). An implantable loop recorder was inserted parasternally in close apposition to the left atrium (LA). After 1-month recovery, sheep were randomized to: 1) a sugar pill (SP)-treated AF control group (n = 15); or 2) an EPL-treated AF group (100 mg/day orally; n = 19). We also used 6 sham-operated animals from previous studies as a reference control group (8,16). The time from pacemaker implantation to terminal assessment was 108.4 ± 11.4 days in SP-treated animals, 125.3 ± 10.9 days in EPL-treated animals, and 193 ± 45.5 days in sham-operated animals. Investigators were blinded to the randomization. Animals were euthanized after 7 days of self-sustained AF without pacing (7-day persistent AF [7d-PeAF]) followed by 1-week observation and terminal ex vivo and in vitro experiments. Sheep that did not reach 7d-PeAF during 23 weeks of tachypacing were euthanized at week 24.

AF PROGRESSION AND FOLLOW-UP. Data were collected weekly from pacemakers, implantable loop recorders, and body surface electrocardiography standard lead II. Power spectral analysis was used to measure dominant frequency (DF) of atrial activation from the intracardiac RA lead and far-field LA signals during AF episodes. Atrial dimensions, mitral and tricuspid regurgitation, ejection fraction, and ventricular and septal dimensions were evaluated echocardiographically every 2 weeks.

STATISTICAL ANALYSES. Normally distributed data are expressed as mean ± SEM, where n represents the number of animals. See the Online Appendix for further details.

RESULTS

AF progression in the sheep model is characterized by continuously increasing markers of electrophysiological and structural remodeling, as well as AF burden, until AF becomes persistent (8,16). To determine whether EPL interferes with such changes, we randomized 34 sheep into daily oral EPL (100 mg; n = 19) or SP (n = 15) treatment (Online Figure 1). We defined 5 time points from the start of tachypacing: 1) first AF episode (1st-AF); 2) first 12-h AF episode (12h-AF); 3) first 1-day AF episode; 4) first continuous 7-day stretch of persistent AF (7d-PeAF); and 5) terminal.

Body weight increased similarly with time in EPL-treated and SP-treated animals (Online Figure 2). No animals developed HF or stroke. On lead II electrocardiography, neither EPL treatment nor SP treatment altered the QT or QTc interval measured at baseline and at final evaluation (Online Figure 3).

EPL MITIGATES ATRIAL DILATION AND CELL ELONGATION DURING AF PROGRESSION. Echocardiographically measured left ventricular ejection fraction and left ventricular end-diastolic volume were unchanged with respect to baseline in both SP-treated and EPL-treated groups (Online Figures 4A to 4C). In contrast, the AF-associated increase in end-