JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 71, NO. 2, 2018
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.11.030

EDITORIAL COMMENT

Neurohormonal Regulation and the Left Atrial Appendage

Still More to Learn*

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The development and increasing use of percutaneous left atrial appendage closure (LAAC) to reduce thromboembolic risk associated with atrial fibrillation has stimulated renewed interest in the broader role of the LAA in normal cardiovascular physiology and response to stress. The heart is a neuroendocrine organ, and the alteration or elimination of a viable LAA may have potentially deleterious effects. The LAA is a source of A-type or atrial natriuretic peptide (ANP) and B-type or brain natriuretic peptide (BNP) that typically promote diuresis, natriuresis, and vasodilation in response to stretch and other stimuli (1-3). Predominantly, ANP is secreted by myocytes throughout the atria, with the appendages accounting for 30% of cardiac sources (4), although storage granules are more dense in the right than the left appendage (5). The predominant source of BNP is ventricular, although the atria seem to contribute more in heart failure and atrial fibrillation. The LAA is richly innervated by both parasympathetic and sympathetic fibers, although not as densely as the LA posterior wall or pulmonary veins (6-8). Both atrial appendages participate in reflex responses to stretch, although removal of the right or both appendages seems to have a greater impact than LAA removal alone (4,9). The precise neural pathways involved are not well-established.

Approaches to percutaneous LAAC differ in their impact on the survival of appendage tissue. Epicardial closure techniques by suture snare at the ostium (Lariat, SentreHEART, Palo Alto, California) leads to progressive atrophy and fibrosis of the appendage (10,11), with subsequent loss of neural and hormonal elements. This finding has not been reported with endocardial occlusion devices (Watchman, Boston Scientific, Marlborough, Massachusetts), which leave the blood supply intact and appendage tissue viable. These differences provide a unique opportunity to explore the physiological impact of a procedure eliminating the LAA (Lariat) with a similar invasive interventional procedure that leaves the LAA viable (Watchman).

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In this issue of the *Journal*, Lakkireddy et al. (12) compared neurohormonal profiles in 38 patients undergoing Lariat suture ligation with 39 patients undergoing Watchman procedures in a single-center, prospective registry. Measurements were made pre-procedure, immediately post device deployment, and at 24 h and 3 months post procedure. Key hormones and biomarkers assayed included those involving natriuresis (N-terminal pro-ANP, N-terminal pro-BNP), adrenergic activation (epinephrine, norepinephrine), the renin-angiotensin-aldosterone system (renin, aldosterone), and metabolism (adiponectin, free fatty acids, insulin, β-hydroxy butyrate, and free glycerols). Although the study was not randomized, both groups of patients had similar baseline clinical characteristics. Collection of blood samples, blood pressure assessment, and management of periprocedural intravenous fluids for both devices followed a common protocol.

Patients with Lariat and Watchman devices demonstrated acute changes in natriuretic peptides during the initial 24 h post procedure, although with different temporal patterns. For the Lariat device, ANP and BNP levels decreased immediately post procedure, then increased above baseline levels at

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* the American College of Cardiology.

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24 h. For the Watchman device, ANP and BNP peaked immediately after device placement, then decreased to near baseline levels at 24 h. However, at 3 months, there were no changes from baseline levels for either peptide for both closure techniques.

The impact of LAAC on natriuretic peptides has been examined previously. For the Watchman device, acute changes in ANP and BNP were observed, similar to those reported by Lakkireddy et al. (13-15). Long-term pro-ANP has been reported to show either a small increase or decrease between baseline and 6 months post procedure (14,15). Bartus et al. (16) reported no change in ANP for patients receiving a Lariat device between baseline and 3 months. For both devices, there were no changes in BNP during long-term follow-up in most studies (14-16), although Cruz-Gonzales et al. (17) report a small decrease at 2 months for the Watchman device. Although acute changes in natriuretic peptides may mediate short-term alterations in blood volume and serum sodium in the periprocedural period, return of these hormone levels to baseline values within a few months indicates that any long-term neurohormonal effects of LAAC are unlikely to be mediated by this mechanism. This finding is not surprising, given that the cardiac sources of both peptides are widely distributed in the atria and elsewhere, and may compensate for the loss of the LAA contribution.

What is most novel in this study, not previously reported, and of potentially greater impact is the finding of persistent declines in epinephrine, norepinephrine, renin, and aldosterone levels lasting at least 3 months post procedure in patients with a Lariat device, whereas these levels were largely unchanged in patients with a Watchman device. The findings in patients with a Lariat device were coupled with a sustained and significant decrease in systolic and diastolic blood pressures (approximately 15% and 12%, respectively), which began early post procedure and were maintained at the end of 3 months of follow-up. The persistent decrease in blood pressure confirms similar observations made by these investigators in a previously reported Lariat cohort (18), and does not seem to occur in patients with a Watchman device, either in this study, or in a previous report (15). The mechanisms for these more persistent changes in patients with a Lariat device remain unclear.

The authors propose that neurohormonal modulation by the LAA may be mediated by 2 pathways, a natriuretic peptide pathway (mostly short-term effects), and an additional pathway, potentially neurally mediated, which may account for more long-term effects. They speculate that the interruption or modification of neural reflexes, either by destruction of afferent fibers within the LAA or by injury to peri-LAA ganglionated plexi during Lariat ligation, may account for the differences seen between the Lariat and Watchman devices. This possibility has not been examined specifically in animal models or clinical studies.

The study investigators are to be congratulated for a carefully performed, comparative study of the impact of 2 different approaches to LAAC on cardiac neurohormonal regulation and blood pressure that provides provocative new findings. These observations require confirmation in larger studies, with a much longer follow-up. Given the complex and interdependent relationships between various regulatory systems, it may be premature to conclude that elimination of the LAA alone will lead to lasting inhibition of the renin-angiotensin-aldosterone system and sustained decreases in blood pressure. Although this line of inquiry seems to be promising, and there are potential clinical benefits, there is still much more to learn.

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KEY WORDS ANP, appendage closure, hypertension, left atrial appendage, renin aldosterone