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Left Atrial Appendage Closure and Systemic Homeostasis

The LAA HOMEOSTASIS Study

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ABSTRACT

BACKGROUND The impact of left atrial appendage (LAA) exclusion, comparing an epicardial LAA or an endocardial LAA device, on systemic homeostasis remains unknown.

OBJECTIVES This study compared the effects of epicardial or endocardial LAA devices on the neurohormonal profiles of patients, emphasizing the roles of the renin-angiotensin-aldosterone system and the autonomic nervous system.

METHODS This is a prospective, single-center, observational study including 77 patients who underwent LAA closure by an epicardial ($n = 38$) or endocardial ($n = 39$) device. Key hormones involved in the adrenergic system (adrenaline, noradrenaline), renin-angiotensin-aldosterone system (aldosterone, renin), metabolic system (adiponectin, free fatty acids, insulin, β-hydroxybutyrate, and free glycerols), and natriuresis (atrial and B-type natriuretic peptides) were assessed immediately before the procedure, immediately after device deployment, at 24 h, and at 3 months follow-up.

RESULTS In the endocardial LAA device group, when compared with baseline blood adrenaline, noradrenaline and aldosterone were significantly lower at 24 h and 3 months ($p < 0.05$). There was no significant change in levels post-endocardial LAA device implantation. After epicardial LAA device implantation, there were significant increases in adiponectin and insulin, with decreased free fatty acids at 3 months. There was no significant change in these levels post-endocardial LAA device. N-terminal pro-A-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide were significantly decreased in the acute phase after epicardial LAA device implantation, which subsequently normalized at 3 months. Post endocardial LAA device implantation, the levels increased immediately and normalized after 24 h. Systemic blood pressure was also significantly lower at all time points after epicardial LAA device implantation, which was not seen post-endocardial LAA device implantation.

CONCLUSIONS There are substantial differences in hemodynamics and neurohormonal effects of LAA exclusion with epicardial and endocardial devices. Further studies are required to elucidate the underlying mechanism of these physiological changes. (J Am Coll Cardiol 2018;71:135–44)

The left atrial appendage (LAA) is a derivative of the primitive fetal atrium (1). It is largely considered a vestigial structure with a limited contribution to the mechanical function of the left atrium (LA). Several studies have identified the role of the LAA in thromboembolic stroke in patients with atrial fibrillation (AF). Elimination of the LAA from the systemic circulation, either with endocardially deployed occluder devices or an epicardial suture/clip, could potentially remove the largest

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ANP = atrial natriuretic peptide

ANS = autonomic nervous system

BNP = B-type natriuretic peptide

DBP = diastolic blood pressure

LA = left atrium

LAA = left atrial appendage

RAAS = renin-angiotensin-aldosterone system

SBP = systolic blood pressure

source of thrombus in the heart in patients with AF (2). More recently, this approach has gained increasing popularity for stroke prophylaxis (2). Whereas the endocardial occluders mostly create a mechanical barrier between the LAA and LA without eliminating the LAA body completely, the epicardial excluders cause necrosis and fibrosis of the LAA body distal to the point of ligation or clipping. Preliminary studies have shown that epicardial LAA ligation could result in temporary fluid retention and long-term blood pressure reduction in patients with AF (3).

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The current body of knowledge about the role of the LAA in neurohormonal modulation is largely limited. The LAA is a well-known source of atrial natriuretic peptide (ANP), which plays an important role in natriuresis (4). Obviously, the changes in systemic volume status, exercise, and atrial stretch regulate ANP secretion, facilitating systemic fluid-salt balance (5). With the advent of LAA exclusion approaches for mechanical thromboprophylaxis, several questions have been raised regarding the role of the LAA in normal human physiology. Whether elimination of the LAA has any deleterious effects on the human body by compromising the contributions of the LAA are unknown to medical science at this time.

Recent observational studies have shown that epicardial LAA device deployment can be safely and effectively performed in AF patients with increased risk of bleeding with oral anticoagulation (6). A substudy from these investigators has shown that epicardial exclusion of the LAA results in an early and persistent decrease in systolic blood pressure (SBP) (3). There was an early decline in serum sodium, which normalizes at long-term follow-up. The underlying mechanisms leading to these changes are not entirely clear. No such changes have been reported with endocardial LAA occluders. Although the LAA is a well-known source of ANP, it is not clear if there are other chemicals it secretes that could potentially affect various systems in the human body. ANP is also known to influence the renin-angiotensin-aldosterone system (RAAS), glucose and lipid metabolism, and the salt-fluid balance. Whether these neurohormonal changes are primarily mediated by or independent of ANP is largely unknown. To delineate the mechanistic underpinning of these changes, we aimed to investigate the broader neurohormonal profile of these patients, with a particular emphasis on the role of the RAAS and autonomic nervous system (ANS), comparing the impact of epicardial versus endocardial closure using the epicardial and endocardial LAA exclusion systems.

METHODS

A total of 77 patients were included in this study. This was a prospective, single-center registry of patients undergoing endocardial LAA occlusion with Watchman (Boston Scientific, Marlborough, Massachusetts) and epicardial LAA exclusion with Lariat (Sentreheart, Redwood City, California). Eligible patients met the following inclusion criteria: 1) age 18 years or older; 2) nonvalvular AF; 3) at least 1 risk factor for embolic stroke ($CHADS_2$ [congestive heart failure, hypertension history, age ≥75 years, diabetes mellitus history, and previous stroke or transient ischemic attack] ≥1); 4) poor candidate or ineligible for long-term oral anticoagulation therapy (e.g., labile international normalized ratio level, noncompliant, contraindicated) and/or oral anticoagulation failure (i.e., transient ischemic attack or stroke while on warfarin therapy); 5) transthoracic echocardiogram performed within 1 year before LAA exclusion; and 6) transthoracic echocardiogram within 30 days after the procedure.

Patients were excluded from the study if they met any of the following exclusion criteria: 1) history of cardiac surgery; 2) severe pectus excavatum; 3) myocardial infarction within 3 months; 4) prior embolic event within the past 30 days; 5) New York Heart Association functional class IV heart failure symptoms; 6) history of thoracic radiation; 7) atrial septal defect; 8) patent foramen ovale with atrial septal aneurysm; or 9) mechanical prosthetic heart valve.

All patients underwent a screening contrast cardiac computed tomography scan to assess the LA size and LAA geometry. Based on the information from computed tomography scans, additional exclusion criteria included: 1) LAA width >40 mm; 2) a superiorly oriented LAA with the LAA apex directed behind the pulmonary trunk; 3) bilobed LAA or multilobed LAA in which lobes were oriented in different planes exceeding 40 mm; and 4) a posteriorly rotated heart, as described previously. The institutional review board at the University of Kansas approved the protocol. Informed consent was obtained from all the patients.

PERCUTANEOUS SUTURE EXCLUSION OF THE LAA USING THE EPICARDIAL LAA DEVICE. LAA exclusion was performed using the epicardial LAA device, as described previously, in 38 patients (7,8). All patients undergoing the epicardial LAA closure procedure received up to 1,000 ml of intravenous bolus of