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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 epicardial 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

normal saline infusion and 500 ml in patients with known history of systolic left ventricular dysfunction. Additional fluid bolus was at the discretion of the anesthesiologist, depending on the blood pressure.

PERCUTANEOUS LAA OCCLUSION USING THE ENDOCARDIAL LAA DEVICE. LAA occlusion was performed using the endocardial LAA device in 39 patients, as described previously (9,10). All patients undergoing the endocardial LAA procedure received up to 1,000 ml of intravenous bolus of normal saline infusion and 500 ml in patients with known history of systolic left ventricular dysfunction. Additional fluid bolus was at the discretion of the anesthesiologist, depending on blood pressure.

BLOOD SAMPLE COLLECTION AND ASSESSMENT OF NEUROHORMONAL PROFILE. Blood samples were collected according to a standardized method immediately before the procedure, at completion of the procedure, 24 h, and at 3 months in a supine position. Pre-procedure blood samples were collected after overnight fasting on all patients. Post-procedural blood samples at 24 h were collected after fasting for at least 6 h. Blood samples at 3 months were collected in the clinic after overnight fasting. All patients were instructed to maintain their routine diets and not to take any additional salt or carbohydrate loading up to 48 h before the blood draw. Serological assays were carried out to assess the levels of various hormones (Online Appendix). These assays were aimed to assess the hormones and biomarkers involved in the adrenergic system (adrenaline, noradrenaline), RAAS (aldosterone, renin), metabolic system (adiponectin, insulin, free fatty acids, β-hydroxybutyrate, and free glycerols), and natriuretic peptides (ANP and B-type natriuretic peptide [BNP]). Care was taken to use the same assay in all patients at different time lines. Assay analysis was performed in the same laboratory using the same standard protocol.

CLINICAL FOLLOW-UP. SBP, diastolic blood pressure (DBP), and heart rate were assessed at baseline 3 weeks before the procedure in the clinic setting, pre-procedural in the triage area on the day of the procedure, immediately post-procedure (in the recovery area), 24 h post-procedure just before discharge on the medical floor, and at the 3-month follow-up in the clinic. All blood pressure recordings were performed with patients in the supine position by the registered nurse using a blood pressure cuff with an automated blood pressure recording machine. Diuretic agents were held on the day of the procedure in all patients. The rest of the blood pressure medications were routinely continued. No changes were allowed in any antihypertensive regimen during the 3-month follow-up unless deemed clinically necessary.

TABLE 1 Baseline Characteristics of the Included Patients

	Epicardial LAA Device (N = 38)	Endocardial LAA Device (N = 39)	p Value
Age, yrs	70 ± 9.60	72 ± 8.10	0.3
Male	31 (82)	24 (61)	0.08
Body mass index, kg/m^2	30.60 ± 5.90	29 ± 4.10	0.1
Coronary artery disease	22 (58)	25 (64)	0.6
Hypertension	38 (100)	38 (97)	0.9
Diabetes	11 (29)	7 (18)	0.2
Congestive heart failure	5 (13)	10 (26)	0.2
$CHADS_2$ score	2.50 ± 1.08	2.5 ± 1.50	0.9
CHA_2DS_2-VASc	3.70 ± 1.64	3.9 ± 1.90	0.6
HAS-BLED	3.13 ± 1.60	3.5 ± 1.20	0.2
Type of atrial fibrillation			0.3
Paroxysmal	17 (44)	19 (49)	
Persistent	12 (32)	10 (26)	
Longstanding persistent	9 (24)	7 (18)	
Echocardiography			
LVEF, %	54.50 ± 12.30	49.30 ± 19.02	0.1
LA size, cm	4.50 ± 0.64	4.20 ± 0.50	0.1
Outpatient antihypertensive medications	36 (95)	38 (97)	0.6

Values are mean ± SD or n (%).

$CHADS_2$ = congestive heart failure, hypertension history, age ≥75 years, diabetes mellitus history, and previous stroke or transient ischemic accident; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category (female); HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, age >65 years, drugs or alcohol; LA = left atrium; LAA = left atrial appendage; LVEF = left ventricular ejection fraction.

STATISTICAL ANALYSIS. Normally distributed continuous variables are expressed as mean ± SD and median and interquartile range (difference between the upper [Q3] and lower [Q1] quartiles). Continuous variables were compared using nonparametric tests such as Wilcoxon rank sum tests and Fisher exact tests for between-group comparisons and Wilcoxon signed rank tests for within-group comparisons. Categorical variables were compared using chi-square tests. Statistical analysis was performed using IBM SPSS Statistics, version 24 (IBM, Armonk, New York). A p value ≤0.05 was statistically significant.

RESULTS

BASELINE DATA. A total of 77 patients were prospectively followed over 3 months after LAA occlusion with either an epicardial or endocardial LAA device. Baseline characteristics are described in Table 1. There was no significant difference between baseline characteristics in the 2 groups. The mean age was 70 ± 9.6 years and 72 ± 8.1 years in the epicardial and endocardial LAA device groups, respectively

TABLE 2 Impact of LAA Closure on the Adrenergic System and RAAS

	Pre-Procedure	Immediately Post-Procedure	24 h Post-Procedure	3 Months Post-Procedure	p Value (Baseline vs. 3 Months)
Epicardial LAA device (N = 38)					
Adrenaline, pg/ml	60.49 (45.31)	48.30 (50.32)	30.30 (58.14)	31.80 (41.72)	<0.01
Noradrenaline, ng/ml	73.85 (82.75)	42.05 (51.68)	36.93 (71.87)	36.40 (66.68)	<0.01
Aldosterone, ng/dl	4.22 (9.91)	8.67 (14.16)	6.84 (15.07)	0.72 (7.80)	<0.01
Renin, pg/ml	52.90 (51.19)	45.35 (89.95)	33.57 (136.30)	18.30 (34.57)	<0.01
Endocardial LAA device (N = 39)					
Adrenaline, pg/ml	14.50 (12.49)	14.23 (17.94)	13.80 (12.54)	13.82 (12.64)	0.09
Noradrenaline, ng/ml	50.36 (58.40)	55.42 (83.03)	54.24 (101.42)	38.43 (96.56)	0.68
Aldosterone, ng/dl	13.34 (6.89)	14.25 (7.23)	13.04 (3.83)	13.63 (3.99)	0.40
Renin, pg/ml	22.04 (30.96)	26.68 (49.37)	22.32 (61.72)	25.42 (44.47)	0.19

Values are median (interquartile range [difference between the upper (Q3) and lower (Q1) quartiles]). pmol/l to ng/dl conversion factor is 27.7.
LAA = left atrial appendage; RAAS = renin-angiotensin-aldosterone system.

(p = 0.3). There was no significant difference in mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65-74 years, sex category [female]) (3.7 ± 1.64 vs. 3.9 ± 1.9; p = 0.6) and HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, age >65 years, drugs or alcohol) score (3.13 ± 1.6 vs. 3.5 ± 1.2; p = 0.2) in the epicardial and endocardial LAA device groups, respectively. In the epicardial and endocardial LAA device groups, there was no significant difference in mean left ventricular ejection fraction (54.5 ± 12.3% vs. 49.3 ± 19%) and LA size (4.5 ± 0.64 cm vs. 4.2 ± 0.5 cm; p = 0.1). Hypertension was the most common comorbidity (100% vs. 97%; p = 0.9) followed by coronary artery disease (58% vs. 64%; p = 0.6) and diabetes (29% vs. 18%; p = 0.2) in both groups. The most common type of AF was nonparoxysmal (56% vs. 51%; p = 0.3) in the epicardial and endocardial LAA device groups. There was no significant difference between patients presenting in sinus rhythm (49% vs. 48%; p = 0.9) between the 2 groups. There was no significant difference between the amount of saline volume administered in the epicardial and endocardial LAA device groups (0.8 ± 0.4 l vs. 0.76 ± 0.5 l; p = 0.9). There was no difference in the amount of contrast media used during the procedure 32 ± 15 ml vs. 37 ± 12 ml; p = 0.8) between the epicardial and endocardial LAA device groups.

IMPACT OF LAA CLOSURE ON THE ADRENERGIC SYSTEM. The key hormones involved in the adrenergic system (adrenaline and noradrenaline) were successfully measured at baseline and during follow-up after epicardial and endocardial LAA device implantation.

EPICARDIAL LAA DEVICE CLOSURE. In the epicardial LAA device group, compared with the median levels of adrenaline before the procedure (60.49 [IQR: 45.31] pg/ml), there was no significant difference from the levels obtained immediately after the procedure (48.3 [IQR: 50.32] pg/ml; p > 0.05). However, there was a significant decrease in these levels 24 h after the procedure (30.3 [IQR: 58.14] pg/ml) compared with the pre-epicardial LAA device baseline (60.49 [IQR: 45.31] pg/ml; p < 0.05). This difference persisted when assessed 3 months after the procedure (31.8 [IQR: 41.7] pg/ml; p < 0.001). However, the levels of noradrenaline were significantly lower immediately after the procedure (42.05 [IQR: 51.68] ng/ml) when compared with the pre-epicardial LAA device baseline (73.85 [IQR: 82.75] ng/ml; p < 0.05). This difference persisted when assessed at 24 h (36.93 [IQR: 71.87] ng/ml; p < 0.05) and at 3 months (36.4 [IQR: 66.6] ng/ml; p < 0.05) after the procedure (Table 2).

In the endocardial LAA device group, compared to the levels of adrenaline before the procedure (14.5 [IQR: 12.49] pg/ml), there was no significant difference from the levels obtained immediately after the procedure (14.23 [IQR: 17.94] pg/ml; p > 0.05). Furthermore, there was no significant change in these levels 24 h after the procedure (13.8 [IQR: 12.5] pg/ml) compared with the pre-endocardial LAA device baseline (14.5 [IQR: 12.49] pg/ml, p > 0.05). There was no significant difference, even at the 3-month follow-up (13.8 [IQR: 12.6] pg/ml, p > 0.05), compared with baseline. There was also no significant difference in the levels of noradrenaline, post-procedure (55.4 [IQR: 83.0] pg/ml, p > 0.05) at 24 h (54.24 [IQR: 101.4] pg/ml; p > 0.05) and at 3 months (38.4 [IQR: 96.5] pg/ml; p > 0.05) compared with baseline (50.36 [IQR: 58.4] pg/ml; p > 0.05) (Table 2).

TABLE 3 Impact of LAA Closure on Lipid and Glucose Metabolism

	Pre-Procedure	Immediately Post-Procedure	24 h Post-Procedure	3 Months Post-Procedure	p Value (Baseline vs. 3 Months)
Epicardial LAA device (N = 38)					
Adiponectin, μg/ml	20.71 (30.08)	19.32 (32.33)	20.71 (33.99)	25.83 (44.47)	<0.01
Free fatty acids (mmol/l)	0.02 (0.15)	0.02 (0.11)	0.02 (0.02)	0.02 (0.05)	0.02
β-hydroxybutyrate, mM	13.81 (4.25)	14.42 (3.92)	12.73 (5.47)	12.35 (4.35)	0.14
Free glycerol, μM	4.50 (11.98)	5.91 (9.58)	4.29 (9.56)	3.99 (8.61)	0.04
Insulin, mIU/l	3.34 (1.70)	3.87 (1.80)	5.03 (8.09)	5.57 (4.57)	<0.01
Glucose, mg/dl	109.04 (31.52)	107.04 (36.25)	104.52 (26.04)	109.03 (30.52)	0.95
Endocardial LAA device (N = 39)					
Adiponectin, μg/ml	1.18 (7.64)	1.26 (7.67)	1.21 (7.37)	1.25 (7.54)	0.48
Free fatty acids, mmol/l	ND	ND	ND	ND	ND
Beta-hydroxybutyrate, mM	0.51 (0.46)	0.48 (0.45)	0.18 (0.34)	0.27 (0.46)	0.17
Free glycerol, μM	31.72 (30.13)	39.32 (20.91)	21.52 (12.93)	22.30 (18.57)	0.02
Insulin, mIU/l	2.93 (1.22)	2.61 (1.20)	7.65 (11.95)	3.59 (4.41)	0.20
Glucose, mg/dl	118.42 (23.03)	118.25 (22.02)	120.74 (16.81)	110.52 (19.62)	0.19

Values are median (interquartile range).
LAA = left atrial appendage; ND = not done.

IMPACT OF LAA CLOSURE ON THE RAAS SYSTEM. The key hormones involved in the RAAS (aldosterone and renin) were successfully measured before and during follow-up after epicardial and endocardial LAA device implantation (Table 2).

Epicardial LAA device closure. There was no significant difference in the levels of aldosterone before (4.22 [IQR: 9.91] pg/ml) and immediately after (8.67 [IQR: 14.16] pg/ml; $p > 0.05$) the procedure. However, when assessed 24 h after the procedure (6.84 [IQR: 15.07] pg/ml), the levels were significantly lower compared with the pre-epicardial LAA device baseline (4.22 [IQR: 9.91] pg/ml; $p < 0.05$). This difference persisted when assessed at 3 months after the procedure (0.72 [IQR: 7.80] pg/ml; $p < 0.001$). Similarly, the levels of renin before the procedure (52.9 [IQR: 51.19] pg/ml) were not significantly different when compared with the levels immediately after the procedure (45.35 [IQR: 89.95] pg/ml; $p > 0.05$) or at 24 h post-procedure (33.57 [IQR: 136.3] pg/ml; $p < 0.05$). However, when compared with the pre-epicardial LAA device baseline (52.9 [IQR: 51.19] pg/ml), the levels of renin were significantly lower 3 months after the procedure (18.3 [IQR: 34.57] pg/ml; $p < 0.05$) (Table 2).

Endocardial LAA device closure. There was no significant difference in the levels of aldosterone before (13.34 [IQR: 6.89] pg/ml) device deployment when compared with immediately after (14.25 [IQR: 7.23] pg/ml; $p > 0.05$), at 24 h (13.0 [IQR: 3.83] pg/ml; $p > 0.05$), and at 3 months (13.6 [IQR: 3.99] pg/ml; $p > 0.05$). Similarly, the levels of renin before the procedure (22.0 [IQR: 30.96] pg/ml) were not significantly different when compared with the levels immediately after the procedure (26.68 [IQR: 49.37] pg/ml; $p > 0.05$), at 24 h post-procedure (22.32 [IQR: 61.7] pg/ml; $p > 0.05$), or at 3 months (25.0 [IQR: 44.47] ± 101.4 pg/ml; $p > 0.05$) (Table 2).

IMPACT OF LAA EXCLUSION ON LIPID METABOLISM. The hormones involved in lipid metabolism, such as adiponectin, free fatty acids, β-hydroxybutyrate, free glycerol, insulin, and glucose, were successfully measured (Table 3).

Epicardial LAA device closure. When compared with the levels of adiponectin before the epicardial LAA device procedure (20.7 [IQR: 30.08] μg/ml), there was no significant difference from the levels obtained immediately after the procedure (19.3 [IQR: 32.2] μg/ml; $p > 0.05$) or 24 h after the procedure (20.71 [IQR: 33.99] μg/ml; $p > 0.05$). However, there was a significant increase in the levels of adiponectin 3 months after the procedure (25.8 [IQR: 44.47] μg/ml; $p < 0.05$). Corresponding changes in the levels of free fatty acids were also assessed. There was no significant change in the levels of free fatty acids when assessed before (0.025 [IQR: 0.15] mmol/l) and immediately after the procedure (0.02 [IQR: 0.11] mmol/l; $p > 0.05$). However, there was a significant decrease in free fatty acid levels 24 h (0.018 [IQR: 0.02] mmol/l; $p < 0.05$) or 3 months after the procedure (0.019 [IQR: 0.05] mmol/l; $p < 0.05$). In contrast, there were no significant changes in the levels of β-hydroxybutyrate (mM) and free glycerol (μM) at any time point (Table 3).

Endocardial LAA device closure. When compared with the levels of adiponectin before the endocardial

TABLE 4 Impact of LAA Closure on Natriuretic Peptides and Electrolytes

	Pre-Procedure	Immediately Post-Procedure	24 h Post-Procedure	3 Months Post-Procedure	p Value (Baseline vs. 24 h Post-Procedure)
Epicardial LAA device					
NT-proANP, pg/ml	129.12 (135.61)	73.22 (89.91)	289.92 (159.24)	123.73 (135.35)	<0.01
NT-proBNP, pg/ml	235.35 (229.86)	187.72 (208.51)	317.73 (151.98)	216.35 (220.59)	0.01
Sodium, mm/l	139.14 (4.18)	136.65 (3.78)	131.64 (4.32)	137.92 (3.91)	<0.01
Potassium, mm/l	4.32 (0.43)	3.94 (0.94)	4.12 (0.75)	3.95 (0.67)	0.11
Magnesium, mg/dl	1.85 (0.27)	1.87 (0.27)	1.92 (0.13)	1.94 (0.81)	0.84
Creatinine, mg/dl	1.08 (0.27)	1.07 (0.27)	1.06 (0.41)	1.13 (0.27)	0.40
Endocardial LAA device					
NT-proANP, pg/ml	68.9 (75.71)	111.4 (106.4)	61.4 (72.8)	69.6 (84.5)	0.97
NT-proBNP, pg/ml	166.40 (130.90)	205.90 (237.20)	180.00 (67.16)	169.70 (92.90)	0.38
Sodium, mm/l	138.05 (3.10)	139.80 (4.59)	138.10 (4.32)	139.70 (3.24)	0.90
Potassium, mm/l	4.30 (1.10)	4.50 (4.32)	4.50 (0.54)	4.20 (0.67)	0.80
Magnesium, mg/dl	1.90 (0.27)	1.80 (0.27)	1.90 (0.13)	1.90 (0.27)	0.90
Creatinine, mg/dl	1.18 (0.27)	1.07 (0.27)	1.36 (0.45)	1.12 (0.27)	0.60

Values are median (interquartile range).
LAA = left atrial appendage; NT-proANP = pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

LAA device procedure (1.18 [IQR: 7.64] μg/ml), there was no significant difference from the levels obtained immediately after the procedure (1.26 [IQR: 7.67] μg/ml; $p > 0.05$), 24 hours after the procedure (1.21 [IQR: 7.37] μg/ml; $p > 0.05$), or at 3 months (1.25 [IQR: 7.54] μg/ml; $p > 0.05$). Free fatty acid levels were not assessed in the endocardial LAA device group. When compared with the levels of free glycerol before the endocardial LAA device procedure (31.7 [IQR: 30.1] μM), there was no significant difference from the levels obtained immediately after the procedure (39.3 [IQR: 20.9] μM; $p > 0.05$). However, at 24 h after the procedure, free glycerol levels (21.5 [IQR: 12.9] μM; $p < 0.05$) were significantly lower compared with pre-procedure levels. This decrease persisted at 3 months follow-up when compared with baseline (22.3 [IQR: 18.57] μM; $p < 0.05$). There was no significant change in the levels of β-hydroxybutyrate (mM) at any time point (Table 3).

IMPACT OF LAA EXCLUSION ON GLUCOSE METABOLISM. Insulin, which is involved in the metabolism of glucose, was successfully measured at various times (Table 3).

Epicardial LAA device closure. When compared with the levels of insulin before the epicardial LAA device procedure (3.34 [IQR: 1.70] mIU/l), there was no significant difference from the levels obtained immediately after the procedure (3.87 [IQR: 1.80] mIU/l; $p > 0.05$). However, there was a significant increase in the levels of insulin 24 h after the procedure (5.03 [IQR: 8.09] mIU/l; $p < 0.05$). This increase persisted when checked 3 months after the procedure (5.57 [IQR: 4.57] mIU/l; $p < 0.05$). The corresponding changes in the levels of glucose were also assessed. There was no significant change in the levels of glucose when assessed before or after the procedure at any time point (Table 3).

Endocardial LAA device closure. When compared with the levels of insulin before the endocardial LAA device procedure (2.93 [IQR: 1.22] mIU/l), there was no significant difference from the levels obtained immediately after the procedure (2.61 [IQR: 1.20] mIU/l; $p > 0.05$). However, at 24 h, there was a significant increase in insulin levels (7.65 [IQR: 11.95] mIU/l; $p < 0.05$), which decreased at 3 months (3.59 [IQR: 4.41] mIU/l; $p > 0.05$) when compared with pre-procedure insulin levels. There was no significant change in the levels of glucose when assessed before or after the procedure at any time point (Table 3).

IMPACT OF LAA CLOSURE ON NATRIURETIC PEPTIDE LEVELS. Blood samples for assaying ANP and BNP levels were drawn at 4 time points, as described in the Methods section (Table 4).

Epicardial LAA device closure. When compared with pre-epicardial LAA device levels (129.1 [IQR: 135.6] pg/ml), the concentration of ANP was significantly lower immediately after the procedure (73.2 [IQR: 89.9] pg/ml; $p < 0.05$). Twenty-four h after the procedure, the levels of ANP (289.9 [IQR: 159.2] pg/ml; $p < 0.05$) were significantly higher when compared with the pre-epicardial LAA device baseline (129.1 [IQR: 135.6] pg/ml). However, these levels returned to the pre-epicardial LAA device baseline when assessed 3 months after the procedure (123.7 [IQR: 135.3] pg/ml;

TABLE 5 Impact of LAA Closure on Systemic Blood Pressure

	Baseline Blood Pressure	Pre-Procedure Blood Pressure	Immediately Post-Procedure	24 h Post-Procedure	3 Months Post-Procedure	p Value (Baseline vs. 3 Months)
Epicardial LAA device (N = 38)						
SBP, mm Hg	137.50 (16.20)	138.60 (20.10)	115.40 (18.60)	122.60 (22.20)	117.90 (12.80)	<0.01
DBP, mm Hg	80.00 (8.37)	81.90 (14.90)	71.20 (13.50)	72.90 (14.90)	70.90 (14.95)	<0.01
Endocardial LAA device (N = 39)						
SBP, mm Hg	144.00 (16.80)	143.60 (16.80)	125.90 (21.06)	142.90 (16.87)	142.90 (7.96)	0.90
DBP, mm Hg	85.20 (19.03)	84.40 (14.95)	75.20 (11.30)	85.90 (19.50)	81.90 (3.10)	0.60

Values are median (interquartile range).
DBP = diastolic blood pressure; LAA = left atrial appendage; SBP = systolic blood pressure.

$p > 0.05$). BNP levels (pg/ml) displayed similar changes (Table 4).

ENDOCARDIAL LAA DEVICE CLOSURE. When compared with pre-endocardial LAA device levels (68.9 [IQR: 75.71] pg/ml), the concentration of ANP was significantly higher immediately after the procedure (111.4 [IQR: 106.4] pg/ml; $p < 0.05$). Twenty-four h after the procedure (61.4 [IQR: 72.8] pg/ml) and at 3 months (69.6 [IQR: 84.5], pg/ml), the levels of ANP were not significantly different when compared with the pre-endocardial LAA device baseline. BNP levels (pg/ml) displayed similar changes (Table 4).

IMPACT OF LAA CLOSURE ON SYSTEMIC BLOOD PRESSURE. Epicardial LAA device closure. SBP at baseline (137.5 [IQR: 16.2] mm Hg), before the epicardial LAA device procedure (138.6 [IQR: 20.1] mm Hg), showed a persistent decrease when measured immediately after (115.4 [IQR: 18.6] mm Hg), 24 h after (122.6 [IQR: 22.2] mm Hg), and 3 months after the procedure (117.9 [IQR: 12.8] mm Hg) compared with baseline. Similar changes in DBP were noted (Table 5).

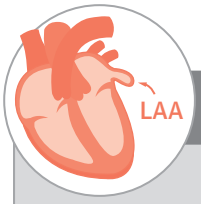
Endocardial LAA device closure. SBP at baseline (144 [IQR: 16.8] mm Hg) before the endocardial LAA device procedure (143.6 [IQR: 16.8] mm Hg) showed a significant decrease when measured immediately after the procedure (125.9 [IQR: 21.06] mm Hg; $p < 0.05$). However, at 24 h after the procedure (142.9 [IQR: 16.87] mm Hg; $p > 0.05$) and 3 months after the procedure (142.9 [IQR: 7.96] mm Hg, $p > 0.05$), there was no significant change compared with baseline. Similar changes were noted in DBP (Table 5).

DISCUSSION

SALIENT FINDINGS. There are several neurohormonal and homeostatic implications after LAA closure with the epicardial and endocardial LAA devices. The major findings of our study include the following (Central Illustration). 1) After epicardial LAA device closure, ANP and BNP levels significantly decreased immediately post-procedure, increased at 24 h, and again normalized at 3 months. After endocardial LAA device implantation, the levels significantly increased immediately post-procedure and continued to normalize at 24 h and at 3 months. 2) Epicardial LAA device closure also led to down-regulation of the adrenergic system and RAAS, and also results in a significant decrease in the systemic blood pressure. No such effects were noted after endocardial LAA device implantation. 3) Epicardial LAA device closure increased levels of adiponectin, insulin, and free fatty acids. No such effects were seen post-endocardial LAA device implantation.

ROLE OF EPICARDIAL LAA DEVICE EXCLUSION IN MODULATING ADRENERGIC OUTPUT AND RAAS. Despite strict adherence to the protocol, there is wide variation in reported values for adrenaline (the reference range in our laboratory is 0 to 900 pg/ml) between the epicardial and endocardial LAA device groups, likely from unmeasured confounding factors, including volume status, antihypertensive medications, duration of fasting, and stress related to the procedure. The sympathetic nervous system plays an important role in the regulation of systemic blood pressure (11). The interaction of natriuretic peptides with the adrenergic system is poorly understood. Some early research suggests that increased ANP activity leads to a reduction in systemic aldosterone levels. The current study is the first to suggest a possible interaction between natriuretic peptides and adrenaline. The LAA is densely innervated by the ANS; however, the role of the ANS in modulation of natriuretic peptides is not known. The current study suggests that exclusion of the LAA with the epicardial LAA device may attenuate the release of adrenaline via a negative feedback mechanism. This study is hypothesis-generating and will be confirmed in a larger cohort of patients undergoing LAA exclusion.

CENTRAL ILLUSTRATION **Role of LAA in Neurohormonal Modulation**



Impact of Left Atrial Appendage (LAA) Closure Using the Epicardial and Endocardial Devices

Levels, compared to prior to procedure:	Post-procedure with epicardial device			Post-procedure with endocardial device		
	0 hours	24 hours	3 months	0 hours	24 hours	3 months
Adrenaline	No change —	↓	↓	—	—	—
Noradrenaline	↓	↓	↓	—	—	—
Aldosterone	—	↓	↓	—	—	—
Renin	—	—	↓	—	—	—
Adioponectin	—	—	↑	—	—	—
Free glycerol levels	—	—	—	—	↓	↓
Insulin	—	↑	↑	—	↑	—
Atrial and brain natriuretic peptides	↓	↑	—	↑	—	—
Systemic blood pressure	↓	↓	↓	↓	—	—

Substantial differences in hemodynamics and neurohormonal impacts.
Further studies are required to elucidate the underlying mechanism of these physiologic changes.

Lakkireddy, D. et al. J Am Coll Cardiol. 2018;71(2):135–44.

The effect of epicardial versus endocardial closure systems on atrial natriuretic peptide, B-type natriuretic peptide, various components of the renin-angiotensin-aldosterone system, and lipid and glucose metabolism. ↑ = increased; ↓ = decreased; LAA = left atrial appendage.

CORRELATION BETWEEN ANP AND RAAS. ANP inhibits the RAAS, and when the LAA is ligated with an acute increase in ANP, levels of RAAS markers should go up. Subsequently, with normalization of ANP, RAAS markers should also normalize. However, we observed that with LAA ligation, the RAAS markers continue to be down-regulated, suggestive of a mechanism that is probably independent of ANP alone. Perhaps the LAA and surrounding fat pad necrosis affect the autonomic inputs and outputs that regulate the systemic RAAS. Similarly, we observed that post-endocardial LAA device implantation, ANP and BNP significantly increase

immediately post-procedure, which is attributed to atrial stretch and injection of dye into the LAA. This finding is consistent with a prior report (12). This area needs further exploration to understand the impact of afferent and efferent inputs from the peri-LAA neural ganglionic structures, baroregulatory centers, and RAAS. It is important to note that, in our results, there is wide variation in the reported aldosterone level values between the epicardial and endocardial LAA devices at all times. The differences are due to variation in volume status, antihypertensive medications, kidney function, and concomitant comorbid conditions. These differences in reported units should not affect the overall results because there was strict adherence to a protocol regarding timing of blood draws, assay, and blood analysis. Furthermore, some variation in ANP levels reported (reference range, 20 to 77 pg/ml) between the 2 groups can be explained by differences in unmeasured confounding factors at baseline, such as minor variation in comorbid conditions, volume status, and use of antihypertensive medications, among others.

ROLE OF THE LAA IN REGULATING GLUCOSE AND FAT METABOLISM. This is the first study to suggest that LAA exclusion could modulate fat and glucose metabolism. We postulate that the LAA is an active endocrine organ that provides feedback via interaction with ANS. The epicardial fat has been implicated in the pathogenesis of various cardiac conditions. We postulate that the LAA, owing to its dense autonomic innervation, plays an important role in the modulation of insulin and adiponectin. The removal of the LAA by the epicardial LAA device or surgery leads to changes that result in lipolysis. Down-regulation of the RAAS probably up-regulates beta cells and results in increased insulin levels and decreased glucose levels after LAA exclusion. Similar effects were not seen post-endocardial LAA device. The variation reported in adiponectin values (reference range, 2 to 37 μg/ml), free glycerol (reference range, 1 to 10,000 μM), and insulin levels (reference, <25 mIU/l) between the epicardial and endocardial LAA device groups at baseline may be due to differences in underlying confounding factors such as body mass index, period of fasting, minor differences in comorbid conditions, sex, and age. These findings need to be confirmed in a larger cohort of patients undergoing LAA exclusion.

IMPACT OF LAA EXCLUSION IN THE REGULATION OF SYSTEMIC BLOOD PRESSURE. Acutely, the reduction in blood pressure is probably related to significant diuresis and natriuresis. The sustained drop in blood pressure during subacute and long-term follow-up is probably related to the down-regulation of the RAAS. It is well known that stretch receptors in the cardiac chambers regulate the intravascular volume and systemic blood pressure. An important component of this regulation is the Bezold-Jarisch reflex, which is activated in response to increased intravascular volume, leading to stretching of the ventricles and atria, and thus activating the afferent limb of the reflex (13). The interaction and the role of the LAA during the Bezold-Jarisch reflex are not known; however, further studies are needed to assess these findings.

IMPACT OF LAA EXCLUSION ON RAAS DOWN-REGULATION. Electrical exclusion of the LAA, either surgically or with an epicardial ligation system, has been shown to positively benefit the overall rhythm control in persistent AF (14–16). As we are aware, RAAS up-regulation is a common finding in patients with AF. LAA elimination may influence the evolution of the atrial substrate by not only eliminating the potential focal triggers, regional re-entry from structural heterogeneity, but also from possible down-regulation of the RAAS, as is seen in the current study. This opens a larger dialog on whether LAA elimination should be considered as an adjunctive therapy in patients with nonparoxysmal AF on a routine basis. The ongoing U.S. Food and Drug Administration–sponsored LAA Ligation Adjunctive to PVI for Persistent or Longstanding Persistent Atrial Fibrillation [NCT02513797]) trial may answer this question in the days to come (17).

STUDY LIMITATIONS. The major limitation of this study is its smaller study cohort. The most important limitation is the lack of specific information regarding antihypertensive medications in each group that could potentially affect our results. However, there was no significant difference in comorbid conditions, such as hypertension, coronary artery disease, diabetes, and congestive heart failure, between the 2 groups that would have influenced the choice of antihypertensive agents in either group. Despite these limitations, the data show several interesting new findings that were not previously reported. Because of limited information on this subject, several hypothetical mechanistic assumptions were made that need to be tested in future studies. This study opens a window of knowledge as to how a primordial embryological remnant such as the LAA can play a major role in various aspects of systemic homeostasis. In patients with AF, elimination of the LAA could be very beneficial in down-regulating the RAAS, eliminating potential triggers/re-entry, and reducing LA volume, thereby changing the evolution of AF and the underlying substrate. Whether LAA ligation should be considered for effective blood

pressure control in AF patients who have drug-resistant hypertension is worth further exploration.

CONCLUSIONS

There are substantial differences in hemodynamics and neurohormonal effects of LAA exclusion with epicardial or endocardial LAA devices. Further studies are required to elucidate the underlying mechanism of these physiological changes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Device-based exclusion of the LAA is an evolving alternative to oral anticoagulation for prevention of thromboembolism in patients with AF. Some closure devices reduce ANP levels, downregulate the renin-angiotensin-aldosterone and adrenergic activity, lower arterial blood pressure and may diminish the burden of recurrent AF.

TRANSLATIONAL OUTLOOK: Further studies are required to elucidate the mechanisms underlying the neurohormonal consequences of LAA closure by various methods.

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KEY WORDS atrial fibrillation, LAA exclusion, neurohormonal regulation

APPENDIX For a listing of the normal reference range of all the key hormones, please see the online version of this article.