# Influence of Left Atrial Appendage Amputation on Natriuretic Peptides—A Randomized Controlled Trial

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## Abstract

**Background** Closure or amputation of the left atrial appendage (LAA) is a common therapy for atrial fibrillation (AF). As the LAA is a hormone-producing organ, however, amputation is still somewhat controversial. We examined patients after surgical AF therapy with or without LAA amputation to determine the influence of LAA amputation on pro-atrial natriuretic peptide (proANP) and B-type natriuretic peptide (BNP) plasma levels and on clinical severity of heart failure.

**Methods** Twenty-one consecutive patients were prospectively randomized to either undergo LAA amputation ($n = 10$) or no LAA amputation ($n = 11$) between 05/2015 and 10/2015. All patients underwent coronary and/or valve surgery and concomitant AF surgery with either cryoablation ($n = 3$) or radio frequency ablation ($n = 17$). ProANP and BNP levels were measured preoperatively and until 800 days postoperatively.

**Results** Baseline proANP values were comparable between the groups (without LAA amputation: 4.2 ± 2.1 nmol/L, with LAA amputation: 5.6 ± 3.6 nmol/L). Postoperatively, proANP levels rose markedly in both groups. Even after LAA amputation, proANP levels remained elevated for 7 days postoperatively but fell to baseline levels at day 31 and remained on baseline level at 800 days postoperatively. ProANP levels in the LAA amputation group (5.8–9.7 nmol/L) were not significantly lower than in the group without LAA amputation (9.2–14.1 nmol/L; $p = 0.357$). BNP levels also rose after surgery in both groups until day 7. At 800 days after surgery, BNP levels were back at baseline levels in both groups. Clinical follow-up at 2 years postoperatively showed no difference in heart failure symptoms or need for heart failure medication between the groups.

**Conclusion** In contrast to commonly held beliefs about the endocrine and reservoir functions of the LAA, there seems to be no clinically relevant detrimental effect of LAA amputation on natriuretic peptide levels and severity of heart failure until up to 2 years postoperatively.

**Keywords**
- arrhythmia therapy
- heart failure
- molecular biology
- physiology

## Introduction

Patients undergoing surgical therapy for atrial fibrillation (AF) often undergo concomitant closure or amputation of the left atrial appendage (LAA), because it is regarded as the "most lethal human appendage."[1] While there is an ongoing discussion regarding the best treatment strategy for surgical LAA management,[2] catheter-based LAA closure has already found widespread acceptance in the cardiology community.[3] In patients with surgical closure of the LAA via either exterior

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or interior approach, a rate of 10 to 20% ineffective closures has been described,[4,5] leading to an even higher risk of stroke than without LAA closure.[6] Because the most successful technique of LAA closure is surgical excision,[7] patients at our center are treated with complete surgical LAA amputation as described previously.[8]

Although an accepted procedure, amputation of the LAA is still a topic of discussion. While Kamohara et al showed improved left atrial function following LAA amputation,[9] Tabata et al showed markedly reduced compliance, elevated LA pressure, and elevated transmitral pressure gradients following occlusion of the LAA.[10] Furthermore, the LAA is a hormone-producing organ.[11,12] Atrial natriuretic peptide (ANP) is released by atrial cardiomyocytes in response to high blood volume. It acts to reduce the water and sodium loads on the circulatory system, thereby reducing blood pressure. B-type natriuretic peptide (BNP) is produced by myocardial cells and has diuretic, natriuretic, and vasodilatory actions. N-terminal pro-BNP is often used as a biomarker for heart failure patients. Until now, there is no data available on the influence of LAA amputation on postoperative natriuretic peptide levels. Therefore, we aimed to determine the influence of LAA amputation on ANP and BNP plasma levels as well as on renal function after surgery in this exploratory study.

## Materials and Methods

### Study Design

The present study was a prospective, randomized, controlled, double-blind, single-center study.

### Study Population

All adult patients with preoperative diagnosis of AF scheduled to undergo cardiac surgery with cardiopulmonary bypass and concomitant AF treatment were eligible. A total of 21 consecutive patients scheduled for heart surgery with concomitant AF therapy were prospectively randomized undergo LAA amputation ($n = 10$) or no LAA amputation ($n = 11$) in a single center.

### Randomization

The patients were included into this study preoperatively (ClinicalTrials.gov identifier: NCT03816410). Randomization was conducted in a 1:1 fashion by a computer-based online randomization system (clinvestigator.com, New York, United States). All eligible patients during the time frame between 05/2015 und 10/2015 were screened and invited to participate in the trial. The operating surgeon received the randomization allocation via e-mail preoperatively. Clinical follow-up until up to 2 years postoperatively was conducted using telephone calls or personal visits to the patients.

### Surgical Procedure

All patients underwent coronary and/or valve surgery and AF surgery with either cryoablation (AtriCure Cryo Ice, Atricure Europe, Amsterdam, Netherlands, $n = 3$) or radio frequency (RF) ablation (Estech Revolution, Estech, Winchester, Ohio, United States, $n = 17$). After establishing extracorporeal circulation (aorta/right atrium), the LAA was managed according to the randomized group allocation: in the intervention group, LAA amputation was performed as described previously.[8] Briefly, an autologous pericardial patch was harvested and incised longitudinally. This patch was pulled over the LAA and put down to its base in a skirt-like fashion. Thereafter, a continuous mattress suture including and fixating the pericardial patch was placed along the LAA base. The LAA was then amputated directly above the patch. Then, a continuous running suture including the patch was performed to safely close the LAA amputation stump. Completeness of LAA amputation (defined as LAA remnant $<10$ mm) was confirmed by transesophageal echocardiography. In the control group, the LAA was left untouched.

The ablation lines included pulmonary vein isolation and an extended left atrial lesion set according to standardized patterns.[13] In patients with long-standing persistent AF, additional right-sided ablation was performed on the beating heart during reperfusion. We performed cryoablation in mitral valve procedures and RF ablation in all other procedures.

### Outcomes

The primary outcomes of this study were proANP and BNP serum levels until 800 days postoperatively. Secondary outcomes included clinical stage of heart failure and survival until 2 years postoperatively. The clinical follow-up was conducted using telephone calls or personal visits to the patients.

### Laboratory Analyses

ProANP and BNP levels were measured preoperatively and at eight postoperative time points (1: at time of skin closure, 2: at 12 hours, 3: at 24 hours, 4: at 4 days, 5: at 5 days, 6: at 7 days, 8: at 31 days, 9: at 800 days). The samples were collected at all time points in both serum vials for proANP and ethylene diamine tetraacetic acid vials for BNP. After collection, the vials were transported to the laboratory at room temperature and processed within 45 minutes. BNP levels were measured via immunoassay (Siemens Centaur, Erlangen, Germany). For proANP measurements from serum, the solid components were removed via centrifugation and the sera were frozen at $-24$°C. All serum samples were tested for proANP levels at the end of the sampling period using enzyme-linked immunosorbent essay (ELISA). We measured proANP because it is more stable than ANP and its serum concentration is proportional to the amount of ANP. ProANP is formed by cleaving the signal peptide of the prohormone, pre-proANP, so that the serum concentration of proANP correlates with ANP production. The half-life of proANP in serum, however, is 60 to 120 minutes, which is significantly longer than that of α-ANP (with a half-life of 3–4 minutes); thus, proANP levels can be measured more accurately. The proANP kit from Biomedica and ELISA was used to analyze the samples; in addition, microplates coated with polyclonal sheep anti-proANP antibodies were used (Biomedical ELISA assay, Biomedical, Vienna, Austria).

 

For both proANP and BNP measurements, a calibration curve was constructed from the values of standardized reference samples. Using this calibration curve, the concentrations in the samples were determined. The optical density of the blank value was subtracted accordingly from the optical density readings of the standards and the samples. From the duplicate sample values, an average value was calculated. Samples that were out of range were diluted appropriately and measured with the next measurement cycle.

Renal function was quantified by estimating the glomerular filtration rate at baseline, immediately postoperatively, and on postoperative days 1, 2, and 6 using the Cockroft-Gault equation. Postoperative acute kidney injury was quantified at these time points using the Acute kidney Injury Network (AKIN) criteria. Serum activity of creatine kinase, isoform MB (CK-MB), and serum levels of troponin I were quantified at the same postoperative time points.

### Ethics

The local ethics committee approved the study. Each patient gave separate informed consent for this sub before enrollment. A 1:1 computed randomization was conducted. The operating surgeon received instructions upon LAA amputation via automated e-mail from the randomization system. All site investigators except the surgeon were blinded to group assignment of each patient. The study was conducted in accordance with the Declaration of Helsinki.

### Statistics

In this exploratory setting, no sample size calculation was conducted. Statistical analyses were conducted using SPSS Version 22 (IBM, Armonk, New York, United States), GraphPad Prism version 6 software (GraphPad Software, Inc., La Jolla, California, United States), and R version 3.1.2. Numeric parameters were analyzed as mean ± standard deviation unless stated otherwise. Group comparisons were made using Fisher's exact test, the chi-square test, or Student's *t*-test, as appropriate. Statistical significance was assumed at the level of $p < 0.05$. The effects of LAA amputation versus no LAA amputation, biatrial versus LA ablation, and cryoablation versus RF ablation (independent variables) on postoperative proANP and BNP levels (repeated measurements; dependent variables) were estimated by multivariate regression using generalized linear models with time as within-subject factor and the respective independent variable as between-subjects factor.

## Results

Twenty-one patients underwent randomization, were treated accordingly, and were analyzed for the primary end point. Baseline characteristics were comparable between the groups except for a tendency for more severe renal impairment in the group not undergoing LAA amputation (►**Table 1**). In both groups, the majority of patients received

**Table 1** Baseline characteristics

| | LAA amputation ($n = 10$) | No LAA amputation ($n = 11$) | *p* Value |
|---|---|---|---|
| Age (years); mean ± SD | 74 ± 5 | 74 ± 7 | 0.92 |
| Male gender; *n* (%) | 5 (50) | 9 (82) | 0.12 |
| Body mass index (kg/m$^2$); mean ± SD | 29 ± 3 | 28 ± 4 | 0.89 |
| Preoperative NYHA stadium; *n* (%) | | | 0.13 |
| I | 1 (10) | 0 | |
| II | 7 (70) | 4 (36) | |
| III | 2 (20) | 6 (55) | |
| IV | 0 | 1 (9) | |
| Glomerular filtration rate (mL/min); mean ± SD | 75 ± 20 | 60 ± 19 | 0.095 |
| Dialysis before surgery; *n* (%) | 1 (10) | 0 | 0.78 |
| Preoperative anticoagulation; *n* (%) | | | 0.26 |
| Warfarin | 4 (40) | 6 (55) | |
| Direct oral anticoagulants | 6 (60) | 5 (45) | |
| Diabetes mellitus; *n* (%) | 2 (20) | 5 (45) | |
| Arterial hypertension; *n* (%) | 10 (100) | 10 (91) | 0.33 |
| AF type; *n* (%) | | | 0.53 |
| Paroxysmal | 5 (50) | 7 (64) | |
| Persistent | 5 (50) | 4 (36) | |
| Cerebrovascular occlusive disease; *n* (%) | 2 (20) | 3 (27) | 0.70 |
| History of stroke; *n* (%) | 1 (10) | 0 | 0.92 |

Abbreviations: AF, atrial fibrillation; LAA, left atrial appendage; NYHA, New York Heart Association, SD, standard deviation.

 

**Table 2** Intraoperative data

| | LAA amputation ($n = 10$) | No LAA amputation ($n = 11$) | $p$ Value |
|---|---|---|---|
| Surgical procedures; *n* (%) | | | 0.18 |
| CABG | 5 (50) | 4 (36) | |
| Aortic valve surgery | 1 (10) | 2 (18) | |
| Aortic valve surgery + CABG | 2 (20) | 4 (36) | |
| Mitral valve surgery + CABG | 2 (20) | 1 (9) | |
| Ablation mode; *n* (%) | | | 0.52 |
| Radiofrequency ablation | 7 (70) | 9 (82) | |
| Cryoablation | 3 (30) | 2 (18) | |
| Ablation extension; *n* (%) | | | 0.41 |
| Biatrial | 5 (50) | 4 (36) | |
| Left atrial | 5 (50) | 7 (64) | |
| Extracorporeal circulation time (min; mean ± SD) | 120 ± 32 | 128 ± 39 | 0.93 |
| Aortic clamping time (min; mean ± SD) | 75 ± 38 | 75 ± 32 | 0.97 |
| Duration of surgery (min; mean ± SD) | 211 ± 38 | 210 ± 46 | 0.93 |

Abbreviations: CABG, coronary artery bypass graft surgery; LAA, left atrial appendage; SD, standard deviation.

LA RF ablation according to our strategy described above. The procedural profile and duration of intraoperative steps were similar in the two groups (►**Table 2**).

Mean baseline proANP values (►**Table 3**) were comparable in the two groups (LAA amputation: 4.2 ± 2.1 nmol/L, no LAA amputation: 5.6 ± 3.6 nmol/L; $p = 0.56$). ProANP levels rose as a result of surgery in both groups (►**Fig. 1**). ANP levels returned to baseline values by the 31st postoperative day only in the group with LAA amputation. During the first 7 days after surgery, proANP levels in the LAA amputation

**Table 3** ANP and BNP levels over time

| | LAA amputation ($n = 9$) | No LAA amputation ($n = 8$) | $p$ Value |
|---|---|---|---|
| ProANP (nmol/L); mean ± SD | | | |
| Preoperative | 4.23 ± 2.13 | 5.63 ± 3.58 | 0.56 |
| Skin closure | 11.6 ± 3.70 | 10.9 ± 9.40 | 0.64 |
| 12 hours | 5.82 ± 3.18 | 9.23 ± 5.73 | 0.25 |
| 24 hours | 6.33 ± 3.50 | 10.6 ± 5.26 | 0.35 |
| 4 days | 6.97 ± 2.37 | 14.1 ± 9.97 | 0.10 |
| 5 days | 6.79 ± 3.10 | 13.6 ± 6.87 | 0.09 |
| 7 days | 9.78 ± 6.34 | 12.9 ± 7.81 | 0.53 |
| 31 days | 4.73 ± 1.50 | 9.87 ± 7.18 | 0.28 |
| 800 days | 3.34 ± 1.12 | 5.08 ± 2.86 | 0.74 |
| BNP (nmol/L); mean ± SD | | | |
| Preoperative | 156 ± 108 | 356 ± 343 | 0.39 |
| Skin closure | 118 ± 77.4 | 287 ± 319 | 0.52 |
| 12 hours | 240 ± 153 | 570 ± 508 | 0.58 |
| 24 hours | 317 ± 169 | 619 ± 675 | 0.26 |
| 4 days | 335 ± 240 | 596 ± 455 | 0.28 |
| 5 days | 359 ± 139 | 676 ± 685 | 0.19 |
| 7 days | 407 ± 211 | 595 ± 529 | 0.27 |
| 31 days | 223 ± 148 | 713 ± 1309 | 0.13 |
| 800 days | 137 ± 67 | 209 ± 144 | 0.73 |

Abbreviations: ANP, Atrial natriuretic peptide; BNP, B-type natriuretic peptide; LAA, left atrial appendage; SD, standard deviation.

 

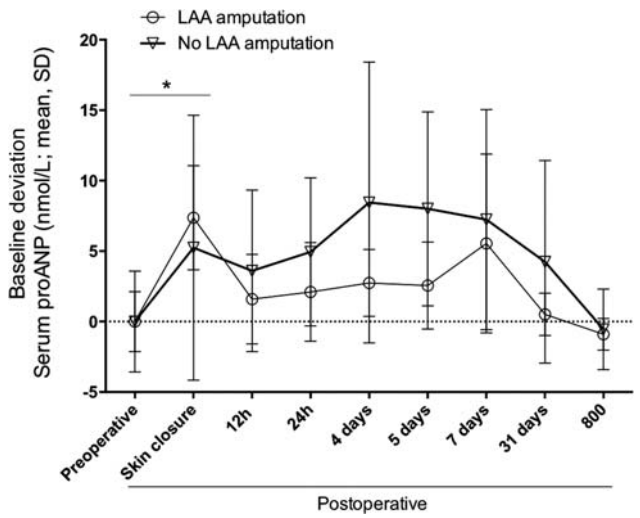


**Fig. 1** ProANP serum levels. Values are standardized to the preoperative baseline values. Abbreviations: LAA, left atrial appendage; proANP, proatrial natriuretic peptide; SD, standard deviation. *proANP levels rose significantly compared with the baseline value in both groups.

group tended to be lower than in the nonamputation group. At 800 days postoperatively, proANP levels were similar in both groups (LAA amputation group: 3.4 nmol/L; control group 5.1 nmol/L; $p = 0.74$) and had returned approximately to the baseline levels. The overall statistical analysis using a general linear model revealed that the difference between the postoperative proANP levels in the two groups was not statistically significant ($p = 0.42$).

BNP levels rose after surgery in both groups until day 7 (►**Fig. 2**). At 31 days after surgery, BNP levels fell only in the patients with amputated LAA (►**Fig. 2**). However, at 800 days postoperatively, BNP levels were slightly lower than at baseline with no significant difference between the groups (LAA amputation group: 137 ± 67 nmol/L; control group: 209 ± 144 nmol/L; $p = 0.73$). Overall, there were no significant differences in BNP levels between patients with versus without LAA amputation ($p = 0.39$) as determined by the general linear model (►**Table 3**).

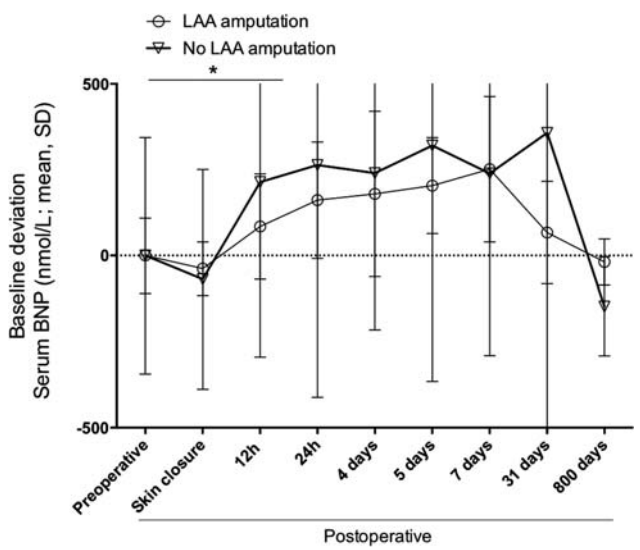


**Fig. 2** BNP serum levels. Values are standardized to the preoperative baseline values. Abbreviations: BNP, B-type natriuretic peptide; LAA, left atrial appendage; SD, standard deviation. *BNP levels rose significantly compared with the baseline value in both groups.

Mean postoperative proANP and BNP levels did not correlate with the duration of cardioplegic arrest ($R^2 = 0.0043$, $p = 0.86$ [proANP], $R^2 = 0.0023$, $p = 0.91$ [BNP]) or with the duration of extracorporeal circulation ($R^2 = 0.0026$, $p = 0.90$ [proANP], $R^2 = 0.0073$, $p = 0.64$ [BNP]). There was also no difference between proANP and BNP levels when comparing patients undergoing LA versus biatrial ablation (data not shown).

Maximum creatinine levels were not different in the two groups (LAA amputation: 1.6 ± 1.3 mg/dL; no LAA amputation: 1.7 ± 1.5 mg/dL; $p = 0.81$). Minimum glomerular filtration rates were also similar (LAA amputation: 54.1 ± 18.0 mL/min, no LAA amputation: 57.3 ± 27.9 mL/min; $p = 0.73$). Kidney injury according to the AKIN criteria occurred in two patients (1× AKIN II, 1× AKIN III) in the amputation group and in two patients (2× AKIN II) in the nonamputation group.

Cardiac injury was assessed by determining the maximum levels of CK-MB and troponin. In the LAA amputation group, values tended to be higher (CK-MB 93.4 ± 63.9 U/L, troponin 42.7 ± 59.9 µg/L) than in the nonamputation group (CK-MB 74.4 ± 38.9 U/L, troponin 24.4 ± 17.8 µg/L) without reaching statistical significance ($p$[CK-MB] = 0.42; $p$[troponin] = 0.34).

There were no deaths or stroke during the 31-day postoperative period (►**Table 4**).

Clinical follow-up at 2 years postoperatively was complete for 20 of 21 patients (95%). By that time, three patients had died (LAA amputation group: 1/10 vs. control group: 2/10; $p = 0.59$). Two deaths were caused by septic multiorgan

**Table 4** Postoperative outcomes

| | LAA amputation ($n = 10$) | No LAA amputation ($n = 11$) | $p$ Value |
|---|---|---|---|
| 31-day mortality; *n* (%) | 0 | 0 | 1.00 |
| Stroke; *n* (%) | 0 | 0 | 1.00 |
| Freedom from AF at discharge; *n* (%) | 8/9 (89) | 8/10 (80) | 0.60 |
| Acute renal failure; *n* (%) | | | 0.51 |
| No | 8 (80) | 9 (82) | |
| AKIN I | 0 | 0 | |
| AKIN II | 1 (10) | 2 (18) | |
| AKIN III | 1 (10) | 0 | |
| Length of ICU stay (days); mean ± SD | 6.7 ± 6.3 | 4.4 ± 2.9 | 0.25 |
| Length of hospital stay (days); mean ± SD | 12.7 ± 7.8 | 11.2 ± 3.9 | 0.57 |

Abbreviations: AKIN, Acute Kidney Injury Network; ICU, intensive care unit; LAA, left atrial appendage; SD, standard deviation.

 

**Table 5** Heart failure medication at 2 years postoperatively

| | LAA amputation ($n = 9$) | No LAA amputation ($n = 8$) | $p$ Value |
|---|---|---|---|
| Diuretics | 8 (89) | 6 (75) | 1.00 |
| Angiotensin-converting enzyme inhibitors | 3 (33) | 2 (25) | 1.00 |
| Aldosterone-receptor blocking agents | 1 (11) | 2 (25) | 1.00 |
| Beta-blockers | 7 (78) | 7 (88) | 1.00 |

Abbreviation: LAA, left atrial appendage.

failure, and one death occurred due to a farming accident. Among the surviving patients, no rehospitalization for heart failure was reported. All patients were on some extent of heart failure medication without differences between the groups (►**Table 5**). Almost all patients were free of heart failure symptoms, except for two patients (one in each group), who reported ongoing heart failure symptoms (peripheral edema, shortness of breath on exercise and orthopnea).

## Discussion

The main result of our study was that in patients undergoing LAA amputation, proANP levels rose after the procedure and did not return to baseline levels until the 31st postoperative day. However, they normalized to baseline levels by 800 days postoperatively. We observed similar kinetics for BNP levels after LAA amputation. The clinical follow-up until 2 years postoperatively demonstrated no differences in clinical heart failure severity or increased need for heart failure medication in patients who had their LAA amputated. These results can be interpreted in a way, that even after amputation of a part of the LA and destruction of atrial regions by ablation, the heart as an endocrine organ can still maintain liquid balance through ANP and BNP secretion. Stöllberger et al emphasized the endocrine function of the LA and warned against external amputation or internal occlusion of the LAA.[12] In our study, we did not observe that LAA amputation lowered ANP values, and there was also no difference in renal dysfunction between patients undergoing LAA amputation and those without LAA amputation.

Interestingly, Brueckmann et al noted a dramatic decrease in ANP serum levels as early as day 1 after catheter ablation without LAA amputation.[14] In the surgical environment, we observed the opposite effect (►**Fig. 1**). This difference may be partly explained by the observation of Jiang et al, who found that ANP does not function as a biomarker for ablation success in patients with structural heart disease, although it is predictive in patients with lone AF, that is, the group of patients studied by Brueckmann et al.[15] Information regarding ANP levels in patients with structural heart disease compared with that of healthy subjects is not available.

Our findings regarding BNP levels are not easy to interpret. We measured BNP levels early and serially and did not see a decrease toward baseline levels in the first 7 days after surgery, whether or not the LAA was amputated. However, BNP levels on postoperative day 31 were higher than baseline in the nonamputated group, whereas BNP levels in the LAA amputation were at baseline values.

BNP levels fell in patients with successful atrial ablation, but could serve as a marker for ablation success over a long time period.[16] The study of Seiler et al cannot be directly compared with ours because they performed endocardial ablation and did not remove the LAA.[17] Berendes et al showed a firm correlation between duration of cardioplegic arrest time and postoperative BNP and ANP levels.[18] Our study did not confirm this correlation; furthermore, there was no difference in BNP and proANP levels between patients undergoing LA or biatrial ablation, respectively.

The levels of CK-MB and troponin in our patients were higher compared with patients not undergoing ablation, but this is not surprising as thermal destruction of atrial tissue would be expected to show some effect on the heart. Incomplete removal of the LAA as well as suturing it from the inside or ligating from the outside leads to a failed LAA occlusion in 10 to 20% of patients.[5] Therefore, we decided to remove the LAA completely using a technique we described previously that did not increase the incidence of bleeding or other complications.[8] While the current guideline recommends device exclusion of the LAA rather than the cut-and-sew technique,[19] we used the latter because it is safe and much less costly than if the exclusion quality is monitored by TEE (no LAA leftovers, stump $< 1$ cm).

There is a consensus that LA ablation as a concomitant procedure to cardiac surgery is only acceptable if it does not increase patient risk.[19] It has already been shown that it does not.[2,20] We can now add another facet to the ablation story concerning the LAA management. Surgical complete LAA amputation does not lead to ANP loss and therefore does not 1result in fluid imbalance or renal dysfunction when compared with surgery without LAA amputation.

### Limitations

The main limitation of this study is that this is a very small study that is not sufficiently powered to detect small effects of the LAA amputation. Thus, the probability of a type 2 error is high. If more patients had been included, there smaller differences between the natriuretic peptide level courses might have turned out to be statistically significant. Furthermore, the study did not evaluate imaging-derived functional cardiac parameters (diastolic dysfunction, LA transport function, LA reservoir function, LA volume) and rhythm outcome data. These parameters might be relevant confounders influencing ANP and BNP levels postoperatively. They should be evaluated in follow-up studies. However, the clinical data suggest at least that no large clinical differences of heart failure symptoms were present between the groups. Finally, the proANP and BNP courses shown in this study are, to our knowledge, the first ever descriptions in the setting after surgical LAA amputation. These values could be used as

 

reference marks for further studies investigating natriuretic peptide courses after AF surgery.

In clinical practice, the value of LAA management is currently unclear and the results of LAAOS-III are eagerly awaited.[21] Until then, the present results suggest to rebut concerns about relevant adverse endocrine effects when weighing the risks and benefits of surgical LAA management.

### Ethics Approval and Consent to Participate

The study was approved by the ethical committee of the Faculty of Medicine at Justus Liebig University Giessen, Germany. The trial was designed and conducted in accordance with the Declaration of Helsinki. Patients gave informed consent for study participation prior to enrollment.

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### Competing Interests

The authors declare that there are no conflicting financial or nonfinancial interests with relevance to this manuscript.

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Philippe Grieshaber and Borros Arneth contributed equally to this work: PG collected the clinical data and samples, BA conducted the laboratory analyses. PG and BA wrote the manuscript together.

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