Chronic atrial fibrillation ablation impact on endocrine and mechanical cardiac functions

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Aims
Assess the impact of persistent/permanent atrial fibrillation (AF) ablation on endocrine and mechanical cardiac functions.

Methods and results
In all, 43 patients (40 males, 53 ± 12 years) undergoing persistent/permanent AF ablation had atrial (ANP) and brain natriuretic peptide (BNP) measurements before day 1, 3, and 3 months after ablation. In the same period of time transthoracic echocardiography was performed. With a mean radiofrequency delivery of 98 ± 29 min, sinus rhythm (SR) was restored in 30 patients (70%) without DC shock. ANP decreased significantly (P < 0.001) with restoration of SR and then increased until day 3 post ablation without reaching the level observed during AF. At 3 months, ANP was significantly lower than day 3 reaching normal value in 28 (65%) patients and being ≤ 7 pg/mL in 4 (9%). The BNP followed the same trend with normal BNP level in 23 (53%) patients at 3 months. Identifiable atrial filling waves on the pulsed Doppler transmitral recordings performed between day 2 and day 4 after the procedure were seen in 18 patients (42%). At 3 months, 39 (95%) of the patients with SR during echocardiography had a significant A wave.

Conclusion
SR following persistent/permanent AF ablation is associated with a dramatic decrease in natriuretic peptides. At 3 months, despite relatively extensive atrial ablation, endocrine and mechanical cardiac functions are significantly improved.

Keywords
Chronic atrial fibrillation • Catheter ablation • Natriuretic peptides • ANP • BNP • Cardiac function

Surgical chronic atrial fibrillation (CAF) ablation with the Cox–Maze Procedure is associated with significant atrial damage (multiple atriotomy incisions and excision of both atrial auricles) and fluid retention with pulmonary oedema.1–4 It has been hypothesized that this may be the result of a postoperative decrease in the atrial natriuretic peptide (ANP).5

Persistent/permanent AF is amenable to catheter ablation,6,7 but requires extensive radiofrequency (RF) lesions delivered in both atria and in the coronary sinus.8 The impact on endocrine and/or mechanical atrial function is largely ignored. This study evaluates heart endocrine secretion and atrial active contraction following CAF ablation.

Methods

Patients’ characteristics
All patients with persistent or permanent AF attending for catheter ablation in the 10-month study period were eligible for the study. Patients were excluded if they had prior catheter ablation for AF, or were unable to attend follow-up. Of the 77 patients who attended for their initial AF ablation, 28 patients were excluded prior to entering the study due to being unable to adhere to the follow-up protocol. In addition, six patients were excluded as they did not complete the 3-month blood test.

The study population consisted of 43 patients (40 men; mean age 53 ± 12 years) referred for ablation of persistent (n = 15) or perma-
Biosense Webster) to achieve the desired power delivery, while sim-irrigation rates of 5–60 mL/min (0.9% saline via a Cool Flow pump, (PV isolation) and 30–40 W (atrial tissue except in posterior LA) using coronary sinus), ablation of atrial tissue, and linear LA ablation. electrical isolation of other thoracic veins (superior vena cava and involved up to 4 steps: electrical isolation of pulmonary veins (PVs), electrical cardioversion for persistent AF, with four being resistant to blocker therapy. Thirty-eight patients underwent a prior attempt at arrhythmic drugs (AAD) prior to the ablation procedure. Twenty-four months (range: 1 month to 6 years) and failed 3.2

<table>
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<th>Table 1 Baseline characteristics of the population (quantitative parameters are expressed as mean ± SD)</th>
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HTA, hypertension; AF, atrial fibrillation; AAD, anti-arrhythmic drugs; LVEF, left ventricular ejection fraction; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin-2 receptor blockade.

nent AF (n = 28) at a single institution. Baseline characteristics are reported in Table 1. These patients were in AF for a median of 11 months (range: 1 month to 6 years) and failed 3.2 ± 1.2 anti-arrhythmic drugs (AAD) prior to the ablation procedure. Twenty-four patients (56%) had AAD at the time of ablation and 28 (65%) a beta-blocker therapy. Thirty-eight patients underwent a prior attempt at electrical cardioversion for persistent AF, with four being resistant to electrical cardioversion. Mean heart rate on holter monitoring in AF was 91 ± 19 b.p.m. (50–132 b.p.m.; median: 90) before the procedure and was assessed between day 1 and day 4 after the procedure and at 3 months. Five patients had a left ventricular ejection fraction (LVEF) <50% (41 ± 8%). All patients provided written informed consent.

**Ablation procedure**

All patients had effective anticoagulation for at least 1 month, and transesophageal echocardiography was performed to exclude left atrial (LA) thrombus before ablation. Oral anticoagulation was replaced by intravenous heparin 48 h before and ceased 6 h before the procedure. After transseptal access, an intravenous bolus of heparin (50 IU mg/kg body weight) was administered and repeated 3–4 h later.

The ablation of the LA was performed as previously described and involved up to 4 steps: electrical isolation of pulmonary veins (PVs), electrical isolation of other thoracic veins (superior vena cava and coronary sinus), ablation of atrial tissue, and linear LA ablation.

RF energy was delivered at each site or area with a power of 20–30 (PV isolation) and 30–40 W (atrial tissue except in posterior LA) using irrigation rates of 5–60 mL/min (0.9% saline via a Cool Flow pump, Biosense Webster) to achieve the desired power delivery, while simultaneous attention to adequate temperature was maintained.

**Study protocol**

Blood samples from the antecubital vein of all patients were obtained before ablation, then on day 1, day 3, and 3 months after ablation. Samples were drawn after subjects were supine for at least 6 h, and blood was collected into tubes containing EDTA (1.5 mg/mL), promptly centrifuged, and stored at −80°C until final analysis. ANP and brain natriuretic peptide (BNP) concentrations were determined using immunoradiometric assay kits (Shionoria, Osaka, Japan). Normal ranges were for ANP 7–31 pg/mL and for BNP (male: 5.3–18.2 pg/mL; female: 6.7–18.6 pg/mL). The intra-assays variations were <6.3% for ANP and <2.7% for BNP. The inter-assays variations were <5.7% for ANP and <4.2% for BNP. Troponin Ic (normal range <0.5 ng/mL (Innolite)) was systematically evaluated the day after the procedure.

All patients were monitored in the hospital for at least 5 days after their procedure. Body weight and urine output were measured daily until discharge. All patients had a transthoracic echocardiogram (TTE) between day 1 and day 4 after the ablation with measurement of the LA (parasternal diameter) and left ventricular (LV) dimensions, and Doppler velocity on mitral, aortic, and tricuspid flow in sinus rhythm (SR). Late diastolic peak velocity (peak A wave velocity) was recorded by pulsed-wave Doppler echocardiography from the apical four-chamber view, with the sample positioned between the tips of the mitral leaflets by averaging three consecutive cycles in patients with SR. LVEF was measured with the Simpson method. All measurements were performed in accordance with the American Society of Echocardiography recommendations.

**Follow-up**

Patients were periodically re-evaluated at 1, 3, 6, and 12 months, after which, in the absence of AF or symptoms, the referring physician provided the follow-up data. At each review, TTE, exercise testing, and ambulatory 48 h monitoring were performed to evaluate the presence of asymptomatic arrhythmias. In the event of recurrent symptomatic or asymptomatic arrhythmia, patients were offered an additional ablation after a trial of drug therapy.

After 3 months free of arrhythmia, ANP and BNP were measured again. Seven patients with arrhythmia recurrence but no redo procedure, had blood samples drawn at 3 months post ablation.

**Statistical analysis**

All variables are reported as mean ± SD. χ² test was used for qualitative variables. Comparison between groups was performed with the Student’s t-test or, when data were not normally distributed, the Mann–Whitney U test. Evaluation of quantitative values within groups was assessed, when appropriate, by an ANOVA F-test to account for the inflation of the experimentwise Type I error due to multiple testing followed by Student’s paired t-test without adjusting the significance level (ANP, BNP, Echo data, weight, mean heart rate were compared from previous studies that have demonstrated significant changes in BNP/ANP in patients undergoing cardioversion for AF.9–12

**Results**

**AF ablation**

Mean RF delivery and procedure time were 98 ± 29 and 266 ± 88 min, respectively. RF applications restored SR in 30 patients (70%) without DC shock. Mean heart rate after ablation was 74 ± 12 vs. 91 ± 19 b.p.m. before (P < 0.001). Mean Troponin Ic level the day after the procedure was 11 ± 4 ng/mL (6–22 g/ mL). Due to catheter irrigation with saline (3.0 ± 1.5 L) during the procedure, volume overload was responsible for weight
changes (Figure 1). Return to baseline weight was observed at day 3.

At 3 months, mean heart rate was 72 ± 12 b.p.m., 36 (84%) patients were free of AF or atrial tachycardia (AT) (28 with AAD); two patients were in AT at that time and other five were in SR with paroxysmal atrial arrhythmia. Concerning the other drugs, 28 had beta-blocker or calcium inhibitor, 17 had angiotensin converting enzyme inhibitor or angiotensin-2 receptor blocker.

After a mean follow-up of 18 ± 5 months, 36 patients (84%) were free of AF or AT (six with AAD) with 1.4 procedures (29 patients had only one).

Plasma ANP and BNP levels
Mean ANP and BNP levels at baseline, day 1, day 3, and 3 months are reported in Figure 1.

At baseline, nine (21%) and eight (19%) patients had, respectively, normal ANP and BNP levels despite AF. ANP and BNP levels were correlated at baseline (r = 0.622, P < 0.001, Figure 2), but there was no significant correlation between ANP or BNP level before ablation with the duration of AF, Troponin level post ablation or duration of RF delivery. However, weak but significant correlations were found between ANP or BNP levels and LA dimension (r = 0.423, P = 0.02; r = 0.528, P < 0.001) and between BNP level and LVEF (r = 0.482, P = 0.002).

ANP decreased significantly (P < 0.001) with restoration of SR and then increased until day 3 post ablation without reaching the level observed during AF. At 3 months, ANP was significantly lower than on day 3 reaching normal value in 26 (65%) patients and being <7 pg/mL in four (9%) (Figures 1 and 3A).

The BNP followed the same trend as shown in Figures 1 and 3B with normal BNP level in 23 (53%) patients at 3 months.

No significant correlations were observed between ANP or BNP levels at baseline and AF or AT recurrence during follow-up. There was no significant difference neither concerning natriuretic peptide secretion (ANP and BNP) between patients with or without recurrence at 3 months or at the end of the follow-up.

However, two patients with AT at the 3 months blood test had high ANP and BNP levels (169 and 88 pg/mL for ANP and 134 and 45 pg/mL for BNP).

Echo data
Identifiable atrial filling waves on the pulsed Doppler transmitral recordings performed between day 2 and day 4 after the procedure were seen in 18 patients (42%) (Table 2).

Patients with no A wave soon after the procedure had a significantly higher Troponin Ic blood level (11 ± 2 vs. 7 ± 1 ng/mL, P = 0.04) and a higher RF duration (110 ± 20 vs. 77 ± 35 min, P = 0.004) but not a longer AF duration (14 ± 10 vs. 12 ± 21 months in patients with A wave—P = 0.72). At 3 months, 39 (95%) of the patients with SR during echocardiography had a significant A wave. Of the two patients with no A wave, one had mild mitral stenosis. The second patient recovered an A wave at 6 months. Overall, A wave velocity improved significantly at month 3 (Table 2). Parasternal LA diameter decreased significantly during the same period of time (Table 2). Concerning left ventricle parameters, reductions of end-diastolic and end-systolic diameters were not significant, but improvement in ejection fraction and BNP secretion were (Table 2 and Figure 1).

Discussion
This study demonstrates that endocrine heart function as judged from ANP and BNP is restored 3 month after an ablation procedure in most patients. This is associated with significant restoration of mechanical atrial function. Of patients undergoing catheter ablation of persistent/permanent AF, 65 and 53%, respectively, had ANP and BNP levels within normal range at 3 months despite a large amount of RF delivery. Neither ANP nor BNP levels observed in the days following the ablation procedure were valid predictors of AF/AT recurrence. Active atrial contraction was present in 39 of 41 patients (95%) with SR during the echo at 3 months.
Natriuretic peptides secretion is not uniform depending on the haemodynamic condition. Previous studies have shown that (i) in SR, ANP was mainly produced by the atria and BNP by the ventricles13,14 (ii) in lone AF, ANP and BNP were mainly produced by the atria15, and (iii) in patients with AF associated with decreased LVEF or structural heart disease, ANP and BNP were mainly produced by the ventricles.13 Rossi et al.16 demonstrated that AF was an independent determinant of higher N-ANP levels in case of LV dysfunction, but not of BNP which was strongly determined by LVEF. Similar to electrical cardioversion, AF ablation decreases natriuretic peptides levels by restoring SR. 3 – 11,13 – 16 The kinetics of these peptides after ablation shows a substantial decrease when compared with the Cox–Maze procedure.5 After catheter ablation, natriuretic peptides secretion recovers within 3 days, concomitantly with delayed fluid overload elimination. Fujiwara et al.9 showed a gradual increase in ANP levels in patients with AF from the fourth hour to 5 days after cardioversion, concomitant with an increase in atrial filling fraction. Wozakowska-Kaplon et al.10 reported similar findings. Therefore, stunning of the atria after AF cardioversion does not involve only atrial contraction, but also endocrine function.

Another important point is the improvement of BNP profile after ablation, even in patients with baseline ‘normal’ LVEF by restoration and maintenance of SR. Improvements of diastolic and systolic function have been reported post AF (paroxysmal and chronic) ablation in patients with lone AF suggesting that AF could be the cause of systolic but also diastolic dysfunction.17 Atrial and ventricular remodelling post CAF ablation (2), may play a role in this phenomenon.

Previous studies on AF ablation and natriuretic peptides included patients with paroxysmal AF who underwent PV isolation (PVI) alone, which is a more limited procedure compared with the one in the present study. Date et al.12 found that BNP decreased significantly after PVI only in patients with no recurrence in a population without structural heart disease, but whether blood tests were performed in SR or in arrhythmia was not clear. Conversely, Yamada et al.11 showed for the same population and procedure that ANP and BNP levels were significantly reduced after PVI independent of PAF recurrence. They concluded that the relief of the AF burden by successful PVI significantly reduced elevated plasma ANP and BNP levels. Despite the fact that this population and the procedures are quite different from our study, we report similar findings than Yamada et al.11 with an improvement in natriuretic peptides level at 3 months compared with day 3 (all these blood samples were done in SR) independently of transient AF/AT recurrences.

Finally, recovery of atrial mechanical function is a major goal in the treatment of AF. In patients with Cox–Maze procedure

| Table 2 | Evolution of echo parameters after ablation (quantitative parameters are expressed as mean ± SD) |
|---|---|---|
| Echo in SR just after ablation (n = 43) | Echo in SR at 3 months (n = 41) | P-value |
| LA size (mm) | 47 ± 8 | 41 ± 8 | < 0.001 |
| Presence of A wave | 18 (42%) [36 ± 11] | 39 (95%) [43 ± 11] | < 0.001 |
| (if present average in cm/s) | | | |
| LVDD (mm) | 55 ± 6 | 53 ± 5 | 0.67 |
| LVDs (mm) | 38 ± 7 | 34 ± 5 | 0.77 |
| Ejection fraction (%) | 59 ± 8 | 64 ± 6 | < 0.001 |

LA, left atrium; LVDD, end-diastolic left ventricle diameter; LVDs, end-systolic left ventricle diameter.
without structural heart disease, 50–72.5% of the patients recover an A wave between 3 months to 1 year, whereas Lemola et al. found that LA circumferential catheter ablation was impairing atrial function in paroxysmal AF, their results on CAF were unclear (LA ejection fraction of 23 ± 13% few months after ablation) due to the lack of baseline atrial function measurement. Loss of active atrial contraction can be detrimental with haemodynamic and thromboembolic consequences. Our study shows that CAF ablation restores and maintains SR and restores active atrial contraction. The superior atrial function observed with the catheter-based procedure compared with the surgery may be due to a less traumatic approach tailored to the patients’ arrhythmias avoiding unnecessary lesions. In addition, the preservation of the LA appendage may improve atrial function compared with Maze procedure in which the LA appendage was removed (A wave at 6 months 100 vs. 72.5%).

**Study limitations**

We do not have a control group with persistent/permanent AF and without ablation, but the literature is quite prolific on natriuretic peptides after cardioversion. Our population is relatively small, but the mean number of patients included in studies on natriuretic peptides and AF conversion or ablation is 41 going from 15 to 66. We have included patients with and without altered LVEF. BNP is not independently associated with AF and is strongly determined by LV function for which it is an independent marker. But we used it as a marker of LV function improvement. Finally, it may be difficult to assess asymptomatic AF and despite thorough follow-up we may have missed some short lasting asymptomatic atrial arrhythmia episode.

**Conclusion**

SR following CAF ablation is associated with a dramatic decrease in natriuretic peptides. At 3 months, despite relatively extensive atrial ablation, endocrine and mechanical atrial function are all significantly improved.

**Conflict of interest:** none declared.

**References**


CLINICAL VIGNETTE

Unicuspid aortic valve: an interesting presentation

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A 52-year-old male presented with acute onset chest pain and ST-segment elevation myocardial infarction (Panel A). An urgent cardiac catheterization was performed which showed a filling defect in the left anterior descending (LAD) artery (Panel B). After failure at attempts to reperfuse the LAD, the patient underwent emergency cardiopulmonary bypass surgery with a left internal mammary graft to LAD. He was found to have clam shell-like severely calcified unicuspid aortic valve (Panels C and D) that was replaced with a porcine valve. Very hard, embolic material was found at the bifurcation of the diagonal LAD which was later determined to be calcium. The embolic calcium is thought to have originated from the calcified unicuspid aortic valve.

Patient was also found to have a dilated, calcified ascending aorta (5.8 cm in diameter) that was electively replaced 5 months later.

Unicuspid aortic valve is a rare, but well-described paediatric congenital anomaly. In a retrospective series, the incidence of unicuspid aortic valve on echocardiography was found to be 0.02% in adults. This population was also shown to have significant ascending aortic dilatation requiring accompanying aortic transplant while replacing the valve. Another observation has been the abundance of calcification associated with unicuspid valve.

Dyspnoea on exertion, angina, and few cases of monocular blindness due to retinal artery emboli have been described as some presenting symptoms.

To our knowledge, this is the first case report of acute myocardial infarction with a calcium embolus from a unicuspid aortic valve. Panel A. A 12-lead ECG showing ST-segment elevation in leads V2–V4 (arrows). Panel B. A coronary angiography of the left anterior descending artery showing a filling defect (arrow) suggestive of an embolus. Panel C. Severe calcification demonstrated on the unicuspid aortic valve. Arrow indicates the possible source of embolus in this patient. Panel D. A post-aortic valve replacement operation specimen of a clam shell-like unicuspid aortic valve (arrow).

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