Characterization of Cardiac Brain Natriuretic Peptide Release in Patients With Paroxysmal Atrial Fibrillation Undergoing Left Atrial Ablation

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Background—Paroxysmal atrial fibrillation (PAF) is associated with elevated levels of brain natriuretic peptide (BNP). The exact cardiac source and implications of this are currently unknown, as are the effects of left atrial ablation on cardiac BNP release. We sought to investigate BNP levels at different cardiac sites in PAF patients before and after left atrial ablation and compare these with a non–atrial fibrillation control cohort.

Methods and Results—Twenty PAF patients (52±10 years, 70% men; left ventricular ejection fraction, 55±3%) undergoing ablation were studied, BNP levels were measured at different cardiac sites before and after ablation and compared with a control cohort undergoing ablation for left lateral accessory pathways (10 patients, 41±11 years; left ventricular ejection fraction, 55±4%). In both cohorts, the coronary sinus BNP levels were the greatest. The PAF cohort had significantly greater BNP levels than the control cohort at all sites before and after ablation. Ablation of the left atrium was associated with a significant decrease in coronary sinus BNP levels (P=0.05) and transcardiac BNP gradient (P=0.03). This was not observed in the control cohort.

Conclusions—BNP levels are elevated in PAF, with the highest levels in the coronary sinus. Ablation of the left atrium was associated with an immediate decrease of BNP levels, implicating this as the source. (Circ Arrhythm Electrophysiol. 2010;3:18-23.)

Key Words: ablation ■ atrium ■ natriuretic peptides

Atrial fibrillation (AF) is the most common sustained arrhythmia and creates a large burden to healthcare worldwide.1 Recent advances in management of AF include nonpharmacological therapies such as ablation in the left atrium.1 This procedure typically isolates pulmonary veins electrically and modifies left atrial substrate to potentially cure paroxysmal AF. The impact of this procedure on the cardiac neurohormonal system is not completely understood.

Clinical Perspective on p 23

Brain natriuretic peptide is released from the ventricle in heart failure in response to increases in left ventricular pressure and volume,3 and its level in the peripheral venous blood has been associated with morbidity and mortality in heart failure. In patients with AF and normal ventricular function, the levels of BNP have also been demonstrated to be elevated; the exact cardiac origin and implications of this are not understood. The origin of BNP in AF may be the atria,4 although this has not been confirmed. Furthermore, decreases in peripheral venous BNP 3 months after left atrial ablation5,6 have been observed. The acute effects on chamber specific cardiac BNP production are unknown.

In this study, we sought to characterize the acute effects of ablation on chamber specific BNP levels in AF patients undergoing left atrial ablation to gain insight into the source of production and the acute affect of left atrial ablation.

Methods

Patient Populations

Twenty consecutive patients with paroxysmal AF who were undergoing left atrial ablation as part of their AF management were enrolled to participate. Ten consecutive patients who were undergoing ablation of a left lateral accessory pathway via a transseptal approach served as controls. All patients had normal left ventricular function and were able to give informed consent. Demographic and clinical parameters were collected on each patient. The study was approved by the ethics committee of the University of Western Ontario and London Health Sciences Center (London, Ontario, Canada).

Ablation Procedure

Each procedure was performed under general anesthesia or heavy sedation in the postabsorptive state in all patients. The atrial ablation procedure for paroxysmal AF adopted in this study has been published elsewhere.1 In short, a double transseptal puncture was...
performed and a circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, Calif) and 3.5-mm Navistar Thermocoil ablation catheter (Biosense Webster) were passed to the left atrium. A nonfluoroscopic anatomic map (CARTO, Biosense Webster) was then made and merged to a 64-slice CT scan of the left atrium as previously described. A wide antral circumferential ablation was performed of both left and right sided pulmonary veins, achieving electric isolation confirmed with the circular mapping catheter. In the control cohort, a single transseptal puncture was performed and a 4-mm radiofrequency ablation catheter (Celsius, Biosense Webster) was passed to the mitral annulus, where accessory pathway radiofrequency ablation was performed in the usual way. The ablation times in both cohorts were recorded. Assessment of the left atrial diameter was by echocardiography using the M-mode cross-sectional atrial diameter in the parasternal long-axis view. Left ventricular ejection fraction was also assessed echocardiographically using a Simpson biplane method or gated cardiac blood pool scanning. These assessments were performed within 3 months of the ablation procedure in both cohorts.

Blood Sampling

A luminal coronary sinus catheter and a radial arterial line were used for coronary sinus and peripheral arterial sampling, respectively. Sampling from the right ventricle and right atrium was performed via the transseptal guiding sheaths before transseptal puncture. Peripheral venous sampling was performed via the femoral introducer sheath. Sampling was performed simultaneously from the right ventricle, the right atrium, the peripheral vein, the coronary sinus, and the peripheral radial artery. Sampling was then completed from the left atrium after transseptal puncture within 10 minutes of the first sampling. Immediately after, left atrial ablation sampling was repeated from the left atrium. Both the transseptal catheters were removed to the right heart, and simultaneous sampling of the right atrium, right ventricle, peripheral femoral vein, coronary sinus and peripheral radial artery was then performed within 10 minutes of the left atrial sampling. Sampling for the control cohort was collected in the same manner.

Blood samples were collected into ice-chilled tubes containing an ethylenediaminetetra-acetic acid (EDTA). After centrifugation at 4°C, plasma samples were stored at −70°C until assayed. Before assaying, the plasma samples were thawed on ice. The AXSYM BNP Assay (Abbott Diagnostics, Abbott Park, Ill) was used to measure plasma BNP; this assay uses a microparticle enzyme immunoassay designed to measure plasma BNP and has been correlated with the point of care TRIAGE Assay (Biosite, San Diego, Calif). Previous research by the current author has demonstrated significant changes in BNP measurements with this assay within 10 minutes of an intervention. All levels for BNP are expressed as picogram per milliliter pg/mL, and as absolute levels. The assay is insensitive to BNP levels <15 pg/mL and as such a level <15 was assigned a value of zero.

A transcardiac veno-arterial gradient BNP gradient was calculated as follows:

\[ \text{Transcardiac BNP gradient (pg/mL)} = \text{CS}_{\text{BNP}} (\text{pg/mL}) - \text{LA}_{\text{BNP}} (\text{pg/mL}) \]

where \( \text{CS}_{\text{BNP}} \) represents coronary sinus (venous level) BNP level and \( \text{LA}_{\text{BNP}} \) represents left atrial (arterial level) BNP level.

In addition, a transpulmonary veno-arterial BNP gradient was also calculated in the control and PAF cohorts before and after ablation as follows:

\[ \text{Transpulmonary BNP gradient (pg/mL)} = \text{LA}_{\text{BNP}} (\text{pg/mL}) - \text{RV}_{\text{BNP}} (\text{pg/mL}) \]

where \( \text{LA}_{\text{BNP}} \) represents left atrial (venous level) BNP level and \( \text{RV}_{\text{BNP}} \) represents right ventricular (arterial level) BNP level.

<table>
<thead>
<tr>
<th>Table 1. Demographic Parameters in PAF Versus Control Cohort</th>
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<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Class III AAD</td>
</tr>
<tr>
<td>Class I AAD</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Left atrial size, mm</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; AAD, antiarrhythmic drugs; LVEF, left ventricular ejection fraction.

Hemodynamic Measurements

At each sampling time systolic and diastolic blood pressure was recorded (in mm Hg) along with heart rate in beats per minute. In addition, cardiac rhythm was recorded before and after ablation.

Statistical Analysis

Data are presented as mean value±standard deviation if normally distributed and as median and interquartile range (25th and 75th percentiles) if nonnormally distributed, unless otherwise stated. Statistical analysis and graphical presentation was performed using statistical software (SigmaStat, version 2.03, Chicago, Ill). Within-group data were compared using a paired \( t \) test and between-group data were compared using an unpaired \( t \) test for normally distributed data. Nonnormally distributed unpaired data were analyzed with a Mann–Whitney test and paired nonnormally distributed data were analyzed with a Wilcoxon signed rank test. Categorical data were compared using a Fisher exact test. Comparisons of data at multiple sites between AF patients and control subjects were performed using the Wilcoxon Mann–Whitney test with correction for multiple measures by the method of Benjamini and Hochberg. A probability value of \(<0.05\) was considered statistically significant.

Results

Baseline Patient Characteristics and Hemodynamics Before and After Ablation

Baseline patient characteristics for both cohorts are listed in Table 1. The paroxysmal AF cohort of 20 patients had an average age of 52±10 years, with 60% men and a left ventricular ejection fraction (LVEF) of 55±3%. The control cohort of 10 patients had an average age of 41±11 years, with 60% men and LVEF 55±4%. These groups were well matched with respect to sex and LVEF, except the paroxysmal AF cohort was significantly older (\( P=0.01 \)). With respect to other demographic parameters, not unexpectedly, the PAF cohort had greater prevalence of hypertension and greater use of class I and III antiarrhythmic drugs. Also, left atrial size was larger in the AP diameter, although both groups were in the normal range. Likewise, serum creatinine was slightly higher in the PAF group, probably because of increased age, but well within the normal range.

Ablation times, measurement of blood pressure, and heart rate in both the left atrial ablation and control cohorts are presented in Table 2. There were no significant differences (\( P>0.05 \)) in blood pressure and heart rates before and after ablation between the control and PAF cohort. Ablation times in both cohorts were as follows: PAF cohort, 2619±1022
seconds versus control, $349 \pm 258$ seconds; $P<0.001$. Two patients in the PAF cohort were in atrial fibrillation before ablation; all other patients in the cohort were in sinus rhythm at the time of ablation. Each patient in the PAF cohort except the $2$ in atrial fibrillation at the time of ablation had not had a symptomatic paroxysm for at least $48$ hours before the ablation. All patients in the control cohort were in sinus rhythm and did not have AF. No patient in the control group had a symptomatic paroxysm of SVT for at least $48$ hours before ablation. SVT was, however, induced in all patients before ablation.

### Assessment of BNP Levels

#### PAF Cohort Before and After Ablation Compared With Control Cohort Before and After Ablation

The site-specific BNP levels in both the control and PAF cohort for both preablation and postablation are presented and compared in Table 3. Compared with the control cohort, the PAF cohort had significantly greater ($P<0.05$) site-specific comparisons of BNP levels at all sites before ablation. After ablation, the PAF cohort had significantly greater site-specific comparisons of BNP levels ($P<0.05$) except for the right ventricular level ($P=0.10$) and right atrial level ($P=0.06$), which were greater but not significantly so.

A comparison of BNP values at all sites in both cohorts before ablation demonstrated that the preablation coronary sinus (CS) BNP level in the PAF cohort was significantly greater ($P<0.001$) than all other sites measured in both cohorts. A comparison of all sites in both cohorts after ablation demonstrated that the postablation CS BNP level in the PAF cohort was significantly greater ($P<0.001$) than levels at all other sites.

#### PAF Cohort: Before Versus After Ablation

Before ablation, in the PAF cohort, the highest BNP levels were measured in the CS ($181 \text{ [104 to 614]} \text{ pg/mL}$). A comparison of the BNP levels at all the $6$ sites before ablation demonstrated that CS BNP was significantly greater ($P=0.001$) than all other sites. CS BNP levels decreased after ablation (before, $181 \text{ [104 to 614]} \text{ pg/mL}$; after, $142 \text{ [81 to 274]} \text{ pg/mL}$; $P=0.05$) (Figure). After ablation, the highest BNP levels were measured in the CS ($142 \text{ [81 to 274]} \text{ pg/mL}$), and a comparison of BNP levels at all $6$ sites after ablation also demonstrated that the CS BNP level was significantly greater ($P<0.001$) than all other sites measured. Otherwise, chamber-specific BNP levels showed a nonsignificant decrease after ablation.

#### Control Cohort: Before Versus After Ablation

In the control cohort, comparison of BNP levels measured at all $6$ sites before ablation demonstrated that the CS BNP level was significantly greater than all other sites ($P=0.005$); however, after ablation, a comparison of all sites were not significantly different from each other. In addition, BNP levels did not significantly change ($P>0.05$) before versus after ablation in the CS (Figure) or at other sites measured.

### Transcardiac and Transpulmonary BNP Gradients

The transcardiac BNP gradients before versus after ablation for the PAF ablation cohort decreased significantly: before AF ablation, $253 \pm 329$ pg/mL; after AF ablation, $172 \pm 334$ pg/mL; $P=0.03$. In the control cohort, the transcardiac gradient before versus after ablation approached significance: preablation BNP, $41 \pm 45$ pg/mL; postablation BNP, $25 \pm 39$ pg/mL; $P=0.08$. The comparison of transcardiac BNP gradient between the PAF cohort and the control cohort revealed the transcardiac BNP gradient was significantly higher in the PAF cohort compared with the control cohort before ($P=0.01$) and after ablation ($P=0.003$).

The transpulmonary BNP gradient did not significantly alter in the PAF cohort or the control cohort before versus after ablation: before AF ablation, $11 \pm 32$ pg/mL; after AF ablation, $18 \pm 29$ pg/mL; $P=0.11$.

### Table 2. Blood Pressure and Heart Rate PAF Ablation Cohort Versus Control Cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-PAF</th>
<th>Pre-Control</th>
<th>$P$ Value</th>
<th>Post-PAF</th>
<th>Post-Control</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>110±20</td>
<td>116±20</td>
<td>0.92</td>
<td>116±24</td>
<td>114±27</td>
<td>0.92</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>68±13</td>
<td>69±13</td>
<td>0.92</td>
<td>71±18</td>
<td>73±12</td>
<td>0.75</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>79±13</td>
<td>81±20</td>
<td>0.84</td>
<td>85±18</td>
<td>93±20</td>
<td>0.48</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>75±24</td>
<td>73±9</td>
<td>0.83</td>
<td>80±19</td>
<td>74±17</td>
<td>0.26</td>
</tr>
</tbody>
</table>

$SBP$ indicates systolic blood pressure; $DBP$, diastolic blood pressure; $MAP$, mean arterial pressure; $HR$, heart rate.

### Table 3. Cardiac BNP Levels Measured Before and After Ablation in Control and PAF Cohort

<table>
<thead>
<tr>
<th>Site Level, pg/mL</th>
<th>Pre-PAF</th>
<th>Pre-Control</th>
<th>$P$ Value</th>
<th>Post-PAF</th>
<th>Post-Control</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral vein</td>
<td>77 (35–126)</td>
<td>17 (0–48)</td>
<td>0.03</td>
<td>70 (40–113)</td>
<td>21 (4–53)</td>
<td>0.047</td>
</tr>
<tr>
<td>Radial artery</td>
<td>83 (37–134)</td>
<td>10 (0–56)</td>
<td>0.03</td>
<td>78 (46–140)</td>
<td>12 (0–68)</td>
<td>0.02</td>
</tr>
<tr>
<td>Right atrium</td>
<td>67 (39–120)</td>
<td>25 (0–52)</td>
<td>0.046</td>
<td>78 (33–121)</td>
<td>37 (18–52)</td>
<td>0.06</td>
</tr>
<tr>
<td>Left atrium</td>
<td>85 (42–122)</td>
<td>30 (0–63)</td>
<td>0.04</td>
<td>80 (37–133)</td>
<td>23 (0–56)</td>
<td>0.04</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>84 (35–123)</td>
<td>21 (0–54)</td>
<td>0.05</td>
<td>69 (33.5–110)</td>
<td>36 (19–76)</td>
<td>0.10</td>
</tr>
<tr>
<td>CS</td>
<td>181 (104–614)</td>
<td>58 (18–99)</td>
<td>0.005</td>
<td>142 (81–274)</td>
<td>36 (14–78)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Data presented as median and interquartile range (25th and 75th percentiles).*
Discussion

In this study, we demonstrated elevations in BNP levels in patients undergoing left atrial ablation for PAF as compared with those with SVT, with the most elevated levels in the coronary sinus. In addition, we demonstrated an immediate acute significant decrease in coronary sinus BNP levels and transcardiac BNP gradient after ablation of the left atrium, suggesting the atria as the likely source of the BNP. The exact origin and cause of elevated BNP levels observed in PAF patients with normal systolic left ventricular function remains unknown. Previous research has demonstrated acute decreases in peripheral venous BNP at day 1 and up to 3 months after AF ablation and suggested that BNP levels after ablation may be a marker for successful outcome. These studies along with the current study suggest a possible association with BNP and the pathogenesis of PAF. Further research is needed to establish an exact cause and effect. It may be that BNP release is initiated by factors such as mechanical strain in the atria and the ventricle, potentially associated with the atrial fibrillation and/or concomitant diastolic dysfunction. Accordingly, it has been demonstrated that BNP gene expression is stimulated by mechanical strain in animal models. The release of BNP in AF abates when the arrhythmia is terminated, such as after electric cardioversion, implying an arrhythmia specific induction of BNP release.

Elevated BNP in AF patients has also been demonstrated in non–heart failure patients in a substudy of the Breathing Not Properly Study, and the authors suggested that higher levels >200 pg/mL should be used as a cutoff for the diagnosis of heart failure in AF patients. This disparity was not demonstrated in the same study in heart failure patients in which AF was not an independent discriminator of BNP level. A study by Rossi et al corroborated this finding demonstrating that left ventricular function was the main determinant of BNP levels and not AF in a heterogeneous heart failure population. BNP in patients with chronic AF with preserved left ventricular function, however, has been correlated to left atrial volume index and left ventricular mass index and AF duration. Our current study also establishes the association of paroxysmal atrial fibrillation with normal left ventricular systolic function with increased BNP. The site-specific measurements in this study also provide insight as to BNP release in PAF. In the nonfailing heart, the source of BNP is believed to be in the atrium, and BNP mRNA has been found in the left atrial wall. Ablation of the left atrium was not associated with an acute increase in left atrial BNP levels as may have been expected with release secondary to cytolysis from ablation. The current data suggest BNP levels in PAF are driven by the coronary sinus level and release into the coronary sinus is acutely decreased with radiofrequency ablation of left atrial tissue implicating the atria and not the ventricles as the source of BNP in PAF. Hemodynamics measured did not differ significantly before and after ablation between the cohorts; however, the changes in BNP observed with radiofrequency ablation in the PAF cohorts may have resulted from affects of radiofrequency ablation on secondary (nonatrial) sites, which were not assessed. The coronary sinus drains the left ventricle and hence values in the coronary sinus increase with heart failure. The increased production of BNP in heart failure would appear to be secondary to induced ventricular production. The coronary sinus also drains the lateral and posterior left atrium and the left atrial appendage, and these areas of the left atrium drained by the coronary sinus may be responsible for elevated levels of BNP observed.

Our PAF and control cohorts were well matched with respect to factors such as sex, body mass index, and LVEF, known to affect peripheral venous BNP. Factors that were different between the cohorts included age, left atrial size, incidence of hypertension, renal function, and usage of antiarrhythmic drugs. To our knowledge, there are currently no data to associate class I and III antiarrhythmic drugs directly with alterations in cardiac BNP release. With respect to the age difference, an 11-year age difference in mean ages can be associated with an increase in peripheral venous BNP levels. The increase has been demonstrated only to be in the order of 1.4-fold per 10 years and is very unlikely to account for the greater differences observed between the cohorts in the current study. Advanced age predicts elevated BNP levels and is believed secondary to increased diastolic dysfunction and poorer renal function. The differences in renal function in the current study are both within normal range and are most likely age related. Deterioration in renal function predominantly affects pro-BNP, which is exclusively cleared by the kidney and its clearance is affected during chronic renal disease, which is not characteristic of our cohorts. The significant increase in left atrial size (to upper limits of normal) and incidence of hypertension in the AF cohort in comparison to the control cohort are both typically associated with AF and potentially may account for

![Figure](http://circep.ahajournals.org/fig-1006.png)
the differences in BNP observed in this study, as both may be associated with diastolic heart dysfunction. We did not formally quantify diastolic dysfunction in our current study; however, it may be inferred in the AF cohort by the increased left atrial size in comparison to the control cohort and along with the greater incidence of hypertension. Previous research has associated AF with diastolic heart dysfunction, which was observed to resolve when sinus rhythm was restored with catheter ablation.\(^{26,27}\) As alluded to earlier, it is currently unclear which is the precipitant or antecedent. Again, the observed decrease in cardiac BNP release after ablation in this study implies the source of increased BNP in diastolic heart dysfunction may be the atria. The magnitude of difference observed in the AF is also similar to transcardiac gradients albeit differently measured observed in aortic stenosis patients with diastolic dysfunction.\(^{28}\)

The transcardiac and transpulmonary BNP gradient estimations are novel measurements of BNP cardiac release and pulmonary BNP metabolism. Transcardiac BNP gradient has been used previously by the current author to assess differences in cardiac BNP release in heart failure subjects in sinus rhythm and AF in response to exercise;\(^{10}\) however, to our knowledge, transpulmonary BNP gradients have not been used to assess a PAF cohort and control cohort in such a manner. BNP may be metabolized in the lung by tissue neutral endopeptidases and BNP receptors on the pulmonary vasculature and as such may contribute to elevated BNP levels observed in pulmonary conditions and hypoxic states.\(^{29,30}\) The clinical validity of transcardiac and transpulmonary levels in the current setting does require further research; however, the transcardiac gradient in particular would appear to be the best acute assessment of cardiac BNP release. Predominantly studies of the physiological effects on cardiac BNP release have assessed peripheral venous BNP, which introduces the potential for interference from possible noncardiac sources, inability to gauge acute changes accurately, and no allowance for effects of peripheral BNP clearance and metabolism. In 2 previous studies\(^{31,32}\) in heart failure patients, the transcardiac BNP gradient has been assessed, and it is from some of these data\(^{32}\) that the ventricular source of BNP in heart failure has been inferred.

**Limitations**

In both our control and PAF cohorts, we do not have constant ECG documentation of heart rhythm in the 48 hours before the procedure and as such cannot exclude asymptomatic paroxysms before ablation affecting the initial BNP levels. The assay we used in this study measures acute change in BNP levels over minutes to hours, unlike the pro-BNP assay. The acute sensitivity of the assay to changes in BNP level, however, would serve to limit the effect of preceding arrhythmias. In addition, preceding arrhythmias are unlikely to have affected the change in BNP levels in response to ablation observed in this study.

**Conclusions**

Our findings demonstrate the source of BNP in PAF patients with normal systolic ventricular function is structures drained by the coronary sinus, most likely the left atrium, and that therapies such as radiofrequency ablation of the left atrium can acutely decrease cardiac BNP release.

**Disclosures**

None.

**References**


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14. Liang F, Gardner DG. Mechanical strain activates BNP gene transcription by the coronary sinus, most likely the left atrium, and that


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18. Deleted in proof.


Brain natriuretic peptide (BNP) levels were measured at different cardiac sites before and after ablation in 20 patients undergoing left atrial ablation as part of their treatment for paroxysmal atrial fibrillation (PAF). These levels before and after ablation were compared with a control group of 10 patients undergoing ablation of a left lateral accessory pathway. The study demonstrated elevated BNP levels in the PAF group at all sites measured compared with the control group. The highest levels were demonstrated in the coronary sinus and significantly decreased in the PAF group after ablation but not in the control group. In addition transcardiac and transpulmonary BNP gradients were greater in the PAF group. These data demonstrate elevated BNP levels in association with PAF, in particular in the coronary sinus, which appear to be the site of cardiac BNP release in PAF. In addition, the decrease in BNP levels in the coronary sinus after left atrial ablation in PAF group indicates this may be the source of BNP in PAF. This study also implies an acute association between PAF and cardiac BNP release that can be modified by radiofrequency ablation of the left atrium. This may have potential implications for the pathophysiology of atrial fibrillation and mechanism of benefit associated with left atrial ablation.
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