Incidence, timing, and characteristics of acute changes in heart rate during ongoing circumferential pulmonary vein isolation

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Aims Previous studies showed that catheter ablation of atrial fibrillation (AF) results in vagal denervation with an increase in average heart rate (HR) and a reduced overall HR variability (HRV) at follow-up. We analysed acute ablation-induced changes in HR and short-term HRV during percutaneous circumferential pulmonary vein isolation (CPVI). We also studied whether observed changes were predictors of successful outcome after first CPVI.

Methods and results A total of 46 patients (35 men, 55 ± 10 years) undergoing CARTO and computed tomography-guided CPVI for symptomatic AF were studied. Circumferential pulmonary vein isolation was performed under general anaesthesia by widely encircling the left and right pulmonary veins during sinus rhythm (SR). Radiofrequency (RF) current (35W, 48 ± C) was applied with a 3.5 mm open irrigated tip catheter (Navistar Thermocool, Biosense Webster, Diamond Bar, CA, USA). Time- and frequency-domain analysis of short-term HRV was performed using 5 min electrocardiogram (ECG) recordings obtained at the beginning and the end of the CPVI procedure. Sinus rhythm cycle length was monitored continuously during CPVI. Circumferential pulmonary vein isolation was performed with 119 ± 25 RF applications. Mean HR increased from 54 ± 8 to 62 ± 9 bpm (P < 0.001). Heart rate variability was significantly reduced (SDNN from 34 ± 30 ms to 14 ± 17 ms, P < 0.001, RMSSD from 27 ± 22 ms to 13 ± 14 ms, P < 0.001) with a marked change in sympathovagal balance towards less vagal activity (low frequency (LF)/high frequency (HF) ratio from 3.94 ± 0.33 to 4.20 ± 0.17, P < 0.001). Changes in RR interval, SDNN, and LF/HF ratio correlated significantly with RR interval (R = 0.56, P < 0.001), SDNN (R = 0.84, P < 0.001), and LF/HF ratio (R = −0.74, P < 0.001) at baseline. There were acute changes during ablation in HR and HRV at the antero-superior junction between the left atrium (LA) and the right superior pulmonary vein (RSPV) in 36 patients (78%). Both HR and HRV at baseline and changes in HR/HRV were comparable between successful (n = 36) and failed (n = 10) patients.

Conclusion (i) Percutaneous CPVI induces acute acceleration of HR and attenuation of short-term HRV (indicating vagal denervation during the procedure). (ii) Acute changes in HR and its variability invariably occur during RF energy delivery at the antero-superior junction between the LA and the RSPV. (iii) The degree of HR and short-term HRV changes depend on the vagal tone at the beginning of the procedure. (iv) In contrast to previously reported changes in overall HRV, acute changes in HR during the procedure are no predictors of long-term clinical outcome after CPVI.

KEYWORDS
Atrial fibrillation; Ablation; Autonomic nervous system

Introduction Alterations of autonomic function resulting in an increased heart rate (HR) and decreased overall heart rate variability (HRV) have been described as a consequence of radiofrequency (RF) ablation for different types of supraventricular tachycardia.¹³ Since RF ablation of triggers within a pulmonary vein (PV) or at the junction between the left atrium (LA) and the PV (LA–PV junction) is used to eliminate atrial fibrillation (AF), several authors have demonstrated a significant raise in HR and a reduction of overall HRV, both signs of vagal denervation, after catheter ablation of AF.⁴⁻⁶ The most common
Occurrence.

Several observations suggest that vagal denervation is related to the higher success rate of the procedure and higher percentage of AF-free patients at follow-up.5–10

No study has yet described the incidence, timing, and characteristics of acute changes in HR during ongoing ablation. Therefore, in this study we analysed the short-term HR and HRV at the beginning and the end of the procedure. Sinus rhythm cycle length (SRCL) was monitored continuously during circumferential pulmonary vein isolation (CPVI) to discover whether HR changes were gradual or acute and at which stage of the procedure changes occurred.

Methods

Patient population

We studied 46 consecutive patients (76% men, mean age 55 ± 10 years) with symptomatic AF who were referred for CPVI between May 2004 and February 2006. Written consent was obtained from all patients. Patient characteristics are shown in Table 1. The mean history of AF was 5.8 ± 6.3 years. Except for one patient, all patients had paroxysmal (3.9 ± 2.8 paroxysms a week) or short-standing persistent AF. All patients were resistant to anti-arrhythmic drugs (2.6 ± 0.8 drugs). Twenty-one of the 46 patients had underlying heart disease, including 13 patients with hypertensive heart disease. There were no patients with overt sick sinus syndrome.

To accurately measure changes in HR and HRV, all patients had to be in sinus rhythm (SR) during baseline mapping, ablation, and remapping. In case of AF at the beginning of procedure, SR was restored by electrical cardioversion.

Circumferential pulmonary vein isolation

Treatment with β-blocking agents and all other anti-arrhythmic drugs except amiodarone was discontinued at least four to five half-lives before the ablation procedure. Patients were treated by CPVI under general anaesthesia with propofol, remifentanil, and cisatracurium in continuous infusions according to body weight. All patients were endotracheal intubated and mechanically ventilated. To maintain normal body temperature, a Cathlab Bear Hugger was used to cover the thorax and upper limbs. Further setup consisted of arterial pressure monitoring and urinary catheterization. Inotropic agents were not used during the procedure.

Transoesophageal echocardiography was used to guide a double trans-septal puncture (Brockenbrough needle, St Jude Medical Sheath, MA, USA) after which heparin was administered. Target-activated clotting time was between 350 and 400 s. The presence of PV potentials was assessed with a circular mapping catheter. A 7 Fr catheter with 3.5 mm deflectable irrigated tip (Navistar Thermocool, Biosense Webster, Diamond Bar, CA, USA) was used for mapping and ablation. We used a non-fluoroscopic electro-anatomical mapping system (CARTO, Biosense Webster) to create a three-dimensional baseline map of the LA during SR. The ostia of the PVs were identified by fluoroscopic visualization of the catheter tip entering the cardiac silhouette during pull-back out of the PV with simultaneous sudden decrease in impedance and appearance of atrial potentials. To facilitate further mapping, a three-dimensional reconstruction of the LA gained with multislice computed tomography (CT) scan was merged with the CARTO map (CARTO Merge, Biosense Webster). The average deviation between the CARTO map and CT image was just 2.0 ± 1.0 mm.

After construction of the baseline map, CPVI was performed by point-wise application of RF energy (20–35 W, 30 s, and temperature limit 48°C). For adequate cooling, saline was infused through the catheter at 20 mL/min during ablation. The PVs were subsequently encircled with contiguous circumferential lines at a distance of 10–20 mm from the PV ostia (except for the anterior side of the left PVs where the ostial ridge was targeted). Ablation was initiated by encircling the left PVs starting postero-inferior at the antrum of the left inferior PV. The right PVs were encircled starting from postero-superior, finishing CPVI anterior at the junction between LA and right superior PV (RSPV).

The endpoint for AF ablation in each patient was the elimination of PV potentials during SR. If necessary, additional touch up ablation on the perimeter of the circle was performed. Per protocol, each study ended with a remapping of the LA (i.e. voltage map projected on the original three-dimensional geometry) during SR.

Post-ablation follow-up

After ablation, all patients were heparinized for 24 h after which coumarine therapy was restarted for a minimum of 3 months. Previously failing anti-arrhythmic drugs were given for 3 months after which anti-arrhythmic therapy was tapered off. Follow-up included a clinical visit and a 12-lead electrocardiogram (ECG) recorded at discharge, 3, 6, 9, 12, 18, and 24 months. Continuous 24-h Holter monitoring and CT scan of the heart were performed on clinical indication.

Heart rate variability

To study short-term HRV, a continuous 5 min 12-lead ECG recording was made in all patients at the beginning and end of the procedure (before and after CPVI). These short-term recordings contain sufficient data to assess HR and short-term HRV, especially when using frequency-domain analysis.11 Artefacts and ectopic beats were filtered using custom-made software (Medtronic, Bakken Research Centre, The Netherlands). Only normal sinus beats were used for HRV analysis. Time- and frequency-domain analysis was performed with ‘HRV analysis software’, v1.1.1.1, developed by the Biomedical Signal Analysis Group, Department of Applied Physics of the University of Kuopio, Finland.12 Calculated time-domain HRV parameters included standard deviation (SD) of normal-to-normal (SDNN) RR intervals as estimate of the overall HRV, root-mean-square of differences of adjacent normal RR intervals (RMSSD) as estimate of the

Table 1 Patient characteristics

<table>
<thead>
<tr>
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<th>Mean ± SD or count (%)</th>
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<tr>
<td>Number of patients</td>
<td>46</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male patients</td>
<td>35 (76%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (24%)</td>
</tr>
<tr>
<td>History of AF (years)</td>
<td>5.8 ± 6.3</td>
</tr>
<tr>
<td>AF</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>37 (80%)</td>
</tr>
<tr>
<td>Short-standing persistent AF</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Paroxysms per week</td>
<td>3.9 ± 2.8</td>
</tr>
<tr>
<td>Number of AAD used</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>21 (45%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (13%)</td>
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</tbody>
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Notes: AF, atrial fibrillation; AAD, anti-arrhythmic drugs.

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short-term component of HRV, and the percentage of adjacent RR interval pairs that differed $> 50$ ms ($pNN50$).

A quantitative geometrical analysis of RR intervals was performed for every patient by means of Poincaré plots based on consecutive RR intervals before and after CPVI. The SD of the points perpendicular to the line at 45° to the normal axis (line-of-identity) describes short-term variability ($SD1$), which is related to vagal tone. The SD along the line-of-identity ($SD2$) describes long-term variability.13,14

Frequency-domain analysis of HRV was obtained by means of Fast Fourier transform of the RR intervals. Spectral power (ms$^2$) was calculated within the following frequency bands: very low-frequency band (0.0–0.04 Hz), low-frequency band (LF; range 0.04–0.15 Hz), and high-frequency band [high frequency (HF); range 0.15–0.40 Hz].15 SDNN, RMSSD, $SD1$, and HF are known to reflect parasympathetic activity, and the LF/HF ratio reflects the sympathovagal balance.11–16

Acute ablation-induced changes in heart rate parameters

To detect acute ‘beat-to-beat’ changes in HR and its variability, SRCL was plotted using the CARTO system’s point list. This list consists of all consecutive mapping points taken throughout the procedure (baseline, ablation, and remap) with all their corresponding data, including cycle length. During each ablation, one point was taken randomly during the 30 s duration of RF energy delivery. These data were exported to a custom-made algorithm to plot SRCL evolution throughout the procedure. Artefacts and ectopic beats were filtered out. Acute HR acceleration was defined as a sudden shortening in SRCL of $> 50$ ms, between two consecutive CARTO points, that persisted through the rest of the procedure. Standard deviation of SRCL was used as a marker for HR variation. If shortening of SRCL was observed during ablation, the location of the ablation catheter tip was retrieved on the CARTO three-dimensional map.

Statistical analysis

Data are given as mean ± SD. Differences between groups were determined by the paired Student’s t-test. Correlation was estimated with the Pearson’s coefficient. Serial measurements were analysed by ANOVA with repeated measures (Friedman test, Dunn’s post-test). A P-value of < 0.05 was considered as statistically significant.

Results

Procedure parameters and clinical outcome

Circumferential pulmonary vein isolation in this series was performed in 46 patients with a mean procedure time of $3.5 ± 1.2$ h. Fluoroscopy time was $24 ± 12$ min. The CARTO baseline map was created with 139 ± 32 points. After a mean number of 119 ± 25 RF applications (RF time 52 ± 10 min), the endpoint of electrical isolation was achieved in all PVs. There was one limited cerebrovascular accident with full recovery within 48 h. After the first procedure and a mean follow-up of 23 ± 5 months (range 16–34 months), 78% of the patients remained free of symptomatic AF without anti-arrhythmic drugs.

After a mean follow-up of 70 ± 82 days, the average RR interval (on a random surface ECG) was 848 ± 123 ms and significantly shorter than RR before CPVI (969 ± 122 ms, $P < 0.01$).

Heart rate and short-term heart rate variability before and after circumferential pulmonary vein isolation

Compared with baseline, HR and HRV parameters were significantly changed after CPVI (Table 2). Heart rate was higher at the end of the procedure (54 ± 8 vs. 62 ± 9 bpm; $P < 0.001$). RR interval shortened from 1141 ± 190 to 982 ± 158 ms ($P < 0.001$). Similarly, compared to before ablation, all time-domain variables of HRV were significantly changed after ablation: $SDNN$ shortened from 34 ± 30 to 14 ± 17 ms ($P < 0.001$), RMSSD from 27 ± 22 to 13 ± 14 ms ($P < 0.001$), and $pNN50$ from 9 ± 12 to 4 ± 12 ms ($P < 0.05$). The quantitative geometrical analysis from the Poincaré plots showed a decrease in mean short-term variability ($SD1$) from 20 ± 16 to 9 ± 10 ms ($P < 0.001$) after CPVI, whereas long-term variability ($SD2$) decreased from 43 ± 41 to 17 ± 23 ms ($P < 0.001$). A representative example of a Poincaré plot before and after ablation is given in Figure 1 (upper panels). The strong reduction in dispersion of the consecutive RR intervals illustrates how both short- and long-term HRV were attenuated after CPVI.

Frequency-domain analysis exhibits the same modification of sympathovagal balance towards less vagal tone. High-frequency power reduced relatively more (683 ± 426 ms$^2$ before vs. 458 ± 230 ms$^2$ after CPVI, $P < 0.001$) when

<table>
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<tr>
<th>Table 2</th>
<th>Heart rate and short-term heart rate variability</th>
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<tbody>
<tr>
<td></td>
<td>Before ablation (mean ± SD)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>RR (ms)</td>
<td>1141 ± 190</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>34 ± 30</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>27 ± 22</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>9 ± 12</td>
</tr>
<tr>
<td>Short-time variability (SD1) (ms)</td>
<td>20 ± 16</td>
</tr>
<tr>
<td>Long-time variability (SD2) (ms)</td>
<td>43 ± 41</td>
</tr>
<tr>
<td>LF power (ms$^2$)</td>
<td>2646 ± 1386</td>
</tr>
<tr>
<td>HF power (ms$^2$)</td>
<td>683 ± 426</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>3.94 ± 0.33</td>
</tr>
</tbody>
</table>

HR, heart rate; RR, heart rate interval during sinus rhythm; SDNN, standard deviation of consecutive normal-to-normal intervals; RMSSD, root-mean-square of differences of adjacent normal RR intervals; pNN50, percentage of adjacent RR interval pairs that differed $> 50$ ms; LF/HF, ratio between low-frequency and high-frequency power.

Statistical analysis

Data are given as mean ± SD. Differences between groups were determined by the paired Student’s t-test. Correlation was estimated with the Pearson’s coefficient. Serial measurements were analysed by ANOVA with repeated measures (Friedman test, Dunn’s post-test). A P-value of < 0.05 was considered as statistically significant.
compared with LF power (2646 ± 1386 ms² before vs. 1899 ± 917 ms² after CPVI, \(P < 0.001\)), resulting in a significantly higher LF/HF ratio after CPVI (3.94 ± 0.33 vs. 4.2 ± 0.17, \(P < 0.001\)). Figure 1 (lower panels) shows Fast Fourier transform results illustrating the reduction in both LF and HF power and change in LF/HF ratio (same patient as upper panel). 

In Figure 2, the relation between the degree of ablation-induced HR/HRV changes and HR/HRV values at baseline is plotted. There was a significant correlation between \(\Delta-\text{RR interval} \text{ and RR interval at baseline} (R = 0.56, P < 0.001)\), between \(\Delta-\text{SDNN} \text{ and SDNN at baseline} (R = 0.84, P < 0.001)\), and between \(\Delta-\text{LF/HF} \text{ and LF/HF ratio at baseline} (R = -0.74, P < 0.001)\).

When comparing successfully ablated patients (\(n = 36\)) with failed (\(n = 10\)) procedures, we did not observe a significant difference in baseline HR and HRV or \(\Delta-\text{HR} \text{ and } \Delta-\text{HRV}\) (Table 3).

### Acute ablation-induced changes in heart rate and heart rate variability

Using the SRCL data from the CARTO point list, we observed that there were acute changes in HR and its variability during ongoing ablation in 36 of 46 patients (78%). A representative example of acute ablation-induced HR acceleration is given in Figure 3. In the left panel, SRCL throughout the procedure is plotted (consecutive CARTO points). Throughout baseline mapping and during the major part of the ablation procedure, SRCL had a mean cycle length of 1058 ms with a moderate variation in SRCL (SD = 55 ms). At the near-end of the ablation procedure, during RF application antero-superior of the LA–RSPV junction (right panel, CARTO point #343), SRCL suddenly shortened and the shorter SRCL persisted (mean 805 ms) through the remainder of the ablation procedure and during remap. As can be seen from the plot, there was also a clear attenuation of the variability of the SRCL after acceleration (SD = 17 ms). For all 36 patients in whom acute ablation-induced HR acceleration was seen, SRCL shortened from 1153 ± 173 ms before to 978 ± 154 ms after acceleration (−15%, \(P < 0.001\)), whereas mean SD-SRCL decreased from 90 ± 34 to 43 ± 36 ms (\(P < 0.01\)).

Patients in whom acute acceleration was observed were characterized by a higher vagal tone at baseline: baseline HR 52 ± 7 bpm (\(P < 0.04\), compared with 58 ± 11 in non-

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**Figure 1** Short-term heart rate variability at the beginning and end of the ablation procedure (5 min sinus rhythm recordings). The Poincaré plot (upper panels) reveals marked reduction of dispersion of consecutive RR intervals after circumferential pulmonary vein isolation, with a reduction in both short-term and long-term heart rate variability. Frequency-domain analysis (lower panels) shows a marked reduction in high-frequency power, resulting in a higher low frequency/high frequency ratio (indicating vagal denervation). SD1, level of short-term heart rate variability; SD2, level of long-term heart rate variability; LF, low frequency; and HF, high frequency.
accelerating patients) and baseline LF/HF 3.9 ± 0.35 (P = 0.064, compared with 4.08 ± 0.16 in non-accelerating patients).

There was no significant difference in clinical success between patients with acute ablation-induced HR acceleration (78%, 28/36) and those without acute HR acceleration (90%, 9/10, P = 0.66, NS).

In all 36 patients with acute HR acceleration, acceleration occurred during RF ablation antero-superior of the LA–RSPV junction. A representative example is given in Figure 4 (LA CARTO Map with CT integration). On the LA map, the site of acute ablation-induced HR acceleration was located at the LA–RSPV junction, 15 mm away from the RSPV ostium and 10 mm superior from the inter-PV ridge. The bipolar electrogram recorded at this site consistently showed a fragmented potential with multiple high-frequency components in all patients (Figure 4, inlay). In Figure 5, we have plotted the distribution of all sites where ablation-induced acute HR acceleration was observed (black dots). For all 36 patients, the mean distance to the RSPV ostium and the inter-PV ridge was 17 ± 5 and 12 ± 2 mm, respectively.

Interestingly, HR acceleration occurred also during ablation antero-superior of the LA–RSPV junction in the one patient in whom the sequence of RF lesions was deliberately altered and ablation was started at this particular region.

### Ablation-induced vagal responses

Marked ablation-induced vagal reflexes were observed in 7 of 46 patients (17%). Sinus bradycardia (HR < 40 bpm) was elicited during RF application in 6 of 7 patients (average maximal RR interval 2793 ± 1012 ms), whereas hypotension (systolic blood pressure <90 mmHg) was observed in 1 of 7 patients.

All vagal reflexes occurred at the left PVs and preferentially during ablation at the postero-inferior junction between the LA and the left inferior PV (Figure 5, black triangles). The ablation-induced vagal reflex was never followed by acute HR acceleration. In the 7 patients with a

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**Table 3 Heart rate and short-term HRV in successful and failed ablation**

<table>
<thead>
<tr>
<th></th>
<th>All procedures (n = 46)</th>
<th>Successful ablation (n = 36)</th>
<th>Failed ablation (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HR (bpm)</td>
<td>54 ± 9</td>
<td>55 ± 8</td>
<td>51 ± 10</td>
<td>0.19, NS</td>
</tr>
<tr>
<td>Baseline SDNN (ms)</td>
<td>34 ± 30</td>
<td>34 ± 32</td>
<td>32 ± 16</td>
<td>0.87, NS</td>
</tr>
<tr>
<td>Baseline RMSSD (ms)</td>
<td>28 ± 22</td>
<td>27 ± 22</td>
<td>31 ± 24</td>
<td>0.59, NS</td>
</tr>
<tr>
<td>Baseline pNN50 (%)</td>
<td>14 ± 21</td>
<td>7 ± 10</td>
<td>15 ± 19</td>
<td>0.11, NS</td>
</tr>
<tr>
<td>Baseline LF power (ms²)</td>
<td>2646 ± 1387</td>
<td>2644 ± 1412</td>
<td>2655 ± 1399</td>
<td>0.98, NS</td>
</tr>
<tr>
<td>Baseline HF power (ms²)</td>
<td>684 ± 427</td>
<td>686 ± 452</td>
<td>668 ± 321</td>
<td>0.90, NS</td>
</tr>
<tr>
<td>Baseline LF/HF ratio (%)</td>
<td>3.94 ± 0.33</td>
<td>3.95 ± 0.33</td>
<td>3.92 ± 0.32</td>
<td>0.81, NS</td>
</tr>
<tr>
<td>Δ-HR (bpm)</td>
<td>9 ± 6</td>
<td>9 ± 7</td>
<td>9 ± 5</td>
<td>0.99, NS</td>
</tr>
<tr>
<td>Δ-SDNN (ms)</td>
<td>20 ± 20</td>
<td>20 ± 21</td>
<td>17 ± 20</td>
<td>0.71, NS</td>
</tr>
<tr>
<td>Δ-RMSSD (ms)</td>
<td>14 ± 21</td>
<td>15 ± 20</td>
<td>13 ± 25</td>
<td>0.79, NS</td>
</tr>
<tr>
<td>Δ-pNN50 (%)</td>
<td>4 ± 14</td>
<td>4 ± 14</td>
<td>4 ± 24</td>
<td>0.91, NS</td>
</tr>
<tr>
<td>Δ-LF power (ms²)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.48, NS</td>
</tr>
<tr>
<td>Δ-HF power (ms²)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.56, NS</td>
</tr>
<tr>
<td>Δ-LF/HF ratio</td>
<td>0.25 ± 0.44</td>
<td>0.23 ± 0.45</td>
<td>0.34 ± 0.4</td>
<td>0.50, NS</td>
</tr>
</tbody>
</table>

HR, heart rate; RR, heart rate interval during sinus rhythm; SDNN, standard deviation of consecutive normal-to-normal intervals; RMSSD, root-mean-square of differences of adjacent normal RR intervals; pNN50, percentage of adjacent RR interval pairs that differed >50 ms; LF/HF, ratio between low-frequency and high-frequency power.
vagal reflex, the freedom of AF was not significantly different from the 39 patients without a vagal reflex.

**Discussion**

**Main findings of the present study**

(i) Percutaneous CPVI results in acute acceleration of HR and changes of short-term HRV. (ii) The degree of changes in both HR and HRV is determined by the vagal tone (or predominance) of the patient at the beginning of the procedure. (iii) Heart rate acceleration and attenuation of HRV occurred acutely and invariably during delivery of RF energy at the antero-superior junction between the LA and the RSPV and was not related to the occurrence of elicited vagal reflexes. (iv) In contrast to previously reported changes in overall HRV, acute changes in HR during the procedure are no predictors of long-term clinical outcome after CPVI.

**Short-term changes in heart rate and heart rate variability after catheter ablation for atrial fibrillation**

Many authors have previously shown that both ostial and circumferential PV ablation result in an increase in mean HR and a decrease in overall HRV at follow-up, suggesting...
parasympathetic nervous withdrawal, enhanced sympathetic activity, or a combination of both after catheter ablation of AF. Hsieh et al. described transient changes in mean HR, maximum HR, and HRV due to autonomic dysfunction in 30 patients who underwent focal AF ablation. One month after the procedure, all HRV variables returned to baseline. Similar changes in HR and overall HRV were described by Pappone et al. in 297 AF patients who underwent circumferential PV ablation. Heart rate variability parameters were analysed at 1 week, and at 1, 3, and 6 months after ablation. In this series, HRV parameters returned to baseline values after 6 months. Similarly, Nilsson et al. analysed HR at 1, 3, 6, 9, and 12 months after PV isolation and described an increase in HR that persisted at least 12 months after the procedure. However, none of the above studies analysed the timing and the location characteristics of acute ablation-induced changes in HR/HRV parameters. As a result, the underlying mechanism of the changes in HR/HRV remains speculative. A first hypothesis is that HR/HRV changes are mediated by a cardiac sympathovagal reflex caused by non-selective LA ablation (so-called cardiocardiac reflexes via central neurons). In the same way as HR and HRV alter after myocardial infarction, non-selective LA ablation might result in a change in chamber geometry leading to an increase in sympathetic afferent activity, in turn leading to an inhibition of vagal efferent activity to the heart, including the sino-atrial node (SAN). However, since it is unknown to what degree ablation for AF causes changes in the geometry of the LA, it is not clear if this hypothesis is correct. A second hypothesis is that, during delivery of RF energy, parasympathetic fibres of the intrinsic cardiac autonomic nervous system (ANS) are ablated, resulting in vagal denervation of the LA, the SAN, and atrioventricular (AV) node. Several authors have demonstrated in canine and human heart how the intrinsic cardiac ANS forms a network of GPs concentrated within epicardial fat pads with mutual connecting ganglia. In particular, the regions: (i) between superior vena cava and aortic root (SVC–Ao fat pad); (ii) at the junction between inferior vena cava and both atria; (iii) inferior to the right inferior PV (inferior right GP); (iv) superior and medial to the left superior PV (superior left GP); (v) inferior to the left inferior PV (left inferior GP); and (vi) of the fat pad between the caudal end of the SAN and the LA–RSPV junction (right anterior GP, RAGP), contain a high density of ganglia. Within these ganglia, sympathetic and parasympathetic fibres destined to innervate SAN and AV node are co-located, making it impossible to selectively target either vagal or sympathetic nerves during ablation. However, since vagal tone prevails under resting conditions and both HR and HRV are largely dependent on vagal modulation, ablation around the PVs may modify ganglia and their connections, resulting in HR acceleration and HRV attenuation during SR, both signs of vagal denervation. Indeed, data from Pappone et al. suggest that LA ablation in the vicinity of PV’s could result in a vagal reflex (acetylcholine release), whereas continued ablation leads to destruction and vagal denervation. However, the same authors observed vagal reflexes in only 102 of 297 (34%) patients, whereas changes in HR and HRV were observed in the population as a whole. Similarly, we demonstrated that vagal reflexes were not followed by acute changes in HR/HRV, suggesting that ablation-induced vagal reflexes and changes in HR/HRV are two distinct entities. Based upon our results on the timing and location characteristics of acute changes in HR/HRV, we hypothesize that changes in HR and HRV are the result of selective ablation in the close vicinity of the RAGP. This hypothesis is further supported by the recent work of Hou et al. who depict the RAGP as a modulator of the extrinsic autonomic nerve input, receiving input from both the right and left vagosympathetic trunk and from the superior left GP before efferent neurons proceed to SAN. Ablation at the antero-superior junction between the LA and the RSPV may therefore destroy efferent vagal neurons from the RAGP projecting onto the SAN, resulting in the acute changes observed in HR and HRV.

Although the RAGP region was— in all but one patient—the last to be ablated, it seems unlikely that acceleration occurred because, at this stage, all local GPs were denervated. Besides, one would expect a more gradual onset of HR acceleration instead of the acute acceleration we observed while ablating in the RAGP region. Similarly, given the consistent observation of acute alterations in HR/HRV during ablation at the antero-superior LA–RSPV junction, it seems unlikely that changes in HR/HRV are due to progressive elimination of ectopic beats, previous cardioversion or changes in volume load, pain sensation, or degree of sedation. Furthermore, it is unlikely that acute changes in HR and its variability are due to RF-induced sympathetic tone because this stimulation is not expected to persist after cessation of RF delivery. Finally, it is unlikely that RF ablation would directly result in a pacemaker-shift within the sinus node area independent of the changes observed in autonomic tone.

Changes in heart rate and heart rate variability after catheter ablation of atrial fibrillation: beneficial or bystander?

Many authors have previously studied the relationship between the intrinsic cardiac nervous system’s sympathovagal balance and the initiation and maintenance of AF. It has been suggested that catheter ablation-induced vagal denervation of the LA (lengthening of atrial effective refractory period, wavelength, and reduction in dispersion) could be beneficial in suppressing AF in patients with paroxysmal AF. The above findings were supported by the clinical observation of Pappone et al. who demonstrated a higher success in patients with evidenced abolition of vagal reflexes (direct vagal denervation of the left atria). In the present study, however, we suggest that changes in short-term HR/HRV are a result of ablation-induced modulation of efferent vagal neurons projecting onto the SAN rather than direct vagal denervation of the LA. Although prevention of sinus bradycardia could be beneficial in suppressing vagotonic AF, we did not observe a relation between observed changes in HR and short-term HRV and clinical outcome after catheter ablation of AF. Therefore, we hypothesize that changes in HR and its variability have no effect in relation to the clinical outcome after catheter ablation of AF. These findings seem to contrast previous studies reporting on the predictive value of overall HRV (24 h recordings). Although Pappone et al. reported no predictive value of changes in HR or HRV per se, a transient higher degree of HRV attenuation was observed in patients without AF recurrence. Similarly, in the study by Nilsson.
et al., in which HR remained significant higher even after 12 months follow-up, changes in overall HRV were a marker for success. The discrepancy in results might be explained by the assessment of short-term HRV by 5 min recordings in the present study, because this limited recording does not allow assessment of all components that contribute to overall HRV. On the other hand, we believe that the use of short-term HRV was dictated by the nature of the present investigation because of its reproducibility and because detailed information about autonomic modulation of RR intervals at a precise moment in time might be obscured by the averaging procedure which is used in long-term recordings.

**Clinical implications**

Although the direct clinical implication of the present study for current AF ablation seems limited, the study does offer novel insights into the mechanisms of acute autonomic denervation after catheter ablation of AF. In contrast to previous reports, we suggest that the increased HR and decreased HRV observed after AF ablation are the results of changes in efferent vagal input to the sinus node (after ablation of the RAGP) and not necessarily the result of local vagal denervation of regions responsible for AF.

Our study also describes a new phenomenon of autonomic modulation during AF ablation, adding a new aspect to a diversity of autonomic responses during ablation. In contrast to the well-known vagal reflexes, which are easily recognizable but only rarely seen, our findings point to a potentially novel method to consistently identify the presence of autonomic fibres (which supply the sinus node). The potential anti- or pro-arrhythmic effect of ablating these fibres in neurally mediated arrhythmias needs to be investigated.

**Limitations of the study**

We used 5 min ECG recordings before and after ablation to gain information about autonomic changes. Although these recordings are sufficient for short-term HRV analysis, especially when focus is on the frequency domain, they cannot give information about overall HRV evolution for which 24 h recordings are needed.

Although 12-lead ECG recordings at follow-up did show an increase in resting HR, we have no consistent long-term data on HR/HRV. Differences in Holter equipment in the referring hospitals complicated consequent gathering of follow-up data on HR and HRV.

All patients in our study underwent CPVI under general anaesthesia and mechanical ventilation. This does influence respiratory sinus arrhythmia and thus HRV derived from ECG data recorded during the procedure. However, this limitation applies to all our patients both at baseline and after CPVI.

Although no patient had overt sinus node disease, it is possible that some patients had some degree of sinus node dysfunction. In these patients, HR and HRV are not mainly determined by the autonomic tone.

**References**


Conflict of interest: none declared.


