Insights from preclinical ultra high-density electroanatomical sinus node mapping

Andreas Bollmann*†, Sebastian Hilbert†, Silke John, Jedrzej Kosiuk, and Gerhard Hindricks

Department of Electrophysiology, Heart Center, Leipzig, Strümpellstr. 39, Leipzig 04289, Germany

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Aims
Although sinus node modification by catheter ablation is an established therapy for the treatment of inappropriate sinus tachycardia, there is incomplete understanding of sinus node anatomy and function but also limited electroanatomical mapping data. Recently, an automatic, ultra high-resolution mapping system has been presented to accurately and quickly identify right atrial (RA) geometry and activation patterns but detailed assessment of sinus node activation has not been performed which was one aim of this study. Preclinical experiences are compared with previous sinus node mapping studies in animals and humans, and potential clinical implications for catheter ablation are discussed.

Methods and results
In anaesthetized and ventilated 14 pigs, 30 endocardial and 2 epicardial RA maps were generated using the Rhythmia™ mapping system without complications and earliest activation sites (EAS) and sinus break-out (SBO) were determined. At baseline, EAS and SBO were located anterior to the middle (n = 6) or lower third (n = 8) of the crista terminalis exhibiting a unicentric activation pattern in all cases. Conduction pathways were directed anterior, posterior, superior, or inferior with substantial inter-individual variation in direction, pathway distance, and conduction time. Orciprenaline, propranolol, or amiodarone shifted endocardial activation with considerable variation between animals with inconsistent patterns. Multicentric activation was found in one case after orciprenaline infusion. Sequential endocardial and epicardial high-density mapping of the RA was performed in two animals and showed a high congruence of the sinus node activation in the endo- and the epicardial map.

Conclusion
Ultra high-density mapping allows fast, simple, and very detailed assessment of sinus node activation. Future studies are clearly needed to evaluate novel mapping and ablation strategies for an improved understanding of sinus node disease and better outcomes.

Keywords
Sinus node • Cardiac mapping • Catheter ablation

Introduction
Sinus node modification by catheter ablation is an established therapy for the treatment of drug-refractory inappropriate sinus tachycardia (IST) with moderate long-term results.1,2 This may—in part—be explained by incomplete understanding of sinus node anatomy and function but also limited electroanatomical mapping data. So far, the latter has been obtained in both animals and humans using either contact mapping with moderate spatial resolution1–4 or non-contact mapping.5,6

Recently, an automatic, high-resolution mapping system has been presented to accurately and quickly identify right atrial (RA) geometry and activation patterns in 10 dogs1 but detailed assessment of sinus node activation has not been performed.

Methods
Animal preparations
All animal experiments have been conducted according to relevant national and international guidelines. Protocols for the use of animals in this study were approved by the Animal Ethics Committee of the University of Leipzig and the federal state of Saxony. Fourteen consecutive pigs
(German saddle breed, 13 females, and 1 male) weighing 45–77 kg were anaesthetized and mechanically ventilated. For premedication all animals received an intramuscular dose of 0.02 mg/kg atropine, 0.5 mg/kg midazolam, and 15 mg/kg ketamine. For intubation a dose of 4 mg/kg propofol was given intravenously. All experimental procedures were carried out under inhalation anaesthesia with isoflurane and monitoring of body temperature. Pain was alleviated with an initial dose of 2 mg/kg and a maintenance dose of 2–4 mg/kg/h of fentanyl. The right carotid artery was cannulated for monitoring arterial pressure; the left femoral artery and the right femoral vein were cannulated with 9 Fr sheaths for catheter placement. A 6 Fr eight-pole catheter was positioned in the coronary sinus under fluoroscopic guidance. A second 6 Fr eight-electrode catheter was retrograde positioned in the left ventricular apex for anatomical guidance and backup pacing.

A 6 Fr sheath was positioned through the right jugular vein in the atrial orifice of the superior vena cava for drug administration.

**Electroanatomical mapping system**

Electroanatomical maps of the right atrium (RA) were created using the Rhythmia™ system (Boston Scientific, Inc.). The mapping system has been described in detail previously. In brief, a mini basket (1.8 cm diameter), containing eight splines of eight electrodes (total 64 electrodes, 2.5 mm spacing) is used to collect mapping data. The system automatically acquires electrograms and location information based on a predefined set of beat acceptance criteria. Beats are included in the map based on cycle length stability, relative timing of reference electrograms, electrode location stability, and respiratory gating. The criteria are selected by the operator before beginning the map. An activation map is obtained without the need for manual annotation. For electrograms with multiple potentials, the system considers the timing of electrograms in the surrounding area to select the potential to use for timing annotation.

The outer most electrodes are used for creating the surface geometry. Inclusion or exclusion of electrograms into the group of surface electrograms is based on the distance from the surface geometry (1–5 mm) which can be set by the operator. All electrograms are stored for later review. By selecting individual electrograms with a virtual roving probe it is possible to determine and mark a region of interest such as crista terminalis.

**Figure 1** Determination of EAS (left panel) and SBO (right panel). For better visualization of the sinus node area, the time frame (colour bar) is reduced to a narrow window from −75 ms to −61 ms in relation to the reference (CS 1–2). Please note the location of both sites anterior to the lower third of the crista terminalis (black dots) that are magnified in the corresponding inlets. While the EAS (white dot) is defined by the earliest QS morphology that can be appreciated in unipolar electrogram ‘E5’, SBO is defined by the earliest rS (roving probe). Earliest activation site and SBO precede the reference electrogram by 72 ms and 69 ms and the onset of P wave (lead aVL) by 25 and 22 ms, respectively.

**What’s new?**

- With the use of a novel ultra high-density mapping system, detailed endocardial and epicardial assessment of sinus node activation is feasible.
- Earliest activation sites and sinus break-out points are highly variable under baseline conditions and after pharmacological challenges with unpredictable patterns.
- Multicentric activation is the result of beat-to-beat cycle length variation.

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† Multicentric activation is the result of beat-to-beat cycle length variation.
Definitions relevant to sinus node mapping

When performing activation mapping during sinus rhythm several terms are commonly used to describe mapping results: (i) location of the earliest activation site (EAS) defined as the earliest unipolar electrogram with a ‘QS’ pattern, (ii) location of sinus break-out (SBO) as earliest unipolar electrogram with a ‘RS’ pattern. Earliest activation site and SBO locations are usually expressed relative to the crista terminalis in the superoinferior and anteroposterior dimension (Figure 1).

Activation is defined as unicentric if one EAS is present and multicentric if two or more EAS with activation time difference ≤5 ms separated by a distance of >10 mm are observed. The path between EAS and SBO is defined as a conduction route and its conduction time can be measured.

Results

Right atrial ultra high-resolution maps were successfully acquired in all cases without complications. Baseline measurements are summarized in Table 1. Median baseline sinus cycle length was 660 ms (range 487–970 ms) and median acquisition time was 11:31 min (5:14–34:37 min). During that time 8.078 (3.313–22.818) data points were automatically annotated without manual correction.

Earliest activation site and SBO were located anterior to the cristaterminalis in all cases without complications. Baseline measurements are summarized in Table 1. Median baseline sinus cycle length was 660 ms (range 487–970 ms) and median acquisition time was 11:31 min (5:14–34:37 min). During that time 8.078 (3.313–22.818) data points were automatically annotated without manual correction.

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Table 1 Baseline measurements

<table>
<thead>
<tr>
<th>Pig</th>
<th>Time (min)</th>
<th>Data points (n)</th>
<th>RA volume (ml)</th>
<th>Sinus CL (ms)</th>
<th>Location of EAS and SBO</th>
<th>Distance CT/EAS (mm)</th>
<th>Distance CT/SBO (mm)</th>
<th>Conduction pathway</th>
<th>Conduction time EAS/SBO (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10:37</td>
<td>5555</td>
<td>57</td>
<td>537</td>
<td>Lower CT</td>
<td>4.79</td>
<td>6.02</td>
<td>Inferior-anterior</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>12:47</td>
<td>4135</td>
<td>70</td>
<td>840</td>
<td>Mid CT</td>
<td>4.47</td>
<td>6.19</td>
<td>Inferior</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>13:39</td>
<td>5473</td>
<td>65</td>
<td>640</td>
<td>Lower CT</td>
<td>5.53</td>
<td>5.03</td>
<td>Inferior</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>14:43</td>
<td>8096</td>
<td>73</td>
<td>537</td>
<td>Lower CT</td>
<td>9.90</td>
<td>8.45/9.48</td>
<td>Inferior and superior</td>
<td>5/2</td>
</tr>
<tr>
<td>5</td>
<td>5:14</td>
<td>6229</td>
<td>94</td>
<td>790</td>
<td>Mid CT</td>
<td>3.1</td>
<td>3.30</td>
<td>All directions</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>5:20</td>
<td>3314</td>
<td>53</td>
<td>800</td>
<td>Lower CT</td>
<td>6.3</td>
<td>9.1</td>
<td>All directions</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>11:31</td>
<td>8708</td>
<td>91</td>
<td>700</td>
<td>Lower CT</td>
<td>9.5</td>
<td>7.2</td>
<td>All directions</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>12:08</td>
<td>22818</td>
<td>99</td>
<td>720</td>
<td>Lower CT</td>
<td>3.62</td>
<td>4.18</td>
<td>Superior</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>8:20</td>
<td>6460</td>
<td>49</td>
<td>487</td>
<td>Mid CT</td>
<td>1.36</td>
<td>1.72</td>
<td>All directions</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>10:27</td>
<td>16126</td>
<td>109</td>
<td>925</td>
<td>Lower CT</td>
<td>2.40</td>
<td>4.95</td>
<td>All directions</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>15:47</td>
<td>11309</td>
<td>88</td>
<td>650</td>
<td>Mid CT</td>
<td>6.39</td>
<td>5.34</td>
<td>All directions</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>34:37</td>
<td>13397</td>
<td>76</td>
<td>660</td>
<td>Mid CT</td>
<td>7.75</td>
<td>7.16</td>
<td>Superior</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>25:49</td>
<td>15659</td>
<td>122</td>
<td>970</td>
<td>Mid CT</td>
<td>1.87</td>
<td>2.20</td>
<td>Superior</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>8:11</td>
<td>8078</td>
<td>60</td>
<td>490</td>
<td>Lower CT</td>
<td>7.56</td>
<td>9.27</td>
<td>Superior</td>
<td>3</td>
</tr>
</tbody>
</table>

RA: right atrium; CL: cycle length; CT: crista terminalis; EAS: earliest activation site; SBO: sinus break-out.
However, one has to keep in mind that the dominant pacemaker within the sinus node may precede the local electrogram by up to 60 ms and that its location does not predict the location of the pacemaking cells. Taken together, these studies suggest that the compact anatomical size of the sinus node is not congruent with its functional characteristics. Thus, complex conduction out of the sinus node and the potential failure of the earliest site of activation to spatially correspond with the earliest site of activation within the node have significant implications for IST catheter ablation which is discussed below.

Furthermore, activation sites are affected by a variety of factors including autonomic status, antiarrhythmic drug use, and sinus node remodelling that must be considered. It has been known for long that modulation of the autonomic tone induces shifts in activation sites. For instance, isoproterenol or aminophylline infusion preferentially shifts activation to more cranial sites, while esmolol results in downward shifts. This was also observed in our experiments with different drugs but with considerable variation between animals as described before under comparable experimental conditions. Furthermore, amiodarone has been found to cause dysfunction of the superior sinus node which was associated with EAS downward shift at baseline and after sympathetic stimulation.

Both acute and chronic sinus node remodelling has been studied. While the former was induced by rapid pacing, the latter was analysed in patients with heart failure, atrial flutter, atrial fibrillation, or sinus node disease. Concordant findings were more caudal activation, slower conduction along preferential pathways, blunted response to sympathetic activation, and a reduction in activation sites which is also discussed below.

However, whether the observed endocardial activation shifts are due to shifts within the pacemaking complex, shifts of the exit pathways, or a combination of both has not been clarified by current mapping studies. Although detailed assessment of EA, SBO, and conduction routes at baseline and after pharmacologic drug challenges as illustrated here is feasible, if this transforms into better understanding of the individual human sinus node anatomy and function in the clinical setting remains to be determined.

**Unicentric vs. multicentric activation**

The sinus node has the capacity for multicentric activation as suggested by previous experimental and mapping studies. As discussed and illustrated above, several factors affect EAS and intra-individual changes with different interventions can be observed.

However, whether multicentric EAS are the results of true simultaneous activations or of beat-to-beat variation has not been clearly addressed. Using spatially limited, sequential point-by-point mapping, multicentric activation has been identified in healthy individuals but also in different patient groups with heart failure, atrial fibrillation, and sinus node dysfunction. Interestingly, EAS were more numerous in healthy controls than in patients with heart failure or atrial fibrillation. Furthermore, the presence of sinus node dysfunction was associated with even more reduced multicentric activation in the latter group.

In contrast, when using high-density, non-contact mapping for single beat analysis in 31 individuals, there was no simultaneously occurring EAS points. However, the intra-individual beat-to-beat EAS location was variable in the range of up to 41 mm.

In our series, we have observed multicentric activation in only one case after orciprenaline infusion, while in all other maps unicentric activation was found.

Based on those and previous findings, we believe that the described multicentric activation results from beat-to-beat variation. When using the Rhythmia™ or other mapping systems strict beat acceptance criteria based on the fixed cycle length may be used, which in turn may result in unicentric activation and subsequent changes in its location with different heart rates. Consequently, one could speculate that the reduction in EAS in different cardiac pathologies is not only an expression of sinus node disease but also a reflection of reduced heart rate variability that is often accompanied in heart failure or atrial fibrillation.

**Epicardial mapping**

The sinus node is a complex, three-dimensional structure that consists of densely packed specialized pacemaker cells in a connective tissue matrix with a predominantly subepicardial location. Importantly, there are up to 10 radiations from the node into the atrial myocardium extending towards the superior caval vein, terminal crest, or the subepicardium. Consequently, mapping and ablation of the sinus node from the epicardium has been suggested which is also deemed necessary in some cases due to the proximity of the sinus node to the phrenic nerve. In this study of five patients representing the largest series so far, epicardial mapping and complete sinus node ablation from both the endo- and epicardium were feasible but no mapping data were provided.

In our series, we have performed endocardial and epicardial high-density mapping of the RA in two animals. Both cases showed a high congruence of the sinus node activation in the endo- and the epicardial map. This mapping strategy suggests the feasibility of this
approach for detailed assessment of sinus node activation which seems attractive if endocardial mapping and ablation are not possible or unsuccessful.

Clinical implications

Current catheter ablation approaches to IST require complete ablation of the cranial part of the sinus node. Thus, a large mean area of $12 \times 19$ mm needs to be ablated with the use of either 8 mm or cooled-tip catheters. Interestingly and importantly, in a substantial number of patients the successful ablation site has been reported to be not the earliest but a site that was a mean of 7 mm away from the earliest site. This finding supports the notion that not only modulation of the compact node and its paranodal area but also of sinoatrial conduction pathways is a major contributor to IST ablation success. Unfortunately, acute success rates of endocardial ablation may be as low as 75% with an additional recurrence rate of up to 27% sometimes requiring epicardial ablation.11

These observations highlight the need for better and more detailed understanding of sinus node activation resulting in improved mapping and ablation techniques. In that vein, ultra high-density mapping allows fast, simple, and very detailed assessment of sinus node activation as expressed by EAS, SBO, and activation routes. Clearly, future studies are needed to confirm our observations and more importantly, to evaluate novel mapping and ablation strategies in the clinical context for the individual patient. In this environment, different acceptance criteria for automatic beat inclusion need to be evaluated. As briefly discussed above, strict acceptance criteria will result in patterns comparable to previous point-by-point mapping systems and may even be necessary for mapping of unstable rhythms (e.g. atrial tachycardia). Strategies that incorporate both settings, e.g. global mapping with wider criteria followed by fine mapping in the area of interest with strict criteria are possible and need to be tested.

Beyond the established indication in IST, assessment of heart rate modulation in other cohorts is warranted. For instance, pharmacological heart rate modulation with beta-blockers or ivabradine has been shown to improve outcomes in heart failure patients.12 Future studies will determine whether or not this may also be possible with catheter ablation.

Supplementary material

Supplementary material is available at Europace online.

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