Characterization of Left Atrial Activation in the Intact Human Heart

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Background—The patterns of activation of the human left atrium (LA), how they relate to atrial myocardial architecture, and their role in arrhythmogenesis remain largely unknown.

Methods and Results—Left atrial endocardial activation was mapped in 19 patients with a percutaneous noncontact mapping system. Earliest endocardial breakthrough during sinus rhythm (SR) occurred more frequently in the septal (63%, principally posteroseptal) than anterosuperior (37%) LA and varied little with isoproterenol or high right atrial pacing rate. Regardless of site of breakthrough, LA activation was characterized in all patients by propagation around a variably complete line of functional conduction block, descending on the posterior wall from the roof, passing between the ostia of the superior and then inferior pulmonary veins (PVs) before turning septally, passing below the oval fossa, and merging further anteriorly with the septal mitral annulus. Examination of the myocardial architecture in 10 normal adult postmortem hearts revealed an abrupt change in subendocardial fiber orientation along a line following the same course. During episodes of focal initiation of atrial fibrillation (AF), interaction was observed between wavefronts entering the LA from PVs and this functional line of conduction block that resulted in LA macroreentry or formation of daughter wavefronts.

Conclusions—The LA endocardium has complex but characteristic patterns of activation during sinus rhythm, pacing, and AF initiation by PV ectopy that are determined largely by the functional properties of atrial musculature. These findings have important implications for both pacing and ablative strategies for the prevention of initiation of AF. (Circulation. 2003;107:733-739.)

Key Words: atrium • fibrillation • conduction • arrhythmia • mapping

Because of the limitations of conventional endocardial activation mapping and the difficulties encountered in epicardial mapping of the posterior left atrium (LA) and interatrial septum, detailed examination of the patterns of activation of the entire human LA has not been possible to date.

In the right atrium (RA), differential conduction of specific regions gives rise to preferential patterns of activation,1 of which atrial anatomy and myocardial architecture are major determinants. The functional properties of RA anatomic features, such as the crista terminalis and eustachian ridge, provide the basis for conduction block under certain conditions.2–4 With increasing focus on improving the efficacy of percutaneous treatment strategies for atrial fibrillation (AF), a more detailed understanding of the anatomic basis for differential LA activation has become essential.

In considering AF as being dependent on triggers, initiators, and perpetuators,5 much is known about triggering by ectopic activity and the processes of electrophysiological remodeling that perpetuate the arrhythmia. On the basis of this understanding, important percutaneous and surgical treatments have been developed, but these remain incompletely effective or associated with excessive morbidity. However, better knowledge of the sequence of left atrial activation and the way in which triggering ectopic activity interacts with the LA to initiate AF will help evolve treatment strategies aimed specifically at the initiating process.

Detailed anatomic studies of interatrial connections and LA and pulmonary venous (PV) architecture5–8 have provided some insight into the possible anatomic basis for preferential LA conduction. The aim of the present study was to address the hypothesis that there are preferential patterns of LA activation derived from the functional properties of atrial myocardial architecture, and that the consequent distinctive patterns interact characteristically with PV ectopy in the initiation of AF.

Methods

Patient Population

The study population consisted of 21 consecutive patients (16 men), aged 55±10 years, who underwent left atrial noncontact mapping for paroxysmal AF. Three patients had a history of hypertension and left ventricular (LV) hypertrophy, and another three had moderate mitral regurgitation. Two patients had significant impairment of LV syst-
tolic function. The remaining patients (n=12) were free from structural heart disease. Overall, LV fractional shortening was 30±8%, and LA size 4.2±0.9 cm.

Protocol
The local ethics committee approved the study, and written informed consent was obtained from the patients. Patients were studied under local anesthesia in the postabsorptive state, with all antiarrhythmic drugs discontinued for ≥5 days.

The noncontact mapping system (EnSite 3000; Endocardial Solutions Inc) used in this study has previously been described in detail.9–11 The multielectrode array and a conventional mapping catheter were deployed transseptally in the LA, patients were anticoagulated, and detailed LA geometry was acquired.

Nine of 10 patients in AF at the beginning of the procedure were successfully internally cardioverted, under midazolam sedation, with a low-energy internal cardioversion system (Alert PA System, EP MedSystems, Inc). The remaining patient could not be cardioverted and was excluded, as was one further patient in whom technical problems prevented data acquisition during sinus rhythm (SR).

Mapping and Pacing
Data were obtained during SR in 19 patients. Reconstructed and selected contact electrograms and derived isopotential and isochronal activation maps from 10 consecutive beats from each of 3 randomly selected segments of SR were analyzed. In patients who had been in AF at the beginning of the study, SR data were collected at least 15 minutes after cardioversion to minimize any effects caused by the cardioversion. Isoproterenol was administered during SR in 13 patients.

Data were also obtained during pacing at cycle lengths (CLs) ranging from 30 ms below sinus rate to 400 ms, at 100-ms decrements, from the high right atrium (HRA), coronary sinus (CS), and from the right side of the interatrial septum (RAS). Pacing over a wider range of CL down to 200 ms, and from additional sites including the 4 PVs, LA roof and appendage, and the mitral annulus (MVA), was performed to further examine the functional properties of lines of conduction block in 10 of the patients. Pacing from all sites was performed at just above threshold amplitude. Episodes of AF initiation were recorded in 11 patients.

Variables were analyzed with t tests if they conformed to a normal distribution and Mann-Whitney U tests if not. Comparisons between more than 2 groups were made with one-way ANOVA, whereas proportions analysis was used to compare independent binomial proportions. Results are shown as mean±SEM.

Examination of Heart Specimens
Ten structurally normal postmortem heart specimens from patients aged 24 to 65 years were examined for architectural features that might influence conduction. The LA chamber of these hearts measured 33±3 mm. The endocardium was carefully stripped to reveal the arrangement of the underlying myocardial fibers. Regions of abrupt change in myofiber orientation in the venous portion were noted by measuring the locations relative to the PV orifices. The roof of the LA between the left and right PVs was removed in two hearts and sectioned transmurally from superior to inferior orifices to confirm the changes in orientation of the subendocardial myofibers. Ten-micron-thick sections taken at 1-mm intervals were mounted and stained with Masson’s trichrome.

Results
Sinus Rhythm
Onset of LA Activation: LA Endocardial Breakthrough
During SR, earliest endocardial LA breakthrough occurred on the posterosetal wall adjacent to the ostia of the right PVs in 10 patients (53%)—adjacent to either the right superior (RS) PV ostium (6 patients, 32%) or right inferior (RI) PV (4 patients, 21%). Earliest breakthrough at the anterosuperior LA wall, consistent with the position of Bachmann’s bundle,

was seen in 7 patients (37%). The remaining 2 patients (10%) had earliest breakthrough near the oval fossa or the region of the septal MVA (Figure 1A). Unipolar electrograms recorded from sites of earliest breakthrough had a QS morphology.
In 4 of the patients with posteroseptal and 1 patient with anterior breakthrough, later (by 28±8 ms) breakthrough at the other site occurred. Only one patient showed a significant shift in endocardial breakthrough during SR, from the region of Bachmann’s bundle to a site adjacent to the RIPV ostium, at longer sinus CL.

**LA Activation Patterns**

Left atrial activation during SR was characterized by the presence of a consistent but variably complete line of conduction block that extended from the LA roof, descending on the posterior LA wall between the ostia of the superior PVs (21±3 mm from the RS and 24±3 mm from the left superior [LS]) and then between the ostia of the inferior PVs (19±3 mm from the RI and 26±4 mm from the left inferior [LI]) before turning septally, passing below the ostium of the RIPV, and proceeding anteriorly to cross the interatrial septum just below the oval fossa; the line completed its course by merging with the septal part of the mitral annulus (Figure 2, see also Figure 5C). The posterior part of the line (from the roof to the region of the oval fossa) measured 41±3 mm along the endocardial surface, whereas the continuing anterior part (from the oval fossa to and along the length of the MVA) measured 51±5 mm. The line was identified by reconstructing isochronal and serial isopotential maps in sinus rhythm. Conduction block was defined as conduction delay of ≥30 ms, associated with wavefront turning. Local double potentials were always present in the region of conduction block, both on reconstructed and, where available, contact electrograms (Figure 2E).

From the point(s) of earliest breakthrough during SR, activation proceeded both septally and laterally: In 15 patients (79%), the line was complete, and excitatory wavefronts propagating septally could not cross the interatrial septum in a craniocaudal direction; wavefronts propagating laterally wrapped around the lateral LA before turning inferoseptally to complete LA activation near the posteroseptal MVA. In the remaining 4 patients (21%), the septal part of the line was incomplete, allowing craniocaudal wavefront propagation along the interatrial septum. LA activation was completed with collision of wavefronts in the posterolateral LA.

P-wave duration, the time interval from P-wave onset to earliest LA breakthrough, and LA activation time (LAAT),
LA Activation During SR and Pacing

<table>
<thead>
<tr>
<th>No.</th>
<th>CL, ms</th>
<th>P-Wave Onset to Earliest LA Breakthrough, ms</th>
<th>Pacing Stimulus to Earliest LA Breakthrough, ms</th>
<th>LA Activation Time, ms</th>
<th>P-Wave Duration, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>19</td>
<td>783±31</td>
<td>...</td>
<td>65±4</td>
<td>134±3</td>
</tr>
<tr>
<td>SR isoproterenol</td>
<td>13</td>
<td>600±20</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
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<td>700–400</td>
<td>...</td>
<td>55±4</td>
<td>60±5</td>
</tr>
<tr>
<td>Pace RAS</td>
<td>12</td>
<td>700–400</td>
<td>...</td>
<td>22±4‡</td>
<td>61±4</td>
</tr>
<tr>
<td>Pace CS</td>
<td>14</td>
<td>700–400</td>
<td>...</td>
<td>40±4‖</td>
<td>54±3</td>
</tr>
</tbody>
</table>

SR indicates sinus rhythm; HRA, high right atrium; RAS, right interatrial septum; and CS, coronary sinus.

*P=0.016 and ‡P<0.0001 vs SR.
†P=0.0001 vs HRA and P=0.012 vs CS pace.
§P=0.0001 vs SR and HRA pace; P=0.0006 vs CS pace.
‖P=0.042 vs HRA pace.

from earliest LA breakthrough to completion of LA activation (Table), did not differ significantly with breakthrough site or between patients with single and multiple sites of LA breakthrough. Isoproterenol shortened the LAAT and P-wave duration (Table) but had no significant effect on areas of conduction block.

Pacing From the HRA, RAS, and CS at 700 to 400 ms

During HRA pacing (14 patients), LA endocardial breakthrough was as in SR regardless of pacing CL, except in 2 patients in whom pacing led to a change in breakthrough to a septal position (Figure 1B). The line of conduction block seen during SR remained unchanged in all patients during HRA pacing, irrespective of CL or site of earliest breakthrough.

RAS pacing resulted in earliest LA endocardial breakthrough in the region of the oval fossa in 8 of 12 patients (Figure 1C). The pattern of activation closely resembled that seen during SR, with the same line of conduction block present in 11 of 12 patients (complete in 8). RAS pacing was followed by rapid LA breakthrough and associated with P-wave shortening compared with SR and pacing from other sites (Table).

During CS pacing (14 patients), earliest LA breakthrough occurred near the MVA in all patients (Figure 1D and E). Later points of LA breakthrough (by 23±8 ms), also around the MVA, were seen only during pacing from the distal CS in 4 patients. Interestingly, P-wave duration was significantly shorter during pacing from the proximal than distal CS (113±2 versus 135±11 ms; P=0.035). The line of conduction block seen during SR was also present during CS pacing in 11 of 14 patients (complete in 6 and incomplete in 5, Figure 3A and B) and absent in 3 patients. A characteristic feature of CS pacing was that LA breakthrough occurred on the opposite side of the line of conduction block compared with SR and RA pacing. As a result, when the line of conduction block was complete, the activation sequence of the LA was reversed compared with SR, with latest activation at the roof anterior to the RSPV ostium. Differential behavior of the line of block was observed during pacing from CS compared with HRA in 6 patients—in 3, the anterior part of the line allowed conduction during CS but not HRA pacing, whereas in 2, the converse was true. In one patient with a complete line during HRA pacing, no conduction block was observed during CS pacing.

Pacing at Shorter Cycle Lengths and From Additional Sites

The main line of conduction block described above remained remarkably stable with CL shortening down to 200 ms during pacing from the HRA, RAS, and CS. However, pacing from 4.4±0.7 additional sites demonstrated that the line was much less likely to be present during pacing from lateral locations, including the left PVS or lateral roof, than more septal locations, including the right PVS or septal MVA (7 of 22 [32%] versus 13 of 20 [65%], P=0.037, Figure 4). When pacing maneuvers did modify the line, clear shortening or absence of the anterior, septal, or posterior portions of the line was observed, but with slowing of conduction through these regions.

Secondary Lines of Conduction Block

Secondary lines of conduction block were seen in a minority of patients during SR and pacing at 700 to 400 ms. An anterior line extending from the anterior MVA toward the LA appendage (LAA) and a posterior line extending from the posterior MVA toward the LIPV were observed during SR in 9 and 4 patients, respectively. Progressive CL shortening down to 300 ms had little effect on the development of additional lines of conduction block. At even shorter CL, however, development of new functional lines of conduction block was observed.

LA Activation During PV Ectopy and Initiation of AF

During activation of the LA by >500 runs of ectopic beats (65% from PVS, 22% LA, 13% RA), the same main line of conduction block was observed, but with variations in degree of completeness, depending predominantly on the source of ectopy. In 28 episodes, continuing rapid ectopic activity was followed by initiation of atrial fibrillation. In these episodes, AF initiation was preceded either by the formation of LA macroreentrant circuits with varying stability, of which the same line formed one or more barriers, or by the formation of daughter wavefronts that escaped through small breaks in the line, with the remainder of the line protecting the daughter wavefront from collision with the main wavefront.
additional 15 episodes, AF appeared to be focally driven by continuing rapid ectopy with some variability in the main line of conduction block that resulted in varying patterns of LA activation.

Examination of Postmortem Hearts
The subendocardial fibers of all hearts had longitudinal or oblique orientations relatively perpendicular to the plane of the mitral orifice and circularly arranged fibers that were more parallel to the mitral orifice. The longitudinal fibers were arranged in broad bands.

The most obvious broad band of longitudinal fibers was formed by the “septopulmonary bundle.” This originated in the anterior interatrial groove on the anterior LA wall behind the anterior interatrial band (Bachmann’s bundle) and passed to the roof before descending posteriorly and then inferoseptally between the PV ostia toward the septal mitral annulus, where it became less distinct. The lateral margin of the bundle, as it passed between the PV ostia (28±6, 13±4, 26±7, and 14±4 mm from the RS, LS, RI, and LI, respectively) toward the septal MVA, formed a line that marked an abrupt change in subendocardial fiber orientation. Fiber orientation changed from longitudinal with a vertical orientation septal to the line, to oblique and circumferential lateral to the line (Figure 5). Histology confirmed the changes in fiber orientation in the subendocardium and also revealed crossover arrangements deeper in the wall. This line, which was seen in all hearts, also marked a change in LA wall thickness, this being thicker toward the septum (1.4±0.5 mm) and thinner laterally (0.7±0.4 mm, P=0.0015). Another area of change in subendocardial fiber orientation was observed adjacent to the anterior MVA in 7 of 10 hearts, whereas abundant fatty tissue was observed above the posterior MVA in 6 of 10 hearts.

Discussion
To our knowledge, this is the first description of characteristic preferential activation patterns in the human LA. In the present study, posterior interatrial connections, as described in recent studies of human atrial anatomy, were found to be at least as important as Bachmann’s bundle in right-to-left interatrial conduction during SR. Irrespective of the site of earliest breakthrough, the pattern of LA activation was predominantly determined by a principal line of conduction block. The line, although evident in every patient in SR, showed some variation in extent and completeness and was even absent under some paced conditions, and is therefore at least in part functional. It appears to be related to an abrupt change in LA subendocardial fiber orientation and wall thickness at the lateral margin of the septopulmonary bundle described by Papez in 1914, as this traverses the posterior LA between the PVs toward the septal mitral annulus, where it merges with this anatomic barrier. The identification of
additional lines of conduction block in a proportion of patients is in keeping not only with our anatomic findings, but also with a recently described “isthmus” between the MVA and LIPV.13

Although epicardial mapping has been used extensively to assess atrial activation both in animals and intraoperatively in humans,14–17 access to the interatrial septum and the posterior atria between the caval and pulmonary veins has prevented complete epicardial mapping17 and general anesthesia may influence conduction.18 Recent publications have shown that left-to-right interatrial conduction occurs predominantly through Bachmann’s bundle,19,20 and we have previously shown that during AF, after periods of electrical silence, the RA consistently reactivates from the region of Bachmann’s bundle, sometimes with additional breakthrough at the CS ostium or oval fossa.20

Despite the difficulties in left atrial mapping noted above, the predominantly epicardial studies of LA activation15,17 have suggested that the principal route of epicardial LA activation during SR is through Bachmann’s bundle, although this was not a universal finding.14,16 A recent study also identified posteroseptal pathways involved in SR activation of the LA endocardium.21 Although Bachmann’s bundle appeared to be the predominant interatrial connection, technical limitations may have reduced the accuracy of mapping in the posteroseptal LA and the region of the RIPV ostium.22

The present study has shown that there are indeed multiple connections capable of right-to-left atrial conduction and that posterior communications play a major role, in contrast to left-to-right conduction. This raises the intriguing possibility that differential right-to-left, versus left-to-right, interatrial conduction pathways may promote interatrial macroreentry, which may have a role in the maintenance of atrial fibrillation. Interruption of interatrial communications, both surgically in humans23 and by means of catheter ablation in animal models, has been proven to be a successful, if challenging, strategy to treat AF.

Connections around the MVA, presumably related to perforating coronary sinus fibers, activated the LA during pacing from the proximal and distal CS.6 Connections near the true interatrial septum had a dominant role during pacing from the RAS, such that right-to-left interatrial conduction was fastest and P-wave duration shortest during pacing from this site. These findings have important implications with regard to choice of pacing sites for atrial resynchronization to suppress AF.

In identifying characteristic patterns of LA activation that are present during SR and pacing from multiple sites and that interact with pulmonary vein and atrial ectopy in the process of initiation of atrial fibrillation, the results of this study have important implications for both pacing and ablative strategies to prevent initiation of this complex arrhythmia.

**Study Limitations**

The signals recorded with the EnSite system predominantly reflect endocardial activation and may not detect differential patterns of epicardial LA activation. Because LA noncontact mapping cannot be justified in entirely normal human subjects, it is impossible to be certain that the patterns of activation observed in this population of patients with paroxysmal AF are normal. Nonetheless, the presence of an anatomic basis for the line of conduction block in normal postmortem hearts suggests that similar patterns of LA activation may be expected in the normal population.

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References


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