Interatrial conduction in the mechanisms of atrial fibrillation: from anatomy to cardiac signals and new treatment modalities

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Areas of slow conduction and conduction block are important prerequisites for re-entry known to underlie atrial fibrillation (AF). Experimental and clinical data show that AF is associated with global lowering of atrial propagation velocity and the presence of defects in the interatrial conduction routes. The increasing data from anatomical studies demonstrate the possible prerequisites for conduction disturbances that could be primarily because of anatomical variability in interatrial connections or because of age-related development of fibrotic changes in the atrial musculature. More detailed descriptions of the structure and function of the interatrial connections other than Bachmann's bundle have become available and, as a result, the role of these connections in the mechanisms of AF is increasingly appreciated. Interatrial pacing studies show promising results, but further studies on larger amounts of materials are required in order to identify the population of patients who would benefit more effectively from this treatment as well as the optimal pacing technique. Therefore, more extensive documentation is required before therapeutic modalities aimed at improving interatrial conduction will become a part of the clinical routine in the management of AF patients.

KEYWORDS
Atrial fibrillation; Interatrial conduction; Anatomy

Conduction velocity in the mechanisms of atrial fibrillation

The role of triggers in the initiation and maintenance of atrial fibrillation (AF) is well appreciated. However, the likelihood that a trigger can initiate the arrhythmia that would sustain itself requires an arrhythmic substrate in the atria and depends on the length of the wavelet defined as the product of the effective refractory period and the conduction velocity. Therefore, the wavelength must be shorter than the available substrate dimensions for re-entry to occur. In addition, the shorter wavelength increases the number of wavelets that could co-exist in the given atrial dimensions and thus increasing the likelihood that AF would sustain itself. This mechanism underlying AF has been confirmed in animal experiments and clinical studies that were recently reviewed by Nattel et al.1

Slow conduction in the atria can be diffuse, presumably either caused by fibrosis that is age-related2 or caused by coexisting conditions such as heart failure or hypertension.1 However, the conduction defect can also be local, critically located in one of the interatrial pathways of which Bachmann’s bundle is the most well known. Indeed, the association between Bachmann’s bundle block and AF has been shown in several studies.3,4 Researches during recent years have further improved our knowledge of the anatomy of the interatrial connections and highlighted previously neglected areas.

The purpose of this review is to present the available data on the structure and function of interatrial connections as well as possible therapeutic modalities aimed at improving interatrial conduction in the management of AF patients.

Anatomy of the interatrial pathways

To the best of our knowledge, the first comprehensive description of the human heart and of the anatomy of the muscle bundles connecting the right and left atria had been found in an atlas published by Bourgery.5 It, one of the most lavishly illustrated anatomical and surgical
treatises ever published, contains 726 illustrations by the artist Nicolas-Henri Jacob, a student of the neoclassical painter Jacques-Louis David.

Figure 1, reproduced from the atlas, clearly demonstrates that, in the mid-nineteenth century, there was knowledge about the cardiac musculature including the circumferential muscle bundle located at the anterior wall of the left atrium and connecting the right and left atrial appendages (Figure 1A). It was later named after George Bachmann who discovered its participation in the interatrial propagation of electrical impulses. Since then, this superior interatrial route has traditionally been considered a major pathway for the fast interatrial activation spread. Animal experiments have demonstrated that with a conduction velocity almost twice as high as the major part of the atrial myocardium (1.66 vs. 0.88 m/s), the effective refractory period of Bachmann’s bundle is significantly longer than that of the right and left atrium (163 vs. 101 and 108 ms, respectively). Consequently, Bachmann’s bundle may become blocked at a pacing rate when the adjacent atrial tissue can still be activated. This represents a potential substrate for re-entry with participation of Bachmann’s bundle that has been documented experimentally.

Catheter ablation techniques and the ability to treat arrhythmic targets with very high precision have revived the interest in cardiac anatomy. Over the past 10 years, the anatomy of the interatrial connections has been studied by several groups. It was found that, in addition to Bachmann’s bundle, muscular bundles exist on the inferior atrial surface near the coronary sinus (CS) and posteriorly in the vicinity of right upper and right lower pulmonary veins. In fact, these structures can also be seen on the same page of the nearly 150-year-old atlas of anatomy (Figure 1B). Muscular sleeves extending from the right atrium on the musculature of CS and further via distinct and isolated bundles from the CS to the left atrial wall represent another substrate for interatrial conduction, alternative to Bachmann’s bundle. The number, location, and thickness of these interatrial connections are reported to be extremely variable, suggesting that the anatomical variability may partly explain why some individuals develop interatrial conduction defects whereas others do not.

Function of the interatrial pathways
Surprisingly, little evidence exist in regard to the function of interatrial connections in humans. Soon after the introduction of electroanatomical mapping in clinical practice, Roithinger et al. reported that transseptal conduction occurs not only via Bachmann’s bundle but also via other connections located either in the vicinity of the CS or fossa ovalis. This finding has later been confirmed by others, but it does not answer the question whether all these bundles are relevant for conduction during sinus rhythm in humans.

Figure 1 Superior (A) and inferior (B) view of the human heart. (A) Superior interatrial route (Bachmann’s bundle) travels from the superior part of the right atrium near the ostium of the vena cava superior to the upper part of the left atrium (*). Aorta and pulmonary artery are removed; (B) components of the inferior interatrial route: asterisk denotes muscular bundles between the right atrium near the orifice of the vena cava inferior and the inferior surface of the left atrium; Δ denotes interatrial bundles in the vicinity of the coronary sinus orifice (coronary sinus is removed). Reproduced from Bourgery.
The issue has been addressed in five studies that used either electroanatomical or non-contact mapping of the left atrium (Table 1). Of those studies, three reported conduction over Bachmann’s bundle during sinus rhythm in the vast majority of the studied individuals. The two other studies documented that an inferior route may also serve as a preferential route for interatrial conduction, suggesting that the importance of Bachmann’s bundle may have been overestimated. Yet another study published as an abstract in 2005 reported the absence of conduction over Bachmann’s bundle during sinus rhythm in 5 of 13 patients with paroxysmal AF. Interestingly, our group has not been able to identify Bachmann's bundle using a serial slicing technique in about half of the heart specimens, i.e. in 7 of 15 cases in our initial report and in 9 of 21 cases in an expanded series 3 years later. In another report by Becker et al., fibro-fatty degeneration of Bachmann’s bundle was common among patients with a history of AF.

Conduction during ectopic atrial rhythms seems to be depending entirely on the anatomical proximity of the arrhythmia focusing on certain interatrial pathways as studied using atrial pacing. This has recently been confirmed for left atrial focal tachycardias originating from pulmonary veins ostia that propagate to the right atrium predominantly via the posterior interatrial connections and not via Bachmann’s bundle.

One should bear in mind, however, that, except for one small study, left atrial mapping has been performed on patients admitted for ablation of AF. Thus, electrophysiology of normal interatrial conduction in healthy humans still remains largely unexplored.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean age, years</th>
<th>Diagnosis</th>
<th>Mapping technique</th>
<th>Conduction via Bachmann’s bundle (%)</th>
<th>Conduction via posterior/inferior connections (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Ponti et al.</td>
<td>7</td>
<td>37</td>
<td>WPW, no AF</td>
<td>Electro-anatomical</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Markides et al.</td>
<td>19</td>
<td>55</td>
<td>Paroxysmal AF</td>
<td>Non-contact</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td>Lemery et al.</td>
<td>20</td>
<td>54</td>
<td>Paroxysmal AF</td>
<td>Non-contact</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Betts et al.</td>
<td>9</td>
<td>46</td>
<td>Paroxysmal AF</td>
<td>Non-contact</td>
<td>22</td>
<td>78 (five at RUPV and two at RIPV)</td>
</tr>
<tr>
<td>Lemery et al.</td>
<td>35</td>
<td>56</td>
<td>Paroxysmal AF</td>
<td>Electro-anatomical</td>
<td>88</td>
<td>31, near FO 93, near CS</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CS, coronary sinus; FO, fossa ovalis; RUPV, right upper pulmonary vein; RIPV, right inferior pulmonary vein.
Atrial conduction defects in patients with atrial fibrillation

A number of non-invasive techniques exist that could be used for assessment of atrial conduction. The one most readily available in clinical practice is the standard 12-lead ECG, where P-wave duration and morphology can serve as indices of atrial conduction. In 1985, Bayes de Luna et al. described an advanced interatrial block with retrograde activation of the left atrium associated with histories of atrial tachyarrhythmias. Such interatrial block is seen on the surface ECG as a wide (> 120 ms) and biphasic P-wave in the inferior leads. Although the prevalence of this advanced block is relatively low, the partial interatrial block defined as a P-wave longer than 120 ms with possible notched morphology is a much more common finding, and a recent report documented those in ~40% of hospitalized patients.

More sophisticated P-wave signal-averaging techniques have demonstrated an association between prolonged P-waves and a history of AF. Our group has shown that a history of lone AF was associated with particular P-wave morphology, primarily the presence of the biphasic (−/+ ) P-waves in the orthogonal Z-lead corresponding to the reverse (+/− ) morphology in the V1–V2 chest leads and thus suggesting the presence of a conduction delay in the posterior interatrial bundles affecting the way the activation wavefront travels between the atria. In a recent study, similar findings were obtained using the same unfiltered P-wave signal-averaged ECG technique in the cohort of patients with hypertrophic obstructive cardiomyopathy known for their higher risk of developing AF. Compared with healthy controls, patients with cardiomyopathy more often showed biphasic (−/+ ) P-wave morphology in the lead Z indicating defective conduction via the posterior interatrial connections as well as biphasic (+/− ) P-waves in the inferior lead Y meeting criteria for complete interatrial block. (Figure 3). Using high-density electroanatomical mapping in the proximal CS during sinus rhythm, we have confirmed that conduction velocity of the inferior route was indeed lower in AF patients compared with patients without a history of AF.

However, it is important to note that solid data linking histological substrates to deteriorated atrial conduction and higher propensity of AF are still lacking. Diffuse structural abnormalities such as vacuolar degeneration, inflammatory changes, and fibrosis were reported in patients with lone AF. Critically located lesions have recently been shown by Becker et al. who described the presence of an extensive fibro-fatty replacement of Bachmann’s bundle in patients with a history of AF. Our group has not been able to document differences either in the structure or in the location of interatrial connections associated with a history of AF.

Is there a way to improve impaired conduction?

Pharmacological approach

Pharmacologically enhanced atrial conductivity could be beneficial for those patients with AF who have this mechanism.

Figure 3 P-wave morphologies in the orthogonal Frank leads illustrating the expression in the VCG of the most common variants of interatrial conduction. P-wave duration is shortest in the left panel and longest in the right. Left: positive X and Y and negative Z with negative or isoelectric terminal portion of the P-wave, common in healthy subjects; Middle: positive X and Y, but biphasic −/+ in Z. Positive terminal portion of the P-wave in the lead Z suggests that depolarization of the left atrium propagates from its anterior part (insertion of Bachmann’s bundle) backwards with no or minimal contribution from the posterior/inferior interatrial bundles. This type is common in patients with paroxysmal AF and patients with hypertrophic cardiomyopathy; Right: positive X, biphasic +/− Y, and biphasic −/+ Z as in advanced interatrial block with retrograde left atrial activation.
linked to the arrhythmia development. This forms an attractive target for clinical research. The studies of substances that enhance the conductivity of atrial tissue have now become available, but their protective effect against AF, as observed in experiments, was quite limited.\textsuperscript{21} Meanwhile, once fibrotic changes become established in the atrial myocardium, a significant improvement in atrial conduction properties is probably not achievable. However, some experimental data suggest that ACE inhibitors may attenuate development of fibrosis in the canine model of CHF.\textsuperscript{32} In clinical studies, P-wave duration was significantly reduced by rennin–angiotensine system inhibitors in patients with arterial hypertension, suggesting an improvement in interatrial conduction.\textsuperscript{33,34} It was not clear, however, whether this shortening of the P-wave had any effect on a predisposition to AF.

The issue was addressed in two clinical trials where blockers of the rennin–angiotensine system were tested on AF patients demonstrating that irbesartan\textsuperscript{35} and enalapril\textsuperscript{36} in addition to amiodarone improved sinus rhythm survival after electrical cardioversion of persistent AF. The documented abilities of these drugs to affect structural atrial changes\textsuperscript{32} make them attractive targets for future research. However, in a recent placebo-controlled CAPRAF study, candesartan alone was not effective in reducing the recurrence rate after electrical cardioversion of AF.\textsuperscript{37}

**Atrial resynchronisation by pacing**

Discussion of the interventions aimed at improving atrial conduction would not be complete without a brief overview of the special pacing modalities used in the management of AF. Shortening of atrial activation can be achieved either by pacing the right and the left atria separately with electrodes in right atrial appendage (RAA) and distal CS (bifascicular pacing) or by pacing RAA and the ostium of CS (dual-site right atrial pacing). Although initial attempts with bifascicular\textsuperscript{38,39} and dual-site right atrial\textsuperscript{40} pacing showed promising results, the results of a lager trial were not conclusive.\textsuperscript{41} Technical complexity of dual-site atrial pacing methodology further complicates its clinical use.

Single-site interatrial septal pacing represents a simpler\textsuperscript{42} and therefore potentially more attractive approach to improve deteriorated interatrial conduction aimed at a reduction of AF burden. However, no consensus has yet been achieved with regard to the selection of the optimal pacing site (Table 2).

Bailin et al.\textsuperscript{43} in a controlled, randomized study demonstrated that pacing in the vicinity of Bachmann’s bundle was superior to the conventional RAA pacing in terms of progression of paroxysmal AF into its permanent form during a 1-year follow-up. However, the choice of the pacing site did not affect the number of paroxysms of AF measured by the number of mode-switch episodes in pacemaker memory.

Pacing in the vicinity of the posterior–inferior interatrial route (i.e. near CS ostium or posterior to fossa ovalis) was assessed in several randomized trials. Padeletti et al.\textsuperscript{44} showed that pacing at the triangle of Koch had a better potential to prevent AF than conventional pacing at RAA. This could not be confirmed in a later performed multicenter ASPECT trial.\textsuperscript{45} However, in this trial, septal lead position varied among investigators and the relative efficacy of individual septal lead locations (low, middle, or high septal) could not be evaluated. In another multicenter trial by De Voogt et al.\textsuperscript{46} (OASES), low atrial septal pacing in combination with an atrial overdrive pacing algorithm demonstrated an advantage compared with pacing from the high right atrium. Findings from the most recent trial by Hermida et al.\textsuperscript{47} have also supported the concept of a positive effect of low atrial septal pacing for reduction of AF burden. Similar findings were obtained in a smaller observational study.\textsuperscript{48}

Given the complexity and structural variability of interatrial routes, it is unlikely that a single pacing electrode location would fit all patients with paroxysmal AF. No direct comparison of the antiarhythmic effects of the single-site pacing at the superior or the inferior interatrial septum has been published either. Attempts to identify the exact location of the interatrial routes for optimization of septal pacing are being made, using a search for either locating the earliest breakthrough site on the right atrial septum during left atrial pacing\textsuperscript{49} or finding a pacing site at the interatrial septum that is associated with the shortest activation time at the high right atrium and distal CS.\textsuperscript{50} The clinical value of these approaches has yet to be confirmed.

**Table 2** Single-site interatrial septal pacing studies in the management of paroxysmal AF

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Mean follow-up, months</th>
<th>IAS pacing site</th>
<th>Control pacing site</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailin et al.\textsuperscript{43}</td>
<td>120</td>
<td>12</td>
<td>High IAS</td>
<td>RAA</td>
<td>IAS pacing associated with fewer permanent AF at 1 year</td>
</tr>
<tr>
<td>Padeletti et al.\textsuperscript{44}</td>
<td>46</td>
<td>3</td>
<td>Low IAS</td>
<td>RAA</td>
<td>AF burden and number of AF paroxysms per month lower in the IAS group</td>
</tr>
<tr>
<td>Kale et al.\textsuperscript{48}</td>
<td>28</td>
<td>6</td>
<td>Low IAS</td>
<td>No control</td>
<td>Observational study. Subjective improvement in 19 patients, complete suppression or marked improvement of AF in 17 patients</td>
</tr>
<tr>
<td>Padeletti et al.\textsuperscript{45}</td>
<td>298</td>
<td>6</td>
<td>Low, middle, and high IAS</td>
<td>RAA</td>
<td>No difference between septal and non-septal electrode location. Individual efficacy of different septal positions could not be evaluated</td>
</tr>
<tr>
<td>De Voogt et al.\textsuperscript{46}</td>
<td>209</td>
<td>6</td>
<td>Low IAS</td>
<td>RAA</td>
<td>Reduction of AF burden in IAS group</td>
</tr>
<tr>
<td>Hermida et al.\textsuperscript{47}</td>
<td>124</td>
<td>16</td>
<td>Mid-IAS above CS</td>
<td>RAA</td>
<td>AF-free survival increased by septal pacing</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; IAS, interatrial septum; RAA, right atrial appendage.
Conclusions
Areas of slow conduction and re-entry block are important prerequisites for re-entry known to underlie AF. Experimental and clinical data show that AF is associated with global lowering of atrial conduction velocity and the presence of local conduction defects critically located in the vicinity of interatrial conduction routes. The increasing amounts of data that currently become available from anatomical studies demonstrate possible prerequisites for conduction disturbances that could either be primarily because of the anatomical variability of interatrial connections or, secondary, because of the age-related development of fibrotic changes in the atrial musculature. The ability of rennin–angiotensine system blockers to attenuate fibrosis has recently been documented in experimental studies showing a beneficial effect in AF patients, possibly giving rise to the development of a ‘structural therapy’ of AF. Promising results from the interatrial septal pacing studies also warrants further studies on a larger material. The section of patients that would benefit from this treatment is still poorly defined and the selection of a pacing technique is still poorly defined and the selection of a pacing technique is therefore required before therapeutic modalities aimed at improving interatrial conduction will become a part of clinical routine in the management of AF patients.

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References


