Impact of the arrhythmogenic potential of long lines of conduction slowing at the pulmonary vein area

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BACKGROUND Areas of conduction delay (CD) or conduction block (CB) are associated with higher recurrence rates after ablation therapy for atrial fibrillation (AF).

OBJECTIVE Thus far, there are no reports on the quantification of the extensiveness of CD and CB at the pulmonary vein area (PVA) and their clinical relevance.

METHODS Intraoperative high-density epicardial mapping of the PVA (interelectrode distance 2 mm) was performed during sinus rhythm in 268 patients (mean ± SD [minimum–maximum] 67 ± 11 [21–84] years) with and without preoperative AF. For each patient, extensiveness of CD (conduction velocity 17–29 cm/s) and CB (conduction velocity <17 cm/s) was assessed and related to the presence and type of AF.

RESULTS CD and CB occurred in, respectively, 242 (90%) and 183 (68%) patients. Patients with AF showed a higher incidence of continuous conduction delay and block (CDCB) lines (AF: n = 37 [76%]; no AF: n = 132 [60%]; P = .046), a 2-fold number of lines per patient (CD: 7 [0–30] vs 4 [0–22], P < .001; CB: 3 [0–11] vs 1 [0–12], P = .003; CDCB: 2 [0–6] vs 1 [0–8], P = .004), and a higher incidence of CD or CB lines ≥6 mm and CDCB lines ≥16 mm (P = .011, P = .025, and P = .027). The extensiveness of CD, CB, and CDCB could not distinguish between the different AF types.

CONCLUSION Patients with AF more often present with continuous lines of adjacent areas of CD and CB, whereas in patients without AF, lines of CD and CB are shorter and more often separated by areas with normal intra-atrial conduction. However, a considerable overlap in the amount of conduction abnormalities at the PVA was observed between patients with a history of paroxysmal and persistent AF.

KEYWORDS Atrial fibrillation; Conduction; Epicardial mapping; Pulmonary veins; Sinus rhythm

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Introduction
The pulmonary vein area (PVA) has been of particular interest in the pathophysiology of atrial fibrillation (AF) ever since Haïssaguerre et al demonstrated bursts of rapid ectopic beats as triggers for spontaneous AF. Since then, treatment strategies for AF mainly focus on the isolation of the PVA by endocardial and/or epicardial ablation. Yet, recurrence rates are considerable for both patients with paroxysmal AF and those with persistent AF and are likely the result of either reconnection or transition of AF from a trigger-driven to a more substrate-driven disease.7

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To date, AF recurrences after ablation procedures remain difficult to predict. Yet, fibrosis at the left atrial (LA) posterior wall, resulting in conduction delay (CD) or conduction block (CB), appears to be associated with higher recurrence rates.3,4 It has been suggested that the assessment of electropathology, including low voltages, fractionation, and conduction abnormalities, during sinus rhythm (SR) at the PVA may facilitate the identification of target sites for ablation or can be used to predict AF recurrences after ablation therapy.5–9

In several mapping studies, a line of CB running vertically between the right and left pulmonary veins during SR was identified.10–12 This CB line varied between patients in its continuity and could in some patients be altered by pacing, indicating that it was partly functional in nature.10–12 Furthermore, this line was more frequently observed in patients with AF or mitral valve regurgitation.11,12 On the basis of histological findings in postmortem hearts, the authors suggested that abnormal conduction was the result of a change in myocardial fiber direction.10 Aside from this
line of CB, other areas of conduction disorders were observed in only a minority of patients.10–12 However, the degree and extent of conduction abnormalities during SR at the PVA have never been quantified and correlated with the different types of AF as defined by the European Society of Cardiology guidelines.13 The goals of the present intraoperative high-resolution epicardial mapping study were therefore to detect and quantify conduction abnormalities at the PVA in a large cohort of patients during SR and to investigate the association with AF persistence.

Methods

Study population
The study population consisted of 268 successive adult patients undergoing elective coronary artery bypass grafting, aortic or mitral valve surgery, or a combination of valvular and bypass grafting surgery. This study was approved by the institutional medical ethical committee (MEC2010-054/MEC2014-393). Written informed consent was obtained from all patients, and clinical data were extracted from electronic patient files. A detailed description of the methods is provided in the Supplemental Material.

Epicardial high-resolution mapping
Epicardial high-resolution mapping of the PVA was performed during SR from the transverse sinus along the borders of the right and left pulmonary veins down toward the atrioventricular groove (Figure 1), as previously described.14 Local activation maps of the right and left pulmonary veins during SR were constructed by annotating the steepest negative slope of atrial potentials recorded at every electrode (see also Supplemental Figure 1). Heterogeneity in conduction was determined by quantifying the amount, number, and length of lines of CD, CB, and continuous conduction delay and block (CDCB) and its differences between patient groups on a 2 mm resolution scale. Lines of CD and CB were defined as time differences (Δt) of, respectively, 7–11 and ≥12 ms between adjacent electrodes.15,16

Statistical analysis
Normally distributed data are presented as mean ± SD (minimum–maximum). Skewed data are presented as median (minimum; interquartile range; maximum) and analyzed using Mann-Whitney U tests. Categorical data are expressed as numbers and percentages and analyzed using the χ² test.
A longitudinal line of CD or CB running vertically between the left and right pulmonary veins from superior to inferior positions was observed in 14 patients (5%), though varying in its continuity and length. Typical examples of activation maps and corresponding isochrones and CD/CB maps of these patients are shown in Figure 3. The incidence of this line was similar between patients without and with AF (P = .295), as well as between patients with IHD and those with (i)VHD (P = .503). However, this line was more often observed in patients with LA dilation (n = 6 [10%]) than in patients without LA dilation (n = 8 [4%]) (P = .048). As displayed in Table 2, multivariate regression analysis revealed only the presence of AF episodes as an independent predictor of long lines of CD and CB at the PVA; clinical characteristics including IHD, (i)VHD, LA dilation, sex, BMI, older age, and left ventricular dysfunction were not.

### Association between AF and heterogeneity in conduction

The upper panel of Figure 4 displays typical examples of activation maps and the corresponding CD/CB maps obtained from a patient without AF and a patient with AF.

Patients with AF more often have continuous lines of CDCB as compared with patients without AF, as demonstrated in the middle left panel (AF: n = 37 [76%]; no AF: n = 132 [60%]; P = .046). The number of lines of CD, CB, and CDCB in patients with AF was approximately 2-fold the number observed in patients without AF (CD: 7 [0–30] vs 4 [0–22], P < .001; CB: 3 [0–11] vs 1 [0–12], P = .003; CDCB: 2 [0–6] vs 1 [0–8], P = .004).

As demonstrated in Figure 4, the incidence of both CD and CB lines ≥6 mm was higher in patients with AF than in patients without AF (CD: 69% [n = 34] vs 49% [n = 108], P = .011; CB: 59% [n = 29] vs 42% [n = 91], P = .025). The maximum length of continuous CDCB lines in patients with AF ranged from 8 to 72 mm, whereas in patients without AF this length ranged from 4 to 42 mm; CDCB lines ≥16 mm occurred more often in patients with AF (n = 20 [41%] vs n = 50 [25%]; P = .027).

Hence, the presence of AF episodes was strongly associated with increased heterogeneity in conduction, marked not only by a higher incidence of CB and CDCB but also by a higher number of lines of CD, CB, and CDCB and more importantly longer lines of CD, CB, and CDCB.

Thus, patients with AF more often present with continuous lines of adjacent areas of CD and CB, whereas in patients without AF, lines of CD and CB are more often separated by areas with normal intra-atrial conduction. These findings were validated in an age- (5-year range),
BMI- (2-kg/m² range), sex-, and type of surgery–matched case-control analysis (AF N=35, No AF N=35).

In addition, patients who developed de novo AF in the early postoperative phase (70 patients without preoperative AF [32%]) showed a trend toward more CB lines (P < .055), a higher number of continuous CDCB lines (P < .030) at the PVA, and a trend toward a higher incidence of long CB lines (>6 mm) (P < .073).

Severity of conduction abnormalities vs clinical AF classification

Figure 5 provides typical examples of PVA activation combined with the corresponding CD and CB maps obtained from 2 patients with paroxysmal AF and 2 patients with persistent AF; the amount of conduction abnormalities in 1 patient with paroxysmal AF is even higher than in the patient with persistent AF.

Figure 5 shows that there is a large interindividual variation in the amount of conduction abnormalities in both paroxysmal and persistent AF groups. There is also no difference between patients with paroxysmal AF and patients with persistent AF in the number of CD, CB, and CDCB lines (P = .442, P = .535, and P = .951). Also, incidences of CD, CB, and CDCB were similar (P = .204; P = .835, and P = .708); receiver operating characteristic curve analyses could not identify a cutoff value for the length of lines distinguishing patients with persistent AF from those with paroxysmal AF. The duration of AF history was similar for patients with paroxysmal AF and those with persistent AF (P = .429).

Hence, although this is only a small group of patients, the overlap in the severity of conduction abnormalities suggests that severity of conduction abnormalities at the PVA does not seem to clearly differentiate patients with paroxysmal AF from patients with persistent AF.

Discussion

Key findings

Intraoperative high-resolution epicardial mapping of the PVA during SR for the first time quantified and characterized different types of conduction abnormalities and related it to the presence of AF episodes. Current data demonstrated that patients with AF have more and longer lines of CD, CB, and CDCB, whereas in patients without AF, short lines (<6 mm) of CD and CB separately are more diffusely present. Furthermore, the severity of conduction abnormalities at the PVA during SR does not differentiate between patients with paroxysmal AF and those with persistent AF.

Conduction abnormalities at the PVA

To our knowledge, only 3 previous studies have investigated conduction abnormalities at the posterior wall of the LA in humans during SR. In an endocardial noncontact mapping study by Markides et al., conduction at the LA was analyzed during SR in 19 patients with a history of paroxysmal AF. They observed a vertical line of CB (inter-electrode time interval 30 ms) extending from the LA roof.
across the posterior LA wall turning septally below the ostium of the right inferior pulmonary vein proceeding anteriorly toward the septal mitral annulus.\textsuperscript{10} This CB line was present in all patients, though varied in its continuity, particularly during pacing.\textsuperscript{10} In a minority of patients, the CB line disappeared completely during pacing.\textsuperscript{10} On the basis of histological findings in postmortem hearts, Markides et al\textsuperscript{10} suggested that the line of CB was caused by an abrupt change in myocardial fiber orientation at the subendocardium.

Roberts-Thomson et al\textsuperscript{11} performed epicardial mapping during SR in 34 patients without AF. They observed a similar
Multivariate analysis

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AF = atrial fibrillation; CB = conduction block; CD = conduction delay; CI = confidence interval; IHD = ischemic heart disease; (i)VHD = ischemic and valvular heart disease; LA = left atrial; LVF = left ventricular function; OR = odds ratio.

In a subsequent study, epicardial SR mapping after electrocardioversion in 16 patients without AF and 5 patients with persistent AF showed a similar vertical CD line in 2 patients without AF whereas this was observed in 4 patients with AF.11 However, when pacing from different sites, the CD line now appeared in all patients.11 In contrast to these previous studies, we observed conduction abnormalities scattered across the PVA with no clear predilection site. Lines of CD occurred in almost all patients and CB in approximately 70% of the population. The fact that the aforementioned studies did not observe any other lines of CD or CB at the PVA is remarkable, especially since study populations consisted of patients with IHD, patients with AF, and patients with LA dilation due to mitral regurgitation. In all these patients, areas of fibrosis would be expected, particularly at the LA posterior wall. Our CB criteria correspond with a conduction velocity of <17 cm/s, which is in the range of the CD criteria of Roberts-Thomson et al. Therefore, although our cutoff criteria are slightly more sensitive, the higher incidence of CD/CB cannot be totally explained by differences in cutoff values. Yet, the higher resolution of the mapping system used in the present study may be the explanation for this discrepancy, as it contains the unique ability to identify lines of CD and CB with a minimum length of 2 mm. Furthermore, we did not set a minimum length or wavefront propagation criterion for lines of CD and CB, as opposed to previous studies.

In our cohort, only a minority of patients showed a longitudinal line running downward between the left and right pulmonary veins, which might be similar to the line observed in previous studies. However, this line varied in length and continuity and practically never consisted of a line of CB running continuously from the superior to the inferior of the posterior wall. The precise nature of this line so far remains unclear. If, as suggested by previous studies, a histological change in fiber direction would be the underlying cause, we would expect it to occur in the majority of patients during SR.

**Conduction abnormalities and AF**

In correspondence to previous studies, increased amounts of CD, CB, and CDCB at the PVA were observed in patients with AF. In patients with AF, a higher incidence of CB,
CDCB, and an almost 2-fold number of separate CD, CB, and CDCB lines per patient was observed. Also, CD, CB, and CDCB lines extended over larger areas.

These observations suggest a critical role for the spatial distribution of conduction abnormalities in AF development. A certain length of an area of abnormal conduction is required for reentry to occur; this phenomenon was first demonstrated by Ortiz et al17 in 7 canine hearts with sterile pericarditis. In this study, the critical role of the length of an area of functional block in the right atrial free wall was observed. In the case of stable atrial flutter, a functional CB line of 24 mm was observed, enabling reentry to occur.17 When the cycle length decreased, areas of slow conduction disappeared, resulting in a shorter line of functional CB with a mean length of 16 mm.17 This resulted in unstable reentrant circuits migrating across the atrial wall, giving rise to AF.17 When the atrial wall already contains continuous long lines of structural CD and CB, it is likely more vulnerable to reentry circuits to occur or for areas of functional block to connect, thereby reaching the critical length for AF initiation.

Figure 4 Differences in electrophysiology between patients without and with AF. Upper panels: Typical examples of activation maps of a patient without AF and a patient with AF. Middle and lower panels: Patients with AF show more electrophysiology at the pulmonary vein area. Patients with AF particularly show a higher incidence of CB and CDCB, a higher number of CD, CB, and CDCB lines per patients, and also longer lengths of CD (blue lines), CB (red lines), and CDCB lines. Color classes per 10 ms. AF = atrial fibrillation; CB = conduction block; CD = conduction delay; CDCB = continuous conduction delay and block.
The future of AF therapy

Despite the fact that conduction abnormalities are more profound in patients with AF, the clinical categories of AF do not correspond with the amount of conduction disorders at the PVA during SR. In a previous study, we demonstrated a considerable intra-atrial variation in the distribution of conduction disorders across the right atrium and LA, indicating that a low amount of CB at the PVA does not necessarily implicate a low amount of CB at other atrial regions.\(^{18}\)

Hence, either the arrhythmogenic substrate underlying AF is not located at the PVA in these patients or, although CD and CB measured during SR are indicators of structural conduction abnormalities, functional conduction disorders may only be revealed during triggers or AF.

To date, ablation treatment strategies for AF focus primarily on isolation of the pulmonary veins.

However, recurrence rates remain unsatisfactory. Recent studies have shown the complex and heterogeneous etiology
of fractionated potentials, providing a possible explanation of the low success rate of ablation therapy targeting these complex fractionated potentials.

Furthermore, recent studies have revealed that aside from the well-known effects of increased renin-angiotensin-system activation, cardiac endothelin-1 levels may play an important role in AF pathogenesis. Endothelin-1 expression, promoting myocyte hypertrophy and interstitial fibrosis, was increased during AF compared to SR. Particularly, endothelin-1 levels were higher at the LA and in patients with VHD, leading to the presumption that this may play a substantial role in the vulnerability of these patients for AF development. Also, increased endothelin-1 levels are regarded as an important factor in AF persistence. As endothelin-1 production is stretch mediated, atrial regions subjected to greater wall stress may also produce higher levels of endothelin-1, thereby leading to regional differences in conduction abnormalities.

Study limitations

Whether general anesthesia influences conduction is yet to be investigated; however, as a standard anesthetic protocol was used for all patients, equal dispersion of possible effects can be assumed. The number of patients with AF was relatively small; thereby, when comparing patients with persistent and paroxysmal AF, conclusions should be drawn cautiously. In addition, although late gadolinium enhancement- magnetic resonance imaging (LGE-MRI) is a feasible technique to detect cardiac fibrosis, it was logistically and financially not possible to perform LGE-MRI before surgery in these patients.

Conclusion

Intraoperative high-resolution epicardial mapping of the PVA during SR for the first time quantified and characterized different types of conduction abnormalities and demonstrated that the presence of AF episodes is associated with continuous lines of adjacent areas of CD and CB, whereas in patients without AF, lines of CD and CB are shorter and more often separated by areas with normal intra-atrial conduction. Patients with AF showed a 2-fold number of CD, CB, and CDCB lines per patient, which also extended over longer lengths. This study demonstrated a considerable overlap in the amount of conduction abnormalities at the PVA between patients with a history of paroxysmal and persistent AF. Studies quantifying the extensiveness of electrophatology by various parameters, including conduction abnormalities, may contribute to the future development of a more accurate risk estimation of recurrent AF after ablation therapy and will thereby enable more patient-tailored care in the future.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.10.027.

References