Impact of the Arrhythmogenic Potential of Long Lines of Conduction Slowing at the Pulmonary Vein Area

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ABSTRACT

Background: Areas of conduction delay (CD) or block (CB) are associated with higher recurrence rates after ablative therapy for atrial fibrillation (AF). Thus far, there are no reports on 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 (SR) in 268 patients (67±11 (21-84) years) with and without preoperative AF. For each patient, extensiveness of CD (17-29 cm/s) and CB (<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. AF patients showed a higher incidence of continuous CDCB lines (AF: N=37 (76%); No AF: N=132 (60%); *P*=0.046), a two-fold number of lines per patient (CD: 7 (0-30) vs 4 (0-22), *P*<0.001; CB: 3 (0-11) vs 1 (0-12), *P*=0.003; CDCB: 2 (0-6) vs 1 (0-8), *P*=0.004) and a higher incidence of CD or CB lines ≥6 mm and CDCB lines ≥16 mm (*P*=0.011, *P*=0.025, *P*=0.027). Extensiveness of CD, CB, CDCB could not distinguish between the different AF types.

Conclusions: AF patients 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. Between patients with a history of paroxysmal and persistent AF, however, a considerable overlap in the amount of conduction abnormalities at the PVA was observed.

INTRODUCTION

The pulmonary vein area (PVA) has been of particular interest in the pathophysiology of atrial fibrillation (AF) ever since Haïssaguere et al. demonstrated bursts of rapid ectopic beats as triggers for spontaneous AF.[1] Since then, treatment strategies for AF mainly focus on isolation of the pulmonary vein area by endocardial and/or epicardial ablation. Yet, recurrence rates are considerable for both patients with paroxysmal and persistent AF and are likely the result of either reconduction or transition of AF from a trigger driven to a more substrate driven disease.[2] To date, AF recurrences after ablation procedures remain difficult to predict. Yet, fibrosis at the left atrial posterior wall, resulting in conduction delay or block, appears to be associated with higher recurrence rates.[3, 4] It has been suggested that assessment of electropathology - including low voltages, fractionation and conduction abnormalities - during SR at the PVA may facilitate identification of target sites for ablation or can be used to predict AF recurrences after ablative therapy.[5–9]

In several mapping studies, a line of conduction block (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] Based on histological findings in post-mortem 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 ESC guidelines.[13] The goal of the present intraoperative high-resolution epicardial mapping study was therefore to detect and quantify conduction abnormalities at the PVA in a large cohort of patients during sinus rhythm (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 was extracted from electronic patient files.

Mapping procedure

Epicardial high-resolution mapping of the PVA was performed during SR from the sinus transversus along the borders of the right and left pulmonary veins (PVR and PVL) down towards the atrioventricular groove (Figure 1), as previously described in detail.[14] Local activation maps of PVR and PVL 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 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 ms and ≥12 ms between adjacent electrodes.[15, 16]

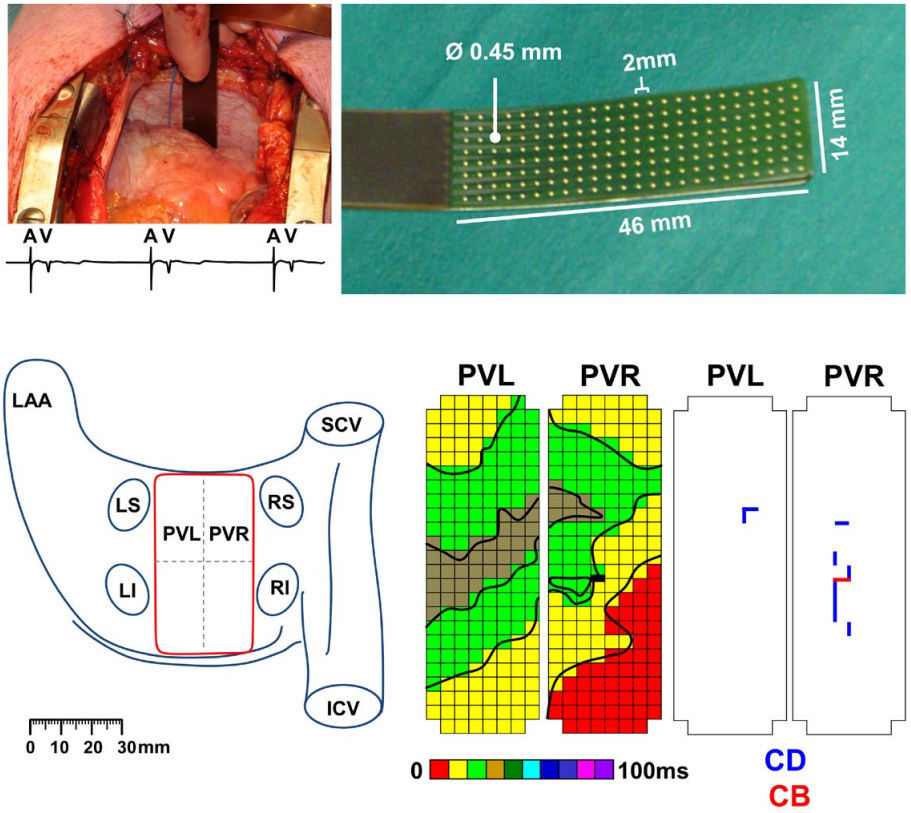

Figure 1. Mapping of the pulmonary vein area.
Top: Mapping of the pulmonary vein area with a 192-electrode array and corresponding electrograms recorded during 5 seconds of SR. Bottom: Schematic view of the pulmonary vein area (PVA) (left) and activation maps and conduction delay/block map (right, CD: blue lines, CB: red lines). A, atrial; V, ventricular; LAA, left atrial appendage; SCV, superior caval vein; ICV, inferior caval vein; PVL, pulmonary veins left; PVR, pulmonary veins right; LS, left superior; LI, left inferior; RS, right superior; RI, right inferior; CD, conduction delay; CB, conduction block.

Statistical analysis

Normally distributed data are described by mean±SD (minimum-maximum). Skewed data are described by median (minimum; interquartile range; maximum) and analyzed by Mann-Whitney U tests. Categorical data are expressed as numbers and percentages and analyzed with χ^2 or Fisher exact test when appropriate. ROC-curves for the difference in CD and CB lengths were constructed and cut-off values were based on sensitivity >50% and 1-specificity <50%. Multivariate regression analysis was performed to identify independent predictors for CD and CB. A *P*-value <0.05 was considered statistically significant.

RESULTS

Study population

Characteristics of the study population (N=268, 196 male (73%), 67±11 (21-84) years, BMI 28±5 (18-55) kg/m^2) are summarized in Table 1. Patients had either IHD (N=157, 59%) or (i) VHD (N=111, 41%; only valvular disease: N=63 (24%)). LA dilation was present in 58 patients (22%) and 49 patients (18%) had a history of AF. Most patients had a normal left ventricular function (N=203, 76%) and used class II antiarrhythmic drugs (AAD) (N=183, 68%).

Incidence of conduction delay and conduction block

Most patients showed lines of CD (N=242, 90%) and CB (N=183, 68%) at the PVA during SR. The number of lines of CD (4 (0-30)) was significantly higher than of CB lines (1 (1-12); *P*<0.001), though the maximum length of CB lines was longer (CD: 6 (2;4-10;20) mm; CB: 8 (2;4-12;44) mm; *P*<0.001, Figure 2). A clear turning point was observed at a length of ≥8 mm, from which point on, the incidence of CB lines exceeded the incidence of CD lines. Most patients also had continuous lines of CDCB (N=169 (63%), median no. 1 (0-6)); maximum length: 14 (4-72) mm.

A longitudinal line of CD or CB running vertically between the left and right pulmonary veins from superior to inferior 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*=0.295), as well as between IHD and (i) VHD patients (*P*=0.503). However, this line was more often observed in patients with LA dilation (N=6 (10%) than patients without LA dilation N=8 (4%), *P*=0.048). As displayed in Table 2, multivariate regression analysis revealed only the presence of AF episodes as an independent predictor for long lines of CD and CB at the PVA; clinical characteristics, including IHD, (i)VHD, LA dilation, gender, BMI, older age and LV dysfunction were not.

Table 1. Patient characteristics

Number of patients	268
Age (years)	67±11 (21–84)
Male	196 (73)
BMI (kg/m^2)	28±5 (18-55)
Underlying heart disease	N (%)
IHD	157 (59)
(i)VHD	111 (41)
Aortic valve stenosis	69 (26)
Aortic valve insufficiency	6 (2)
Mitral valve insufficiency	36 (13)
Left Atrial Dilation >45mm	58 (22)
History of AF	49 (18)
Paroxysmal	38 (14)
Persistent	11 (4)
Left ventricular function	
Normal	203 (76)
Mild dysfunction	52 (19)
Moderate dysfunction	11 (4)
Severe dysfunction	2 (1)
Antiarrhythmic drugs	197 (74)
Class I	2 (1)
Class II	183 (68)
Class III	12 (5)
Class IV	3 (1)

AF = atrial fibrillation; BMI = body mass index; IHD = ischemic heart disease; VHD = valvular heart disease; (i) VHD = ischemic and valvular heart disease.

Association between atrial fibrillation and heterogeneity in conduction

The upper panel of Figure 4 displays typical examples of activation maps and 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 compared to patients without AF, as demonstrated in the middle left panel (AF: N=37, 76%; No AF: N=132, 60%; *P*=0.046). The number of lines of CD, CB and CDCB in patients with AF was approximately two-fold the number observed in patients without AF (CD: 7 (0-30) vs 4 (0-22), *P*<0.001; CB: 3 (0-11) vs 1 (0-12), *P*=0.003; CDCB: 2 (0-6) vs 1 (0-8), *P*=0.004 respectively). As demonstrated in Figure 4, the incidence of both CD and CB lines ≥6 mm was higher in patients with AF compared to patients without AF (CD: 69% (N=34) vs. 49% (N=108), *P*=0.011; CB: 59% (N=29) vs. 42% (N=91), *P*=0.025 respectively). Maximum lengths of continuous CDCB lines in patients with AF ranged from 8 to 72 mm, whereas in patients without AF these lengths ranged from 4 to 42 mm; CDCB lines ≥16 mm occurred more often in patients with AF (N=20 (41%) versus N=50 (25%), *P*=0.027).

Table 2. Analysis of risk factors for CD and CB maximum length in the upper 50th percentile

	CD			CB		
Univariate Analysis	OR	95%CI	*P*	OR	95%CI	*P*
Age (per year)	1.026	0.999-1.053	0.060	1.005	0.982-1.028	0.700
Male gender	0.602	0.339-1.067	0.082	0.961	0.547-1.688	0.891
(i)VHD	1.183	0.696-2.011	0.535	0.797	0.478-1.330	0.386
IHD	0.846	0.497-1.437	0.535	1.254	0.752-2.093	0.386
LA dilation	1.347	0.725-2.503	0.346	0.702	0.373-1.319	0.271
LVF (compared to normal function)						
mild dysfunction	1.390	0.726-2.659	0.320	1.162	0.620-2.179	0.640
moderate dysfunction	1.500	0.423-5.322	0.530	0.697	0.179-2.711	0.603
severe dysfunction	2.625	0.161-42.69	0.498	1.859	0.115-30.17	0.663
AF history	2.082	1.097-3.950	0.025	1.630	0.869-3.057	0.128
Multivariate Analysis						
Age (per year)	1.020	0.993-1.048	0.139			
Male gender						
(i)VHD						
IHD				1.370	0.792-2.370	0.260
LA dilation				0.670	0.347-1.292	0.232
LVF (compared to normal function)						
mild dysfunction						
moderate dysfunction						
severe dysfunction						
AF history	1.872	0.971-3.609	0.061	1.967	1.005-3.851	0.048
Hosmer and Lemeshow	0.808			0.778		

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

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, AF patients 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/m^2 range), gender and type of surgery matched case–control analysis (AF-No AF, 35-35). In addition, patients who developed de novo AF in the early postoperative phase (N=70, 32% of patients without preoperative AF) showed a trend towards more CB lines (*P*=0.055), a higher number of continuous CDCB lines (*P*=0.030) at the PVA and a trend towards a higher incidence of long CB lines >6 mm (*P*=0.073).

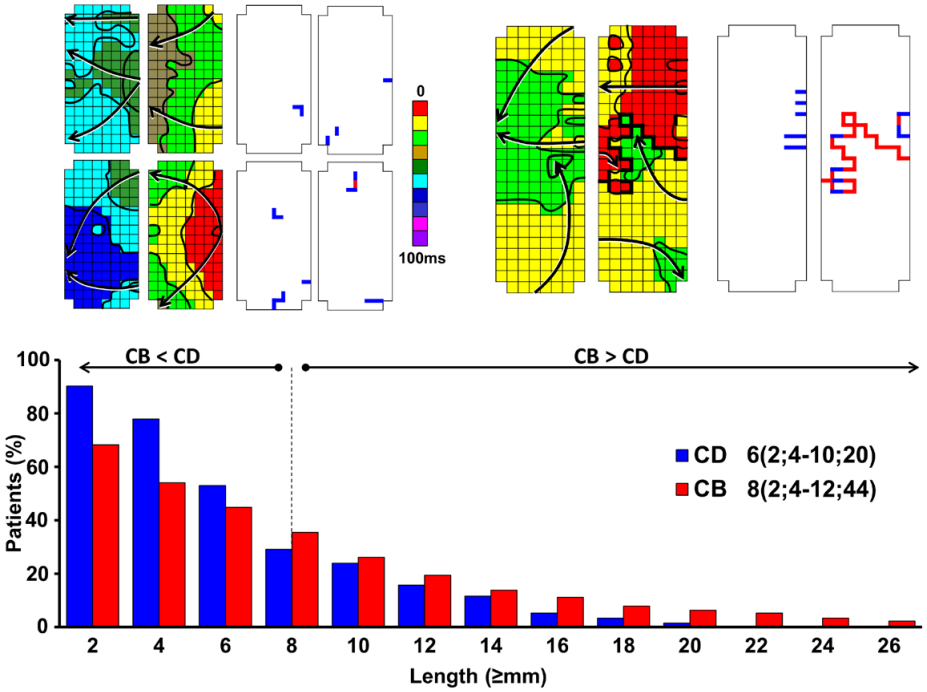

Figure 2. Characteristics of conduction delay and block.
Activation maps showing the typical difference between lines of conduction delay (blue lines) and lines of conduction block (red lines): lines of conduction block occur less frequently, yet extent over longer lengths. A turning point was observed at a length of 8 mm, as displayed in the lower panel. CD, conduction delay; CB, conduction block. Color-classes per 10 ms.

Severity of conduction abnormalities versus clinical atrial fibrillation classification

Figure 5 provides typical examples of PVA activation combined with corresponding CD and CB maps obtained from 2 patients with paroxysmal AF and 2 patients with persistent AF; the amount of conduction abnormalities in the one patient with paroxysmal AF is even higher than in the patient with persistent AF. Figure 5 shows that there is a large inter-individual variation in the amount of conduction abnormalities in both the paroxysmal and persistent AF group. There is also no difference between patients with paroxysmal AF and persistent AF in the number of CD, CB, CDCB lines (P=0.442, P=0.535 and P=0.951). Also, incidences of CD, CB and CDCB were similar (P=0.204, P=0.835 and P=0.708); nor could ROC-curve analyses identify a cut-off value for the length of lines distinguishing patients with persistent AF from paroxysmal AF. Duration of AF history was similar for patients with paroxysmal and persistent AF (P=0.429). Hence, although this is only a small group of patients, the overlap in severity of conduction abnormalities suggests that severity of conduction abnormalities at the PVA does not seem to clearly discriminate patients with paroxysmal AF from patients with persistent AF.

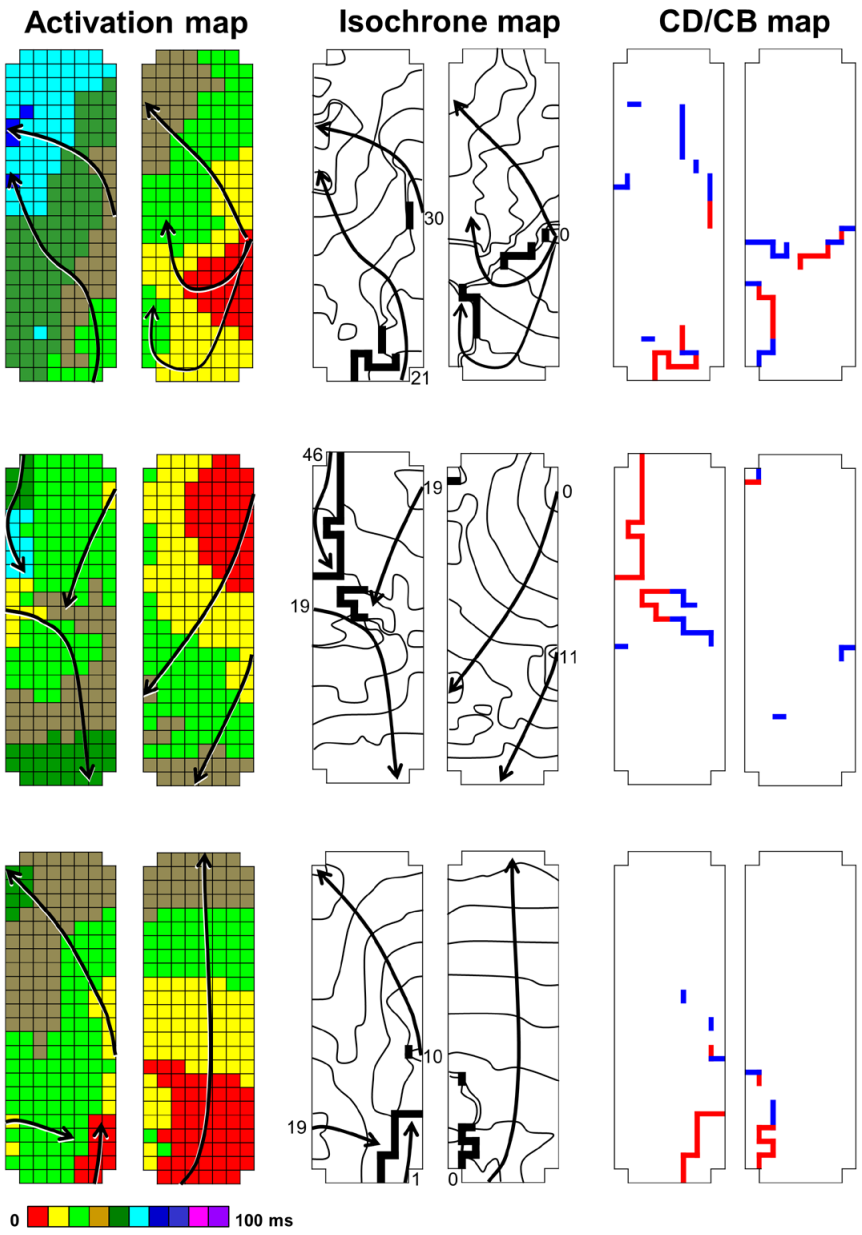

Figure 3. Longitudinal line of conduction delay/ block between the right and left pulmonary veins. Typical examples of activation maps with a line of CD (blue lines), CB (red lines) or CDCB running downwards between the right and left pulmonary veins, varying in its continuity. Corresponding isochrone maps (per 5 ms) and CD/CB maps are shown next to the activation maps. Arrows indicate the main wave trajectory; local activation times are provided next to the arrows. Lightning bolts indicate areas of simultaneous activation. Color-classes per 10 ms.

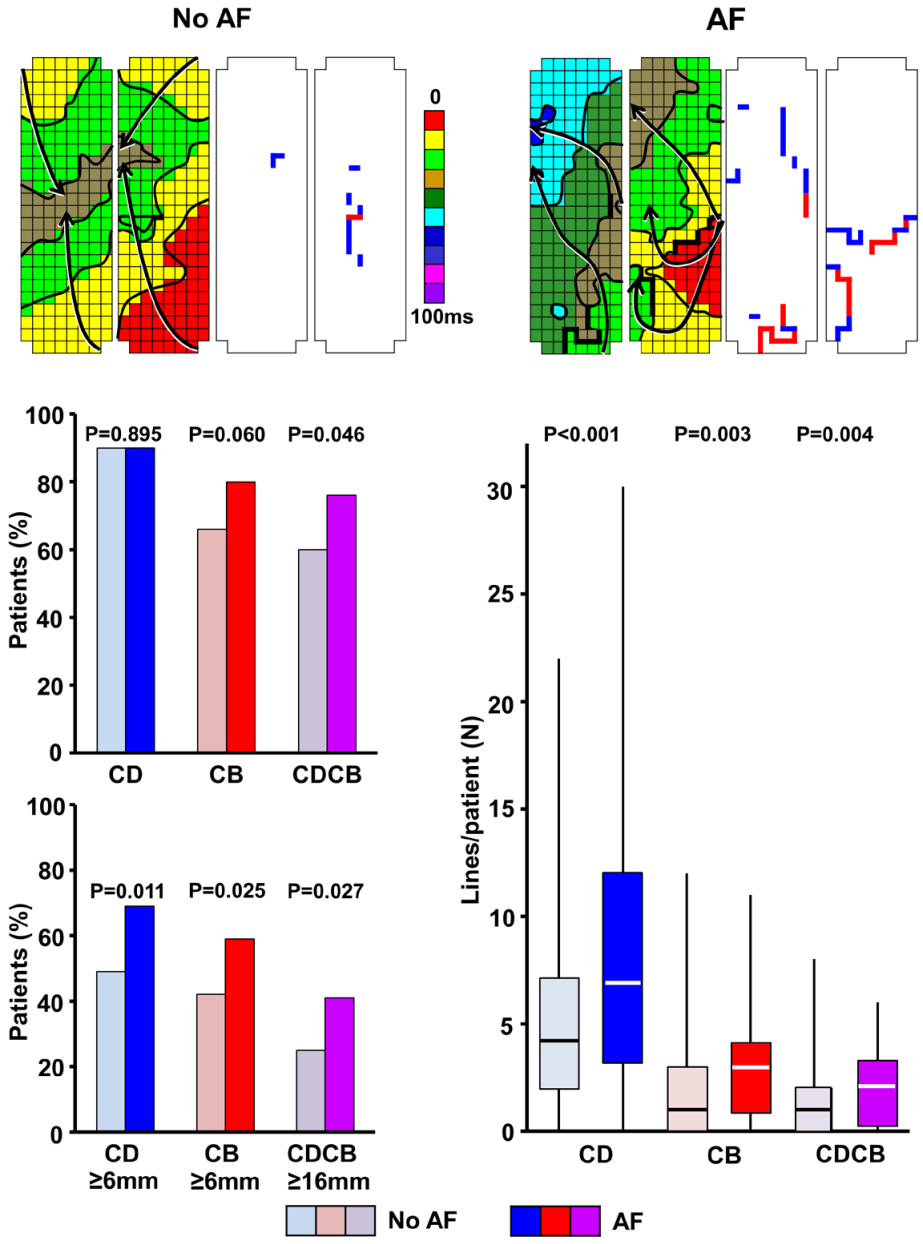

Figure 4. Differences in electropathology between patients without and with atrial fibrillation.
Top: Typical examples of activation maps of a patient without AF and a patient with AF. Patients with AF show more electropathology at the PVA, as displayed in the middle and bottom panels. AF patients particularly show a higher incidence of CB and continuous 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. AF, atrial fibrillation; CD, conduction delay; CB, conduction block; CDCB, continuous conduction delay and block. Color-classes per 10 ms.

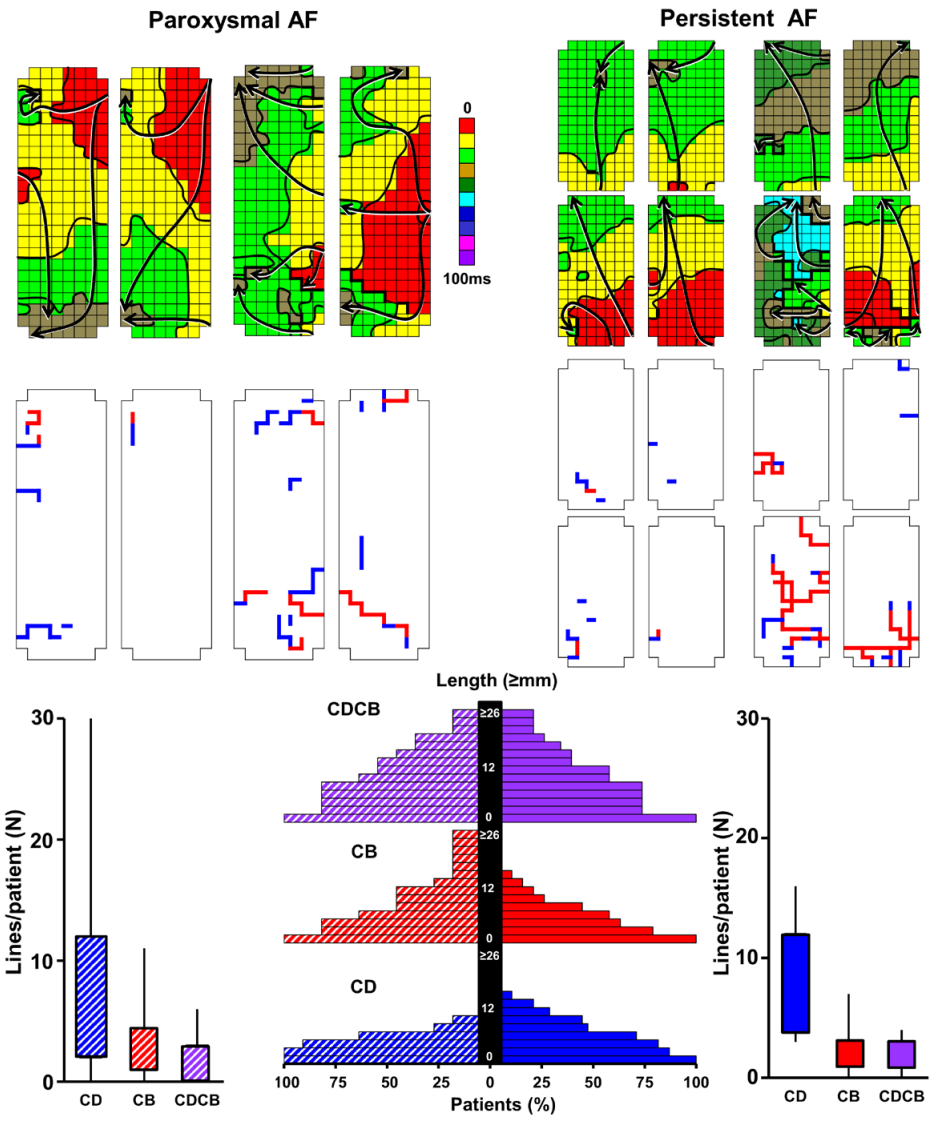

Figure 5. Overlap in electropathology between paroxysmal and persistent atrial fibrillation.
The top left panel shows activation maps of an IHD and VHD patient with paroxysmal AF both diagnosed 3 months prior to surgery. Corresponding CD/CB maps (CD: blue lines, CB: red lines) show a relatively small amount of CD/CB in the first patient, whereas the second patient has a large amount of CD/CB. The top right panel shows activation maps of patients with persistent AF. Both patients underwent mitral valve surgery and were diagnosed with persistent AF respectively 3 and 6 months prior to surgery; both patients underwent electrocardioversion to SR prior to mapping. In this case also the one patient has a relatively small amount of electropathology, whereas the other patient has a large amount of CD/CB. Hence, a considerable overlap in the amount of conduction disorders is observed between paroxysmal and persistent AF, which is also quantified in the bottom panel showing the number of lines per patient and the distribution of lengths of these lines. Color-classes per 10 ms.

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 continuous 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 discriminate between patients with paroxysmal and persistent AF.

Conduction abnormalities at the pulmonary vein area

To our best 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.[10] They observed a vertical line of conduction block (interelectrode 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 towards the septal mitral annulus.[10] This CB line was present in all patients, though varied in its continuity, particularly during pacing from different sites.[10] In a minority of patients, the CB line disappeared completely during pacing.[10] Based on histological findings in postmortem hearts they suggested that the line of CB was caused by an abrupt change in myocardial fiber orientation at the subendocardium.[10]

Roberts-Thomson et al. performed epicardial mapping during SR in 34 patients without AF.[11] They observed a similar line of functional CD, defined as a conduction velocity between 10-20 cm/s, running vertically across the PVA, though only occurring in a minority of 5 patients.[11] In contrast to the findings of Markides et al., during pacing from superior and inferior positions at the PVA the line of CD now appeared in all patients.[11] 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 of the AF patients.[12] However, when pacing from different sites, the CD line again appeared in all patients without AF and the number of CD lines increased in patients with AF to a maximum of 3 vertical lines running parallel to each other across the PVA.[12] Though the findings of Markides et al. and Roberts-Thomson et al. appear to contradict each other, it may be concluded that this line of CD was more evident in AF patients and was, at least in part, functional, as it varied during different pacing conditions. Moreover, besides the vertical line of abnormal conduction, no other CD/CB lines were observed in these studies.

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 seventy percent 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 IHD patients, AF patients 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 <17 cm/s, which is in the range of the CD criteria of Roberts-Thomson et al. Therefore, although our cut-off criteria are slightly more sensitive, the higher incidence of CD/CB cannot be totally explained by differences in cut-off values. Yet, the higher resolution of the mapping system used in current 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 downwards 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 atrial fibrillation

In correspondence to previous studies, increased amounts of CD, CB and CDCB at the PVA were observed in AF patients. In AF patients, a higher incidence of CB, continuous CDCB and an almost two-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 re-entry to occur; this phenomenon was first demonstrated by Ortiz et al. in 7 canine hearts with sterile pericarditis.[17] In this study, the critical role of the length of an area of functional block in the right atrial free wall was observed. In case of stable atrial flutter, a functional CB line of 24 mm was observed, enabling re-entry 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 re-entrant 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 re-entry circuits to occur or for areas of functional block to connect, thereby reaching the critical length for AF initiation.

The future of atrial fibrillation 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 and left atrium, 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, ablative 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 ablative therapy targeting these complex fractionated potentials.[19]

Furthermore, recent studies have revealed that, aside from well-known effects of increased renin-angiotensin-system activation, cardiac endothelin-1 levels may also play an in important role in AF pathogenesis.[20] Endothelin-1 expression, promoting myocyte hypertrophy and interstitial fibrosis, was increased during AF compared to SR.[20] Particularly, endothelin-1 levels were higher at the LA and in patients with VHD, leading to the presumption this may play a substantial role in the vulnerability of these patients for AF development.[20] 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 a regional differences in conduction abnormalities.[20]

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 AF patients was relatively small; thereby, when comparing patients with persistent and paroxysmal AF, conclusions should be drawn cautiously. In addition, although LGE-MRI is a feasible technique to detect cardiac fibrosis, it was logistically and financially not possible to perform LGE-MRI prior to 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 dem-

onstrated that 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. AF patients showed a two-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 of the extensiveness of electropathology by various parameters, including conduction abnormalities, may contribute to the future development of a more accurate risk estimation of recurrent AF after ablative therapy and will thereby enable more patient tailored care in the future.

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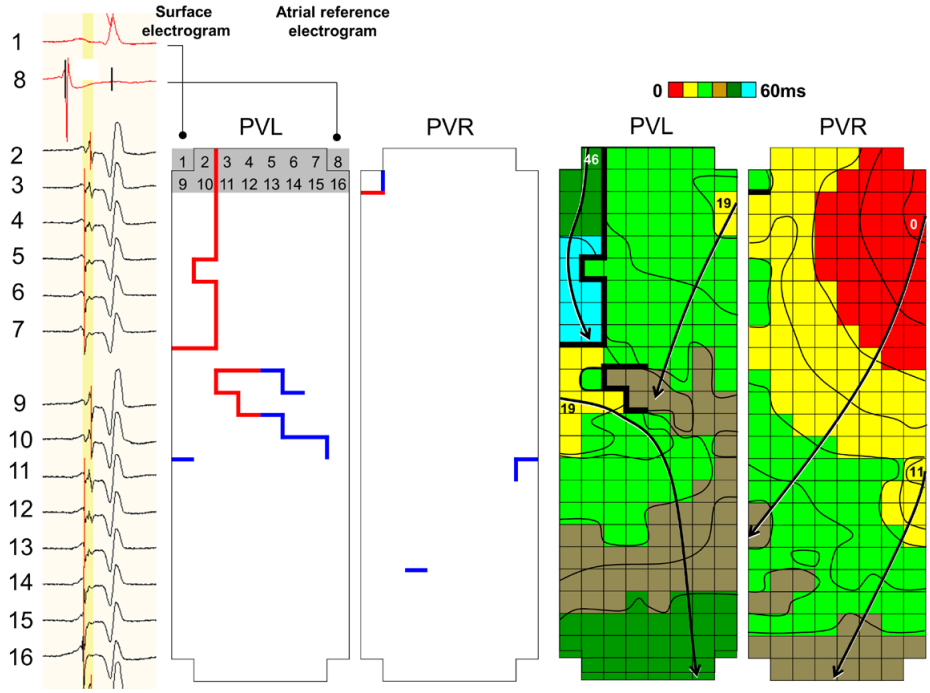
SUPPLEMENTAL MATERIAL CHAPTER 8



Supplemental Figure 1. Identification of conduction abnormalities.
From left to right, first a sample of potentials recorded simultaneously from the first 2 rows of electrodes on the electrode array at the left PVA is shown. The surface electrogram and the atrial reference electrogram are recorded on electrode 1 and 8 respectively. The steepest negative slope is annotated by a red marking and indicates the local activation time. Note the clear difference in the position of the red marking between electrode 2 and 3 and between electrode 10 and 11. Following, the conduction delay and block map is shown, in which the line of conduction block between electrodes 2 and 3 and between electrodes 10 and 11 is visualized by a red line, which is also identifiable by the shift in color-class (per 10 ms) in the activation map and by the crowding of isochrones (per 5 ms) at these areas.