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Direction-dependent conduction abnormalities in the chronically stretched atria

Christopher X. Wong[1†], Bobby John[1,2†], Anthony G. Brooks[1], Sunil T. Chandy[2], Pawel Kuklik[1], Dennis H. Lau[1], Thomas Sullivan[1], Kurt C. Roberts-Thomson[1], and Prashanthan Sanders[1*]

[1]Centre for Heart Rhythm Disorders (CHRD), University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; and [2]Department of Cardiology, Christian Medical College, Vellore, India

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Aims There is increasing evidence of the role direction-dependent conduction plays in the arrhythmogenic interaction between ectopic triggers and abnormal atrial substrates. We thus sought to characterize direction-dependent conduction in chronically stretched atria.

Methods and results Twenty-four patients with chronic atrial stretch due to mitral stenosis and 24 reference patients with left-sided accessory pathways were studied. Multipolar catheters placed at the lateral right atrium, crista terminalis, and coronary sinus (CS) characterized direction-dependent conduction along linear catheters and across the crista terminalis. Bi-atrial electroanatomic maps were created in both sinus rhythm and an alternative wavefront direction by pacing from the distal CS. This allowed an assessment of conduction velocities, electrogram, and voltage characteristics during wavefronts propagating in different directions. While differing wavefront directions caused changes in both chronic atrial stretch and reference patients ($P < 0.001$ for all), these direction-dependent changes were greater in chronic atrial stretch compared with reference patients, who exhibited greater slowing in conduction velocities ($P = 0.09$), prolongation of bi-atrial activation time ($P = 0.04$), increase in number ($P < 0.001$) and length ($P < 0.001$) of lines of conduction block, increase in fractionated electrograms ($P < 0.001$), and decrease in voltage ($P = 0.08$) during left-to-right compared with right-to-left atrial activation. These direction-dependent changes were associated with a greater propensity for chronically stretched atria to develop atrial fibrillation ($P = 0.02$).

Conclusions Atrial remodelling in chronic atrial stretch exacerbates physiological direction-dependent conduction characteristics. Our data suggest that the greater direction-dependent conduction seen in patients with chronic atrial stretch may promote arrhythmogenesis due to ectopic triggers from the left atrium.

Keywords Atrial fibrillation • Direction dependence • Atrial stretch • Atrial substrate • Arrhythmia

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Introduction

The development of atrial fibrillation (AF) involves a complex interplay of triggering activity, perpetuating factors, and underlying substrate. Our understanding of the triggering of ectopic activity and the processes of electrophysiological remodelling that perpetuate AF has been advanced considerably in recent years.[1] Similarly, there is emerging evidence of the significant structural changes present in the atria with conditions known to predispose to AF.

Structural remodelling has been shown in experimental settings to cause considerable directional effects on conduction, over and above that seen in healthy tissue. Spach and co-workers[2,3] observed that ageing leads to greater changes in conduction during differing wavefront directions, with an increase in fractionated and low-voltage electrograms as a result of 'zigzag' propagation. Similarly,

† These authors contributed equally.

* Corresponding author. Centre for Heart Rhythm Disorders (CHRD), Department of Cardiology, Royal Adelaide Hospital, Adelaide, SA 5000, Australia. Tel: +61 882222723; fax: +61 882222722, Email: prash.sanders@adelaide.edu.au

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Verheule *et al.*[4,5] used optical mapping to reveal conduction slowing and heterogeneity present during differing wavefront direction in a canine model of chronic atrial dilatation, but not present in controls.

A recent clinical study has suggested that direction-dependent conduction may explain in part how ectopic triggers create conduction slowing and heterogeneity conducive to arrhythmogenesis.[6] We have previously studied patients with chronic atrial stretch due to mitral stenosis (MS) and observed significant structural remodelling and widespread conduction abnormalities.[7] The goal of the present study was to further characterize the importance of propagation direction to arrhythmogenesis in patients with chronically stretched atria. We hypothesized that conduction changes caused by differing wavefronts might be exacerbated by underlying atrial structural abnormalities.

Methods

Study population

This study comprised 24 patients with rheumatic MS undergoing percutaneous balloon mitral commissurotomy and a reference group of 24 patients with structurally normal hearts undergoing radiofrequency ablation for left-sided accessory pathways. Patients with MS were selected on the basis of having severe MS with a mitral valve area of <1.5 cm^2 with significant symptoms (New York Heart Association class ≥ 2) and mitral valve morphology suitable for percutaneous balloon mitral commissurotomy as determined by the Wilkins criteria (score <10). Patients were excluded if they had any suggestion of other structural heart disease (coronary artery disease or left ventricular dysfunction), or hypertension. No patients in either group had a history of AF or had utilized amiodarone in the previous 6 months. The clinical characteristics and baseline electrophysiological data from the cohort of MS patients included in this study have been presented elsewhere.[7]

All anti-arrhythmic medication was ceased ≥ 5 half-lives prior to the study. All patients provided written informed consent to the study, which was approved by each institutional Clinical Research and Ethics Committee.

Electrophysiological study

Electrophysiological study was performed in the post-absorptive state with sedation utilizing midazolam. In patients with MS, the study protocol was performed before percutaneous balloon mitral commissurotomy, while in the reference group this was done after accessory pathway ablation. The following catheters were positioned for the study protocol: (i) a 10-pole catheter (2-5-2 mm inter-electrode spacing, Daig Electrophysiology, Minnetonka, MN, USA) within the coronary sinus (CS) with the proximal bipole at the CS ostium as determined in the best septal left anterior oblique position; (ii) a 20-pole catheter (2-5-2 mm inter-electrode spacing, Daig Electrophysiology) placed along the lateral right atrium (RA); (iii) a 20-pole 'crista' catheter (1-3-1 mm inter-electrode spacing, Biosense-Webster, Diamond Bar, CA, USA) placed along the crista terminalis with the distal tip superiorly such that the second bipole lay at the junction of the superior vena cava and right atrium, stabilized by a long sheath (CSTA, Daig Electrophysiology) to ensure close apposition to the posterolateral right atrium; and (iv) a roving 10-pole catheter (2-5-2 mm interelectrode spacing, Biosense-Webster) position within the left atrium via a single transseptal puncture. This catheter was stabilized with the use of a long sheath (Preface, Biosense-Webster) and positioned at the left atrial roof.

Electroanatomic mapping

Electroanatomic maps were created of both atria during (i) sinus rhythm and (ii) in an alternative wavefront direction by pacing the distal CS at a rate slightly faster than sinus rhythm (50 ms shorter than sinus cycle length) to ensure constant capture. This provided an assessment of atrial conduction characteristics during wavefront propagating in different directions, as previously described.[6] The electroanatomic mapping system has been previously described in detail; the accuracy of the sensor position has been previously validated and is 0.8 mm and 5°.[8] In brief, the system records the surface electrocardiogram (ECG) and bipolar electrograms filtered at 30–400 Hz from the mapping and reference catheters. Endocardial contact during point acquisition was facilitated by electrogram stability, fluoroscopy, and the catheter icon on the CARTO system. Points were acquired in the auto-freeze mode if the stability criteria in space (≤ 6 mm) and local activation time (≤ 5 ms) were met. Mapping was performed with an equal distribution of points using a fill-threshold of 15 mm. Local activation time was manually annotated to the peak of the largest amplitude deflection on bipolar electrograms; in the presence of double potentials this was annotated at the largest potential. If the bipolar electrogram displayed equivalent steepest positive and negative deflections, the steepest negative deflection on the simultaneously acquired unipolar electrogram was used to annotate the local activation time. Points not conforming to the surface ECG P-wave morphology or $<75\%$ of the maximum voltage of the preceding electrogram, and thus likely to be erroneous, were excluded. Regional conduction velocity and bipolar voltage was analysed as previously described and are detailed in the following text.[9–13]

Direction-dependent conduction velocity

Isochronal activation maps (5 ms intervals) of the atria were created during both sinus rhythm and pacing from the CS. Direction-dependent conduction velocities were determined in the direction of wavefront propagation (least isochronal crowding), as previously described.[10–13] In brief, an approximation of conduction velocity was determined by expressing the distance between two points as a function of the difference in local activation time. Mean direction-dependent conduction velocity for each region was determined by averaging the conduction velocity between five pairs of points, as previously described. To evaluate differences in regional direction-dependent conduction velocities, each atrium was segmented using previously validated offline software.[14] The right atrium was segmented as high- and low-lateral, high- and low-posterior, high- and low-septal, and anterior. The left atrium was segmented as posterior, anterior, septal, inferior, lateral, and roof.

Total bi-atrial activation time and direction-dependent conduction

The effect of conduction directionality on conduction time was assessed by measuring total bi-atrial activation time during sinus rhythm and distal CS pacing. The anisotropy index was calculated by dividing the longest activation time by the shortest activation time.[15–17]

Complex electrograms and lines of conduction block

During sinus rhythm and CS pacing, the proportion of points demonstrating complex electrograms was determined using the following definitions: (i) fractionated signals—complex activity of ≥ 50 ms

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duration; and (ii) double potentials—potentials separated by an isoelectric interval where total electrogram duration was ≥50 ms. A line of double potentials of at least four anatomically contiguous signals was considered to represent a line of conduction block.[18,19]

Direction-dependent bipolar voltage

The bipolar voltage of points during sinus rhythm and CS pacing was exported for analysis. For the purposes of evaluating regional direction-dependent voltage differences, each atrium was segmented as noted in the preceding text.

Direction-dependent conduction times

The effect of conduction directionality on conduction time was assessed along linearly placed catheters at the CS, lateral right atrium, and left atrial roof in proximal–distal direction and distal–proximal direction by pacing the proximal bipole (9,10) and determining the conduction time to the distal bipole (1,2), and vice versa. Conduction time at each site was averaged over 10 beats during stable capture at 600 ms cycle lengths. The anisotropy index was calculated by dividing the longest conduction time by the shortest conduction time.[15–17]

Direction-dependent conduction characteristics at the crista terminalis

To determine the direction dependence of conduction characteristics at the crista terminalis, the number of bipoles on the crista terminalis catheter with discrete double potentials separated by an isoelectric interval or complex fractionated activity of ≥50 ms duration, and the maximum electrogram duration, were determined during sinus rhythm, pacing at 600 ms intervals and extrastimulus from the distal CS.

Inducibility of atrial fibrillation

Vulnerability to AF by single extrastimulus was noted during electrophysiological testing. Atrial fibrillation was defined as irregular atrial activity lasting >30 s.

Statistical analysis

Continuous variables are reported as mean ± standard deviation. Categorical variables are reported as number and percentage. Proportions were compared using Fisher's exact test. Comparisons between means were analysed using paired or unpaired *t*-tests. A mixed effects model was used to assess group (MS and reference) and rhythm (pacing vs. sinus rhythm) main effects, and a group × rhythm interaction. Patient ID and the interaction between patient ID and rhythm/group were modelled as random effects to account for nested data within each patient and repeated measures between rhythms. A mixed effects model was also used to investigate the regional variation in measured parameters, with region (seven right atrial and six left atrial) and rhythm modelled as fixed effects and patient ID as a random effect. Model residuals were visually inspected for normality to ensure an appropriate model fit. Statistical tests were performed using SPSS 16 (SPSS Inc., Chicago, IL, USA) and statistical significance was set at $P < 0.05$.

Results

Baseline details

Baseline patient characteristics are summarized in *Table 1*. Groups were well matched for age, sex, and left ventricular function. Patients with MS had significantly larger left atria ($P < 0.0001$), and increased left atrial pressure ($P < 0.0001$) compared with reference patients.

Electroanatomic mapping

A total of 448 ± 104 points/patient were analysed in the left atrium and right atrium during both sinus rhythm and pacing from the distal CS using electroanatomic mapping.

Direction-dependent conduction velocities

During distal CS pacing, both MS and reference patients demonstrated a slowing in conduction velocity compared with sinus rhythm ($P < 0.001$), with a trend towards a greater slowing in patients with MS ($P = 0.09$, *Figure 1A*). Although there was no significant regional interaction ($P = 0.9$), there was a consistent decrement in regional conduction velocity during distal CS pacing in patients with MS (*Figure 2*).

Total bi-atrial activation times and direction-dependent conduction

During distal CS pacing, both MS and reference patients demonstrated a prolongation in bi-atrial activation time compared with sinus rhythm ($P < 0.001$). This increase was significantly greater in patients with MS compared with reference ($P = 0.04$, *Figure 1B*). Patients with MS also had a greater anisotropy index than reference patients (1.23 ± 0.13 vs. 1.12 ± 0.10, $P < 0.05$).

Table 1 Baseline characteristics

	Mitral stenosis ($n = 24$)	Reference ($n = 24$)	*P* value
Age (years)	31.5 ± 8.6	34.2 ± 11.0	0.3
Male sex (%)	33.3	58.3	0.1
Left atrial size			
Longitudinal (mm)	56.2 ± 5.6	43.7 ± 4.1	<0.0001
Transverse (mm)	50.1 ± 3.9	33.9 ± 4.2	<0.0001
Volume (mL)	77.8 ± 14.3	24.2 ± 5.1	<0.0001
Right atrial size			
Longitudinal (mm)	46.6 ± 2.6	41.5 ± 5.1	<0.0001
Transverse (mm)	26.7 ± 3.1	31.9 ± 3.3	<0.0001
Volume (mL)	18.3 ± 8.9	20.1 ± 8.9	0.5
Left ventricular ejection fraction (%)	62.8 ± 9.4	64.4 ± 8.5	0.3
Left ventricular size			
End-diastolic diameter (mm)	40.5 ± 7.2	44.8 ± 6.9	0.01
End-systolic diameter (mm)	27.8 ± 5.1	28.0 ± 4.5	0.6
Pressures			
Left atrial (mmHg)	24.0 ± 7.6	5.0 ± 4.0	<0.0001
Pulmonary artery (mmHg)	39.3 ± 15.6	18.1 ± 8.4	<0.0001

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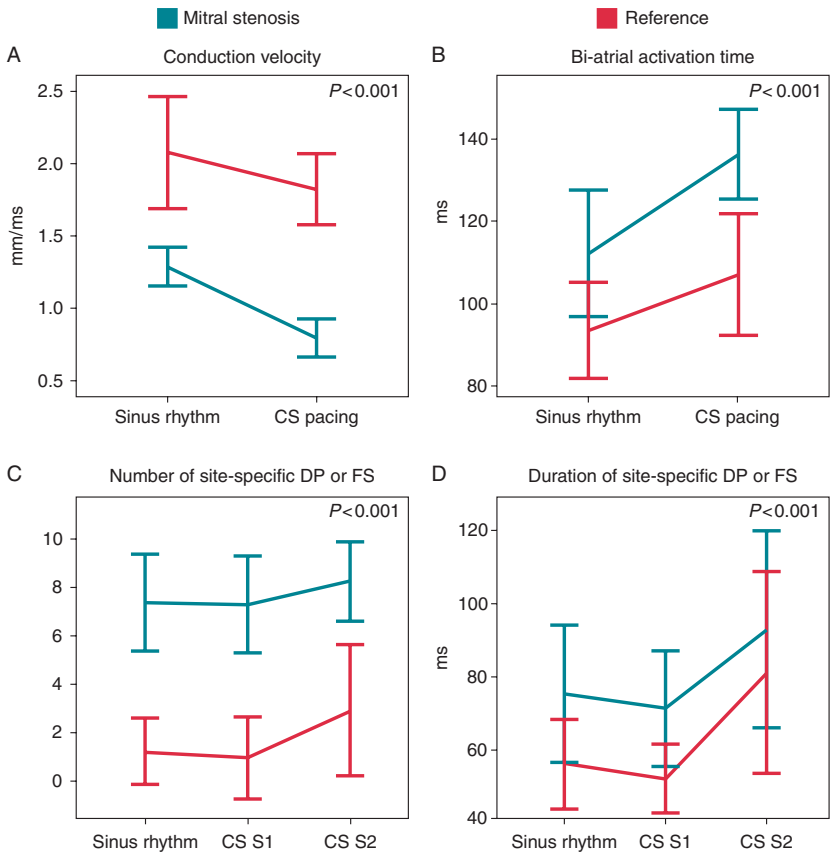

Figure 1 Direction-dependent conduction velocity, bi-atrial activation time, and conduction characteristics at the crista terminalis during sinus rhythm and coronary sinus pacing. The rhythm main effect *P* value is shown for each plot. (*A*) Mean (±SD) direction-dependent conduction velocity (top left). There was a trend to greater direction-dependent slowing in patients with mitral stenosis ($P = 0.09$). (*B*) Mean (±SD) direction-dependent bi-atrial activation time (top right). Patients with mitral stenosis demonstrated a greater prolongation during coronary sinus pacing ($P = 0.04$). (*C* and *D*) Mean (±SD) number (bottom left) and maximum duration (bottom right) of double potentials (DP) or fractionated signals (FS) along the crista terminalis during sinus rhythm, pacing at 600 ms (S1) and with the earliest captured extrastimulus (S2) from the coronary sinus.

Complex electrograms and lines of conduction block

During distal CS pacing, both MS and reference patients demonstrated significantly greater number of double potentials and fractionated signals on electroanatomic mapping compared with sinus rhythm ($P < 0.001$). This increase in number from sinus rhythm to distal CS pacing was significantly greater in patients with MS ($P < 0.001$, *Figure 3A*).

Furthermore, during distal CS pacing both MS and reference patients demonstrated an increase in number and length of lines of conduction block compared with sinus rhythm ($P < 0.001$). This increase in number and length during pacing was significantly greater in patients with MS compared with reference ($P = 0.001$, *Figure 3C* and *D*).

Direction-dependent voltage abnormalities

During distal CS pacing, both MS and reference patients demonstrated a decrease in mean bipolar voltage during pacing compared with sinus rhythm ($P < 0.001$), with a trend towards a greater decrease in patients with MS ($P = 0.08$, *Figure 3B*). This decrement was consistently observed across all regions of both atria ($P = 0.1$; *Figure 2C* and *D*).

Direction-dependent conduction times

The difference in conduction time along the catheters at the lateral right atrium, left atrial roof, and CS according to the direction of pacing (proximal-to-distal or distal-to-proximal) was significantly greater in patients with MS compared with reference patients (11.9 ± 7.7 vs. 2.8 ± 4.5 ms, $P < 0.001$; *Table 2*). Patients with MS also had a greater anisotropy index than reference patients (1.33 ± 0.26 vs. 1.06 ± 0.08, $P < 0.001$; *Table 2*). However, there was no significant interaction between patient group and site of conduction measurement ($P = 0.2$), suggesting a consistently greater degree of direction-dependent conduction differences at these sites in patients with MS.

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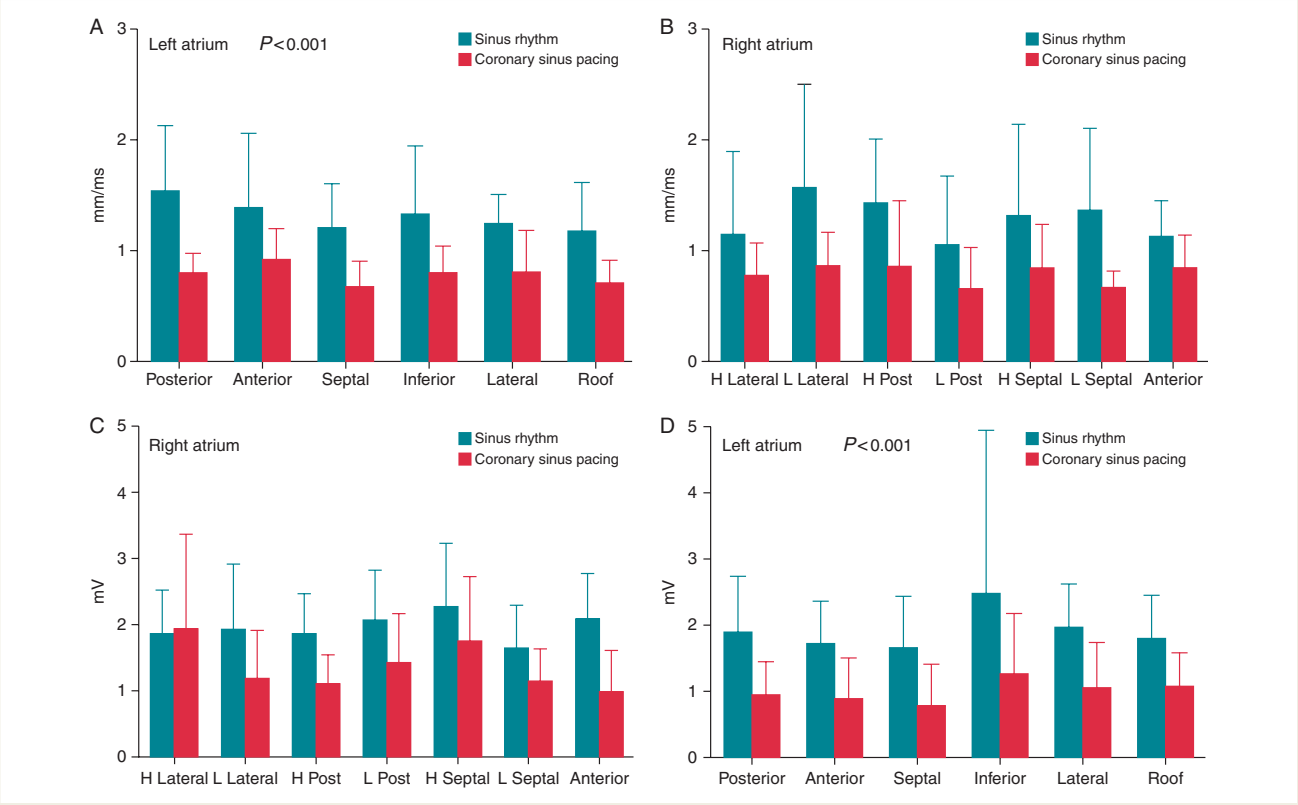

Figure 2 Regional direction-dependent conduction velocities and bipolar voltages. The rhythm main effect *P* value is shown for each analysis. H = high; L = low; Post = posterior. (*A* and *B*) Mean (±SD) conduction velocities of the six left atrial and seven right atrial regions from the electroanatomic maps in mitral stenosis patients during both sinus rhythm and pacing. (*C* and *D*) Mean (±SD) bipolar voltages of the six left atrial and seven right atrial regions from the electroanatomic maps in mitral stenosis patients during both sinus rhythm and pacing.

Direction-dependent conduction characteristics at the crista terminalis

Site-specific conduction abnormalities at the crista terminalis increased in number and duration from sinus rhythm to distal CS pacing and extrastimulus in both MS and reference patients ($P < 0.001$, *Figure 1C* and *D*). While MS patients had greater number and duration of direction-dependent conduction abnormalities than reference patients at all time points ($P < 0.001$), the degree of rhythm-specific number and duration of direction-dependent conduction abnormalities were similar in both MS and reference patients ($P = 0.2$).

Vulnerability for atrial fibrillation

Patients with MS developed AF more frequently during electrophysiological study than reference patients (42.7 vs. 0%, $P = 0.02$).

Discussion

Major findings

This study presents detailed new information on the electrophysiological and electroanatomic conduction abnormalities present during differing wavefront directions in patients with chronically stretched atria compared with a reference cohort. It demonstrates that direction-dependent conduction is accentuated in these patients with diseased substrates compared with reference patients, and this may contribute to arrhythmogenesis. The major findings observed during ectopic wavefront direction consistent with direction-dependent conduction in patients with chronic atrial stretch are as follows:

(1) Slower conduction velocities and longer bi-atrial activation times.
(2) Greater direction-dependent conduction at the crista terminalis and evidence of other lines of conduction block.
(3) An increase in the proportion of complex electrograms and lower bipolar voltage, suggesting zig-zag and circuitous propagation.
(4) Greater anisotropic index on both electrophysiological and electroanatomical mapping.
(5) Greater pronouncement of these direction-dependent conduction abnormalities in patients with chronic atrial stretch compared with reference patients.
(6) Greater susceptibility of patients with chronic atrial stretch for the development of AF.

Thus, the present study suggests that the underlying structural remodelling in patients with chronic atrial stretch due to MS exacerbates direction-dependent conduction, and that this may explain in part the propensity for these patients to develop AF when ectopic triggers from the left atrium initiate differing conduction wavefronts.

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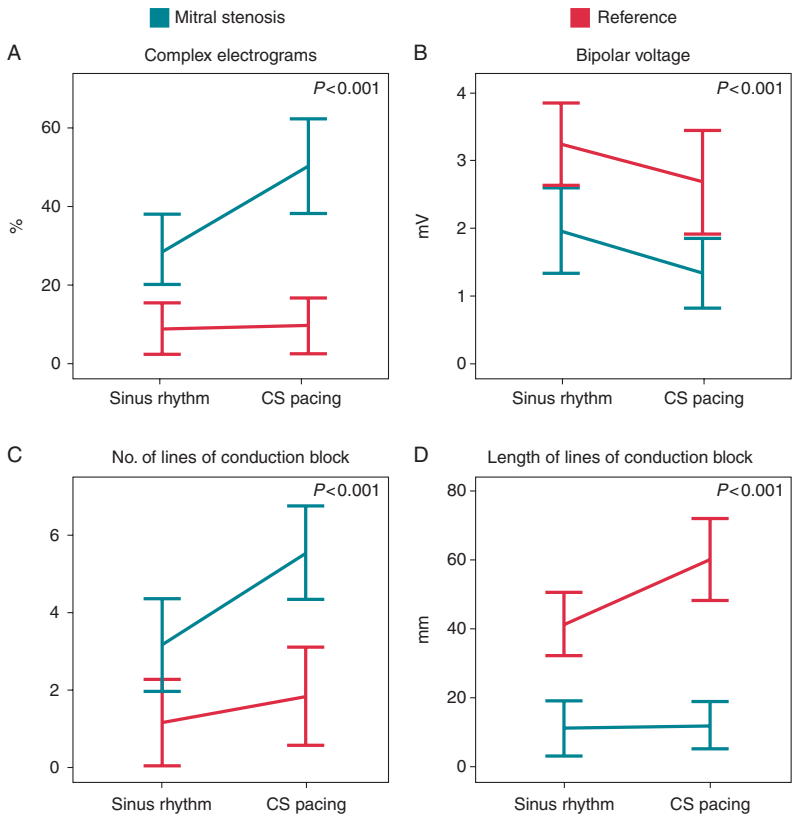

Figure 3 Effect of propagation direction on the proportion of complex electrograms, bipolar voltage, and lines of conduction block during sinus rhythm and coronary sinus pacing. The rhythm main effect *P* value is shown for each plot. (*A*) Mean percentage (±SD) of double potentials and fragmented signals (top left). During coronary sinus pacing, patients with mitral stenosis demonstrated a significantly greater direction-dependent increase in these complex electrograms from sinus rhythm compared with reference patients ($P < 0.001$). (*B*) Mean (±SD) bipolar voltage (top right). During coronary sinus pacing, there was a trend to a greater direction-dependent decrease in bipolar voltage in mitral stenosis compared with reference patients ($P = 0.08$). (*C* and *D*) Mean (±SD) number (bottom left) and length (bottom right) of lines of conduction. During coronary sinus pacing, these parameters increased more in mitral stenosis than reference patients ($P < 0.001$).

Direction-dependent conduction in cardiac myocytes

That structural anisotropy of cardiac tissue plays a critical role in direction-dependent conduction differences was first described by Spach and co-workers.[2,20] These investigators emphasized that while the parallel arrangement of cardiac myocytes could contribute to uniform structural anisotropy, where there is uniform propagation in all directions and smooth extracellular waveforms, 'non-uniform' anisotropy could occur in some regions. In a series of elegant experiments, non-uniform anisotropy, where transverse propagation is interrupted such that adjacent fascicles are excited in a markedly irregular sequence, was shown to be associated with structural separation of muscle bundles due to collagenous septa. These findings are particularly relevant in the atria, however, where a degree of non-uniform anisotropy is found normally. While atrial cardiac myocytes demonstrate tight coupling of gap junctions and connexin proteins between cells in the longitudinal direction, with the majority being primarily located at the ends of myocytes, there is a comparable absence of side-to-side electrical couplings between parallel myocardial fibres.[21] Given the importance of these intercellular communication for conduction,[22] this results in irregular activation of adjacent fibres during propagation transverse to the longitudinal axis of fibres. As a result of this irregular activation, atrial conduction velocity is slowed and electrogram fractionation is observed.[3]

Structural remodelling and directional conduction differences

Experimental studies have demonstrated that continued AF results in a shortening of the effective refractory period and conduction slowing.[23,24] These data described how these perpetuating factors combine to maintain AF, giving rise to the concept that 'AF begets AF'.[24] However, it is increasingly understood that this rate-related remodelling is unlikely to form the underlying substrate which initially predisposes to the development of AF. Indeed, several investigators have now demonstrated that in conditions predisposed to arrhythmia there is 'atrial remodelling of a different sort', where marked interstitial fibrosis was associated with significant conduction heterogeneity.[25–29] Similarly, Verheule *et al.*[4,5] observed profound conduction abnormalities due to

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Table 2 Direction-dependent conduction times and anisotropy index

Site of linearly placed catheter	Mitral stenosis	Reference	*P* value
Direction-dependent conduction			
Lateral right atrium (ms)	7.5 ± 6.8	2.5 ± 2.7	<0.05
Left atrial roof (ms)	12.9 ± 6.8	3.3 ± 4.7	<0.001
Coronary sinus (ms)	14.4 ± 8.5	2.7 ± 5.7	<0.001
Anisotropy index			
Lateral right atrium	1.16 ± 0.21	1.03 ± 0.02	0.01
Left atrial roof	1.31 ± 0.19	1.07 ± 0.07	<0.01
Coronary sinus	1.43 ± 0.32	1.08 ± 0.01	<0.01

structural remodelling in a canine model of mitral regurgitation, and that the differing propagation directions could unmask underlying structural remodelling to promote arrhythmogenesis. Furthermore, Spach *et al.*[20] have described how in ageing human atrial bundles there is an increasing presence of collageneous septa and non-uniform anisotropy which results in variable conduction patterns sensitive to different location and timing of stimuli. More recently, a computational study of atrial tissue utilizing a two-dimensional model of coupled myocytes further expanded on the notion that underlying structural remodelling can exacerbate anisotropic conduction.[30] This study confirmed previous experimental findings linking structural remodelling and direction-dependent conduction abnormalities, finding that increasing microfibrosis reducing side-to-side electrical coupling produced increasing fractionation, decreasing electrogram voltage, and slower conduction velocities. From their data, they also suggested that these parameters could possibly be used to discriminate the substrate and characteristics of fibrosis present. Such characteristics have been utilized for the dynamic identification of arrhythmogenic substrate in the clinical setting.[31]

We have previously shown that the atria in patients with chronic atrial stretch due to MS are characterized by significant structural remodelling.[7] While AF is well known to cause electrical remodelling, the importance of structural remodelling is increasingly being recognized. Atrial stretch is an important contributor to such structural remodelling, not only in patients with MS, but also in patients with hypertension, heart failure, and other conditions predisposing to AF. Such structural remodelling includes atrial enlargement, cellular hypertrophy, dedifferentiation, fibrosis, apoptosis, and myolysis.[32] In the present study, we demonstrated that this underlying structural remodelling is associated with marked direction-dependent conduction abnormalities. Our data showed that patients with chronic atrial stretch demonstrated a greater degree of direction-dependent conduction compared with reference patients as evidenced by differences in conduction velocity, linear conduction times, atrial activation times, electrogram fragmentation, site-specific conduction delays, and bipolar voltages. We posit that these changes are likely to be a result of increasingly complex pathways of propagation spreading in a zig-zag fashion during abnormal propagation direction, as suggested by previous studies.[33] Such direction-dependent conduction which results from structural remodelling has also been observed in the ventricles during myocardial infarction, creating the substrate for re-entry.[34] Conduction asymmetry has also been observed elsewhere in patients with MS and importantly, like other conduction abnormalities, may be attenuated with reversal of atrial stretch.[35,36] Importantly, while we observed some degree of similar findings in reference patients, these were less pronounced than in patients with chronic atrial stretch.[21] Thus, our findings are consistent with previous studies suggesting that the effects of wavefront direction on conduction are greater in diseased substrates characterized by interstitial fibrosis and a loss of side-to-side electrical coupling than they are in healthy tissue.[5]

Implications

The development of AF is a complex interaction between triggers, perpetuators, and substrate. While the importance of ectopic triggers and other factors perpetuating arrhythmia, such as rate-related electrical remodelling, has been well studied, less is known about the interaction between such triggering ectopic activity and disease substrates. Our data highlight that direction-dependent conduction is accentuated by the substrate of chronically stretched atria. Such conduction abnormalities are likely to contribute the initiation of AF episodes by differing wavefronts from ectopic triggers, such as that from the left atrium, in the absence of rate-related remodelling.

Study limitations

While the abnormalities observed in this study are proposed to contribute to the substrate predisposing to AF in patients with chronic atrial stretch, the development of clinical AF is complex and depends not only on substrate but also on other factors such as triggers and perpetuators that were not addressed by this study.[1,7,9–13,24,27,37,38] This study provides detailed electrophysiological and electroanatomic properties of the atria which are consistent with experimental data. However, in the context of this clinical study, we were unable to provide the associated histological analysis which has been elegantly presented elsewhere.[39] Reference patients had left-sided accessory pathways; this condition is associated with an increased risk of developing AF. However, we did not feel it would be appropriate to subject individuals who may have been more ideal reference patients (e.g. healthy volunteers or patients with atrioventricular nodal reentry) to unnecessary invasive procedures. Finally, the direction-dependent changes in chronic atrial stretch due to rheumatic MS may be different in other conditions that lead to chronic atrial stretch.

Conclusion

Structural remodelling of the atria due to chronic atrial stretch is associated with an increase in direction-dependent conduction. In these patients with chronic valvular heart disease free from arrhythmia, our findings highlight the critical interplay between underlying disease substrates and differing wavefront directions, such as that emanating from ectopic triggers, in creating conduction slowing and heterogeneity conducive to the development of AF.

Conflict of interest: K.C.R.-T. has served on the advisory board of St Jude Medical. P.S. reports having served on the advisory board

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of St. Jude Medical, Bard Electrophysiology, Biosense-Webster, Medtronic, Sanofi-Aventis, and Merck. P.S. reports having having received lecture fees from St. Jude Medical, Bard Electrophysiology, Biosense-Webster, Medtronic, and Merck, and research funding from St. Jude Medical, Bard Electrophysiology, Biosense-Webster, and Medtronic.

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References

1. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
2. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. *Circ Res* 1986;**58**:356–71.
3. Spach MS, Dolber PC, Heidlage JF. Influence of the passive anisotropic properties on directional differences in propagation following modification of the sodium conductance in human atrial muscle. A model of reentry based on anisotropic discontinuous propagation. *Circ Res* 1988;**62**:811–32.
4. Verheule S, Wilson E, Everett Tt, Shanbhag S, Golden C, Olgin J. Alterations in atrial electrophysiology and tissue structure in a canine model of chronic atrial dilatation due to mitral regurgitation. *Circulation* 2003;**107**:2615–22.
5. Verheule S, Wilson E, Banthia S, Everett THt, Shanbhag S, Sih HJ *et al.* Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. *Am J Physiol Heart Circ Physiol* 2004;**287**:H634–44.
6. Wong CX, Stiles MK, John B, Brooks AG, Lau DH, Dimitri H *et al.* Direction-dependent conduction in lone atrial fibrillation. *Heart Rhythm* 2010;**7**:1192–9.
7. John B, Stiles MK, Kuklik P, Chandy ST, Young GD, Mackenzie L *et al.* Electrical remodelling of the left and right atria due to rheumatic mitral stenosis. *Eur Heart J* 2008;**29**:2234–43.
8. Gepstein L, Hayam G, Ben-Haim SA. A novel method for nonfluoroscopic catheter-based electroanatomical mapping of the heart. In vitro and in vivo accuracy results. *Circulation* 1997;**95**:1611–22.
9. Roberts-Thomson KC, John B, Worthley SG, Brooks AG, Stiles MK, Lau DH *et al.* Left atrial remodeling in patients with atrial septal defects. *Heart Rhythm* 2009;**6**:1000–6.
10. Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH *et al.* Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the 'second factor'. *J Am Coll Cardiol* 2009;**53**:1182–91.
11. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB *et al.* Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* 2003;**108**:1461–8.
12. Sanders P, Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A *et al.* Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling. *Circulation* 2004;**109**:1514–22.
13. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK *et al.* Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol* 2004;**44**:109–16.
14. Kuklik P, Szumowski L, Zebrowski JJ, Walczak F. The reconstruction, from a set of points, and analysis of the interior surface of the heart chamber. *Physiol.l Meas* 2004;**25**:617–27.
15. Eijsbouts SC, Majidi M, van Zandvoort M, Allessie MA. Effects of acute atrial dilation on heterogeneity in conduction in the isolated rabbit heart. *J Cardiovasc Electrophysiol* 2003;**14**:269–78.
16. Roberts-Thomson KC, Stevenson IH, Kistler PM, Haqqani HM, Goldblatt JC, Sanders P *et al.* Anatomically determined functional conduction delay in the posterior left atrium relationship to structural heart disease. *J Am Coll Cardiol* 2008;**51**:856–62.
17. Roberts-Thomson KC, Stevenson I, Kistler PM, Haqqani HM, Spence SJ, Goldblatt JC *et al.* The role of chronic atrial stretch and atrial fibrillation on posterior left atrial wall conduction. *Heart Rhythm* 2009;**6**:1109–17.
18. Love BA, Collins KK, Walsh EP, Triedman JK. Electroanatomic characterization of conduction barriers in sinus/atrially paced rhythm and association with intra-atrial reentrant tachycardia circuits following congenital heart disease surgery. *J Cardiovasc Electrophysiol* 2001;**12**:17–25.
19. Jais P, Shah DC, Haissaguerre M, Hocini M, Peng JT, Takahashi A *et al.* Mapping and ablation of left atrial flutters. *Circulation* 2000;**101**:2928–34.
20. Spach MS, Miller WT 3rd, Dolber PC, Kootsey JM, Sommer JR, Mosher CE Jr. The functional role of structural complexities in the propagation of depolarization in the atrium of the dog. Cardiac conduction disturbances due to discontinuities of effective axial resistivity. *Circ Res* 1982;**50**:175–91.
21. Saffitz JE, Kanter HL, Green KG, Tolley TK, Beyer EC. Tissue-specific determinants of anisotropic conduction velocity in canine atrial and ventricular myocardium. *Circ Res* 1994;**74**:1065–70.
22. Guerra JM, Everett THt, Lee KW, Wilson E, Olgin JE. Effects of the gap junction modifier rotigaptide (ZP123) on atrial conduction and vulnerability to atrial fibrillation. *Circulation* 2006;**114**:110–8.
23. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* 1995;**91**:1588–95.
24. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;**92**:1954–1968.
25. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999;**100**:87–95.
26. Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Worthington M, Rajendram A *et al.* Short-term hypertension is associated with the development of atrial fibrillation substrate: a study in an ovine hypertensive model. *Heart Rhythm* 2010;**7**:396–404.
27. Lau DH, Mackenzie L, Kelly DJ, Psaltis PJ, Brooks AG, Worthington M *et al.* Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electro-structural correlate in a conscious chronically instrumented ovine model. *Heart Rhythm* 2010;**7**:1282–90.
28. Kistler PM, Sanders P, Dodic M, Spence SJ, Samuel CS, Zhao C *et al.* Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation. *Eur Heart J* 2006;**27**:3045–56.
29. Lau DH, Psaltis PJ, Carbone A, Kelly DJ, Mackenzie L, Worthington M *et al.* Atrial protective effects of n-3 polyunsaturated fatty acids: a long-term study in ovine chronic heart failure. *Heart Rhythm* 2011;**8**:575–582.
30. Jacquemet V, Henriquez CS. Genesis of complex fractionated atrial electrograms in zones of slow conduction: a computer model of microfibrosis. *Heart Rhythm* 2009;**6**:803–10.
31. Strickberger SA, Knight BP, Michaud GF, Pelosi F, Morady F. Mapping and ablation of ventricular tachycardia guided by virtual electrograms using a noncontact, computerized mapping system. *J Am Coll Cardiol* 2000;**35**:414–21.
32. De Jong AM, Maass AH, Oberdorf-Maass SU, Van Veldhuisen DJ, Van Gilst WH, Van Gelder IC. Mechanisms of atrial structural changes caused by stretch occurring before and during early atrial fibrillation. *Cardiovasc Res* 2011;**89**:754–65.
33. Koura T, Hara M, Takeuchi S, Ota K, Okada Y, Miyoshi S *et al.* Anisotropic conduction properties in canine atria analyzed by high-resolution optical mapping: preferential direction of conduction block changes from longitudinal to transverse with increasing age. *Circulation* 2002;**105**:2092–8.
34. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, de Jonge N *et al.* Slow conduction in the infarcted human heart. 'Zigzag' course of activation. *Circulation* 1993;**88**:915–26.
35. Coronel R, Langerveld J, Boersma LV, Wever EF, Bon L, van Dessel PF *et al.* Left atrial pressure reduction for mitral stenosis reverses left atrial direction-dependent conduction abnormalities. *Cardiovasc Res* 2010;**85**:711–8.
36. John B, Stiles MK, Kuklik P, Brooks AG, Chandy ST, Kalman JM *et al.* Reverse remodeling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. *J Am Coll Cardiol* 2010;**55**:1217–26.
37. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G *et al.* Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol* 2011;**57**:1745–51.
38. Lau DH, Psaltis PJ, Mackenzie L, Kelly DJ, Carbone A, Worthington M *et al.* Atrial remodeling in an ovine model of anthracycline-induced nonischemic cardiomyopathy: remodeling of the same sort. *J Cardiovasc Electrophysiol* 2011;**22**:175–82.
39. Unverferth DV, Fertel RH, Unverferth BJ, Leier CV. Atrial fibrillation in mitral stenosis: histologic, hemodynamic and metabolic factors. *Int J Cardiol* 1984;**5**:143–54.

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