Autonomic and surgical substrate modulation of atrial fibrillation
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Chapter 3

Atrial fibrosis and conduction slowing in the left atrial appendage of patients undergoing thoracoscopic surgical pulmonary vein isolation for atrial fibrillation

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Chapter 3

ABSTRACT

Introduction
Atrial fibrosis is an important component of the arrhythmogenic substrate in patients with atrial fibrillation (AF). We studied the effect of interstitial fibrosis on conduction velocity (CV) in the left atrial appendage of patients with AF.

Methods
Thirty-five left atrial appendages were obtained during AF surgery. Preparations were superfused and stimulated at 100 beats per minute. Activation was recorded with optical mapping. Longitudinal CV (CVL), transverse CV (CVT), and activation times (>2 mm distance) were measured. Interstitial collagen was quantified and graded qualitatively. The presence of fibroblasts and myofibroblasts was assessed immunohistochemically.

Results
Mean CVL was 0.55±0.22 m/s, mean CVT was 0.25±0.15 m/s, and the mean activation time was 9.31±5.45 ms. The amount of fibrosis was unrelated to CV or patient characteristics. CVL was higher in left atrial appendages with thick compared with thin interstitial collagen strands (0.77±0.22 versus 0.48±0.19 m/s; p=0.012), which were more frequently present in persistent patients with AF. CVT was not significantly different (p=0.47), but activation time was 14.93±4.12 versus 7.95±4.12 ms in patients with thick versus thin interstitial collagen strands, respectively (p=0.004). Fibroblasts were abundantly present and were associated with the presence of thick interstitial collagen strands (p=0.008). Myofibroblasts were not detected in the left atrial appendage.

Conclusions
In patients with AF, thick interstitial collagen strands are associated with higher CVL and increased activation time. Our observations demonstrate that the severity and structure of local interstitial fibrosis is associated with atrial conduction abnormalities, presenting an arrhythmogenic substrate for atrial re-entry.
INTRODUCTION

In patients with atrial fibrillation (AF), an increased amount of fibrosis is found in the atria. Atrial fibrosis is an important component of the arrhythmogenic substrate in patients with AF. Fibrosis can be arrhythmogenic by increasing the extracellular matrix collagen content, separating atrial myocytes, and increasing the length of activation pathways, or by direct fibroblast–cardiomyocyte coupling resulting in an increased passive electric load to the cardiomyocytes. In particular, myofibroblasts—differentiated fibroblasts that develop during pathological stimuli—contribute to the pathological fibrotic remodeling and couple directly with cardiomyocytes have been described. The changes in fibrosis formation and (myo)fibroblast–cardiomyocyte interaction can facilitate re-entry after a premature beat emanating from the pulmonary veins. The effect of the quantity and the structural organization of fibrosis on atrial conduction abnormalities in man is unknown. Animal experiments show an increase in the heterogeneity of conduction as a result of increased interstitial fibrosis. We studied the amount and organization of interstitial fibrosis and investigated the effect of interstitial fibrosis on conduction characteristics in the left atrial appendages (LAAs) from patients with AF.

METHODS

Thoracoscopic surgery

Thirty-five LAAs were obtained from patients with AF during thoracoscopic surgery, as described before. The patient characteristics are shown in Table. The study was in accordance with the declaration of Helsinki and approved by the Institutional Review Board. All patients gave written informed consent. The LAAs were removed using an endoscopic stapling device (Endo Gia stapler, Tyco Healthcare Group). The tissue samples were transported to the optical mapping setup in 100-mL cooled superfusion fluid (Na+, 155.5 mmol/L; K+, 4.7 mmol/L; Ca2+, 1.45 mmol/L; Mg2+, 0.6 mmol/L; Cl−, 136.6 mmol/L; HCO3−, 27 mmol/L; PO43−, 0.4 mmol/L; glucose, 11.1 mmol/L; and heparin, 1000 IE).

Optical mapping

Preparations were submerged in a tissue bath. The superfusion fluid was kept at a temperature of 36.5°C to 37.5°C and oxygenized with a mixture of 95% O2 and 5% CO2 to maintain a pH of 7.4. All LAAs were stimulated at 100 beats per minute at twice diastolic threshold with a pulse width of 2 ms using an epicardial electrode. In 6 LAAs preparations, short-coupled premature stimuli were applied and optical mapping recordings were made of the shortest conducting S1–S2 interval. The preparation was equilibrated for ≥30 minutes. Di-4-ANEPPS (Tebu Bio) was used as a membrane potential-sensitive fluo-
rescent dye. A contraction uncoupler 2 to 10 mmol/L 2-3-butanedione monoxime (DAM; Sigma-Aldrich, B0753) was added if motion artifacts precluded recording of fluorescent action potentials (n=7). A MiCAM Ultima camera (SciMedia USA Ltd) was used to record epicardial images of an area of 1 cm² with a resolution of 100×100 pixels and a sample time of 0.5 ms. Images were stored using MiCAM Ultima Experiment Manager. A custom-made analysis program based on MATLAB R2006b (The MathWorks, Inc) was used to construct epicardial activation maps. The occurrence of motion artifacts precluded analysis of the repolarization of the LAA.

**Measurement of conduction velocity**

Local activation times (ATs) were determined from the steepest upstrokes of the optical action potential at each pixel. Activation maps were constructed from local ATs. To assess conduction velocity (CV), a line was drawn in the activation map in the direction of the activation wavefront (Figure 1). Subsequently, ATs were plotted against the distance from the stimulation site. This relation allowed for identification of the latency close to the stimulation site and breakthrough of multiple wave fronts at larger distance of the stimulation site. CV was calculated from the slope of the linear portion of the relation between distance to the stimulation site and AT. Local longitudinal CV (CVL) and local transverse

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**Table 1. – Patient Characteristics**

<table>
<thead>
<tr>
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<th>LAA (n=35)</th>
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<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>58±9</td>
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<tr>
<td>Male, n (%)</td>
<td>20 (57)</td>
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<tr>
<td>Years of AF, mean ± SD, years</td>
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<td>Type AF</td>
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<td>Paroxysmal, n (%)</td>
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<tr>
<td>Persistent, n (%)</td>
<td>23 (66)</td>
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<td>CHADSVASc, median, limits</td>
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<td>0-1</td>
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<td>≥2</td>
<td>19 (54)</td>
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<td>Medication</td>
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<tr>
<td>Flecainide, n (%)</td>
<td>11 (31)</td>
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<td>Beta-blockers, n (%)</td>
<td>19 (54)</td>
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<tr>
<td>Sotalol, n (%)</td>
<td>7 (20)</td>
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<tr>
<td>Amiodarone, n (%)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Calcium-antagonists, n (%)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Echocardiographic atrial volume index, mean ± SD, mL/m²*</td>
<td>41±13</td>
</tr>
</tbody>
</table>

* *Atrial volume indexed for the body surface area of the patient determined <6 months before surgery.*

**AF: atrial fibrillation, SD: standard deviation.**
Atrial Fibrosis and Conduction in Patients With AF

CV (CVT) were calculated from the line starting at the point of earliest activation along, which activation spread most rapidly, and the line perpendicular to that respectively, assuming that this represented fiber direction. In addition, to assess the influence of fibrotic barriers on gross transverse conduction delay in the LAA, the AT was measured along an arbitrarily chosen 2 mm line on the activation maps perpendicular to the fiber direction at the site of greatest transverse conduction slowing (Figure 1).

Collagen quantification and organization

After optical mapping, the LAAs were frozen at −80°C with liquid nitrogen. Slides were prepared from the recording area of the LAA. Picrosirius red staining was performed for visualization and quantification of interstitial collagen in 32 LAAs. Three to 5 photographs

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**Figure 1.** – A, Illustration of an activation map with a line drawn in direction of the activation wavefront. In the graph (B) the activation times (ATs) are plotted against the distance from the stimulus site. The latency (L) and potential breakthrough (Br) of multiple wave fronts are identified. The slope of the linear portion of the relation between distance and AT (a) is used to calculate the conduction velocity (CV). C, Typical example of an activation map (1 cm²) of left atrial appendage (LAA). The isochronal lines are 2 ms apart and color scale is in ms; red represents the earliest and purple the latest activation. The graph (D) shows the ATs along the solid and striped lines in the activation map, which are drawn perpendicular to the isochronal lines for longitudinal and transverse conduction, respectively.

*CVL: longitudinal CV, CVT: transverse CV, S: stimulation*
from each section of randomly selected areas were taken of non-overlapping fields at ×10 magnification. The percentage of interstitial collagen of the total tissue (collagen and cardiomyocytes) was determined, after manual exclusion of epicardial, endocardial and perivascular fibrosis.\textsuperscript{11,12} Two independent observers (blinded to the origin of the sections) assessed the width of interstitial collagen strands (ICS) qualitatively (Figure 2). The width of the ICS was assessed and qualified as predominantly containing either thin (±<0.01 mm) or thick fibrotic strands (±≥0.01 mm).

\textbf{Figure 2.} – A, Example of the picrosirius red staining of a left atrial appendage (LAA) with thick interstitial collagen fibers (ICS). The red color represents collagen and the yellow/orange staining represents cardiomyocytes. B, A LAA with thin ICS.
Fibroblast histology

Fibroblasts were identified with anti-vimentin antibody (1:2000, DAKO, M0725) and an indirect peroxidase (3-amino-9-ethylcarbazole peroxidase) was used as the substrate in 27 LAAs. Sections were faintly counterstained with additional hematoxylin staining and 3 to 5 photographs of different, randomly selected areas were taken of non-overlapping fields at ×20 magnification. The density of fibroblasts in the tissue was semiquantitatively assessed optically by 2 independent observers, blinded for section origins, based on the density of fibroblasts scattered throughout the tissue area (excluding microvessels). Two groups were identified (intermediate, ±<30% of tissue area and many, ±>30% of tissue area). All immunohistochemical staining included the use of positive and negative controls with omission of the primary antibody and stained using the same techniques.

Myofibroblast histology

α–smooth muscle actin (α-SMA) antibody’s (1:800, Sigma, A2547) was used for staining of myofibroblasts in 27 LAAs. Because α-SMA stains pericytes and vascular smooth muscle tissue as well, an anti-CD31 antibody staining (1:500, DAKO, M0823) was performed to stain endothelial cells. Cell nuclei were stained with Sytox green (1:1000, Molecular Probes, S-7020). The combination of co-staining of α-SMA and CD31 indicates microvasculature. Isolated α-SMA positive cells in the interstitium were considered to be myofibroblasts. Three to 5 photographs of different areas were taken of non-overlapping fields at ×20 and ×40 magnification in each LAA to identify interstitial myofibroblasts. All immunohistochemical staining included the use of positive and negative controls with omission of the primary antibody and stained using the same techniques.

Statistics

Data are presented as mean ± standard deviation for normally distributed continuous variables or median and empirical limits for non-normally distributed variables. Categorical variables are presented in numbers with percentages. Differences were determined using an independent Student t test for normally distributed data or a Mann–Whitney U test for non-normally distributed data. To assess correlation in normally distributed data, the Pearson was used and in case of nonparametric data Spearman’s was used. p<0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics version 20.
RESULTS

Conduction velocity
Mean CVL was 0.55±0.22 m/s and mean CVT was 0.25±0.15 m/s. Median anisotropy was 3.1 (1.05–13.4). CVL and CVT were not significantly different in patients with paroxysmal or persistent AF (CVL: p=0.25 and CVT: p=0.51). Other patient characteristics were not associated with CVL or CVT. In particular, the use of sodium channel blocking drugs flecainide and amiodarone were not related to CVL (p=0.94) or CVT (p=0.14). Mean AT was 9.31±5.45 ms. AT was not different between patients with paroxysmal or persistent AF (p=0.15). Patient characteristics, including the use of sodium channel blocking drugs flecainide and amiodarone were not associated with AT (p=0.76). A total of 7 LAAs required DAM to reduce motion artifacts. CVL (p=0.47), CVT (p=0.28), and AT (p=0.62) between the LAAs exposed to DAM and other LAAs were similar.

Figure 3. – Effect of a short coupled extrastimulus on conduction. A, activation map (1 cm2) of the left atrial appendage (LAA) during pacing at 600 ms, isochrones at 2 ms. B, Activation map of a short coupled extrastimulus of 250 ms. Over the red line crossing a line of block, apparent conduction velocity (CV) is 0.06 m/s. The black line shows the true direction of the activation wavefront, circumventing the line of block, with an apparent CV of 0.23 m/s. C, Associated optical tracings of action potentials under the red line in (B). The maximum dv/dt (activation times) are marked with circles, which show conduction block along the line.
In the 6 LAAs with premature stimulation (shortest S1–S2 interval; mean 250 ms [200–260 ms]), CVL was 0.44 m/s [0.33–0.56 m/s] at baseline and 0.30 m/s [0.15–0.40 m/s; p=0.046] at shortest S1–S2 interval. CVT was 0.24 m/s [0.46–0.06 m/s] at baseline and 0.16 m/s (0.05–0.25 m/s; p=0.12) at shortest S1–S2 interval. AT increased significantly from 4.73 ms (3.33–6.90 ms) to 8.08 ms (4.35–13.33 ms; p=0.028). Activation maps of the shortest captured S1–S2 interval showed prolonged ATs and clear lines of conduction block, that were absent during stimulation at basic cycle length. Figure 3 shows 2 representative activation maps from the same LAA. In this LAA, the CVL was 0.46 m/s and CVT was 0.27 m/s at baseline. Note that at the short-coupled premature stimuli the activation pattern shows a zig-zag pattern, calculated CVL was 0.15 m/s and CVT was 0.13 m/s, whereas the apparent CV along line C is 0.06 m/s. However, if we follow the activation wavefront (line D), circumventing the area of conduction block, apparent CV along the activation wavefront is 0.23 m/s.

**Interstitial fibrosis**

In 4 LAAs, severe artifacts precluded the semiquantitative analysis of interstitial collagen. In the remaining 28, the collagen content was 16.8±7.5%. There was no significant difference in the percentage of collagen between patients with paroxysmal and persistent AF (p=0.22). CVL and CVT were not associated with the amount of collagen (CVL: p=0.098 and CVT: p=0.91). However, a larger degree of transverse conduction delay was observed in patients with a high amount of collagen (AT: p=0.015). Other clinical characteristics of the patients, including left atrial size were not associated with the interstitial collagen content.

After qualitative assessment, 24 LAAs contained mainly thin ICS, whereas 8 LAAs had a mainly thick ICS. Thick strands were more often found in patients with a high degree of interstitial collagen content (mean 14.0% versus 21.1%; p=0.027). In addition, 7 of the 8 patients with thick ICS had persistent AF. CVL was higher in patients with thick ICS of 0.77±0.22 m/s compared with thin ICS of 0.48±0.19 m/s (p=0.012). CVT was not significantly different between samples with thick ICS and thin ICS (0.24±0.14 m/s compared with 0.22±0.16 m/s; p=0.47; Figure 4). However, AT was significantly higher in patients with thick ICS compared with patients with thin ICS (14.93±6.93 versus 7.95±4.12 ms; p=0.004).

**Fibroblast histology**

Fibroblasts were abundantly present (intermediate, n=10 and many, n=17). A high density of fibroblasts was associated with a high CVL as shown in Figure 5 (intermediate, 0.44±0.11 m/s versus many, 0.71±0.24 m/s; p=0.007). No differences were observed in CVT (intermediate, 0.21±0.09 m/s versus many, 0.30±0.20 m/s; p=0.66) and AT (in-
Figure 4. – Influence of the quantity and quality of fibrosis on conduction velocity (CV) and activation time (AT). A, No correlation between the amount of fibrosis and longitudinal CV (CVL) and transverse CV (CVT), but correlation with AT (p=0.015). B, Qualitative analysis reveals that a higher CVL is observed in samples with thick interstitial collagen fibers (ICSs) between cardiomyocytes (p=0.012). No influence of width of interstitial fibrosis is found on CVT. A longer AT is observed in the patients with thick ICS (p=0.004).
Atrial Fibrosis and Conduction in Patients With AF

Figure 5. – A, Section of a left atrial appendage is shown with intermediate fibroblast staining. B, Section with a high number of fibroblasts. C, High number of fibroblasts was associated with a higher longitudinal CV (CVL; p=0.007), whereas no difference is found in transverse CV (CVT). CV: conduction velocity.

Intermediate, 9.67±3.95 ms versus many, 10.64±6.68 ms; p=0.90). Furthermore, all the specimens with thick ICS also had many fibroblasts (p=0.008).

Myofibroblast histology
The combination of α-SMA and CD31 staining revealed a significant amount of interstitial atrial microvasculature, composed of CD31 positive smooth muscle cells bordered by a rim of α-SMA positive pericytes. Myofibroblasts could not be identified in the LAA (n=27) because no isolated α-SMA positive interstitial cells were present (Figure 6).
**DISCUSSION**

This study shows that the structural local components of fibrosis, specifically the collagenous interstitial matrix, played an important role in modulating CVL and CVT in LAAs obtained from patients undergoing antiarrhythmic surgery for AF. Patients with persistent AF or high degree of interstitial collagen had predominantly thick ICS. This was associated with increased CVL, whereas local CVT was not affected. In spite of increased CVL, more transverse activation delay was present in these preparations and areas of activation block occurred, leading to zig-zag conduction. More pronounced slowing of conduction was observed after short-coupled stimuli. They also induced lines of conduction block, which were absent under baseline stimulation. Fibroblasts were abundantly present in the human LAA, and was associated with thick ICS and a high CVL. No myofibroblasts were detected in the LAAs.

**The role of fibrosis in the arrhythmogenic substrate of AF**

The patients undergoing thoracoscopic surgery for AF had a mean amount of 16.8% fibrosis. In a study investigating patients with AF with or without mitral valve disease 7.6% fibrosis was reported in the LAAs of patients with lone AF and 10.7% in patients with mitral valve disease using similar methods of fibrosis quantification. The patients in our
study are patients with highly symptomatic AF with an indication for surgical treatment. The high amount of fibrosis in our patients might be explained by large atria, older age, and a greater predominance of persistent AF compared with earlier studies. However, no single patient characteristic was associated with the amount of fibrosis in the LAA in our data. In our patients, the organization of interstitial collagen rather than the amount was associated with conduction changes. The contribution of fibrosis to the arrhythmogenic mechanism has been extensively studied in monolayers of cultured myocytes, animal models, and in human ventricular myocardium. In our experiments, we observed the induction of activation delay, caused by propagation of the activation front around inexcitable barriers of collagen. In these LAAs, CV was only modestly affected, possibly because of increased transverse fiber separation. This may result in a heterogeneity of conduction, such as the occurrence of unidirectional conduction block and re-entry, facilitating both the induction and the maintenance of AF. At baseline, pacing some LAAs showed a high anisotropy and activation delay. High anisotropy might facilitate the development of AF because of ectopic foci. In the presence of short-coupled premature stimuli, such as during AF, lines of conduction block developed, and the activation wavefront propagated around this area of block (Figure 3).

CV is also determined by excitability and coupling, mediated by the voltage-gated sodium channels and connexins, respectively. Therefore, we cannot fully exclude that changes in CV between patients might be related to changed function or expression of the voltage-gated sodium channels and (lateralization of) connexins. However, a severe reduction in functional gap junction, as well as a reduced voltage gated sodium channels would result in a reduced CV, whereas we observed an increase in CVL and a unaffected CVT. These findings illustrate the local arrhythmogenic effect of fibrosis in the pathophysiology of AF, but our data do not permit conclusions about the question whether fibrosis is a result or the cause of AF.

The role of fibroblasts in the substrate of AF
A high density of fibroblasts in the LAA was associated with thick ICS, suggesting a local increase of extracellular matrix deposition. The increased extracellular matrix results in a separation between cardiomyocytes and subsequently in an increase in CVL. In in-silico models, fibroblasts have been described to act as passive electric load and to depolarize cardiomyocyte resting membrane potential through gap junctional coupling with myocytes. However, only the myofibroblast, a differentiated form of the fibroblast, connects to cardiomyocytes in in-vitro cell layer models. This connection can result in discontinuous slow conduction and induces spontaneous electric activity. Our observations argue against such a mechanism in the patients that we studied because CVL was increased in the presence of a high density of fibroblasts, which is not expected if reduced direct coupling is present. Alternatively, fibroblasts might exert their influences
on CV by a paracrine mechanism. In cell-cultures, a significant paracrine effect was found on CV, resulting in reduced CV. However, our data showed an increase in CVL in the presence of many fibroblasts, thus it is unlikely that the paracrine influences on CV have a major role in these patients.

**The role of myofibroblasts in the substrate of AF**

In response to pathological stimuli, fibroblasts differentiate into myofibroblasts. In our selected population of patients with symptomatic AF and enlarged atria undergoing thoracoscopic surgery for AF, no myofibroblasts were detected in the LAAs. However, myofibroblasts might play a more prominent role in other, more acute, causes of AF (eg, valvular AF, AF after ischemia, and experimental models) or in the earlier phases of AF. There, the myofibroblasts might contribute to an increase in extracellular matrix and subsequently differentiate to inactive fibrocytes in a later phase of the disease.

**Clinical implications**

The major finding of our study is that in patients with AF, an arrhythmogenic substrate for atrial re-entry is present, caused by the deposition of collagen. It may be conceivable that thick collagen strands anchor rotors that sustain human AF. Identification of the patients with severely affected fibrotic atria might help to guide therapeutic decision-making. Recent studies using noninvasive characterization of the fibrotic phenotype using MRI have shown an inverse relation between the success of catheter ablation for AF and the amount of fibrosis present in the atrium. Although present imaging techniques allow the detection of large areas of fibrosis, future developments might increase the resolution and enable the detection of smaller fibrotic strands.

Fibrosis consists of a dynamic substrate of fibroblasts and extracellular matrix in which collagen turnover is between 3% and 5% per day. A reduction in extracellular matrix secretion by fibroblasts or the prevention of the formation or migration of myofibroblasts, could possibly reduce or alter the deposition of collagen and could be a potential target of upstream therapy. Studies already have already demonstrated a moderate effect of upstream therapy in the setting of primary prevention. However, it is unclear whether secondary prevention can induce reverse remodeling and dissolve this arrhythmogenic substrate.

**Limitations**

Because of the nature of surgery, we could obtain only LAAs, but no left atrial samples without cardioplegia for the electrophysiological experiments. Also, we were not able to obtain issue from healthy control patients. It is unclear whether the LAA myocytes are different from the rest of the atrium. The distribution and amount of interstitial collagen in the LAA probably reflects the fibrotic changes in the left atrium, although no study has
investigated the distribution of fibrotic remodeling throughout the entire human atrium. However, a similar amount of (increased) fibrosis was observed at different parts of the left atrium in patients with AF. Our model of the LAA provides a unique opportunity to study the atrial substrate in patients with AF.

All patients underwent the procedure under general anesthesia and remained on antiarrhythmic drugs. These drugs could have influenced the electrophysiological findings in the LAA. However, no relation of the antiarrhythmic drugs with CV, especially sodium channel blocking drugs was observed.

After administration of DAM to the superfusion medium, a certain degree of motion artifact remained. Although DAM can influence the electrophysiological properties of the LAA, the LAA samples that received DAM were limited (n=7), were evenly distributed among the groups and did not deviate from results of samples without DAM. Because of motion artifacts induced by LAA contraction, determination of action potential characteristics other than the upstroke (ie, repolarization) could not be reliably performed.

CONCLUSIONS

In patients undergoing thoracoscopic surgery for AF, the structural local interstitial components of fibrosis modulate conduction in the LAA. Patients with persistent AF had more thick interstitial fibrotic strands, which was associated with an increased longitudinal CV, consistent with a separation of myocardial fibers. Local transverse conduction was not affected by these fibrotic strands, but activation delay was present because of areas of activation block. Slowing of conduction and increased areas of conduction block were observed after short-coupled stimuli, but were absent under baseline stimulation. Fibroblasts were abundantly present in the human LAA and were associated with thick interstitial fibrotic strands and increased longitudinal conduction. However, myofibroblasts were absent in the human LAAs. Our observations demonstrate that the severity and structure of local interstitial fibrosis is associated with atrial conduction abnormalities, presenting an arrhythmogenic substrate for atrial re-entry.

ACKNOWLEDGMENTS

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Chapter 3

REFERENCES


