



Universiteit
Leiden
The Netherlands

Mapping and ablation of atrial tachyarrhythmias : from signal to substrate

Groot, N.M.S. de

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chapter 5

Conduction Properties of Fibrillation Waves in the Epicardial Plane in Patients with Acute and Chronic Atrial Fibrillation

Natasja MS de Groot

Richard M. Houben, Robert Klautz, Jerry Braun,
Joep LRM Smeets

Maurits A. Allessie, Martin J. Schalij



Abstract

Introduction: The goal of this study was to quantify the degree and spatial distribution of local conduction abnormalities in the epicardial plane during induced atrial fibrillation (acute AF, AAF) in patients with normal atria and during chronic AF (CAF) in patients with valvular heart disease.

Methods: Epicardial mapping during cardiac surgery (244 electrode-array, inter-electrode distance 2.25 mm) of the right atrial free wall was performed during AAF in patients ($n = 20$, age 31 ± 12 yrs) with normal atria and no history of AF and during CAF in patients with valvular disease ($n = 14$, age 64 ± 11 yrs). Episodes of 8 seconds of AF were analyzed. Local conduction velocity during AF was measured by constructing conduction velocity vectors in areas of 3×3 electrodes for assessment of the degree of conduction anisotropy. Local conduction delays were measured in order to determine the average local conduction delay (P50) and the relative inhomogeneity index ($P5-P95/P50$). Conduction block was defined as a local conduction delay > 30 ms, corresponding with a conduction velocity < 7.5 cm/s.

Results: Comparing AAF and CAF patients, CAF was characterized by a lower conduction velocity (AAF: 51 ± 8 cm/s, CAF: 27 ± 8 cm/s, $p < 0.0001$), a higher degree of conduction anisotropy (anisotropy ratio: CAF 1.44 ± 0.17 versus AAF 1.22 ± 0.07 , $p < 0.001$), a larger inhomogeneity in conduction, (relative inhomogeneity index: AAF 0.51 ± 0.15 [0.3-0.8] versus CAF 1.05 ± 0.28 [0.71-1.71], $p < 0.01$) and a higher incidence of conduction block (AAF: $3 \pm 3\%$, CAF: $26 \pm 11\%$, $p < 0.001$). Conduction block occurred more frequently in patients with dilated atria ($r = 0.80$, $p < 0.0001$) and a higher anisotropy ratio ($r = 0.67$, $p < 0.0001$). A higher incidence of epicardial breakthroughs (AAF: 1.49 ± 0.82 /beat, CAF: 0.24 ± 0.25 /beat) was related with a higher incidence of conduction block ($r = 0.81$, $p < 0.001$).

Conclusion: Conduction during CAF is characterized by slowing of conduction, enhanced inhomogeneity in conduction, increased conduction anisotropy and a high incidence of conduction block. The relation between conduction block and epicardial breakthroughs supports the hypothesis that the thin subepicardial layer is damaged in patients with CAF.

Introduction

Propagation of electrical impulses through myocardium is determined by membrane properties, tissue structure and wavefront geometry.¹⁻⁵ Conduction abnormalities play a crucial role in both genesis and perpetuation of tachyarrhythmias and they are the result of functional and/or anatomical properties of the myocardium.⁶

Functionally determined conduction abnormalities can be due to e.g. spatial dispersion in excitability or refractoriness.⁷⁻⁹ Conduction is also affected by interstitial fibrosis and the presence of insulating collagenous septa between atrial muscle bundles giving rise to non-uniform anisotropic conduction.⁹ Non-uniform tissue anisotropy due to interstitial fibrosis is thought to be a major cause of local conduction disturbances resulting in slow conduction, uni-directional conduction block and eventually initiation of reentry.

The likelihood of conduction abnormalities to occur is increased by ageing, dilatation or the presence of structural heart diseases as they alter both functional and anatomical properties of the myocardium.⁹⁻¹⁶

Several studies have demonstrated that patients with intra-atrial conduction abnormalities are more prone to sustained atrial fibrillation (AF).^{6,17} Patterns of activation during acutely induced, self-terminating AF in young patients without structural heart diseases is characterized by a beat-to-beat change in the location of areas of conduction block.¹⁸

These conduction abnormalities were purely functional in nature. It can be expected that conduction in older patients with underlying cardiac diseases and dilated atria is additionally affected by alterations of atrial structure. Therefore, it will be more likely that there are preferential sites for conduction abnormalities to occur. Local conduction abnormalities due to pathological alterations of myocardial tissue might be the key factor by which acutely induced, self-terminating AF progresses into persisting AF.

Recently, Houben et al. proposed that the subepicardial layer plays a leading role in propagation of fibrillation waves.¹⁹ In chapter 4, we suggested that a higher incidence of epicardial breakthrough during chronic AF (CAF) compared to induced atrial fibrillation could be attributed to injury of this subepicardial layer. It could be hypothesized that injury of the subepicardial layer also gives rise to abnormalities in conduction.

This study was performed to quantify the degree and spatial distribution of local conduction abnormalities in the epicardial plane during induced atrial fibrillation (acute AF, AAF) in patients with normal atria and during chronic AF (CAF) in patients with valvular heart disease by performing epicardial high density mapping of the right atrial free wall.

Methods

Study Population

Epicardial mapping studies were performed in 34 patients during open chest surgery. Twenty patients (14 male, age 31 ± 12 yrs) underwent cardiac surgery for interruption of an accessory pathway. All patients had normal sized atria (left atrial diameter 38 ± 6 mm) and no history of valvular disease or coronary artery disease. A more detailed description of this study population has been given previously.¹⁸

Fourteen patients (7 male, age 64 ± 11 [47-80] yr) underwent cardiac surgery for valvular disease (mitral valve: $n = 12$, aortic valve: 2). Coronary artery disease was present in 4 patients. Left atrial dimension and left ventricular ejection fraction estimated by trans-thoracic echocardiography was respectively 60 ± 9 [47-72] mm and 54 ± 12 [35-66] %. The time interval between the first documentation of an AF episode and the moment of cardiac surgery ranged from 1 to 9 years. Anti-arrhythmic drugs were used by 9 patients (β -blocker and digoxin: 5, verapamil: 1, digoxin: 2, cordarone: 1).

Mapping of Atrial Fibrillation

Epicardial recordings were acquired before patients were put on cardiopulmonary bypass.

In the AAF patients, AF was induced by programmed electrical stimulation using electrodes sutured to the right atrial appendage.

The right atrial free wall was mapped with a spoon shaped electrode, containing 244 unipolar electrodes (diameter 0.3 mm, inter-electrode distance 2.25 mm, mapping area 36X36 mm). This device was held manually on the middle of the right atrial free wall.

A silver plate positioned inside the thoracic cavity served as an indifferent electrode.

Unipolar fibrillation electrograms and a surface ECG lead were stored on a computer disk for off-line analysis (amplification: gain 1000, filtering: bandwidth 1-500 Hz, sampling rate: 1KHz, analogue to digital conversion: 12 bits).

Data Analysis

Episodes of 8 seconds were off-line analysed using specialized mapping software. Fibrillation maps were constructed as described in chapter 2. Local activation times were detected automatically by a computer algorithm and edited manually if necessary.

At each electrode, fibrillation intervals were assessed by measuring the time between activations by consecutive fibrillation waves. Median AFCL was determined from all fibrillation intervals recorded by the 244 unipolar electrodes during 8 seconds of AF.

Anisotropy in Conduction

To study the relation between conduction abnormalities and propagation direction, the degree of anisotropy in conduction was determined. In every map, local conduction ve-

locity during AF was measured by constructing conduction velocity vectors in areas of 3x3 electrodes (4.5x4.5 mm, upper panel Figure 1).

An ellipse was fitted through all local conduction velocity vectors obtained during 8 seconds of AF. Conduction in perpendicular directions with respectively the highest and lowest velocity were assigned as 'longitudinal' and 'transverse' conduction velocity. The ratio between the two axes was used to assess the degree of local anisotropy in conduction at each electrode (lower left panel). An anisotropy map was then constructed by plotting the anisotropy ratio at every electrode (lower right panel). The orientation of the lines indicates the direction of the fastest local conduction velocity and the length indicates the local anisotropy ratio.

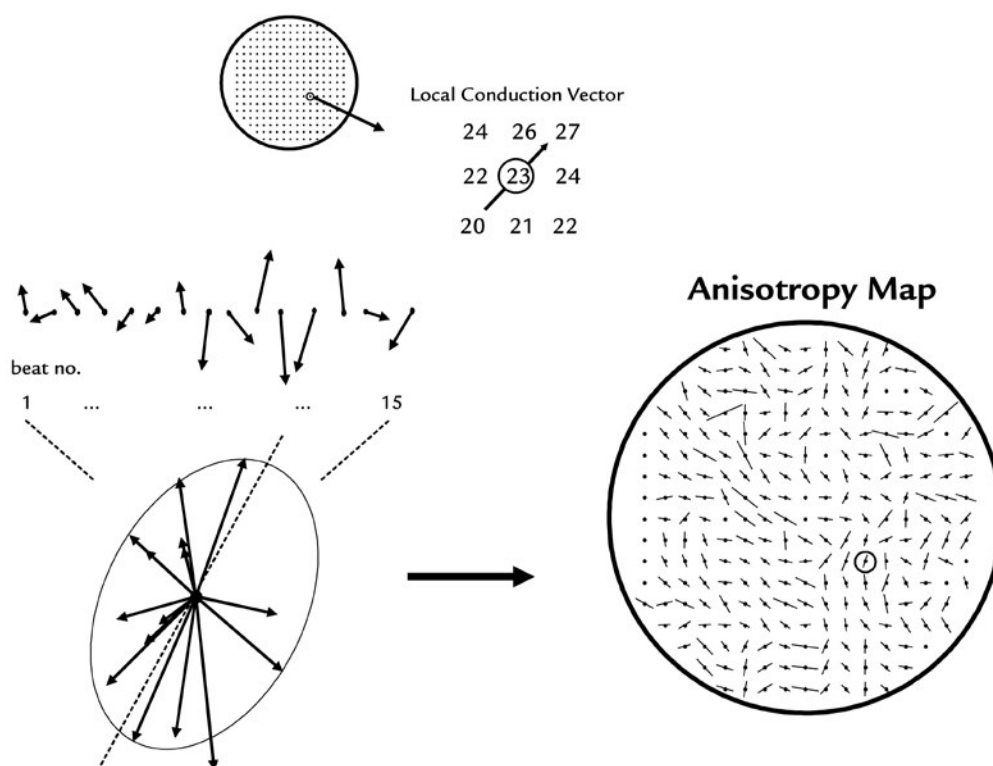


Figure 1.

Method for determination of local anisotropy in conduction.

Upper panel: local conduction velocity vectors were constructed in areas of 3x3 electrodes (4.5x4.5 mm). *Lower left panel:* conduction velocity vectors shown for one electrode during 15 consecutive beats; an ellipse was fitted through all local conduction velocity vectors. Conduction in perpendicular directions with the highest and lowest velocity represents respectively the 'longitudinal' and 'transverse' conduction velocity. The ratio between the 2 axes of the ellipse was used to assess the degree of local anisotropy in conduction. *Lower right panel:* The anisotropy map shows the anisotropy ratio for every electrode. Orientation of the lines indicates the direction of the fastest local conduction velocity and the length of the lines indicate local anisotropy ratio.

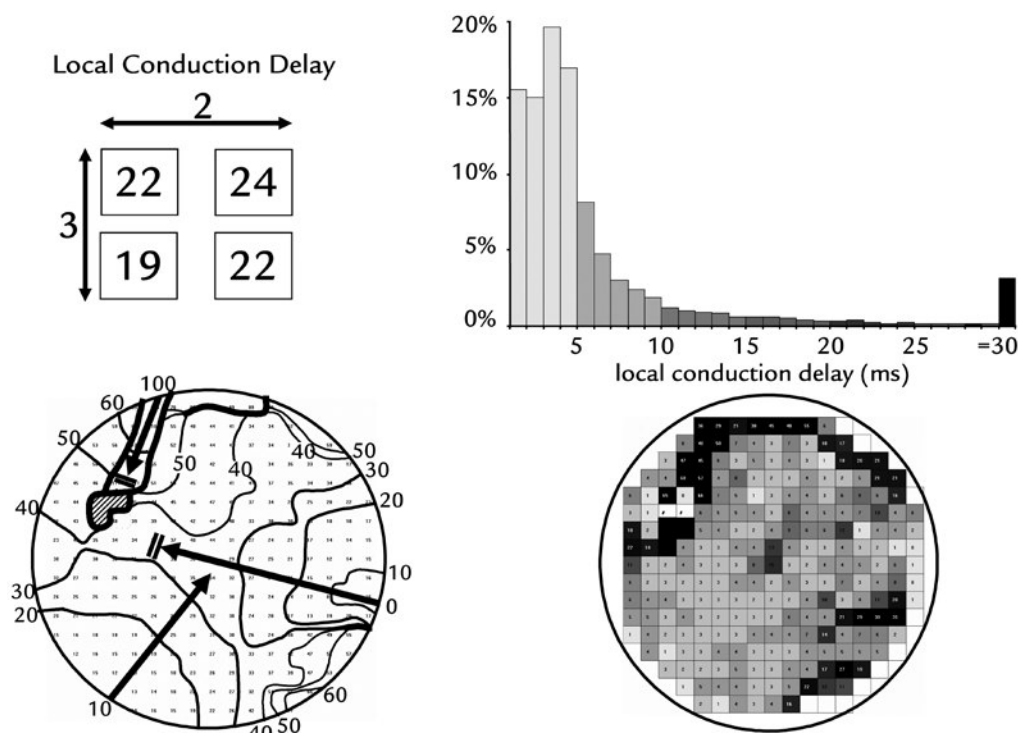


Figure 2.

Measurement of local conduction delay.

Upper panel: The local conduction delay is the difference in activation time between neighboring electrodes and is calculated in areas of 2X2 electrodes. The local conduction delay histogram shows the relative incidence of all conduction delays measured during 8 seconds of AF and was used for determination of the median local conduction delay (P50) and the relative inhomogeneity index (P5-P95/P50).

Lower panel: Example of fibrillation map and corresponding local conduction delay map demonstrating the spatial dispersion in conduction delays.

Local Conduction Delays

Fibrillation maps were used to measure local conduction delays. Local conduction delay is the difference in activation time between neighbouring electrodes and is calculated in areas of 2X2 electrodes (upper left panel Figure 2). All local conduction delays recorded during 8 seconds of AF were plotted in a histogram (Figure 2, upper right panel).

For each patient, the median local conduction delay (P50) and the relative inhomogeneity index (P5-P95/P50) was determined. The relative inhomogeneity index was used to analyse inhomogeneity in conduction independent of conduction velocity.²⁰

Conduction block was defined as a local conduction delay of more than 30 ms, corresponding with a conduction velocity of less than 7.5 cm/s. In order to determine the spatial distribution of conduction abnormalities, local conduction delay maps were constructed for each fibrillation map (Figure 2, lower panel). A local conduction delay map

shows the maximum difference in activation time for each electrode. All local conduction delay maps constructed during 8 seconds of AF were summated for localizing preferential areas of conduction block. For this purpose, the incidence of conduction block at every electrode was determined.

Statistical Analysis

All data are expressed as mean $\pm$ standard deviation, range or percentage. Students T-tests were used to evaluate differences between AAF and CAF patients. Pearson's correlation (r) was used to study relations between different variables. A probability level of 5% was considered statistically significant.

Results

Local Conduction Velocity

The upper panel in Figure 3 shows isochronal maps of the right atrial free wall constructed during AAF (left) and CAF (right). During AAF, two fibrillation waves enter the mapping array from opposite direction and fuse. The area behind the line of conduction block (thick black line) is activated by another wavefront. During CAF, multiple wavelets propagating in various directions are separated by lines of conduction block. In addition, epicardial breakthroughs (*) are present. The lower panel shows the corresponding local conduction velocity maps. The vectors show conduction direction and the magnitude of conduction velocity (length of the vector). Local conduction velocity vectors in the AAF map indicated two main propagation directions. The area where local conduction velocity vectors were absent, represents the line of conduction block. Most local conduction velocity vectors were equal in length, implying that local conduction velocity throughout

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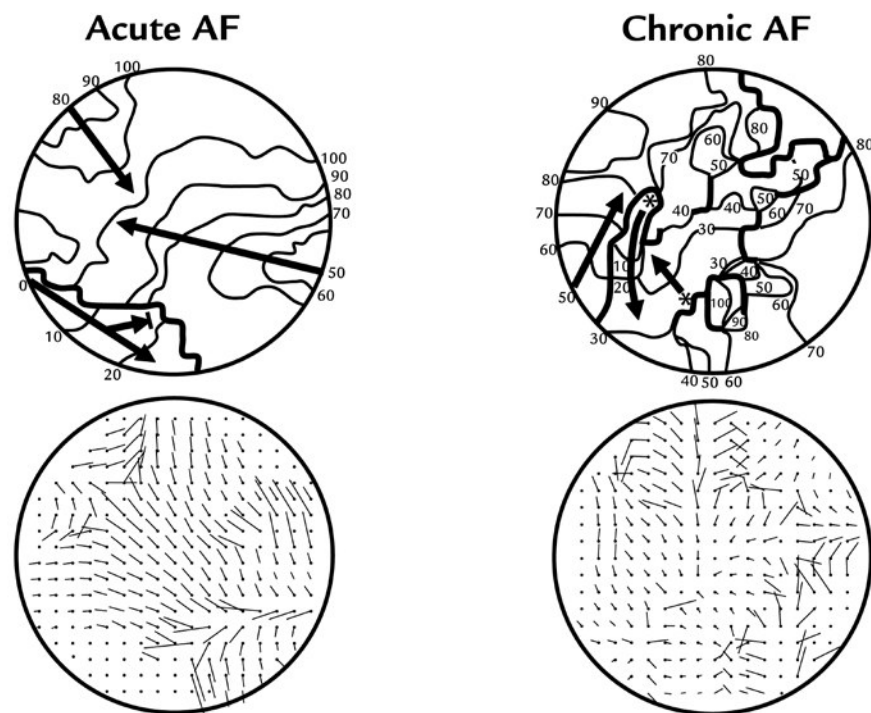


Figure 3.

Upper panel: typical example of isochronal map of the right atrial free wall obtained from one AAF and CAF patient. Lower panel: corresponding local conduction velocity vector map. The vectors show conduction direction and magnitude of conduction velocity (length of the vector).

the mapping area was equivalent. In the CAF map, local conduction velocity was reduced (shorter vectors) and the local propagation directions were more diverse (variable vector directions). Absence of local conduction velocity vectors at several sites is caused by multiple areas of conduction block.

The averaged median conduction velocity during CAF was lower than during AAF (AAF: 51 ± 8 cm/s, CAF: 27 ± 8 cm/s, $p < 0.001$). There was no relation between the averaged median AFCL (AAF: 159 ± 29 (120-232) ms, CAF: 182 ± 26 (151-231) ms) and conduction velocity ($r = -0.16$, $p = 0.4$). In 5 CAF patients who were successfully cardioverted to sinus rhythm, conduction velocity immediately measured after cardioversion was higher (CAF: 37 ± 16 cm/s versus SR: 68 ± 8 cm/s, $p = 0.01$).

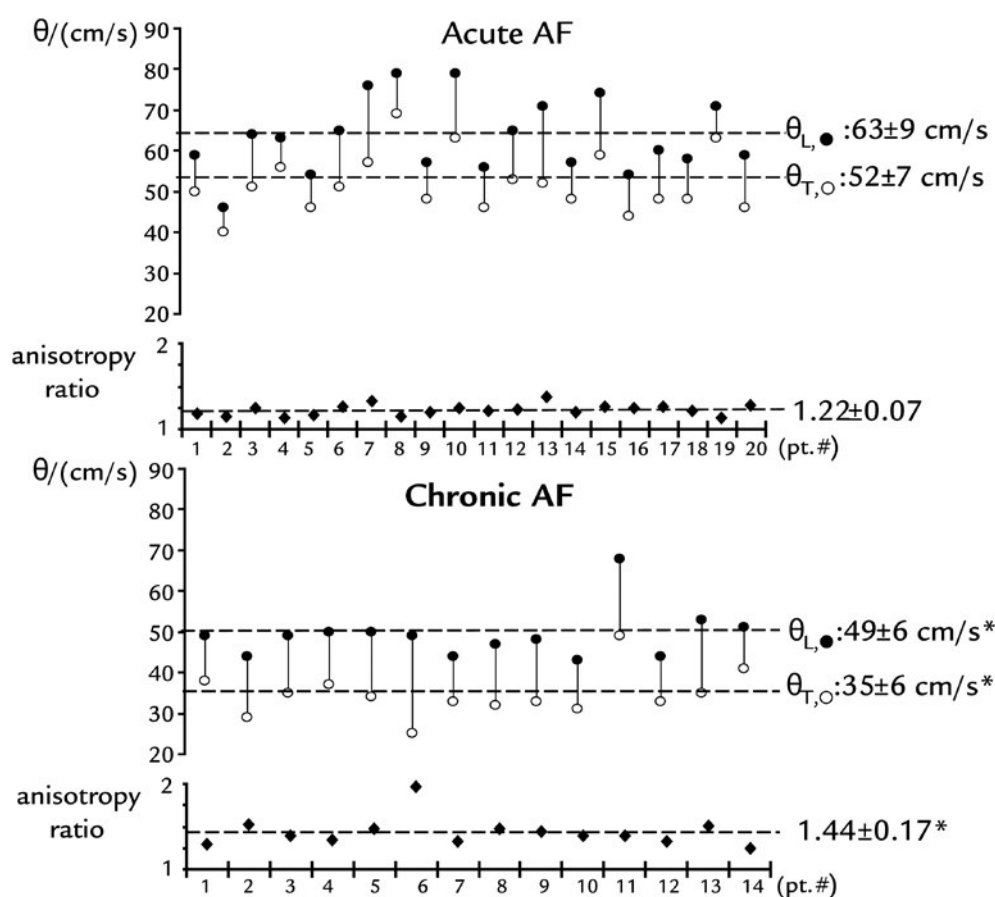


Figure 4.

Longitudinal (●, θ_L) and transverse (○, θ_T) conduction velocity and conduction anisotropy ratio (●) for every AAF (upper panel) and CAF (lower panel) patient separately. During CAF, conduction velocity was lower and the degree of conduction anisotropy was higher * $p < 0.001$

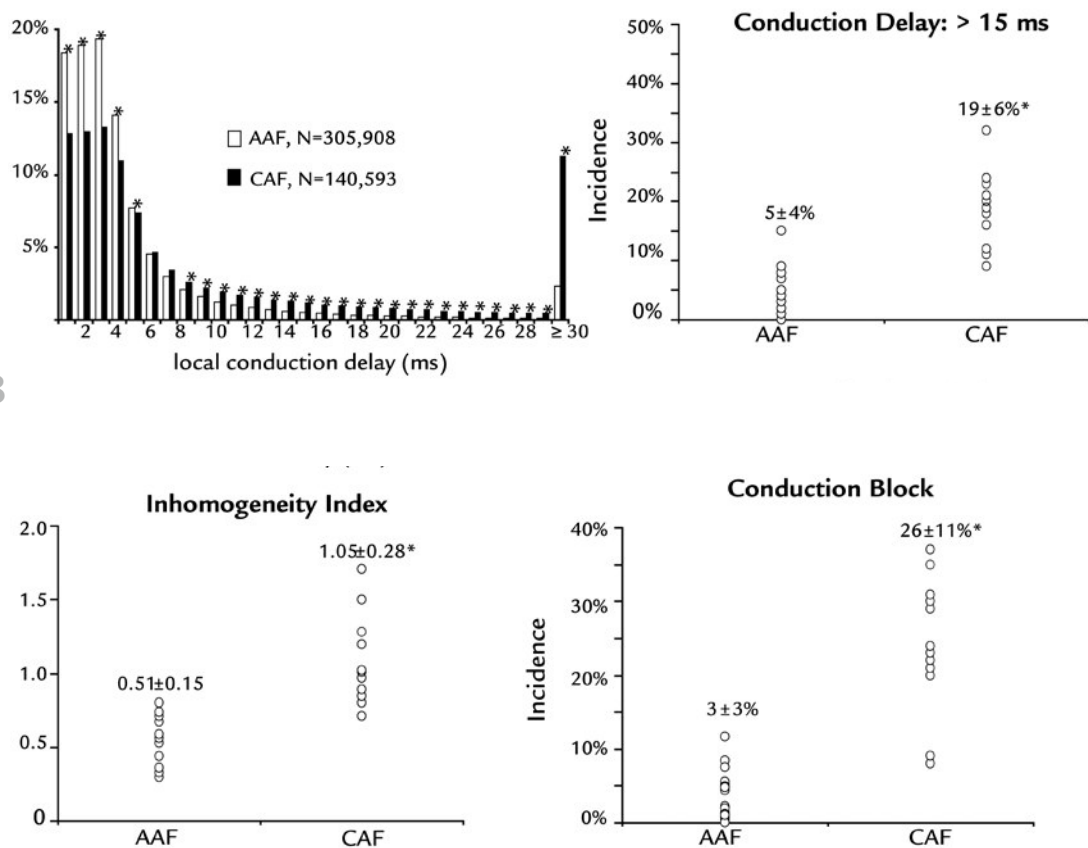


Figure 5.

Upper left panel: relative frequency distribution of local conduction delays over a distance of 2.25 measured during AAF and CAF. Incidence of local conduction delay > 15 ms (upper right panel), inhomogeneity in conduction (lower left panel) and incidence of local conduction block (lower right panel) for every AAF and CAF patient individually.

* $p < 0.001$.

Directional Differences in Conduction Velocity

The 'longitudinal', 'transverse' conduction velocity and corresponding anisotropy ratios for every AAF and CAF patient is demonstrated in Figure 4. Within the AAF and CAF group, there is an inter-individual variation in both longitudinal and 'transverse' conduction velocity. 'Longitudinal' and 'transverse' conduction velocities during CAF were lower than during AAF (AAF: $\theta_L 63 \pm 9$ (46-79) cm/s, $\theta_T 52 \pm 7$ (40-69) cm/s, CAF: $\theta_L 49 \pm 6$ (43-68) cm/s, $\theta_T 35 \pm 7$ (25-49) cm/s, $p = 0.01$). The anisotropy ratio in the AAF patients ranged from 1.13 to 1.37 (1.22 ± 0.07) and in the CAF patients from 1.24 to 1.96 (1.44 ± 0.17). Though there is overlap in the degree of anisotropy between the AAF and CAF patients, there was a higher degree of directional differences in conduction velocity during CAF ($p = 0.001$).

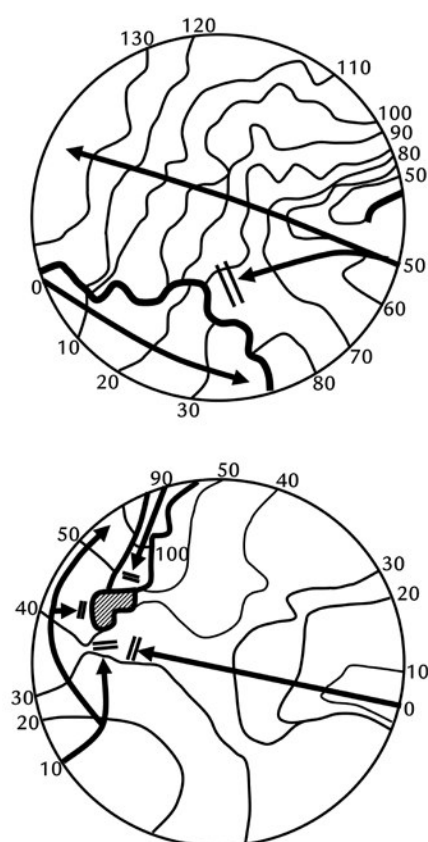


Figure 6.

Isochronal maps of the right atrial free wall demonstrating 2 different types of conduction block occurring during AF: bi-directional conduction block (upper panel) and an island of intra-atrial conduction block (lower panel). Isochrones are drawn at 10 milliseconds intervals, thick lines represent bi-directional conduction block and the dashed area is the island of intra-atrial conduction block. Arrows indicate main activation direction.

Local Conduction Delays

The relative frequency distribution of local conduction delays over a distance of 2.25 measured during AAF ($n = 305,908$) and CAF ($n = 140,593$) is shown in the upper left panel of Figure 5. The averaged local conduction delay was 1.8 ± 0.4 (1.3-2.2) ms/mm during AAF and 3.8 ± 1.1 (2.2-5.8) ms/mm during CAF ($p < 0.001$). There was a higher incidence of local conduction delays > 8 ms in the CAF patients. Slowing of conduction (local conduction delays > 15 ms) in every patient separately is shown in the upper right panel. Comparing AAF and CAF patients, slowing of conduction occurred more frequently during CAF ($19 \pm 5\%$ versus $5 \pm 4\%$, $p < 0.0001$). Also, inhomogeneity in conduction was larger in the CAF patients (AAF: 0.51 ± 0.15 [0.3-0.8] versus CAF: 1.05 ± 0.28 [0.71-1.71], $p < 0.01$).

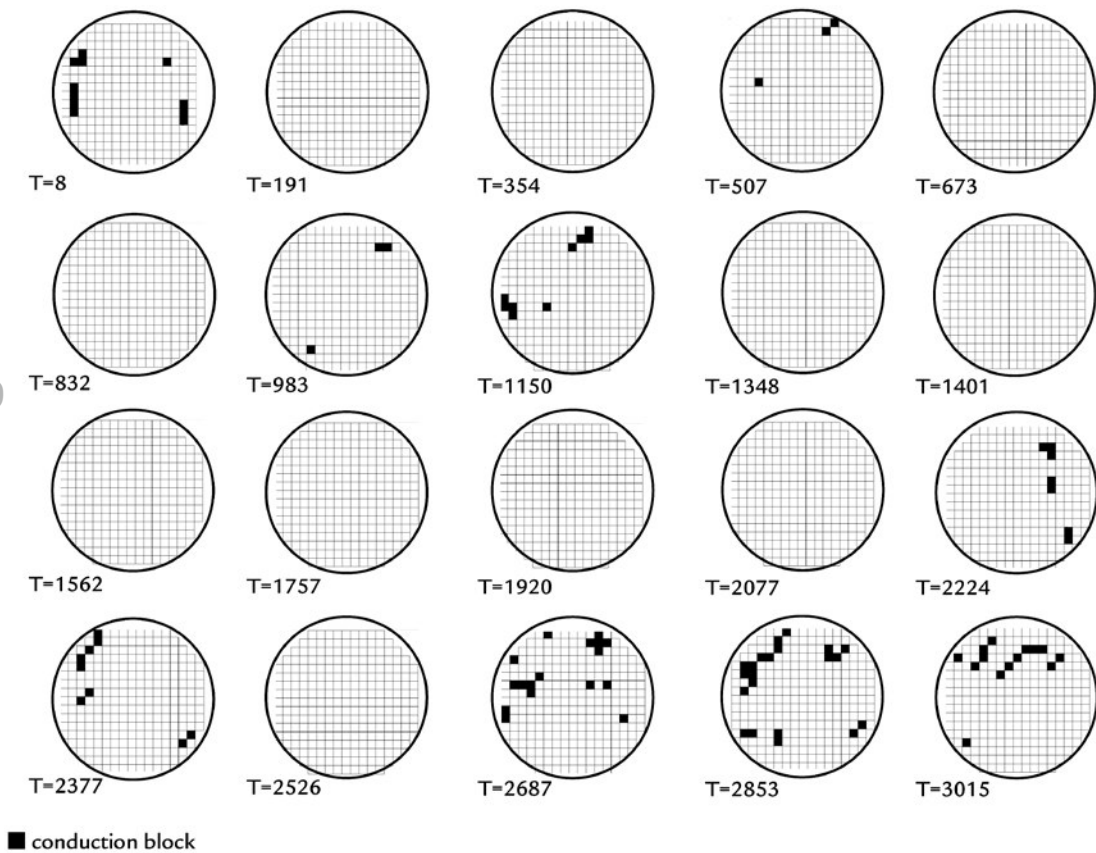


Figure 7.

Twenty consecutive maps demonstrating the location of areas of conduction block (black) in a representative AAF patient.

Fibrillation maps in Figure 6 shows two different types of conduction block observed during AF. In the upper panel, propagation of a fibrillation wave is partly blocked in the lower part of the mapping area. The area behind the line of conduction block is activated by a wavefront propagating from another direction (*bi-directional conduction block*). In the lower panel, a small part of the mapping area is not activated despite the presence of multiple wavefronts approaching this area from different directions (*island of intra-atrial conduction block*). Conduction block, either a bi-directional conduction block or an island of intra-atrial conduction block occurred more frequently during CAF (AAF: $3 \pm 3\%$, CAF: $26 \pm 11\%$, $p < 0.001$, Figure 5, lower right panel).

Conduction block occurred more frequently in patients with dilated atria ($r = 0.80$, $p < 0.001$) and a higher anisotropy ratio ($r = 0.67$, $p < 0.001$). In chapter 2, we determined the incidence of epicardial breakthroughs in this study population (AAF: $1.49 \pm 0.82/$

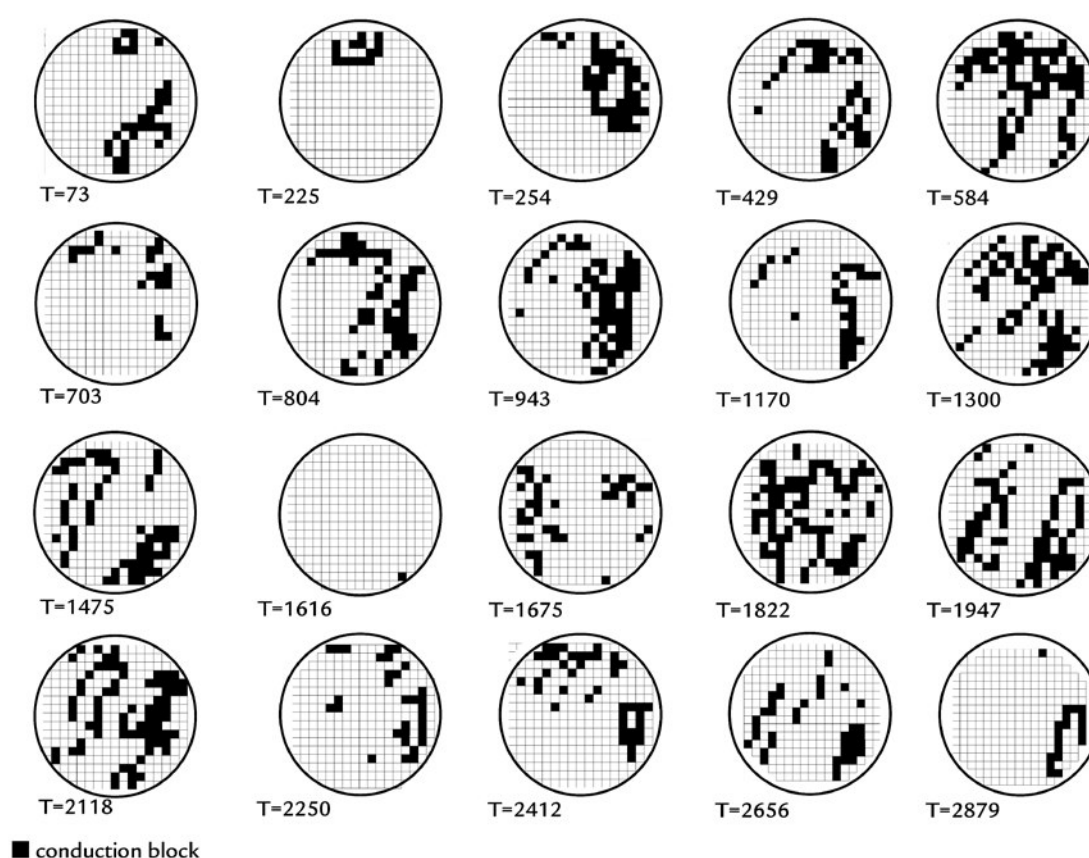


Figure 8.

Twenty consecutive maps demonstrating the location of areas of conduction block (black) in a representative CAF patient.

beat, CAF: $0.24 \pm 0.25/\text{beat}$). Conduction block occurred more frequently in patients with a higher incidence of epicardial breakthroughs ($r = 0.81$, $p < 0.001$).

Representative examples of conduction delays maps of 20 consecutive 'beats' obtained from one representative AAF and CAF patient are demonstrated in respectively Figure 7 and 8. Black colored regions indicate areas where conduction of fibrillation waves was blocked in at least one direction.

In the AAF patient, only small areas of conduction block were present at several sites of the mapping area. In a large number of beats, conduction block did not occur. In previous studies it was demonstrated that the location of areas of conduction block changed from beat-to-beat and that conduction block in the AAF group was functional in nature. In the CAF patient, there were multiple, large areas of conduction block present throughout the mapping area and areas of conduction block were present in most beats.

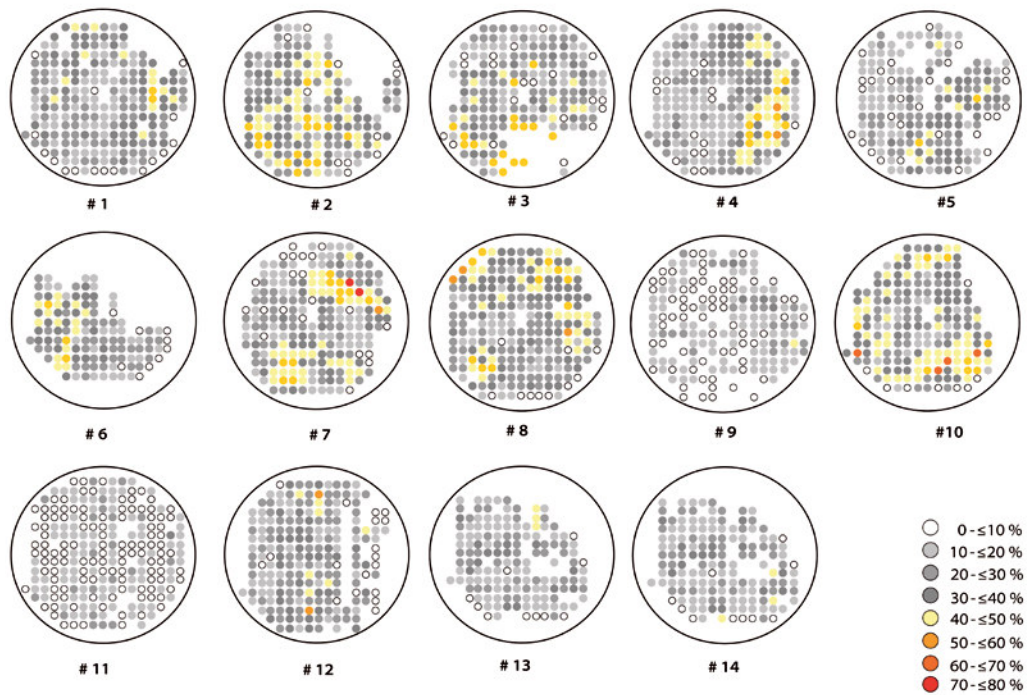


Figure 9.

Spatial distribution of the incidence of conduction block for every CAF patient. Regional differences in the occurrence of conduction block were present in all patients.

In order to study whether there were preferential sites for conduction block to occur in the CAF patients, the incidence of conduction block at every electrode during 8 seconds of AF was determined. The spatial distribution of the incidence of conduction block for every CAF patient is demonstrated in Figure 9. Regional differences in the occurrence of conduction block were found in all patients. In some of them, conduction block at certain areas occurred in 50-80% of the beats.

Discussion

This study evaluated differences in conduction properties of epicardial fibrillation waves at the right atrial free wall during induced AF in young patients with normal sized atria and during CAF in older patients with dilated atria and valvular heart disease. The main finding is that compared to AAF, CAF was characterized by slowing of conduction, enhanced inhomogeneity in conduction, increased conduction anisotropy and a higher incidence of conduction block. The incidence of conduction block was related with left atrial diameter and the degree of conduction anisotropy. Conduction block occurred more frequently in patients with a higher incidence of epicardial breakthroughs.

Inhomogeneity in Conduction

Propagation of an electrical impulse is altered when active or passive cell membrane properties are affected. Conduction velocity of fibrillation waves in the CAF patients was significantly lower than in the AAF patients. Though a decrease in conduction velocity is known to be rate dependent, we did not find a relation between conduction velocity and AFCL. On the contrary, conduction velocity during CAF was reduced in the presence of a relative longer median AFCL compared to the AAF patients.

Impairment of propagation can be the result of reduced membrane excitability caused by a decrease in the inward sodium current. Immediately after cardioversion, there was a considerable increase in conduction velocity, implying that if conduction abnormalities were due to depressed membrane excitability, this reduction in excitability was only transient in nature. Temporary reduction in membrane excitability during AF occurs when the depolarization wave interacts with the refractory tail of another wavelet.

Regional differences in membrane excitability can also be caused by a spatial dispersion in refractoriness and action potential duration, which has shown to be present in patients with AF.^{8,21,22}

Cardiac Anisotropy

Another major determinant of myocardial conduction is cardiac anisotropy.⁹ The degree of anisotropy in this study was related with the incidence of conduction block. Anisotropy of cardiac tissue is the result of cell shape of the cardiomyocyte, connectivity, arrangement and density of inter-cellular connections.²³ Cardiac anisotropy is influenced by ageing and structural heart diseases. In isolated human atrial tissue, anisotropy ratios measured at a microscopic scale as high as 5 were reported.²⁴ However, in the CAF group, directional differences in conduction velocity were low and differences in the degree of anisotropy of atrial tissue at the right atrial free wall between AAF and CAF patients appeared to be moderate. This finding is consistent with a study performed by Verheule et al. who demonstrated that in a canine model of chronic dilatation due to mitral regurgitation, direction-dependent conduction abnormalities were not present in the right atrium, but only

in the left atrium.²⁵ Whether directional differences in conduction velocity are present in the left atrium in humans with AF, needs to be further investigated.

Patients in the CAF group were significantly older than patients in the AAF group. Several researchers have studied the relation between senescence and electro-physiological changes in the atrium.¹⁰⁻¹⁴ Spach demonstrated that ageing was associated with an increase in interstitial fibrosis resulting in a decrease in side-to-side electrical coupling thereby giving rise to non-uniform anisotropy.²⁴ In well-coupled continuous atrial tissue, the preferential direction of conduction block with advancing age changed from longitudinal to transversal due to age-dependent changes in wavefront curvature.¹⁰ In patients, endocardial electro-anatomical mapping studies demonstrated that ageing was associated with regional slowing of conduction and conduction delay.¹⁴ All these electro-physiological changes occurring with ageing contribute to remodeling of tissue anisotropy which affects myocardial conduction and increases the likelihood of conduction abnormalities to occur. Alterations in gap junctional properties have been described patients with AF but the results of these studies are inconsistent and the effect of connexin expression on atrial conduction velocity remains largely unknown.²⁶⁻²⁹

All CAF patients had valvular heart disease. Augmentation of atrial fibrosis, due to chronic stretch caused by valvular heart disease or alterations of atrial structure by AF itself could account for a higher incidence of conduction abnormalities during CAF.^{30,31}

It can be expected that there are preferential sites for conduction abnormalities to occur in patients with atrial fibrosis. In case of the presence of a structural discontinuity and multiple wavelets propagating randomly through the atrium, 50% of the fibrillation waves propagating towards this structural barrier will be blocked. If the incidence of conduction block is higher than 50%, it is most likely that conduction block is structurally determined. If the incidence of conduction block is less than 50%, conduction block is either more functional in nature or there are preferential conduction directions. In several CAF patients, conduction block in some regions occurred in 50-80% of the beats indicating that conduction block was structural determined.

Epicardial Breakthrough and Conduction Block

Conduction block occurred more frequently in patients with a high incidence of epicardial breakthrough of fibrillation waves. In a previous study, we suggested that the higher incidence of epicardial breakthrough observed during CAF compared to AAF could be attributed to injury of the thin subepicardial layer which is assumed to play a leading role in propagation of fibrillation waves.¹⁹ Injury of this subepicardial layer giving rise to structural discontinuities may also be the cause of the increased inhomogeneity in conduction observed in the CAF patients. Abnormalities in conduction of fibrillation waves may result in delayed excitation of the epicardium giving endocardial fibrillation waves the opportunity to activate the epicardial layer. On the other hand, we demonstrated in

chapter 4 that most epicardial breakthroughs prematurely activated the epicardial layer. Conduction block is therefore more likely to occur as atrial tissue at the epicardial surface might still be refractory.

Conclusion

Conduction properties of fibrillation waves at the right atrial free wall during CAF in older patients with dilated atria and valvular heart disease is characterized by slowing of conduction, enhanced inhomogeneity in conduction, increased conduction anisotropy and a high incidence of conduction block. Preferential sites for conduction block observed in some patients with CAF indicate that conduction block is more structural in nature.

The incidence of conduction block was related to left atrial diameter, the degree of anisotropy and the incidence of epicardial breakthroughs. The relation between conduction block and epicardial breakthroughs supports the hypothesis that the thin subepicardial layer is damaged in patients with CAF.

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