Mapping and ablation of atrial tachyarrhythmias : from signal to substrate

Groot, N.M.S. de

chapter 2

Analysis of Temporal Irregularity of Atrial Fibrillation Cycle Length

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Abstract

Introduction: The exact mechanism of irregularities in atrial fibrillation cycle length (AFCL) is unknown. The aim of this study was to elucidate the mechanisms causing beat-to-beat changes in AFCL during induced (acute AF, AAF) and chronic human AF (CAF).

Methods: Epicardial mapping studies of the right atrial free wall were performed during AAF in patients (n = 20, 14 male, age 31 ± 12 yrs) with normal atria and during CAF in patients with valvular heart disease (n = 13, 7 male, age 66 ± 9 yrs.) using a 244 unipolar electrode array (3.6 cm diameter). At the center of the mapping area, AFCL was determined by measuring the time between activation by consecutive fibrillatory waves. Temporal variations in AFCL were related with beat-to-beat changes in conduction of fibrillatory waves.

Results: Median AFCL was longer and more irregular (P95-P5)/P50) during CAF (185 ± 28 ms and 75 ± 24 versus 157 ± 26 ms and 41 ± 17) compared to AAF. Beat-to-beat changes in conduction included no changes in conduction (AAF: 30 ± 18%, CAF: 10 ± 13%, p = 0.001), alterations in conduction velocity/path (CV/CP, AAF: 34 ± 15%, CAF: 15 ± 12%, p = 0.001) changes in conduction direction (CD, AAF: 12 ± 13% versus CAF: 7 ± 4%, p<0.001) or epicardial breakthrough (EB, AAF: 24 ± 22%, CAF: 68 ± 26%, p = 0.001). Comparing AAF and CAF patients, only the degree of irregularities caused by epicardial breakthroughs was higher during CAF (p<0.001). The degree of irregularities in AFCL caused by these changes in conduction is summarized in **Table 1**.

	CV/CP (ms)	CD (ms)	EB (ms)
AAF	23 ± 13	25 ± 20	41 ± 25#
CAF	23 ± 17	15 ± 14	78 ± 14*

p = 0.005, * p = 0.001

Conclusion: Compared to induced AF in young patients with normal atria, median AFCL was longer and more irregular during CAF in older patients with valvular heart disease. Epicardial breakthroughs are major determinants of irregularities in AFCL and the larger beat-to-beat variation in fibrillation intervals found during CAF is caused by the higher incidence of epicardial breakthroughs.

Introduction

Atrial fibrillation (AF) is characterized by a continuously changing activation pattern of the atria. Moe et al. were the first to demonstrate that AF could be the result of two different mechanisms.[1] In their experiments they showed that AF could either depend on a single, frequently discharging focus (*fibrillatory conduction*) or that AF persisted independently from the site where it was initiated *(true fibrillation)*. Moe postulated that true fibrillation was due to the presence of multiple, randomly re-entering wavelets.[2] This concept was later experimentally confirmed by Allessie et al. who demonstrated that, in isolated canine atria, the atria were excited by multiple, wandering wavelets.[3]

However, more recent, experimental and clinical mapping studies not only have been supportive for multiple wavelets as a mechanism of AF but also for a 'focal mechanism' perpetuating AF.[4-7]

Atrial fibrillation cycle length (AFCL) is the interval between successive fibrillatory waves and can only be measured directly from epicardial or endocardial atrial electrograms. AFCL is determined by the action potential duration (refractory period) and an excitable period.

If AF depends on a high frequency *regular* discharging source, irregularities in fibrillation intervals occur when parts of the atria can not follow the high activation rate in a 1:1 manner.[5] Irregularities in AFCL can also be due to variation in the excitation frequency of the source itself. If AF is perpetuated by multiple wavelets, irregularities in AFCL can be explained by beat-to-beat changes in conduction of the fibrillatory waves. This results in variable excitable periods due to different "waiting times" for the next fibrillatory wave to arrive. Variation in the excitable period in turn gives rise to interval dependent changes in conduction velocity and action potential duration.[8]

The goal of this study was to elucidate the mechanism of beat-to-beat changes in AFCL during induced (acute AF, AAF) and chronic AF (CAF) in patients. The relative contribution of beat-to-beat changes in conduction properties of fibrillatory waves like changes in conduction velocity, activation pathway, direction of propagation or epicardial breakthroughs to the irregularities in fibrillation intervals was explored. Furthermore, we assessed to which degree irregularities in AFCL could be explained by beat-to-beat changes in conduction within a mapping area of 3.6X3.6 cm.

Methods

Study Population

Recordings of AAF were obtained from patients (n = 20, 14 male, age 31 ± 12 years) during open chest surgery for interruption of an accessory pathway. All patients had normal sized atria (left atrial diameter 38 ± 6 mm) and no history of valvular or coronary artery disease. A more detailed description of this study population has been given previously.[9] Recordings of CAF were obtained from patients (n = 13, 7 male, age 66 ± 9 years) with valvular disease undergoing cardiac surgery. All CAF patients had AF lasting for more than one year. Left atrial diameter estimated by M-mode echocardiography was 58 ± 9 mm. Characteristics of the CAF patients are summarized in Table 1.

Epicardial Mapping of Atrial Fibrillation

In AAF patients, AF was induced by programmed electrical stimulation using electrodes sutured to the right atrial appendage. Mapping studies were performed before cannulation for cardiopulmonary bypass. In all patients, the right atrial free wall was studied with a spoon shaped electrode containing 244 unipolar electrodes (diameter 0.3 mm, inter-electrode distance of 2.25 mm). A silver disc positioned inside the thoracic cavity served as indifferent electrode. Signals were amplified (gain 1000), filtered (bandwidth 1-500 Hz), and digitized (sampling rate 1 KHz). All electrograms were stored on a computer disk together with a surface electrocardiogram.

Data Analysis

Time periods of 8 seconds were analyzed off-line using a custom-made software package. Local activation times at each electrode were detected by marking the steepest negative deflection of unipolar fibrillation potentials. Time windows were constructed to create fibrillation maps. A time window started at the moment that a fibrillatory wave entered the mapping area and ended when all electrodes were activated one time.
When successive time windows were not separated by a electrically silent period, an overlapping time window was constructed. In this case, a new time window was created each time when the next entering fibrillatory wave activated one of the electrodes for a second time. A total of 56 ± 17 and 37 ± 19 fibrillation maps per patient were constructed during respectively AAF and CAF.

Measurement of Fibrillation Intervals

At each electrode, fibrillation intervals were determined by measuring the time between activations by consecutive fibrillatory waves (Figure 1). All fibrillation intervals in the entire mapping area measured during 8 seconds of AF were used to construct an interval histogram. The irregularity in fibrillation intervals was expressed as (95th - 5th)/50th percentile of the AFCL histogram.

Table 1. **Characteristics of the CAF patients.**

pt no.	age	gender	valvular disease	AAD	LAD (mm)	LVEF (%)	AF duration	CVP (mmHg)
1	68	M	MVD	digoxin	69	37	>2 yrs	15
2	68	M	MVD	digoxin	72	42	>9 yrs	15
3	75	M	MVD	sotalol, digoxin	59	56	> 1 yr	NA
4	54	M	MVD	sotalol, digoxin	56	59	> 1 yr	8
5	69	F	MVD	verapamil+digoxin	47	35	> 5 yrs	16
6	55	F	MVD	–	70	64	> 6 yrs	10
7	67	F	MVD	sotalol, digoxin	49	66	> 1 yr	NA
8	76	F	MVD	sotalol, digoxin	60	64	> 2 yrs	20
9	66	F	AOD	sotalol, digoxin	62	59	> 1 yr	12
10	53	M	MVD	–	58	62	> 1 yr	8
11	58	M	MVD	Sotalol			> 1 yr	NA
12	80	M	AOD	–	56	47	> 1 yr	5
13	70	F	MVD	verapamil+digoxin	42	32	> 2 yr	NA
mean/sd	66 ± 9				58 ± 9	52 ± 13		12 ± 5

M: male, F: female, MVD: mitral valve disease. AOD: aortic valve disease,
AAD: anti-arrhythmic drugs, LAD: left atrial diameter, LVEF: left ventricular ejection fraction, CVP = central venous pressure measured during cardiac surgery.

Discrimination between True Short Fibrillation Intervals and Long Double Potentials

Short fibrillation intervals may cause interpretation difficulties. A short interval between consecutive fibrillation potentials can either be a *true* short fibrillation interval or it can be the result of dissociation of fibrillatory waves under the recording electrode (*false* short fibrillation interval).

Two consecutive fibrillation potentials are considered to represent a *true* short fibrillation interval when none of the potentials are far-field potentials and each potential is the result of propagation of a fibrillatory wave under the recording electrode. An example of a true short fibrillation interval is given in the upper panel of Figure 2. Two fibrillation potentials with an interval as short as 75 ms were recorded at the site indicated by an asterix. In the first isochronal map (left), this site was activated by a fibrillatory wave 22 ms after entering the mapping area. The next fibrillatory wave appeared after 90 ms and activated the mapping site at t = 97 ms (second isochronal map). Hence, the successive activation of this site by fibrillatory waves resulted in a true local fibrillation interval of 75 ms. In each case, the potential was generated by a passing wavefront which conducted to the surrounding tissue.

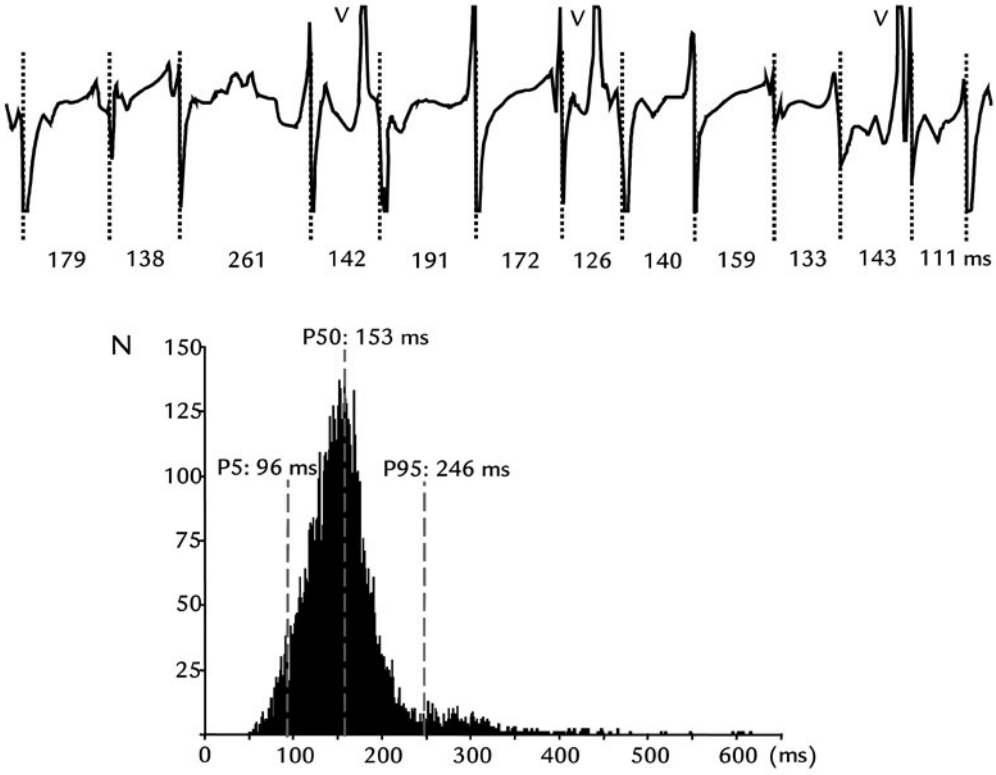

Figure 1.
Measurements of AFCL in an unipolar epicardial electrogram recorded at the right atrial free wall during CAF. Fibrillation intervals were determined by measuring the time between activations by consecutive fibrillatory waves. Corresponding interval histogram constructed during 8 seconds of AF demonstrated a right skewed distribution.
ms = milliseconds, V = far-field ventricular signal.

In the lower panel, an example of a false short fibrillation interval of 75 ms is shown. The electrogram was recorded at site B. This map shows two fibrillatory waves; one is travelling from right to the left side and is blocked in the lower part of the mapping area (thick black line). The other wave activating the atrial tissue travels in the opposite direction. Fibrillation potentials recorded at the left (C) and right (A) side of the line of conduction block (B) are shown in the lower right panel. At the right side of the line of conduction block, only one fibrillation potential is recorded (A). Since this activation wavefront was blocked at site B it did not propagate to electrode C. At electrode C, a fibrillation potential was recorded 75 ms later. Again, the wavefront activating electrode C was blocked and did not propagate to electrode A. The two potentials recorded at mapping site B were obtained from the border of the two wavefronts and represent local dissociation in conduction of fibrillatory waves. These potentials therefore do not represent a true short

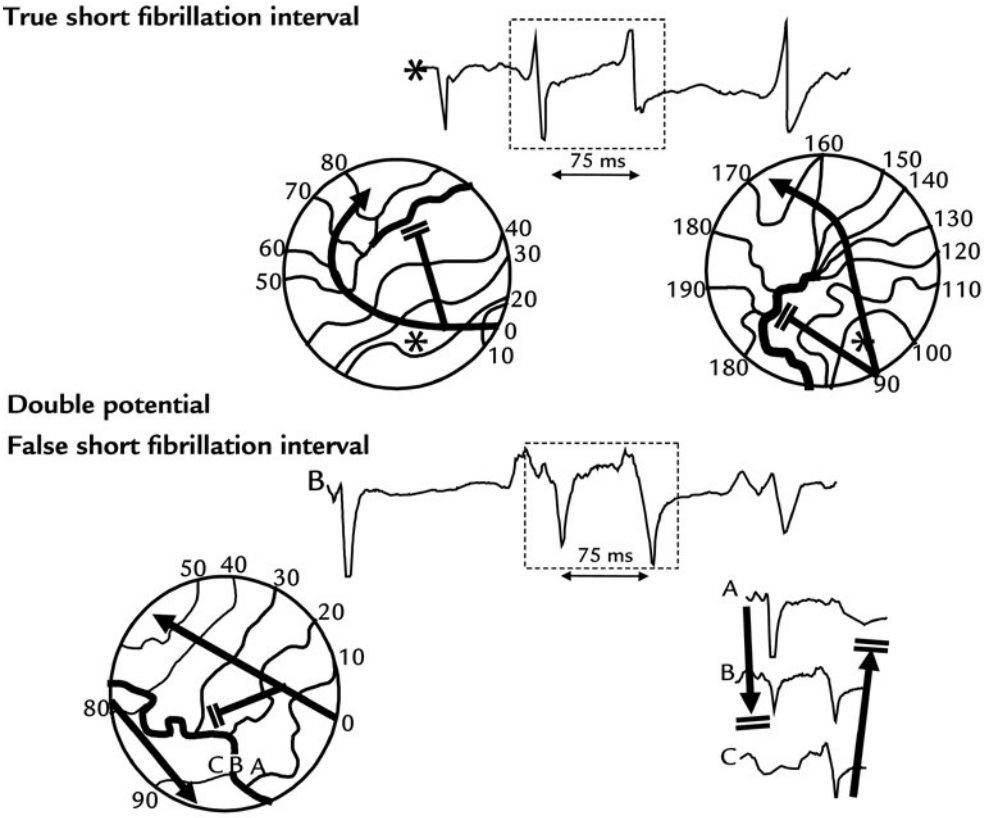

Figure 2.

True short fibrillation intervals (*top*) were discriminated from double potentials with a long time interval between the two different components (*bottom*) using both spatial patterns of activation and electrogram morphology. Isochrones are drawn at 10 milliseconds intervals. Arrows indicate main direction of propagation and thick black lines represent lines of conduction block.
See text for a detailed explanation.

fibrillation interval. Hence, for the accurate measurement of irregularities in AFCL it is essential to distinguish between a true short fibrillation interval and a double potential with a short time interval between the two different components (false short fibrillation interval). This is not possible based on analysis of electrograms only and maps of all fibrillation intervals were therefore checked to exclude false short fibrillation intervals.

Analysis of the Beat-to-Beat Irregularity in AFCL Caused by Changes in Conduction

The relation between beat-to-beat irregularity in AFCL and beat-to-beat changes in conduction was analyzed. For this purpose, the electrode located in the center of the circular mapping area was selected as the distance from each entrance point of a fibrillatory wave in the mapping area to center electrode is equivalent.

In each map ('beat'), the fibrillatory wave activating the center electrode was identified and the moment of entrance of this fibrillatory wave into the mapping area was defined as 0 ms. The conduction time from the entry site of the mapping area to the center electrode was measured. Beat-to-beat changes in conduction time (d-CT) were then correlated with the beat-to-beat changes in AFCL at the center electrode. The cause of beat-to-beat changes in conduction time was analysed for each fibrillation map. For this purpose, fibrillation maps were used to assign a change in the relative activation time of the center of the mapping electrode to one the following events: 1) a difference in beat-to-beat changes in conduction time of < 5 ms (no change), 2) alterations in conduction velocity or length of the pathway to the center electrode, 3) changes in direction of propagation or 4) epicardial breakthrough.

Schematic representations of beat-to-beat changes in conduction are shown in Figure 3. Maps in the upper panel shows 2 successive fibrillatory waves entering the mapping electrode at the same site and propagating towards the center electrode. Changes in conduction time to the center electrode were due to changes in conduction velocity (curved arrow, left) or lengthening of the path to the center electrode (dashed arrow, right) due to a line of conduction block (conduction velocity ≤ 7.5 cm/s, thick black line). Only changes in conduction velocity giving rise to beat-to-beat alterations in conduction times of more

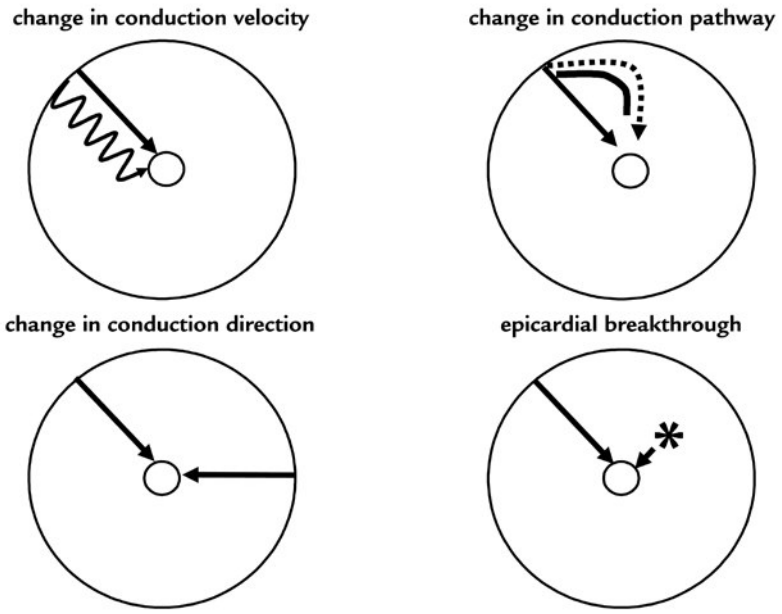

Figure 3.
Schematic isochronal maps demonstrating beat-to-beat changes in conduction of fibrillatory waves to the center electrode in the epicardial plane. The curved arrow indicates slowing of conduction, the thick black line represents a line of conduction block and the asterix an epicardial breakthrough site.

than 5 ms were taken into account. The lower left map shows a change in conduction direction. A change in direction of propagation was defined as a difference of more than 45° between entrances of successive fibrillatory waves into the mapping area. In the lower right map, a schematic representation of an epicardial breakthrough (*) is given. The center electrode is now activated relatively early because of a shorter distance.
In case of an epicardial breakthrough, the degree of pre-excitation of the center electrode by the epicardial breakthrough was calculated. Therefore, the fibrillatory wave activating the center electrode if the EB would not have happened was identified. The shortest distance from the center electrode to the nearest electrode activated by the approaching fibrillatory wave was measured. Next, the expected activation time by the approaching epicardial fibrillatory wave was determined. The expected activation time was calculated by summation of the activation time at the nearest electrode to the center activated by the approaching fibrillatory wave and the expected time required for this approaching depolarization wave to travel to center electrode. The latter was determined by dividing the distance from the last activated electrode to the center electrode by the median conduction velocity. The degree of pre-excitation was then estimated by calculating the difference between the local activation time at the center electrode and the expected activation time.

Statistical Analysis

All data are expressed as mean ± standard deviation. Students T-tests were applied to compare AFCL and irregularity in fibrillation intervals between AAF and CAF patients. Pearson's correlation coefficient (r) was used to examine the relation between beat-to-beat changes in sequences of activation and variation in AFCL. A probability level of 5% was considered statistically significant.

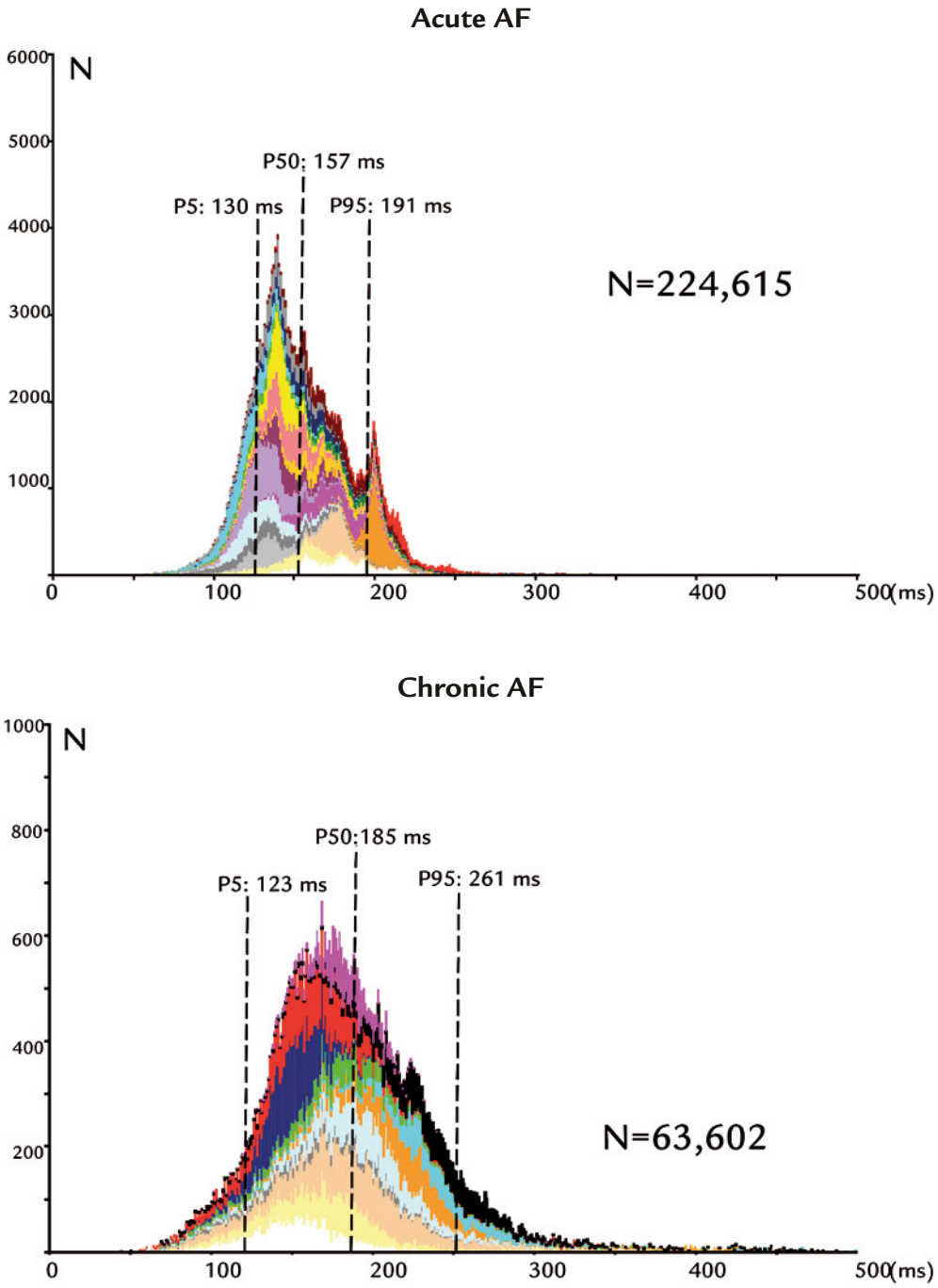

Figure 4.

Cumulative frequency distribution of all fibrillation intervals recorded at the right atrial free wall during AAF and CAF for each patient separately. Each subject is represented by a different color. Comparing the AAF and CAF patients, AFCL was longer and more irregular during CAF.

Results

Irregularity in Fibrillation Intervals at the Right Atrial Free Wall

The cumulative frequency distribution of fibrillation intervals for all AAF and CAF patients is shown in Figure 4. Each patient is represented by a different color. There was no difference between the shortest fibrillation intervals obtained from AAF and CAF patients (AAF: 85 ± 37 (49-171) ms, CAF: 64 ± 23 (42-133) ms, P = 0.08). In 2 ± 2% and 4 ± 3% of the intervals recorded during respectively AAF and CAF, there was an overlap between double potentials and short fibrillation intervals.

During CAF, however, the AFCL was significantly longer than during AAF. The median AFCL in AAF patients ranged from 122 to 215 (157 ± 26) ms and in CAF patients from 149 to 233 (185 ± 28) ms (p = 0.003). Six CAF patients used d-sotalol. The median AFCL in these patients tended to be longer than in the other CAF patients (median AFCL 192 ± 29 ms versus 175 ± 29 ms, p = 0.3).

There was no difference between the P95-P50 and P50-P5 values in both the AAF and CAF group (AAF: P95-P50: 34 ± 14 ms versus P50-P5: 27 ± 10 ms, p = 0.06, CAF: P95-P50: 76 ± 33 ms versus P50-P5: 61 ± 17 ms, p = 0.1) (Table 2). Both P95-P50 and P50-P5 were larger during CAF than during AAF (p<0.001). Comparing the degree of irregularity between AAF and CAF patients, CAF was more irregular ((P95-P5)/P50: CAF: 75 ± 24 (22-98) versus AAF: 41 ± 17(13-80), p = 0.001). There was no correlation between the median AFCL and variation in fibrillation intervals (R = 0.04, p = 0.8).

The most striking difference between the interval histograms of AAF and CAF patients is an elongated tail extending towards the longer fibrillation intervals in the CAF patients. Corresponding fibrillation maps revealed that these long fibrillation intervals were caused by islands of intra-atrial conduction block.

Islands of Intra-Atrial Conduction Block

Figure 5 shows consecutive isochronal maps and unipolar fibrillation electrograms recorded at 3 sites within the mapping area (Δ, O, □). In map A, the 3 sites are activated by a fibrillatory wave propagating from the right to the left side of the mapping area, resulting in registration of a fibrillation potential at all 3 electrodes.

In the following map, a fibrillatory wave entered the mapping area from below and propagated parallel to a line of conduction block (thick black line). This fibrillatory wave fails to elicit a depolarization at several electrodes giving rise to an enclosed area of intra-atrial conduction block (shaded area). The wavefront eventually turned around this area to activate the remainder of the mapping area. The electrode located in the island of intra-atrial conduction block (O) recorded only far-field potentials. In map C, all 3 electrodes are again activated by a passing fibrillatory wave. The occurrence of an island of intra-atrial conduction block in the second beat gave rise to local prolongation of the fibrillation interval (322 ms).

Table 2. **Variation in fibrillation intervals.**

	pt no	no of intervals	P0 (ms)	P5 (ms)	P50 (ms)	P95 (ms)	P95-P5/ P50 (ms)	DP (%)	IAB (%)
AAF	2	10666	84	134	169	225	54	1	9.34
	3	9221	49	102	153	203	67	7	3.90
	4	11154	97	159	176	195	20	0	1.51
	5	8082	80	109	130	160	39	0.4	0.18
	6	10975	50	92	135	199	80	5	3.17
	7	14050	62	102	128	163	48	2	1.40
	8	13444	143	188	201	215	13	0	0
	9	13360	109	143	171	199	33	0	0.15
	10	19282	68	113	132	159	35	0	0.50
	11	9774	80	132	149	168	24	0	0.04
	12	9635	70	131	162	195	40	1	4.01
	14	16618	62	121	148	180	40	1	0.22
	15	14411	58	126	141	174	34	1	1.43
	16	5309	54	97	131	166	53	1	5.20
	17	4794	104	154	185	231	42	1	1.13
	18	14307	55	98	122	159	50	1	4.01
	19	9274	83	124	156	207	53	0	7.38
	20	11727	53	103	140	179	54	5	3.84
	21	11033	168	178	193	214	19	0	0
	25	4287	171	197	215	230	15	0	0
mean/sd		11070 ± 3826	85 ± 37	130 ± 31	157 ± 26	191 ± 25	41 ± 17	2 ± 2	2 ± 3
CAF	1	9968	53	96	153	246	98	6	10
	2	5807	57	110	173	275	96	5	13
	3	9317	66	110	187	290	97	3	15
	4	3396	44	117	170	284	98	8	6
	5	2288	42	91	168	248	93	9	36
	6	6779	62	125	194	264	71	4	12
	7	5968	61	154	218	338	84	4	10
	8	3262	71	161	233	291	56	1	11
	9	3557	66	104	179	244	78	3	19
	10	6596	65	119	149	175	38	0	0.42
	11	7703	49	105	160	218	71	4	21
	12	4730	63	154	232	323	73	2	22
	13	2912	133	158	187	199	22	0	0.27
mean/sd		5560 ± 2472	64 ± 23	123 ± 25	185 ± 28	261 ± 46	75 ± 24	4 ± 3	13 ± 10

DP = double potentials, IAB = islands of intra-atrial conduction block

In the AAF patients, 2 ± 3% of the fibrillation intervals were prolonged by islands of intra-atrial conduction block. In CAF patients, islands of intra-atrial conduction block occurred more frequently (CAF: 13 ± 10 %, $p<0.001$).

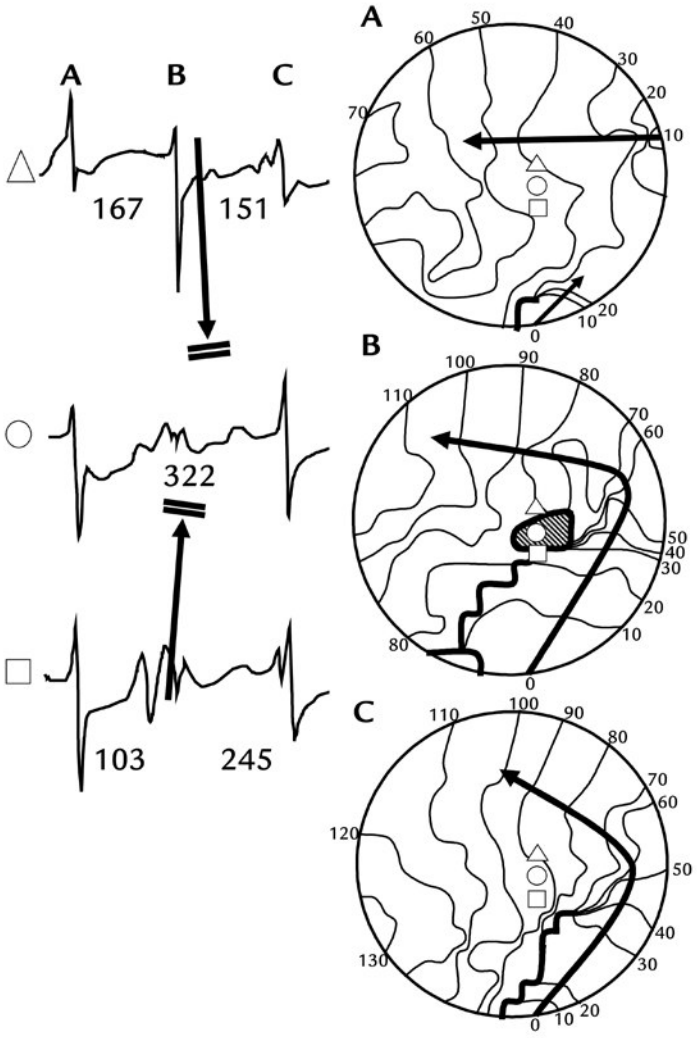

Figure 5.

Three consecutive isochronal maps constructed during AF demonstrating an island of intra-atrial conduction block in map B (dashed area). Isochrones are drawn at 10 ms intervals, thick black lines represent lines of conduction block and arrows indicate main direction of propagation. Unipolar fibrillation electrograms recorded at the 3 different sites (Δ, O, □) in the mapping area during these 3 beats are shown on the left. The island of intra-atrial conduction block gave rise to local prolongation of AFCL (O).

Irregularity in Fibrillation Intervals at the Center Electrode

In order to examine to which degree beat-to-beat changes in conduction can explain the temporal irregularity of AFCL, the relation between AFCL at the center of the mapping array and changes in conduction of fibrillatory waves was studied.

Figure 6 shows the median AFCL together with the 5th and 95th percentile of the AFCL measured at the center of the mapping array for each patient. Both within the AAF and CAF group, there was a considerable inter-individual variation in AFCL (median AFCL: AAF 157 ± 27(117-213) ms, CAF: 182 ± 28(143-228) ms) and irregularity in fibrillation intervals ((P95-P5)/P50: AAF: 44 ± 17(10-72), CAF: 68 ± 13 (45-87)). There was some

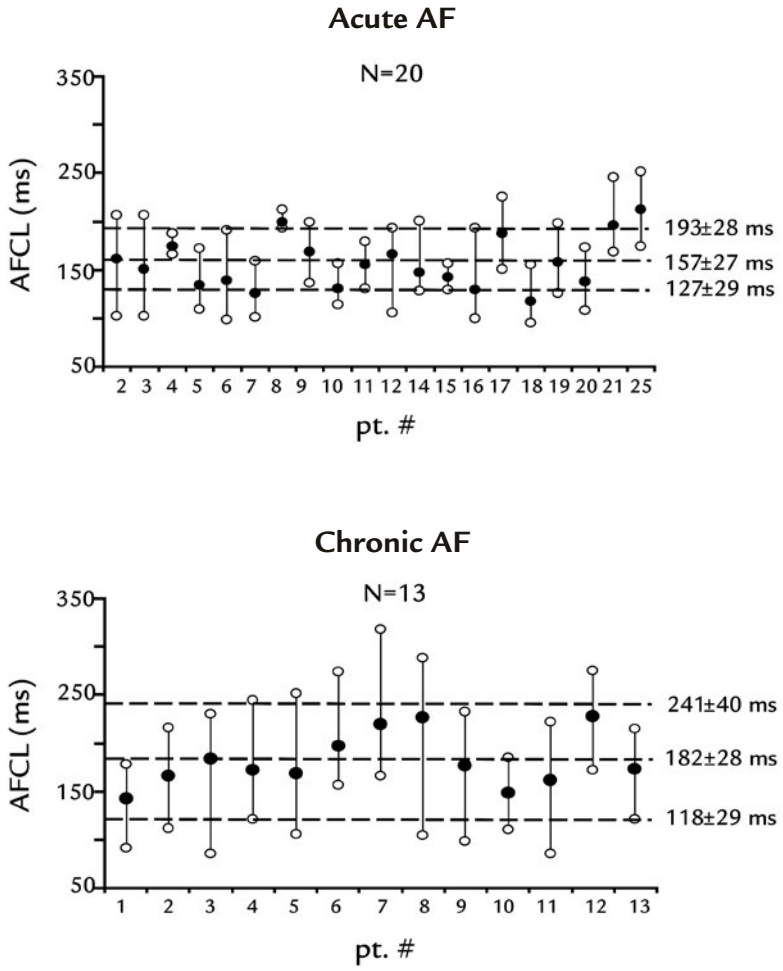

Figure 6.

Median AFCL, 5th and 95th percentile of the AFCL measured at the center of the mapping array for each AAF and CAF patient separately.

overlap of both median AFCL and variation in AFCL between the groups. However, in general, AFCL in the CAF group was longer and more irregular (p = 0.001).
As it is not possible to measure changes in conduction time in case of an islands of intra-atrial conduction block, beats with intra-atrial conduction block occurring at the center electrode were excluded from analysis.

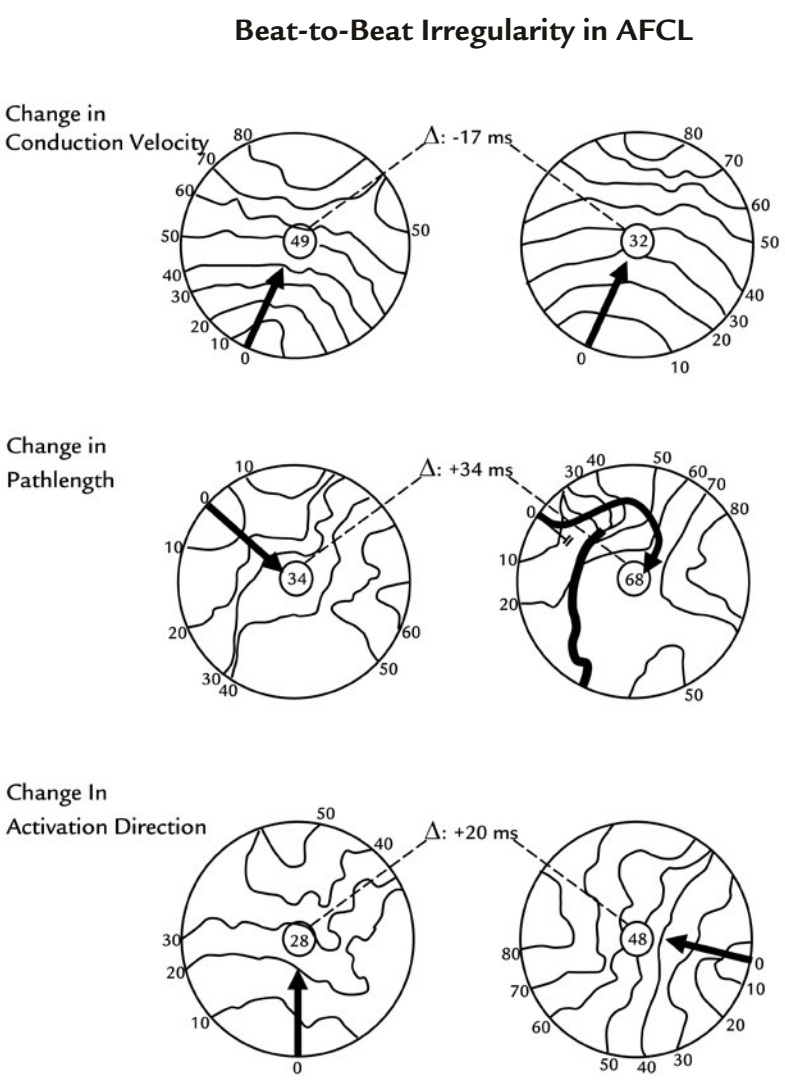

Figure 7.
Consecutive isochronal maps demonstrating beat-to-beat changes in conduction of fibrillatory waves in the epicardial plane. Isochrones are drawn at 10 ms intervals, arrows show main direction of propagation, thick black lines represent lines of conduction block.
See text for a detailed explanation.

Nature of Beat-to-Beat Changes in Conduction

Examples of beat-to-beat changes in conduction of fibrillatory waves are shown in Figure 7 and 8. The upper panel of Figure 7 shows two successive fibrillatory waves entering the mapping area at the same site (linking). The second fibrillatory wave propagated faster, resulting in a beat-to-beat difference in conduction time to the center electrode of 17 ms. The middle panels show the occurrence of a line of conduction block (thick black line) in the second map resulting in lengthening of the pathway to the center electrode. This gave rise to an increase in conduction time of 34 ms. The first map in the lower panels shows a fibrillatory wave entering the mapping area from below and propagating in an upward direction. The next fibrillatory wave entered the mapping electrode from the right and crossed the mapping electrode from right to left side. This change in direction of propagation was associated with an increase in conduction time of 20 ms.

Examples of epicardial breakthrough are shown in Figure 8. In the first map, the center electrode is activated by a fibrillatory wave entering the mapping area from below.

In the following beat, a new wavefront suddenly appeared in the middle of the mapping area (*) and spread more or less centripetally from the site of earliest activation. Since

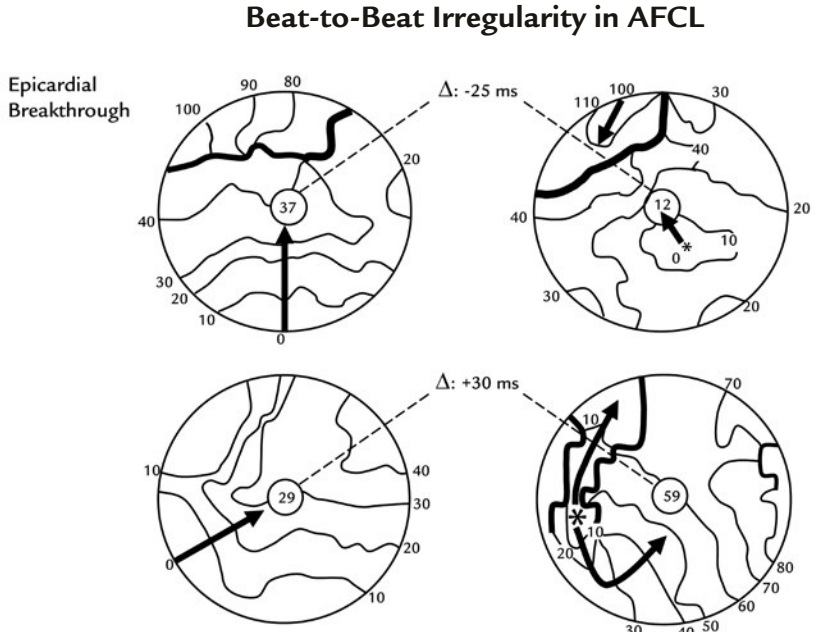

Figure 8.

Consecutive isochronal maps demonstrating beat-to-beat changes in conduction of fibrillatory waves caused by epicardial breakthroughs. Isochrones are drawn at 10 ms intervals, arrows show main direction of propagation, thick black lines represent lines of conduction block and the asterix indicates the origin of an epicardial breakthrough.

See text for a detailed explanation.

the site of this epicardial breakthrough was close to the center electrode the conduction time was decreased by 25 ms. The first map in the lower panel shows a fibrillatory wave activating the center electrode 29 ms after entering the mapping area. In the following beat, an epicardial breakthrough appears (*). The wavefront spreading from the epicardial breakthrough site encountered a line of conduction block (thick black line) around which it must turn before it can activate the center. So, despite an early epicardial breakthrough, the conduction time to the center electrode was increased due to lengthening of pathway.

The relative incidence of the different beat-to-beat changes in conduction causing irregularity in AFCL during AAF and CAF are shown in **Figure 9**.

No changes in conduction of successive fibrillatory waves occurred more frequently during AAF (30 ± 18 (5-66)%) than during CAF (10 ± 13 (0-48)%, p = 0.001). Alterations in conduction time to the center electrode without a change in direction of the fibrillatory waves either due to changes in conduction velocity or path was also more often observed during AAF (AAF: 34 ± 15 (4-56)% versus CAF: 15 ± 12 (0-41)%, p = 0.001). Changes in pathlength to the center electrode due to lines of conduction block occurred rarely both in AAF and CAF patients (AAF: 1 ± 2% and CAF: 2 ± 4%).

Beat-to-beat changes in propagation direction of fibrillatory waves were the underlying cause of irregularities in AFCL in the minority of the beats (AAF: 12 ± 13 (0-54)%, CAF: 7 ± 4 (0-13)%). Epicardial breakthrough was a frequent event during both AAF (24 ± 22 (0-63)%) and CAF (68 ± 26 (0-94)%*, p<0.001). In CAF patients, it was even the most commonly occurring event.

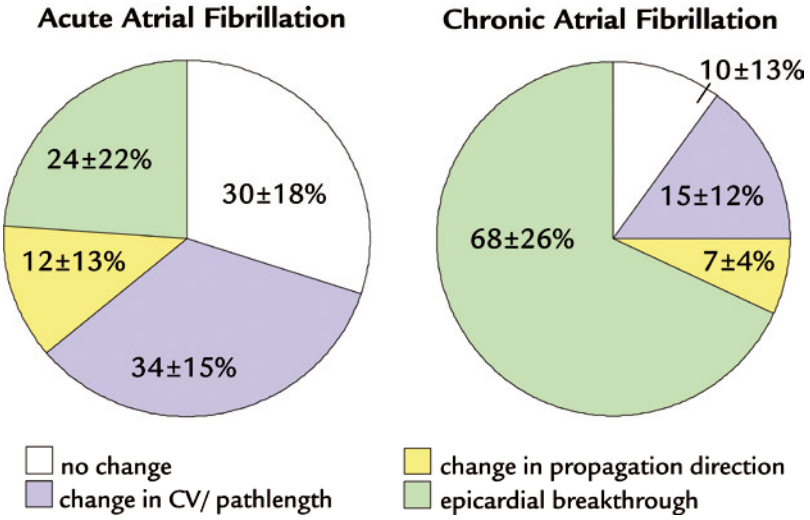

Figure 9.
Incidence of the different beat-to-beat changes in conduction giving rise to variation in AFCL at the center electrode during AAF (left) and CAF (right).

Effects of Beat-to-Beat Changes in Conduction on Irregularity in AFCL

The frequency distribution of the different beat-to-beat changes in conduction of fibrillatory waves on irregularity in AFCL is shown in Figure 10. The contribution of epicardial breakthroughs to irregularities in AFCL could be determined for 28% and 30% of the epicardial breakthroughs during respectively AAF and CAF.

In all other cases, there were no other fibrillatory waves approaching the center electrode.

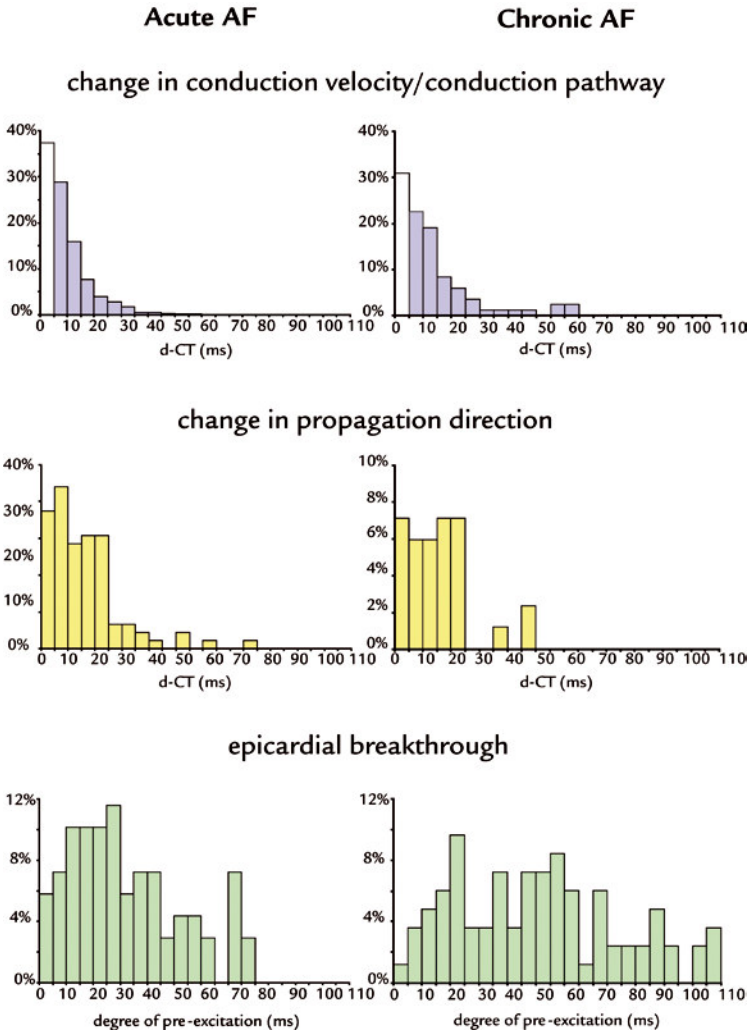

Figure 10.

Relative frequency distribution of the degree of irregularities in AFCL caused by alterations in conduction velocity/pathway (upper panel), changes in propagation direction (middle panel) and epicardial breakthrough (lower panel).

d-CT = beat-to-beat change in conduction time.

During AAF, there was no difference in the degree of irregularity in AFCL caused by changes in conduction velocity/pathway (P100-P0: 23 ± 13 ms) or alterations in propagation direction (P100-P0: 25 ± 20 ms). Irregularities due to epicardial breakthrough were larger (P100-P0: 41 ± 25 ms, p = 0.005). In the CAF group were the effects on variation in AFCL by epicardial breakthrough considerable larger than variation caused by changes in conduction velocity or propagation direction (P100-P0: 78 ± 14 ms versus 23 ± 17 ms and 15 ± 14 ms, p <0.001). Comparing AAF and CAF patients, only the degree of irregularity

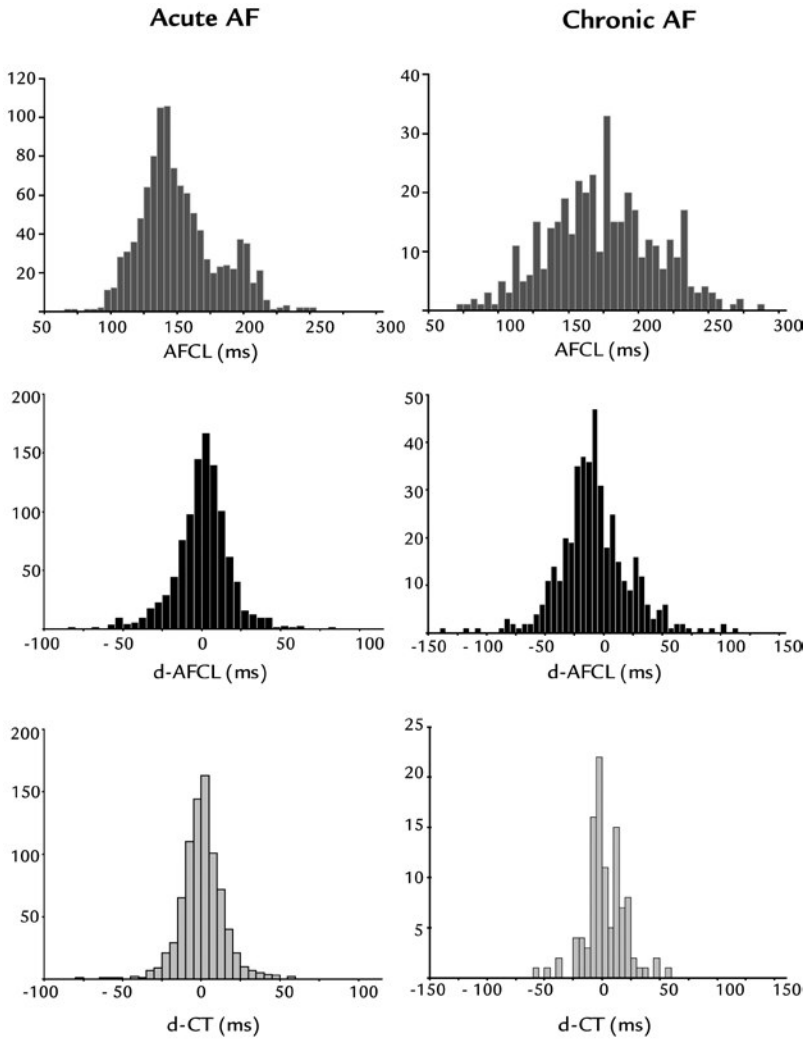

Figure 11.

Upper panel: irregularities in fibrillation intervals at the center electrode during AAF (left) and CAF (right). *Middle panel*: frequency distribution of differences between each recorded fibrillation interval and the median AFCL (d-AFCL). *Lower panel:* frequency distribution of beat-to-beat changes in conduction time due to changes in conduction velocity, activation pathway or propagation direction.

caused by epicardial breakthroughs was higher during CAF ($p < 0.001$). Total variation in conduction time correlated with the degree of irregularities in AFCL ($r = 0.44$, $p = 0.01$).

Irregularities in AFCL explained by Beat-to-Beat Changes in Conduction

Figure 11 summarizes the relation between irregularities in fibrillation intervals and the effects of beat-to-beat changes in conduction of fibrillatory waves during AAF (left) and CAF (right). Interval histograms in the upper panel show all fibrillation intervals recorded at the center electrode in the AAF and CAF patients. The middle and lower panels show a histogram of respectively the difference between each fibrillation interval and the median AFCL (d-AFCL) and beat-to-beat changes in conduction times due to alterations in conduction velocity/pathway and propagation direction (d-CT).

Assuming that irregularities in AFCL are only due to beat-to-beat changes in conduction, irregularities in AFCL at the center electrode are the summation of 1) variation in intervals between wavefronts coming from outside the mapping area and 2) beat-to-beat changes in conduction times from the entry site of the mapping area to the center electrode. Irregularities in fibrillation intervals *outside* the mapping area were estimated by measuring intervals between sites of earliest activation of the mapping area by wavefronts that activate the center electrode during 2 successive beats. The median AFCL of these 'outer' intervals were 156 ± 26 ms during AAF and 180 ± 25 ms during CAF; variations in outer intervals were respectively 49 ± 18 and 72 ± 15 ms. In none of the patients a difference between median AFCL and irregularites in fibrillation intervals in- and outside the mapping area was found.

To determine to which degree irregularities in AFCL could be explained by beat-to-beat changes in conduction in the epicardial plane within an area of 1.8 x 1.8cm, the area of the d-CT and d-AFCL histograms was calculated. Changes in conduction caused by changes in conduction velocity, pathway or propagation direction accounted for respectively 78% and 25% of the irregularities in AFCL at the center electrode during AAF and CAF.

As the degree of pre-excitation of the center electrode could only be calculated for a small number of epicardial breakthroughs the total contribution of epicardial breakthrough to irregularities in AFCL could not be determined. However, as there was no difference in variations in AFCL in- and outside the mapping area, the remaining degree of irregularities in AFCL is most likely be caused by epicardial breakthrough of fibrillatory waves.

Discussion

In this study, differences in irregularities in fibrillation intervals between AAF and CAF patients were evaluated by performing high density mapping studies of the right atrial free wall. The key findings of this study are that 1) compared to induced AF in young patients with normal atria, median AFCL was longer and more irregular during CAF in older patients with valvular heart disease, 2) epicardial breakthroughs are major determinants of irregularities in AFCL, 3) the larger beat-to-beat variation in fibrillation intervals during CAF is caused by a higher incidence of epicardial breakthroughs.

A marked inter-individual variation in median AFCL was found in both groups (AAF: 84 ms, CAF: 93 ms). This finding is consistent with other studies which also described a wide range in fibrillatory frequency in human AF.[9-19]

Mapping studies comparing AFCL during paroxysmal and persistent AF demonstrated that persistence of AF is associated with a shorter AFCL.[10;11;20;21] Shortening of AFCL can be the result of either a decrease in action potential duration or the excitable period. It is well-known that long-standing AF induces shortening of the refractory period ('electrical remodeling'). According to the multiple wavelet hypothesis, shortening of atrial refractoriness or depression of conduction velocity decreases the atrial wavelength. As the wavelength becomes shorter, the atria can contain more wavelets. Due to the increased number of circulating wavelets, the interval between activation by consecutive fibrillatory waves becomes shorter, thereby decreasing the excitable period. Thus, as CAF is associated with electrical remodeling, it was expected that fibrillation intervals in the CAF patients would be shorter than in the AAF patients. However, the results of the present study showed that despite inter-individual differences in fibrillation intervals in the AAF and CAF group, AFCL during CAF was longer and also more irregular.

Surprisingly, there was no difference in the shortest fibrillation intervals measured in AAF and CAF patients. Absence of a difference in the shortest fibrillation interval between AAF and CAF could be explained by the fact that the minimal AF cycle length does not equal the refractory period and that an excitable period may be present.

Longer fibrillation intervals in the presence of electrical remodeling in CAF patients can be explained by a larger excitable period compared to the AAF patients. In case of leading circle reentry as the underlying mechanism of AF, prolongation of the excitable period could be the result of conduction delay caused by wavefronts turning around areas of conduction block. Areas of conduction block in case of random reentry may also give rise to a longer excitable period by lengthening of the pathway of fibrillatory waves thereby giving rise to a longer waiting time for cells to be activated by the next fibrillatory wave.

In the present study, islands of intra-atrial conduction block were indeed more frequently observed during CAF. These islands of intra-atrial conduction block locally prolonged AFCL. The high incidence of conduction block observed in the CAF patients could be the result of for example atrial fibrosis.[22]

The low incidence of lines of conduction block giving rise to lengthening of the conduction pathway as a cause of irregularity in AFCL found in this study does not imply that conduction block during AF was an unusual event. In this study, we only examined the effects of conduction block on variation in AFCL at the *center electrode*. A large number of fibrillatory waves were already blocked before reaching the center electrode and were therefore not taken into account. So in the presence of multiple wavelets, prolongation of AFCL is most likely caused by widening of the excitable period due to the presence of large areas of conduction block throughout the atria.

Irregularities in AFCL

This study provides new insight into the underlying mechanism of beat-to-beat changes in AFCL. Beat-to-beat changes in conduction time represented to which degree beat-to-beat changes in AFCL at the center electrode are due to changes in conduction of fibrillatory waves *within* the mapping area. In all AAF and CAF patients, the median AFCL and variations in AFCL at the center electrode were comparable with the median AFCL and variations in fibrillation intervals of waves entering the mapping area, suggesting that electrophysiological properties of atrial tissue beneath the mapping electrode and in the remainder of the right atrium were similar.

An increase in conduction times beneath the mapping electrode resulted in a larger variation in AFCL. The effect of changes in conduction velocity/pathway or changes in activation direction in AAF and CAF patients were comparable suggesting that conduction characteristics of broad wavefronts during AAF and CAF did not differ. In all patients, irregularities in AFCL caused by epicardial breakthrough were larger than variations caused by changes in conduction velocity or activation direction. There was a higher incidence of epicardial breakthroughs activating the center electrode in the CAF patients compared to the AAF patients and irregularities in AFCL caused by epicardial breakthroughs were larger during CAF than during AAF.

In general, an epicardial breakthrough pre-excites the center electrode and shortens AFCL. However, when conduction of the fibrillatory wave from the epicardial breakthrough origin towards the center is slow, or when the expanding wavefront encounters a line of conduction block around which it must turn, shortening of AFCL is diminished. Epicardial breakthroughs therefore gave rise to a variable degree of pre-excitation of the center electrode and hence a larger variation in AFCL.

Mechanisms of Atrial Fibrillation

When AF is perpetuated by a focal mechanism giving rise to a 1:1 conduction throughout the atria, irregularities in cycle length are only due to irregularities in the excitation frequency. In case of conduction abnormalities in the atria and the presence of a focus, irregularities in AFCL for a given point in the atria are determined by variation in the excitation frequency plus changes in conduction time from the focus to this point.

For each atrial site, beat-to-beat changes in conduction velocity, pathway and propagation direction of fibrillatory waves in an area of 3.6X3.6 cm accounted for 78% and 25% of irregularities in AFCL during respectively AAF and CAF. The remaining degree of irregularities in AFCL could be attributed to epicardial breakthroughs or variation in the excitation frequency of a focus.

The magnitude of beat-to-beat changes in conduction time is directly related with the diameter of the mapping area. As the estimated surface area of the atria in man approximates 60 cm^2, the beat-to-beat changes in conduction times within the atria completely accounted for irregularities in AFCL at the center electrode. This suggests that the presence of a focus contributing to irregularities in AFCL is unlikely.

Study Limitations

Mapping studies were performed during open chest surgery. It is known that cardiac exposure by median sternotomy prolongs AFCL.[23] However, as the circumstances for the mapping procedure are similar for all patients, comparison of fibrillation intervals between AAF and CAF is justified.

Conclusion

Compared to induced AF in young patients with normal atria, median AFCL was longer and more irregular during CAF in older patients with valvular heart disease. In the presence of multiple wavelets, prolongation of AFCL during CAF is most likely caused by widening of the excitable period due to large areas of conduction block throughout the atria. Epicardial breakthroughs are major determinants of irregularities in AFCL and the larger beat-to-beat variation in fibrillation intervals during CAF is due to a higher incidence of epicardial breakthroughs.

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