Mapping and ablation of atrial tachyarrhythmias : from signal to substrate

Groot, N.M.S. de

chapter

13

Fragmented, Long Duration, Low Amplitude Electrograms Characterize the Origin of Focal Atrial Tachycardia

Natasja MS de Groot, Martin J. Schalij

Abstract

Background: Focal Atrial Tachycardias (FAT) originate from areas with poor cell-to-cell coupling. Due to cellular uncoupling extra-cellular potentials become fractionated. The degree of fragmentation may be used to identify the site of origin of FAT prior to catheter ablation. We studied electrical fragmentation in relation to the distance to the site of earliest activity during FAT.

Methods: 3-D electro-anatomical activation/voltage maps obtained from patients (N = 15, 6 male, age 40 ± 14 (19-72) yrs) referred for catheter ablation of FAT were analysed. Bipolar atrial potentials (BP) were categorized according to the number of deflections. The peak-to-peak amplitude and the time interval between the first and last deflection (*fractionation duration*) of each BP were measured.

Results: Eighteen different AT (CL 346 ± 109 (190-550) ms were analysed. The incidence of single potentials ranged from 30 to 81 [59 ± 16]%. The occurrence of double and fractionated potentials ≤ 2 cm of the site of earliest activity ('focal area') was higher compared to the remainder of the atria (67 ± 22% versus 34 ± 14%, $p < 0.001$). Focal area potentials were characterized by a longer duration (49 ± 22ms versus 34 ± 17ms, $p < 0.001$) and a lower peak-to-peak amplitude (0.51 ± 0.43 [0.12-1.7] mV versus 0.94 ± 0.69 [0.22-2.58] mV, $p = 0.03$). Fractionation was not associated with FAT cycle length ($r = -0.26$, $p = 0.29$) or left atrial diameter ($r = 0.47$, $p = 0.30$).

Conclusion: Significant differences in fractionation, fractionation duration and peak-to-peak-amplitude of atrial potentials between the focal area and the remainder of the atria exist. Fractionation and voltage mapping can be used, besides activation mapping, to identify the site of origin of FAT during catheter ablation.

Introduction

Focal atrial tachycardias (FAT) are by definition tachyarrhythmias characterized by repetitive electrical activation originating from a small, circumscribed area from where the remainder of the atria is activated.[1;2] It has been demonstrated that different mechanisms may cause FAT including enhanced automaticity, triggered activity or micro-reentry.[3] Regardless of the underlying mechanism, FAT can be eliminated by catheter ablation in most patients.[4-12] Mapping studies performed in patients with FAT provided insight into the electrophysiological characteristics. Higa et al. demonstrated that FAT originate from areas characterized by low amplitude electrograms.[12] Others reported that low amplitude, fractionated electrograms characterize the successful ablation sites.[13] Based on these observations and the fact that FAT preferentially arise from sites with discontinuities in atrial structure it was hypothesized that cellular uncoupling is a pre-requisite for development of FAT.[12-15] Cellular uncoupling gives rise to local asynchronous activation resulting in fractionation of atrial electrograms. [16] The hypothesis that cellular uncoupling is a prerequisite for development of FAT is supported by computer simulation studies demonstrating that cellular uncoupling results in a diminished electrotonic inhibition thereby allowing a rapidly discharging focus to become manifest.[16-20]

However, fractionation of atrial electrograms is not specific for a FAT origin. Fractionated electrograms are often recorded from multiple sites throughout the atria as electrical fractionation is associated with ageing, dilatation, structural heart disease and atrial arrhythmias.[21-24] Yet, when the hypothesis that poor cell-to-cell coupling is required for FAT to occur is correct, it is likely that the incidence of fractionated atrial electrograms at the FAT origin is higher compared to other atrial sites.

The goal of this study was therefore to quantify the degree of fractionation of bipolar atrial electrograms obtained from patients with FAT and to study characteristics of atrial electrograms in relation to the distance to the site of earliest activation during FAT using 3-dimensional bipolar electro-anatomical activation maps.

Methods

Study Population

The study population comprised 15 consecutive patients (6 Male, 40 ± 14(19-72) yrs) referred for catheter ablation of FAT. Hospital records were reviewed with respect to clinical presentation, cardiac diseases, history of hypertension, previous cardiac surgery, anti-arrhythmic drugs usage and hemodynamic function.

Mapping and Ablation Procedure

The mapping and ablation procedure was guided by the 3-dimensional electro-anatomical mapping system (CARTO™, Biosense Webster, USA) in all patients. This mapping technology has been described in detail previously.[25;26] Mapping and ablation was performed with a 7F Navistar catheter (4mm tip, 2 bipolar electrode pairs, inter-electrode distance 2 mm, Biosense Webster, USA). All bipolar electrograms were filtered between 10 and 400 Hz and sampled at 1kHz.

If patients were in sinus rhythm at the onset of the ablation procedure, atrial tachycardia was induced using standard programmed electrical stimulation manoeuvres. The construction of activation/voltage maps during tachycardia started with designation of anatomical structures. Local activation times were determined by marking the earliest onset of bipolar potentials and peak-to-peak amplitudes of atrial potentials were automatically measured for construction of bipolar voltage maps.[14] In case of fractionated potentials, the peak-to-peak amplitude of the largest deflection was measured. All markings were visually verified and annotations were adjusted manually if necessary.

Global mapping of the atria was performed to elucidate the mechanism of the tachycardia. A FAT activation map was characterized by a wavefront originating from a circumscribed region from where its spreads to the remainder of the atrium. Detailed mapping within this region was aimed at identifying the site of earliest activity in relation to the P wave on the surface electrocardiogram. Radiofrequency current was applied at the site of earliest activation for 60 sec (maximum tip temperature set at 70° C, maximum output 50 Watt).

Follow-up

After hospital discharge, all patients visited the out-patient clinic 4 to 6 weeks after the ablation procedure. Long-term outcome was evaluated by clinical symptoms, the resting surface electrocardiogram and 24-hour Holter monitoring.

Fractionation of Atrial Potentials

Electrograms were analysed when the variability in cycle length, local activation time and beat-to-beat difference of the catheter's location were respectively < 2%, < 3ms and < 4mm. A stable beat-to-beat morphology of consecutive atrial potentials was also visually verified. Electrograms distorted by far-field electrical activity were excluded from analysis.

Atrial potentials were categorized according to the number of deflections. Single potentials were defined as potentials consisting of one negative deflection with R and S waves of variable amplitudes. Double potentials contain 2 consecutive negative deflections and fractionated potentials consist of 3 or more consecutive negative deflections. The incidence of single, double and fractionated potentials was determined for each patient. The time interval between the first and last deflection ('*fractionation duration*') and the peak-to-peak amplitude of each double or fractionated potential was measured.

The distance to the site of earliest activity with respect to the surface p wave was measured for each atrial potential in order to study characteristics of atrial potentials in relation to the FAT origin.

Statistical Analysis

All data are expressed as mean ± standard deviation. Pearson's correlation coefficient and (in) dependent student's T-tests were used to validate significance of the data acquired. A probability level of 5% was considered statistically significant.

Table 1. **Characteristics of the study population**

pt no.	age	gender	cardiac disease	incessant AT
1	72	M	MVD, HT	Y
2	43	F	MVD, AOVD	Y
3	58	M	MVD	Y
4	34	F		Y
5	22	F		N
6	44	F		N
7	52	F	MVD	N
8	41	F	HT	N
9	39	F	AVSD	N
10	49	M	ASD-II + PS	N
11	29	F	TA + PS	Y
12	26	F	TGA + VSD	after AFL
13	19	M	ccTGA + VSD + PS	after AFL
14	30	M	monoV + monoA + TGA + PS	N
15	36	M	ASD + TGA + TA + PS	Y

M: male, F: female, MVD: mitral valve disease, AOVD: aortic valve disease, ASD: atrial septal defect, AVSD: atrioventricular septal defect, PS: pulmonary stenosis, TA: tricuspid atresia, TGA: transposition of the great arteries, ccTGA = corrected congenital TGA, monoA = mono-atrium, monoV = mono-ventricle, HT = hypertension.

Table 2. **Classification of bipolar potentials recorded during FAT.**

	Bipolar Potentials (N = 118 ± 64)		
pt no.	**SP (%)**	**DP (%)**	**FP (%)**
1	61	12	27
2	52	33	16
3	79	16	5
4	73	26	1
5	81	18	1
6	81	19	0
7	45	29	26
	42	39	19
8	42	46	12
	65	28	7
9	61	30	9
10	44	32	25
11	59	28	13
	30	23	47
12	79	19	2
13	46	21	32
14	62	21	18
15	62	24	14

SP: single potentials, DP: double potentials, FP: fractionated potentials.

Results

Study Population

Clinical characteristics of the study population (N = 15, 6 male, age 40 ± 14 (19-72) yrs) are summarized in Table 1. Seven patients had prior cardiac surgery for congenital heart disease and 4 for acquired mitral valve disease. Hypertensive heart disease was present in two subjects. Left atrial diameter estimated by M-mode echocardiography ranged from 3.5 to 5.3 [4.3 ± 1.0] mm.

Mapping Procedure

Eighteen different atrial FAT (CL 346 ± 109 (190-550) ms) were studied and treated by catheter ablation. Only 1 FAT originated from the left atrium. FAT was incessant in 6 patients. In two patients, FAT appeared after ablation of a typical atrial flutter. Eight FAT were induced with fixed rate pacing; isoproterenol infusion was additionally required in one patient. In two patients, FAT was induced with atrial extra stimuli. In 2 other patients, a new FAT originating from another area emerged after ablation of the presenting tachycardia. In one patient, 2 ablation procedures for different FAT were performed with an interval of 5 years.

Fractionation of Atrial Potentials

The degree of fractionation as measured in 2250 bipolar atrial potentials recorded during the 18 different FAT is shown in Figure 1. The incidence of single potentials (non fractionated) in the right atrium ranged from 30 to 81 [59 ± 16]% (Table 2). The incidence

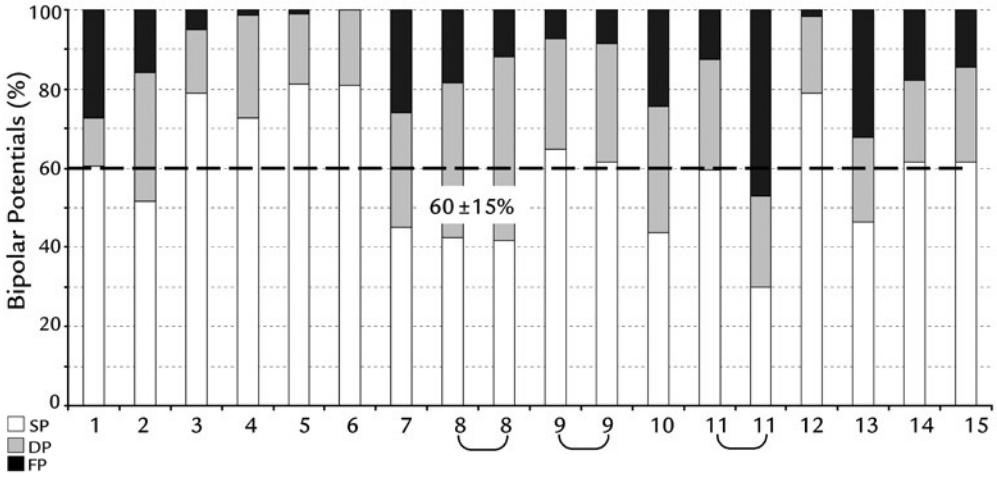

Figure 1.
Incidence of bipolar atrial potentials consisting of 1, 2 and 3 or more deflections for each patient separately. SD = single potentials, DP = double potentials, FP = fractionated potentials

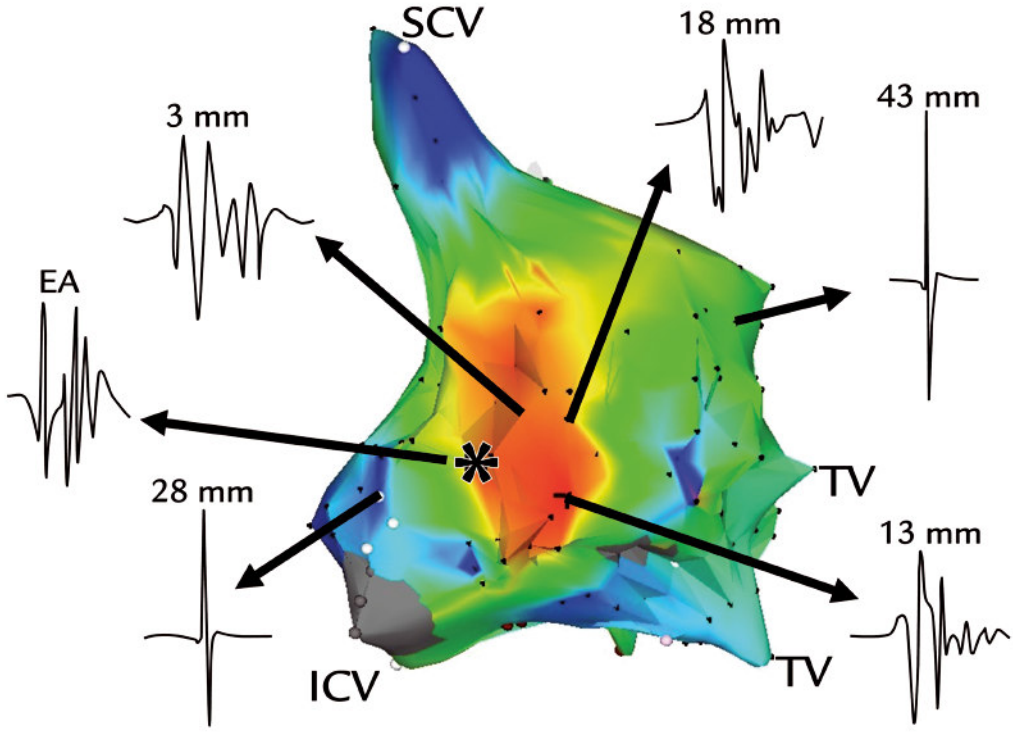

Figure 2.
Bipolar activation map of the right atrium (right lateral view), demonstrating a FAT originating from the lateral free wall. Examples of fractionated atrial potentials recorded within 2 cm distance ('focal area') are shown outside the map. Most atrial potentials obtained within a distance of less than 2 cm from the site of earliest activation are fractionated.

of double potentials was higher than the incidence of fractionated potentials (double potentials: 26 ± 8%; fractionated potentials: 15 ± 13%, $p<0.005$). There was no difference in the degree of fractionation between patients with and without congenital heart disease ($p = 0.4$) or between patients with or without a history of prior cardiac surgery ($p = 0.18$). Fractionation was not associated with tachycardia cycle length ($r = -0.26$, $p = 0.29$) or left atrial diameter ($r = 0.47$, $p = 0.30$).

A typical example of a right atrial activation map (pt no 7) during FAT originating from the lateral free wall is shown in **Figure 2**. Atrial potentials recorded at varying distances from the FAT origin are shown outside the activation map. Nearly all atrial potentials recorded within a distance of 2 cm from the site of earliest activation were fractionated. Electrograms recorded at the site of earliest activation of all eighteen different FAT are given in **Figure 3**; in each patient, the electrogram representing the site of origin consisted of fractionated atrial potentials.

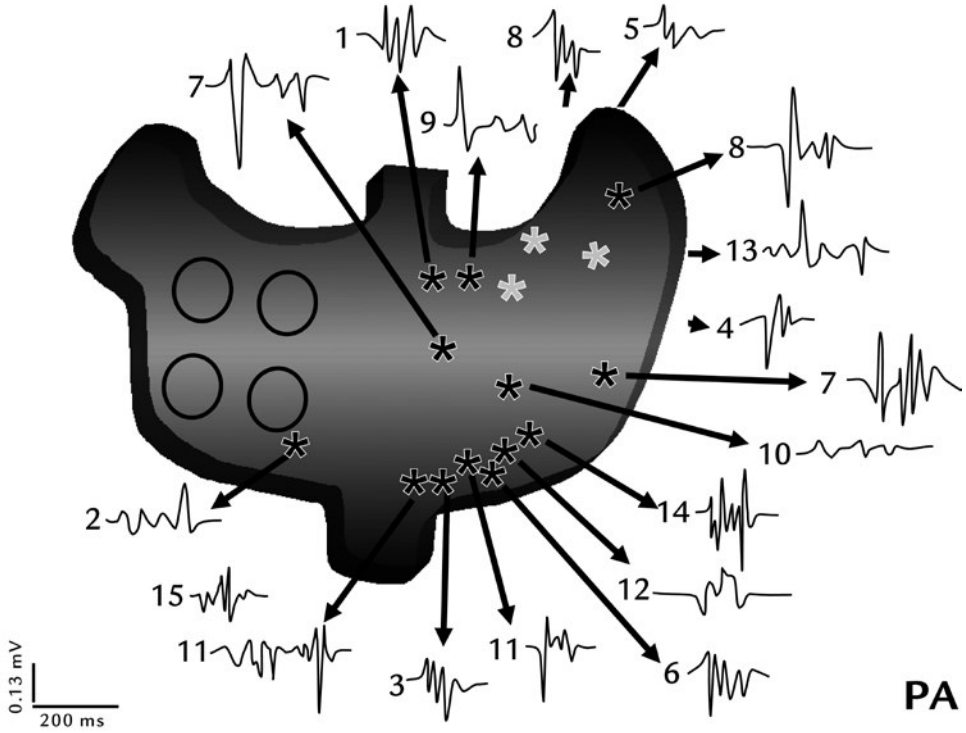

Figure 3.

Schematic representation of the atria. Electrograms recorded at the site of earliest activation during the 18 FAT. The location of sites of earliest activation are marked with a black asterix. Sites located at the anterior part of the right atrium are marked with a grey asterix. During each FAT, the origin was characterized by a fractionated atrial potential.

Interestingly, in all patients, the incidence of double and fractionated potentials decreased with increasing distance from the site of origin ($r = -0.88$, $p < 0.001$); in other words, the degree of fractionation within 2 cm of the site of origin was significantly higher compared the degree of fractionation at longer distances. Therefore, mapping sites located within 2 cm from the site of origin were classified to belong to the 'focal area'. Electrograms recorded at all other sites were named the 'remaining area'.

The degree of fractionation of bipolar potentials obtained recorded from the focal area ($N = 26 \pm 16$) and the remainder of the atrium ($N = 92 \pm 54$) for each individual FAT is shown in **Figure 4** (upper panel). The incidence of double and fractionated bipolar potentials within the focal area ranged from 17 to 100 [67 ± 23]%. Double and fractionated potentials were more frequently recorded within the focal area than in the remainder of the atria (67 ± 22% versus 34 ± 14%, $p < 0.001$). In patients *without* congenital heart disease, a high number of double and fractionated potentials within the focal area was associated with ageing ($r = 0.85$, $p = 0.004$).

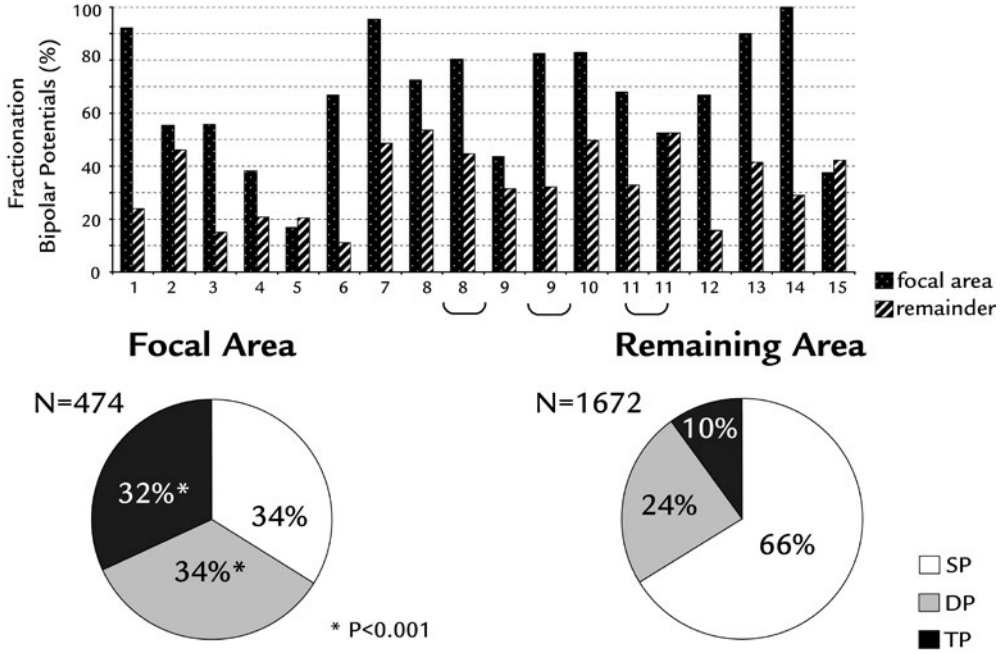

Figure 4.
Incidence of bipolar atrial potentials consisting of 1, 2 and 3 or more deflections for each patient separately (bars) and for the entire study population (pies). The incidence of atrial potentials containing 2 or more deflections in the focal area was significantly higher than in the remainder of the atrium.

Within the focal area, there was no difference between the number of double (34 ± 19%) and the number of fractionated potentials (32 ± 30%, p = 0.8). In the remainder of the atria, fractionated potentials were less frequently recorded than double potentials (p <0.001).

Fractionation Duration

From the signals shown in the previous figures it is apparent that not only the degree of fractionation is higher near the site of origin but also the duration is longer compared to signals recorded at a longer distance. The frequency distributions of the fractionation duration of atrial potentials obtained from the focal area and the remainder of the atrium are given in Figure 5 (upper panel).

Fractionation duration of all double and fractionated potentials recorded within the focal area was longer than the signal duration recorded from the remainder of the atrium (49 ± 22 ms versus 34 ± 17 ms, p <0.001).

Fractionation duration of atrial potentials recorded in patients with congenital heart disease was not different than the fractionation duration recorded in the other patients (45 ± 22 ms versus 37 ± 17 ms, p = 0.26).

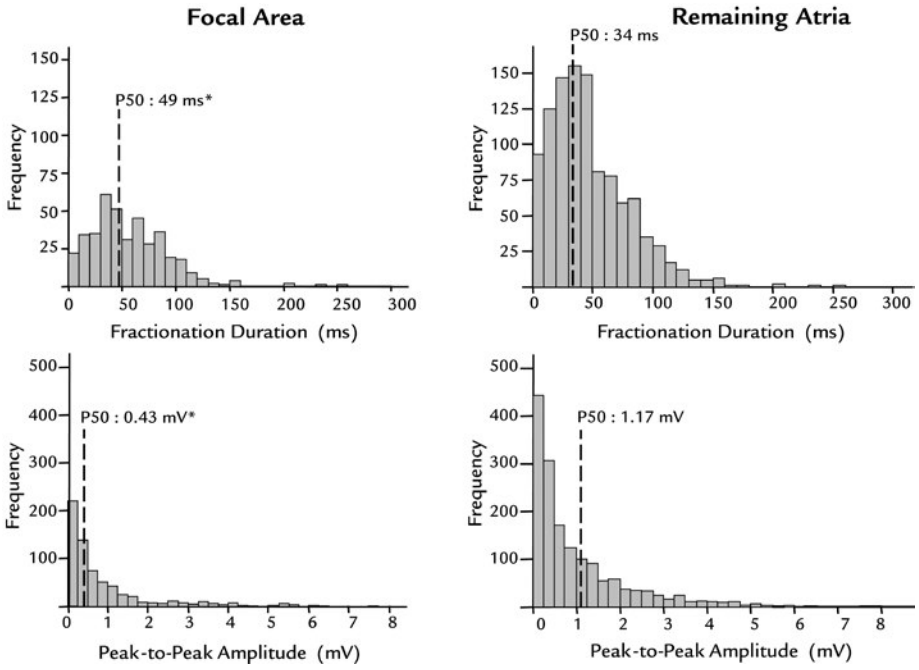

Figure 5.
Upper panels: frequency distribution of the incidence of fractionation duration of atrial potentials obtained from the focal area (left) and remainder of the atria (right).
Lower panels: frequency distribution of the incidence of peak-to-peak amplitudes of atrial potentials obtained from the focal area and the remainder of the atria.

Peak-to-Peak Amplitude

The frequency distributions of the peak-to-peak amplitude of bipolar electrograms recorded from the focal area and the remainder of the atrium are shown in Figure 5 lower panels. The peak-to-peak amplitude of bipolar atrial potentials recorded from the focal area were significantly lower than the peak-to-peak amplitude of bipolar atrial potentials recorded from the remainder of the atria (focal area: 0.51 ± 0.43 [0.12-1.7] mV versus remainder of the atria: 0.94 ± 0.69 [0.22-2.58] mV, p = 0.03).
Amplitudes of atrial potentials obtained from patients with a history of cardiac surgery were lower than from patients without prior surgery (0.95 ± 0.70 mV versus 0.45 ± 0.32 mV, p = 0.01).

Ablation Procedure and Follow-Up

Seventeen FAT (94%) were successfully ablated (termination during ablation and not inducible after ablation). There was no termination during ablation in one patient and this patient had to be cardioverted to sinus rhythm. During a follow-up period of 25 ± 25 months, recurrences were observed in two patients.

Discussion

The key finding of this study is that within a distance of less than 2 cm from the site of earliest endocardial activity during FAT, bipolar potentials are characterized by a high degree of fractionation, prolonged fractionation duration and low peak-to-peak amplitudes.
We analysed characteristics of atrial potentials in relation to the distance to the site of earliest activity during FAT. Several studies reported the presence of fractionated electrograms at successful ablation sites of FAT but up till now no study evaluated differences in fractionation between the focal area and the remainder of the atrium.[14]
The results of this study support the hypothesis that a certain degree of cellular uncoupling (reflected by a high degree of fragmentation, long signal duration and low amplitudes) is required for the development of FAT thereby providing further insight into the aetiology of FAT.

Fractionation of Atrial Potentials

In our study population, a significant number of fractionated atrial potentials was recorded in all patients. One might argue that due to the natural tendency to acquire more sampling points within the so-called focal area the degree of fractionation was (at least partly) associated with the relatively high sampling density within this area. However, in all patients, the number of atrial potentials recorded in the remainder of the atria was at least 4 times higher than the number of points recorded within the focal area thereby limiting the effect of high density mapping within the focal area.
Fractionated atrial potentials consist of multiple small, rapid deflections reflecting asynchronous activation of atrial tissue surrounding the recording electrode.[27] Local asynchronous activation has been observed during sinus rhythm and atrial arrhythmias.[21-23;28-31] Experimental studies have demonstrated that fractionation is either anatomically (heterogeneity in atrial structure) or functionally (dispersion of refractory period) determined.[16]
As bipolar electrogram represent the difference between two unipolar electrograms – most likely also fractionated – bizarre complexes may be recorded. The severity of fractionation probably reflects the amount of interstitial fibrosis, affecting intra-atrial conduction. It is unlikely that these slow components were caused by poor contact as electrograms were only analyzed when the variability in cycle length, local activation time and beat-to-beat difference of the catheter's location were respectively < 2%, < 3ms and < 4mm and when a stable beat-to-beat morphology of consecutive atrial potentials was visually verified. The fact that ablation at sites from which relative slow extra-cellular potentials were recorded resulted in elimination of the focal atrial tachycardia indicated that there was local conduction, though perhaps only through deeper layers of the atrial wall.
Interestingly, in our study, the incidence of fractionated atrial potentials in patients with congenital heart disease was not higher than in the patients without congenital heart disease. As atrial tissue in congenital heart disease patients is affected by prior cardiac sur-

gery and hemodynamic overload, higher incidence of fractionated atrial potentials was therefore expected. However the non-congenital group was older (46 ± 15 yrs) than the congenital group of patients (33 ± 15, P = 0.07). As ageing is associated with increased fractionation this may explain the finding that the degree of fractionation was the same in both groups.

FAT were defined as tachycardias characterized by a focal spread of activation originating from a localized area. Focal activity could be due to triggered activity, enhanced automaticity or micro-reentry. The high degree of fractionation indicated that poor cell-to-cell coupling at the origin was present in most patients. Reduced cell-to-cell coupling may facilitate conduction abnormalities and this finding therefore may support micro-reentry as the underlying mechanism of FAT. The activation maps did not support "macro"-reentry as a possible mechanism as in none of the patients a circulating wavefront around a macroscopic anatomical structure or a functional line of conduction block was recorded.

Focal Area

From **Figure 3**, it seems that focal areas in this study population were not only confined to trabeculated regions of the right atrium such as the crista terminalis. Some sites appeared to be located more to the smooth posterior wall. It could be hypothesized that in case of volume or pressure overload, the thin postero-septal wall may be stretched even more than the trabeculated antero-lateral part of the right atrium. Stretch enhances tissue anisotropy and hence increased the likelihood for AT to occur.[32]

The number of fractionated atrial potentials declines with increasing distance from the focal area. Bipolar potentials recorded within a distance of less than 2 cm from the site of earliest endocardial activity were characterized by a high incidence of fractionated potentials, a longer fractionation duration and a lower peak-to-peak-amplitude compared to the remainder of the atria. Furthermore, fractionated atrial potentials were recorded from successful ablation sites in all patients. These findings support the postulation that cellular uncoupling is a pre-requisite for the elucidation of a FAT. The sparse side-to-side electrical coupling impairs conduction – though not resulting in conduction block – and reduces electronically inhibition of focal activity.

The findings of this study also imply that the substrate of FAT comprises a considerable larger area than only the site with the earliest endocardial activity which is targeted for ablation.

Unfortunately, based on our data we can not give a definitive explanation for this finding. Yet, the results of our study suggested that electro-pathological changes affected a larger area than generally thought. This hypothesis is supported by the study of Kammeraad et al reporting that the recurrence rate of FAT after a successful catheter ablation is significant which could be explained the fact that new FAT arise from other sites within the fractionated area.[33]

The high incidence of fractionated potentials due to local dissociation in conduction around the site of earliest activation is consistent with the observation of expansion of FAT in patients through a preferential conduction pathway. [12]

Study Limitations

The number of recorded atrial potentials – particularly in the focal area – was determined by the complexity of the ablation procedure. The natural tendency to increase the sampling density within the focal area might have affected the degree of fractionation although in all patients at least 4 times more points were acquired from the remaining atria than from the focal area. As unipolar potentials are frequently affected by far-field electrical activity, only bipolar atrial potentials were used for analysis. As it is known that fractionation of atrial potentials depends on direction of activation and that the activation direction during sinus rhythm differs from FAT we only studied fractionation during FAT and not during sinus rhythm. However, based on the findings of this study, it may be of interest to compare fractionation during FAT and sinus rhythm.

Clinical Implications

The area around the site of earliest activation of FAT is characterized by an increased incidence of fractionated potentials, a prolonged fractionation duration and a lower peak-to-peak-amplitude. Hence, fractionation and voltage mapping can be used, besides activation mapping, to identify the site of origin of FAT during catheter ablation. The results of our study further supports the hypothesis that a certain degree of cellular uncoupling is required for the development of a FAT thereby providing further insight into the aetiology of FAT.

References

1. Chen SA, Tai CT, Chiang CE et al. Focal atrial tachycardia: reanalysis of the clinical and electrophysiologic characteristics and prediction of successful radiofrequency ablation. J Cardiovasc Electrophysiol. 1998;9:355-365.
2. Saoudi N, Cosio F, Waldo A et al. A classification of atrial flutter and regular atrial tachycardia according to electrophysiological mechanisms and anatomical bases - A statement from a Joint Expert Group from the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and electrophysiology. European Heart Journal. 2001;22:1162-1182.
3. Chen SA, Chiang CE, Yang CJ et al. Sustained atrial tachycardia in adult patients. Electrophysiological characteristics, pharmacological response, possible mechanisms, and effects of radiofrequency ablation. Circulation. 1994;90:1262-1278.
4. Hoffmann E, Reitmann C, Nimmermann P et al. Clinical experience with electroanatomic mapping of ectopic atrial tachycardia. Pace-Pacing and Clinical Electrophysiology. 2002;25:49-56.
5. Wetzel U, Hindricks G, Schirdewahn P et al. A stepwise mapping approach for localization and ablation of ectopic right, left, and septal atrial foci using electroanatomic mapping. European Heart Journal. 2002;23:1387-1393.
6. Bhatia A, Sra J, Dhala A et al. Radiofrequency catheter ablation of atrial tachycardia using noncontact computerized mapping system. Circulation. 2000;102:527.
7. Cavaco D, Adragao P, Morgado F et al. Electronanatomical mapping and ablation of atrial tachycardias with the CARTO system. Rev Port Cardiol. 2002;21:407-418.
8. Gupta AK, Maheshwari A, Thakur RK et al. Catheter ablation of atrial tachycardia using a real-time position management mapping system. Indian Heart J. 2003;55:75-77.
9. Rodriguez E, Callans D, Kantharia B et al. Basket catheter localization of the origin of atrial tachycardia with atypical morphology after atrial flutter ablation. Pacing Clin Electrophysiol. 2000;23:269-272.
10. Schmitt H, Weber S, Schwab JO et al. Diagnosis and ablation of focal right atrial tachycardia using a new nigh-resolution, non-contact mapping system American Journal of Cardiology. 2001;87:1017-+.
11. Kottkamp H, Hindricks G, Breithardt G et al. Three-dimensional electromagnetic catheter technology: electroanatomical mapping of the right atrium and ablation of ectopic atrial tachycardia. J Cardiovasc Electrophysiol. 1997;8:1332-1337.
12. Higa S, Tai CT, Lin YJ et al. Focal atrial tachycardia: new insight from noncontact mapping and catheter ablation. Circulation. 2004;109:84-91.
13. Lesh MD, Van Hare GF. Status of ablation in patients with atrial tachycardia and flutter. Pacing Clin Electrophysiol. 1994;17:1026-1033.
14. Weiss C, Willems S, Rueppel R et al. Electroanatomical mapping (CARTO (R)) of ectopic atrial tachycardia: Impact of bipolar and unipolar local electrogram annotation for localization the focal origin. Journal of Interventional Cardiac Electrophysiology. 2001;5:101-107.
15. Kalman JM, Olgin JE, Karch MR et al. "Cristal tachycardias": origin of right atrial tachycardias from the crista terminalis identified by intracardiac echocardiography. J Am Coll Cardiol. 1998;31:451-459.
16. Joly D, Savard P, Roberge FA et al. Simulation and experimental studies of the factors influencing the frequency spectrum of cardiac extracellular waveforms. J Electrocardiol. 1990;23:109-125.
17. Joyner RW. Modulation of repolarization by electrotonic interactions. Jpn Heart J. 1986;27 Suppl 1:167-183.
18. Joyner RW, Wang YG, Wilders R et al. A spontaneously active focus drives a model atrial sheet more easily than a model ventricular sheet. Am J Physiol Heart Circ Physiol. 2000;279:H752-H763.
19. Tan RC, Joyner RW. Electrotonic influences on action potentials from isolated ventricular cells. Circ Res. 1990;67:1071-1081.
20. Wagner MB, Golod D, Wilders R et al. Modulation of propagation from an ectopic focus by electrical load and by extracellular potassium. Am J Physiol. 1997;272:H1759-H1769.

21. Centurion OA, Fukatani M, Konoe A et al. Electrophysiological Abnormalities of the Atrial Muscle in Patients with Sinus Node Dysfunction Without Tachyarrhythmias. International Journal of Cardiology. 1992;37:41-50.
22. Centurion OA, Fukatani M, Konoe A et al. Different Distribution of Abnormal Endocardial Electrograms Within the Right Atrium in Patients with Sick Sinus Syndrome. British Heart Journal. 1992;68:596-600.
23. Centurion OA, Isomoto S, Fukatani M et al. Relationship Between Atrial Conduction Defects and Fractionated Atrial Endocardial Electrograms in Patients with Sick Sinus Syndrome. Pace-Pacing and Clinical Electrophysiology. 1993;16:2022-2033.
24. Konoe A, Fukatani M, Tanigawa M et al. Electrophysiological Abnormalities of the Atrial Muscle in Patients with Manifest Wolff-Parkinson-White Syndrome Associated with Paroxysmal Atrial-Fibrillation. Pace-Pacing and Clinical Electrophysiology. 1992;15:1040-1052.
25. Gepstein L, Hayam G, Ben Haim SA. A novel method for nonfluoroscopic catheter-based electroanatomical mapping of the heart. In vitro and in vivo accuracy results. Circulation. 1997;95:1611-1622.
26. Gepstein L, Evans SJ. Electroanatomical mapping of the heart: basic concepts and implications for the treatment of cardiac arrhythmias. Pacing Clin Electrophysiol. 1998;21:1268-1278.
27. Spach MS, Barr RC. Effects of cardiac microstructure on propagating electrical waveforms. Circ Res. 2000;86:E23-E28.
28. Shimizu A, Fukatani M, Tanigawa M et al. Intra-atrial conduction delay and fragmented atrial activity in patients with paroxysmal atrial fibrillation. Jpn Circ J. 1989;53:1023-1030.
29. Shimizu A, Centurion OA. Electrophysiological properties of the human atrium in atrial fibrillation. Cardiovasc Res. 2002;54:302-314.
30. Tanigawa M, Shimizu A, Matsumoto Y et al. Electrophysiologic Characteristics of Right Atrial Electrograms During Sinus Rhythm in Patients with Paroxysmal Atrial-Fibrillation. Japanese Circulation Journal-English Edition. 1988;52:927.
31. Tanigawa M, Fukatani M, Konoe A et al. Prolonged and Fractionated Right Atrial Electrograms During Sinus Rhythm in Patients with Paroxysmal Atrial-Fibrillation and Sick Sinus Node Syndrome. Journal of the American College of Cardiology. 1991;17:403-408.
32. Eijsbouts SC, Majidi M, van Zandvoort M et al. Effects of acute atrial dilation on heterogeneity in conduction in the isolated rabbit heart. J Cardiovasc Electrophysiol. 2003;14:269-278.
33. Kammeraad JAE, Balaji S, Oliver RP et al. Nonautomatic focal atrial tachycardia: Characterization and ablation of a poorly understood arrhythmia in 38 patients Pace-Pacing and Clinical Electrophysiology. 2003;26:736-742.