Mapping and ablation of atrial tachyarrhythmias : from signal to substrate

Groot, N.M.S. de

Summary and Conclusions

Summary

Atrial tachyarrhythmias (AT) have become an important problem in cardiology due to the ever-growing patient population presenting with different types of AT. The only curative treatment option of AT is catheter or surgical ablation therapy. Knowledge of the mechanism underlying the AT is essential for determination of the ablation strategy. However, ablative therapy is frequently not successful which may be caused by insufficient understanding of the mechanism of the arrhythmia.

The aim of this thesis in general was to increase our knowledge of arrhythmogenesis of various atrial tachyarrhythmias (AT), including atrial fibrillation, type I atrial flutter and focal atrial tachycardias by performing endocardial and epicardial mapping studies in humans in order to improve ablation strategies.

In **chapter 1**, we reviewed experimental and clinical mapping studies of AT and we discussed the relationship between atrial anatomy and pathogenesis of AT. This review demonstrates that as a consequence of the limited number of mapping studies of human AF performed sofar, the exact mechanism underlying AF is still not completely understood. First, patterns of activation have never been examined in patients with chronic AF. Second, despite the recent introduction of electrogram-guided AF ablation therapy, the relation between electrogram morphology and abnormalities in conduction has never been analyzed. Also, electrophysiological characteristics of different types of AF have never been compared. We therefore performed epicardial high density mapping of the right atrial free wall with a spoon-shaped electrode (244 unipolar electrodes, inter-electrode distance 2.25 mm) during open chest surgery in order to study electrophysiological differences between patients with normal atria and induced atrial fibrillation (acute AF) and patients with valvular heart disease and chronic atrial fibrillation (chronic AF). The outcome of these studies is presented in **chapter 2** to **5**.

The aim of the study described in **chapter 2** was to unravel the mechanism of beat-to-beat changes in fibrillation intervals and to study differences in fibrillation intervals during acute and chronic AF.

AF intervals histograms of the entire mapping area were constructed by measuring intervals between successive fibrillation waves directly from unipolar atrial electrograms. At the center of the mapping area, temporal variations in AF cycle length (AFCL) were related with beat-to-beat changes in conduction of fibrillation waves including no changes in conduction, alterations in conduction velocity/path, changes in conduction direction or epicardial breakthrough. By comparing intervals histograms constructed during acute AF and chronic AF, it was demonstrated that fibrillation intervals during chronic AF were longer and more irregular. Epicardial breakthroughs were the major cause of irregularities in AFCL and occurred more frequently during chronic AF. This accounted for the higher degree of irregularity in AFCL during chronic AF compared to acute AF. The fact that fibrillation intervals in the chronic AF patients were longer though chronic AF is associated

with electrical remodeling suggests that a larger excitable period must be present. We hypothesized that in the presence of multiple wavelets, widening of the excitable period is most likely caused by large areas of conduction block throughout the atria. These areas of conduction block lengthen the pathway of fibrillation waves or give rise to local conduction delay at turning points. This hypothesis was supported by our finding that islands of conduction block were more frequently observed in the chronic AF patients.

In **chapter 3**, we characterized the morphology of fibrillation electrograms obtained from patients with induced AF in order to gain insight into the electropathological substrate of atrial fibrillation. For this purpose, the RS difference of each fibrillation potential was measured. This analysis revealed a marked predominance of S waves. We suggested that this S wave predominance resulted from the thin epicardial layer of myocardium providing an electrical bridge between the thicker endocardial muscle bundles. We also explored other causes of S-wave predominance including tissue anisotropy and wavefront curvature. However, there was no relation between RS differences and local wavefront curvature or conduction anisotropy. Computer simulations demonstrated that transmural activation in an epicardial to endocardial direction provided indirect evidence that the thin epicardial layer of atrial myocardium plays an important role in propagation of fibrillation waves.

In **chapter 4**, we studied characteristics of epicardial breakthroughs observed during AAF and CAF. Epicardial breakthroughs occurred as non-repetitive events at multiple sites within the mapping area, preceded by fibrillation intervals of variable lengths. Breakthrough of a fibrillation wave usually resulted in pre-excitation of atrial tissue but expansion of the epicardial breakthroughs was often limited due to the presence of areas of conduction block confining the new fibrillation wave to a small area.

Epicardial breakthroughs should therefore not be regarded as focal sources of AF, though they give rise to focal activity. The results of this study are most consistent with transmural propagation of fibrillation waves as the mechanism underlying epicardial breakthrough. Epicardial breakthroughs occurred more frequently in the chronic AF patients compared to the acute AF patients, indicating that transition from paroxysmal AF to persistent AF might be the result of progression from 2-dimensional to 3-dimensional conduction. The higher degree of local pre-excitation of the epicardial breakthroughs during chronic AF suggests that there is a larger dissociation between the endocardial and epicardial layer which could be attributed to electro-pathological alterations of the myocardium. This finding supports the hypothesis of electro-pathological alterations in the thin subepicardial layer leading propagation of fibrillation waves in patients with chronic AF. In case of injury of the subepicardial layer, epicardial patterns of activation are determined by the complex network of the pectinate muscles. This mechanism could account for the diffuse distribution of epicardial breakthroughs and the wide variety of epicardial breakthroughs coupling intervals found in this study.

In **chapter 5**, we analyzed conduction properties of fibrillation waves during acute AF and chronic AF by quantifying the degree and spatial distribution of local conduction abnormalities. Comparing conduction characteristics of fibrillation waves between acute AF and chronic AF, conduction during chronic AF was characterized by a lower conduction velocity, a higher incidence of conduction block, a higher degree of conduction anisotropy and a larger inhomogeneity in conduction. Analysis of the spatial variation in conduction block in the chronic AF patients demonstrated that conduction blocked preferentially at some sites, suggesting that conduction in these areas was more structurally determined. Conduction block was associated with atrial dilatation, the degree of conduction anisotropy and epicardial breakthrough. Conduction block in the epicardial plane during chronic AF could be attributed to injury of the thin subepicardial layer resulting in structural discontinuities and hence to abnormalities in conduction. In the previous chapter we postulated that the occurrence of epicardial breakthrough could be explained by damage of the subepicardial layer. The relation between conduction block and epicardial breakthrough as demonstrated in this study further supports the hypothesis of the leading role of the thin subepicardial layer in propagation of fibrillation waves.

In **chapter 6**, we introduce a new mapping tool. The degree and duration of fractionation of unipolar fibrillation potentials was measured in order to study whether acute AF and chronic AF differ in incidence of fractionation and fractionation duration. Regional differences in fractionation and fractionation duration were visualized with maps demonstrating fractionation and fractionation duration/potential for each recording site. Comparing characteristics of fibrillation potentials recorded during acute AF and chronic AF, the incidence of long double and fractionated potentials was higher and fractionation duration was longer in the CAF patients. Fractionation maps demonstrated that fractionated electrograms with longer fractionation duration were also recorded by a larger number of electrodes during CAF. High density fractionation mapping might become a new diagnostic tool as it can be used to discriminate between different types of AF.

In order to individualize AF treatment, the mechanism of AF in each individual patient should be analyzed. For this purpose, multi-site high density mapping is required in order to identify focal sources or to localize areas of conduction abnormalities. We therefore developed a unique epicardial multi-site high density mapping approach by performing total mapping of the atria with a hand-made, so-called "finger-tip" electrode in patients with chronic AF. This is the first high density mapping study of the *entire* atria in humans with chronic AF. In **chapters 7 and 8**, this small 1 cm^2 template containing 60 unipolar electrodes (inter-electrode distance of 1.5 mm) was used to map the atria epicardially in patients with chronic AF. In **chapter 7**, we analyzed characteristics of fibrillation waves propagating across bachmann's bundle in humans with chronic AF. Fibrillation maps demonstrated considerable inter-individual differences in patterns of activation. Consequently, there was also an inter-individual variation in the degree of conduction block,

epicardial breakthrough and fractionation of fibrillation potentials. In some patients, there were directional differences in the incidence of fractionation and conduction block. The findings of this study indicate that the role of bachmann's bundle during AF varies from patient to patient and it can therefore be expected that the effects from therapies e.g. ablation or preventive pacing may also differ between patients.

In **chapter 8**, we performed total mapping of the atria in patients with chronic AF by shifting the mapping electrode over the epicardium and recording episodes of 10 seconds at each mapping site. The purpose of the present study was to evaluate this new multi-site high density mapping approach for assessing intra-atrial differences in fractionation characteristics of fibrillation potentials, conduction block and conduction anisotropy.

This study demonstrated that there were large intra-atrial variations in the degree of fractionation, fractionation duration, AF cycle length, conduction block and conduction anisotropy during chronic AF and that these parameters varied considerably over only small distances. Also, there were large inter-individual differences in the degree of fractionation at various mapping sites. These findings indicate that there must be an inter-individual variation in the location of the arrhythmogenic substrate perpetuating AF. Hence, multi-site high density mapping is thus essential. Epicardial multi-site, high density fractionation mapping might therefore become an important tool for identification and subsequent ablation of the arrhythmogenic substrate perpetuating AF in patients undergoing open chest surgery.

In **chapter 9**, the use of a new endocardial mapping technique for the first time applied in patients referred for catheter ablation of various tachyarrhythmias was described. This mapping system allowed real-time three-dimensional positioning of mapping/ablation catheters.

In **chapter 10 to 13**, 3-dimensional endocardial mapping studies of late, post-operative atrial tachyarrhythmias in patients with surgically corrected or palliated congenital heart defects were performed in order to facilitate ablation of these complex arrhythmias.

In **chapter 10**, a 3-dimensional electro-anatomical mapping system (CARTO™) was used to construct bipolar voltage maps during post-operative AT (patient group) and atrioventricular reciprocating tachycardia (control group). Peak-to-peak amplitudes of bipolar electrograms were measured and compared between the patient and control group.

As the lowest voltage measured in the control group was 0.1 mV, this value was used as the upper limit of low voltage areas in patients with congenital heart disease. By using the 0.1 mV cut-off value, low voltage areas were delineated in patients with congenital defects in order to identify crucial pathways of conduction in reentrant circuits embedded within scar tissue which served as target sites for ablation.

In **chapter 11**, we analyzed how the recording technique affected the outcome of catheter ablation procedures in patients with congenital heart defects. For this purpose, 3-dimensional unipolar and bipolar voltage and activation maps were constructed during

atrioventricular nodal reentrant tachycardia, focal atrial tachycardia, atrial flutter and scar-related atrial reentrant tachycardia. Peak-to-peak amplitudes of both unipolar and bipolar electrograms were compared between the different groups. Unipolar voltages were equally distributed in patients with atrial flutter and post-operative AT. Bipolar voltages ≤ 0.1 mV were only found in patients with congenital heart defects. Hence, bipolar voltage maps should be used in order to successfully ablate post-operative AT.

In **chapter 12**, we studied the mechanism underlying post-operative AT in a large cohort of patients with complex congenital heart defects by analyzing 3-dimensional electro-anatomical activation/voltage maps. Not only macro-reentrant mechanisms giving rise to atrium flutter or scar-related AT were observed, but also focal mechanisms underlying post-operative AT were present. At the origin of these focal AT, circumscribed areas with heterogeneous conduction were found. Delineation of these areas of conduction abnormalities resulted in elimination of the focal AT.

In a following study (**chapter 13**), we quantified the degree of fractionation of bipolar atrial electrograms obtained from patients with focal AT and we studied 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. Our study population consisted of patients with congenital heart defects and patients without detectable heart disease. The area around the site of earliest activation of a FAT is characterized by an increase in the incidence of fractionated potentials, prolonged fractionation duration and a lower peak-to-peak-amplitude. Hence, fractionation and voltage mapping can besides activation mapping be used to identify the site of origin of FAT. The results of our study also 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.

In **chapter 14,** we present a case-report demonstrating an ablation procedure of a focal atrial tachycardia in a Fontan patient guided by fusion of electroanatomical activation maps and multi-slice computed tomography. This technique visualizes the position of the catheter in relation to the endocardium, thereby improving delineation of scar tissue which may facilitate ablation of complex post-operative AT.

Conclusions

- Compared to induced AF in young patients with normal atria, chronic AF in older patients with valvular heart disease is characterized by:
  - a higher incidence of epicardial breakthroughs
  - a larger beat-to-beat variation in fibrillation intervals
  - slowing of conduction
  - enhanced inhomogeneity in conduction
  - increased conduction anisotropy
  - a higher incidence of conduction block
  - a higher incidence of fractionated potentials and prolonged fractionation duration
- Irregularities in fibrillation intervals are mainly caused by epicardial breakthroughs. Conduction block occurred more frequently in patients with a higher incidence of epicardial breakthroughs supporting the hypothesis that the thin subepicardial layer is damaged in patients with CAF.
- Chronic AF is associated with transmural conduction of fibrillation waves. When there is a transmural propagation of fibrillation waves, the atria can contain more wavelets thereby stabilizing AF.
- Fractionation and fractionation delay maps visualize regional differences in fractionation and fractionation duration. Hence, fractionation fingerprints and fractionation (delay) maps are useful tools to identify the electro-pathological substrate of AF and to guide selective ablative therapies.
- In humans with chronic AF, there is an inter-individual variation in patterns of activation across Bachmann's Bundle as reflected by variation in heterogeneity in conduction and fractionation of fibrillation potentials.
- Epicardial high density mapping shows that there is an intra-atrial and inter-individual variation in electrophysiological characteristics including patterns of activation, fractionation and heterogeneity in conduction.
- The arrhythmogenic substrate perpetuating AF varies between patients implying that AF treatment needs to be individualized.
- The use of 3-dimensional electro-anatomical mapping systems facilitates mapping and ablation of atrial tachyarrhythmias.
- The arrhythmogenic substrate of late post-operative atrial tachyarrhythmias in patients with congenital heart defects is often bordered by areas of scar tissue.
- By using a bipolar voltage cut-off value of 0.1 mV during late post-operative atrial tachyarrhythmias low voltage areas can accurately be delineated in order to identify crucial pathways of conduction in reentrant circuits embedded within scar tissue which serve as target sites for ablation.

- Late post-operative atrial tachyarrhythmias in patients with congenital heart defects are not only caused by a macro-reentrant mechanisms giving rise to atrial flutter or scar-related AT but also by a focal mechanism.
- Fractionation and voltage mapping can – besides activation mapping – be used to identify the origin of focal AT.
- Mapping should always be the gold standard for diagnosing and treating AT.