New items in the electrophysiologist's toolbox

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APPENDIX A

SUMMARY

A.1 Introduction

Atrial fibrillation (AF) is characterized by irregular electrical activation of, and conduction in the atria and irregular activation of the ventricles. With an incidence ranging between 0.21 and 0.41 per 1.000 persons/year, AF is already the most common arrhythmia, but its incidence is still growing. It is estimated that AF will affect 14-17 million people worldwide by 2030. AF is a progressive disease with a clear need for early treatment. Using technology for smart employment of resources should help coping with the growing number of AF patients in the oncoming years. Smart employment means distribution of the right treatment to the right patient to ensure adequate AF control with minimal interventions. This thesis presents techniques that, in the future, could help in treating AF patients.

A.2 New tools

The trigger responsible for AF is most commonly found in the pulmonary veins (PVs). A common technique to treat AF is to remove the AF trigger by electrical isolation of the PVs (PVI). Patients may show AF recurrence after PVI because of an electrical reconnection of the PV, or because an AF trigger exists outside of the PVs. **Chapter 2** presented a method to investigate if the P-wave measured at different body surface locations provides an accurate measure for the timing and location of the ultimate left-atrial activations. Determining the P-wave properties correctly is important, because it can provide information on the electrical status of the atrium. The link between atrial conduction and P-wave morphology can be revealed by expanding the dataset presented in **Chapter 2**. The link between atrial conduction and P-wave morphology may then be used to monitor reconnection status of PVs non-invasively, for instance by comparing a body surface map recorded before the PVI procedure to a body surface map recorded during follow-up. Increased knowledge of PV-reconnection status, or the existence of an AF trigger outside the PVs shown by a lack of PV reconnection, could potentially help in selecting the right ablation method for the patient, thereby reducing ablation times and increasing the success rate of ablation procedures.

If there is no trigger in the PV regions, methods to detect AF inducing and AF sustaining mechanisms located outside the PVs are needed. The ideal technique to find these AF mechanisms does not focus on one specific characteristic of the recorded signals (for instance, the dominant frequency or voltage), but instead considers the total spatiotemporal signal. **Chapter 3** presented such a technique to analyze atrial endocardial mapping data by looking for repetitive patterns. Repetitive patterns are expected near localized and stable AF sources independently from their mechanisms (be it ectopic focal discharges or local reentries) and have been found to assist in identifying anatomical structures harboring preferential conduction paths, thereby reflecting the underlying bundle structure of the atria. **Chapter 3** used recurrence plots to detect repetitive patterns in 60 seconds of high density contact mapping data recorded in a goat model. A method was presented to determine if individual repetitive intervals are one time occurrences, or if repetitive intervals repeat over time. The results of **Chapter 3** showed the occurrence of repetitive patterns, and that the maximum duration of repetitive patterns as well as the size of the regions containing the most dominant repetitive pattern decrease with prolonged AF duration in a goat model.

The methodology of searching for repetitive patterns as presented in **Chapter 3** was applied to human data in **Chapter 4**. Atrial data was recorded using epicardial high-density grid recordings.

Recurrence plots were generated based on 10s of mapping data to study repetitiveness in paroxysmal and persistent AF patients. The repetitive patterns were classified into conduction pattern categories. Repetitive patterns could be identified in the majority of patients and in equal numbers for paroxysmal and persistent AF. The duration of repetitive patterns was longer in pAF patients compared to persAF patients. The majority of repetitive patterns were peripheral waves, often with conduction block, while breakthroughs and reentries occurred less frequently. The findings of **Chapter 3** and **4** may reflect well-described changes of the atrial substrate under the influence of AF, where prolonged AF leads to more complex atrial substrate indicated by a higher degree of block and a higher degree of electrical dissociation. This complex substrate may cause repeating AF patterns to become less stable in time and location. Repetitive patterns may represent different AF sources or AF drivers, which are independently able to perpetuate AF. In the future, with a wide enough coverage of the atria, recurrence mapping can possibly reveal the dominant drivers of a repeating pattern, and ablation at this location may cause conversion of AF to sinus rhythm. The analysis of stable repetitive patterns may also allow recordings at different sites in the atria to be used to reconstruct a composite activation map during AF, something which so far is only possible during stable activation patterns like atrial flutter or sinus rhythm. These composite AF activation maps could help increase the spatial coverage of standard mapping catheters.

The creation of contiguous ablation lines leads to a higher PVI success rate compared to PVI with non-contiguous ablation lines. However, robustness of ablation lines is not always accurately verifiable during the procedure. Means to ensure robust ablation lines can prevent AF recurrence, and thereby progression of AF, but also reduce the workload of electrophysiologists by reducing the number of redo PVI procedures. A method to evaluate the quality of ablation lines was discussed in **Chapter 5** where the use of adenosine to reveal dormant conduction during PVI was investigated in a large European retrospective database. The results showed a small benefit in rhythm outcome when adenosine is used and that adenosine is used in only 10.2% of all cases. Although our results showed a beneficial effect of adenosine use on rhythm outcome in selected subgroups, the source of the data (a registry not build for the purpose of adenosine evaluation) precluded strong recommendations for adenosine use. In the months following the publication of **Chapter 5**, multiple studies regarding this topic have been published that underline our conclusion that adenosine testing and the subsequent ablation of dormant conduction show a beneficial effect on long-term PVI outcome. Therefore it may be reasonable to make adenosine testing a standard part of PVI protocols.

A.3 Conclusion

This thesis showed several methods towards improving the workup for and ablation of AF. The future of non-pharmacological AF management should become easier by performing more detailed invasive and non-invasive electrophysiological measurements. Before the techniques presented in this thesis can be implemented, clinical trials have to be passed in which the ability to detect reconnections based on P-wave morphology, as well as the benefit of mapping and ablation based on recurrence maps have to be tested.