Evoluation and technological advances in ablation of complex atrial and ventricular arrhythmias

VALORIZATION

Scope, rationale and socio-economic relevance

The findings presented in this thesis will boost a significant improvement in the clinical efficacy of catheter ablation for complex arrhythmias such as atrial fibrillation (AF) and ventricular tachycardia (VT). As a consequence more patients may be treated effectively with fewer procedures per patient, thus improving the cost-effectiveness of this costly intervention. The revenue of our strategic physiological application of new ablation technology is even broader: it may not only lead to improved cost-effectiveness, but also it has already formed a firm stepping stone for follow-up observational and randomized controlled studies, enhancing on one hand the spread of our findings across centres in Europe (and the rest of the world), and on the other it generated new data to further enhance efficacy and safety of arrhythmia ablation, and formed a trigger for new technological developments as well.

The scope of atrial fibrillation

AF is the most common sustained arrhythmia. In 2010, the estimated worldwide prevalence was 33.5 million.[1,2] Estimates suggest an overall prevalence of approximately 3% in adults aged >20 years[3] and its incidence keeps rising due to better detection of silent AF[4-6], alongside increasing age and conditions predisposing to AF.[7] By 2030, 14–17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year.[3,8,9] AF is a serious public health problem because of its increasing incidence and prevalence in the aging population[10] and its association with elevated risks of cardiovascular events and death.[4,11-15] The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK, and between 6.0–26.0 billion US dollars in the US for 2008,[16,17] driven by AF-related complications (e.g. stroke) and treatment costs (e.g. hospitalizations). These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner. In addition, AF causes a wide variety of symptoms, including fatigue and reduced exercise tolerance, and significantly impairs quality of life.[18] The morbidity and mortality associated with AF provide a rationale to maintain sinus rhythm. Yet to date, rhythm control strategy has failed to demonstrate a beneficial effect on hard endpoints such as a reduction in stroke or mortality rate.[19-20] Ablation of atrial fibrillation has proven to reduce symptoms and improve quality of life, and is superior to antiarrhythmic drugs in obtaining rhythm control.[21-23] Therefore according to current guidelines AF ablation is indicated in symptomatic patients as a second-line treatment after failure of a class I or III antiarrhythmic drug (Class I indication (level of evidence A) in paroxysmal AF, A class IIa indication (level of evidence B) in persistent AF and a class IIb indication (level of evidence C) in long-standing persistent AF.[24] Given that catheter ablation of AF as a first-line treatment is associated with a higher freedom from AF compared with drug therapy,[25-27] current guidelines also state that catheter ablation of AF as a first-line treatment (without a trial of class I of III antiarrhythmic drugs) is indicated in symptomatic paroxysmal (Class IIa – level of evidence B) and

persistent AF patients (Class IIa – level of evidence C; and Class IIb – level of evidence C in case of long-standing persistent AF).[24]

Pulmonary vein isolation

Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF, pulmonary vein isolation (PVI) has become the cornerstone of catheter ablation of AF.[24] Over the past 20 years, the development of AF ablation technologies has been a constant effort to improve the PVI technique. The goal has been to improve patient outcomes, reducing the need for repeat procedures, to reduce procedure times and to increase the safety of the procedure. However, despite these advances and two decades of experience, long-term procedural success rates at curing AF are still suboptimal and may require repeat procedures or hybrid therapy with antiarrhythmic drugs to improve outcome. The reason for these suboptimal results is twofold; on one side the pathophysiological mechanism of AF is still not completely elucidated, and on the other side the ablation tools and techniques still fail to deliver durable and transmural ablation lesions. The cornerstone of ablation of AF is to achieve *durable* electrical isolation of the pulmonary veins.[24] Radiofrequency ablation, the most established ablation technique, aims to achieve PVI by applying circumferential contiguous and transmural point-by-point ablation lesions.[29] Despite achieving nearly always acute procedural PVI, early and late pulmonary vein reconnections are frequent and are associated with increased AF recurrences and the need for repeat ablation procedures.

Mapping drivers in persistent atrial fibrillation

Despite the advances in technology and our insight in the molecular, ionic, and physiological fundamentals of cardiac electrophysiology, the exact mechanism of AF is still not completely elucidated. Mechanisms in how AF is initiated and sustained may differ from patient to patient, and in various AF types (paroxysmal, persistent or permanent). Aside from the technical limitations in delivering qualitative ablation lesions, our limited understanding of the mechanisms that initiate and sustain AF withholds us from being able to cure this arrhythmia. While the outcome of AF ablation in paroxysmal AF is favorable and ensues from elimination of the triggering firing sources that arise predominantly from the pulmonary veins, the results of PVI are inferior in persistent AF. It is therefore perceived that in these patients (additional) ablation targeting the sustaining atrial substrate is necessary in order to improve ablation outcome. The benefit of non-specific ablation strategies (such as linear ablation or ablation of non-specific complex fragmented atrial electrograms)[30-31] has proven modest and therefore research is focusing on patient-tailored substrate ablation that is selectively targeting either the patient's specific anatomical substrate (e.g. fibrosis[32]) or patient specific mechanistic AF drivers. Indeed intra-procedural identification of focal and reentrant AF drivers could pose attractive and patient-specific targets for AF ablation.

Ablation of post-myocardial infarction ventricular tachycardia

For ischemic heart disease patients presenting with VT despite antiarrhythmic drug (AAD) therapy, which often results in ICD therapies (shocks or antitachycardia pacing), therapeutic options include escalating AAD therapy by increasing the dose, changing the drug, adding a new drug, and catheter ablation. In the recent VANISH trial, catheter ablation proved superior to increasing the dose of amiodarone or adding mexiletine.[33] In addition, in 3 large, prospective, multicenter cohort studies, VT ablation in patients with ischemic heart disease and recurrent VT despite AAD treatment ablation resulted in a consistent reduction of VT episodes.[34-36] Based on these results VT ablation in ischemic heart disease has become a Class I indication for patients with recurrence of (symptomatic) monomorphic VT despite AAD treatment.[37] Recently few studies have reported long-term follow-up data of VT ablation, guided predominantly by activation and entrainment mapping,[36,38] but long-term results of alternative strategies such as substrate modification have not been reported.

The novelty of our research and clinical perspectives

In PART I we aimed to contribute to the improvement of catheter ablation of AF. In PART IA we were the first to investigate if the benefits on contact force-sensing catheters maintained after acquiring extensive tip-tissue feedback with these advanced catheters. We found that an extensive learning-period still was no substitute for online contact force sensing.

In PART IB we developed a new protocol to optimize the results of pulmonary vein isolation, termed CLOSE-PVI. CLOSE-PVI proved to be associated with a very high single-procedure freedom from atrial arrhythmia recurrence, even when assessed with continuous cardiac monitoring; with more durable isolation at repeat studies; and without compromising safety. Using this novel ablation concept, efficacy is superior compared to previously published outcomes of PVI performed with either radiofrequency or cryo-energy. However, our favourable results on outcome and safety need to be confirmed in larger studies. As such, our multicenter VISTAX study was designed to assess the reproducibility of CLOSE-PVI across 17 European centers and evaluate the outcome in a larger group of 340 paroxysmal AF patients.[39]

In our striving to optimize PVI results there is growing interest in increasing the ablation power (high-power, short-duration applications) in order to further decrease the procedure time while maintaining/increasing safety. Given that the lesion depth is similar at a specific *ablation index* value (irrespective of the power) using a higher ablation power (45-50 W) is expected to be feasible. The POWER-AF trial was designed to investigate the efficacy and safety of the *'CLOSE'* protocol while using 45 W applications.

Even when point-by-point ablation is meticulously performed according to the strict established criteria, the *'CLOSE'* protocol is still not able to ensure durable PV isolation in 100% of cases. Indeed,

at repeat ablation due to arrhythmia recurrence, we found that 38% of patients still had at least one reconnected vein. This could be due to variables that are not taken into account, such as the tissue thickness or tissue composition. A patient-tailored strategy with adapted ablation characteristics based on pre- or intra-procedural imaging (e.g. with computed tomography or intra-cardiac echo) as well as intra-procedural lesion verification (e.g. with magnetic resonance imaging) might be the next step to improve CLOSE-PVI results.

After optimized index-PVI, even the majority of patients with clinical AF recurrence now present with four isolated pulmonary veins (PVs) during a repeat invasive procedure. On one hand this is the signature of our improvement in achieving durable, effective PVI. On the other hand, this poses several issues. Whereas in the past, repeat ablation for paroxysmal AF generally was straightforward, consisted of closing one or more gaps, had a favorable clinical result and had a shorter, predictable procedure duration. Now, in case of four isolated veins, the preferred ablation strategy is unknown (unless there is an overt non-PV trigger during the procedure), the outcome is worse irrespective of which ablation strategy is chosen, and the procedure time is highly variable (with practical planning issues). Therefore knowing prior to a repeat invasive procedure which patients have a status of four isolated veins is much desired and might – at this time – even lead to deferment of a repeat invasive procedure until all conservative treatment options have been exhausted. Unfortunately there are no distinct non-invasive characteristics that predict the likelihood of finding four isolated veins after AF recurrence. A randomized trial comparing a strategy of detailed invasive evaluation of the atrial substrate (such as high-density voltage mapping, localization/documentation of non-PV atrial extrasystole, …) during index-PVI vs. index-PVI without these invasive diagnostics would therefore be of interest.

In PART IC we applied the same principles of the '*CLOSE'* protocol to left atrial linear ablation, and demonstrated that this ablation strategy is also effective at the roof. The applicability of this ablation strategy could therefore be expanded to linear ablation in order to treat macro-reentrant atrial tachycardia or to isolate arrhythmogenic atrial areas. Only at the posterior mitral isthmus this ablation strategy proved unsuccessful, due to its specific anatomical configuration often necessitating epicardial ablation in order to achieve block. Other strategies, such as a combination with alcoholization of the Vein of Marshall, might increase our success in achieving mitral isthmus block.

In PART ID we investigated a new mapping technique with a high yield of online detection of potential bi-atrial drivers in persistent AF. These potential AF drivers can be automatically analyzed and annotated on a 3D-geometric bi-atrial shell, allowing patient-tailored substrate ablation. However the effect of ablation of was not investigated in our study and further studies are needed to investigate if ablation of these *repetitive atrial activation sequences* would indeed improve clinical outcome.

In PART II we aimed to contribute to the improvement of catheter ablation of ventricular tachycardia (VT) in ischemic heart disease. Our research was the first to publish long-term outcomes of single and multiple ablation procedures targeting modification of the arrhythmogenic substrate (in casu elimination of all *local abnormal ventricular activities* (LAVA)). This technique resulted in a substantial reduction of VT storm, VT burden and need for ICD shocks. Outcomes were improved by implementation of modern mapping technologies such as multi-electrode mapping and integration of pre-procedural imaging. However, the recurrence of previously ablated *LAVA* advocates the importance of effective and durable radiofrequency lesions. Therefore, in order to improve outcomes of VT ablation, further research should aim to develop criteria and/or tools for effective radiofrequency lesion creation in the ventricle. Secondly, while elimination of all *LAVA* was associated with a better outcome, many *LAVA* might be innocent bystanders and are not involved in channels responsible for current or future clinical VTs. Identification of potential VT channels on imaging studies (computed tomography or magnetic resonance imaging) might significantly reduce the amount of radiofrequency delivery, procedures times, avoid unnecessary myocardial destruction and improve arrhythmia-free survival.

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