Atrial tachyarrhythmias

Toward optimizing detection and invasive treatment

Mol, D.

Publication date
2022

CHAPTER 9

SUMMARY ATRIAL TACHYARRHYTHMIAS: TOWARD OPTIMIZING DETECTION AND INVASIVE TREATMENT

SUMMARY

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting millions of people worldwide. The estimated prevalence (2020) of AF among adults in the Netherlands is 2.0%. This number is expected to grow to 3.2% in 2060.[1] The AF prevalence will mainly increase in persons above 75. In the Netherlands, an estimate of 156.500 persons above 75 had AF in 2010, this number is expected to rise to 418.100 persons in 2060.[1] For persons above 55, 8.6% of the males have AF compared to 7.1% of the females. The age-adjusted risk for AF is similar for males and females.[1]

AF has been associated with an increased risk for adverse outcomes and more morbidity.[2-5] Patients with AF have a 2.4-fold higher risk for ischemic strokes, a 96% increased risk of cardiovascular events, a 1.5-fold higher risk for cognitive impairment, and a 1.4-fold higher risk for dementia.[2, 5, 6] Fifty percent of the patients with AF develop left ventricular dysfunction, and AF patients have a 2.4-fold higher risk for cardiovascular death.[2, 4] Also, AF patients have a poorer health-related quality of life compared to the general population and are 2.7 fold more likely to develop depression, anxiety, stress disorder, or receive psychotropic drugs within three months after AF diagnosis.[7, 8] Forty-one – 49% of the AF patients are hospitalised for a cardiovascular cause.[9, 10] Important to note is that AF was the reason in only 4% of these hospitalisations.[9] Symptoms of AF consists of palpitations, dyspnoea, exercise intolerance, chest tightness, syncope or fatigue.[11] However, in 1.4% of the patients aged above 65 years, AF remains undetected, and patients are potentially undertreated.[11, 12]

As mentioned above, patients with AF are carrying a significant disease burden which leads to a 73% increase in health care costs compared to matched individuals.[13, 14] In the Netherlands, the direct annual cost of a female patient with a first AF episode without any comorbidities is 1,544 euros.[14] The presence of underlying heart disease and cardiovascular hospitalisation increases the (direct) annual costs by 1,170 euro and 5,294 euro, respectively.[14]

Approximately 15% of the patients progress from paroxysmal to persistent AF. These patients have more comorbidities compared to those who do not progress.[15] It has been shown that lifestyle changes to lose weight, increasing physical activity, and treating risk factors reduce the AF burden, cardiovascular hospitalisations, and mortality.[16] The 2020 European Society of Cardiology AF guidelines provide a structured AF characterisation using the 4S-AF scheme.[17] 4S-AF indicates Stroke risk assessment, Symptom score, Severity of AF burden and Severity of substrate. Furthermore, the 2020 guideline includes the Atrial fibrillation Better Care (ABC) holistic pathway to optimize the management of AF patients. The ABC pathway consists of Avoiding stroke, Better symptom control, and management of Cardiovascular risk factors and concomitant diseases.[17] The holistic ABC pathway has been shown to lower the risk for all-cause mortality, cardiovascular death, major bleeding, first (cardiovascular) hospitalisation, and multiple hospitalisations.[18]

Aside from preventing adverse events, a decision needs to be made to restore sinus rhythm or accept the arrhythmia. The current guideline state that rate control can be applied in patients with no or minor symptoms.[17] However, the EAST AFNET-4 study data were not included in the current guidelines.[19] The EAST AFNET-4 demonstrated that early rhythm control resulted in a 35% stroke reduction and a 28% lower cardiovascular mortality risk.[19] As various older studies did not find benefit of rhythm control compared to rate control (albeit in an era with different perceptions regarding stroke prevention), this study changed our perspective of rhythm control.[20, 21] Indeed, following the 4S-AF scheme, we have to determine the chance of restoring and maintaining sinus rhythm and whether the patient benefits from rhythm control therapy.

Ablation therapy has become a cornerstone in the invasive rhythm control treatment in AF patients. Ectopic beats originating from the pulmonary veins (PV) have been identified as triggers for AF.[22] Ablation therapy eliminates the propagation of the ectopic beat from the PV to the left atrium. It has been shown that AF ablation is more effective in maintaining sinus rhythm and improving health-related quality of life than anti-arrhythmic drug therapy.[23, 24] Moreover, AF ablation has been suggested to reduce mortality and heart failure hospitalisation in specific heart failure patients.[25, 26] The recently published EARLY AF and the STOP AF studies investigated cryoballoon ablation as first-line therapy in patients with paroxysmal AF.[27, 28] Patients were randomised to cryoballoon ablation or anti-arrhythmic drug therapy. These studies demonstrate that cryoballoon ablation as first-line therapy is also more effective in maintaining sinus rhythm than anti-arrhythmic drugs.[27, 28] Despite this overwhelming evidence on the restoration of sinus rhythm, we have to keep in mind that the CABANA trial did not find any difference between AF ablation and anti-arrhythmic drug therapy for the composite primary endpoint of death, disabling stroke, serious bleeding, or cardiac arrest.[23]

Part I. Detection of Atrial Fibrillation

Opportunistic screening for AF has been shown to reduce stroke risk in patients aged 75 or 76.[29] When screening is performed with mobile devices, it is essential that the hardware to perform the heart rhythm measurement is widely available, easy to use, and has low costs. The automated algorithm requires excellent test characteristics to minimize the number of false positives or false negatives. Also, the population needs

S

to have a substantial pre-test risk for having AF and an increased thromboembolic risk profile. In **Chapter 2** we validated a new automated artificial intelligence AF detection algorithm that uses photoplethysmography (PPG) technology from a smartphone device. The algorithm was developed using data from the Heart-for-Heart campaign. The Heart-for-Heart was a worldwide crowdsourcing campaign that included > 15,000 PPG measurements. Importantly, this algorithm is able to provide an undetermined outcome in cases with any uncertainty, with this, the rate of false positives and false negative results is greatly reduced. For validation, we included 149 patients with AF admitted for elective electro cardioversion. A PPG recording was obtained in all patients before electro cardioversion and in 108 patients after electro cardioversion. This study demonstrated that this novel automated artificial intelligence algorithm had excellent test characteristics in a supervised clinical setting. By omitting measurements with low confidence, sensitivity and specificity increased with 1.8% and 4.6% to 98.1% for both sensitivity and specificity.

Part II. Arrhythmia Free Survival and Improvement of Quality of Life after Atrial Fibrillation and Flutter Ablation

After AF ablation, arrhythmia free survival varies between 50% and 81% depending on the type of AF, follow-up duration, and follow-up method used.[26, 27, 30-35] Patients with persistent forms of AF have more comorbidity, and longer AF episodes advance the left atrial substrate.[36, 37] Atrial fibrosis changes the conduction properties, emerges non-PV AF triggers, and has been associated with more atrial arrhythmia recurrences.[38, 39] However, randomized controlled trials failed to demonstrate benefit of non-PV target ablation in addition to PV isolation.[40-42] The 2020 European Society of Cardiology Atrial Fibrillation Guideline recommends patient-orientated outcomes such as Health-Related Quality of Life (HRQoL) as an essential factor in managing AF patients.[17] Although studies have been investigating outcomes after the second-generation cryoballoon ablation in patients with persistent AF, they are mostly limited to short-term follow-up or data on HRQoL are lacking.[43-45] In **Chapter 3**, we describe a cross-sectional study investigating 148 persistent AF patients who underwent cryoballoon PV isolation. We focus on arrhythmia free survival, AF-related symptoms and HRQoL. On average, patients were followed for 3.7 ± 1.0 years. After cryoballoon ablation, 55% of the patients had an atrial tachyarrhythmia recurrence, including AF in 89% of the patients and atrial tachycardia in 31%. Twenty-four percent of the patients underwent a repeat left atrium ablation and 1.4% a His bundle ablation. In this study, we demonstrate that despite a considerable number of patients with an atrial tachyarrhythmia recurrence, 80% of the patients improved in AF-related symptoms after multiple procedures. Also, at the last follow-up, patients had a good HRQoL (overall AFEQT score 88.9 [IQR 70.4 – 97.2]), and there was no difference in HRQoL between patients at 2, 3, 4 or 5 years follow-up.

During AF ablation, isolation of all PVs is achieved in nearly 100% of the patients.[31] However, PV isolation is durable in only 47% of the patients.[46] Reconnected PVs have been associated with more atrial tachyarrhythmia recurrences compared to patients with durable PV isolation.[46] Repeat AF ablation is performed in 15 - 24% of the patients. Before repeat AF ablation, PV reconnection is observed in up to 90% of patients.[47] Despite this high prevalence of reconnected PVs and the association between PV reconnection and arrhythmia free survival, non-PV target ablation strategies are widely used during repeat AF ablation, and comparative studies are limited.[48-52] In **Chapter 4**, we present a retrospective multicentre comparative assessment of non-PV target ablation (n = 140) versus PV target ablation (n = 140) in patients who underwent their first repeat AF ablation. As this study was non-randomized, we adjusted for covariates that influenced the treatment coefficient by more than 10%. Also, we performed a sensitivity analysis with inversed propensity weights. At 12 months follow-up, patients who underwent non-PV target ablation had significantly more atrial tachyarrhythmia, AF, and atrial tachycardia (AT) recurrences. However, these outcomes were strongly driven by baseline characteristics, and there was no difference in atrial tachyarrhythmia or AF recurrence risk after adjustment. Patients who underwent non-PV target ablation had a 2.2-fold (95% CI 1.18 – 4.42) higher AT recurrence risk. We also show a 2.5-fold (95% CI 1.17 – 5.12) higher risk of experiencing an AF recurrence in patients who underwent non-PV target ablation who had isolated PVs before the repeat AF ablation compared to patients who underwent PV target ablation with reconnected PVs. AF-related symptoms improved in all groups, and anti-arrhythmic drug (AAD) therapy was de-escalated in all groups, except for patients with isolated PVs who underwent non-PV target ablation. The de-escalation in AAD therapy and improvement in AF-related symptoms were most profound in patients who underwent PV target ablation.

The right-sided typical atrial flutter is a cavotricuspid isthmus dependent macro re-entrant tachycardia. Patients with an atrial flutter also have an increased risk for stroke and have similar comorbidity and adverse outcomes as patients with AF.[53] Due to the stability of the propagating re-entrant wave front rate-control is more difficult to establish compared to patients with AF. Right isthmus ablation with an 8-mm tip has shown to be highly effective to achieve isthmus conduction block.[54, 55] However, larger electrodes have worse sensing abilities compared to smaller.[56] In **Chapter 5**, we aimed to explore the additional diagnostic value of 8-mm ablation tips equipped with mini electrodes. Additional diagnostic value was defined as the presence of intracardiac signals on the mini electrode electrogram while absent on the conventional electrogram. We dem-

S

onstrate that ablation catheters equipped with mini electrodes had additional value in 23% of the patients. In addition, in 15% of the patients, ablation resulted in isthmus block while signals on the mini electrode electrogram were lacking. We demonstrate that 8-mm ablation electrodes equipped with mini electrodes were similarly effective in acute procedural success and one-year freedom of atrial flutter. However, in only a minority of the patients, ablation was solely performed guided on the mini electrodes.

Part III. Safety Outcomes of Atrial Fibrillation Ablation

In the Netherlands, the number of patients undergoing AF ablation has increased over the last few years.[57] Recently, studies have shown that PV isolation as a first-line treatment is more effective to maintain sinus rhythm than antiarrhythmic drugs, and that PV isolation can be performed safely in patients with paroxysmal AF.[27, 28] These findings open the gate for early AF ablation leading to more procedures. The generalizability of these data, however, might be limited because safety outcomes of AF ablation differ with patients' characteristics, ablation volume, and study type.[58, 59]

In **Chapter 6**, we present safety outcomes of three different AF ablation modalities, including conventional radiofrequency (RF) ablation, phased-RF ablation, and cryoballoon ablation. We used data from the Netherlands Heart Registration, compromising data from 13,823 patients. This study shows that the complications differ among the ablation strategies. Conventional-RF had the highest incidence of cardiac tamponades (for which an intervention was required) (0.8%) and vascular complications (1.7%). Persistent phrenic nerve palsy occurred in 1.5% of the patients who underwent cryoballoon ablation, but persistent phrenic nerve palsy rarely occurred in patients who underwent AF ablation with the other modalities. This study further demonstrates that females had a 3.0-fold (95% CI 1.98 – 4.45) higher risk to develop a bleeding complication, a 2.0-fold (95% CI 1.03 – 4.00) higher risk to develop a cardiac tamponade, and a 2.2-fold (95% CI 1.39 – 3.51) higher risk to develop a vascular complication. Among the ablation strategies, patients who underwent cryoballoon ablation had the lowest chance of being admitted for repeat left atrial ablation within one year. Patients who underwent phased-RF had the most significant chance of being admitted for repeat left atrial ablation. Furthermore, we present a Letter to the Editor by Jordaens et al. discussing our findings from **Chapter 6** and our response to that letter.[60]

Persistent phrenic nerve palsy is defined as phrenic nerve palsy lasting > 24 hours. Because most phrenic nerve palsies recover within this given period, data on the course of persistent phrenic nerve palsy is limited.[31, 61] In **Chapter 7**, we describe follow-up data from the Netherlands Heart Registration of patients who developed persistent phrenic nerve palsy during AF ablation. Following AF ablation, 54 patients developed proven persistent phrenic nerve palsy. Of those, follow-up data were available in 44 (81.5%) patients. All 44 patients had follow-up data on phrenic nerve palsy related symptoms, and objective follow-up data on the persistence of phrenic nerve palsy was available in 41 (76.0%) patients. After a median follow-up of 203 [113 – 351] days, phrenic nerve palsy recovered fully in 71% of the patients. Eighty-six percent of the patients were free op phrenic nerve palsy related symptoms after a median follow-up of 184 [82 – 359] days. In this study, we found that patients who underwent cryoballoon or thoracoscopic ablation had a 21-fold (95% CI 6.49 – 129.75) and 19-fold (95% CI 4.86–124.41) higher risk for persistent phrenic nerve palsy, respectively. Also, females had a 2.3-fold (95% CI 1.07 – 5.06) higher risk for the occurrence of persistent phrenic nerve palsy.

In **Chapter 8**, we study the 30-day mortality after AF ablation. In total, 25,858 patients underwent AF ablation in one of the 15 value-based health care centres in the Netherlands. The vital status of these patients was derived from the municipal death registration and was available in 99.9%. Fourteen (0.05%) patients died within 30 days. We considered the death as procedure-related in eight (0.03%) patients, non-procedure related in five (0.02%) patients, and the cause of death was unknown in one patient. This extremely low 30-day mortality after AF ablation rate was observed when performed in high volume centres (246 [range 55 – 514] AF ablations/year) with onsite cardiothoracic surgical back-up. Also, the 30-day mortality incidence after AF ablation does not exceed the crude death rate for persons aged between 50 – 80 in the Netherlands.[62]