Pathophysiologic Mechanisms and Catheter Ablation in Atrial Fibrillation

Summary of PhD Thesis

by

Cristina Vaduva, M.D.

Supervisor:

Robert Pap, M.D., Ph.D.

2nd Department of Internal Medicine and Cardiology Centre

Faculty of Medicine, University of Szeged

Doctoral School of Clinical Medicine-Clinical and Experimental Cardiovascular Science

2019

Introduction

Atrial fibrillation (AF) is an arrhythmia of increasing prevalence. Since the identification of trigger activity in the pulmonary vein by Haissaguerre et al, pulmonary vein isolation (PVI) by catheter ablation has become an established therapeutic modality for the treatment of patients with AF. It is a highly effective therapy when PV arrhythmogenicity is responsible for AF. However, when other pathophysiologic mechanisms are involved, the effectiveness of PVI may be limited.

Aims

In the search for ways to improve ablation success, first we conducted a systematic review of the published literature on the long term effectivenes of PVI (success rate, predictors and mechanism of recurrent atrial arrhythmias), then we studied pathophysiologic mechanisms, including atrial wall stretch and ectopic firing underlying AF.

Literature review

To be able to evaluate the very long-term results of atrial fibrillation ablation we conducted a systematic literature review of all relevant studies published until march 2015. We have also analyzed the literature on one of the most important proarrhythmic complications after LA ablation: regular atrial tachycardia or flutter and our own database of patients with paroxysmal and persistent atrial fibrillation ablation.

Experimental Methods

Study group 1

Eleven consecutive patients with manifest or concealed left-sided accessory pathway, without a history of AF (controls) and 16 patients with paroxysmal AF underwent invasive left atrial (LA) pressure monitoring via a transseptal catheter. Simultaneous transthoracic echocardiographic evaluation was undertaken including specle tracking LA strain analysis. The average positive

peak atrial longitudinal strain (PALS), which corresponds to LA reservoir function, was measured. The LA stiffness index (SI) was calculated as mean LA pressure(LAP)/PALS. After baseline measurements simultaneous atrioventricular (AV) pacing was carried out to produce an acute increase in LA pressure. LA effective refractory period (ERP) was determined both during simultaneous AV pacing and during atrial pacing at the same cycle length to control for the effect of the preceding cycle length on atrial ERP.

Study Group 2

Thirty-one consecutive patients undergoing their first PVI for drug-refractory, symptomatic, paroxysmal AF were prospectively studied. The LA and the PVs were mapped through double transseptal puncture. A decapolar circular mapping catheter (CMC) was positioned at the left PV antrum overlying both left PVs, and a 3.5 mm irrigated-tip mapping catheter was positioned on the right PV carina. AF was induced by isoproterenol infusion, starting at 3 μg/min with incremental doses of 5 μg/min until AF was induced, the maximum dose of 20 μg/min

was reached, or the patient developed side effects. Ectopic activity triggering an AF episode was identified, and the origin was determined based on the endocardial activation sequence and by comparison to paced activation sequences from PVs as well as observing LA-PV electrogram reversal. During AF electrograms were recorded from each bipole of the CMC positioned sequentially in all 4 PVs. After fast Fourier transformation (FFT) on two consecutive 5-s episodes recorded by the CMC the frequency spectrum in the 3–15 Hz range was obtained, and the peak with the highest power was determined as the dominant frequency (DF).
After electrical disconnection of all PVs by ablation, each PV was assessed periodically during a 30-min waiting period for the presence of dissociated firing (DiFi).

Study Group 3

Forty patients with paroxysmal AF were enrolled, with the aim being to test at least 30 patients with each drug. Patients were prospectively included and received adenosine (Ado) and isoproterenol (Iso) for induction of AF in a randomized order.

Iso was infused in incremental doses of 3-20μg/min as described above. Ado was administered into the right atrium (RA) via one long transseptal sheath. A quick bolus of 18 mg was given flushed with 5-10 ml of saline. A second dose of 36 mg was administered if AF was not induced after the first dose. Ectopic activity triggering an AF episode was identified and the origin determined based on the endocardial activation sequence, as described above. When sustained AF was induced and did not terminate after a few minutes, DCCV was performed and the second drug was administered after a 5-minute waiting period. In cases when immediate recurrence of AF (IRAF) occurred after DCCV, drug challenge was terminated and we proceeded with ablation. We determined the effectiveness of the two drugs in inducing AF and compared them with each other and spontaneous AF episodes in terms of the location of AF triggers.

Results

Our literature review suggests that success rates following ablation of AF are relatively favorable (50-

70%), however depend on technical aspects of the procedure and the frequency and intensity of arrhythmia monitoring. Ablation of AF may result in regular atrial tachycardias (ATs) or flutter, with variable frequency, depending on the ablation techniques used. The mechanism in the vast majority of cases is reentry related to gaps in prior ablation lines. Conservative therapy is usually not effective; radiofrequency ablation procedure is mostly successful but can be challenging and requires a complex approach.

Acute pressure elevation in controls and patients with AF

In Study Group 1 eleven controls and 16 patients with paroxysmal AF were included. Controls were younger and had smaller LA volume index (LAVI), without further differences in clinical characteristics. Patients with AF had higher mean (mLAP) and peak (pLAP) invasive LA pressures at baseline (8.3±4.7 vs. 5.1± 3.1 mmHg, p=0.048 and 20.8±8.8 vs. 14.6±5.7 mmHg, p= 0.015, respectively), compared to controls. Baseline LA PALS was significantly lower (15.1±5.1 vs. 21.6±6.2 %, p=0.006), while baseline SI was higher

(0.69±0.75 vs. 0.28±0.22, p=0.015), pointing to diminished LA reservoir function in patients with AF. At the same time, LA ERP was longer at baseline in AF patients, compared to controls (242.3±33.4 vs. 211.7±15.6 ms, p=0.017).

During simultaneous AV pacing, mLAP rose by the same extent in controls and AF patients (mean change 12.6±7.4 vs. 12.6±7.5 mmHg, p=0.980). At the same time, LA PALS decreased (from 15.1±5.1 to 11.6±3.3 %, p=0.008) and SI increased (from 0.69±0.75 to 1.29±1.17, p<0.001) in patients with AF, while they remained unchanged in controls (from 21.6±6.2 to 22.9±7.1 %, p=0.405 and from 0.28±0.22 to 0.45±0.43, p=0.10, respectively).

Association between dissociated firing in isolated pulmonary veins and atrial fibrillation

AF triggers were found to originate from the left superior PV (LSVP) in 20 (65 %) patients, from the left inferior PV (LIPV) in 5 (16 %) patients, and from the right PVs in 6 (19 %) patients. Fourteen (45 %) patients had DiFi after PVI in at least one and 7 of them in more

than one PV. It was recorded most commonly from the left upper (84 %) and lower (67 %) and less commonly from the right upper (31 %) PVs. There was no difference in size between PVs with or without DiFi.

Triggering PVs more commonly showed any DiFi, compared to nontriggering PVs (68 vs. 27 %, $p=0.003$) and more commonly had sustained DiFi (53 vs. 0 %, $p<0.001$).

During sustained AF, PVs with any DiFi showed faster maximal DF compared to PVs without DiFi (7.1±1.3 vs. 5.9±1.1 Hz, $p=0.001$). The maximal DF was higher in triggering PVs, compared to nontriggering ones (8.02±1.64 vs. 6.53±1.36, $p<0.001$).

Patients with DiFi after PVI had a longer mean time to recurrent AF after the last procedure compared to those without DiFi at the index procedure (52 vs. 32 months, $p=0.048$).

Isoproterenol versus adenosine for the identification of atrial fibrillation triggers

AF was induced with Iso in 15/32 (47%) and with Ado in 12/30 (40%) patients ($p=0.9$). Iso-triggered AF started

from the left PVs in 11/15 (73%), from the right PVs in 3/15 (20%), from the coronary sinus (CS) in 1/15 (7%) cases. Ado-induced AF episodes originated from the left PVs in 6/12 (50%), from the right atrium (RA) in 4/12 (33%), from the CS in 2/12 (17%) cases. Altogether Iso-induced AF was more likely initiated from the PVs (93%), compared to Ado (50%) (p=0.02). However, Ado-induced non-PV triggers did not show a correlation with spontaneous triggers and were not predictive of arrhythmia recurrence after PVI.

Conclusion

Atrial fibrillation (AF) is an arrhythmia of increasing prevalence. Catheter ablation is an important therapeutic modality for the treatment of patients with AF. Despite a continuous improvement in knowledge and technology PVI is still associated with significant recurrence rate especially in persistent AF. Improvement in the outcome of the procedure can be expected by influencing the mechanisms leading to persistence of AF, better identification of the structures responsible for arrhythmia

initiation and maintenance by drug challenge and monitoring for DiFi. Meticulous care in isolation of arrhythmogenic PVs, as well as ablation of non-PV sources can also improve therapeutic efficiency.

According to our study, increased atrial pressure can result in increased stiffness and wall tension with shortened atrial refractoriness favoring AF maintenance, which further contributes to heightened LA pressure. This way, a vicious circle is established, which may culminate in persistent AF. These results therefore suggest early intervention to prevent the progression of AF.

We have shown that DiFi after PVI can be considered a hallmark of PV arrhythmogenicity pointing to the role of the particular PV both in the initiation and maintenance of AF. When AF is initiated and maintained by PV arrhythmogenicity rather than other mechanisms, PVI should have a better outcome.

Ectopy inducing AF can be identified by drug challenge also, however, according to our results adenosine is likely to induce non-PV triggers without established clinical significance and therefore cannot be

recommended for the identification of trigger sites to guide catheter ablation of paroxysmal AF.

New observations

1. The normal LA can adapt to episodes of acute pressure elevation without a substantial change in reservoir function and ERP. On the other hand, patients with AF show an exaggerated fall in LA reservoir function in response to pressure rise, with an out of proportion increase in wall tension leading to a decline in LA ERP. This mechanoelectric feedback likely further promotes the development of AF.
2. Pulmonary veins with dissociated firing are more likely to have a role as initiators and perpetuators of paroxysmal AF.

3. Adenosine is much more likely, than isoproterenol to induce non-PV triggers, especially from the RA. The clinical significance of these foci, however, is questionable therefore it cannot be recommended for the identification AF triggers.

Publications related to the subject of the thesis

I. Tutuianu C, Szilagy J, Pap R, Sághy L. Very Long-TermResults Of Atrial Fibrillation Ablation Confirm That This Therapy Is Really Effective. J Atr Fibrillation. 2015 Aug 31;8(2):1226. . **IF 0.14**

II. Sághy L, Tutuianu C, Szilágyi J. Atrial tachycardias following atrial fibrillation ablation Curr Cardiol Rev. 2015;11(2):149-56. **IF 1.35**

III. Ágoston G, Szilágyi J, Bencsik G, Tutuianu C, Klausz G, Sághy L, Varga A, Forster T, Pap R. Impaired adaptation to left atrial pressure increase in patients with atrial fibrillation. J Interv Card Electrophysiol. 2015 Nov;44(2):113-8. **IF 1.676**

IV. Tutuianu C, Traykov V, Bencsik G, Klausz G, Sághy L, Pap R. Association between dissociated firing in isolated pulmonary veins and the initiation and maintenance of atrial fibrillation. J Interv Card Electrophysiol. 2016 Jan;45(1):29-35. **IF 1.826**

V. Tutuianu C, Pap R, Riesz T, Bencsik G, Makai A, Saghy L. Is adenosine useful for the identification of atrial fibrillation triggers? J Cardiovasc Electrophysiol. 2018 Oct 29. doi: 10.1111/jce.13779. **IF 2,873**