New items in the electrophysiologist's toolbox

Citation for published version (APA):

van Rosmalen, F. (2021). *New items in the electrophysiologist's toolbox: future improvements for electrophysiological AF treatment*. [Doctoral Thesis, Maastricht University]. Gildeprint Drukkerijen. <https://doi.org/10.26481/dis.20210113fr>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20210113fr](https://doi.org/10.26481/dis.20210113fr)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

New items in the electrophysiologist's toolbox

*future improvements for electrophysiological
AF treatment*

Frank van Rosmalen

Copyright © 2020 by Frank van Rosmalen

Cover design and thesis layout: Frank van Rosmalen & Ben Hermans

Cover figures are downloaded from [freepik.com](https://www.freepik.com) and adjusted by Frank van Rosmalen

Printed by Gildeprint, The Netherlands

ISBN: 978-94-6419-096-0

New items in the electrophysiologist's toolbox

*future improvements for electrophysiological
AF treatment*

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, prof. dr. Rianne M. Letschert,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 13 januari 2021 om 16:00 uur

door

Frank van Rosmalen

geboren op 4 november 1988
te Beilen, Nederland

Promotores

Prof. dr. T. Delhaas

Prof. dr. U. Schotten

Copromotor

Dr. S. Zeemering

Beoordelingscommissie

Prof. dr. K. Vernooy (voorzitter)

Prof. dr. L.V.A. Boersma (St. Antonius Ziekenhuis Nieuwegein/Amsterdam UMC)

Dr. J.M.H. Karel

Prof. dr. F.W. Prinzen

Prof. dr. R. Tavernier (AZ Sint-Jan, Brugge, België)

Financial support by the Dutch Heart Foundation, Hart en vaat onderzoekfonds Limburg and Maastricht University for the publication of this thesis is gratefully acknowledged.

Table of Contents

Chapter 1	General Introduction	7
Chapter 2	Combining endocardial and body surface potentials to interpret the end of the P-wave	17
Chapter 3	A novel tool for the identification and characterization of repetitive patterns in high-density contact mapping of atrial fibrillation	37
Chapter 4	Incidence, prevalence and prajectories of repetitive conduction patterns in human atrial fibrillation	65
Chapter 5	Adenosine usage during AF ablation in Europe and selected long-term findings from the ESC-EHRA EORP atrial fibrillation ablation long-term registry	85
Chapter 6	General Discussion	107
Appendices	A Summary	119
	B Acknowledgements (Dankwoord)	125
	C Curriculum Vitae	131

CHAPTER 1

GENERAL INTRODUCTION

1.1 Background

The heart can be viewed functionally as two electrically activated pumps with the pulmonary and systemic circulations situated in between the pumps. Electric activation starts at the sinoatrial (SA) node located within the posterior wall of the right atrium (RA). Action potentials generated by the SA node spread as a wave throughout the atria. The atria are electrically separated from the ventricles by non-conducting connective tissue except for the atrio-ventricular (AV) node located in the inferior-posterior region of the interatrial septum. The AV node consists of highly specialized conducting tissue that slows the impulse conduction, resulting in a delay of ventricular activation. This delay is important because it allows sufficient time for complete atrial depolarization, contraction, and emptying of atrial blood into the ventricles prior to ventricular activation and contraction. The slow conduction of the AV node also helps to limit the frequency of impulses traveling through the AV node, an important safety feature in case of atrial arrhythmia/tachycardia. For optimal functioning of the heart as a pump it is important that the heart is activated in a constant rhythm, and that the frequency of this rhythm is sufficiently low to allow the ventricles and atria to fill before they contract.

1.1.1 Atrial Fibrillation

Atrial fibrillation (AF) is characterized by irregular electrical conduction in the atria and irregular activation of the atria and ventricles. Exercise capacity of persons in AF is reduced because they do not show rate adaptation, a process where the heart rate responds to the activity level of a person. Moreover, the cardiac pump function is reduced because the ventricles can be activated before ideal filling time has passed.¹ Reduction of cardiac pump function causes impaired blood flow, leading to an increased stroke risk.²

AF is associated with a 1.5 to 2-fold increase in all-cause mortality.³ With a current incidence ranging between 0.21 and 0.41 per 1.000 persons/year, AF is already the most common arrhythmia,⁴ but its incidence is still growing. The ever increasing AF incidence is linked to an increase in incidence of AF risks factors, for instance obesity and high blood pressure. The number of AF cases is increasing worldwide, not only due to the growing AF incidence, but also because the detection rate for AF is higher due to more and better screening techniques.⁵ It is estimated that AF will affect 14-17 million people worldwide by 2030.⁴

Although still not completely understood, mechanisms that initiate or sustain AF are often divided into two categories. Triggers are the first mechanism, they occur as ectopic focal activity which is caused by electrical impulses generated by cells other than the sinus node. The generation of these impulses can be faster than the pacemaker activity of the SA node and can occur anywhere in the atria, thereby disturbing the normal conduction pattern of atrial activation. The majority of focal activity inducing AF is found in the pulmonary vein regions.⁶

Altered electrophysiological properties, sometimes but not always due to altered structural properties of the atria, are responsible for the second mechanism that may initiate or sustain AF. This mechanism is hence often indicated by "AF substrate". Electrophysiological properties can be altered in response to AF risk factors, for instance high blood pressure, but may also be induced by AF itself. Within minutes to hours of AF, electrical changes in atrial tissue can be found, called electrical remodeling.⁷ The high

atrial activation rate causes an array of changes in ion currents that result in shortening of the cellular action potential⁸ allowing the cells to be reactivated sooner than normal.⁹ A second effect of electrical remodeling is that some, but not all, atrial cells are easier to activate.¹⁰ Because the cells can now be activated in rapid succession, and because the activation wave does not spread homogeneously over the cells, the chance of reentry and AF maintenance increases.

Besides electrical remodeling, atria also undergo structural remodeling as a consequence of AF.¹¹ In reaction to increased mechanical loads, the atria become enlarged¹² and a mild form of endomysial fibrosis occurs.^{10,13} Atrial fibrosis causes local conduction heterogeneities, particularly at short activation intervals, favoring reentry and AF maintenance.¹⁴ Both processes contribute to the increasing stability of AF over time,¹⁵ making it a progressive disease with a clear need for early treatment.^{16,17}

1.1.2 Catheter ablation for atrial fibrillation

Catheter ablation aims to remove either the trigger that generates AF, or the circuit that sustains AF once it has started. An ablation catheter is inserted through a vein or artery in the groin and is brought into the atria. The tip of the ablation catheter destroys atrial tissue by applying energy, either in the form of heat or cold.¹⁸ The advantage of catheter ablation is that it is less invasive compared to surgery and, if successful, the patient no longer needs drugs to remain in sinus rhythm. The removal of a trigger can be achieved by electrically isolating areas with triggered activity from the rest of the atria.¹⁹ An example of this is pulmonary vein isolation (PVI), where the pulmonary veins (PVs) are isolated from the atria by destroying a ring of tissue around the entrance of the PVs. By destroying the tissue, the cells can no longer conduct electrical signals and therefore the PVs are electrically isolated from the left atrium. AF reentry can be disrupted by destroying a line of tissue over the atrium that is in the path of the reentry circuit. PVI is currently the cornerstone of catheter ablation for AF, but other options have been tried over the years. In the last decade, research has focused on terminating AF by targeting AF substrate mechanisms that could potentially maintain AF. For example, complex fractionated atrial electrograms (CFAEs)²⁰ have been suggested to represent highly complex AF with a high degree of conduction block. Such areas may generate more fibrillation waves than they absorb. Another option that was explored was rotor ablation²¹ thereby assuming that atrial activation spirals around a central core. However, in the past years it has been shown that neither the addition of CFAE ablation to PVI nor the addition of rotor ablation to PVI consistently and reproducibly increase the long-term rhythm outcome of patients undergoing AF ablation.^{22,23}

1.2 Thesis outline

Around 30% of patients show recurrence of AF within a year of the ablation procedure.²⁴ AF is confirmed by an irregular ventricular rate and a lack of P-waves in the ECG. The morphology of the P-wave changes, depending on where on the body the P-wave is measured. In **Chapter 2**, we present a technique to link the P-wave measured on the body surface to endocardial atrial activations during the course of the P-wave. The P-wave might contain information on the conduction around the pulmonary veins, especially the terminal portion of the P-wave that mostly reflects left-atrial activity. We investigated a technique to find out whether it is possible to find the true end of left atrial activity in the P-wave on the ECG, and which location on the body surface is most suitable to find the end of the P-wave. Accurate measurement of

the P-wave is important since P-wave duration was found to be associated with an increased risk of AF in 12-lead ECG recordings.²⁵ Interestingly, increased AF risk was not only shown for long, but also for short P-wave durations. The mechanism behind this association is still unclear. Therefore, it is interesting to be able to investigate the nature of the relation between total atrial activation time, atrial conduction pattern during sinus rhythm, and the associated P-wave duration.

Although the freezing and heating techniques to destroy atrial tissue are advancing rapidly, the success rate of AF ablation has remained constant over the past decade. Studies have shown that an increasing number of patients who return in AF after PVI still have isolated PVs.^{30–33} This suggests that the trigger, or the atrial source that sustains AF, must be located elsewhere in the atrium. Therefore, it is likely that the recurrence rate of AF is not caused by improper energy delivery to the atrial tissue, but by a lack of mapping methods to locate an AF source outside the PVs. The narrow field of view of currently used mapping catheters may play a role in the difficulty of finding these sources outside of the PV. Multiple studies show that candidate AF sources exhibit repetitive patterns of wave propagation.^{34–38} The existence of stable repetitive patterns during AF would allow recordings of different atrial sites to be combined into a complete overview of repetitive conduction in the atrium. This can be done by recording the atrial wall simultaneously with the repetitive area and then combining the atrial recordings based on the repetitions, as is already common in 3D mapping of stable patterns such as flutters.³⁹ Besides, repetitive conduction patterns are of interest because they might reflect anatomical structures harboring preferential conduction paths and thereby reflect the underlying bundle structure of the atrium.^{37,40,41} For these reasons a mapping technique able to find repetitive patterns may help to study structure-function relationships during fibrillatory conduction. A panoramic view of repetitive conduction may provide new insight in AF mechanisms, with the potential to identify and localize AF sources. **Chapter 3** presents a new technique to analyze atrial mapping data to gain insight into the incidence and conduction characteristics of repetitive patterns of atrial conduction using an AF goat model. The technique uses recurrence plots to represent 60 seconds of high density contact mapping data. The recurrence plot is used to detect repetitive patterns, and a method is presented to determine if individual repetitive intervals are one time occurrences, or if repetitive intervals repeat over time.

In **Chapter 4** we apply the recurrence plot technique to high-density atrial maps of paroxysmal and persistent AF patients to detect repetitive patterns. This chapter presents data on the difference in occurrence and variability of repetitive patterns between paroxysmal and persistent AF patients. The conduction pattern within a recurrent interval is explored by visualizing individual repetitive intervals, and then classifying these intervals in conduction pattern categories. Classification of the patterns can show the activation path responsible for the repetitiveness of the conduction, and may provide information on the underlying structural or functional mechanism causing AF.

Though catheter ablation for AF is worldwide the most commonly performed ablation technique¹⁹, some questions remain to be answered regarding the optimal use of this procedure. One of the questions is whether to use pharmacological agents to check robustness of ablation lines. Catheter ablation uses either heat or cold to destroy tissue. Tissue that is heated or cooled, but not destroyed, can show a temporary loss of function.^{mmmmmm} This may lead to the false conclusion that an ablation line is complete, where it may in fact be able to conduct electrical activity after recovery from the temporary loss of function. It has been demonstrated that complete isolation lines show less recurrence of AF compared to incomplete ablation lines.²⁷ Pulmonary veins can reconnect within 3 months after the ablation, even though the robustness of the ablated line was checked after the PVI procedure by confirming exit block

and a loss of or dissociation of local electrograms in the ablated zone.^{27,28} Adenosine can be used to reveal this so called 'dormant conduction' of tissue during the PVI procedure.²⁹ In **Chapter 5**, we present a study where we used a European multicenter registry to investigate the use of adenosine in Europe. We also present selected long-term findings of adenosine use.

The thesis is concluded in **Chapter 6** with a **General Discussion** in which the findings of the various chapters are put into broader perspective and where the scientific and societal impact of this thesis is discussed.

1.3 References

1. van Gelder IC, Crijns HJGM, Blanksma PK, et al.: Time course of hemodynamic changes and improvement of exercise tolerance after cardioversion of chronic atrial fibrillation unassociated with cardiac valve disease. *Am J Cardiol* 1993;72:560–566.
2. Wolf PA, Abbott RD, Kannel WB: Atrial fibrillation as an independent risk factor for stroke: The framingham study. *Stroke* 1991;22:983–988.
3. Andersson T, Magnuson A, Bryngelsson IL, et al.: All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: A Swedish nationwide long-term case-control study. *Eur Heart J* 2013;34:1061–1067.
4. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S: Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;6:213–220.
5. Schnabel RB, Yin X, Larson MG, et al.: Fifty-Year Trends in Atrial Fibrillation Prevalence, Incidence, Risk Factors, and Mortality in the Community Renate. *Lancet* 2015;386:154–162.
6. Haïssaguerre M, Jais P, Shah DC, et al.: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–666.
7. Allessie MA, Ausma J, Schotten U: Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230–246.
8. Heijman J, Voigt N, Nattel S, Dobrev D: Cellular and Molecular Electrophysiology of Atrial Fibrillation Initiation, Maintenance, and Progression. *Circ Res* 2014;114:1483–1499.
9. Veenhuyzen GD, Simpson CS, Abdollah H: Atrial fibrillation. *CMAJ* 2004;171:755–760.
10. Nattel S, Harada M: Atrial remodeling and atrial fibrillation: Recent advances and translational perspectives. *J Am Coll Cardiol* 2014;63:2335–2345.
11. Schotten U, Neuberger HR, Allessie MA: The role of atrial dilatation in the domestication of atrial fibrillation. *Prog Biophys Mol Biol* 2003;82:151–162.
12. Spach MS, Heidlage JF, Barr RC, Dolber PC: Cell size and communication: Role in structural and electrical development and remodeling of the heart. *Heart Rhythm* 2004;1:500–515.
13. Tan AY, Zimetbaum P: Atrial fibrillation and atrial fibrosis. *J Cardiovasc Pharmacol* 2011;57:625–629.
14. Nattel S, Burstein B, Dobrev D: Atrial Remodeling and Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2008;1:62–73.
15. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA: Atrial Fibrillation Begets Atrial Fibrillation. *Circulation* 1995;92:1954–1968.
16. Kirchhof P, Benussi S, Kotecha D, et al.: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18:1609–1678.
17. Proietti R, Hadjis A, Alturki A, et al.: A systematic review on the progression of paroxysmal to persistent atrial fibrillation: Shedding new light on the effects of catheter ablation. *JACC Clin Electrophysiol* 2015;1:105–115.
18. Kuck K-H, Brugada J, Fürnkranz A, et al.: Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016;374:2235–2245.
19. Calkins H, Hindricks G, Cappato R, et al.: 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:e1–e160.
20. Nademanee K, McKenzie J, Kosar E, et al.: A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;43:2044–2053.
21. Narayan SM, Krummen DE, Rappel W-J: Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol* 2013;23:447–454.
22. Verma A, Jiang CY, Betts TR, et al.: Approaches to catheter ablation for persistent atrial fibrillation.

- N Engl J Med 2015;372:1812–1822.
23. Mohanty S, Mohanty P, Trivedi C, et al.: Long-Term Outcome of Pulmonary Vein Isolation With and Without Focal Impulse and Rotor Modulation Mapping. *Circ Arrhythm Electrophysiol* 2018;11(3):e005789.
24. Schmidt B, Brugada J, Arbelo E, et al.: Ablation strategies for different types of atrial fibrillation in Europe: results of the ESC-EORP EHRA Atrial Fibrillation Ablation Long-Term registry. *EP Eur* 2020;22:558–566.
25. Nielsen JB, Kühl JT, Pietersen A, et al.: P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. *Heart Rhythm* 2015;12:1887–1895.
26. Arentz T, Macle L, Kalusche D, et al.: “Dormant” Pulmonary Vein Conduction Revealed by Adenosine after Ostial Radiofrequency Catheter Ablation. *J Cardiovasc Electrophysiol* 2004;15:1041–1047.
27. Kuck K-H, Hoffmann BA, Ernst S, et al.: Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol* 2016;9:e003337.
28. Linhart M, Alarcon F, Borràs R, et al.: Delayed Gadolinium Enhancement Magnetic Resonance Imaging Detected Anatomic Gap Length in Wide Circumferential Pulmonary Vein Ablation Lesions Is Associated With Recurrence of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2018;11:e006659.
29. Datino T, Macle L, Qi X-Y, et al.: Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation* 2010;121:963–972.
30. Sultan A, Lükér J, Hoffmann B, et al.: Interventional management of recurrent paroxysmal atrial fibrillation despite isolated pulmonary veins: impact of an ablation strategy targeting inducible atrial tachyarrhythmias. *Europace* 2016;18:994–999.
31. Coutiño HE, de Asmundis C, Mugnai G, et al.: Repeat procedures after second-generation cryoballoon ablation as an index procedure for persistent atrial fibrillation: one-year follow-up. *J Interv Card Electrophysiol* 2016;47:365–371.
32. Baldinger SH, Chinitz JS, Kapur S, et al.: Recurrence of Atrial Arrhythmias Despite Persistent Pulmonary Vein Isolation After Catheter Ablation for Atrial Fibrillation. *JACC Clin Electrophysiol* 2016;2:723–731.
33. Szilágyi J, Marcus GM, Badhwar N, et al.: Atrial fibrillation patients with isolated pulmonary veins: Is sinus rhythm achievable? *J Cardiovasc Electrophysiol* 2017;28:754–761.
34. Holm M, Johansson R, Brandt J, Luhrs C, Olsson SB: Epicardial right atrial free wall mapping in chronic atrial fibrillation. Documentation of repetitive activation with a focal spread - A hitherto unrecognised phenomenon in man. *Eur Heart J* 1997;18:290–310.
35. Lee S, Sahadevan J, Khrestian CM, et al.: Simultaneous Batrial High-Density (510-512 Electrodes) Epicardial Mapping of Persistent and Long-Standing Persistent Atrial Fibrillation in Patients: New Insights into the Mechanism of Its Maintenance. *Circulation* 2015;132:2108–2117.
36. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J: Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* 2000;101:194–199.
37. Hansen BJ, Zhao J, Csepe TA, et al.: Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390–2401.
38. Narayan SM, Shivkumar K, Krummen DE, Miller JM, Rappel W-J: Panoramic Electrophysiological Mapping but not Electrogram Morphology Identifies Stable Sources for Human Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:58–67.
39. Shah DC, Jais P, Haïssaguerre M, et al.: Three-dimensional mapping of the common atrial flutter

- circuit in the right atrium. *Circulation* 1997;96:3904–3912.
40. van Hunnik A, Zeemering S, Podziemski P, et al.: Stationary atrial fibrillation properties in the goat do not entail stable or recurrent conduction patterns. *Front Physiol* 2018;9:1–16.
 41. Maesen B, Zeemering S, Afonso C, et al.: Rearrangement of atrial bundle architecture and consequent changes in anisotropy of conduction constitute the 3-dimensional substrate for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:967–975.

CHAPTER 2

COMBINING ENDOCARDIAL AND BODY SURFACE POTENTIALS TO INTERPRET THE END OF THE P WAVE

Frank van Rosmalen, Stef Zeemering, Ulrich Schotten, Tammo Delhaas

In preparation

CHAPTER 3

A NOVEL TOOL FOR THE IDENTIFICATION AND CHARACTERIZATION OF REPETITIVE PATTERNS IN HIGH-DENSITY CONTACT MAPPING OF ATRIAL FIBRILLATION

Stef Zeemering[†], Arne van Hunnik[†], **Frank van Rosmalen**, Pietro Bonizzi, Billy Scaf, Tammo Delhaas, Sander Verheule, Ulrich Schotten

Frontiers in Physiology, October, 2020

[†]Both authors contributed equally

Abstract

Introduction

Electrical contact mapping provides a detailed view of conduction patterns in the atria during atrial fibrillation (AF). Identification of repetitive wave front propagation mechanisms potentially initiating or sustaining AF might provide more insights into temporal and spatial distribution of candidate AF mechanism and identify targets for catheter ablation. We developed a novel tool based on recurrence plots to automatically identify and characterize repetitive conduction patterns in high-density contact mapping of AF.

Methods

Recurrence plots were constructed by first transforming atrial electrograms recorded by a multi-electrode array to activation-phase signals and then quantifying the degree of similarity between snapshots of the activation-phase in the electrode array. An AF cycle length dependent distance threshold was applied to discriminate between repetitive and non-repetitive snapshots. Intervals containing repetitive conduction patterns were detected in a recurrence plot as regions with a high recurrence rate. Intervals that contained similar repetitive patterns were then grouped into clusters. To demonstrate the ability to detect and quantify the incidence, duration and size of repetitive patterns, the tool was applied to left and right atrial recordings in a goat model of different duration of persistent AF (3 weeks AF (3wkAF, n=8) and 22 weeks AF (22wkAF, n=8)), using a 249-electrode mapping array (2.4mm inter-electrode distance).

Results

Recurrence plots identified frequent recurrences of activation patterns in all recordings and indicated a strong correlation between recurrence plot threshold and AF cycle length. Prolonged AF duration was associated with shorter repetitive pattern duration (mean maximum duration 3wkAF: 74 cycles, 95% confidence interval [54-94] vs. 22wkAF: 41 cycles [21-62], $p=0.03$), and smaller recurrent regions within repetitive patterns (3wkAF 1.7cm² [1.0-2.3] vs. 22wkAF 0.5cm² [0.0-1.2], $p=0.02$). Both breakthrough patterns and reentry were identified as repetitive conduction patterns.

Conclusion

Recurrence plots provide a novel way to delineate high-density contact mapping of atrial fibrillation. Dominant repetitive conduction patterns were identified in a goat model of sustained AF. Application of the developed methodology using the new generation of multi-electrode catheters could identify additional targets for catheter ablation of AF.

3.1 Introduction

During atrial fibrillation (AF) electrical conduction patterns in the atria are diverse, variable, and often complex. The complexity of these wave front patterns, i.e. the number of waves that propagate through the atria during each AF cycle, typically increases with AF duration.¹ Catheter ablation of AF aims at isolation of triggers for AF and at elimination of a dominant electrical mechanism that initiates or sustains AF. Current success rates of various approaches to catheter ablation of AF in patients show that there is a need to systematically identify additional targets besides the pulmonary veins (PV), especially in patients undergoing redo procedures after initially successful PV isolation. Several candidate mechanisms, associated detection algorithms, and ablation strategies have been proposed and applied in the last few decades, but this has not yet led to significantly improved long-term ablation outcome.^{2,3}

Proposed candidate sources of AF often show a high degree of repetitiveness. Repetitive focal patterns of activation detected in high-density mapping have been reported in patients with persistent AF^{4,5}, but others found repetitive focal events to be rare⁶. Highly repetitive microreentrant sources were found using optical mapping, both in sheep⁷ and in a small diverse set of human explanted hearts⁸, but also using panoramic contact mapping⁹. Other studies suggest more unstable spatiotemporal behavior of reentrant circuits, driven by an underlying stochastic process of wave generation¹⁰ or clustered at the borders of fibrotic atrial regions¹¹. Repetitive AF sources were also identified in several anatomical locations with a more general approach based on high electrogram morphology similarity and short AF cycle length.^{12,13}

Repetitive conduction is also to be expected in the vicinity of such local drivers. A local source may not always conduct 1:1 to its vicinity but this region is nonetheless expected to exhibit repetitive conduction patterns driven by the source. The presence of repetitive patterns in a region of the atria may furthermore reveal a structure-function relationship at that site, impacted by atrial anatomy^{8,14} or by structural remodeling associated with AF^{15,16}. A repetitive pattern may also be the precursor to (spontaneous) termination of AF¹⁷, or give an indication of the overall state of atrial conduction, i.e. the dynamics of linking of conduction between consecutive activations in different atrial regions¹⁸. Therefore, techniques to reliably identify repetitive conduction patterns can be very instrumental, particularly in the light of recent advances towards electro-anatomical mapping tools with increased spatiotemporal resolution.

In this paper we introduce a method to analyze the incidence and characteristics of repetitive conduction patterns in contact mapping of AF using a recurrence plot, a well-established technique to study the dynamics of complex nonlinear systems¹⁹. We demonstrate the ability of this novel computational tool to detect and quantify repetitive conduction patterns in high-density epicardial mapping in a goat model of AF.

3.2 Materials and Methods

3.2.1 High-density contact mapping in a goat model of AF

In this study we made use of a retrospective dataset, comprised of baseline measurements from a drug provocation study in two groups of 8 goats, in which AF was induced by left atrial burst pacing and maintained for either 3 weeks (3wkAF) or 22 weeks (22wkAF). High-density contact mapping was performed during an open-chest experiment, using a 249-electrode circular mapping array (2.4mm inter-electrode distance, sampling frequency 1039Hz). One-minute recordings of unipolar atrial electrograms were made simultaneously on the right atrial (RA) and left atrial (LA) epicardial wall. Further experimental details can be found in ¹⁴. The study protocol was approved by the local ethics committee and complied with the Dutch and European directives.

3.2.2 Recurrence plot construction to visualize repetitive pattern incidence

Recurrence plots provide a general way to visualize and analyze the temporal behavior of complex nonlinear dynamical systems.¹⁹ It requires the definition of a phase-space trajectory of the dynamical system and a distance function that measures the similarity or distance between any pair of time points on the trajectory. A recurrence then occurs when the distance between two points in time is below a certain threshold. The recurrence rate RR is defined as the fraction of detected recurrences over all comparisons.

We adapted this general definition of recurrence plots to the analysis of atrial electrograms and conduction patterns. The approach is illustrated in **Figure 1** on a recording of beats that were regularly paced from four cardinal directions. First, unipolar atrial electrograms were transformed to activation-phase signals by local activation time annotation, employing a previously published algorithm that assigns local atrial deflections to maximize the likelihood of atrial deflection intervals given an estimated AF cycle length distribution.²⁰ Activation-phase signals (in the range $[-\pi, \pi]$) were constructed by linear interpolation, taking the local activation time as the moment of phase inversion. The phase-space was then defined as the snapshot of the activation-phase of all mapping array electrodes at individual time points. This snapshot can be interpreted as still frame of the local conduction pattern at a given time point. The distance δ_{ij} between two time points i and j on the phase-space trajectory was determined based on the phase angle difference at every electrode, by taking the average of the cosine of each difference, transformed back to a fraction of the activation-phase duration of a single AF cycle (2π). This distance measure was chosen so that the range of differences between two snapshots ($[-2\pi, 2\pi]$) was mapped appropriately: maximum similarity occurred at differences (0, -2π and 2π), while maximum dissimilarity occurred at π and $-\pi$. This also meant that the distance between two snapshots was always symmetric. The resulting distance measure ranged from 0 (two snapshots that were completely in phase) to 0.5 (two snapshots that were half an AF cycle length out of phase).

This transformation of electrograms to activation-phase snapshots, also known as the phase-space embedding, together with the distance function was subsequently used to create a distance matrix in which all activation-phase snapshots within a recording were compared. The distance matrix was

Figure 1. Recurrence plot construction. Block diagram and example of recurrence plot reconstruction for a recording of a paced rhythm. Unipolar electrograms were annotated, converted to activation-phase signals and used to create activation phase snapshots. Next, the distances δ_{ij} between all pairs of snapshots (i, j) were used to construct a distance matrix. The distance threshold δ_{max} was computed based on the maximum recurrence rate per AF cycle RR_{max} (default $RR_{max} = 1$) and applied to the distance matrix to construct a recurrence plot. Consecutive recurrences were eroded, removing false positives from the recurrence plot. HD: high density; LA: left atrium; PCL: pacing cycle length.

transformed to a recurrence plot by imposing an adaptive maximum distance threshold δ_{max} . The distance threshold δ_{max} can be interpreted as the maximum degree to which two snapshots were allowed to be out of phase for a recurrence to occur. This threshold was computed by requiring the recurrence plot to have a recurrence rate that corresponded to a maximum recurrence rate per AF cycle RR_{max} . Default value for RR_{max} was set to 1, equivalent to the recurrence rate per AF cycle that would occur if a single conduction pattern were repeating for the whole length of the recording. The resulting δ_{max} and recurrence rate of the recurrence plot therefore depended on the AF cycle length, the number of time points in the recording, and the distribution of distances in the distance matrix. A formal definition of the distance matrix, recurrence plot construction and distance threshold computation is provided in the **Supplemental methods**, subsection **Distance matrix and distance threshold computation**. Note that this choice for the threshold constituted a sensitive detection of recurrences, which on the one hand ensured that completely regular patterns were detected correctly, but on the other hand also caused false positive recurrence detections (also known as false nearest neighbors in recurrence plot analysis) in recordings with a lower degree of regularity.

3.2.3 Recurrence plot analysis to detect repetitive patterns

Recurrence plots were analyzed to detect the incidence and duration of repetitive patterns. There are a few general features of a recurrence plot that are worth mentioning here. A recurrence plot is always symmetric as it compares all pairs of snapshot within a recording in both directions of time, past and future. The main diagonal represents the comparison of a snapshot with itself and hence is always recurrent. A repeating conduction pattern will form a sequence of consecutive recurrences, i.e. if two activation-phase snapshots are similar, these two snapshots will also be similar when shifted equal (small) amounts in time. This phenomenon is visible in a recurrence plot as a diagonal line.¹⁹ A conduction pattern that repeats consistently for several consecutive AF cycles will show up in the recurrence plot as a square block of diagonal lines around the main diagonal. Due to the sensitive detection of recurrences, diagonal lines may exhibit some “thickness” when the distance between consecutive activation-phase snapshots still falls within the imposed threshold, which leads to aforementioned false positive recurrences. In our analysis this effect was removed by eroding the recurrence plot, effectively replacing consecutive horizontal or vertical snapshot recurrences by a single recurrence at the time point with minimum distance.

The resulting eroded recurrence plot was then used to detect intervals that contained repetitive patterns, as illustrated in **Figure 2**. These intervals were detected by an algorithm that traversed the main diagonal of a recurrence plot and computed the recurrence rate per AF cycle in square blocks of increasing duration around the diagonal at each time point. Recurrence rate was again normalized to the AF cycle length, so that a value of 1 indicated a single recurrence occurring each AF cycle on average. For each time point we stored the duration of the interval that was formed by the square block in the recurrence plot with the maximum recurrence rate. Intervals that contained repetitive patterns were defined as local maxima in the interval duration, with a minimum recurrence rate per AF cycle RR_{min} . The default value of RR_{min} was set to 0.9, corresponding to an average of 0.9 recurrences per AF cycle, to account for short-lasting pattern interruptions and small deviations in AF cycle length. In case of two identified intervals with more than 50% overlap in time, the interval with the longest duration was selected.

Figure 2. Repetitive pattern detection. Intervals containing repetitive patterns were detected by traversing the main diagonal of the recurrence plot and computing the duration of the square block surrounding the diagonal with the maximum recurrence rate at each time point. Intervals with peak duration and a recurrence rate above a minimum recurrence rate per AF cycle RR_{min} (0.9) were selected. In the four detected intervals the average activation time map was constructed, representing the original four pacing directions. For each pattern a heat map was constructed that indicated the average recurrent activation-phase distance δ_k^p for a pattern (p) for each electrode (k) separately. From this heat map the pattern size was computed by determining the area of the electrodes with $\delta_k^p < \delta_{max}$. In this example of a paced rhythm the repetitive patterns were very consistent: almost all electrodes contributed to the repetitive pattern with an average activation-phase distance below the distance threshold. HD: high density; LA: left atrium; PCL: pacing cycle length.

3.2.4 Clustering of similar repetitive patterns

To investigate which identified intervals on the main diagonal of the recurrence plot containing repetitive patterns represented similar or distinct activation patterns, patterns were grouped based on the cross-recurrence rate between intervals. Cross-recurrence rate between two intervals was determined by computing the recurrence rate in the rectangular block in the recurrence plot formed by the respective intervals. The resulting interval similarity matrix, describing the cross-recurrence rate between all pairs of intervals containing repetitive patterns, was clustered using agglomerative hierarchical clustering, a commonly used clustering technique that builds a tree of linked pairs of most similar intervals using a bottom-up approach. Groups of similar patterns were extracted from the hierarchical cluster tree using the same recurrence rate threshold RR_{min} applied in the detection of repetitive patterns.

3.2.5 Repetitive pattern visualization

Repetitive (clustered) patterns were visualized by computing the average of activation-phase snapshots corresponding to recurrences on a vertical line within the corresponding intervals in the recurrence plot. The average activation-phase snapshot was converted to an average activation time map using the estimated AF cycle length, setting the earliest activation time to zero. To identify spatial regions within the mapping array that contributed most to the recurrent behavior of the average pattern, a heat map was constructed that indicated the average recurrent activation-phase distance δ_k^p for a pattern (p) for each electrode (k) separately (see **Supplemental methods**, subsection **Average pattern activation-phase distance**). The size of the most recurrent region was defined as the area covered by electrodes with an average activation-phase distance below the computed adaptive distance threshold δ_{max}^p or a fixed time difference threshold Δt , after converting the average activation-phase distance per electrode to a time difference by multiplying δ_k^p by the AF cycle length.

3.2.6 Statistics

Based on the recurrence plot analysis we determined for each individual recording the adaptive distance threshold δ_{max}^p , the number and duration of intervals containing repetitive patterns and clusters of similar patterns, and the size of most recurrent region. Sensitivity analysis was performed to assess the effect of the thresholds RR_{max} and RR_{min} on the detection of repetitive patterns (see Supplemental Methods, section Sensitivity analysis). Differences between 3wkAF and 22wkAF and LA and RA were tested using mixed ANOVA, employing a significance threshold of 0.05. Correlations between parameters were computed using Spearman's rank correlation coefficient, controlling for AF group and atrium. Algorithms for recurrence plot construction and repetitive pattern detection were implemented in MATLAB²¹. Statistical tests were performed using R²² and the package emmeans²³.

3.3 Results

3.3.1 Application to high-density recordings of AF

The procedure of electrogram activation-phase and snapshot distance matrix computation, recurrence plot construction and repetitive pattern detection was applied to recordings during AF in the goat model. The result of this automated analysis scheme in simultaneous left and right atrial recordings in a single animal is illustrated in **Figure 3**. Intervals containing repetitive patterns are indicated as red square blocks around the diagonal. For both atria, the detected intervals were clustered into groups of similar patterns, of which the three clusters with the longest combined duration (in AF cycles) are shown. For each clustered pattern the average activation time map was determined together with the heat map of the average activation-phase distance per electrode. In this case the right atrium showed a repetitive pattern for many cycles (227), a wave entering from the northeast of the mapping area, alternated with a different pattern (71 cycles), again a wave entering the field of view, but now from the southeast. The third pattern resembled the first, but the distance heat map indicated a more variable pattern at the entrance point of the wave. In contrast, at the same time in the left atrium, the three most prevalent patterns were short lasting, with 32, 28 and 27 cycles respectively. Here the first pattern represented two peripheral waves that collided in the center of the mapping area, and the second and third repetitive focal/breakthrough waves at distinct locations. The heat maps of the patterns in the left atrium indicated a more variable or unstable pattern compared to the right.

3.3.2 Sensitivity analysis of RRmax and RRmin

First, we varied RR_{max} between 0.25 and 2, around the default value of 1, and quantified the effect on the recurrence plot construction: the distance threshold δ_{max} and the recurrence rate of the eroded recurrence plot. We also evaluated the effect of RR_{max} on the detection of repetitive patterns (keeping RR_{min} fixed at the default value 0.9): number of intervals, maximum duration of an interval, maximum pattern duration and pattern size (using the adaptive distance threshold δ_{max} that is determined by the choice of RR_{max}). We repeated this analysis for a range of fixed δ_{max} . Results show that most parameters are moderately affected by changes in RR_{max} . Recurrence plot parameters show an approximately linear response (**Supplemental Figure 1**, Panels A and B), while the parameters related to the detection of repetitive patterns show either a linear (maximum interval and pattern duration), a weak biphasic (number of intervals), or almost no response (pattern size) (**Supplemental Figure 2**). In contrast, using a range of fixed δ_{max} [0.1, 0.25] that corresponded to the range of observed values for the δ_{max} computed from RR_{max} , we observed a much stronger, non-linear response in the eroded recurrence plot recurrence rate (**Supplemental Figure 1**, Panel C) and the pattern detection parameters (**Supplemental Figure 3**). **Supplemental Figure 4** provides an example of recurrence plot construction and repetitive pattern detection for varying values of RR_{max} . Second, we varied RR_{min} between 0.5 and 1.5, while keeping RR_{max} fixed at $RR_{max} = 1$. Results show that choices for RR_{min} close to the default value 0.9 do not change the qualitative interpretation of the results of the pattern identification, most notably for the maximum duration of patterns and the pattern size (**Supplemental Figure 5**).

Figure 3. Example of repetitive pattern detection in simultaneous left (LA) and right (RA) atrial recordings. For both locations the recurrence plot and interval detection (red blocks) are depicted. Those intervals are shown that belong to the three clustered patterns with longest duration (in cycles). Cross-recurrence between intervals belonging to the same cluster is indicated in blue in the recurrence plot. The average activation pattern for each pattern is illustrated, together with the heat map of the average activation-phase distance per electrode.

3.3.3 Repetitive patterns in a goat model of different AF duration

Using $RR_{max} = 1$ and $RR_{min} = 0.9$, repetitive pattern detection was performed in all recordings at baseline in the two groups of 3wkAF and 22wkAF goats to investigate the incidence of repetitive patterns and to detect any potential differences in recurrence characteristics associated with AF duration and atrium. Our main results are summarized in **Figure 4**. The computed distance threshold δ_{max} was strongly correlated with the AF cycle length (correlation -0.62, $p < 0.01$, **Figure 4**, Panel A). The maximum duration (in number of AF cycles) of clustered patterns was longer in 3wkAF than in 22wkAF (mean maximum duration 74 cycles (95% confidence interval [54-94] vs. 41 [21-62] cycles, $p = 0.03$). In **Figure 4**, Panel B we illustrated the diversity in the number of intervals that contained repetitive patterns, as well as the total duration of these intervals during a recording. We observed a wide variety of interval incidence and prevalence, from recordings that showed a low number of intervals that covered only a small portion of the recording duration, to recordings with a small to large amount of intervals that covered almost the entire recording. The number of patterns, where multiple intervals could be grouped into one clusters representing a single pattern, compared to the total coverage of the recording showed similar diversity. Here we only included clusters of patterns where the total duration of the combined intervals exceeded 10 AF cycles. The average size of the most recurrent region per recording (**Figure 4**, Panel C) was slightly smaller in the right atrium (mean size LA 10.9cm² [10.0-11.4] vs. RA 9.5cm² [8.8-10.3], $p = 0.03$), when computed based on the number of electrodes with an average activation-phase distance below the adaptive distance threshold δ_{max} . Pattern region size was much smaller when applying a fixed maximum activation time difference threshold Δt of 10ms between recurrences in detected patterns. Here, differences were found between 3wkAF and 22wkAF (3wkAF 1.7cm² [1.0-2.3] vs. 22wkAF 0.5cm² [0.0-1.2], $p = 0.02$). Sensitivity analysis of Δt indicated that this difference in regions with low average temporal dissociation was consistent for values of Δt between 10-30ms (**Supplemental Figure 5**, Panel B).

3.3.4 Examples of mechanisms detected by recurrence analysis

In **Figure 5** we show two examples to illustrate how this method can detect and visualize candidate AF source patterns. These were selected recordings from the same study in goats, but during infusion of different dosages of the antiarrhythmic drug used. The first example shows a recording that started with a peripheral wave entering from the east (pattern 2), but then switched to a local reentry within the mapping area (pattern 1). Pattern 2 returned after a while, but was intermitted by other, less stable and frequent patterns. Then pattern 3 arose, again a local reentry within the mapping area, comparable to pattern 1, but following a slightly different trajectory. Finally pattern 1 reappeared, followed by pattern 3. The dominant conduction direction per electrode for each of the patterns confirmed their interpretation. The second example shows an extreme case of a repetitive focal/breakthrough wave, where the most spatiotemporal stable pattern (pattern 1) appeared intermittently for a total of 191 cycles. In this example the other intermittent patterns (patterns 2 and 3) were very similar to pattern 1, and only differed slightly in the variation of the radial spread of activation, as indicated by the activation-phase distance heat maps. The dominant conduction direction per electrode for each of the patterns highlights this radial spread originating from the site of the focus/breakthrough activation.

Figure 4. Recurrence detection results in 3wkAF and 22wkAF goats. Panel A: correlation between AF cycle length (AFCL) and the adaptive distance threshold δ_{max} and maximum pattern duration per recording in AF cycles. Panel B: variety of number of detected intervals containing a repetitive interval and clustered patterns compared to the total recording coverage. Only clustered patterns with a combined duration exceeding 10 AF cycles were included. Panel C: Average size of the most recurrent pattern region within each recording, computed using the adaptive distance threshold δ_{max} (left) and a fixed maximum time difference Δt (10ms) applied to the average activation time difference between pattern recurrences (right).

3.4 Discussion

We developed a method to automatically identify repetitive patterns of conduction in high-density mapping of AF. This method can be used to detect the incidence of time intervals containing repetitive patterns, to group intermittent intervals that exhibit similar repetitive patterns, and to visualize these distinct patterns to interpret the mechanism the conduction pattern represents. As an application, repetitive conduction patterns were identified in HD mapping recordings in a goat model of sustained AF, where we identified repetitive patterns in almost all recordings. We also show that the maximum duration of repetitive patterns and the size of the regions containing the most dominant repetitive pattern decreased with prolonged AF duration.

3.4.1 Recurrence analysis as a tool to identify repetitive patterns during AF

Recurrence analysis has been applied to investigate AF characteristics in invasive measurements, based on single electrode bipolar electrogram morphology. Recurrence plots were used to assess the degree of organization present during AF.²⁴ Recurrence quantification analysis was applied to detect complex fractionated atrial electrograms²⁵, to quantify the dynamics of beat-to-beat deflection morphology similarity at several locations in the left and right atrium²⁶, and to distinguish spiral wave reentry from multiple wavelets in bipolar electrograms²⁷. Recurrence plots derived from consecutive AF cycle lengths from an electrogram recorded in the coronary sinus suggested that the underlying AF process is deterministic, rather than stochastic.²⁸ Also alternative methods for the detection of local bipolar electrogram regularity were proposed, again using electrogram morphology, but also by integrating electrogram coupling to quantify local organization²⁹, or by quantifying the repetitiveness of the pattern of complex fractionated atrial electrograms using frequency domain parameters³⁰. The use of a single electrode and bipolar electrograms however limits the amount of spatiotemporal information that can be incorporated in the assessment of the dynamics of the underlying recurrent conduction pattern. In our approach we aimed to not only include temporal dynamics, but also detailed local spatial coherence, by analyzing electrograms from a high-resolution grid of electrodes. Our approach further relies on unipolar electrograms that are insensitive to the direction of conduction. We adopted an activation-phase representation of the electrograms to enable the computation of the distance, or difference, between two snapshots of conduction in time. Other approaches may also be chosen to arrive at this phase-space representation of the conduction patterns, for instance methods that rely on the Hilbert transform of the filtered electrogram.³¹ Caution should be applied however when interpreting the resulting averaged activation-phase patterns, as these approaches tend to blur the true underlying activation patterns, which can lead to the elimination of conduction block.³²

3.4.2 Interpretation and implications of the adaptive recurrence threshold

In our approach we adopted an adaptive distance threshold to transform the distance matrix that describes the difference in activation-phase between each pair of snapshots, to a recurrence plot, that only contains the moments in time when two conduction patterns are sufficiently in phase. The choice for a recurrence plot threshold has to be made carefully: applying a too restrictive threshold will not identify existing recurrences and can lead to the detection of many short, interrupted intervals; a too tolerant threshold will lead to many false positive recurrences, that obscure the underlying structure

Figure 5. Examples of AF mechanisms detected using recurrence analysis. Two conduction patterns associated with candidate AF mechanisms are depicted: an intermittent, unstable local reentry within the mapping area (left) and a repetitive focal/breakthrough wave (right). Intervals containing recurrent patterns are indicated in red blocks, while cross-recurrences between clustered intervals are indicated in blue. The average activation pattern for each pattern is illustrated, together with the heat map of the average activation-phase distance per electrode and the average conduction direction during the pattern duration.

of the recurrence plot.¹⁹ There are several approaches to choosing a recurrence threshold.³³ We used the a priori knowledge of the AF cycle length to choose a threshold that led to a number of recurrences that was to be expected if the underlying pattern was completely regular and repetitive for the whole duration of the recording. In the case of AF this threshold was often too tolerant, which led to sensitive, but not specific detection of recurrent snapshots. The post processing of the resulting recurrence plot, together with the constraints imposed on the detection of repetitive patterns, ensured that these false positives detections were disregarded. Sensitivity analysis indicated that this approach to compute an adaptive distance threshold is a relatively robust choice compared to setting a fixed distance threshold: a small change in RR_{max} led to relatively small and predictable change in δ_{max} and associated pattern detection results, whereas changes in a fixed δ_{max} that was applied to all recordings, led to much more pronounced and unpredictable changes in pattern detection results.

A higher recurrence threshold that still leads to the detection of intervals that contain repetitive intervals can indicate two things: either repetitive patterns are more variable, but still stand out from other intervals with even more disorganized activity, and/or the spatial region within the mapping area where the repetitive pattern is localized is smaller. The application of our method on the goat model data revealed that the threshold is strongly associated with the AF cycle length. This correlation indicated less stable or smaller repetitive patterns in recordings with shorted AF cycle lengths, which corroborates the findings of Schuessler et al., where in a cholinergic model of AF the shortening of the effective refractory period (and cycle length) resulted in an increased number of wave fronts and local reentry circuits³⁴.

3.4.3 Repetitive patterns in AF

Applying the developed methodology to recordings in a goat model of AF, we found that there was a large diversity both in the number of repetitive patterns as well as in the total duration of the recording covered by repetitive patterns. Stability of patterns however seemed to decrease with AF duration, with a lower maximum pattern duration in 22wkAF. The size of the region within the mapping area responsible for the recurrent behavior did also decrease with AF duration (using a fixed threshold of 10ms for the maximum allowed activation time difference between recurrences). This suggests that, while repetitive patterns are still present, the size of the repetitive process becomes smaller with prolonged AF duration. This is largely in line with findings in a comparable goat model of AF.¹⁶ Interestingly we observed switching between different repetitive patterns in several of the examples (**Figures 3** and **5**). This suggests the existence of different states of the atrial conduction during AF, and sudden transitions between these states, as also observed in simulations of AF.^{35,36}

In this study we analyzed mapping data from the epicardium of both atria. Since conduction during AF is a 3D process, signals measured simultaneously on the endocardial wall may show some degree of uncoupling.^{37–39} Independent epi-endocardial repetitive patterns might point to separate drivers in the two layers. It would be of great interest to further investigate whether epi-endocardial coupling occurs during episodes of repetitive activity. Furthermore, electrode array resolution has been shown to significantly impact AF driver identification.⁴⁰ Computation modeling of AF can help to investigate the effect of 3D conduction, dissociation and mapping device on pattern detection, providing that the model incorporates the 3D nature of the atrial anatomy and bundle structure, and exhibits epi-endocardial dissociation to an extent that 3D conduction patterns can be simulated (see for instance ⁴¹).

3.4.4 Recurrence analysis to identify and target AF sources

The detection of AF sources during an AF ablation is a possible extension of the current approach. The examples in Figure 5 show that our approach – in principle – can detect and visualize local candidate mechanism that may drive or initiate AF (e.g. a local reentry or a repetitive focal/breakthrough wave). In patients, ablation of such driver sites may restore sinus rhythm or prevent AF recurrence. As a future perspective, during an ablation procedure, several regions of the atria could be mapped sequentially and repetitive patterns can then be reconstructed for each region. With the use of a common reference, or spatial overlap between asynchronous recordings at different sites, repetitive patterns can be “stitched” together to form a more complete picture of whole atrial repetitive conduction. A similar approach was recently demonstrated in the RADAR trial, where a catheter placed in the coronary sinus (CS) served as the common reference.⁴² A potential limitation of that specific setup is that intervals containing repetitive patterns were detected using only the electrograms from the CS catheter. In contrast, identification of repetitive patterns at partially overlapping sites also enables the detection of candidate AF drivers that do not lead to repetitive electrogram morphology in the CS. Multi-site identification of repetitive patterns will however require recordings with longer duration than currently acquired during an ablation procedure, together with a sufficient incidence and duration of repetitive patterns.

3.4.5 Limitations

The result of the recurrence plot construction and repetitive pattern detection were dependent on the chosen phase-space embedding (local activation-phase computation) and recurrence rate thresholds RR_{max} and RR_{min} . Optimal embedding and threshold values were not investigated in this study. Sensitivity analysis of RR_{max} and RR_{min} indicated that results obtained in the goat model of AF were moderately insensitive with respect to the exact choice for these thresholds. Recordings evaluated in this study were from a goat model of AF, where although AF was persistent, the amount of structural remodeling was most likely limited and the differences between groups subtle. A similar study in patients in different stages of AF (paroxysmal and persistent) is needed to investigate the relationship between AF duration and associated structural remodeling and repetitive pattern incidence and size.

3.5 References

1. de Groot NMS, Houben RPM, Schotten U, et al.: Electropathological Substrate of Long-Standing Persistent Atrial Fibrillation in Patients With Structural Heart Disease. *Circ Arrhythm Electrophysiol* 2010;3:606–615.
2. Verma A, Jiang CY, Betts TR, et al.: Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812–1822.
3. Wong KCK, Paisey JR, Sopher M, et al.: No Benefit of Complex Fractionated Atrial Electrogram Ablation in Addition to Circumferential Pulmonary Vein Ablation and Linear Ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol* 2015;8:1316–1324.
4. Holm M, Johansson R, Brandt J, Luhrs C, Olsson SB: Epicardial right atrial free wall mapping in chronic atrial fibrillation. Documentation of repetitive activation with a focal spread - A hitherto unrecognised phenomenon in man. *Eur Heart J* 1997;18:290–310.
5. Lee S, Sahadevan J, Khrestian CM, et al.: Simultaneous Biatrial High-Density (510-512 Electrodes) Epicardial Mapping of Persistent and Long-Standing Persistent Atrial Fibrillation in Patients: New Insights into the Mechanism of Its Maintenance. *Circulation* 2015;132:2108–2117.
6. de Groot NMS, Allesie MA: Pathophysiology of atrial fibrillation: Focal patterns of activation. *Pacing Clin Electrophysiol* 2019;42:1312–1319.
7. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J: Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* 2000;101:194–199.
8. Hansen BJ, Zhao J, Csepe TA, et al.: Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390–2401.
9. Swarup V, Baykaner T, Rostamian A, et al.: Stability of rotors and focal sources for human atrial fibrillation: Focal impulse and rotor mapping (firm) of AF sources and fibrillatory conduction. *J Cardiovasc Electrophysiol* 2014;25:1284–1292.
10. Dharmapriani D, Schopp M, Kuklik P, et al.: Renewal Theory as a Universal Quantitative Framework to Characterize Phase Singularity Regeneration in Mammalian Cardiac Fibrillation. *Circ Arrhythm Electrophysiol* 2019;12:1–12.
11. Haissaguerre M, Shah AJ, Cochet H, et al.: Intermittent drivers anchoring to structural heterogeneities as a major pathophysiological mechanism of human persistent atrial fibrillation. *J Physiol* 2016;594:2387–2398.
12. Ravelli F, Masè M, Cristoforetti A, et al.: Anatomic localization of rapid repetitive sources in persistent atrial fibrillation: Fusion of biatrial CT images with wave similarity/cycle length Maps. *JACC Cardiovasc Imaging* 2012;5:1211–1220.
13. Ravelli F, Masè M, Cristoforetti A, Marini M, Disertori M: The logical operator map identifies novel candidate markers for critical sites in patients with atrial fibrillation. *Prog Biophys Mol Biol* 2014;115:186–197.
14. van Hunnik A, Zeemering S, Podziemski P, et al.: Stationary atrial fibrillation properties in the goat do not entail stable or recurrent conduction patterns. *Front Physiol* 2018;9:1–16.
15. Maesen B, Zeemering S, Afonso C, et al.: Rearrangement of Atrial Bundle Architecture and Consequent Changes in Anisotropy of Conduction Constitute the 3-Dimensional Substrate for Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:967–975.
16. Verheule S, Tuyls E, Van Hunnik A, et al.: Fibrillatory conduction in the atrial free walls of goats in persistent and permanent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3:590–599.
17. Ortiz J, Igarashi M, Gonzalez HX, et al.: Mechanism of spontaneous termination of stable atrial flutter

- in the canine sterile pericarditis model. *Circulation* 1993;88:1866–1877.
18. Gerstenfeld EP, Sahakian A V., Swiryn S: Evidence for transient linking of atrial excitation during atrial fibrillation in humans. *Circulation* 1992;86:375–382.
 19. Marwan N, Carmen Romano M, Thiel M, Kurths J: Recurrence plots for the analysis of complex systems. *Phys Rep* 2007;438:237–329.
 20. Zeemering S, Maesen B, Nijs J, et al.: Automated quantification of atrial fibrillation complexity by probabilistic electrogram analysis and fibrillation wave reconstruction. *Annu Int Conf IEEE Eng Med Biol Soc* 2012, pp. 6357–6360.
 21. MATLAB: version 1.8.0_181 (R2019a). Natick, Massachusetts: The MathWorks Inc., 2019,.
 22. R Core Team: R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria, 2017.
 23. Lenth R, Buerkner P, Herve M, et al.: emmeans: Estimated Marginal Means, aka Least-Squares Mean [Internet]. 2020.
 24. Censi F, Barbaro V, Bartolini P, et al.: Recurrent patterns of atrial depolarization during atrial fibrillation assessed by recurrence plot quantification. *Ann Biomed Eng* 2000;28:61–70.
 25. Navoret N, Jacquir S, Laurent G, Binczak S: Detection of complex fractionated atrial electrograms using recurrence quantification analysis. *IEEE Trans Biomed Eng* 2013;60:1975–1982.
 26. Ng J, Gordon D, Passman RS, et al.: Electrogram morphology recurrence patterns during atrial fibrillation. *Heart Rhythm* 2014;11:2027–2034.
 27. Hummel JP, Baher A, Buck B, et al.: A method for quantifying recurrent patterns of local wavefront direction during atrial fibrillation. *Comput Biol Med Elsevier Ltd*, 2017;89:497–504.
 28. Aronis KN, Berger RD, Calkins H, et al.: Is human atrial fibrillation stochastic or deterministic? - Insights from missing ordinal patterns and causal entropy-complexity plane analysis. *Chaos* 2018;28:1–11.
 29. Faes L, Ravelli F: A morphology-based approach to the evaluation of atrial fibrillation organization. *IEEE Eng Med Biol Mag* 2007;26:59–67.
 30. Ciaccio EJ, Biviano AB, Whang W, et al.: Differences in repeating patterns of complex fractionated left atrial electrograms in longstanding persistent atrial fibrillation as compared with paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:470–477.
 31. Kuklik P, Zeemering S, Maesen B, et al.: Reconstruction of instantaneous phase of unipolar atrial contact electrogram using a concept of sinusoidal recomposition and hilbert transform. *IEEE Trans Biomed Eng* 2015;62:296–302.
 32. Podziemski P, Zeemering S, Kuklik P, et al.: Rotors Detected by Phase Analysis of Filtered, Epicardial Atrial Fibrillation Electrograms Colocalize With Regions of Conduction Block. *Circ Arrhythm Electrophysiol* 2018;11:e005858.
 33. Zbilut JP, Zaldívar-Comenges JM, Strozzi F: Recurrence quantification based Liapunov exponents for monitoring divergence in experimental data. *Phys Lett A* 2002;297:173–181.
 34. Schuessler RB, Grayson TM, Bromberg BI, Cox JL, Boineau JP: Cholinergically mediated tachyarrhythmias induced by a single extrastimulus in the isolated canine right atrium. *Circ Res* 1992;71:1254–1267.
 35. Iravanian S, Langberg JJ: Critical phase transitions during ablation of atrial fibrillation. *Chaos* 2017;27:093925.
 36. Marcotte CD, Grigoriev RO: Dynamical mechanism of atrial fibrillation: A topological approach. *Chaos* 2017;27:093936.
 37. Gutbrod SR, Walton R, Gilbert S, et al.: Quantification of the transmural dynamics of atrial fibrillation by simultaneous endocardial and epicardial optical mapping in an acute sheep model. *Circ*

- Arrhythm Electrophysiol 2015;8:456–465.
38. Eckstein J, Zeemering S, Linz D, et al.: Transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation: Evidence from simultaneous endo-epicardial high-density activation mapping. *Circ Arrhythm Electrophysiol* 2013;6:334–341.
 39. De Groot N, Van Der Does L, Yaksh A, et al.: Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans. *Circ Arrhythm Electrophysiol* 2016;9:1–7.
 40. Roney CH, Cantwell CD, Bayer JD, et al.: Spatial Resolution Requirements for Accurate Identification of Drivers of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2017;10:1–13.
 41. Gharaviri A, Bidar E, Potse M, et al.: Epicardial Fibrosis Explains Increased Endo–Epicardial Dissociation and Epicardial Breakthroughs in Human Atrial Fibrillation. *Front Physiol* 2020;11:1–15.
 42. Choudry S, Mansour M, Sundaram S, et al.: A multicenter food and drug administration investigational device exemption clinical trial of persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2020;2–12.

3.6 Supplemental methods

3.6.1 Distance matrix and distance threshold computation

The *distance* δ_{ij} between two activation-phase snapshots at time points i and j was determined based on the phase angle difference at each of the N electrodes, by taking the average of the cosine of each difference, transformed back to a fraction of the activation-phase duration of a single AF cycle (2π). Formally:

$$\delta_{ij} = \cos^{-1} \left(\frac{\sum_{k=1}^N \frac{\cos(\varphi_{k,j} - \varphi_{k,i})}{N}}{2\pi} \right)$$

where $\varphi_{k,i}$ denotes the activation-phase of the electrode k at time i , and N the number of electrodes. This definition leads to distance values in the range $[0, 0.5]$. The distance matrix was then formed by computing δ_{ij} for all combinations of i and j , where $ij = 1, 2, \dots, T$, with T being the total number of time points.

Recurrence R_{ij} between two snapshots was computed by imposing a distance threshold δ on the distance matrix:

$$R_{ij} = \begin{cases} 0 & \text{if } \delta_{ij} > \delta \\ 1 & \text{if } \delta_{ij} \leq \delta \end{cases}$$

The *recurrence rate* of a recurrence plot is defined as:

$$RR = \frac{1}{T^2} \sum_{i=1}^T \sum_{j=1}^T R_{ij}$$

We adapted this definition to the *recurrence rate per AF cycle*, computed as the relative number of recurrences per AF cycle over all possible time point comparisons:

$$RR = \frac{T_{AFC}}{T^2} \sum_{i=1}^T \sum_{j=1}^T R_{ij}$$

where T_{AFC} denotes the number of time points per AF cycle.

The *distance threshold* δ_{max} applied to construct the recurrence plot for each recording was computed by selecting the largest value for the threshold δ that led to a given maximum recurrence rate per AF cycle RR_{max} :

$$\delta_{max} = \sup\{\delta \in [0, 0.5] \mid RR \leq RR_{max}\}$$

Since

$$\sum_{i=1}^T \sum_{j=1}^T R_{ij} = \frac{T^2}{T_{AFC}} RR_{max}$$

this is equivalent to computing the percentile of all T^2 distances in the distance matrix that corresponds

to the expected recurrence rate $RR_{max'}$ adjusted for the number of time points per AF cycle T_{AFC} :

$$\delta_{max} = P_{100 \times RR_{min}/T_{AFC}} \{ \delta_{ij} \mid i, j, = 1, \dots, T \}$$

3.6.2 Average pattern activation-phase distance

The average activation-phase distance for each electrode during a repetitive pattern was computed as the average distance at recurrences R_{ij} occurring during a repetitive pattern. Formally, given a pattern p and a corresponding set of time points T_p during which the pattern is detected, the average distance for an electrode k is given by:

$$\delta_k^p = \cos^{-1} \left(\frac{\sum_{i \in T_p} \sum_{j \in T_p} \cos(\varphi_{ki} - \varphi_{kj}) R_{ij}}{\sum_{i \in T_p} \sum_{j \in T_p} R_{ij}} \right) / 2\pi$$

3.6.3 Sensitivity analysis

In this study, results were dependent on two main thresholds: 1) the maximum allowed distance between two activation-phase snapshots (δ_{max}) to construct a recurrence plot from a distance matrix, and 2) the minimal recurrence rate per AF cycle (RR_{min}) of an interval within the recurrence plot for which an interval was assumed to contain a repetitive pattern. The threshold $\delta_{max'}$, the recurrence plot threshold, was determined in a data-driven way for each recording separately, by computing the value of δ_{max} for which recurrence rate of the recurrence plot corresponded to the maximum recurrence rate per AF cycle (RR_{max}). Default values for RR_{max} and RR_{min} were 1 and 0.9 respectively. To assess the sensitivity of the results to the value of these thresholds, we performed recurrence plot construction and repetitive pattern detection for a range of RR_{max} and RR_{min} around the default values. To motivate the choice for a data-driven recurrence plot threshold $\delta_{max'}$ as opposed to an equal, fixed δ_{max} for all recordings, we also performed sensitivity analyses for a range of fixed δ_{max} values. To investigate the use of a fixed time threshold Δt when computing average pattern size, we performed sensitivity analysis on the maximum allowed average time difference per electrode during recurrences within a repetitive activation pattern. In this analysis, the average activation-phase distance for each electrode during a repetitive pattern δ_k^p was converted to time in milliseconds, by multiplying by the estimated AF cycle length of each recording.

3.7 Supplemental figures

Supplemental Figure 1. Panel A: Effect of the maximum recurrence rate ($RR_{\max}$) on the average of the maximum allowed distance between two activation-phase snapshots ($\delta_{\max}$) and change compared to $\delta_{\max}$ at the default value $RR_{\max} = 1$. Panel B: Effect of $RR_{\max}$ on the recurrence rate (RR) per AF cycle of the eroded recurrence plot and change compared to RR at the default value $RR_{\max} = 1$. Panel C: Effect of a fixed $\delta_{\max}$ on the RR of the eroded recurrence plot and difference compared to RR when computed using $\delta_{\max}$ at the default value $RR_{\max} = 1$.

Supplemental Figure 2. Effect of the maximum recurrence rate per AF cycle ($RR_{\max}$) on the detection of repetitive patterns. The minimal recurrence rate per AF cycle ($RR_{\min}$) was held constant in this analysis at $RR_{\min} = 0.9$.

Supplemental Figure 3. Effect of a fixed distance threshold δ_{max} for all recordings to construct a recurrence plot on the detection of repetitive patterns. The minimal recurrence rate per AF cycle (RR_{min}) was held constant in this analysis at $RR_{min} = 0.9$.

Supplemental Figure 4. Example of the effect of various values for the maximum recurrence rate (RR_{max}) on the recurrence plot construction and interval and pattern detection in a single recording. Upper panel: recurrence plots, interval detection (red blocks) and cross-recurrence between intervals belonging to the same cluster (blue blocks), for $RR_{max} = 0.50, 1, 1.5$ and 2 . Lower panel: left: RR_{max} -driven change in δ_{max} and recurrence rate (RR) of the eroded recurrence plot (RP); middle: the number of intervals containing repetitive patterns and maximum interval duration; right: the number of clustered patterns and pattern size (area formed by electrodes with an average activation-phase distance during pattern recurrences below δ_{max}). The minimal recurrence rate per AF cycle (RR_{min}) was held constant in this analysis at $RR_{min} = 0.9$.

Supplemental Figure 5. Panel A: Effect of the minimum recurrence rate per AF cycle of an interval containing a repetitive pattern ($RR_{\min}$) on the detection of repetitive patterns. The maximal recurrence rate per AF cycle ($RR_{\max}$) was held constant in this analysis at $RR_{\max} = 1$. Panel B: Effect of a fixed threshold Δt in milliseconds to compute the size of repetitive patterns. Here the average activation-phase distance for each electrode during a repetitive pattern δ_k^p was converted to time in milliseconds, by multiplying δ_k^p by the estimated AF cycle length of each recording. Repetitive patterns were computed using $RR_{\max} = 1$ and $RR_{\min} = 0.9$.

CHAPTER 4

INCIDENCE, PREVALENCE AND TRAJECTORIES OF REPETITIVE CONDUCTION PATTERNS IN HUMAN ATRIAL FIBRILLATION

Frank van Rosmalen, Bart Maesen, Arne van Hunnik, Ben J.M. Hermans, Pietro Bonizzi, Elham Bidar, Jan Nijs, Jos Maessen, Sander Verheule, Tammo Delhaas, Ulrich Schotten, Stef Zeemering

Europace, accepted for publication

Abstract

Aims

Repetitive conduction patterns in atrial fibrillation (AF) may reflect anatomical structures harboring preferential conduction paths and indicate the presence of stationary sources for AF. Recently, we demonstrated a novel technique to detect repetitive patterns in high-density contact mapping of AF. As a first step towards repetitive pattern mapping to guide AF ablation, we determined the incidence, prevalence and trajectories of repetitive conduction patterns in epicardial contact mapping of paroxysmal and persistent AF patients.

Methods

A 256-channel mapping array was used to record epicardial left and right atrial fibrillation electrograms in persistent (persAF, n=9) and paroxysmal AF (pAF, n=11) patients. Intervals containing repetitive conduction patterns were detected using recurrence plots. Activation movies, preferential conduction direction and average activation sequence were used to characterize and classify conduction patterns.

Results

Repetitive patterns were identified in 33/40 recordings. Repetitive patterns were more prevalent in pAF compared to persAF (pAF: median 59%, interquartile range [41-72] vs. persAF: 39% [0-51], $p<0.01$), larger (pAF: = 1.54 [1.15-1.96]cm² vs. persAF: 1.16 [0.74-1.56]cm², $p<0.001$) and more stable (normalized preferentiality (0-1) pAF: 0.38 [0.25-0.50] vs. persAF: 0.23 [0-0.33], $p<0.01$). Most repetitive patterns were peripheral waves (87%), often with conduction block (69%), while breakthroughs (9%) and re-entries (2%) occurred less frequently.

Conclusion

High-density epicardial contact mapping in AF patients reveals frequent repetitive conduction patterns. In persistent AF patients, repetitive patterns were less frequent, smaller and more variable than in paroxysmal AF patients. Future research should elucidate whether these patterns can help in finding AF ablation targets.

4.1 Introduction

Pulmonary vein isolation (PVI) is a common treatment for atrial fibrillation (AF).^{1,2} In patients with paroxysmal AF, PVI leads to freedom of AF in 59%-89% of patients 12 months after the procedure.³ In patients with persistent AF only 59% show freedom of AF after 18 months. AF recurrence after PVI can be caused by reconnection of pulmonary veins (PVs), but recurrence of AF is also possible while all PVs are still isolated, implying the existence of AF sources outside of the PVs.⁴ To improve the success rate of PVI, the identification of alternative ablation targets outside of the PVs has been explored. Ablation of dominant frequency sites, linear lesion sets, complex fractionated atrial electrograms (CFAE) as well as focal impulse and rotor modulation ablation showed significant improvement in single studies, but in larger trials or meta-analyses their superiority as compared to PVI-only could not consistently be demonstrated.^{3,5-8}

Repetitive focal sources⁹ and micro-reentrant sources^{10,11} have been described as candidate sources of AF. Repetitive conduction patterns are expected to occur close to AF drivers, independent of their actual mechanism (local reentry, ectopic firing, complex conduction with new wave generation). Detection of repetitive conduction patterns may help to localize sources of AF, and thus provide a new strategy for AF driver identification. Repetitive conduction patterns are also of interest because they might reflect anatomical structures harboring preferential conduction paths associated with the underlying bundle structure of the atrium.^{10,12,13} Therefore, a mapping technique able to find repetitive patterns may help study structure-function relationships during fibrillatory conduction. Finally, the analysis of stable repetitive patterns may also facilitate combining recordings at different sites in the atria to reconstruct a composite activation map during AF, so far only feasible during stable activation patterns like atrial flutter or atrial tachycardia. These composite AF activation maps could help to increase the spatial coverage of existing mapping modalities.¹⁴

A technique to detect repetitive patterns in high-density mapping of AF has recently been demonstrated by our group.¹⁵ In the present study, we applied this methodology to investigate the incidence, prevalence and trajectories of repetitive conduction patterns in epicardial mapping data of paroxysmal and persistent AF patients.

4.2 Methods

4.2.1 Patient selection

This study uses a retrospective dataset of 20 patients (persistent AF (persAF), n=9, paroxysmal AF (pAF), n=11) that underwent bi-atrial epicardial mapping.¹⁶ Patients included in this study were referred for open-chest surgery: either cut-and-sew rhythm surgery, coronary bypass grafting, aortic valve surgery or mitral valve surgery. The study protocol was approved by the local ethics committee and informed consent was obtained from each patient before the procedure.

Table 1. Patient characteristics

	Paroxysmal AF (n=11)	Persistent AF (n=9)
Age (year)	68.7 ± 4.2	69.1 ± 5.8
Male (%)	75.0	55.6
Clinical characteristics:		
Nicotine abuse (%)	27.3	44.4
Hypertension (%)	63.6	77.8
Diabetes (%)	9.1	44.4
Peripheral arterial disease (%)	18.2	22.2
Previous MI %	18.2	11.1
Hypercholesterolemia (%)	36.4	44.4
GFR < 60mL/min (%)	18.2	22.22
BMI (kg/m ²)	26.6 ± 4.4	26.9 ± 3.1
NYHA class	2 [1.25-2.75]	2 [2-3]
CHA2DS2-VASc	3 [2-3]	3 [3-6] *
Time since AF diagnosis (year)	7.0 ± 6.9	9.6 ± 6.6
Preoperative CRP (mg/L)	2.3. ± 1.5	3.2 ± 3.7
Surgery:		
CABG	7	4
MVS	1	2
AVS	2	2
Lone AF	1	1
Echocardiography:		
LA diameter (mm)	43.5 ± 8.1	53.1 ± 6.1*
LA volume (cm ³)	79.1 ± 27.5	151.0 ± 55.3*
LAA flow velocity (cm/s)	61.1 ± 25.9	37.6 ± 13.3*
RA volume (cm ³)	53.6 ± 26.1	102.8 ± 32.3*
LVEDD (mm)	52.0 ± 4.4	52.1 ± 5.1
LVESD (mm)	32.8 ± 6.0	34.9 ± 6.8
LVEF (%)	64.3 ± 9.1	61.4 ± 6.4
Drug use:		
Beta-blocker (%)	81.8	77.8
Digoxin (%)	0.0	33.3
Amiodarone/sotalol (%)	63.6	11.1
ACE-inhibitor/ARB (%)	54.5	100*
Calcium channel blocker (%)	27.3	33.3

MI = myocardial infarction; GFR = glomerular filtration rate; BMI = body mass index; NYHA = New York Heart Association; CRP = c-reactive protein; CABG = coronary bypass grafting; MVS = mitral valve surgery; AVS = aortic valve surgery; LA = left atrial; LAA = left atrial appendage; RA = right atrial; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; LVEF = left ventricular ejection fraction; ACE = angiotensin converting enzyme; ARB = angiotensin-receptor blockers. *= p<0.05 vs paroxysmal AF.

4.2.2 Epicardial mapping procedure

The heart was approached via median sternotomy. Two electrode grids were sequentially placed on the atria, one on the free wall of the right atrium (RA) and one in the oblique sinus on the posterior left atrium (LA). Both electrode grids were custom-made, single-use 256-channel grids measuring 22.5mmx22.5mm with an interelectrode distance of 1.5mm. A reference electrode was positioned subcutaneously in the sternotomy opening. In pAF patients in sinus rhythm at the start of the procedure, AF was induced by incremental pacing (300-60ms cycle length). Recording of unipolar electrograms was started 30s after AF induction. For each location (RA and LA), 10s of data was stored using a 1,039 kHz sampling rate.

4.2.3 Electrogram processing

The automated processing and annotation of AF electrograms has been described previously¹⁷. Briefly, all electrograms were high-pass filtered using a third order Chebyshev filter with a cutoff frequency of 0.5Hz to remove baseline drift. Ventricular waves visible in the atrial recordings were detected and removed using single beat QRST-template cancellation. Local activations, characterized by sharp deflections on the electrogram, were detected using unipolar deflection template matching and classified as local activations using a probabilistic algorithm based on the estimated distribution of the AF cycle length (AFCL).

4.2.4 Recurrence plot construction

The methodology used to detect intervals containing repetitive patterns is described in detail in a recent study by Zeemering et al.¹⁵ Unipolar electrograms were transformed to an activation phase signal by treating the local activation time as the moment of phase inversion and using linear interpolation for the time between the phase inversions. This procedure resulted in a signal that represents the phase of the activity in a local electrogram, with values between $-\pi$ and π and allowed for the creation of snapshots that represented the phase of all individual electrodes at one point in time (see **Figure 1**, Panel A). Snapshots at two different points in time were compared by computing the phase difference for every corresponding electrode between the two snapshots. The distance δ_{ij} between two activation-phase snapshots at time points i and j was determined based on the phase angle difference at each of the N electrodes, by taking the average of the cosine of each difference, transformed back to a fraction of the activation-phase duration of a single AF cycle (2π). Formally:

$$\delta_{ij} = \cos^{-1} \left(\frac{\sum_{k=1}^N \frac{\cos(\varphi_{kj} - \varphi_{ki})}{N}}{2\pi} \right)$$

where φ_{ki} denotes the activation-phase of the electrode k at time i . This definition led to distance values between 0 (two snapshots completely in phase) and 0.5 (two snapshots half an AF cycle length out of phase). We used a recurrence plot to visualize whenever a pair of snapshots exhibited an activation-phase distance below a certain distance threshold. Recurrence plots show ‘time’ on both the x and y-axis. Snapshots with a distance smaller than a threshold are recurrences, represented by a dot (see **Figure 1**, panel B&C). As an example, a snapshot at $t=1$ s that recurs at $t=5$ s is shown in the recurrence

Figure 1. The creation of recurrence plots. Panel A shows the signal for one electrode of a mapping grid. The signals consist of two repetitive intervals. The first repetitive interval (red trace) is repeated later in time (blue trace). The signal is converted to a phase signal (straight lines under signal trace), and snapshots consisting of the phase of all electrodes of the grid created. Snapshots are compared, and when the phase difference is below the phase difference threshold, the time points of similar phase snapshots are marked on a recurrence plot (panel B). Panel C shows the recurrence plot for the trace in panel A. AFCL: AF cycle length.

plot by a dot at position (1,5) as well as a dot at position (5,1), since all recurrence plots are symmetric with respect to the diagonal. The threshold for the maximum-allowed activation-phase distance between two snapshots was computed based on the maximum expected number of recurrences. The maximum expected number of recurrences was estimated as the number of recurrences that would occur if a single conduction pattern repeatedly occurred for the full length of the recording, giving rise to on

average one recurrence per AF cycle length for each snapshot. This number therefore depended on the AF cycle length and the sampling frequency of the recording, since a higher sampling frequency results in more snapshots per time. The choice of the distance threshold enabled a sensitive detection of recurrences, which ensured that completely regular patterns with on average one recurrence per AF cycle length were detected correctly. In recordings with a lower degree of regularity, this choice of recurrence plot threshold caused false positive recurrence detections, which were removed in the next stage as explained below.

4.2.5 Repetitive pattern detection

A recurrence plot was generated for every recording, and used to detect the number and duration of repetitive patterns. A conduction pattern that is repetitive for a number of consecutive AF cycles has recurrences with a period of one AF cycle length. In the time interval that contains the repetitive pattern, every snapshot has recurrences with preceding or following snapshots, again with a period of one AF cycle length. This is visible in the recurrence plot as a block of stacked diagonal lines around the main diagonal with a distance of one AF cycle length between the diagonal lines. (Figure 1, panel C). Diagonal lines may exhibit some “thickness” when the distance between consecutive activation-phase snapshots still falls within the computed distance threshold, which leads to aforementioned false positive recurrences. This effect was removed by erosion: replacing consecutive horizontal or vertical recurrences by a single recurrence at the pair of snapshots with minimum distance.

The eroded recurrence plot was used to detect intervals that contained successive repetitive conduction patterns. These intervals were detected by an algorithm that traversed the main diagonal of a recurrence plot and computed the recurrence rate in square blocks of increasing duration around the diagonal at each time point. The recurrence rate is the ‘density’ of a recurrence plot and is computed as the number of detected recurrences divided by all comparisons possible. Square blocks centered on the diagonal with a minimum recurrence rate of 0.9 (corresponding to an average of 0.9 recurrences per AF cycle) were selected as recurrent intervals.

4.2.6 Characterization of repetitive conduction patterns

We computed the preferential (dominant) conduction direction per individual electrode of each repetitive conduction pattern (circular variance of conduction direction, defined as *Pref*).¹⁸ A *Pref* of 1 indicates that all conduction vectors point in the same direction, whereas a *Pref* of 0 implies that all conduction vectors are uniformly pointing in all directions. Within repetitive intervals, the degree of preferentiality and direction of conduction for the mapping array were visualized in preferentiality plots, where arrows indicate the preferential direction, and *Pref* is indicated by a color. The preferentiality plot only shows arrows for electrodes with a *Pref*>0.5, to highlight preferential conduction directions that could be assessed accurately. The size of a repetitive pattern was defined as the number of electrodes with *Pref*>0.5. The preferentiality of conduction direction during a repetitive pattern was defined as the sum of *Pref* over electrodes with a *Pref*>0.5.

Detected repetitive patterns may vary in duration and pattern stability. To compare *Pref* between intervals, we defined normalized preferentiality ($Pref_{norm}$) as an overall measure of AF pattern stability.

$Pref_{norm}$ incorporates pattern duration, size of the high preferential region, and the sum of $Pref$ in the high preferential region into one metric. The duration of the interval is normalized to the total recording duration, the size of the high preferential region is normalized to the total size of the mapping array, and the sum of $Pref$ in the high preferential region is normalized to the sum of the maximum $Pref$ value for every electrode. $Pref_{norm}$ is the product of the normalized duration, normalized high preferential region and normalized sum of $Pref$, and thus has a value between 0 (short/small area/unstable pattern) and 1 (long/large area/stable pattern; see **Supplement**). This implies that intervals in which all electrodes in the

Figure 2. Summary of repetitive interval detection results. There was no significant difference in number of detected intervals between pAF and persAF. Interval duration as percentage of total time, size of high preferential areas, sum of high preferential values as well as the normalized preferentiality show a significant difference between pAF and persAF.

mapping array are part of the repetitive pattern, and where the pattern continues uninterrupted for the total duration of the recording, are assigned a value of one. In contrast, the normalized preferentiality is zero either when no interval containing a repetitive pattern can be found in the recording or no electrodes with a preferentiality >0.5 are present in the repetitive intervals.

The preferentiality plot, average activation sequence plot, and an animation of the activation pattern for each repetitive pattern was generated and visually inspected by three authors (FvR, SZ and US). Patterns were categorized as peripheral wave without block, peripheral wave with block, breakthrough, reentry within the mapping area, or undecided if the pattern did not fit any of the other categories. Definitions for conduction patterns are presented in the **Supplement**.

4.2.7 Statistics

Differences between pAF and persAF patients were analyzed for the number of intervals containing repetitive patterns, the duration of these intervals, the size of the region with $Pref > 0.5$, the sum of $Pref > 0.5$ and the normalized preferentiality $Pref_{norm}$. Normality of variables was tested using the one-sample Kolmogorov-Smirnov test. To test for significant differences between AF groups, a mixed ANOVA was used, employing a significance threshold of 0.05. Multiple comparison tests were performed using Tukey's range test, controlling for AF group and atrium. Descriptive statistics of variables with a normal distribution are reported as mean and standard deviation (SD). Descriptive statistics of other variables are indicated by median, 25th, and 75th percentile.

4.3 Results

Baseline characteristics of all patients are given in **Table 1**. In persAF patients, atrial size was larger, left atrial appendage flow velocity was lower, and CHA2DS2-VASc score and ACE-inhibitors use were higher.

Measurements of all 20 patients were used, resulting in 20 recordings of the left atrium and 20 recordings of the right atrium. Recurrent intervals were found in 33 out of 40 recordings (pAF: 20/22, persAF: 13/18, $p=0.12$). Although the incidence of recurrent intervals did not significantly differ between the paroxysmal and persistent AF group (pAF: median = 3, interquartile range [2-3] vs persAF: median = 2, [0-4], $p=0.29$, **Figure 2**), the prevalence, defined as total repetitive pattern duration as percentage of total recording time, was higher in pAF patients (pAF: median = 59% [41-72] vs persAF: median = 39% [0-51], $p<0.01$). The relation between the number of intervals and the total duration of intervals in a recording is visualized in **Figure 2**, bottom right. The size of repetitive patterns was significantly larger in pAF patients (pAF: median = 1.54 [1.15-1.96]cm² vs persAF: median = 1.16 [0.74-1.56]cm², $p<0.001$, **Figure 2**, top right). Preferentiality of conduction direction during a repetitive pattern was higher in paroxysmal than in persistent AF (pAF: median sum of preferentiality over all electrodes = 114 [77-146], persAF: median sum of preferentiality over all electrodes = 82 [67-114], $p<0.01$). Overall conduction pattern stability was significantly higher in pAF patients (pAF: median = 0.38 [0.25-0.50] vs persAF: median = 0.23 [0-0.33], $p<0.005$, **Figure 2**, bottom center).

The $Pref_{norm}$ varied in the range of 0 to 0.927 (median: 0.303). Seven recordings showed a $Pref_{norm}$ of 0, the lowest non-zero $Pref_{norm}$ was 0.090. **Figure 3** provides examples for left atrial recordings of a recurrence

Figure 3. Examples of recurrence plots and preferentiality plots for high, moderate and low normalized preferentiality recurrent intervals. Top row: Eroded recurrence plots, detected recurrent intervals shown with squares. Middle row: Preferentiality plots of the recurrent interval indicated by the red square in the top row. Bottom row: Average activation time for the interval indicated by the red square in the top row. High $Pref_{norm}$ is associated with a regular recurrence plot showing recurrences for the full recording. The preferentiality plot for the first interval shows a conduction pattern lasting 7.4s (37.5 AF cycle lengths), where the majority of electrodes are involved. The activation wave enters the mapping array from the top right, and leaves at the bottom left. The dark blue color indicates that the direction of conduction is very stable for the duration of the repetitive pattern. The recurrence plot for moderate $Pref_{norm}$ also shows recurrences, but not the entire recording. Two intervals are detected, with a combined duration of 4.28s (24 AF cycle lengths). The preferentiality plot for the first interval shows the activation wave enters from the right and travels to the left, but that the pattern is unstable in the top- and bottom left corner of the mapping array. The lighter blue colors show that the direction of activation is less stable towards the left side of the mapping array, and the transparent colors indicate that for a part of the mapping array the activation direction is too irregular to quantify. The low $Pref_{norm}$ recurrence plot shows irregular recurrences, and only one recurrent interval of 1.66s (10 AF cycle lengths) could be detected. The preferentiality plot for this interval shows that the direction of activation is too irregular to quantify in the majority of the mapping array, but that small regions exhibit regular behavior.

Figure 4. Classification of recurrent intervals in conduction patterns. Top half of the figure shows the occurrence of conduction patterns for paroxysmal and persistent AF. Note that conduction patterns are not mutually exclusive. Bottom half of the figure presents examples of conduction pattern categories. Row three shows the preferentiality map, bottom row shows the average activation time corresponding with the preferentiality map.

plot, preferentiality plot, and average activation sequence for a high (0.927), moderate (0.315) and low (0.104) non-zero normalized preferentiality.

Repetitive patterns were categorized based on their prevailing conduction trajectories. Classification results are shown in **Figure 4**. In right and left atria together, most repetitive patterns were peripheral waves (87%), often with conduction block (69%), while breakthroughs (9%) and reentries (2%) occurred less frequently. Both paroxysmal and persistent AF showed more blocked waves than unblocked waves (pAF: 55% vs 27%, persAF: 92% vs 3%), but blocked waves were more common in persistent AF patients

(pAF: 54%, persAF: 92%). Nine intervals showed a repeating pattern of breakthroughs and peripheral waves (pAF: 11%, persAF: 5%).

4.4 Discussion

We investigated the presence, duration, area, and the trajectories of repetitive conduction patterns in epicardial high-resolution direct contact mapping data of patients with paroxysmal and persistent AF. Repetitive conduction patterns were identified in the majority of patients, both in pAF and persAF. Not only the prevalence of repetitive patterns was higher in pAF patients compared to persAF patients, but also the overall stability of AF patterns. The majority of repetitive patterns were peripheral waves, often with conduction block, while breakthroughs and reentries occurred less frequently.

4.4.1 AF pattern stability and AF complexity

Analysis of recurrent patterns through normalized preferentiality showed that persAF patients exhibit patterns that are more variable compared to pAF patients. These findings may reflect well described changes of the atrial substrate under the influence of AF, where prolonged AF leads to more complex atrial substrate with a higher degree of block and a higher degree of electrical dissociation.¹⁹ This complex substrate may cause repeating AF patterns to become less stable in time and location.

4.4.2 Classification of repetitive patterns

In the present study, five types of repetitive conduction patterns were used: Peripheral with block, peripheral without block, breakthrough, reentry and undecided. Both pAF and persAF patients showed more blocked than unblocked waves, but blocked waves were more common in persAF. Nine intervals showed a repeating pattern of breakthroughs and peripheral waves. Reentries were only found in two intervals.

Classification of the repetitive patterns revealed that the ratio of blocked versus unblocked peripheral waves is higher in the persistent AF group. Uninterrupted peripheral waves were mostly observed in pAF patients, but were almost absent in persAF patients. This indicates that patients with persistent AF have a more complex atrial substrate with a higher incidence of conduction block. Interestingly, nine repetitive patterns were classified as breakthroughs. Repetitive breakthroughs, visible as radial spread of conduction from one point in the mapping array, may represent rapid ectopic firing or endo-epicardial dissociation and might be responsible for the perpetuation of AF.^{9,20-23}

Peripheral waves without conduction block were found relatively more often for paroxysmal AF patients and may indicate a zone of unidirectional conduction that can be part of a macro-reentry circuit, or conduction away from a source. Reentry was observed in 2 patterns (in 2 patients), a relatively small percentage of all repetitive patterns. When the total reentry path of the pattern was visible in at least one reentry cycle, the pattern was classified as reentry to avoid a negative bias against reentries. Pivoting waves (waves from one direction pivoting around a line of block and returning to the same direction without crossing the line of block), seen in 8 intervals (7 patients), were not counted as reentries. The

low incidence of repetitive reentry is in line with an earlier analysis of our dataset where incidence of reentry itself was low.¹⁶ Hansen et al. found a higher prevalence of reentry in isolated human atria along endocardial bundles. Their measurements were however performed in the presence of compounds that shorten the AF cycle length which strongly favors reentry.¹⁰

4.4.3 Potential applications

For many years, attempts have been made to design a mapping approach for alternative AF ablation targets. Well-known examples are dominant frequency mapping²⁴, complex fractionated electrogram mapping²⁵ and rotor mapping²⁶. None of these techniques have so far proven to consistently increase success rates of catheter ablation in AF. The inconsistent results from ablation trials may be partly attributable to technological shortcomings of the mapping techniques used. Our earlier work has documented that fractionation indices used in commercially available mapping systems do neither correlate well among each other nor with the incidence of conduction block.²⁷ Phase analysis of filtered electrograms as usually used in rotor mapping strongly overestimates rotational activity during AF.¹⁶ The fundamental mechanisms driving AF are still heavily debated by key opinion leaders because of the differences in preprocessing methods, analysis and interpretation of fibrillation electrograms.^{9,28} Currently proposed hypotheses are that AF is driven or sustained by: focal activity emanating from varying locations throughout the atria;^{9,29} spiral wave rotors that may change in complexity during the remodelling process^{30,31} (also suggested by studies using ECG-imaging³²); localized stable rotors (showed by using the Focal Impulse and Rotor Modulation (FIRM) approach^{33,34}); multiple wavelets in the three-dimensional architecture of the atrial wall.^{20,35}

In the context of AF ablation beyond PVI, AF sources are particularly interesting when they are stationary or preferentially occur at specific sites. In such cases conduction close to a source should be highly repetitive and propagating away from this source independently from the actual mechanism of the source. Hence, a repetitive pattern detection technique could help identify and localize AF sources. The existence of repetitive patterns during human AF – as demonstrated by the present study – therefore supports the temporary presence of prevailing conduction paths that may be linked to temporarily active, stationary drivers for AF. Ablation of these drivers could be an opportunity to restore sinus rhythm.

Another potential application of this method is the construction of composite AF conduction maps. The presence of repeating patterns allows combining atrial recordings that have been recorded sequentially into one composite activation map showing these repetitive patterns for the whole atrium. This method is commonly used to produce sinus rhythm activation maps based on several separate recordings throughout the atria. Because of the repetitive nature of activation sequences found in this study, this approach may partly be transferable to mapping of AF. The feasibility of such an approach was demonstrated in the recent RADAR trial, where activation patterns identified in the coronary sinus have been used to link sequential but small activation patterns to one larger composite map.¹⁴

4.4.4 Limitations

The mapping arrays used in this study only cover part of the atria. Therefore, we do not know the state of the atria outside of the mapping array. To overcome this limitation, future measurements may use either

a larger mapping array or multiple mapping arrays at the same time, or use a single mapping array and a reference signal to create a composite map from sequentially mapped data.

For this study, only 10s of data was used for the analysis of recurrent patterns. Patterns that are recurrent with pauses longer than 10 seconds between the recurrences would have been missed. Despite our 10s recordings, we did find recurrent intervals in the majority of recordings, suggesting that for this type of analysis relatively short recordings could already provide meaningful data.

Preferentiality plots were used to summarize the conduction pattern of individual recurrent intervals. A possible limitation of using preferentiality plots is the compression of temporal information. When a conduction pattern shows regular conduction from left-to-right for the first half of the recurrent interval, but then changes to right-to-left conduction for the second half of the recurrent interval, the average conduction direction may be too uncertain to quantify. Visual comparison of the preferentiality plots with activation animations showed that this effect was negligible in this dataset.

The threshold used to decide whether two snapshots are similar was adaptive and based on the expected AF cycle length. This led to a sensitive, but not specific detection of repetitive snapshots. Consequently, not all intervals could be categorized as a conduction pattern, although this occurred in only 2 out of 96 cases

4.4.5 Conclusion

High-density epicardial contact mapping in AF patients reveals frequent repetitive conduction patterns. In persistent AF patients, repetitive patterns were less frequent, smaller and more variable than in paroxysmal AF. The majority of repetitive conduction patterns were (blocked) peripheral waves entering from outside the mapping array. Repetitive breakthrough and reentry patterns were observed in a small minority of cases. The existence of repetitive patterns during AF suggests the presence of stationary AF drivers. Future research should elucidate whether detection of repetitive patterns can help to locate AF drivers.

4.5 References

1. Hindricks G, Potpara T, Dagres N, et al.: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020;1–126.
2. January CT, Wann LS, Alpert JS, et al.: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of cardiology/American heart association task force on practice guidelines and the heart rhythm society. *Circulation* 2014;130:e199–267.
3. Calkins H, Hindricks G, Cappato R, et al.: 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:e1–e160.
4. De Pooter J, Strisciuglio T, El Haddad M, et al.: Pulmonary Vein Reconnection No Longer Occurs in the Majority of Patients After a Single Pulmonary Vein Isolation Procedure. *JACC Clin Electrophysiol* 2019;5:295–305.
5. Verma A, Jiang CY, Betts TR, et al.: Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812–1822.
6. Wong KCK, Paisey JR, Sopher M, et al.: No Benefit of Complex Fractionated Atrial Electrogram Ablation in Addition to Circumferential Pulmonary Vein Ablation and Linear Ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol* 2015;8:1316–1324.
7. Mohanty S, Mohanty P, Trivedi C, et al.: Long-Term Outcome of Pulmonary Vein Isolation With and Without Focal Impulse and Rotor Modulation Mapping. *Circ Arrhythm Electrophysiol* 2018;11:1–9.
8. Atienza F, Almendral J, Ormaetxe JM, et al.: Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: A noninferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol* 2014;64:2455–2467.
9. Lee S, Sahadevan J, Khrestian CM, et al.: Simultaneous Batrial High-Density (510–512 Electrodes) Epicardial Mapping of Persistent and Long-Standing Persistent Atrial Fibrillation in Patients: New Insights into the Mechanism of Its Maintenance. *Circulation* 2015;132:2108–2117.
10. Hansen BJ, Zhao J, Csepe TA, et al.: Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390–2401.
11. Narayan SM, Shivkumar K, Krummen DE, Miller JM, Rappel W-J: Panoramic Electrophysiological Mapping but not Electrogram Morphology Identifies Stable Sources for Human Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:58–67.
12. van Hunnik A, Zeemering S, Podziemski P, et al.: Stationary atrial fibrillation properties in the goat do not entail stable or recurrent conduction patterns. *Front Physiol* 2018;9:1–16.
13. Maesen B, Zeemering S, Afonso C, et al.: Rearrangement of atrial bundle architecture and consequent changes in anisotropy of conduction constitute the 3-dimensional substrate for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:967–975.
14. Choudry S, Mansour M, Sundaram S, et al.: A multicenter food and drug administration investigational device exemption clinical trial of persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2020;13:e007825
15. Zeemering S, van Hunnik A, van Rosmalen F, et al.: A Novel Tool for the Identification and Characterization of Repetitive Patterns in High-Density Contact Mapping of Atrial Fibrillation. *Front Physiol* 2020;11:1304.
16. Podziemski P, Zeemering S, Kuklik P, et al.: Rotors Detected by Phase Analysis of Filtered, Epicardial Atrial Fibrillation Electrograms Colocalize With Regions of Conduction Block. *Circ Arrhythm Electrophysiol* 2018;11:e005858.

17. Zeemering S, Maesen B, Nijs J, et al.: Automated quantification of atrial fibrillation complexity by probabilistic electrogram analysis and fibrillation wave reconstruction. *Annu Int Conf IEEE Eng Med Biol Soc* 2012, pp. 6357–6360.
18. Maesen B, Zeemering S, Afonso C, et al.: Rearrangement of Atrial Bundle Architecture and Consequent Changes in Anisotropy of Conduction Constitute the 3-Dimensional Substrate for Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2013;6:967–975.
19. Nattel S, Harada M: Atrial remodeling and atrial fibrillation: Recent advances and translational perspectives. *J Am Coll Cardiol* 2014;63:2335–2345.
20. de Groot NMS, Houben RPM, Schotten U, et al.: Electropathological Substrate of Long-Standing Persistent Atrial Fibrillation in Patients With Structural Heart Disease. *Circ Arrhythm Electrophysiol* 2010;3:606–615.
21. Eckstein J, Zeemering S, Linz D, et al.: Transmural conduction is the predominant mechanism of breakthrough during atrial fibrillation: Evidence from simultaneous endo-epicardial high-density activation mapping. *Circ Arrhythm Electrophysiol* 2013;6:334–341.
22. De Groot N, Van Der Does L, Yaksh A, et al.: Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans. *Circ Arrhythm Electrophysiol* 2016;9:e003648.
23. Aronis KN, Trayanova NA: Understanding AF Mechanisms Through Computational Modelling and Simulations. *Arrhythmia Electrophysiol Rev* 2019;8:210–219.
24. Lazar S, Dixit S, Marchlinski FE, Callans DJ, Gerstenfeld EP: Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. *Circulation* 2004;110:3181–3186.
25. Nademanee K, McKenzie J, Kosar E, et al.: A new approach for catheter ablation of atrial fibrillation: Mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;43:2044–2053.
26. Narayan SM, Krummen DE, Rappel W-J: Clinical Mapping Approach To Diagnose Electrical Rotors and Focal. *J Cardiovasc Electrophysiol* 2013;23:447–454.
27. Lau DH, Maesen B, Zeemering S, et al.: Indices of Bipolar Complex Fractionated Atrial Electrograms Correlate Poorly with Each Other and Atrial Fibrillation Substrate Complexity. *Heart Rhythm* 2015;12:1415–1423.
28. Nattel S, Dobrev D: Controversies about Atrial Fibrillation Mechanisms: Aiming for Order in Chaos and Whether it Matters. *Circ Res* 2017;120:1396–1398.
29. Lee S, Sahadevan J, Khrestian CM, Markowitz A, Waldo AL: Characterization of Foci and Breakthrough Sites During Persistent and Long-Standing Persistent Atrial Fibrillation in Patients: Studies Using High-Density (510-512 Electrodes) Batrial Epicardial Mapping. *J Am Heart Assoc* 2017;6:1–12.
30. Berenfeld O, Jalife J: Mechanisms of Atrial Fibrillation. *Heart Fail Clin* 2016;12:167–178.
31. Jalife J, Berenfeld O, Skanes A, Mandapati R: Mechanisms of atrial fibrillation: mother rotors or multiple daughter wavelets, or both? *J Cardiovasc Electrophysiol* 1998;9:S2-12.
32. Haissaguerre M, Hocini M, Denis A, et al.: Driver domains in persistent atrial fibrillation. *Circulation* 2014;130:530–538.
33. Krummen DE, Baykaner T, Schricker AA, et al.: Multicentre safety of adding Focal Impulse and Rotor Modulation (FIRM) to conventional ablation for atrial fibrillation. *Europace* 2017;19:769–774.
34. Narayan SM, Patel J, Mulpuru S, Krummen DE: Focal impulse and rotor modulation ablation of sustaining rotors abruptly terminates persistent atrial fibrillation to sinus rhythm with elimination on follow-up: A video case study. *Heart Rhythm* 2012;9:1436–1439.
35. Allesie MA, De Groot NMS, Houben RPM, et al.: Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease longitudinal dissociation. *Circ Arrhythm Electrophysiol* 2010;3:606–615.

4.6 Supplemental methods

4.6.1 Normalized preferentiality

The normalized preferentiality was calculated as follows:

$$Pref_{norm} = \frac{\sum Pref_{Pref>0.5}}{\#electrodes_{Pref>0.5}} * \frac{\#electrodes_{Pref>0.5}}{Total \#electrodes} * \frac{Interval \ duration}{Total \ recording \ duration}$$

Where $Pref_{norm}$ is the normalized preferentiality, $\sum Pref_{Pref>0.5}$ is the sum of all preferentiality values >0.5 , $\#electrodes_{Pref>0.5}$ is the number of electrodes where the preferentiality is >0.5 and $\#electrodes_{Pref>0.5}$ is the number of electrodes where the preferentiality is >0.5 .

4.6.2 Conduction pattern definitions

The following definitions were used to visually discriminate conduction patterns based on the preferentiality plot, average activation sequence plot and an animation of the activation pattern.

Peripheral with block:

- **Animation:** Wave entering from outside the mapping array. Wave conduction stops at the same position inside the mapping array for multiple repetitions. Wave cannot pass over the line of block.
- **Average activation sequence plot:** Activation starts from the edge of the mapping array, indicating a wave coming from outside the mapping array. Activation stops at the line of block
- **Preferentiality plot:** Direction of activation points away from the edge of the mapping array, towards the line of block. Preferentiality is high (>0.5) but can be lower close to the block line due to varying activation direction near this area.

Peripheral without block:

- **Animation:** Wave entering from outside the mapping array. Wave travels to the site opposite of the side of entrance of the mapping array with no or very little disturbances in activations.
- **Average activation sequence plot:** Activation starts from the edge of the mapping array, indicating a wave coming from outside the mapping array. Latest activation is on the opposite site of the side of entrance.
- **Preferentiality plot:** Direction of activation points away from the edge of the mapping array, towards the opposite side of the mapping array. Preferentiality is high (>0.5) for (nearly) all electrodes.

Breakthrough:

- **Animation:** Wave originating from inside the mapping array. Wave travels away from the area of first activation.

- **Average activation sequence plot:** Earliest activation is located inside the mapping array. Activations radiate outwards from the earliest activation.
- **Preferentiality plot:** Direction of activation points away from the earliest activated site. Preferentiality can be low close to the breakthrough site, as small variations in breakthrough site location can cause conduction towards opposite sides for electrodes close to the breakthrough site.

Reentry:

- **Animation:** Wave should show reentry within the mapping array. Wave enters the mapping array, turns, and continues over the path of initial entrance. When the total reentry path of the pattern was visible in at least one reentry cycle, the pattern was classified as reentry to avoid a negative bias against reentries. Pivoting waves (waves from one direction pivoting around a line of block and returning to the same direction without crossing the line of block) were not counted as reentries.
- **Average activation sequence plot:** Activation sequence shows circular pattern, with the latest and earliest activation in close proximity.
- **Preferentiality plot:** Direction of activation shows circular direction of activations. Preferentiality can be lower in the part where the beginning and end of the reentry come together.

CHAPTER 5

ADENOSINE USAGE DURING AF ABLATION IN EUROPE AND SELECTED LONG-TERM FINDINGS from the ESC-EHRA EORP Atrial Fibrillation Ablation Long-Term registry

Frank van Rosmalen, Tammo Delhaas, Nikolaos Dagres, Elena Arbelo, Carina Blomström-Lundqvist, Harry J.G.M. Crijns, Antoine Da Costa, Mariusz Pytkowski, Nikita Sharikov, Cécile Laroche, Luigi Tavazzi, Joseph Brugada, Laurent Pison, on behalf of the ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry investigators

Journal of Interventional Cardiac Electrophysiology, April 30, 2020

Abstract

Background

Adenosine can be used to reveal dormant pulmonary vein (PV) conduction after PV isolation (PVI). This study presents a subanalysis of real-world one-year follow-up data from the ESC-EHRA EORP Atrial Fibrillation (AF) Ablation Long-Term registry to analyze the usage of adenosine during PVI treatment in terms of rhythm outcome and safety.

Objective

The registry consists of 104 participating centers in 27 countries within the European Society of Cardiology. The registry data was split into an adenosine group (AG) and a no-adenosine group (NAG). Procedure characteristics and patient outcome were compared.

Results

Adenosine was administered in 10.8% of the 3591 PVI patients included in the registry. Spain, the Netherlands and Italy included the majority of adenosine cases (48.8%). Adenosine was applied more often in combination with open irrigation RF-energy (74.7%) and less often in combination with non-irrigated RF energy (1.6%). After 1 year, a higher percentage of the AG was free from AF compared to the NAG (68.9% vs 59.1%, $p<0.001$). Adenosine was associated with better rhythm outcome in RF ablation procedures, but not in cryo-ablation procedures (freedom from AF: RF: AG: 70.9%, NAG: 58.1%, $p<0.001$, cryo: AG: 63.9%, NAG: 63.8%, $p=0.991$).

Conclusion

The use of adenosine was associated with a better rhythm outcome after one year follow-up and seems more useful in patients treated with RF energy compared to patients treated with cryo energy. Given the improved rhythm outcome at one-year follow-up, it seems reasonable to encourage the use of adenosine during RF AF ablation.

5.1 Introduction

Ablation of the pulmonary veins (PVs) or atrium ideally results in irreversible cell damage and subsequent cell death, but can also temporarily cause reversible cell damage leading to a lower resting potential. Consequently, these non-destroyed cells are more difficult to activate, causing a transient electrical block.¹ Once the resting potential of the non-destroyed cells is restored, the 'dormant conduction' revives. This revival might lead to reconnection of one or more PVs, which is the leading cause of arrhythmia recurrence after PVI.²

It was shown that adenosine can be used to reveal dormant conduction of the PVs after PV isolation by increasing the resting potential of PV cells.¹ Publications on the usefulness and long-term outcome of adenosine use after PVI have come from relatively small clinical trials, observational studies, or randomized controlled trials with conflicting results.³ The current guidelines for the management of atrial fibrillation consider adenosine testing to identify the need for additional ablation to be controversial.⁴ This study presents a subanalysis of the large ESC EORP Atrial Fibrillation Ablation (AFA) Long-Term registry consisting of real-world one-year follow-up data, to analyze the effects of adenosine use during PVI treatment in terms of rhythm outcome and safety.

5.2 Methods

All data were collected from the Atrial Fibrillation Ablation Long-Term registry, a prospective, multinational study (not a randomized clinical trial - RCT) conducted by the EURObservational Research Programme (EORP). The ESC EORP AFA Long-Term registry was previously described elsewhere.⁵ In short, it is a prospective, multicenter observational study of consecutive patients undergoing an ablation procedure for atrial fibrillation (AF) at one of the 104 participating centers in 27 countries within the European Society of Cardiology. All patients included in the registry were enrolled between April 2012 and April 2015 with a maximum of 50 consecutive patients per center. Out of all patients enrolled in the registry, patients with an unclassified type of AF, patients who did not undergo an ablation procedure or patients treated with both radiofrequency (RF) and cryo energy in the same procedure were excluded to be able to perform the analyses presented in this paper. All patients signed an informed consent before data collection and were followed up for one year according to the local clinical practice. The protocol was approved by the national and/or local Institutional Review Boards, according to existing regulations in each country. The registry management, central data quality control and the statistical analysis were performed by the EORP Center of the ESC, which coordinated also a random local auditing of 22% participating centers across 14 countries.

The registry data was split into one group of patients where adenosine was used to check for dormant conduction (adenosine group: AG) and another group of patients where adenosine was not used (no adenosine group: NAG). Since this was an observational registry in which the patients were treated according to the local protocol, the application of adenosine during the ablation procedure as well as the timing of testing after ablation, dosage of adenosine or additional use of isoproterenol were all left at the discretion of the operator. Since adenosine administration was based on the local protocol, it is assumed adenosine was used with the intention to treat and therefore for detecting reconnections and ablation of these reconnections when present. It is assumed additional ablation is performed in PVs only, since adenosine is able to reveal dormant conduction in PV cells, but not in LA cells.¹ For the one

year clinical follow up data, the registry was first split into a cryoballoon group and a radiofrequency energy group, and then into an AG and NAG in order to assess the possible influence of different ablation techniques (point-by-point RF vs cryoballoon) on rhythm outcome.

The 1-year follow-up data of patients enrolled in the in-hospital phase was used for the analyses. Continuous variables were reported as mean $\pm$ standard deviation (SD), or as median with interquartile range (IQR). Group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Group comparisons were made using a chi-square test or Fisher's exact test (if any expected cell count was <5). Plots of the Kaplan–Meier curves for arrhythmia-free survival according to type of AF categories were generated. The survival distributions were compared using the log-rank test. A two-sided P-value < 0.05 was considered statistically significant. All analyses were performed using SAS Statistical Software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

5.3 Results

5.3.1 Study population

In the total number of 3591 patients that underwent AF ablation, adenosine was administered in 367 (10.2%) patients to unmask dormant conduction. 152 patients (4.2%) were excluded because both RF and cryo energy was used in the same procedure, resulting in 3439 patients included for the analysis, of which 360 were treated with adenosine. A large difference between countries was noted. Most adenosine cases were included by centers in Spain, followed by the Netherlands and Italy (respectively 27.5%, 11.2% and 10.1% of total included adenosine cases), whereas centers in Bulgaria, Denmark, Israel, Kazakhstan, Latvia, Romania and Slovenia did not include any adenosine cases (see **Table 3**).

The AG and NAG consisted of 96 (26.7 %) and 654 (21.2%) redo patients respectively. After 1 year, 3179 patients (96.8%) were still in follow-up (10.1% AG, 89.9% NAG). Loss to follow up was 12.8% for the AG and 11.3% for the NAG.

5.3.2 Practice of adenosine use

Although there was a significant difference in longstanding persistent AF between the groups ($p = 0.004$), the ratio of paroxysmal, persistent and long-standing persistent was similar, with the longstanding AF group accounting for a minority of cases in both groups (see **Table 2**). The AG consisted of 71.7% paroxysmal, 26.4% persistent and 1.9% long-standing persistent AF patients, whereas the NAG consisted of 66.9% paroxysmal, 27.6% persistent and 5.5% long-standing persistent AF patients (see **Table 2**).

The AG had a lower number of ablations of fractionated electrogram sites in both the left (AG: 5.1%, NAG: 8.9%, $p = 0.015$) and right (AG: 0.8%, NAG: 3.6%, $p = 0.007$) atrium, as well as fewer left atrial roof lines (AG: 7.9%, NAG: 14.0%, $p = 0.002$) and mitral isthmus lines (AG: 3.1%, NAG: 7.0%, $p = 0.005$) (see **Table 3**).

Whereas the overall use of adenosine was 10.8%, adenosine was applied more often in procedures where open irrigation RF-energy is used (75.8%), while it is less often used in procedures using non-irrigated RF energy (0.3%) or duty-cycled RF energy (0%) (see **Table 3**). Cryo energy was relatively over-represented in the AG (AG: 20.6%, NAG: 15.2%, $p = 0.009$).

Table 1. Adenosine use in Europe

	Total cases	Adenosine	
		Total (% of total within country)	% of total within Europe
Spain	526	101 (19.2)	27.5
Netherlands	242	41 (16.9)	11.2
Italy	314	37 (11.8)	10.1
Austria	41	27 (65.9)	7.4
United Kingdom	48	22 (45.8)	6.0
Russian Federation	467	21 (4.5)	5.7
Belgium	84	20 (23.8)	5.5
Sweden	108	14 (13.0)	3.8
Ukraine	87	13 (14.9)	3.5
Finland	170	13 (7.7)	3.5
Czech Republic	79	11 (13.9)	3.0
Greece	139	9 (6.5)	2.5
Ireland	28	8 (28.6)	2.2
Portugal	44	7 (15.9)	1.9
Poland	338	7 (2.1)	1.9
Hungary	60	5 (8.3)	1.4
Egypt	78	5 (6.4)	1.4
France	152	3 (2.0)	0.8
Germany	204	2 (1.0)	0.5
Belarus	20	1 (5.0)	0.3
Bulgaria	107	0 (0.0)	0.0
Denmark	17	0 (0.0)	0.0
Israel	53	0 (0.0)	0.0
Kazakhstan	30	0 (0.0)	0.0
Latvia	35	0 (0.0)	0.0
Romania	61	0 (0.0)	0.0
Slovenia	66	0 (0.0)	0.0

Procedural effects of adenosine

The use of adenosine did not cause a significantly higher total procedure time (measured from the moment of catheter placement until the moment of catheter removal). There was no significant difference in achievement of only entrance block between the AG and NAG, but all PVs showed significantly more entrance and exit block in the AG when compared to the NAG (see **Table 3**). Administration of adenosine revealed reconnection of PVs in 17.3% of adenosine cases.

5.3.3 Effects of adenosine usage on patient outcome

Adverse events

Procedural adverse events potentially related to adenosine use were rare. The adenosine group showed a higher occurrence of pericarditis (AG: 1.7%, NAG: 0.7%, $p = 0.048$) and pulmonary vein stenosis (AG: 0.6%, NAG: 0.0%, $p = 0.031$, defined as a reduction of the diameter of a PV or PV branch of more than 50%). There was no significant difference for other general, cardiovascular, gastrointestinal, neurological, peripheral/vascular or pulmonary adverse events (see **Supplement Table 1**).

Adverse events at one year are listed in **Supplement Table 2**. One infrequently occurring difference in adverse events at one year follow-up was found to be phrenic nerve damage (AG: 2/304, NAG: 0/2669).

One year follow-up

Follow-up at 12 months after the index procedure showed a significant difference in rhythm outcome between the AG and NAG; a higher percentage of the AG was free from AF compared to the NAG (AG: 69.2%, NAG: 58.9%, $p < 0.001$). Observing a 3-month-blanking period, the AG showed a lower percentage of arrhythmia recurrence during the first year after the index procedure compared to the NAG (AG: 20.8%, NAG: 26.3%, $p = 0.038$) (see **Table 4**).

The one year follow-up rhythm outcome was split into a cryoballoon group (493 patients) and a RF energy (non-irrigated radiofrequency, radiofrequency with closed irrigation or radiofrequency with open irrigation) group (2517 patients). Patients where both cryo and RF energy was used within the same procedure were excluded from the analysis (152 patients). While there was no significant difference in rhythm outcome or arrhythmia recurrence between the AG and NAG for patients treated with cryo energy, the RF energy group showed less paroxysmal AF patients in the AG group (AG: 16.0%, NAG: 28.2%, $p < 0.001$), more patients without AF (AG: 70.9%, NAG: 58.1%, $p < 0.001$) and a lower number of arrhythmia recurrences (AG: 19.2%, NAG: 26.5%, $p < 0.015$) after one year follow-up (see **Table 4**).

There was no significant difference in the number of redo procedures between the AG and NAG ($p = 0.662$), or within the cryo and RF ($p = 0.482$, $p = 0.930$) groups during the first year after the procedure (see **Table 4**).

5.4 Discussion

This real-world registry shows adenosine to be used in only a small number (10.2%) of AF ablation procedures within the 104 participating centers of the ESC-EHRA Atrial Fibrillation Ablation Long-Term registry of the European Society of Cardiology, and that there are large regional differences in adenosine use within Europe. The registry shows significant differences in freedom from arrhythmia after 1 year

Table 2. Baseline characteristics

	Cryo or RF energy			Cryo energy			RF energy					
	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P
Gender (female)	1096/3439 (31.9%)	92/360 (25.6%)	1004/3079 (32.6%)	0.007	185/543 (34.1%)	17/74 (23.0%)	168/469 (35.8%)	0.030	911/2896 (31.5%)	75/286 (26.2%)	836/2610 (32.0%)	0.045
Age ≥65 years (mean, SD)	910/3438 (26.5%)	86/360 (23.9%)	824/3078 (26.8%)	0.241	154/543 (28.4%)	22/74 (29.7%)	132/469 (28.1%)	0.779	57.8 (10.3)	56.1 (10.6)	58.0 (10.2)	0.004
Body Mass Index (kg/m2) (mean, SD)	28.4 (4.5)	27.9 (4.3)	28.5 (4.5)	0.101	28.1 (3.9)	27.6 (3.8)	28.1 (3.9)	0.535	28.5 (4.6)	28.0 (4.4)	28.5 (4.6)	0.143
Left atrial diameter (mm) (mean, SD)	42.6 (6.6)	42.1 (5.4)	42.7 (6.7)	0.310	41.0 (5.9)	41.1 (4.5)	41.0 (6.0)	0.633	59.9 (8.4)	59.9 (7.7)	59.9 (8.5)	0.080
Type of AF:												
Paroxysmal	2318/3439 (67.4%)	258/360 (71.7%)	2060/3079 (66.9%)	0.068	454/543 (83.6%)	66/74 (89.2%)	388/469 (82.7%)	0.163	1864/2896 (64.4%)	192/286 (67.1%)	1672/2610 (64.1%)	0.303
Persistent	946/3439 (27.5%)	95/360 (26.4%)	851/3079 (27.6%)	0.615	79/543 (14.5%)	8/74 (10.8%)	71/469 (15.1%)	0.326	867/2896 (29.9%)	87/286 (30.4%)	780/2610 (29.9%)	0.851
Longstanding persistent	175/3439 (5.1%)	7/360 (1.9%)	168/3079 (5.5%)	0.004	10/543 (1.8%)	0/74 (0.0%)	10/469 (2.1%)	0.372	165/2896 (5.7%)	7/286 (2.4%)	158/2610 (6.1%)	0.013

RF: radiofrequency energy. SD: standard deviation.

and in the number of arrhythmia-related hospitalizations, both in favor of the AG. The very low overall incidence of complications precludes further explanation regarding the cause of these adverse events. Adenosine seems to be more useful in RF patients compared to patients treated with cryo energy.

The low number of adenosine cases might be explained by the adherence to guidelines. Adenosine use was not covered in the guidelines available at the time of inclusion. At the time of writing, the guidelines describe adenosine as “may be considered” and “controversial”.^{2,4}

Multiple studies indicated no significant difference in terms of arrhythmia recurrence between using a cryoballoon or RF catheter. Our results, however, showed that adenosine use was associated with a difference in rhythm outcome between cryoballoon and RF: patients treated with RF energy seem to benefit from adenosine use, whereas patients treated with cryo energy did not. Application of point-by-point RF energy may be technically more challenging compared to the delivery of cryo energy with the use of a cryoballoon. This might lead to more gaps in the ablation line, which is associated with lower long-term ablation success.⁶ Adenosine reveals these gaps, which might explain the difference in outcome between the AG and NAG in the RF group. This outcome is in contrast to the UNDER-ATP study by Kobori et al.⁷ In this study, 2113 AF patients were randomized to RF energy PVI with vs without adenosine. Rhythm outcome after one year follow-up was not statistically different. A possible explanation for this discrepancy can be found in the baseline characteristics of our study. Whereas Kobori et al. report no significant differences in baseline characteristics between the two groups for paroxysmal, persistent and long-standing AF, our AG had a small but significantly higher percentage of paroxysmal AF patients, and a small but significantly lower percentage of long-standing persistent AF patients when compared to the NAG. The differences in baseline characteristics can be explained by the different study designs. Whereas Kobori et al. performed a prospective randomized trial, our study contains data from a retrospective registry and is more focused on adenosine usage, in comparison to outcome.

The ADVICE trial is a multicenter, randomized superiority trial consisting of 534 patients who underwent PVI with adenosine treatment at the end of the procedure.⁸ Patients showing dormant conduction were randomly assigned to additional adenosine-guided ablation or to no further ablation, whereas patients not showing dormant conduction were followed in a separate registry. After one year, there was a significant difference between the groups regarding freedom from any atrial tachyarrhythmia after a single procedure, both with and without the use of anti-arrhythmic drugs. The dormant conduction group with additional ablation outperformed the non-dormant conduction group, which in turn outperformed the dormant conduction group without further ablation. Because the patients in our study who received adenosine after PVI either had no dormant conduction, or the reconnected PV was re-isolated, we can compare our results to the ‘dormant conduction with additional ablation group’ combined with the ‘no dormant conduction registry group’ of the ADVICE trial. The ADVICE trial reports that after one year 63.4% of patients where adenosine was used (the dormant conduction with additional ablation group combined with the no dormant conduction registry group) are free from any atrial tachyarrhythmia after a single procedure. This is comparable to our finding of 68.9% freedom of AF for the AG.

The differences between the UNDER-ATP study, the ADVICE trial and our registry indicate that further research should be undertaken to investigate the effect of adenosine on arrhythmia recurrence after PVI. This should also answer the question whether adenosine should be used in combination with cryoballoon, RF or both, since the registry shows that the use of adenosine is not associated with

improved rhythm outcome in combination with cryoballoon procedures but is currently used more often with cryoballoon procedures than RF procedures.

The UNDER-ATP study and ADVICE trial are responsible for the majority of cases included in two recent systematic reviews and meta-analysis.^{3,9} The meta-analysis of Wang et al. included 22 comparative studies and randomized controlled trials. Although there was significant heterogeneity between investigated studies, the authors conclude that the presence of PV reconnections identified with adenosine (and not ablated) result in poorer rates of freedom from AF, and that administration of adenosine post PVI improves rates of freedom from AF by identifying areas for further ablation. Wang et al. show a comparable outcome to our results (freedom from AF: AG: 67%, NAG: 63% (Wang et al.), versus AG: 68.9%, NAG: 59.1% (this study)). Afzal et al. present a meta-analysis over all RCTs investigating adenosine and PVI. The study included 5 RCTs available, all using RF catheters. The conclusion is that routine use of adenosine to guide PVI does neither improve arrhythmia-free survival nor need for repeat ablation. As noted by the authors of both meta-analyses, their outcome depended on the methodology of the observed studies, and there is a large variation in methods. Patient selection, PVI procedure, adenosine dosage, waiting time after adenosine administration, follow-up duration and follow-up method are (amongst others) variables that ideally should be controlled for. Our results add to the growing body of data by showing that adenosine testing can improve outcome in specific cases in a large, multi-center real world cohort.

A significantly higher occurrence of phrenic nerve damage at 1-year follow-up was observed in the AG, although the absolute numbers are low. Since phrenic nerve damage is reported as the most frequent adverse event for cryoballoon ablations,^{10,11} the fact that cryo energy was used more often in the AG could have caused this difference in adverse events outcome.

If adenosine reveals dormant conduction, extra ablation is needed to close the line isolating the PVs. These extra ablations increase the energy delivered to the PVs, which in turn increases the chance of pericarditis and PV stenosis. This can be a reason for the increase in pericarditis and PV stenosis occurrence in the AG.

The fact that cryo patients do not seem to benefit from the use of adenosine might partially be a procedural reason. Most cryo ablations are PVI-only ablations and do not use a catheter able to target regions outside of the PV, nor make linear lesions. However, we compare these to RF ablations where adenosine is used, and in this group, only a minority (61 out of 353) received LA linear lesions.

Force sensing catheters and ablation index technology were not widely used during the inclusion period of this registry. The use of these techniques might decrease the need for adenosine testing, as research indicates that the quality of point-by-point RF lesions increases significantly by using force sensing catheters and ablation index technology.^{12,13}

5.4.1 Limitations

The main limitations of this registry have already been described previously⁵. A prospective design requiring consecutive inclusion of patients was used to minimize the risk of selection and reporting bias. The EURObservational Research Programme Department of the ESC performed extensive validation and invited external auditors to assure quality and reliability of the data, as mentioned in the

Table 3. Type of procedure and ablation strategy

Type of procedure	Cryo or RF energy			Cryo energy			RF energy					
	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P
First procedure	2685/3439 (78.1%)	263/360 (73.1%)	2422/3079 (78.7%)	0.015	490/543 (90.2%)	70/74 (94.6%)	420/469 (89.6%)	0.174	2195/2896 (75.8%)	193/286 (67.5%)	2002/2610 (76.7%)	<0.001
Redo due to Atrial Fibrillation	660/3439 (19.2%)	94/360 (26.1%)	566/3079 (18.4%)	<0.001	49/543 (9.0%)	4/74 (5.4%)	45/469 (9.6%)	0.242	611/2896 (21.1%)	90/286 (31.5%)	521/2610 (20.0%)	<0.001
Redo due to Left Atrial Flutter/Left Atrial Tachycardia	90/3439 (2.6%)	2/360 (0.6%)	88/3079 (2.9%)	0.010	4/543 (0.7%)	0/74 (0.0%)	4/469 (0.9%)	1.000	86/2896 (3.0%)	2/286 (0.7%)	84/2610 (3.2%)	0.017
Hybrid	4/3439 (0.1%)	1/360 (0.3%)	3/3079 (0.1%)	0.358	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	-	4/2896 (0.1%)	1/286 (0.3%)	3/2610 (0.1%)	0.340
Ablation strategy												
Fractionated electrogram sites in the left atrium	278/3263 (8.5%)	18/353 (5.1%)	260/2910 (8.9%)	0.015	8/533 (1.5%)	0/74 (0.0%)	8/459 (1.7%)	0.607	270/2730 (9.9%)	18/279 (6.5%)	252/2451 (10.3%)	0.042
Fractionated electrogram sites in right atrium	107/3263 (3.3%)	3/353 (0.8%)	104/2910 (3.6%)	0.007	4/533 (0.8%)	0/74 (0.0%)	4/459 (0.9%)	1.000	103/2730 (3.8%)	3/279 (1.1%)	100/2451 (4.1%)	0.013
Left atrial linear lesion												
Roof line	436/3264 (13.4%)	28/353 (7.9%)	408/2911 (14.0%)	0.002	0/533 (0.0%)	0/74 (0.0%)	0/459 (0.0%)	NA	436/2731 (16.0%)	28/279 (10.0%)	408/2452 (16.6%)	0.004
Mitral isthmus line	216/3264 (6.6%)	11/353 (3.1%)	205/2911 (7.0%)	0.005	2/533 (0.4%)	0/74 (0.0%)	2/459 (0.4%)	1.000	214/2731 (7.8%)	11/279 (3.9%)	203/2452 (8.3%)	0.011
Posterior line	137/3199 (4.3%)	16/342 (4.7%)	121/2857 (4.2%)	0.702	0/513 (0.0%)	0/74 (0.0%)	0/439 (0.0%)	NA	137/2686 (5.1%)	16/268 (6.0%)	121/2418 (5.0%)	0.495
Other left atrial linear lesion	99/3264 (3.0%)	6/353 (1.7%)	93/2911 (3.2%)	0.122	0/533 (0.0%)	0/74 (0.0%)	0/459 (0.0%)	NA	99/2731 (3.6%)	6/279 (2.2%)	93/2452 (3.8%)	0.164
Achievement of entrance block												
LSPV	3004/3104 (96.8%)	328/334 (98.2%)	2676/2770 (96.6%)	0.118	510/528 (96.6%)	69/73 (94.5%)	441/455 (96.9%)	0.294	2494/2576 (96.8%)	259/261 (99.2%)	2235/2315 (96.5%)	0.019
LIPV	2939/3030 (97.0%)	323/330 (97.9%)	2616/2700 (96.9%)	0.320	498/516 (96.5%)	66/71 (93.0%)	432/445 (97.1%)	0.087	2441/2514 (97.1%)	257/259 (99.2%)	2184/2255 (96.9%)	0.031

Table 3. Type of procedure and ablation strategy (Continued)

RSPV	2984/3094 (96.4%)	327/334 (97.9%)	2657/2760 (96.3%)	0.127	494/519 (95.2%)	67/72 (93.1%)	427/447 (95.5%)	0.371	2490/2575 (96.7%)	260/262 (99.2%)	2230/2313 (96.4%)	0.015 (5)
RIPV	2953/3083 (95.8%)	323/330 (97.9%)	2630/2753 (95.5%)	0.045	480/507 (94.7%)	67/71 (94.4%)	413/436 (94.7%)	0.781	2473/2576 (96.0%)	256/259 (98.8%)	2217/2317 (95.7%)	0.014
Adenosine												
Use of adenosine at end of procedure	353/3264 (10.8%)	353/353 (100.0%)	0/2911 (0.0%)	<0.001	74/533 (13.9%)	74/74 (100.0%)	0/459 (0.0%)	<0.001	279/2731 (10.2%)	279/279 (100.0%)	0/2452 (0.0%)	<0.001
Adenosine-induced reconnection of PV	61/353 (17.3%)	61/353 (17.3%)	0/0 (0.0%)	-	15/74 (20.3%)	15/74 (20.3%)	0/0 (0.0%)	-	46/279 (16.5%)	46/279 (16.5%)	0/0 (0.0%)	-
Catheter used												
Non-irrigated RF	44/3439 (1.3%)	1/360 (0.3%)	43/3079 (1.4%)	0.082	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	44/2896 (1.5%)	1/286 (0.3%)	43/2610 (1.6%)	0.121
RF with closed irrigation	125/3439 (3.6%)	12/360 (3.3%)	113/3079 (3.7%)	0.747	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	125/2896 (4.3%)	12/286 (4.2%)	113/2610 (4.3%)	0.916
RF with open irrigation	2730/3439 (79.4%)	273/360 (75.8%)	2457/3079 (79.8%)	0.078	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	2730/2896 (94.3%)	273/286 (95.5%)	2457/2610 (94.1%)	0.363
Cryo	543/3439 (15.8%)	74/360 (20.6%)	469/3079 (15.2%)	0.009	543/543 (100.0%)	74/74 (100.0%)	469/469 (100.0%)	NA	0/2896 (0.0%)	0/286 (0.0%)	0/2610 (0.0%)	NA
Duty-cycled RF energy	9/3439 (0.3%)	0/360 (0.0%)	9/3079 (0.3%)	0.610	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	9/2896 (0.3%)	0/286 (0.0%)	9/2610 (0.3%)	1.000
High intensity focused ultrasound	8/3439 (0.2%)	0/360 (0.0%)	8/3079 (0.3%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	8/2896 (0.3%)	0/286 (0.0%)	8/2610 (0.3%)	1.000
Laser balloon	0/3439 (0.0%)	0/360 (0.0%)	0/3079 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2896 (0.0%)	0/286 (0.0%)	0/2610 (0.0%)	NA
Other	3/3 (100.0%)	0/0 (0.0%)	3/3 (100.0%)	NA	-	-	-	-	3/3 (100.0%)	0/0 (0.0%)	3/3 (100.0%)	NA
Procedure:												
Procedure duration (min) (mean, SD)	165.9 (65.8)	161.2 (55.3)	166.5 (66.9)	0.566	138.3 (49.3)	162.6 (60.3)	134.4 (46.3)	<0.001	170.9 (67.1)	160.8 (54.2)	172.0 (68.4)	0.042

LSPV: Left Superior Pulmonary Vein. LIPV: Left Inferior Pulmonary Vein. RSPV: Right Superior Pulmonary Vein. RIPV: Right Inferior Pulmonary Vein. NA: data not available.

Table 4. One year clinical follow-up

	Cryo or RF energy				Cryo energy				RF energy			
	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P
Classification of AF one year after the procedure												
Permanent AF	61/3010 (2.0%)	5/308 (1.6%)	56/2702 (2.1%)	0.596	7/493 (1.4%)	0/71 (0.0%)	7/422 (1.7%)	0.601	54/2517 (2.1%)	5/237 (2.1%)	49/2280 (2.1%)	0.968
Persistent AF	295/3010 (9.8%)	25/308 (8.1%)	270/2702 (10.0%)	0.294	25/493 (5.1%)	2/71 (2.8%)	23/422 (5.5%)	0.558	270/2517 (10.7%)	23/237 (9.7%)	247/2280 (10.8%)	0.593
Paroxysmal AF	825/3010 (27.4%)	62/308 (20.1%)	763/2702 (28.2%)	0.003	145/493 (29.4%)	24/71 (33.8%)	121/422 (28.7%)	0.380	680/2517 (27.0%)	38/237 (16.0%)	642/2280 (28.2%)	<0.001
Long-standing persistent AF	25/3010 (0.8%)	3/308 (1.0%)	22/2702 (0.8%)	0.737	4/493 (0.8%)	0/71 (0.0%)	4/422 (0.9%)	1.000	21/2517 (0.8%)	3/237 (1.3%)	18/2280 (0.8%)	0.441
No AF	1804/3010 (59.9%)	213/308 (69.2%)	1591/2702 (58.9%)	<0.001	312/493 (63.3%)	45/71 (63.4%)	267/422 (63.3%)	0.986	1492/2517 (59.3%)	168/237 (70.9%)	1324/2280 (58.1%)	<0.001
Recurrence (after blanking period)	762/2958 (25.8%)	64/307 (20.8%)	698/2651 (26.3%)	0.038	123/478 (25.7%)	18/68 (26.5%)	105/410 (25.6%)	0.880	639/2480 (25.8%)	46/239 (19.2%)	593/2241 (26.5%)	0.015
Method of documentation												
ECG	804/3029 (26.5%)	66/311 (21.2%)	738/2718 (27.2%)	0.025	120/492 (24.4%)	16/71 (22.5%)	104/421 (24.7%)	0.694	684/2537 (27.0%)	50/240 (20.8%)	634/2297 (27.6%)	0.025
Hospital discharge record	189/3025 (6.2%)	13/311 (4.2%)	176/2714 (6.5%)	0.112	32/490 (6.5%)	2/71 (2.8%)	30/419 (7.2%)	0.294	157/2535 (6.2%)	11/240 (4.6%)	146/2295 (6.4%)	0.277
Transtelephonic monitoring	23/3025 (0.8%)	0/311 (0.0%)	23/2714 (0.8%)	0.161	6/490 (1.2%)	0/71 (0.0%)	6/419 (1.4%)	0.600	17/2535 (0.7%)	0/240 (0.0%)	17/2295 (0.7%)	0.397
Written diagnosis	167/3025 (5.5%)	13/311 (4.2%)	154/2714 (5.7%)	0.274	18/490 (3.7%)	2/71 (2.8%)	16/419 (3.8%)	1.000	149/2535 (5.9%)	11/240 (4.6%)	138/2295 (6.0%)	0.370
Holter	380/3026 (12.6%)	33/311 (10.6%)	347/2715 (12.8%)	0.274	67/491 (13.6%)	12/71 (16.9%)	55/420 (13.1%)	0.388	313/2535 (12.3%)	21/240 (8.8%)	292/2295 (12.7%)	0.075
Implanted monitoring system	57/3025 (1.9%)	5/311 (1.6%)	52/2714 (1.9%)	0.705	15/490 (3.1%)	0/71 (0.0%)	15/419 (3.6%)	0.144	42/2535 (1.6%)	5/240 (2.1%)	37/2295 (1.6%)	0.591

Table 4. One year clinical follow-up (Continued)

Management of recurrence												
Cardioversion	459/1020 (45.0%)	31/85 (36.5%)	428/935 (45.8%)	0.099	63/158 (39.9%)	4/22 (18.2%)	59/136 (43.4%)	0.025	396/862 (45.9%)	27/63 (42.9%)	369/799 (46.2%)	0.610
Redo ablation	223/996 (22.4%)	17/82 (20.7%)	206/914 (22.5%)	0.707	41/154 (26.6%)	3/21 (14.3%)	38/133 (28.6%)	0.169	182/842 (21.6%)	14/61 (23.0%)	168/781 (21.5%)	0.792
Cardiology visit	2507/3031 (82.7%)	256/312 (82.1%)	2251/2719 (82.8%)	0.745	418/493 (84.8%)	48/71 (67.6%)	370/422 (87.7%)	<0.001	2089/2538 (82.3%)	208/241 (86.3%)	1881/2297 (81.9%)	0.087
Emergency room visit	472/3030 (15.6%)	45/312 (14.4%)	427/2718 (15.7%)	0.553	82/493 (16.6%)	10/71 (14.1%)	72/422 (17.1%)	0.533	390/2537 (15.4%)	35/241 (14.5%)	355/2296 (15.5%)	0.701
Hospitalization due to arrhythmia in blanking period	206/420 (49.0%)	12/25 (48.0%)	194/395 (49.1%)	0.914	29/67 (43.3%)	2/4 (50.0%)	27/63 (42.9%)	1.000	177/353 (50.1%)	10/21 (47.6%)	167/332 (50.3%)	0.812
Hospitalization due to arrhythmia outside blanking period	320/420 (76.2%)	14/25 (56.0%)	306/395 (77.5%)	0.015	52/68 (76.5%)	2/4 (50.0%)	50/64 (78.1%)	0.233	268/352 (76.1%)	12/21 (57.1%)	256/331 (77.3%)	0.035
Hospitalization due to other cardiovascular event	96/2969 (3.2%)	9/309 (2.9%)	87/2660 (3.3%)	0.736	11/492 (2.2%)	3/71 (4.2%)	8/421 (1.9%)	0.202	85/2477 (3.4%)	6/238 (2.5%)	79/2239 (3.5%)	0.417
Hospitalization due to non cardiovascular event	166/2970 (5.6%)	20/309 (6.5%)	146/2661 (5.5%)	0.475	31/492 (6.3%)	2/71 (2.8%)	29/421 (6.9%)	0.289	135/2478 (5.4%)	18/238 (7.6%)	117/2240 (5.2%)	0.130
Follow-up duration (months, mean (SD))	13.0 (3.6)	12.3 (2.4)	13.1 (3.7)	0.004	12.8 (2.8)	12.7 (2.5)	12.8 (2.9)	<0.001	13.0 (3.7)	12.2 (2.3)	13.1 (3.8)	0.179
Number of repeat procedures												
1	257/2958 (8.7%)	22/303 (7.3%)	235/2655 (8.9%)	0.662	46/479 (9.6%)	4/68 (5.9%)	42/411 (10.2%)	0.482	211/2479 (8.5%)	18/235 (7.7%)	193/2244 (8.6%)	0.930
2	21/2958 (0.7%)	1/303 (0.3%)	20/2655 (0.8%)		4/479 (0.8%)	0/68 (0.0%)	4/411 (1.0%)		17/2479 (0.7%)	1/235 (0.4%)	16/2244 (0.7%)	
3	3/2958 (0.1%)	0/303 (0.0%)	3/2655 (0.1%)		-	-	-		3/2479 (0.1%)	0/235 (0.0%)	3/2244 (0.1%)	

RF: radiofrequency energy. SD: standard deviation.

methods section. The interpretation of recurrence data may be limited by inhomogeneous and partially insufficient arrhythmia monitoring. Follow-up at one year was performed in 52.8% by clinical visit, 44.2% by telephone contact and 3.0% by contact with the general practitioner, and although 82.7 % of patients had a clinical visit within the first year, ideally all patients would have had one year follow up by clinical visit and Holter monitoring to discover possible asymptomatic recurrence.

The ESC-EHRA EORP Atrial Fibrillation Ablation Long-Term registry was not designed to answer specific questions regarding adenosine dosage, timing or strategy since the criteria for adenosine use, dosage, timing and strategy were all left at the discretion of the operator. This precludes detailed conclusions about specific adenosine strategies.

Another limitation of the registry is that it contains no explicit information whether additional ablation was performed when PV reconnections were found. Since adenosine administration was based on the local protocol, it is assumed adenosine was used with the intention to treat and therefore for detecting reconnections and ablation of these reconnections when present.

Because this registry presents observational data, the possibility of confounding factors that may influence the descriptive study results cannot be excluded. Because of the very low incidence of complications in this registry, it is not possible to provide evidence on possible correlations between complications, ablation techniques and adenosine use. The main focus of the analysis is the use of adenosine within Europe. Since this is not a randomized controlled trial, small but significant differences in baseline characteristics between the AG and NAG might influence the results.

5.5 Conclusion

In conclusion, this observational study shows that, though adenosine is used in only a small number of AF ablation cases, its use is associated with a better rhythm outcome in patients treated with RF energy. Given the very low incidence of complications associated with the use of adenosine, it seems reasonable to encourage the use of adenosine during RF energy AF ablation. These findings need to be confirmed in randomized controlled trials.

5.6 References

1. Datino T, Macle L, Qi X-Y, et al.: Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. *Circulation* 2010;121:963–972.
2. Calkins H, Hindricks G, Cappato R, et al.: 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:e1–e160.
3. Wang N, Phan S, Kanagaratnam A, Kumar N, Phan K: Adenosine Testing After Atrial Fibrillation Ablation: Systematic Review and Meta-analysis. *Hear Lung Circ* 2017;27:601–610.
4. Kirchhof P, Benussi S, Kotecha D, et al.: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18:1609–1678.
5. Arbelo E, Brugada J, Blomström-Lundqvist C, et al.: Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J* 2017;38:1303–1316.
6. Kuck K-H, Hoffmann BA, Ernst S, et al.: Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol* 2016;9:e003337.
7. Kobori A, Shizuta S, Inoue K, et al.: Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: The UNmasking dormant electrical reconduction by adenosine triphosphate (UNDER-ATP) trial. *Eur Heart J* 2015;36:3276–3287.
8. Macle L, Khairy P, Weerasooriya R, et al.: Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. *Lancet* 2015;386:672–679.
9. Afzal MR, Kahaly O, Weiss R, et al.: Expert Review of Cardiovascular Therapy Adenosine triphosphate / adenosine guided pulmonary vein isolation does not improve the outcomes of ablation : a meta-analysis of randomized controlled trials. *Expert Rev Cardiovasc Ther* 2018;16:313–318.
10. Kuck K-H, Brugada J, Fürnkranz A, et al.: Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016;374:2235–2245.
11. Canpolat U, Kocyigit D, Aytemir K: Complications of Atrial Fibrillation Cryoablation. *J Atr Fibrillation* 2017;10:1620.
12. Schaeffer B, Willems S, Meyer C, et al.: Contact force facilitates the achievement of an unexcitable ablation line during pulmonary vein isolation. *Clin Res Cardiol* 2018;107:632–641.
13. Hussein A, Das M, Chaturvedi V, et al.: Prospective use of Ablation Index targets improves clinical outcomes following ablation for atrial fibrillation. *J Cardiovasc Electrophysiol* 2017;28:1037–1047.

5.7 Supplemental tables

Table S1. Adverse events

	Cryo or RF energy				Cryo energy				RF energy			
	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P
Cardiovascular												
Cardiac Arrest	3/3430 (0.1%)	0/360 (0.0%)	3/3070 (0.1%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	3/2887 (0.1%)	0/286 (0.0%)	3/2601 (0.1%)	1.000
Air Embolism	8/3430 (0.2%)	1/360 (0.3%)	7/3070 (0.2%)	0.589	3/543 (0.6%)	0/74 (0.0%)	3/469 (0.6%)	1.000	5/2887 (0.2%)	1/286 (0.3%)	4/2601 (0.2%)	0.407
Endocarditis	0/3430 (0.0%)	0/360 (0.0%)	0/3070 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2887 (0.0%)	0/286 (0.0%)	0/2601 (0.0%)	NA
Myocardial Infarction	0/3430 (0.0%)	0/360 (0.0%)	0/3070 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2887 (0.0%)	0/286 (0.0%)	0/2601 (0.0%)	NA
Cardiac perforation	46/3430 (1.3%)	1/360 (0.3%)	45/3070 (1.5%)	0.084	7/543 (1.3%)	0/74 (0.0%)	7/469 (1.5%)	0.601	39/2887 (1.4%)	1/286 (0.3%)	38/2601 (1.5%)	0.174
Bradycardia Requiring Pacemaker	5/3431 (0.1%)	0/360 (0.0%)	5/3071 (0.2%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	5/2888 (0.2%)	0/286 (0.0%)	5/2602 (0.2%)	1.000
Cardiac Thrombo- embolic Event	2/3430 (0.1%)	1/360 (0.3%)	1/3070 (0.0%)	0.199	1/543 (0.2%)	0/74 (0.0%)	1/469 (0.2%)	1.000	1/2887 (0.0%)	1/286 (0.3%)	0/2601 (0.0%)	0.099
Heart Valve Damage	1/3430 (0.0%)	0/360 (0.0%)	1/3070 (0.0%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	1/2887 (0.0%)	0/286 (0.0%)	1/2601 (0.0%)	1.000
Pericarditis	26/3431 (0.8%)	6/360 (1.7%)	20/3071 (0.7%)	0.048	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	26/2888 (0.9%)	6/286 (2.1%)	20/2602 (0.8%)	0.038
Other	50/3434 (1.5%)	8/360 (2.2%)	42/3074 (1.4%)	0.200	3/543 (0.6%)	0/74 (0.0%)	3/469 (0.6%)	1.000	47/2891 (1.6%)	8/286 (2.8%)	39/2605 (1.5%)	0.132
General												
Allergic Reaction	9/3435 (0.3%)	1/360 (0.3%)	8/3075 (0.3%)	1.000	3/543 (0.6%)	0/74 (0.0%)	3/469 (0.6%)	1.000	6/2892 (0.2%)	1/286 (0.3%)	5/2606 (0.2%)	0.465
Sepsis	1/3436 (0.0%)	0/360 (0.0%)	1/3076 (0.0%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	1/2893 (0.0%)	0/286 (0.0%)	1/2607 (0.0%)	1.000

Table S1. Adverse events (Continued)

Gastrointestinal											
Oesophageal ulceration	2/3437 (0.1%)	1/360 (0.3%)	1/3077 (0.0%)	0.199	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	2/2894 (0.1%)	1/2608 (0.0%)	0.188
Oesophageal Fistula or perforation	1/3437 (0.0%)	0/360 (0.0%)	1/3077 (0.0%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	1/2894 (0.0%)	1/2608 (0.0%)	1.000
Neurological											
Stroke	1/3437 (0.0%)	0/360 (0.0%)	1/3077 (0.0%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	1/2894 (0.0%)	1/2608 (0.0%)	1.000
TIA	8/3436 (0.2%)	1/360 (0.3%)	7/3076 (0.2%)	0.588	3/543 (0.6%)	0/74 (0.0%)	3/469 (0.6%)	1.000	5/2893 (0.2%)	4/2607 (0.2%)	0.406
Phrenic Nerve Damage	13/3436 (0.4%)	4/360 (1.1%)	9/3076 (0.3%)	0.039	11/543 (2.0%)	4/74 (5.4%)	7/469 (1.5%)	0.050	2/2893 (0.1%)	2/2607 (0.1%)	1.000
Vagal nerve injury	0/3436 (0.0%)	0/360 (0.0%)	0/3076 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2893 (0.0%)	0/2607 (0.0%)	NA
Peripheral nerve injury	0/3436 (0.0%)	0/360 (0.0%)	0/3076 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2893 (0.0%)	0/2607 (0.0%)	NA
Peripheral/Vascular											
AV fistula	14/3435 (0.4%)	2/360 (0.6%)	12/3075 (0.4%)	0.652	1/542 (0.2%)	0/74 (0.0%)	1/468 (0.2%)	1.000	13/2893 (0.4%)	11/2607 (0.4%)	0.373
DVT	0/3433 (0.0%)	0/360 (0.0%)	0/3073 (0.0%)	NA	0/542 (0.0%)	0/74 (0.0%)	0/468 (0.0%)	NA	0/2891 (0.0%)	0/2605 (0.0%)	NA
Peripheral thromboembolic event	0/3433 (0.0%)	0/360 (0.0%)	0/3073 (0.0%)	NA	0/542 (0.0%)	0/74 (0.0%)	0/468 (0.0%)	NA	0/2891 (0.0%)	0/2605 (0.0%)	NA
Pseudoaneurysm	16/3433 (0.5%)	1/360 (0.3%)	15/3073 (0.5%)	1.000	3/542 (0.6%)	0/74 (0.0%)	3/468 (0.6%)	1.000	13/2891 (0.4%)	12/2605 (0.5%)	1.000
Hematoma or bleeding requiring evacuation or transfusion	12/3434 (0.3%)	0/360 (0.0%)	12/3074 (0.4%)	0.627	4/543 (0.7%)	0/74 (0.0%)	4/469 (0.9%)	1.000	8/2891 (0.3%)	8/2605 (0.3%)	1.000
Bleeding requiring transfusion	4/3433 (0.1%)	2/360 (0.6%)	2/3073 (0.1%)	0.057	1/542 (0.2%)	1/74 (1.4%)	0/468 (0.0%)	0.137	3/2891 (0.1%)	2/2605 (0.1%)	0.268

Table S1. Adverse events (Continued)

Pulmonary												
Hemothorax	1/3437 (0.0%)	0/360 (0.0%)	1/3077 (0.0%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	1/2894 (0.0%)	0/286 (0.0%)	1/2608 (0.0%)	1.000
Pneumothorax	2/3437 (0.1%)	0/360 (0.0%)	2/3077 (0.1%)	1.000	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	2/2894 (0.1%)	0/286 (0.0%)	2/2608 (0.1%)	1.000
Pulmonary vein damage/ dissection	0/3437 (0.0%)	0/360 (0.0%)	0/3077 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2894 (0.0%)	0/286 (0.0%)	0/2608 (0.0%)	NA
Pulmonary vein stenosis	3/3437 (0.1%)	2/360 (0.6%)	1/3077 (0.0%)	0.031	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	3/2894 (0.1%)	2/286 (0.7%)	1/2608 (0.0%)	0.027
Pleural Effusion	5/3437 (0.1%)	1/360 (0.3%)	4/3077 (0.1%)	0.425	1/543 (0.2%)	0/74 (0.0%)	1/469 (0.2%)	1.000	4/2894 (0.1%)	1/286 (0.3%)	3/2608 (0.1%)	0.341
Pulmonary embolism	0/3437 (0.0%)	0/360 (0.0%)	0/3077 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2894 (0.0%)	0/286 (0.0%)	0/2608 (0.0%)	NA
Pulmonary vein thrombosis	0/3437 (0.0%)	0/360 (0.0%)	0/3077 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2894 (0.0%)	0/286 (0.0%)	0/2608 (0.0%)	NA
Pneumonia	0/3437 (0.0%)	0/360 (0.0%)	0/3077 (0.0%)	NA	0/543 (0.0%)	0/74 (0.0%)	0/469 (0.0%)	NA	0/2894 (0.0%)	0/286 (0.0%)	0/2608 (0.0%)	NA
Other	54/3436 (1.6%)	10/360 (2.8%)	44/3076 (1.4%)	0.052	7/543 (1.3%)	2/74 (2.7%)	5/469 (1.1%)	0.245	47/2893 (1.6%)	8/286 (2.8%)	39/2607 (1.5%)	0.131

RF: radiofrequency energy.

Table S2. Adverse events at one year follow-up

	Cryo or RF energy			Cryo energy			RF energy					
	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P	Total	Adenosine	No adenosine	P
Permanent pacemaker implantation	23/131 (17.6%)	1/15 (6.7%)	22/116 (19.0%)	0.468	0/24 (0.0%)	0/5 (0.0%)	0/19 (0.0%)	NA	23/107 (21.5%)	1/10 (10.0%)	22/97 (22.7%)	0.686
Cardiovascular	31/3057 (1.0%)	3/314 (1.0%)	28/2743 (1.0%)	1.000	3/494 (0.6%)	0/71 (0.0%)	3/423 (0.7%)	1.000	28/2563 (1.1%)	3/243 (1.2%)	25/2320 (1.1%)	0.744
Cardiac Arrest	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Air Embolism	1/3057 (0.0%)	0/314 (0.0%)	1/2743 (0.0%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1.000
Endocarditis	1/3057 (0.0%)	0/314 (0.0%)	1/2743 (0.0%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1.000
Myocardial Infarction	2/3057 (0.1%)	0/314 (0.0%)	2/2743 (0.1%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	2/2563 (0.1%)	0/243 (0.0%)	2/2320 (0.1%)	1.000
Cardiac perforation	6/3057 (0.2%)	0/314 (0.0%)	6/2743 (0.2%)	1.000	1/494 (0.2%)	0/71 (0.0%)	1/423 (0.2%)	1.000	5/2563 (0.2%)	0/243 (0.0%)	5/2320 (0.2%)	1.000
Bradycardia Requiring Pacemaker	5/3057 (0.2%)	0/314 (0.0%)	5/2743 (0.2%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	5/2563 (0.2%)	0/243 (0.0%)	5/2320 (0.2%)	1.000
Cardiac Thromboembolic Event	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Heart Valve Damage	1/3057 (0.0%)	0/314 (0.0%)	1/2743 (0.0%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1.000
Pericarditis	4/3057 (0.1%)	1/314 (0.3%)	3/2743 (0.1%)	0.352	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	4/2563 (0.2%)	1/243 (0.4%)	3/2320 (0.1%)	0.329
Other	14/3057 (0.5%)	2/314 (0.6%)	12/2743 (0.4%)	0.648	1/494 (0.2%)	0/71 (0.0%)	1/423 (0.2%)	1.000	13/2563 (0.5%)	2/243 (0.8%)	11/2320 (0.5%)	0.353
General	3/3057 (0.1%)	1/314 (0.3%)	2/2743 (0.1%)	0.278	1/494 (0.2%)	1/71 (1.4%)	0/423 (0.0%)	0.144	2/2563 (0.1%)	0/243 (0.0%)	2/2320 (0.1%)	1.000
Allergic Reaction	2/3057 (0.1%)	1/314 (0.3%)	1/2743 (0.0%)	0.195	1/494 (0.2%)	1/71 (1.4%)	0/423 (0.0%)	0.144	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1.000
Sepsis	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA

Table S2. Adverse events at one year follow-up (Continued)

Gastrointestinal	4/3057 (0.1%)	1/314 (0.3%)	3/2743 (0.1%)	0.352	2/494 (0.4%)	1/71 (1.4%)	1/423 (0.2%)	0.267	2/2563 (0.1%)	0/243 (0.0%)	2/2320 (0.1%)	1.000
Oesophageal Fistula or perforation	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Oesophageal ulceration	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Neurological	8/3057 (0.3%)	3/314 (1.0%)	5/2743 (0.2%)	0.041	3/494 (0.6%)	2/71 (2.8%)	1/423 (0.2%)	0.055	5/2563 (0.2%)	1/243 (0.4%)	4/2320 (0.2%)	0.393
Stroke	1/3057 (0.0%)	0/314 (0.0%)	1/2743 (0.0%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1.000
TIA	5/3057 (0.2%)	1/314 (0.3%)	4/2743 (0.1%)	0.419	1/494 (0.2%)	0/71 (0.0%)	1/423 (0.2%)	1.000	4/2563 (0.2%)	1/243 (0.4%)	3/2320 (0.1%)	0.329
Phrenic Nerve Damage	2/2973 (0.1%)	2/304 (0.7%)	0/2669 (0.0%)	0.010	2/480 (0.4%)	2/68 (2.9%)	0/412 (0.0%)	0.020	0/2493 (0.0%)	0/236 (0.0%)	0/2257 (0.0%)	NA
Vagal nerve injury	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Peripheral nerve injury	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Peripheral-vascular	21/3057 (0.7%)	1/314 (0.3%)	20/2743 (0.7%)	0.717	5/494 (1.0%)	0/71 (0.0%)	5/423 (1.2%)	1.000	16/2563 (0.6%)	1/243 (0.4%)	15/2320 (0.6%)	1.000
AV fistula	8/2973 (0.3%)	0/304 (0.0%)	8/2669 (0.3%)	1.000	3/480 (0.6%)	0/68 (0.0%)	3/412 (0.7%)	1.000	5/2493 (0.2%)	0/236 (0.0%)	5/2257 (0.2%)	1.000
DVT	2/3057 (0.1%)	0/314 (0.0%)	2/2743 (0.1%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	2/2563 (0.1%)	0/243 (0.0%)	2/2320 (0.1%)	1.000
Peripheral thromboembolic event	1/3057 (0.0%)	0/314 (0.0%)	1/2743 (0.0%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1.000
Pseudoaneurysm	9/2973 (0.3%)	1/304 (0.3%)	8/2669 (0.3%)	1.000	3/480 (0.6%)	0/68 (0.0%)	3/412 (0.7%)	1.000	6/2493 (0.2%)	1/236 (0.4%)	5/2257 (0.2%)	0.450
Hematoma or bleeding requiring evacuation or transfusion	3/3057 (0.1%)	0/314 (0.0%)	3/2743 (0.1%)	1.000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	3/2563 (0.1%)	0/243 (0.0%)	3/2320 (0.1%)	1.000
Bleeding requiring transfusion	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA

Table S2. Adverse events at one year follow-up (Continued)

	10/3057 (0.3%)	1/314 (0.3%)	9/2743 (0.3%)	1,000	2/494 (0.4%)	1/71 (1.4%)	1/423 (0.2%)	0.267	8/2563 (0.3%)	0/243 (0.0%)	8/2320 (0.3%)	1,000
Pulmonary												
Hemotorax	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Pneumotorax	3/3057 (0.1%)	0/314 (0.0%)	3/2743 (0.1%)	1,000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	3/2563 (0.1%)	0/243 (0.0%)	3/2320 (0.1%)	1,000
Pulmonary vein damage/dissection	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Pulmonary vein stenosis	4/3057 (0.1%)	0/314 (0.0%)	4/2743 (0.1%)	1,000	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	4/2563 (0.2%)	0/243 (0.0%)	4/2320 (0.2%)	1,000
Pleural Effusion	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Pulmonary embolism	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Pulmonary vein thrombosis	0/3057 (0.0%)	0/314 (0.0%)	0/2743 (0.0%)	NA	0/494 (0.0%)	0/71 (0.0%)	0/423 (0.0%)	NA	0/2563 (0.0%)	0/243 (0.0%)	0/2320 (0.0%)	NA
Pneumonia	3/3057 (0.1%)	1/314 (0.3%)	2/2743 (0.1%)	0.278	2/494 (0.4%)	1/71 (1.4%)	1/423 (0.2%)	0.267	1/2563 (0.0%)	0/243 (0.0%)	1/2320 (0.0%)	1,000
Other	48/3057 (1.6%)	6/314 (1.9%)	42/2743 (1.5%)	0.628	9/494 (1.8%)	1/71 (1.4%)	8/423 (1.9%)	1,000	39/2563 (1.5%)	5/243 (2.1%)	34/2320 (1.5%)	0.411

RF: radiofrequency energy.

CHAPTER 6

GENERAL DISCUSSION

6.1 General discussion

Management of atrial fibrillation (AF) consists of anticoagulation, optimal treatment of cardiovascular co-morbidities and risk factors, and symptom control achieved by either electrical or pharmacological cardioversion or pharmacological rate control.¹ One of the first treatments of AF was ablation of the atrioventricular junction, thereby uncoupling the electrical conduction system of the atria from the ventricles.^{2,3} This treatment stops irregular AF activations from reaching the ventricle, but also prevents adaptation of the heart rate to exercise. The first AF treatment with preservation of exercise capacity was the Cox-Maze procedure. This procedure involved transmurals incisions that walled-off sections of the atria, including the pulmonary veins (PVs), and created a path to guide the electrical activity from the sinoatrial node to the atrioventricular node.⁴ The success rate was high, 93% of patients were arrhythmia free without antiarrhythmic medication after 3-102 months.⁵ Despite the high success rate, the Cox-Maze procedure was mostly used as add-on procedure for open chest surgeries (bypass graft surgery, valve replacement) instead of primary therapy for AF due to the invasiveness of the procedure and the high complication rate.^{6,7} Catheter ablation was used as minimal invasive alternative to create linear lesions in the atria without having to open the chest. After the discovery that most of the triggers causing AF reside within the PVs⁸, treatment shifted from ablation of endocardial linear lesions to endocardial electrical isolation of the PVs. After decades of research and practice, catheter ablation to cure AF is still not effective in a large percentage of patients. Analysis of a registry by the European Society of Cardiology revealed that, when considering all types of AF, 34.2% of AF patients in Europe treated with catheter ablation had an episode of atrial arrhythmia during the 12-month follow-up period.⁹

The success of catheter ablation for the treatment of AF depends on many factors, both during the ablation procedure as well as before and after. The focus of this thesis is the non-pharmacological electrophysiological AF management, including population-wide screening for AF, non-invasive pre- and post-procedural evaluation, invasive electro-anatomical mapping, and ablation-procedure techniques. These topics are addressed in the following sections.

6.1.1 Screening

Population-wide structural screening for AF is currently not performed. AF is commonly only diagnosed after patients present with symptoms, but can be present long before. Symptom severity can vary from asymptomatic forms, light symptoms, such as palpitations or fatigue, to severe complications such as stroke. Screening and early intervention of AF has the potential to avoid complications that otherwise substantially contribute to morbidity and mortality of AF patients.¹⁰ Furthermore, early intervention of AF may stop the progression of AF from paroxysmal to persistent or permanent AF.¹¹ Postponing intervention to the stage of persistent or permanent AF is associated with a lower success rate for the eventual catheter ablation and a higher rate of AF related complications. Population-wide screening for AF has become feasible due to new screening devices. These devices can be consumer electronics such as watches or other wrist-worn wearables, or custom AF screening devices built for high-volume patient screening. AF sensing watches¹² and AF screening devices¹³ have been proven highly sensitive for AF detection. A cost-effectiveness study for the MyDiagnostic AF screening device showed an increase in quality-adjusted life years combined with a reduction in overall cost of healthcare when screening was performed in a population at risk.¹⁴ A recent review on population-wide AF screening mentions enthusiasm for screening, but warns that there are key issues that must be resolved. These issues

include which populations to screen, with what device, using what screening methodology, for how long to screen, and what duration or burden of AF is sufficient to justify initiation of anticoagulant treatment.¹⁵ Population-wide screening should be cost-effective and not overburden the healthcare system. Since the incidence of AF increases with age¹⁶, effectiveness of screening can be improved by selecting an older population for screening. There is a tradeoff between duration of the measurement, technique used for the measurement and the logistics of screening. Sensitivity of AF detection increases with longer and non-intermittent measurements, while specificity increases by manual review of recorded rhythms. Long measurements not only require long battery life, but also signal storage capacity for later review of the signals. Furthermore, recording over a longer time requires the distribution and collection of screening devices. The ideal population-wide screening would use a patient's own device for screening. If irregularities in rhythm are detected, the patient will be referred to their general practitioner for follow-up. This approach ensures population-wide coverage with long registrations, while minimizing the burden on the healthcare system. Efficiency becomes important when more patients are referred for AF management due to better screening. This thesis presents new methods that, in the future, may be used for more efficient AF treatment. Adenosine can help making robust ablation lines, thereby reducing the need for redo ablations. Non-invasive pre- and post-procedural evaluation can potentially aid in choosing the right approach for AF ablation, shortening the procedure time and reducing the need for redo ablations. The mapping of repetitive patterns may in the future assist in finding AF sources, increasing the success rate of AF ablation. These techniques are discussed in the next sections.

6.1.2 Non-invasive pre- and post-procedural evaluation

Non-invasive imaging techniques are used to plan PVI procedures. MRI or CT imaging provide anatomical information such as the number of PVs and their branching pattern, PV ostial measurements, LA dimensions and possible anatomic anomalies. Gaps in ablation lines have been shown by using delayed gadolinium enhancement MRI in a research setting.¹⁷ This information on atrial status before starting an ablation procedure may help the electrophysiologist in choosing the most appropriate ablation approach. ECG imaging (ECGi) is a technique where signals recorded on the body surface are back-projected to show activations on the atrial anatomy. The use of ECGi as non-invasive imaging technique for AF is currently under investigation.^{18,19} Body surface signals can also be linked directly to recorded atrial activations, negating the use of a back-projection algorithm. This thesis focused on the P-wave as non-invasive atrial evaluation technique. Utilization of non-invasive signals, such as the ECG P-wave in body surface recordings, can aid in pre-ablation or pre-redo ablation decision making. As an example, if the analysis of P-wave morphology would allow the detection of PV reconnection, the electrophysiologist may opt for a cryoballoon for efficient re-isolation. If P-wave analysis does not show reconnection, the electrophysiologist may decide to choose a multi-electrode grid catheter for increased mapping coverage, or a radiofrequency catheter to enable the creation of spot ablations in the LA away from the PVs. In **Chapter 2**, we 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. Especially the last part of the P-wave can contain information on PV isolation status because the left PV region is one of the latest activated regions in the left atrium. Deviation of normal P-wave duration, either longer or shorter, is associated with an increased risk of AF and risk of AF recurrence after PVI. However, the mechanism behind this association is unclear. Better knowledge on how the total atrial activation time can be estimated from the P-wave is needed to identify

the mechanism responsible for this association.

In the future, by extending the work in **Chapter 2** and adding more data, the underlying activation pattern of short, normal and long P-waves can be quantified. By linking the body surface recordings to endocardial local activation times, it would be possible to estimate what part of the atrium corresponds to a certain point in time on the body surface P-wave. This information would enable both the detection of divergent P-wave morphologies and the linking of these deviations to atrial regions. A change in P-wave morphology can then be attributed to, for instance, the region of the pulmonary veins. This link between P-wave morphology and endocardial activation patterns may then be used to monitor reconnection status of PVs non-invasively. The knowledge if a recurrence stems from a reconnection or originates outside of the PV area could potentially help in selecting the right ablation method for the patient, thereby reducing ablation times and increasing the success rate of ablation procedures.

6.1.3 Invasive electro-anatomical mapping

Recent studies show that all PVs are still electrically isolated in 8-62% of patients undergoing a redo ablation for recurrent AF.²⁰⁻²⁴ Mapping and ablating outside the PVs did not consistently reduce recurrence rate so far, certainly not in patients with persistent AF. Neither adding linear lesions, nor ablation of complex fractionated areas or the mapping and ablation of rotors resulted in improvement in rhythm outcome.²⁵ For these patients it is important to be able to identify AF sources located outside of the PVs.

Chapter 3 introduces a method to automatically identify and characterize repetitive conduction patterns in high-density contact mapping in a goat model. **Chapter 4** applies this methodology to human data. The technique to identify and characterize repetitive conduction patterns does not focus on one specific characteristic of the recorded signals (for instance, the dominant frequency), but instead considers the total spatiotemporal signal and searches for repetitive patterns. Repetitive patterns are expected near localized and stable AF sources independently from its mechanisms (be it ectopic focal discharges or local reentries). Besides, repetitive patterns have also been found to assist in identifying anatomical structures harboring preferential conduction paths and thereby reflect the underlying bundle structure of the atrium.²⁶ Our results showed the existence of multiple patterns over time in the same recording. Switching between different repetitive patterns within the same recording was observed. A different pattern can be viewed as a different conduction state of the atrium. The different states may represent different AF sources or AF drivers, which are independently able to perpetuate AF. 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.

In **Chapter 3** It was shown that AF patients show repeating patterns. The patterns in persistent AF patients have a shorter duration and involve a smaller area when compared to paroxysmal AF patients. It is likely that this difference in AF recurrences is related to the higher complexity of AF in patients with persistent AF reflecting the presence of a structural substrate in these patients.

All recordings in **Chapter 3** and **4** are made with disposable high-density grids that measure the epicardial side of the atrium. The mapping approach has to be usable with endocardial signals to become clinically relevant. Since repetitive patterns can be detected independent of mapping catheter shape,

testing this methodology can be done on signals measured on the endocardial side of the atrium during standard mapping procedures. Best results are expected when the mapping catheter is in a stable position on the atrial wall during the measurement to prevent drift. The spacing of the electrodes on the mapping catheter is also important, as a larger electrode spacing may not be able to pick up subtle repeating patterns. New commercially available high-density mapping catheters, for example the advisor HD grid (Abbot) with a 4x4-electrode grid, may already be usable for this mapping approach. Future work should look into the spatial stability of repeating atrial patterns. If repeating patterns in the atria show high spatial stability, maps of small atrial regions measured in sequence could be combined to create a map of the total atrium. 3D atrial modeling can help answering the question whether repetitive patterns can identify AF sources. High spatial resolution atrial 3D models can show electrograms of all locations on the atrial surface at the same time.²⁷ The influence of drivers on the recurrent patterns can be investigated by modelling different drivers. Using this modeling approach, the influence of multiple, moving or alternating sources on repetitive atrial patterns can be studied for all locations on the left atrium.

6.1.4 Ablation-procedure techniques

The creation of contiguous ablation lines leads to a higher PVI success rate compared to PVI with non-contiguous ablation lines.²⁸ The most common way to check for proper electrical isolation is by pacing in the isolated PV, and checking presence of exit block or entrance block.²⁹ However, robustness of ablation lines is not always accurately verifiable during the procedure.^{17,30} Means to ensure robust ablation lines can prevent AF recurrence, and thereby progression of AF.

The focus of this thesis was not the creation of ablation lines, but a method to evaluate the quality of ablation lines. In **Chapter 5** we investigated the use of adenosine to reveal dormant conduction during PVI. The results show a small benefit in rhythm outcome when adenosine is used. In an expert consensus statement on catheter- and surgical ablation of AF, published in the same year as the first results of the real world registry used in **Chapter 5**, 61% of the expert group uses adenosine, compared to only 10% in the registry. This can be an indication that real world practice needs time to adapt to new ideas. During the writing and publication of the **Chapter 5**, evidence for the use of adenosine during PVI was contradictory.³¹⁻³³ Although our results showed a beneficial effect of adenosine use on rhythm outcome, 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.^{30,34} Therefore it may be reasonable to make adenosine testing a standard part of PVI protocols under certain circumstances. This, however, has to be preceded by a study in the cost effectiveness of adenosine testing. Adenosine testing adds time to ablation procedures, and an optimum has to be found between using adenosine for all patients, or to select patients that might benefit the most from this technique. Patient selection could be based on factors like non-standard PV anatomy, previous ablations, AF type or a combination of these factors.

6.2 Impact of our research on the scientific field and society

By publication of our methods, we enable researchers from other groups to learn from our work and to expand upon it towards better AF care. In this thesis, multiple methods have been presented.

Chapter 2 introduces a method to combine endocardial data and body surface data recorded on different points in time to study the link between atrial activation and body surface P-waves. The methods of **Chapter 2** pave the way for further investigation towards the link between the activation sequence of the atrium and the P-wave morphology as measured on the body surface. The understanding of this link is important for the interpretation of body surface signals. The P-wave is a composite signal, consisting of the depolarization and repolarization of both atria. Future research may unravel where changes in P-wave morphology are localized in the atrium, making the ECG an even more powerful tool. P-wave analysis has potential to become a tool for patient stratification. For instance, a change in P-wave morphology could be attributed to the region of the pulmonary veins. If a change in P-wave morphology indicates a change only at the location of the pulmonary veins, the patient may show a reconnected PV instead of a focal AF trigger outside of the PV region. Patients stratified as having no AF triggers outside the PVs can be treated without extensive atrial mapping, thus saving time, whereas an indication of non-PV triggers justifies extensive atrial mapping.

Chapter 3 presents a new method to analyze atrial recordings based on repetitive signals. The chapter shows how the technique works on a goat model, and explains the choices for threshold settings. **Chapter 4** uses the method presented in **Chapter 3** and applies it to human data. It is shown that paroxysmal and persistent AF patients show different levels of AF complexity, and that repetitive intervals can be categorized in different conduction patterns. The analysis of recurrent patterns on the atria opens up a new path of atrial mapping and possibly leads to new targets for AF ablation. The presentation of the methods to find recurrent patterns in atrial recordings is a first step. Based on the first findings that distinct patterns can be discerned, future research should focus on quantification of patterns and/or measurements with a good spatial and temporal coverage, either direct or through sequential mapping. A first step towards the employment of recurrent analysis in the clinic is the use of 3D modelling to study the response of recurrent patterns to different AF sources.

Chapter 5 provides insights in the use of adenosine to reveal dormant conduction during PVI procedures. The publication of our findings add data to the discussion whether adenosine has beneficial effects on long-term rhythm outcome. Our data shows that adenosine has a positive effect on patient outcome, but that the use of adenosine is not common practice in Europe. The use of adenosine should ensure a low recurrence rate for patients and a reduction of procedures and redo procedures, thereby easing the growing burden of AF patients on the healthcare system worldwide.

The societal impact of the work presented in this thesis lies in future implementation. AF is a growing epidemic and it is estimated that AF will affect 14-17 million people worldwide by 2030.³⁵ 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.

6.3 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. Future workup for AF patients could be looking as follows. Patients eligible for an AF ablation procedure could undergo non-invasive measurements, for which **Chapter 2** may provide a first step, to be categorized as isolated PVs or not. Ablation-naïve patients without any suspicion for AF triggers outside the PV area, or patients that show a reconnection after a previous PVI qualify for extensive mapping, in the future possibly using the repetitive pattern mapping techniques described in **Chapters 3** and **4**. This mapping approach may guide the clinician to the source or the anatomical pathway responsible for maintaining AF. Patients that are suspected for non-PV triggers, or patients that underwent PVI but show no signs of reconnection despite AF recurrences can be treated with regular PVI methods, with the addition of adenosine to prevent recurrences, as discussed in **Chapter 5**. Before this workflow can be implemented, clinical trials have to be passed. The ability to detect reconnections based on P-wave morphology, as well as the benefit of mapping and ablation based on recurrence maps has to be proven.

6.4 References:

1. Hindricks G, Potpara T, Dagres N, et al.: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020;1–126.
2. Scheinman MM, Morady F, Hess DS, Gonzalez R: Catheter-induced ablation of the atrioventricular junction to control refractory supraventricular arrhythmias. *JAMA* 1982;248:851–855.
3. Gallagher JJ, Svenson RH, Kasell JH, et al.: Catheter Technique for Closed-Chest Ablation of the Atrioventricular Conduction System. *N Engl J Med* 1982;306:194–200.
4. Cox JL, Schuessler RB, D'Agostino HJ, et al.: The surgical treatment of atrial fibrillation: III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;101:569–583.
5. Cox JL, Schuessler RB, Lappas DG, Boineau JP: An 8 1/4 -year clinical experience with surgery for atrial fibrillation. *Ann Surg* 1996;224:267–275.
6. Ad N: The Cox-Maze procedure : History , results , and predictors for failure. *J Interv Card Electrophysiol* 2007;20:65–71.
7. Prystowsky EN: The history of atrial fibrillation: The last 100 years. *J Cardiovasc Electrophysiol* 2008;19:575–582.
8. Haïssaguerre M, Jaïs P, Shah DC, et al.: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–666.
9. Arbelo E, Brugada J, Blomström-Lundqvist C, et al.: Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J* 2017;38:1303–1316.
10. Freedman B, Potpara TS, Lip GYH: Stroke prevention in atrial fibrillation. *Lancet* 2016;388:806–817.
11. Kato T, Yamashita T, Sagara K, Iinuma H, Fu LT: Progressive nature of paroxysmal atrial fibrillation - Observations from a 14-year follow-up study. *Circ J* 2004;68:568–572.
12. Wasserlauf J, You C, Patel R, et al.: Smartwatch Performance for the Detection and Quantification of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2019;12:e006834.
13. Tieleman RG, Plantinga Y, Rinkes D, et al.: Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace* 2014;16:1291–1295.
14. Jacobs MS, Kaasenbrood F, Postma MJ, Van Hulst M, Tieleman RG: Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands. *Europace* 2018;20:12–18.
15. Khurshid S, Healey JS, McIntyre WF, Lubitz SA: Population-Based Screening for Atrial Fibrillation. 2020;143–154.
16. Lloyd-Jones DM, Wang TJ, Leip EP, et al.: Lifetime risk for development of atrial fibrillation: The framingham heart study. *Circulation* 2004;110:1042–1046.
17. Linhart M, Alarcon F, Borràs R, et al.: Delayed Gadolinium Enhancement Magnetic Resonance Imaging Detected Anatomic Gap Length in Wide Circumferential Pulmonary Vein Ablation Lesions Is Associated With Recurrence of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 2018;11:e006659.
18. Azpilicueta J, Chmelevsky M, Potyagaylo D: ECGI in atrial fibrillation: A clinician's wish list. *J Electrocardiol* 2018;51:S88–S91.
19. ClinicalTrials.gov [Internet]. Identifier NCT03836092. ECGI in Patients With Persistent Atrial Fibrillation. <https://ClinicalTrials.gov/show/NCT03836092>.
20. Sultan A, Lüker J, Hoffmann B, et al.: Interventional management of recurrent paroxysmal atrial fibrillation despite isolated pulmonary veins: impact of an ablation strategy targeting inducible atrial tachyarrhythmias. *Europace* 2016;18:994–999.

21. Coutiño HE, de Asmundis C, Mugnai G, et al.: Repeat procedures after second-generation cryoballoon ablation as an index procedure for persistent atrial fibrillation: one-year follow-up. *J Interv Card Electrophysiol* 2016;47:365–371.
22. Baldinger SH, Chinitz JS, Kapur S, et al.: Recurrence of Atrial Arrhythmias Despite Persistent Pulmonary Vein Isolation After Catheter Ablation for Atrial Fibrillation. *JACC Clin Electrophysiol* 2016;
23. Szilágyi J, Marcus GM, Badhwar N, et al.: Atrial fibrillation patients with isolated pulmonary veins: Is sinus rhythm achievable? *J Cardiovasc Electrophysiol* 2017;28:754–761.
24. De Pooter J, Strisciuglio T, El Haddad M, et al.: Pulmonary Vein Reconnection No Longer Occurs in the Majority of Patients After a Single Pulmonary Vein Isolation Procedure. *JACC Clin Electrophysiol* 2019;5:295–305.
25. Verma A, Jiang CY, Betts TR, et al.: Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812–1822.
26. Hansen BJ, Zhao J, Csepe TA, et al.: Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390–2401.
27. Gharaviri A, Bidar E, Potse M, et al.: Epicardial Fibrosis Explains Increased Endo-Epicardial Dissociation and Epicardial Breakthroughs in Human Atrial Fibrillation. *Front Physiol* 2020;11:1–15.
28. Kuck K-H, Hoffmann BA, Ernst S, et al.: Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol* 2016;9:e003337.
29. Calkins H, Hindricks G, Cappato R, et al.: 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017;14:e275–e444.
30. Andrade JG, Deyell MW, Nattel S, et al.: Prevalence and clinical impact of spontaneous and adenosine-induced pulmonary vein reconnection in the Contact-Force vs. Cryoballoon Atrial Fibrillation Ablation (CIRCA-DOSE) study. *Heart Rhythm* 2020;17:897–904.
31. Kobori A, Shizuta S, Inoue K, et al.: Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: The UNmasking dormant electrical reconnection by adenosine triphosphate (UNDER-ATP) trial. *Eur Heart J* 2015;36:3276–3287.
32. Macle L, Khairy P, Weerasooriya R, et al.: Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. *Lancet* 2015;386:672–679.
33. McLellan AJA, Kumar S, Smith C, et al.: The role of adenosine following pulmonary vein isolation in patients undergoing catheter ablation for atrial fibrillation: a systematic review. *J Cardiovasc Electrophysiol* 2017;24:742–751.
34. Zeng LJ, Shi L, Tian Y, et al.: Pace capture and adenosine triphosphate provocation are complementary rather than mutually exclusive methods to ensure durable pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2019;30:815–823.
35. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S: Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;6:213–220.

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.

APPENDIX B

ACKNOWLEDGEMENTS (DANKWOORD)

Na iets meer dan vier jaar het idee te hebben gehad dat ik nog lang niet klaar was, ben ik dat nu ineens toch. Het is gelukt, er is een thesis geproduceerd. Dit is uiteraard niet slechts mijn eigen werk, velen hebben hier in meer of mindere mate een bijdrage aan geleverd. Ik wil de personen die behulpzaam zijn geweest, in welke vorm dan ook, hartelijk danken voor het ondersteunen van mijn tijd in Maastricht.

Zonder **Tammo** was deze tijd nooit begonnen. Ik wil je dan ook bedanken dat je me de kans hebt gegeven om, hoewel ik destijds vooral ervaring op had gedaan op neurologisch gebied, te werken aan een thesis over cardiologie en techniek. Als mede-Drent kun je redelijk direct zijn in de communicatie, en ik kan het zeer waarderen dat je er geen moeite mee had als ik af en toe dezelfde communicatiemethode hanteerde.

Uli, hoewel niet vanaf het prille begin betrokken bij mijn promotie, ben ik blij dat ik van je kennis gebruik heb mogen maken. Jij kunt als geen ander het overzicht houden over verschillende studies en het veld, en wist hiermee sturing te geven aan mijn lopende projecten. Je kon, zelfs met mijn soms minimale beschrijvingen van datasets, meteen doorgronden wat er mogelijk was met de data, en tegen welke problemen we aan konden lopen. Ik bewonder je visie en het streven naar goed opgezette, goed uitgevoerde en goed opgeschreven studies.

Stef, jij hebt mij de afgelopen vier jaar, naast het doen van onderzoek, ook veel bijgeleerd over signaalanalyse en code schrijven. In het begin was het licht frustrerend dat ieder idee dat ik samen met Ben bedacht, vijf jaar eerder al door jou en Uli was gepubliceerd. Later werd dit een voordeel, omdat een deel van de code die voor die studies gebruikt was, zeer bruikbaar bleek voor mijn onderzoek. Ik ben ervan overtuigd dat ik door het werken met jou, en het aanpassen en werken met je code, een betere onderzoeker ben geworden. Ik spreek met Ben tegenwoordig over kladversies, en versies die aan 'Stef-standaarden' voldoen. Dank ook de vlugge reacties op e-mails, soms nog sneller dan je out-of-office reply.

Ik wil **Laurent** bedanken voor de stoomcursus elektrofysiologie. Ik was vanaf het eerste moment onder de indruk van je kennis en de manier waarop je die deelde met anderen. Ik heb veel geleerd door naar je te luisteren tijdens procedures, en tijdens onze overlegmomenten op de stafgang. Ik heb je tijdens onze samenwerking altijd als zeer vriendelijk ervaren en had nog veel van je kennis over signalen gebruik willen maken. Ook toen mijn promotie meer naar de technische kant ging heb ik nog altijd veel aan je kennis gehad.

Prof. Vernooy, prof. Prinzen, prof. Tavernier, prof. Boersma en **dr. Karel**, leden van de beoordelingscommissie, wil ik bedanken voor het vlot en kritisch nalezen van mijn thesis.

Hoewel mijn tijd in Maastricht nooit was begonnen zonder Tammo, had ik Tammo nooit leren kennen zonder **Ben**. Ik denk dat we elkaar voor het eerst hebben ontmoet bij het ECTM in Enschede, waar het mijn taak was om je in te werken. Die gunst heb je ruimschoots mogen retourneren. Doordat je een jaar PhD plus duizend cardiologie-stages in Maastricht op mij voor liep, was je de perfecte eerste halte voor veel van mijn vragen de afgelopen vier jaar. Ik heb veel gehad aan je pragmatische aanpak en je efficiëntie in het komen tot oplossingen. Ondanks dat we uiterlijk redelijk van elkaar verschillen, zijn er genoeg mensen die ons door elkaar halen. Ik vind dat (qua inhoud!) een compliment voor mij. Vele kwesties zijn opgelost in onze tweepersoons focusgroep, en sommige van deze kwesties waren zelfs relevant voor een van onze theses.

Er is een grote kans dat ik tijdens mijn verdediging enkele kilo's zwaarder was geweest als **Aurore** er niet was geweest. Hoewel je zeer tactisch mensen met chocola naar je kantoor lokt, ben je ook zo coulant om deze extra calorieën er samen af te willen sporten. Er is niemand met wie ik zoveel kilometers heb afgelegd, zoveel kilo's heb verplaatst of zoveel balletjes tegen een muur heb geslagen als jij. Ik (en niet alleen ik) hebben veel met/om je kunnen lachen, onder andere door je brede kennis van vuurwerk en 'the worm'. Ik heb nog nooit iemand zich zo snel zien aanpassen aan een compleet nieuw land, en niemand zo snel een derde taal zien leren als jij, erg knap.

Moving to a new city where you don't know people is always a challenge. I was very happy to meet **Lauren**, who on my first day at the lab asked if I wanted to join a game of laser tag that same evening. This was the start of meeting many fun people, many fun activities, and many drinks. Thank you for being the social glue for many people including me, and for shifting my work/life balance a bit more to the latter.

Sjeng en **Maarten** wil ik bedanken voor het bescheiden houden van mijzelf. Vaak als ik iets denk te weten over een willekeurig onderwerp, weet minimaal een van jullie hier nog een heleboel meer over. **Letty**, dank voor de gezelligheid en de afleiding binnen en buiten het lab, en als perfecte vervanger van Sjeng als mijn cubicle-genoot, aangezien jullie evenveel moeite hebben met woorden als 'langs' en 'naast'. **Myrthe**, bedankt voor de (bijna) altijd vrolijke 'goedemorgen' de schattige muizenslides en alle tips over strijken. Ik wil **Raoul** bedanken voor het doorstaan van zijn uitzicht de afgelopen vier jaar. **Erik**, bedankt voor het bier brouwen, het bier drinken, tips over klussen en het lenen van gereedschap. **Bennis**, ik denk niet dat ik ooit de kwaliteit van je animaties kan vergeten, evenals je talent voor dichten en je glasheldere uitleg als je nieuwe technieken presenteerde. **Tijmen**, dank voor het mij doen inzien dat ik niet gebouwd ben voor het hooggebergte, **Koen** (Keon) voor je rustgevende uitstraling 's ochtends, **Shaiv** thanks for teaching me about good food, **Mehrdad** thank you for the coffee corner conversations and the great smells coming from the microwave. **Tim**, **Nick**, **Anneloes**, **Pamir**, **Joost**, **Koen**, **Wouter** en alle **studenten** door de jaren heen, dank voor de goede tijd en de waardevolle commentaren op presentaties. **Claudia**, **Melania**, **Ahmed**, **Afrak** and **Feddo**, who form a fresh new cohort of PhDs in the lab, I hope you have as much fun during your time in Maastricht as I did. **Claire** bedankt voor het regelen van allerlei soorten zaken, de pepernoten en de roddels.

Matthias Zink, **Suzanne Philippens** en het **vaatkamerpersoneel** wil ik graag bedanken voor de samenwerking omtrent alle praktische zaken, en omdat jullie het bij tijd en wijle prima vonden dat ik een poosje in de weg kwam staan bij diverse onderzoeken.

Ik wil de deelnemers aan de AMA-meetings bedanken voor het scherpe commentaar op onze plannen en ons gepresenteerde werk. Naast mijn promotieteam waren dat **Ben**, **Arne**, **Sander**, **Pietro**, **Dominik**, **Marisevi**, **Bart**, **Vannessa**, **Dominique** en **Miranda**.

Het is helaas niet gelukt om **Timon** als onderdeel van TBFF ook naar het zuiden af te laten zakken. Er komt zelfs weer iemand richting het Noorden. Op zoek naar een golfbaan halverwege...

Dank, ook namens mijn gestel, aan **Peter**, **Sabine**, **Niek**, **Aurore**, **Maarten**, **Sjeng**, **Tijmen**, **Alberto**, **Job**, **Letty**, **Koen**, **Bart** en heel misschien **Bennis** voor het vormen van BM2wielers. Jullie hebben mij aan het fietsen gekregen en gehouden. Een subgroep hiervan, plus **Robin**, dank voor de vroege ochtend-squash-sessies.

Mannen (en aanhang) uit Beilen, het is erg fijn om me na al die jaren nog altijd welkom te voelen bij een vriendengroep in een dorp waar ik al meer dan 10 jaar niet meer woon. Erg leuk dat ik nog altijd mee mag doen met pub-quizen in de kroeg en jaarlijkse uitstapjes naar (voor mij soms minder) verre oorden.

Olivier en **Michel**, dank voor het op peil houden van mijn RSI. Ik heb me erg vermaakt tijdens het klussen aan jullie paleizen. Mocht ik mezelf nog eens aan een upgrade wagen dan weet ik jullie te vinden.

Peter, Rianne, Dorien en **Juriaan**, bedankt voor alle ongein verspreid over twee landen, zowel voor de individuele ontmoetingen in huiselijke kring en op campings, als de groepsessies in de kroeg met afsluitende snackbarsoap.

Lieve **papa** en **mama**. Zonder jullie was het niet gelukt. De voorbereiding voor de laatste vier jaar begon natuurlijk al jaren eerder, en jullie hebben altijd alles gedaan om te helpen. Alle verhuizingen, mijn afwezigheid op momenten dat het druk was, mijn frustraties die ik soms met jullie deel, jullie hebben veel meegekregen van wat er allemaal speelde. Het advies was steevast 'doorgaan, het komt wel goed', en dat werkt heel aardig tot nu toe. Ik ben blij dat jullie altijd bereikbaar zijn, als ik er even geen zin meer in heb, maar ook voor nuttige vragen over planten en vlekken in kleding, of het voor de tiende keer opzoeken of ik nou wel of geen waterpokken heb gehad als kind.

Marlies en **Leo** hebben ook vaak aan mogen horen wat er allemaal gebeurde in het verre zuiden. Ik heb veel gehad aan jullie mening over uiteenlopende zaken, de leuke ontspannen gesprekken, tegenwoordig ook met **Carlijn**, en het klusgeweld waarmee in minimale tijd mijn appartement is verbouwd. Door jullie ervaring weet ik dat ik zelden de eerste ben die een bepaald probleem op moet lossen, en dat er altijd een mogelijkheid is om dat op een goede manier te doen.

Lieve **Maartje**, jij hebt op menig manier bijgedragen aan de totstandkoming van deze thesis. Misschien zonder dat je het zelf door hebt gehad, heb je ervoor gezorgd dat ik soms even afleiding had, dat ik soms een nieuw idee kreeg doordat ik je (waarschijnlijk voor de zoveelste keer) aan het vertellen was wat ik probeerde te doen. De leuke dingen tussen het werken door, maar ook de aansporing om, als ik er bijna was, niet te dralen maar het gewoon af te maken hebben mij enorm geholpen. Bovenal ben ik gewoon graag met je samen. Alleen al daarom verdien je een plek in het dankwoord.

APPENDIX C

CURRICULUM VITAE

About the author

Frank van Rosmalen was born on November 4, 1988 in Beilen, the Netherlands. He finished primary school without obtaining his multiplication tables diploma, but he obtained his pre-university (VWO) degree in 2007 in both the Nature & Health (Natuur & Gezondheid) and the Nature & Science (Natuur en Techniek) track at the dr. Nassau College Quintus in Assen.

Frank continued to study Technical Medicine. He obtained his bachelor degree in 2012, followed by his master degree in 2015. During his clinical research internships for the master track 'Medical Sensing & Stimulation', he visited five departments. He first worked on a disposable breath conduction system for use with electronic nose systems for asthma screening at the department of Pulmonology at the Amsterdam Medical Center. He then worked on patient specific determination of optimal PEEP using electrical impedance tomography at the Intensive Care department at the Erasmus Medical Center in Rotterdam. He continued his internships with working on the automated detection of local clinically relevant information in patients with diabetic foot problems using infra-red images at the department of Vascular Surgery at Zorggroep Twente hospital in Almelo, followed by an internship on the topic of multi-region intracranial spectral characterization of sleep stages and REM-onset using depth electrodes at the Epilepsy Unit of the Montreal Neurological Institute in Montreal. Frank finished his master degree with a thesis on the automatic detection of the High Frequency Oscillation-zone in epilepsy using magnetoencephalography, which was written based on his work done at the department of Clinical Neurophysiology at the University Medical Center Utrecht and the department of Magnetoencephalography of the Free University Medical Center in Amsterdam.

After his graduation, Frank started at the department of Biomedical Engineering and the Cardiology department at Maastricht University with research focusing on the application of signal analysis in atrial fibrillation. The department of Physiology joined the collaboration, and the result of the collaboration, supervised by prof. Delhaas, prof. Schotten and dr. Zeemering, can be found in this thesis.

Frank will continue his career as technical physician and researcher at the Intensive Care department of the Maastricht University Medical Center+.

List of publications

Peer reviewed journals

- van Rosmalen F, Maesen B, van Hunnik A, Hermans BJM, Bonizzi P, Bidar E, Nijs J, Maessen J, Verheule S, Delhaas T, Schotten U, Zeemering S: Repetitive patterns in high-density mapping of atrial fibrillation in patients. *Europace* 2021, accepted for publication.
- Hermans BJM, Zink MD, van Rosmalen F, Crijns HJGM, Vernooy K, Postema P, Pison L, Schotten U, Delhaas T: Pulmonary vein isolation in a real-world population does not influence QTc. *Europace* 2021, accepted for publication.
- Zeemering S, van Hunnik A, van Rosmalen F, Bonizzi P, Scaf B, Delhaas T, Verheule S, Schotten U: A novel tool for the identification and characterization of repetitive patterns in high-density contact mapping of atrial fibrillation. *Front Physiol* 2020;11:570118.
- Tas J, van Gassel RJJ, Heines SJH, Mulder MMG, Heijnen NFL, Acampo-de Jong MJ, Bels JLM, Bennis FC, Koelmann M, Groven RVM, Donkers MA, van Rosmalen F, Hermans BJM, Meex SJR, Mingels AMA, Bekers O, Savelkoul PHM, Oude Lashof AML, Wildberger JE, Tijssen FH, Buhre WFFA, Sels JWEM, Ghossein-Doha C, Driessen RGH, Kubben PL, Janssen MLF, Nicolaes GAF, Strauch U, Geyik Z, Delnoij TSR, Walraven KHM, Stehouwer CDA, Verbunt JAMCF, van Mook WNKA, van Santen S, Schnabel RM, Aries MJH, van de Poll MCG, Bergmans DCJJ, van der Horst ICC, van Kuijk SMJ, van Bussel BCT: Serial measurements in COVID-19-induced acute respiratory disease to unravel heterogeneity of the disease course: design of the Maastricht Intensive Care COVID cohort (MaastrICChT). *BMJ Open* 2020;10:e040175.
- van Rosmalen F, Delhaas T, Dagres N, Arbelo E, Blomström-Lundqvist C, Crijns HJGM, Da Costa A, Pytkowski M, Sharikov N, Laroche C, Tavazzi L, Brugada J, Pison L: Adenosine usage during AF ablation in Europe and selected long-term findings from the ESC-EHRA EORP Atrial Fibrillation Ablation Long-Term registry. *J Interv Card Electrophysiol Journal of Interventional Cardiac Electrophysiology*, 2020.
- Vroomen M, van Rosmalen F, Schröder J, Philippens S, Delhaas T, Crijns HJG, Pison L: Ten-year follow-up after endocardial point-by-point cryoablation for paroxysmal atrial fibrillation. *Acta Cardiologica*, 2020;1:1–6.
- van Klink N, van Rosmalen F, Nenonen J, Burnos S, Helle L, Taulu S, Furlong PL, Zijlmans M, Hillebrand A: Automatic detection and visualisation of MEG ripple oscillations in epilepsy. *NeuroImage Clin Elsevier*, 2017;15:689–701

Conference proceedings and (poster) presentations

- Bonnizi P, Zeemering S, van Rosmalen F, Schotten U, Karel J: Noninvasive Assessment of Spatio-Temporal Recurrence in Atrial Fibrillation. 28th European Signal Processing Conference (EUSIPCO 2020) Amsterdam.
- van Rosmalen F, Zeemering S, Maesen B, Maessen J, Delhaas T, Schotten U: Electrophysiological characteristics of repetitive conduction patterns in patients with atrial fibrillation. Heart Rhythm San Diego, 2020, pp. S383–S476.
- van Rosmalen F, Pison L, Delhaas T, Crijns HJGM, Zeemering S, Schotten U: Local Atrial Conduction Velocity During Pacing as Indication of Atrial Fibrillation Substrate Complexity. Computing in Cardiology (CinC) 2019, Singapore.
- van Rosmalen F, van Klink N, Zijlmans M, Hillebrand A: Automatic identification of the epileptogenic zone based on high frequency oscillations in MEG. 31st International Epilepsy Congress, 2015, Istanbul, Turkey, Epilepsia, 56 (Suppl. 1):3–263, 2015