Impact of catheter ablation of atrial fibrillation on the left atrium

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Contents

Chapter 1

1.1 GENERAL INTRODUCTION

What is known about the impact of catheter ablation of atrial fibrillation on the left atrium?

Based on (chapter 6)
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Submitted

Catheter ablation with radiofrequency energy as a treatment for atrial fibrillation (AF) is commonly performed worldwide [1]. It may involve only pulmonary vein isolation or it may employ a more extensive approach with additional ablation in the left atrium (LA). Its success in eliminating AF has been proven in many studies [2-6], however, its impact on the LA itself remains uncertain. Although several studies have looked into this subject by analyzing LA size and function, they report diverse results and are difficult to compare due to different applied methods (imaging techniques, ablation techniques, etc) [7, 8].

It is well known that AF causes remodeling of the atria on several levels [9, 10]. First, electrical remodeling takes place, which is characterized by changes in atrial refractoriness and atrial conduction due to changes in intracellular Ca^{2+} handling. Electrical remodeling is completely reversible once sinus rhythm is restored [11, 12]. Second, contractile remodeling occurs with loss in atrial contractility, leading to atrial dilatation and an increased risk of thrombus formation. Contractile remodeling is reversible as well after cessation of AF [13, 14]. And third, structural remodeling takes place, which involves myocyte cell loss with diffuse atrial fibrosis. Structural remodeling tends to persist after restoration of sinus rhythm [14, 15].

Two main factors may be responsible for the possible changes in hemodynamic parameters of the LA following catheter ablation of AF: remodeling, either by ongoing AF or reverse remodeling by restoration of sinus rhythm, and ablation induced LA fibrosis. However, it remains uncertain to what degree these factors may influence the LA.

This introduction contains an overview of the literature, known up till now, that addressed the topic of the impact of catheter ablation of AF on the LA and evaluated changes in LA size and/or LA function following ablation or evaluated the amount of LA fibrosis post-ablation.

Impact of catheter ablation on the development of left atrial fibrosis

Catheter ablation of AF with radiofrequency energy results in thermal damage of the LA myocardium. It causes myocardial necrosis followed by inflammatory infiltrates that result in replacement or scarring fibrosis of the myocardial wall [16, 17].

Visualization of left atrial fibrosis

Delayed enhancement magnetic resonance imaging (MRI) is able to depict regions of scar or injured tissue in the myocardium due to altered washout kinetics of a contrast agent (a gadolinium based agent)[18, 19]. The physiological principles of delayed enhancement MRI are based on an increased volume of distribution for gadolinium and a prolonged wash-out because of a decreased capillary density in myocardial fibrosis. Consequently, the increase in concentration of gadolinium within fibrotic tissue will cause T1 shortening resulting in a bright signal on T1-weighted magnetic resonance images. Although delayed enhancement MRI has been successfully used to identify scarring of the left ventricle, imaging of the LA has posed a greater challenge since the LA wall may be up to five times thinner than the left ventricular myocardium [20]. Nevertheless, in 2007 Peters et al published a study in which they reported their initial experience using delayed enhancement MRI to depict LA fibrosis after catheter ablation of AF [20]. They identified a partial to complete circumferential delayed enhancement pattern for the left inferior pulmonary vein (PV) in patients after PV antrum isolation. One year later, these results were confirmed by McGann et al who showed hyperenhancement of the LA wall in all patients post-ablation [21]. Evidence that these areas of LA fibrosis post-ablation are actually correlated to catheter ablation has been provided by Taclas et al [22]. They stated that 80% of their ablation sites on the Carto model corresponded with LA fibrosis detected with delayed enhancement MRI. Only 1% of LA fibrosis was present outside ablation areas marked by the Carto system. Additionally, Segerson et al described a highly significant correlation between the total LA radiofrequency delivery time and the percentage of LA fibrosis quantified by delayed enhancement MRI [23].

Impact of left atrial fibrosis on the left atrium

The abovementioned publications offer substantial proof that catheter ablation of AF results in fibrosis of the LA wall. However, does this ablation induced LA fibrosis have a possible unfavorable effect on LA function? Wylie et al performed delayed enhancement MRI to visualize LA fibrosis after ablation and they found a strong linear correlation between the decrease in LA ejection fraction and LA fibrosis volume after catheter ablation, suggesting that ablation induced fibrosis may have a detrimental effect on LA function [24].

However, further research concerning the influence of ablation induced fibrosis on LA function is lacking. The positive side of ablation induced fibrosis is a favorable outcome. Several studies have shown that the amount of LA fibrosis post-ablation is related to the outcome of the ablation procedure [23, 25, 26]. For example, Segerson et al mentioned a significant relationship between the number of pulmonary veins (PVs) encircled by delayed enhancement and clinical success of catheter ablation of AF [23]. Their analysis revealed a relative reduction of 38% in AF recurrence rate for each PV that was encircled. In addition, progressive increases in post-ablation posterior LA wall fibrosis reduced AF recurrence rates with a hazard ratio of 0.65 in their statistical analysis. So although a certain amount of ablation induced LA fibrosis is necessary to have a successful outcome of the ablation procedure, it should be born in mind that this ablation induced fibrosis may potentially impair LA function.

Impact of catheter ablation on left atrial size

Methods to assess left atrial size: Several measures to determine LA size exist in the literature. A widely used measurement of LA size is the anteroposterior diameter derived from the parasternal long-axis view with echocardiography. Some clinical centers use this diameter to select AF patients for treatment with catheter ablation, since an increased diameter has been shown to correlate with a worse outcome [27-29]. However, this diameter inaccurately represents true LA size since the LA often has an asymmetrical shape and the enlargement, seen in patients with AF, does not occur in a uniform fashion [30]. In addition, the American Society of Echocardiography has recommended quantification of LA size by a biplane method rather than using a one-dimensional measurement [31]. Biplane methods to assess LA size make fewer assumptions and are therefore more accurate, but still underestimate true LA size [32]. The most accurate method to assess LA size is LA volume calculated by Simpson's rule. This method involves manual tracing of LA area on each available slice and has been shown to correlate closely with true LA size obtained by post mortal assessment [33, 34]. Additionally, this method should be employed with either computed tomography (CT) or MRI, since echocardiography has shown to systematically underestimate LA volume compared to CT or MRI [35]. All the abovementioned imaging techniques and methods to assess LA size are used in the studies addressing the impact of catheter ablation of AF on LA size, and this partly accounts for the diversity in their results [8]. Consequently, it may be wise to particularly value the studies that have used the most precise method to estimate LA size (Simpson's rule by either CT or MRI) [36-40]. But even these studies report contradictory results. Lemola et al noticed a significant decrease in LA volume in patients with a successful outcome and no decrease in LA volume in patients with AF recurrences after catheter ablation [40]. A more recent study performed by Jahnke et al reported similar results [36]. However, Perea et al revealed a significant decrease of LA volume in all patients regardless of outcome of catheter ablation [39].

Catheter ablation technique

Catheter ablation as a treatment for AF has evolved rapidly, from a rather simple procedure targeting only the PVs to more complex procedures targeting multiple triggers and performing substrate modification. Not long after the PVs were identified as triggers that initiated AF, an ablation approach was introduced by Haissaguerre et al designed to electrically isolate the PVs [41, 42]. This segmental PV isolation involved delivery of radiofrequency energy very close to the PV ostia. The recognition of both PV stenosis as an important complication of segmental PV isolation and the PV antrum as an additional site of AF initiation, resulted in the development of PV antrum isolation. This involves wide continuous circumferential ablation surrounding left and right PVs in pairs [43, 44]. Furthermore, additive ablation strategies have been created to further improve outcome of catheter ablation of AF, especially in patients with (longstanding) persistent AF. These strategies include additional linear ablation in the LA mimicking the Cox Maze-III [45-47], for example the roof line and the mitral isthmus line, and ablation of areas with complex fractionated atrial electrograms (CFAEs) in both atria [48].

It can be assumed that segmental PV isolation would result in far less ablation induced fibrosis than PV antrum isolation with additional linear ablation and ablation of CFAEs in the LA. To the best of our knowledge, two studies exist in which only segmental PV isolation was performed and the change in LA volume after ablation was examined. Jayam et al noticed a significant reduction in LA volume in the total study population, regardless of clinical outcome [49]. However, Tsao et al reported opposing results [50]. They observed a borderline reduction of LA volume in the group with a successful outcome and an increase in LA volume in the group with AF recurrences. Nevertheless, as will be discussed in the next section, this may be influenced by the totally different time intervals used to measure LA volume. Jayam et al assessed LA volume approximately 2 months after ablation, while Tsao et al performed the post-ablation measurements at a mean of 21 months after ablation.

There are also conflicting results on what impact PV antrum isolation with additional linear ablation in the LA has on LA size [38-40, 51-57]. For instance, in the study by Tops et al PV antrum isolation was combined with a roof line and a mitral isthmus line and they reported a decrease of LA volume in patients with a successful outcome and an increase of LA volume in patients with AF recurrences [57]. Similar results were found in the study by Lemola et al 40. Delgado et al and Perea et al performed PV antrum isolation and additional linear ablation in their study population, including a roof line, a mitral isthmus line and a posterior line, and noticed a decrease in LA volume in all patients [39, 53]. Finally, one study could be found in which they not only performed PV antrum isolation and additional linear ablation, but also performed ablation of CFAEs in the LA [37]. They reported a decrease of LA volume in the total study population but they did not perform a subanalysis with regard to LA volume and outcome of catheter ablation.

Timing of post-ablation left atrial size assessment

LA size after ablation of AF may vary because different ablation techniques are employed and different methods are used to assess it. Additionally, the timing of the post-ablation assessment of LA size is also of significant importance. As previously mentioned, the main factors influencing LA size after ablation are development of ablation induced fibrosis, reverse remodeling by restoration of sinus rhythm, or ongoing remodeling by AF. These factors may show a different progression over time. Badger et al performed delayed enhancement MRI in patients with AF who underwent catheter ablation to visualize ablation induced fibrosis [58]. The delayed enhancement MRI scans were made 24 hours, 3 months, 6 months, and 9 months after catheter ablation in order to examine the response of ablation induced fibrosis over time. They found that ablation induced fibrosis appears to have formed by 3 months post-ablation with no recovery or reduction of fibrosis after that time point.

The effect of the heart rhythm, either by restoration of sinus rhythm or relapse of AF, on the LA is rather an ongoing process. Restoration of sinus rhythm reverts the process of LA enlargement in patients with AF and therefore leads to a gradual decrease in LA size [59]. In contrast, persistence of AF may lead to further remodeling with dilatation of the LA [60, 61]. In the study of Suarez et al patients with lone AF were followed for 6 years and showed an increase in LA size compared to baseline measurements [61].

The studies by Donal et al and Jahnke et al only included successful cases (patients with a successful outcome after the ablation procedure) in the long-term follow-up [36, 51]. Both studies measured LA volume at 3 and 12 months after catheter ablation of AF and noticed a progressive decrease in LA volume in these successful cases, consistent with the information above concerning reverse remodeling of the LA by restoration of sinus rhythm. Interestingly enough, Rodrigues et al measured LA volume at one day and 8 months after ablation and did not see a decrease in LA volume at all, whether patients had recurrences of AF or not [62]. The study performed by Tsao et al has the longest time interval between catheter ablation of AF and post-ablation assessment of LA size [50]. They measured LA volume 21 months after ablation and reported a borderline reduction in the successful cases and a dilatation of the LA in the patients with AF recurrences.

Three articles exist in which very comparable methods were used [38-40]. They all performed PV antrum isolation with additional linear ablation, they measured LA volume using the Simpson's rule and MRI or CT, and they measured post-ablation LA volume at 4-6 months after catheter ablation. However, the results of these 3 articles could not be more different. Whereas Tsao et al reported no significant change in LA volume after ablation in the total study population [38], Perea et al noticed a significant decrease of LA volume in all patients, regardless of clinical outcome [39]. And finally, Lemola et al stated that LA volume decreased only in patients with a successful outcome of the ablation procedure [40].

Impact of catheter ablation on left atrial function

Methods to assess left atrial function

LA function is mainly determined by three phases during the cardiac cycle [63, 64]. First, during ventricular systole (or atrial diastole) the LA operates as a reservoir receiving blood from the PVs. Thereafter, during the early phase of atrial systole the LA functions as a conduit for passive transfer of blood to the left ventricle. Finally, during the second phase of atrial systole the LA actively pumps blood into the left ventricle. Most articles that analyze LA function before and after catheter ablation of AF employ the LA ejection fraction (LA EF) as a representative of LA function, which is calculated by LA EF = [(LAmax - LAmin)/LAmax] x 100. As the LA EF is comprised of both the passive and the active phase of the atrial systole, a more precise method divides the LA EF into the passive atrial emptying fraction, as an index of LA conduit function, and the active atrial emptying fraction, as an index of LA active contraction [65-67]. Other methods exist to determine LA function, for example peak transmitral A wave velocity [63]. However, only 3 articles employed these different methods [51, 68, 69], and comparison is difficult because of the very different study protocols.

Since LA EF and the active and passive atrial emptying fractions are derived from LA volume measurements, it is of significant importance to take into account which method and imaging technique has been used to obtain these volumes. As discussed previously, the most precise method to estimate LA volume is applying the Simpson's rule with either CT or MRI. One must consider, however, that CT imaging results in radiation exposure. Although CT protocols exist with a reduced amount of radiation, these protocols involve prospective gating and are therefore unsuitable for LA EF assessment. When examining the articles that have used the most precise method to calculate LA EF, we found the following results. Jahnke et al and Tsao et al reported similar results [36, 38]. They noted an increase in LA EF in patients with a successful outcome of catheter ablation and no change in LA EF in patients with AF recurrences. Perea et al, however, revealed no change in LA EF in patients with a successful outcome and a decrease in LA EF in patients with AF recurrences [39].

Few articles exist in which, in addition to LA EF, the passive and active atrial emptying fractions of the LA were calculated [24, 53, 70]. Delgado et al showed preservation of LA function in the total study population finding no change in LA EF or active atrial emptying fraction in all patients, regardless of clinical outcome [53]. In contrast, in the study by Marsan et al a deterioration of LA pump function was found in patients with AF recurrences [70]. They reported an increase in LA EF and active atrial emptying fraction in patients with a successful outcome and a decrease in LA EF and active atrial emptying fraction in patients with AF recurrences. And finally, Wylie et al noted a significant decrease of LA EF, passive and active atrial emptying fraction in the total study population [24].

Catheter ablation technique

As discussed previously, the extensiveness of the ablation procedure used in different studies is of importance, since it influences the degree of post-ablation induced fibrosis that can affect LA function. To our knowledge, in 5 studies only PV antrum isolation was performed with no additional ablation [24, 36, 62, 70, 71]. Two of these studies noticed an increase of LA EF after catheter ablation in patients with a successful outcome [36, 70], with a decrease of LA EF in patients with AF recurrences in one study [70] and no change in LA EF in patients with AF recurrences in the other study [36]. In the remaining 3 studies, no subanalysis was performed with regard to the effect of outcome of catheter ablation on LA function [24, 62, 71]. Interestingly, these studies again reported diverse results. Rodrigues et al and Wylie et al showed a decline in LA EF in the total study population [24, 62]. Additionally, Wylie et al performed delayed enhancement MRI to visualize LA fibrosis after ablation and they found a strong linear correlation between the decrease in EF and LA fibrosis volume after catheter ablation, suggesting that ablation induced fibrosis may have a detrimental effect on LA function [24]. However, an improvement in LA EF in the total group was found in the study by Verma et al [71]. These last three studies used different imaging techniques, including echocardiography, MRI and CT, but the remaining part of their study protocol is rather comparable.

Analysis of the studies that performed PV antrum isolation with additional linear ablation in the LA does not provide much clarity either. Most studies reported no difference in LA function after ablation in patients with AF recurrences [38, 52, 53, 56]. But Perea et al, measuring LA EF by the most precise method, noticed a decrease in LA EF after ablation in patients with AF recurrences [39]. Results are more diverse when looking at LA EF after catheter ablation in patients with a successful outcome. Studies report either no change in LA EF in these successful cases [39, 53] or even an improvement in LA EF [38, 56]. Although not one of these studies has reported a decrease in LA EF in patients with a successful outcome after extensive ablation, it is still not clear whether LA function may not be impaired by catheter ablation. For example, Choi et al measured LA EF in patients with AF after cardioversion (ECV group) and in patients with AF after extensive ablation (ABL group) [52]. They noticed no change in LA function in the ABL group, but LA EF improved significantly in the ECV group.

Timing of post-ablation left atrial function assessment

In addition to LA size, LA function after catheter ablation is also influenced by the development of ablation induced fibrosis, reverse remodeling by restoration of sinus rhythm, or ongoing remodeling by AF. However, the recovery of LA function after restoration of sinus rhythm occurs at a faster rate than the reversion of LA enlargement. Depending on the duration of AF prior to conversion and the mode of conversion to sinus rhythm (pharmacological or electrical cardioversion), LA function improves between 1 week and 1 month [52, 72-74]. Van Gelder et al measured LA function in patients with chronic AF directly after cardioversion, and 1 week, 1 month and 6 months thereafter [74]. They already described an improvement of LA function at 1 week which remained unchanged thereafter.

As stated previously, according to Badger et al, ablation induced fibrosis appears to have formed by 3 months post-ablation with no recovery or reduction of fibrosis after that time point [58]. However, they did not perform additional delayed enhancement MRI between 24 hours and 3 months after ablation. Wylie et al already found a strong linear correlation between the decrease in LA EF and LA fibrosis using measurements between 30 and 60 days after catheter ablation [24]. This suggests that the effect of ablation induced fibrosis may be expected well before 3 months post-ablation.

A few studies reported results that agree with the information mentioned above regarding reverse remodeling. Jahnke et al mentioned a recovery of LA EF at one month post-ablation in the group with a successful outcome, which did not change at 3 months post-ablation [36]. The patients with AF recurrences did not show a recovery of LA EF during the total follow-up. In the study by Marsan et al, patients with a successful outcome showed no change in LA EF 3 days after catheter ablation, but they showed a significant improvement 3 months post-ablation [70]. In the same study, the patients with AF recurrences showed a decrease of LA EF at 3 months after ablation which was not seen at 3 days post-ablation. These studies confirmed that LA function can show a recovery between a few days and 1 month post-ablation if sinus rhythm is restored. However, articles exist that showed the opposite. The total study population in the study by Choi et al did not show any improvement in LA EF after ablation with a follow-up duration of 8 months [52]. And Perea et al described no change in LA EF at 4-6 months post-ablation in patients with a successful outcome and a decline in LA EF in patients with AF recurrences [39]. The results of these last mentioned studies may suggest that an effect of ablation induced fibrosis plays a role which may counteract the effect of reverse remodeling. An interesting detail that corresponds with this theory is that PV antrum isolation with additional ablation was performed in the last mentioned studies, while only PV antrum isolation was done in the study by Jahnke et al and Marsan et al who noticed an improvement in LA function [36, 39, 52, 70].

Summary

Catheter ablation of AF may have several effects on the LA. First of all, it gives rise to ablation induced fibrosis which can be visualized by delayed enhancement MRI. Research has shown that at least a certain amount of ablation induced fibrosis is necessary in order to get a successful outcome. However, ablation induced fibrosis may also have a negative effect on LA function post-ablation although this remains inconclusive. Second, catheter ablation of AF affects LA size but it is uncertain to what degree and in what manner. It is important to measure LA size using a precise method and to take into consideration what ablation technique is performed and at what time interval LA size is measured post-ablation. However, even after taking these parameters into account, the literature regarding LA size after ablation varies considerably. Additionally, the impact of catheter ablation on LA function, mainly expressed as LA EF, is still open for debate. Although not many studies reported a decrease of LA function after ablation in patients with a successful outcome, it is still unsure whether LA function may not be impaired by catheter ablation.

Other variables than those discussed above may have affected LA size and function after ablation and may have been responsible for the diversity in the literature, for example type of AF, presence of structural heart disease, and definition of outcome. However, analyzing the impact of these variables was outside the scope of this work.

In conclusion, although it has been proven that catheter ablation of AF results in ablation induced LA fibrosis, we are still relatively in the dark regarding the impact of catheter ablation of AF on LA size and function. More studies are needed that examine LA size and function after catheter ablation of AF with standardized methods, preferably measuring LA size and function by applying Simpson's rule with CT or MRI.

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1.2 OUTLINE OF THE THESIS

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1.2 Outline of the thesis

Radiofrequency catheter ablation as a treatment for patients with atrial fibrillation (AF) is a well established treatment option. The success of catheter ablation in eliminating AF has been proven in many studies. However, the effect of catheter ablation on the left atrium (LA) itself is still uncertain. The aim of this thesis was to establish the changes in LA size and function after catheter ablation of AF in order to determine the impact of catheter ablation on the LA.

Part 1
Imaging of the left atrium in patients with atrial fibrillation

In the first part of this thesis several methods and imaging techniques will be described which can be used to quantify LA size. In chapter 2, a simple and widely used representative of LA size, the anteroposterior diameter by echocardiography, will be analyzed. This diameter is thought to be an inaccurate representative of LA size, but is still widely used in clinical practice. For that reason, we will compare this diameter to LA volume by computed tomography (CT) calculated with the Simpson's rule (multiple slice method) in order to analyze its accuracy. The Simpson's rule is considered to be the gold standard since it correlates closely with post mortal LA size assessment. However, the Simpson's rule is time consuming making it less suitable for clinical practice. Therefore, in chapter 3 and 4 alternatives to the Simpson's rule will be analyzed which are much easier and faster to obtain. In chapter 3, a method that involves measuring 3 diameters of the LA will be validated by correlating it to the gold standard. CT images will be used for both methods. In chapter 4, the area length method, originating from the echocardiography, will be compared to the gold standard with magnetic resonance imaging (MRI).

Part 2
Clinical implications of the left atrium in patients with atrial fibrillation undergoing catheter ablation

The second part of this thesis will focus on the clinical implications of the LA in patients with AF treated with catheter ablation. The first chapter of this part, chapter 5, will only focus at LA size at baseline and will describe the predictive value of LA size at baseline in patients undergoing catheter ablation of AF. Several studies have shown that the baseline LA anteroposterior diameter by echocardiography predicts clinical outcome after AF ablation. Since the LA diameter may not be an accurate representative of LA size, we were interested whether LA volume assessed by the gold standard with CT may also have predictive value. In addition, pulmonary venous anatomy is examined to assess its predictive value.

Chapter 6 reviews the literature that analyzed LA size and function after catheter ablation of AF. This review will demonstrate the great diversity that exists within these articles.

The remaining chapters (chapter 7 and 8) will concentrate on the main topic of this thesis: the impact of catheter ablation of AF on the LA. In chapter 7, our initial results on the observed changes in LA volume after AF ablation will be reported and the correlation of these changes with clinical outcome. This study functioned as a pilot study for the study mentioned in chapter 8 which is an expansion of the study mentioned in chapter 7. In chapter 8, the changes in LA volume as well as in LA function will be observed after catheter ablation of AF in a much larger cohort of AF patients. In addition, a small subset of patients underwent delayed enhancement MRI with the aim to visualize ablation induced fibrosis in the LA. With these last studies we strive to determine the impact of catheter ablation of AF on the LA.

Part 1

Imaging of the left atrium in patients with atrial fibrillation

Chapter **2**

Correlation of left atrial diameter by echocardiography and left atrial volume by computed tomography

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Abstract

Introduction

For patients undergoing catheter ablation of atrial fibrillation, left atrial size is a predictor of recurrence of atrial fibrillation during follow-up. For this reason, major clinical trials have used a left atrial diameter (LAD) of more than 5.0 or 5.5 cm, assessed by echocardiography, as an exclusion criterion for patients deemed candidates for ablation of atrial fibrillation. However, whether LAD accurately reflects true left atrial size has not been systematically investigated. Therefore, the purpose of this study was to test the hypothesis that LAD, measured by echocardiography, accurately correlates to left atrial volume measured by CT.

Methods and results

We included 50 patients (mean age 56 ±12 years, 5 female) with symptomatic atrial fibrillation (40% paroxysmal, 60% persistent), referred for catheter ablation. In each patient transthoracic echocardiography was performed. Additionally, all patients underwent CT using a 64-slice CT scanner. Left atrial volume was calculated by manually tracing left atrial area on each CT cross-sectional image.

Patients had a mean LAD measured by echocardiography of 4.5 ±0.7 cm, ranging from 2.9 to 5.7 cm. Left atrial volume measured by CT ranged from 67 ml to 270 ml with a mean value of 146 ±49 ml. A poor correlation was noted between LAD and left atrial volume, r=0.49 (p<0,001).

Conclusion

LAD measured by echocardiography correlates poorly with left atrial volume measured by CT in patients with atrial fibrillation. As a result, selecting patients with atrial fibrillation for treatment with catheter ablation should not be based on an echocardiographic derived LAD alone.

Introduction

During the past decade a significant number of studies have been performed which demonstrated that atrial fibrillation (AF) results in electrical and structural remodeling of the atria [1-4]. This process of remodeling results clinically in an increased likelihood for development of persistent AF and a lower response rate to pharmacologic and non-pharmacologic therapy. From a structural perspective, the process of remodeling results in left atrial (LA) dilation. Morillo and colleagues demonstrated that atrial size increases over six weeks in an animal model of AF [1]. Similar findings have been seen in humans [5-7].

Catheter ablation of AF has emerged as an important treatment option for patients with AF. A number of predictors of a lower response rate have been identified and include patient age, the presence of persistent AF, the length of time a patient has been continuously in AF, structural heart disease, and LA size [8-13]. Because of this relationship between LA size and outcome, many clinical trials have restricted enrollment to patients with a left atrial diameter (LAD) ≤5.0 or 5.5 cm [12,14-16].

The purpose of our study was to test the hypothesis that LAD, determined by transthoracic echocardiography (TTE), accurately correlates to LA volume by comparing it with LA volume measured by computed tomography (CT). If our hypothesis is confirmed, this would provide additional justification for including or excluding patients from consideration for treatment with catheter ablation based on an echocardiographic derived LAD.

Methods

Patient population

This cross-sectional study included 50 patients with symptomatic AF who were referred to our center for catheter ablation. They were admitted for their first radiofrequency ablation procedure which involved pulmonary vein isolation guided by Cartomerge electroanatomical mapping. The patient had TTE performed prior to catheter ablation. A cardiac CT was obtained to evaluate LA and pulmonary vein anatomy. All 50 patients gave informed consent according to a protocol approved by the Institutional Review Board of the Johns Hopkins Medical Institutions.

Left atrial size assessment

In each patient two-dimensional TTE with M-mode and Doppler was performed at a mean of 5 months prior to CT scanning. Images were obtained from parasternal long-

and short-axis views, apical 4-chamber, 2-chamber and long-axis views. The M-mode derived anteroposterior LAD was measured from the parasternal long-axis according to the American Society of Echocardiography as shown in Figure 1 [17].
Additionally, each patient underwent contrast-enhanced CT scanning using a 64-slice CT scanner (Aquillon, Toshiba Medical Systems Corporation, Tochigi, Japan). The CT scan was performed during a single breath-hold at the end-expiratory phase as described previously [18]. CT scanning was achieved after 120-140 ml of contrast media (Isovue, Bracco Diagnostics, Inc., Princeton, New Jersey, USA) was injected at an infusion rate of 3 ml/sec. The duration of scanning was approximately 10 seconds and scanning was retrospectively gated to the cardiac cycle.
Reconstruction of images was performed every 10% of the R-R interval with slice thickness of 1.0 mm. The reconstructed images were transferred to a commercially available workstation (Vitrea 2, Vital images, Minneapolis, Minnesota, USA) for measurement. In patients who were in sinus rhythm during scanning the phase corresponding with the end-diastole of the atria, just before mitral valve opening, was selected for assessment [19]. If patients were in AF or atrial flutter at the time of scanning the phase which appeared to have the largest LA volume was chosen for evaluation.
Subsequently, LA volume was measured using the selected phase of the cardiac cycle and the Vitrea 2 workstation. The method to assess LA volume in the present study has been used in prior studies to measure LA volume with CT or magnetic resonance imaging (MRI) [20-23]. This assessment has shown to be very closely related to true LA size obtained by post mortal assessment (r=0.99) [24,25]. Using this method the area of the LA was manually traced on each cross-sectional image of the CT scan from the roof of the LA to the level of the mitral annulus (Figure 2).

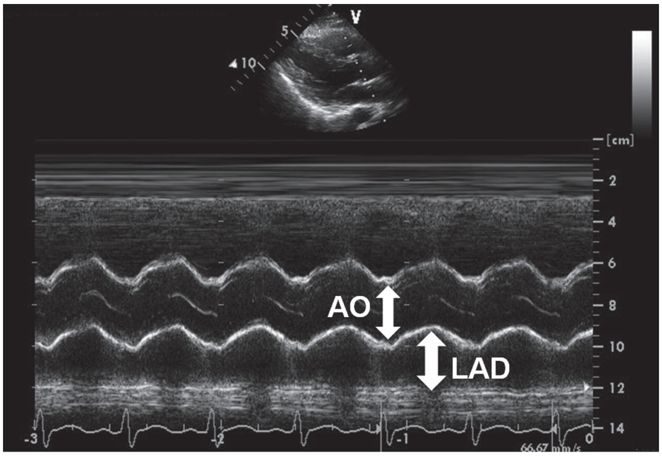

Figure 1. Measurement of the left atrial diameter from M-mode, guided by a parasternal long-axis view (upper half). AO= aorta, LAD= left atrial diameter.

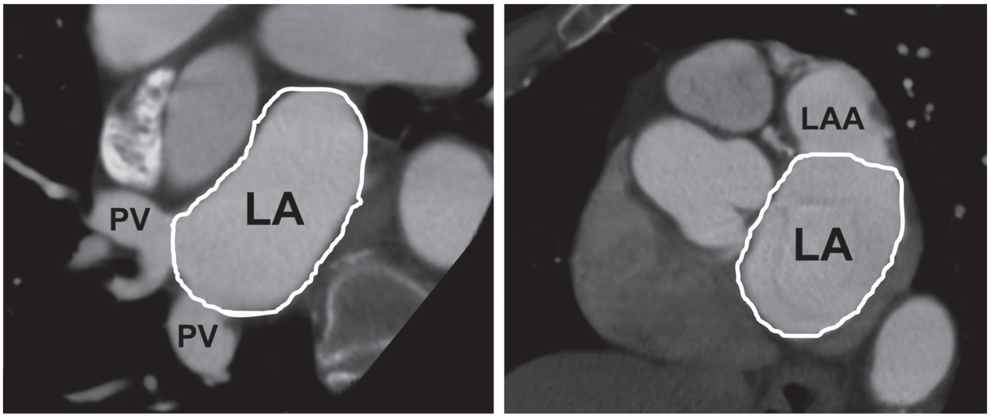

Figure 2. Oblique axial planes in a patient with atrial fibrillation. The white line demonstrates the manually tracings of the left atrium, excluding the pulmonary veins (left panel) and the left atrial appendage (right panel). LA= left atrium, LAA= left atrial appendage, PV= pulmonary vein.

The pulmonary veins and the left atrial appendage were excluded from the LA at their ostia. The mitral annulus was excluded at the level of insertion of the mitral valve leaflets. With the obtained areas of the LA, volume was calculated automatically.

Statistical methods

Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation, counts or percentages, as appropriate. Continuous variables were compared with the unpaired t-test. Intra-observer variability was determined by calculating the mean difference between the first and the second measurement, and by calculating a Pearson correlation coefficient (r). To measure the strength of the correlation between the LAD measured by echocardiography and LA volume measured by CT, a Pearson correlation coefficient was determined. A p-value below 0.05 was considered statistically significant.

Results

Baseline patient characteristics

The study population consisted of 50 patients with AF. AF was paroxysmal in 20 patients (40%) and persistent in 30 patients (60%). Forty-five patients (90%) were male. The mean age was 56 ±12 years. Patients experienced symptomatic AF for 6 ±6 years, which was refractory or intolerant to a mean of 1.4 ±0.9 antiarrhythmic drugs. Among the 50 participants in this study cardiovascular disease was present.

Eighteen patients (36%) had hypertension. Coronary artery disease was found in four patients (8%) and valvular disease was present in five patients (10%).

Left atrial size

Patients had a mean LAD measured by echocardiography of 4.5 ±0.7 cm, ranging from 2.9 to 5.7 cm. In ten patients (20%) the LAD was more than 5.0 cm and three of these patients had a LAD of more than 5.5 cm. LAD in patients with paroxysmal AF was significantly smaller than LAD in patients with persistent AF, 4.1 ±0.5 cm vs 4.7 ±0.6 cm ($p < 0.01$).

During CT scanning 30 patients (60%) were in sinus rhythm, 19 (38%) were in AF and one patient (2%) experienced atrial flutter. LA volume measured by CT ranged from 67 ml to 270 ml with a mean value of 146 ±49 ml. Keller and colleagues measured LA volume in healthy subjects and therefore provide us with an idea of normal LA volume and LA enlargement (26). They used the exact same method as in our study to measure volume in 21 healthy subjects and reported a mean LA volume of 67 ml with a range of 25 to 110 ml. Based on these results, we would consider a LA to be moderately enlarged if the LA volume was less than 50% above the upper limit of normal (<165 ml) and severely enlarged if LA volume was equal to or more than 50% above the upper limit in this study (≥165 ml). Thus, in our series of 50 patients, 25

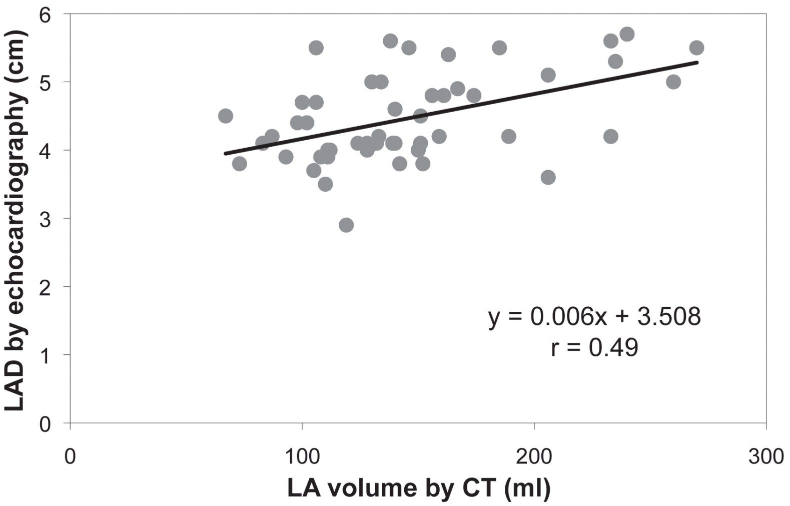

Figure 3. Correlation of left atrial diameter (LAD) measured by echocardiography and left atrial (LA) volume measured by CT.

patients (50%) had a moderately enlarged LA and 12 patients (24%) had a severely enlarged LA. Patients with paroxysmal AF had a significantly smaller LA volume than patients with persistent AF, 124 ±29 ml vs 160 ±54 ml ($p<0.01$). Ten random blinded reassessments were performed to calculate the intra-observer variability in LA volume. A mean difference between first and second assessment was reported of 2.2 ±1.2% (ranging from 0.5% to 4.7%), with a correlation of $r=1.00$ ($p<0.001$).

Correlation of left atrial diameter and left atrial volume

Shown in Figure 3 is the relationship between LAD measured by echocardiography and LA volume measured by CT. A poor correlation was noted, $r=0.49$ ($p<0,001$). Various cutoffs of the LAD did not demonstrate a better correlation than the one achieved in the total study population. The LAD of the ten patients with a LAD of more than 5.0 cm corresponded with diverse LA volumes. The LA volume of these patients ranged from 107 ml to 270 ml. Within this group, the three patients with a LAD of more than 5.5 cm had a LA volume of 138 ml, 233 ml and 240 ml. Among the 40 patients with a LAD equal to or less than 5.0 cm LA volume varied between 67 ml and 260 ml.

Discussion

In our study LAD measured by echocardiography and LA volume determined by CT were compared in 50 patients with AF admitted to our institution for treatment with catheter ablation. The results of this study demonstrated only a weak correlation between LAD and LA volume. Of particular importance is the finding that patients with a LAD of more than 5.0 cm, who might have been excluded for catheter ablation according to selection criteria in many centers, showed a wide range in LA volume. Furthermore, mean LA volume in the total study population was 146 ±49 ml with a range of 67 ml to 270 ml. According to the results of the study of Keller and colleagues, 74% of the patients included in our study had a moderately or severely enlarged LA volume of >110 ml [26]. These patients had a mean LAD of 4.5 ±0.7 cm while the patients with a normal LA volume (≤110 ml) had a mean LAD of 4.3 ±0.5 cm ($p=0.20$).

LAD measured by M-mode echocardiography is a widely used, simple, and convenient measurement of LA size. The purpose of this study was to determine if LA size, as assessed by LAD correlates with LA volume as assessed by CT. The results revealed a poor correlation, suggesting that LAD does not correspond to LA size and LA enlargement. This finding most likely reflects the fact that the LA is an asymmetrical shape and that enlargement does not occur in a uniform fashion because of the

physical constraints of the spine and the sternum [27,28]. In contrast to this one-dimensional method, prior research has shown that LA volume by two-dimensional echocardiography provides a more accurate measurement of LA size [28]. Consequently, the American Society of Echocardiography has recommended quantification of LA size by biplane two-dimensional echocardiography instead of using a one-dimensional measurement [17]. However, two-dimensional echocardiographic methods systematically underestimate LA volume when compared with CT or MRI quantitation [25,29,30].
To date, there has been only one prior study which has examined the relationship between CT and echocardiography. The results of this study, Vandenberg et al, are in contrast to our results [25]. Vandenberg and colleagues compared LAD by M-mode echocardiography and LA volume by CT and noted a correlation of r=0.82. They performed similar methods of measuring LAD and LA volume but only examined 16 subjects. There are several potential explanations for the differing results of our study with that of Vandenberg et al. First, the distinct difference in sample size may be responsible for the discrepancy in results. Second, the study population in the study of Vandenberg and colleagues differed because of the inclusion of healthy subjects. And finally, this prior study did not provide information on the indication for the CT scan in the patients included in this study.

Limitations

This study was not designed to evaluate the long term efficacy of catheter ablation of AF. As a result we cannot directly compare the relative efficacy of LA diameter as assessed by echocardiography versus LA volume as assessed by CT imaging in predicting recurrence of AF following catheter ablation. A second limitation is the time interval between echocardiography and CT scanning. Echocardiography was obtained 5 months prior to CT imaging. However, Suarez and colleagues reported an increase in LAD in patients with AF of 14.7% over 6.2 years and Wożakowska-Kaplon showed an increase in LAD in patients with AF of 3.4% over 5 years [7,31]. In this context, a period of 5 months would result in an increase in LAD of less than 1 or 2% and therefore would be very unlikely to significantly alter the results of our study. Furthermore, the patient's rhythm during echocardiography was not available for this study which produced another limitation. Finally, there is a small possibility of overestimation of LA volume by CT which may have influenced the reported correlation of LAD and LA volume. This overestimation can be caused by inclusion of a part of the left atrial appendage since it is not always possible to define the exact border of this structure, or incorporation of area formed by the confluence of the pulmonary veins [28].

Clinical implications

The results of this study are of clinical importance to those involved with catheter ablation of AF. It is striking that many clinical centers use LA size, as assessed by the echocardiography derived LAD, to select and/or exclude patients with AF for treatment with catheter ablation. Our results have shown that an echocardiography derived LAD correlates poorly with LA volume as assessed by three dimensional CT imaging. These findings therefore draw attention to the widespread clinical practice of relying on standard echocardiography to select appropriate candidates for AF ablation. Not only are some patients with relatively preserved atrial size being excluded from undergoing catheter ablation of AF at many centers, other patients with markedly dilated left atria are undergoing this procedure.

Conclusion

LAD measured by echocardiography correlates poorly with LA volume measured by CT in patients with AF. As a result, selecting patients with AF for treatment with catheter ablation should not be based on an echocardiographic derived LAD alone.

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Chapter 3

Validation of a simplified method to determine left atrial volume by computed tomography in patients with atrial fibrillation

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Abstract

The success of catheter ablation of atrial fibrillation (AF) is highly dependent on a pre-procedural assessment of the size and shape of the left atrium. The most precise method to determine left atrial (LA) volume by CT requires manually tracing the LA area of each cross-sectional image. This is a labor intensive and time-consuming technique. The purpose of this study was to compare LA volume derived from using the 'gold standard' multiple slice technique, with the one estimated by using three orthogonal LA dimensions in patients with AF. The patient population was comprised of 100 patients referred for catheter ablation of AF (87 male, mean age 57 ±12 years). AF was paroxysmal in 49 patients and persistent in 51. Each patient underwent CT prior to catheter ablation and LA volume was measured using the two methods. LA volume measured by the multiple slice technique had a mean value of 136 ±46 ml. According to the simpler estimation approach, mean LA volume was 112 ±41 ml. A close correlation was noted between atrial volume determined with the two methods of $r=0.91$ ($p<0.001$). There was a mean underestimation of LA volume by the estimation technique of 17 ±13%. In conclusion, the results of this study reveal that LA volume determined using an estimation approach correlates closely with true LA volume as determined using the gold standard multiple slice approach. This estimation approach underestimates true LA volume by approximately 20%.

Introduction

There is general agreement that the most precise method to determine LA volume is by manually tracing the area of the LA on each cross-sectional image of the CT scan [1,2]. This technique takes into account that the LA is an asymmetrical shape and therefore provides an accurate assessment of LA volume [3]. However, this method is extremely labor intensive and time-consuming, limiting its use as a clinical or research tool. The present study validated a simpler estimation method of determining LA volume that has been proposed by Ho and colleagues [4]. According to this alternative technique, LA volume can be rapidly estimated by measuring 3 dimensions of the LA and employing a mathematical calculation. It is striking that although Ho et al developed this estimation method nearly 10 years ago, and many subsequent studies have employed this estimation method to determine LA volume, no validation studies have been performed [5,6]. In this study we compare for the first time LA volume using the 'gold standard' multiple slice technique, with the simpler estimation approach which was proposed by Ho et al.

Methods

This study included 100 patients who were referred to our institution for catheter ablation of AF. These patients had symptomatic AF and were admitted for their first radiofrequency catheter ablation procedure. Each patient underwent cardiac CT prior to catheter ablation to evaluate LA and pulmonary vein anatomy. All patients gave informed consent according to a protocol approved by the Institutional Review Board of the Johns Hopkins Medical Institutions.

Each patient underwent contrast-enhanced CT scanning using a 64-slice CT scanner (Aquillon, Toshiba Medical Systems Corporation, Tochigi, Japan). Image acquisition was achieved as reported in detail previously [7]. Briefly, CT scanning was performed during one breath-hold at the end-expiratory phase after intravenous injection of 120-140 ml contrast material (Isovue, Bracco Diagnostics, Inc., Princeton, New Jersey, USA) at an infusion rate of 3 ml/sec. The duration of acquisition was approximately 10 sec. Scanning was retrospectively gated to the cardiac cycle.

Images were reconstructed every 10% of the cardiac cycle with a slice thickness of 1 mm. The images were then transferred to a commercially available workstation (Vitrea 2, Vital images, Minneapolis, Minnesota, USA) for assessment of LA volume. Fifty patients were in sinus rhythm during CT scanning and the phase corresponding with the end-diastole of the atria, just before mitral valve opening, was selected for evaluation [8]. Forty-nine patients were in AF and 1 patient experienced atrial flutter during scanning. Within these patients the phase which appeared to have the largest LA volume was selected for assessment. The cardiac phase most frequently selected for assessment was 40% in 53 patients, followed by 30% in 26 patients, 50% and 60% both in 10 patients and 70% in 1 patient.

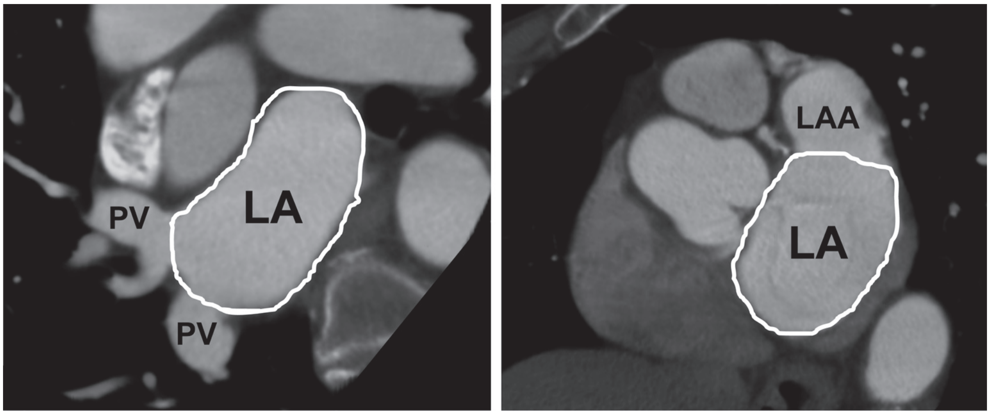

Figure 1. The multiple slice technique. The white line demonstrates the manually tracings in axial planes, excluding the pulmonary veins (left panel) and the left atrial appendage (right panel) at their ostia. LA = left atrium, LAA = left atrial appendage, PV = pulmonary vein.

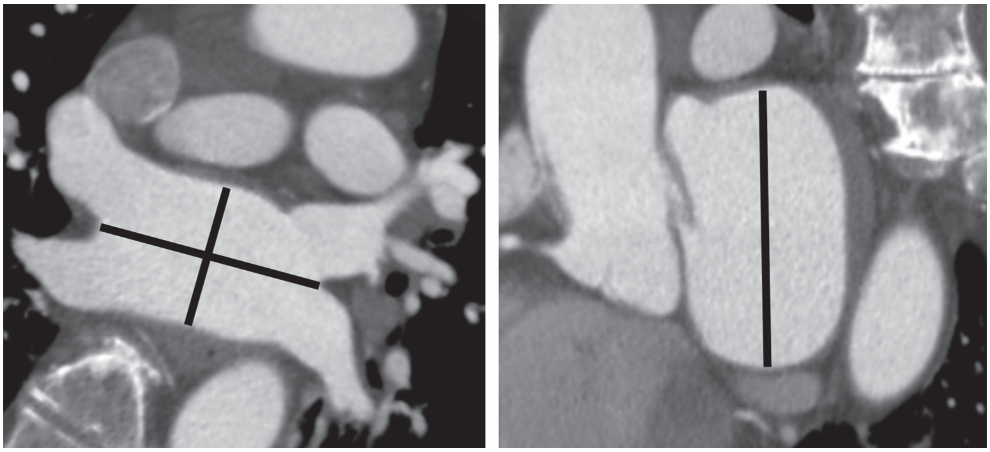

Figure 2. Orthogonal dimensions of the LA according to the technique of Ho et al. Left panel: oblique axial view of the LA. The transverse diameter was defined as the distance between the midpoints of the right and left sides of the pulmonary veins. The anteroposterior diameter was measured at the midpoint of the transverse diameter. Right panel: sagittal image of the LA. The longitudinal diameter was measured at the midpoint of the transverse diameter.

In each patient LA volume was measured using two different techniques. These measurements were performed with the selected phase of the cardiac cycle and the Vitrea 2 workstation.

First, LA volume was estimated by the multiple slice technique. This method has been performed in prior studies using CT or MRI [9-12]. With this method LA area was manually traced on each cross-sectional image of the CT scan from the roof of the LA to the level of the mitral annulus (Figure 1). Pulmonary veins and the left atrial appendage were excluded from the LA area at their ostia. The mitral annulus was excluded at the point of insertion of the mitral valve leaflets. LA volume was calculated automatically after all LA areas were obtained.

Second, LA volume was assessed by the estimation approach, the technique of Ho and colleagues [4]. Three orthogonal dimensions of the LA were recorded (transverse, anteroposterior and longitudinal) as demonstrated in Figure 2. Oblique axial images were used for measuring the transverse (TA) and the anteroposterior (AP) diameter. The measurement of the transverse diameter was defined as the distance between the midpoints of the right and left sides of the pulmonary veins. The anteroposterior dimension was measured at the midpoint of the transverse diameter. The longitudinal (L) diameter was measured at the midpoint of the transverse diameter in a sagittal view of the LA. A formula was used to calculate LA volume: Volume = $\pi \times TA \times AP/2 \times L/2$.

Both assessments were completed by one examiner blinded to any previous measurement of LA volume. Ten random blinded reassessments were performed to calculate intra-observer variability.

Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation, counts or percentages, as appropriate. Continuous variables were compared with the unpaired t-test or the paired t-test. Intra-observer variability was determined by calculating the mean difference between the first and the second measurement. A Pearson correlation coefficient (r) was calculated to determine the correlation of the two methods of measuring LA volume. A p-value <0.05 was considered statistically significant.

Results

The study population consisted of 100 patients with symptomatic AF. Eighty-seven patients were male and the mean age was 57 ±12 years. AF was paroxysmal in 49 patients and persistent in 51 patients. The mean duration of AF was 7 ±6 years and AF was refractory or intolerant to a mean number of 1.7 ±0.9 antiarrhythmic drugs. Forty-eight patients had a history of hypertension. Coronary artery disease was found in 10 patients and valvular disease was seen in 11 patients.

LA volume measured by the gold standard multiple slice technique had a mean value of 136 ±46 ml with a range of 63 ml to 270 ml. According to the estimation approach, mean LA volume in patients was 112 ±41 ml, ranging from 49 ml to 270 ml. LA volume measured by the estimation approach was significantly smaller than LA volume according to the gold standard technique, $p < 0.001$. Intra-observer variability was

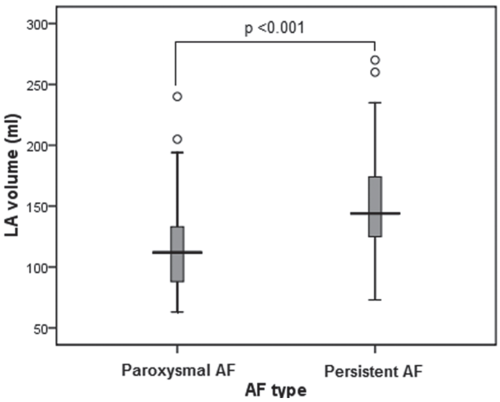

Figure 3. Distribution of LA volumes in patients with paroxysmal AF and persistent AF, measured by the multiple slice technique.

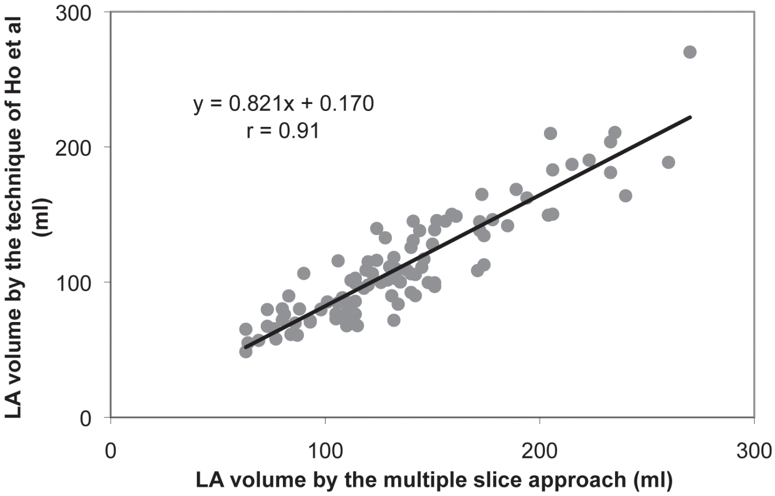

Figure 4. Correlation of LA volume measured by the multiple slice approach and LA volume measured by the estimation approach.

calculated for each method with 10 random blinded reassessments. Using the multiple slice technique intra-observer variability ranged from 0.5% to 4.7% with a mean of 2.2 ±1.2%. With the estimation approach intra-observer variability had a mean value of 4.7 ±2.2% with a range of 2.3% to 9.4%.

Shown in Figure 3 is the distribution of LA volumes in patients with paroxysmal AF and patients with persistent AF. LA volume, measured with the multiple slice technique, was significantly smaller in patients with paroxysmal AF than LA volume in patients with persistent AF (116 ±37 ml versus 154 ±46 ml respectively, p<0.001).

Shown in Figure 4 is the relationship between LA volume as determined using the gold standard multiple slice approach and the estimation approach. An excellent correlation in LA volume determined using these two approaches was noted (r=0.91, p<0.001). Correlation of the two methods did not differ much between patients who were in AF or atrial flutter during CT scanning (n=50) and patients who were in sinus rhythm during CT scanning (n=50), r=0.92 and r=0.87 respectively. You can appreciate that the estimation approach results in an underestimation in true LA volume by 17 ±13%. In fact, among the 100 patients in our study, LA volume was less using the estimation approach in 91% of patients.

Discussion

The present study validated a simplified estimation technique for determination of LA volume which was proposed by Ho and colleagues. Although this technique was initially developed almost a decade ago, and has been employed in multiple studies since that time, no validation studies have ever been performed to validate this technique [5,6]. Our gold standard, the multiple slice technique, has been used in prior studies to assess LA volume with CT or with MRI (9-12). This method has shown to be very closely related to true LA size obtained by post mortal assessment (r=0.99) [1,2].

To our best knowledge, no prior study has examined the relation between the multiple slice method and the estimation technique proposed by Ho et al to determine LA volume. The results of this study reveal that LA volume determined using the estimation approach correlates closely with true LA volume as determined using the multiple slice technique. Therefore, the estimation technique offers a good alternative to the more labor intensive multiple slice approach. However, it is important to recognize that the estimation technique results in a significantly smaller LA volume with a mean underestimation of LA volume of 17% and one should bear this in mind when applying this method. This underestimation may be explained by the complex LA anatomy. The three dimensions, used with the estimation approach, make the LA resemble an ovoid cylinder and do not account for the frequently observed asymmetry of the LA [3].

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Chapter **4**

Left atrial volume and function assessment by magnetic resonance imaging

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Abstract

Introduction

In patients with atrial fibrillation undergoing catheter ablation, magnetic resonance imaging (MRI) can determine left atrial (LA) volume and function before and after ablation. The most accurate, but time consuming, method to determine LA volume is the multiple slice method (MSM) which involves manual tracing of LA area on each slice. The area length method (ALM) offers a simplified, but unvalidated, alternative for LA volume assessment by MRI. The aim of this study was to compare LA volume and function assessment by ALM with MSM.

Methods and Results

MRI was performed before and after catheter ablation in 40 patients with atrial fibrillation (30 male, mean age 57 years). All patients had sinus rhythm during imaging. In total, 72 MRI scans were available. LA end-diastolic and end-systolic volumes (EDV respectively ESV) were measured by both methods. LA function was determined by calculating LA ejection fraction (EF = (EDV-ESV)/EDV).

Measured by ALM, mean LA EDV and ESV were significantly lower than using MSM (102ml and 49ml versus 111ml and 65ml respectively, $p<0.001$) with a larger difference in mean ESV than EDV (16ml versus 9ml). This resulted in an overestimation of LA EF by ALM with a mean of 11% (54% by ALM and 42% by MSM, $p<0.001$). ALM correlated well with MSM for LA EDV and ESV ($r=0.77$ respectively 0.85) and showed no significant difference in intraobserver and interobserver variability.

Conclusion

ALM significantly underestimates LA volumes and overestimates LA function, but correlates well with the more accurate MSM.

Introduction

Assessment of left atrial (LA) volume and function is important for selection and follow-up of patients undergoing catheter ablation for atrial fibrillation (AF). Various techniques are available using different imaging modalities. The most precise technique to measure LA volume is the multiple slice method (MSM) with magnetic resonance imaging (MRI) or computed tomography. This technique involves manual tracings of LA area on each cross-sectional image and has shown to be very closely related to true LA size obtained by post mortal assessment [1, 2]. However, this technique is time consuming making it less suitable for daily clinical practice and multi-slice images of the LA are not usually available in clinical settings.

Simplified methods are available for LA volume and function assessment, for instance the single plane area length method (ALM). This method has been used to determine LA and left ventricular size with echocardiography [3] and has also been applied for quick evaluation of left ventricular volume and function with MRI [4-7]. However, ALM has not yet been validated for LA volume assessment with MRI. The purpose of the present study was therefore to compare LA volume and function derived from ALM with values derived from the more accurate MSM. This study was designed as a substudy of research still in progress, which aims to investigate the impact of pulmonary vein antrum isolation (PVAI) on the LA. This substudy is meant to determine whether ALM offers a useful alternative to measure LA volume and function in patients with AF in daily practice.

Methods

Patient population

Patients with AF accepted for PVAI were included in this study. These patients routinely undergo MRI of the heart and pulmonary veins before and approximately 4 months after catheter ablation. Computed tomography is only performed in cases of MRI contraindications such as a pacemaker, intracardiac defibrillator, or claustrophobia. Inclusion criteria for this substudy were patients with symptomatic paroxysmal or persistent AF, refractory to at least two antiarrhythmic drugs, who underwent cardiac cine MRI scan prior to and/or a few months following catheter ablation. In addition, scanning had to be performed during normal sinus rhythm in order to be able to determine LA function.

Magnetic resonance imaging

Patients underwent gadolinium-enhanced MRI scanning using a 1.5 Tesla MRI system (Philips Medical Systems, Best, the Netherlands) with a cardiac synergy coil for radiofrequency signal reception. Imaging was performed with the patients in supine position with ECG gating. A breath-hold balanced steady-state free-precession cine MRI was performed to cover the entire LA in the short axis view with on average 10-12 slices (average acquisition time 3 minutes). In addition, a single slice steady-state free-precession cine MRI was performed in two-chamber and four-chamber orientations (average acquisition time 20 seconds). Retrograde ECG gating was used to achieve 35 phases per R-R interval for the short axis view and 50 phases per R-R interval for the four-chamber and two-chamber views. Scan parameters were as follows: TR = 3.1 ms, TE = 1.53 ms, RF flip angle 55°, Field-Of-View (FOV) 350x277 mm, matrix size 192x150, slice thickness 8 mm, and gap + slice 8 mm. Gadovist was administrated at a dose of 0.2 ml/kg and with an infusion rate of 1.5 ml/s. MR angiograms (MRA) were obtained with single breath-hold three-dimensional fast spoiled gradient-echo imaging in coronal view. MRA acquisition was manually started after visualizing the contrast bolus in the left ventricle and giving a breath-hold command. Scan parameters were: TR = 4 ms, TE = 1 ms, RF flip angle 35°, FOV 400 mm, matrix size 272x173, slice thickness 3 mm, and gap + slice 1.5 mm. The average acquisition time was approximately 20 seconds.

4

Left atrial volume and function assessment

LA volume and function were assessed offline using commercially available software (ViewForum, Philips Medical Systems, Best, the Netherlands). Phases representing

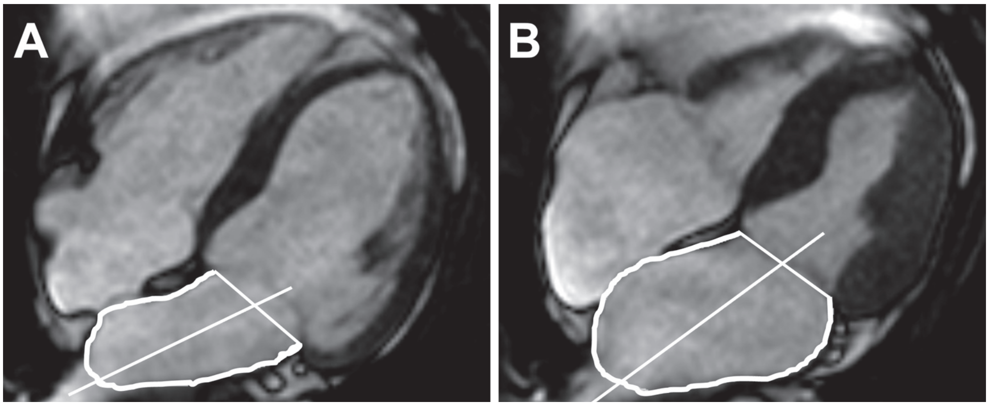


Figure 1. Semi-automatic outlining of the left atrium with the area length method in the four-chamber view. Panel A represents the atrial end-systolic phase and panel B represents the atrial end-diastolic phase.

the end-systole (minimum LA volume at mitral valve closure) and the end-diastole (maximum LA volume just before mitral valve opening) of the atria were selected for LA volume assessment [8]. First, single plane ALM was used to estimate end-systolic and end-diastolic volumes (ESV respectively EDV) of the LA in the four-chamber plane. ALM is based on a rotational ellipsoid with volume calculated as: volume = 0.85 x area^2/length [4-7]. LA area was manually encircled in the mid-atrial slice as is demonstrated in Figure 1. The point of insertion of the mitral valve leaflets was taken to be the atrioventricular border. The long axis was automatically drawn by the software from the middle of the atrioventricular border to the posterior wall of the LA but could be corrected manually if necessary. LA volume was then calculated with the abovementioned formula.

Second, the multiple short axis images were used to measure ESV and EDV of the LA with MSM. LA area was manually encircled on each image, excluding the left ventricle at the atrioventricular border as described above (Figure 2). Pulmonary veins were excluded at their ostia and the left atrial appendage was excluded at its base [9]. LA volume was automatically calculated from all the included slices.

Subsequently, LA function was determined by calculating LA ejection fraction with the following formula: ejection fraction = (EDV-ESV)/EDV. All measurements were completed by a single investigator in a blinded fashion. Intra-observer variability was determined by performing twenty at random blinded reassessments of LA volume (ESV and EDV). Interobserver variability was assessed by selecting a second investigator who performed twenty at random blinded assessments of LA volume as well.

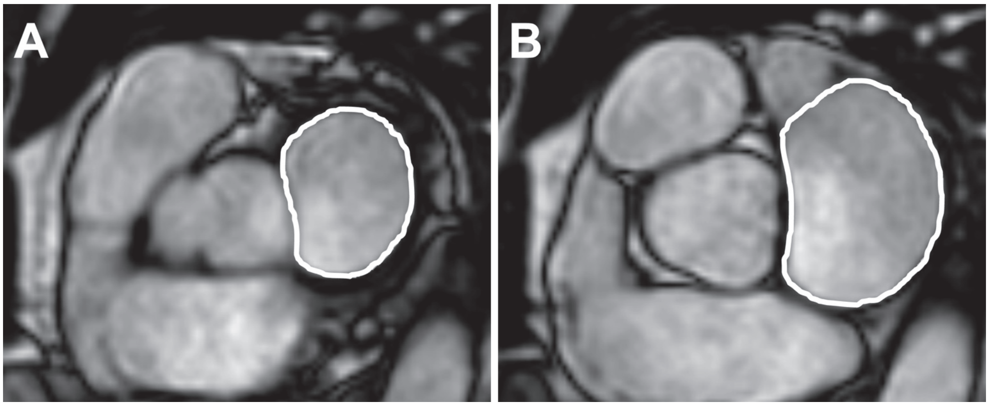


Figure 2. Manual tracings of the left atrium with the multiple slice method in the short axis view. Panel A represents the atrial end-systolic phase and panel B represents the atrial end-diastolic phase in one slice.

Statistical methods

Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation, counts or percentages, as appropriate. Continuous variables were compared with either a Student's t-test or a paired t-test. Intraobserver and interobserver variability were determined by calculating the mean difference between both measurements. A Pearson correlation coefficient (r) was calculated to determine the correlation of the two methods for LA volume and function assessment. A p-value below 0.05 was considered statistically significant.

Results

Baseline patient characteristics

Forty patients with paroxysmal or persistent AF, admitted for PVAI, were selected for this substudy. The baseline characteristics of these patients are shown in the table. The mean age of the study population was 57 ±9 years and most patients were male (75%). AF was paroxysmal in 70% and persistent 30% of patients. A quarter of the included patients had hypertension and structural heart disease was present in a minority of the study population (10%).

Table 1 Patient characteristics

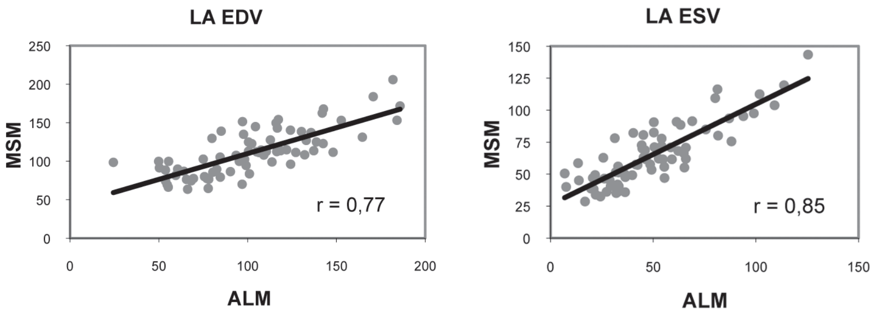
N	40
Age (years)	57 ±9
Male	30 (75%)
Type of atrial fibrillation	
Paroxysmal	28 (70%)
Persistent	12 (30%)
Duration of atrial fibrillation (years)	7 ±6
Body mass index	26 ±4
Hypertension	10 (25%)
Structural heart disease	4 (10%)
Dilated cardiomyopathy	1 (2.5%)
Ischemic cardiomyopathy	3 (7.5%)

Values are given as mean ± standard deviation or number (%).

Left atrial volume and function

Of the 80 included MRI scans, 72 scans were available for LA volume and function assessment. The remaining 8 MRI scans could not be used due to incomplete images of the LA. Measured by ALM, mean LA EDV and ESV of the total study population were 102 ±35 ml and 49 ±26 ml, respectively. With the more accurate MSM, LA EDV and ESV had mean values of 111 ±31 ml and 65 ±24 ml, respectively. As can be appreciated, LA volumes were significantly smaller when applying ALM compared to volumes obtained with MSM ($p<0.001$), with a larger difference in mean ESV compared to mean EDV (16 ml versus 9 ml). This resulted in a significant overestimation of the LA ejection fraction by ALM with a mean of 11 % (mean ejection fraction was 54 ±13 % by ALM and 42 ±10 % by MSM, $p<0.001$).

Correlation between the two methods was calculated for each parameter (EDV, ESV, and ejection fraction) and is shown in Figure 3. A good and significant correlation was found ranging from r = 0.77 for LA EDV ($p<0.001$) to r = 0.85 for LA ESV ($p<0.001$). Intraobserver variability was calculated and a mean difference between first and second assessments was found of 6 ±5% for ALM and 5 ±4% for MSM ($p=0.44$). Interobserver variability was determined using twenty at random blinded assessments performed by a second investigator. Mean difference between assessments of both investigators was 4 ±4% for ALM and 6 ±5% for MSM ($p=0.10$).



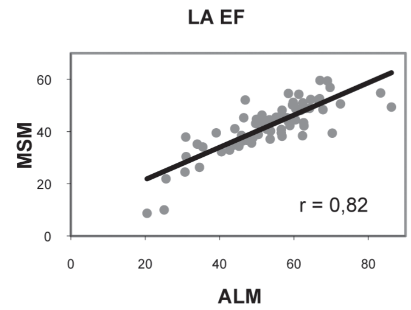


Figure 3. Correlation of the area length method (ALM) and the multiple slice method (MSM) for left atrial end-diastolic volume (LA EDV), left atrial end-systolic volume (LA ESV), and left atrial ejection fraction (LA EF).

Discussion

This study aimed to determine whether ALM offers a useful and reliable method to measure LA volume and function with MRI in daily practice. In total, 72 MRI scans were evaluated and LA EDV, ESV, and ejection fraction were assessed with both ALM and MSM. MSM has proven to be the most precise technique to measure LA volume and was considered to be the golden standard [1, 2]. However, this method is time consuming. It takes approximately 10 minutes to measure LA volume with the MSM compared to roughly one minute when using the ALM. In addition, LA volume by the MSM cannot always be obtained due to lack of multi-slice images of the LA. A good correlation of the two methods was found with regard to both LA volumes and function (Pearson correlation coefficient ranged from 0.77 to 0.85). Therefore, also taken the disadvantages of the MSM into consideration, ALM offers a useful alternative to the MSM. Nevertheless, it should be taken into consideration that the ALM significantly underestimates LA volumes and overestimates LA function when this method is applied. Single plane ALM is a widely used, simple and convenient estimation of volume of ellipsoid organs. Initially, this method has been employed for quick evaluation of LA and left ventricular volume by echocardiography [3, 10]. This method makes less geometric assumptions than the M-Mode derived LA anteroposterior diameter which has shown to correlate poorly with true LA volume assessed by computed tomography [11]. Later on, ALM was applied to measure left ventricular volume and function with MRI and several studies have demonstrated that ALM in this setting generated accurate and reproducible results [6, 7, 12]. However, these results could not be transferred to the right ventricle since Hergan et al reported that ALM significantly underestimated right ventricular volume compared to more precise methods [7]. The most likely reason for this is the different anatomical situation of the right ventricle which does not symbolize an ellipsoid but is wrapped around the left ventricle.

Our study was the first study to compare LA volumes and function measured by ALM with MSM as golden standard using MRI. In spite of the good correlation of both methods that was found, ALM significantly underestimated LA volume and overestimated LA ejection fraction. This underestimation of LA volume may be explained by the fact that the LA does not represent a simple ellipsoid but a complex asymmetrical hollow body that is therefore less suitable for the simple ALM [13]. Additionally, LA volume in this study has been assessed only in patients with AF who are more likely to have an enlarged LA due to electrical and structural remodeling [14]. Since LA enlargement does not occur in a uniform fashion due to the physical constraints of the spine and the sternum, the LA body may be even more asymmetrical within these patients compared to a healthy population [15].

Limitations

The present study was not designed to discuss the impact of catheter ablation of AF on the LA. This was a substudy which aimed to validate a simplified method for LA volume and function assessment with MRI in patients with AF. Therefore, no results are mentioned regarding pre and post ablation LA volumes and function and no outcomes of the ablation procedure are reported.

In this study 8 MRI scans were excluded due to incomplete images of the LA. Although MRI is thought to be one of the most valuable and accurate imaging modalities, artifacts may still occur which may limit the use of this technique.

LA volume and function was only assessed in patients with AF undergoing PVAI. Therefore, extrapolation of the results to the general population may not be accurate.

Conclusion

ALM correlates closely with MSM when measuring LA volume and function with MRI in patients with paroxysmal and persistent AF. ALM therefore offers a useful alternative to the time consuming MSM. However, it is important to take into account that ALM may significantly underestimate LA volume and overestimate LA ejection fraction.

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Part 2

Clinical implications of the left atrium in patients with atrial fibrillation undergoing catheter ablation

Chapter 5

5.1 ORIGINAL ARTICLE

Does left atrial volume and pulmonary venous anatomy predict the outcome of catheter ablation of atrial fibrillation?

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Abstract

Introduction

Pre-procedural factors may be helpful in selecting patients with atrial fibrillation (AF) for treatment with catheter ablation and in making an assumption regarding their prognosis. The aims of this study were to investigate whether left atrial (LA) volume and pulmonary venous (PV) anatomy, evaluated by computed tomography (CT) prior to ablation, will predict AF recurrence following catheter ablation.

Methods and Results

We included 146 patients (mean age 57 ±11 years, 83% male) with symptomatic AF (55% paroxysmal, 18% persistent, 27% longstanding persistent). All patients underwent CT scanning prior to catheter ablation to evaluate LA volume and PV anatomy. Circumferential PV isolation was performed guided by Cartomerge electroanatomical mapping. Outcome was defined as complete success, improvement, or failure.

After a mean follow-up of 19 ±7 months, complete success was achieved in 59 patients (40%) and 38 patients (26%) demonstrated improvement. LA volume was found to be an independent predictor of AF recurrence with an adjusted OR of 1.14 for every 10 ml increase in volume (95% CI 1.00-1.29, p=0.047). PV variations were equally distributed among the different outcomes of the ablation procedure, and therefore univariate analysis did not identify PV anatomy as a predictor of outcome.

Conclusion

LA volume is an independent predictor of AF recurrence after catheter ablation. Additionally, PV anatomy did not have any effect on outcome. These findings suggest that an assessment of LA volume may be incorporated into the pre-procedural evaluation of patients being considered for AF ablation.

Introduction

Catheter ablation has emerged as an important treatment option for patients with atrial fibrillation (AF). However, there is a wide variety in success rates reported after catheter ablation and recurrences of AF remain an important problem [1]. Prior studies have identified a number of predictors of outcome following AF ablation including age, type of AF, hypertension, sleep apnea syndrome, and left atrial (LA) diameter [2-6]. We and others have recently shown that LA diameter, as assessed with conventional echocardiography, correlates poorly with true LA volume as determined by computed tomographic (CT) imaging [7, 8]. The purpose of this study, therefore, was to determine whether LA volume, as determined using CT imaging, predicts outcome after catheter ablation of AF. We also sought to determine if specific patterns and variants of pulmonary venous (PV) anatomy may be predictive of the success or failure of AF ablation.

Methods

Patient population

Patients with symptomatic AF referred to our center for treatment with catheter ablation between May 2005 and May 2007 were considered possible candidates for this study. Patients were enrolled if they were admitted for their first radiofrequency ablation procedure which involved circumferential PV isolation guided by Cartomerge electroanatomical mapping. Additional inclusion criteria were a cardiac CT prior to ablation for evaluation of LA and PV anatomy and a follow-up duration with a minimum of six months. The protocol was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions and all patients provided informed consent.

Computed tomography

Each patient underwent contrast-enhanced CT scanning within 24 hours of their ablation procedure using a 64-slice CT scanner (Aquillon, Toshiba Medical Systems Corporation, Tochigi, Japan). CT scanning was achieved as reported in detail previously [9]. Briefly, image acquisition was performed during one breath-hold at the end-expiratory phase after intravenous injection of 120-140 ml contrast media (Isovue, Bracco Diagnostics, Inc., Princeton, New Jersey, USA) at an infusion rate of 3 ml/sec. The duration of scanning was approximately 10 seconds and scanning was retrospectively gated to the cardiac cycle.

CT images were reconstructed every 10% of the cardiac cycle with a slice thickness of 1 mm. The reconstructed images were transferred to a commercially available workstation (Vitrea 2, Vital images, Minneapolis, Minnesota, USA) for evaluation of LA and PV anatomy. Eighty patients (54.8%) were in sinus rhythm during scanning and the phase corresponding with the end-diastole of the atria, just before mitral valve opening, was selected for evaluation [10]. Sixty-five patients (44.5%) were in AF and one patient (0.7%) experienced atrial flutter during image acquisition. In these patients, the phase which appeared to have the largest LA volume was selected for assessment.

Image analysis

Image analysis was performed by a single investigator in a blinded fashion with the selected phase of the cardiac cycle and the Vitrea 2 workstation.

First, LA volume was calculated. The method to measure LA volume used in this study has been used in prior studies with both CT and magnetic resonance imaging (MRI) as imaging techniques [11-14]. This method has shown to be very closely related to true LA size as obtained by post mortal assessment (r=0.99) [8, 15]. LA area was manually traced, as demonstrated in Figure 1, on each cross-sectional image of the CT scan from the roof of the LA to the level of the mitral annulus. PVs were excluded at their ostia and the LA appendage was excluded at its base. The mitral annulus was taken to be the atrioventricular border, and therefore the mitral annulus was excluded at the point of insertion of the mitral valve leaflets. LA areas were automatically calculated and summed to obtain LA volume. Twenty random blinded reassessments were

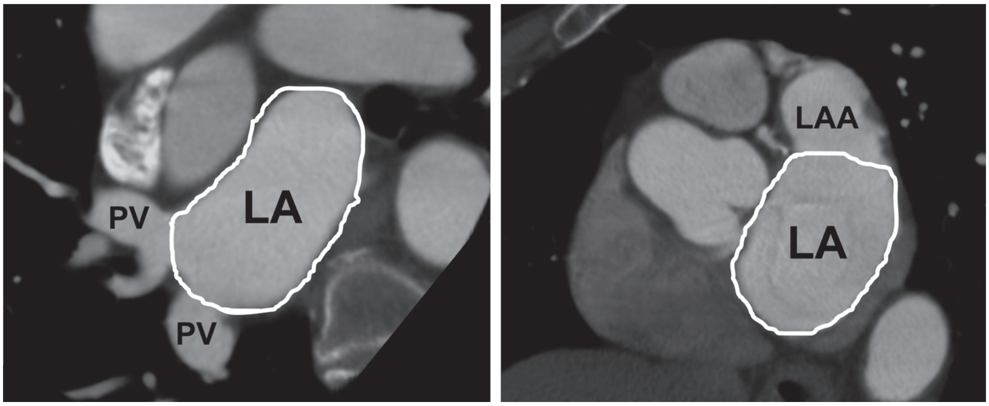

Figure 1. Assessment of left atrial volume using oblique axial planes. The white line demonstrates the manually tracings of the left atrium, excluding the pulmonary veins (left panel) and the left atrial appendage (right panel). LA = left atrium, LAA = left atrial appendage, PV = pulmonary vein.

performed to determine intra-observer variability. A mean difference between first and second assessment was reported of 2.7 ±1.7%, ranging from 0% to 6.0%.
Second, PV anatomy was evaluated. The number and distribution of PVs were recorded for each patient, including the left and right superior PV, the left and right inferior PV, and the presence of PV variations, for example a common left or right trunk, and left or right sided accessory PVs (Figure 2). A common trunk was defined as a superior and inferior PV that join proximal to the LA resulting in a single atriopulmonary venous junction. An accessory PV has its own independent atriopulmonary venous junction separate from the superior and inferior PVs and is named for the pulmonary lobe or segment that it drains [16].

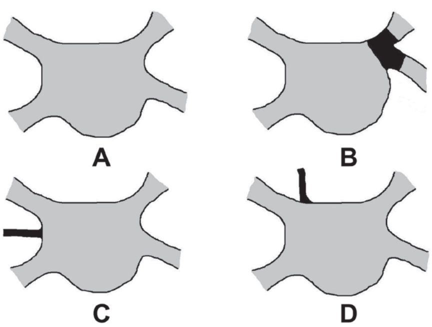

Figure 2. Schematic overview of variations in pulmonary venous anatomy. The dark parts indicate different anatomical variations. A = Conventional pulmonary venous anatomy with four separate veins, B = Common left trunk, C = Right middle accessory pulmonary vein, D = Right superior accessory pulmonary vein.

Catheter ablation procedure and patient follow-up

The approach employed for catheter ablation of AF at Johns Hopkins Hospital has been previously reported [17, 18]. A wide area circumferential approach was used with a primary endpoint of PV isolation as assessed using a circular multielectrode mapping catheter (Lasso, Biosense Webster, Inc., or Orbiter PV, Bard Electrophysiology, Lowell, Massachusetts, USA) [19].
Each patient was seen in the outpatient clinic three months following the ablation procedure and at this visit rhythm status was determined using history and ECG. If patients had symptoms suggesting the presence of PV stenosis, a CT or MRI was acquired to evaluate these symptoms. Antiarrhythmic drug therapy was continued for at least two months following catheter ablation and was discontinued thereafter in patients who became free of AF during follow-up. When patients reported symptoms suggestive of AF recurrence during follow-up, event monitoring was performed. Since many included patients did not live in close proximity to this region of the country, they were allowed follow-up through their local cardiologist. Therefore, long-term follow-up data were obtained by direct telephone interview of all patients.

The following definitions were used in the present study. Complete success was defined as recommended by the HRS Consensus Document on AF ablation as the absence of AF or any other atrial tachyarrhythmias lasting 30 seconds or longer, off antiarrhythmic drug therapy [20]. The first three months following ablation was a blanking period during which AF recurrences were not evaluated. Improvement was defined as either ≥ 90% reduction of AF burden with no antiarrhythmic drug therapy, or absence or ≥ 90% reduction of AF burden while receiving previously ineffective antiarrhythmic drugs, after the blanking period. Clinical success was determined by combining the patients with complete success and improvement. Failure was defined as failure to achieve either end point.

Statistical Methods

Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation, counts or percentages, as appropriate. Intra-observer variability was determined by calculating the mean difference between the first and the second measurement. Univariate and multivariate analysis were performed to identify predictors of outcome of catheter ablation. In univariate analysis, an independent t-test was used for continuous variables analysis and a chi square test was used for discrete variables analysis. Variables tested in the univariate analysis were selected for multivariate analysis which was performed with a logistic regression analysis. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The patient population was comprised of 146 patients with symptomatic AF who underwent catheter ablation and met the enrollment criteria for this study. The baseline patient characteristics are summarized in Table 1. Most patients were male (121 patients, 83%). The mean age was 57 ±11 years. Paroxysmal AF was present in 80 patients (55%). The remaining patients had either persistent AF (26 patients, 18%) or longstanding persistent AF (40 patients, 27%). Longstanding persistent AF was defined as continuous AF of greater than one year duration [20].

Outcome of catheter ablation

The mean follow-up duration of the study population was 19 ±7 months. A repeat procedure was performed in 15 patients (10%) because of recurrences of AF. At the end of the follow-up period complete success was achieved in 59 patients (40%) and 38 patients (26%) met the definition of improvement. These 97 patients (66%) demonstrated clinical success. Catheter ablation was unsuccessful in 49 patients (34%).

Left atrial volume and pulmonary venous anatomy

The mean LA volume in the total study population was 127 ±39 ml with a range of 63 to 270 ml. LA volume was significantly smaller in patients with paroxysmal AF than in patients with persistent or longstanding persistent AF, 114 ±33 ml versus 133 ±33 ml ($p=0.01$) and 150 ±42 ml ($p<0.001$) respectively. LA volume was not influenced by the duration of AF prior to catheter ablation, $p=0.42$.

With regard to the PV anatomy, conventional PV anatomy, with 4 separate PVs, was present in 86 patients (59%) (Table 2). The remaining patients had a PV variation. The most common observed PV variation was a right middle accessory PV in 34 patients (23%) and the second most frequent PV variation was a common left trunk which was present in 24 patients (16%). No patients had a left accessory PV and only one patient (0.7%) had a common right trunk.

Predictors of recurrence of atrial fibrillation

Univariate and multivariate analysis were performed to identify whether LA volume predicts outcome of catheter ablation. Outcome was divided in patients without recurrences of AF (complete success) and patients with recurrences of AF (improvement or failure) following catheter ablation. Variables selected for univariate

Table 1 Baseline patient characteristics

Patients	146
Age (years)	57 ±11
Male gender	121 (83%)
Type of AF	
Paroxysmal	80 (55%)
Persistent	26 (18%)
Longstanding persistent	40 (27%)
Duration of AF (years)	7 ±6
Ineffective AADs	1.5 ±0.9
Structural heart disease	35 (24%)
Hypertension	68 (47%)

Values are given as mean ± standard deviation or number (%).
AAD = antiarrhythmic drug, AF = atrial fibrillation.

analysis were age, gender, hypertension, structural heart disease, type and duration of AF, and LA volume. Predictors of AF recurrence following catheter ablation with univariate analysis included LA volume (p=0.020) and duration of AF (p=0.024) (Table 3). Multivariate analysis revealed that LA volume was an independent predictor of AF recurrence with an adjusted odds ratio of 1.14 for every 10 ml increase in volume (95% CI 1.00-1.29, p=0.047). In addition, duration of AF prior to catheter ablation was identified as an independent predictor of AF recurrence with an adjusted odds ratio of 1.08 (95% CI 1.00-1.17, p=0.038).

Table 2 Distribution of pulmonary venous anatomy

Pattern of PV anatomy	Prevalence
Conventional anatomy*	86 (59%)
Common left trunk	24 (16%)
Common right trunk	1 (0.7%)
Left sided accessory PVs	0
Right sided accessory PVs	40 (27%)
Superior accessory PV	6 (4%)
Middle accessory PV	34 (23%)
Multiple middle accessory PVs	2 (1.4%)
Inferior accessory PV	0

Values are given as number (%). * Conventional anatomy = single right and left superior and inferior pulmonary veins that drain into the left atrium without accessory veins. PV = pulmonary vein/venous.

Table 3 Predictors of recurrence of atrial fibrillation

Variables	Univariate analysis *p value*	Multivariate analysis *p value*
Age	0.596	
Gender	0.688	
Hypertension	0.130	
Structural heart disease	0.102	
Type of AF	0.820	
Duration of AF	0.024	0.038
LA volume	0.020	0.047
Conventional PV anatomy	0.198	
Common left trunk	0.133	
Right sided middle accessory PV	0.917	
Right sided superior accessory PV	0.625	

A p-value < 0.05 was considered statistically significant. AF = atrial fibrillation, *LA = left atrial, PV = pulmonary vein/venous.*

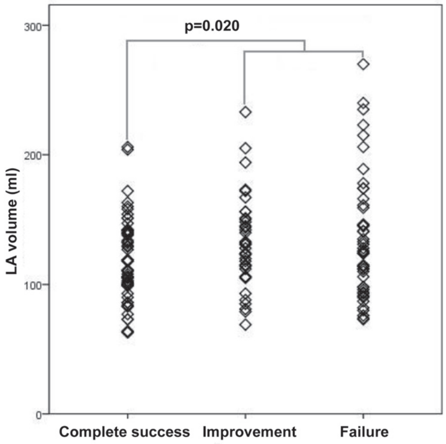

Figure 3. Distribution of left atrial volume among the different outcomes of the ablation procedure.

The distribution of LA volume among the different outcomes of the ablation procedure is shown in Figure 3. Patients with complete success had a mean LA volume of 118 ±32 ml, patients who met the definition of improvement had a mean LA volume of 132 ±35 ml, and patients who failed the ablation procedure had a mean LA volume of 135 ±47 ml. Among the 10 patients with a LA volume of greater than 200 ml complete success was achieved in 2 patients (20%). In contrast, complete success was achieved in 7 of 22 patients (32%) with a LA volume between 150 and 200 ml and in 50 of 114 patients (44%) with a LA volume less than 150 ml.

The impact of PV anatomy on the outcome of catheter ablation of AF was also evaluated. Patients were categorized into those with a conventional PV anatomy, a common left trunk, and right sided middle and superior accessory PVs. PV variations were equally distributed among the different outcomes of the ablation procedure. Univariate analysis did not identify PV anatomy as a predictor of outcome after AF ablation (Table 3).

Discussion

The aims of the present study were to investigate whether LA volume and PV anatomy predict the outcome of AF ablation. The results of our study revealed that LA volume is an independent predictor of recurrences of AF after AF ablation with an adjusted odds ratio of 1.14 for every 10 ml increase in volume. Additionally, PV anatomy did not have any effect on the outcome of catheter ablation of AF. PV variations were equally distributed among patients with AF recurrence or no AF recurrence.

To the best of our knowledge this is the first study to evaluate whether true LA volume, as measured by manually tracing LA area on CT prior to ablation, predicts outcome of catheter ablation of AF. In contrast, a number of studies have evaluated LA diameter, as assessed with conventional echocardiography, as a predictor of outcome of AF ablation. The results of these studies are contradictory. Some studies reported LA diameter by echocardiography to be an independent predictor of AF recurrence following catheter ablation [2, 3, 5]. However, other studies reported opposing results [4, 21, 22].

There have been two prior studies which have examined the relationship between LA volume and the outcome of AF ablation. Shin and colleagues used echocardiography to measure LA volume and reported that LA volume was a predictor of AF recurrence after catheter ablation (p=0.01) [23]. In addition, Maciel et al used the CARTO system to determine LA volume. They also identified LA volume to be an independent predictor of AF recurrence (p<0.001) [24]. Consistent with the studies of Shin et al and Maciel et al, LA volume was identified as an independent predictor of outcome following AF ablation in our study. It is reassuring that the results are steady and consistent with the two prior studies which have assessed LA volume with echocardiography and electroanatomic mapping. The consistency of the reported relationship between LA volume, regardless of how assessed, is striking. This is particularly true when contrasted with the varying results of studies which have evaluated the relationship of LA diameter, as assessed with conventional echocardiography, with the outcome after AF ablation.

Surprisingly, LA volume prior to catheter ablation was correlated to outcome and AF type, however, univariate analysis did not identify AF type as a predictor of outcome. This is striking because many studies have found AF type to be associated with outcome of catheter ablation, reporting a higher success rate in patients with paroxysmal AF compared to patients with persistent AF [25]. The similar success rates found in patients with different AF types within our study population may be explained by the small number of patients within the subgroups or the association of AF type with other predictors of outcome. Additionally, several other studies could not confirm a relation between AF type and outcome of catheter ablation as well [2, 6, 26]. For instance, Cheema and colleagues reported a success rate of 48%, 36%, and 50% in patients with paroxysmal, persistent, or permanent AF respectively (p=0.90) [26].

Furthermore, our study examined for the first time the relationship between PV anatomy and the outcome of AF ablation. The distribution of anatomical variants of PV anatomy in our study is very consistent with prior studies which have reported that four distinct PV ostia are present in approximately half to two thirds of patients, and that the remaining patients have one or more anatomical variants [27, 28]. What is unique about our study is that we examined the relationship between the pattern of PV anatomy and the outcome of AF ablation. The results of our study did not find PV anatomy to be predictive of outcome.

Conclusion

The results of the present study demonstrate that LA volume is an independent predictor of outcome following AF ablation. For each 10 ml increase in volume the risk of AF recurrence increased by 14%. This finding, together with the results of prior studies, suggest that an assessment of LA volume may be incorporated into the pre-procedural evaluation of patients being considered for AF ablation to be able to make an assumption regarding their prognosis. In addition, LA volume assessments should also be included as a covariate in future clinical trials of AF ablation.

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5.2 EDITORIAL

Predicting outcome from AF ablation: size of the chamber, or is tissue the issue?

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5.2 Editorial comment

Despite tremendous advances in the field of percutaneous catheter ablation for atrial fibrillation (AF), several concerns continue to limit more widespread acceptance, particularly as a first-line therapy. The absence of a focused ablation target, variable anatomy of the left atrium, and the need for vigilant monitoring of catheter location and anticoagulation make the procedure more technically challenging than ablation for other supraventricular arrhythmias. The accompanying lower success rates and marginally higher complication rates have made the identification of robust, preoperative markers for successful outcomes a priority.

The type of AF is an accepted marker of outcome.[1,2] Poorer success has been observed in patients with persistent compared with paroxysmal AF, particularly when segmental, ostial, or complex fractionated atrial electrogram (CFAE) approaches are employed.[3,4] However, when wider-area circumferential lesion sets are created, particularly in conjunction with defragmentation and/or linear lesions, the predictive value of the type AF is less clear. Some studies show no correlation with outcome at all.[5-7] Duration of AF may be a better marker with very longstanding AF generally associated with the poorest outcomes.

Patient comorbidities are also predictive of poor ablation outcome. Hypertension, sleep apnea, age, congestive heart failure (CHF), and hypertrophic cardiomyopathy are all associated with greater recurrence rates although several single, high-volume center studies produced very respectable outcomes in elderly and obese patients.[5,7-11] Importantly, most of these markers do not adequately distinguish subjects in whom ablation should categorically be avoided.

Given the large surface area covered by ablation lesion sets and the need to create conduction block, one would predict that left atrial (LA) geometry would be an important factor in procedural success. Four discrete pulmonary venous (PV) ostia are not always present and may represent a minority of anatomies.[12] PV variants including a common left trunk and accessory PVs, particularly associated with the right pulmonary vein (RPV) complex are observed in up to 44% of patients.[13] Little data exist regarding the impact of such variants on ablation outcomes.

LA dimension (LAd) has been a predictor of ablation outcomes in multiple studies and is used as an exclusion criterion in many randomized ablation trials.[5,14] However, other reports fail to show correlation between LAd and procedural results.[15,16] Why might this be? While LAd is a strong predictor of cardiovascular events, including the development and progression of AF, it is a poor overall predictor of LA volume (LAV), the true representation of LA size.[17] Not surprisingly, LAV, particularly when indexed, is a more robust predictor of CV events than LAd.[18] The anterior-posterior LAd measures the most constrained dimension of LA size. The spine and the ventricles constrain expansion in the anteroposterior (AP) dimension. Much of the enlargement in the LA occurs transversely and in a cranio-caudal direction. Thus, LAd may vastly underestimate pathologic LA enlargement. In one study, an LAd of 42 mm was associated with LAVs ranging from 40 to 120 mL.[19]

In this issue of the Journal, Hof et al.20 report results of their single-center study examining the role of LAV and PV anatomy in predicting outcome following AF ablation. The computed tomography (CT) scans of 146 sequential patients undergoing circumferential PV isolation aided by CT integration were examined. The LA border was traced on sequential CT images excluding the PVs at their ostia and the left atrial appendage (LAA) at its base. The areas were calculated and summed to create an LAV, a method they previously validated.21 CTs were also assessed for PV variants that were present in 41% of patients, the most frequent being a common left pulmonary vein (LPV) trunk in 16% and any accessory RPV in 27%. Procedural outcomes after at least 6 months were classified as complete success (no atrial arrhythmias lasting >30 seconds after a 3-month blanking period, off antiarhythmic [AA] drugs), improvement (no AF on an AA drug or >90% reduction in AF burden on or off an AA drug) and failure.

There was no correlation between the presence of variant PV anatomy and outcome. Variants were equally distributed among the different outcome groups. Mean LAV of the population was 127 ± 39 mL. Among the 40% with complete success, the mean LAV was 118 ± 32 mL compared with 132 ± 35 mL and 135 ± 47 mL in the patients showing improvement and failure, respectively. Among the 10 patients with very large LAV (>200 mL), complete success was seen in only 20%. In contrast, complete success was achieved in 32% with LAV 150–200 mL and 44% with LAV <150 mL. In multivariate analysis, only duration of AF and LAV were predictors of AF recurrence with an adjusted odds ratio of 1.14 for every additional 10 mL volume increase. Interestingly, improvement as an outcome was not correlated with LAV.

It is not entirely surprising that variant PV anatomy did not adversely impact ablation success. Wider-area circumferential lesion sets can easily incorporate most accessory veins and essentially the same lesion set is created, save carinal lesions, whether a common left trunk or discrete left ostia are present. PV variants would be more likely to be of significance in ostial or segmental ablation approaches or when preoperative imaging is unavailable, limiting the likelihood of recognizing the presence of a variant anatomy. It is also possible that this finding was due to lack of statistical power.

Four other groups have measured LAV in patients undergoing catheter ablation and all report correlation with procedural outcome.[22-25] The Hof study showed the largest odds ratio, likely because their report included the largest cohort with the widest range

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of LAVs.20 There are several limitations. The success rates seem low compared with other studies. This may be explained by reporting based on a single ablation procedure and the quite large LAVs represented in the cohort - as large as 3 times the size seen in the other 4 studies. Finally, the impact of LA size on procedural complications was not discussed.

So why is LAV a strong and reproducible predictor of ablation success? It is possible the finding reflects a purely mechanical effect. A larger LAV yields a larger LA surface area and thus amore extensive substrate to modify. Similarly, a larger volume is associated with greater wall stress and thickness, rendering the tissue more resistant to transmural lesion formation.

In my opinion, LAV enlargement more likely represents a patient's state of or susceptibility to adverse LA remodeling. AF itself, hypertension, diastolic and systolic CHF, as well as other pathologies, can trigger a negative-remodeling process that invokes alterations in gene expression leading to structural and electrophysiologic changes manifest by increased LA size, fibrosis, and altered conduction properties.[26] Regardless of the trigger, this remodeling further increases the likelihood of persistent AF and may reduce the likelihood of successful ablation. LAV enlargement may mark a final common pathway of any process that negatively remodels the LA, and the extent of LAV enlargement may reflect not only the trigger itself but a patient's susceptibility to remodeling. Verma et al. showed a strong correlation between LA remodeling in the form of scar, as measured by low-voltage regions during electroanatomic mapping, and recurrence of AF postablation.[27] Thus, preoperative imaging that could characterize the degree of LA tissue remodeling could be quite useful. In their study, LAd correlated with the burden of scar but was not a predictor in multivariate analysis. However, LAV was not measured. It is possible that scar burden would have closely correlated with LAV.

A recent paper by Oakes et al. sheds further light on this issue.[24] They performed magnetic resonance imaging (MRI) studies with delayed-enhancement imaging on 81 patients undergoing PV antral isolation. Compared with normal controls who had less than 2% of their atria with delayed enhancement, a marker of myopathic scar, subjects with AF could be grouped as having minimal (mean, 8.0 ± 4.2%), moderate (21.3 ± 5.8%), and extensive enhancement (50.1 ± 15.4%). While enhancement in subjects with minimal levels clustered around the PVs, posterior wall and septum, in those with greater levels of pathology, the patterns were more diffuse.

The location and degree of enhancement was found to correlate with low-voltage regions found by electroanatomic mapping during the index procedure. After a minimum of 6 months follow-up, multivariate analysis showed the extent of enhancement, that is, pathologic remodeling and scar, the most robust marker of procedural failure. Interestingly, LAV was also an independent predictor of recurrence.

It is worth noting that in the Oakes study, persistent AF was a much weaker predictor of AF recurrence than the degree of LA enhancement. In Hof, AF recurrence was not correlated with type of AF at all, as seen in several other studies. It is conceivable that persistent AF is a poorer surrogate for the extent of atrial remodeling than LAV enlargement or scar burden and that there is overlap in the degree of remodeling among many patients with paroxysmal versus persistent AF. Perhaps future studies will find that those with moderate remodeling will have same ablation outcome regardless of type of AF. Duration of AF may be a better predictor of recurrence than AF type since it may reflect the duration of exposure to pathologic atrial remodeling.

How can we incorporate these data into practice? These studies highlight the importance of preoperative imaging. While Hof did not randomize patients to the presence or absence of CT imaging, it is reasonable to conclude that preoperative mapping of PV anatomy may prevent detrimental impact of PV variants on procedural outcome.

More importantly, imaging for LAV and evidence of pathologic remodeling appear to be reproducible predictors of AF recurrence postprocedure. Delayed-enhancement imaging will need further validation and refinement before widespread adoption. The technique requires well-trained operators and failed to provide interpretable data in 37/118 (31%) of those initially scanned for the Oakes study. We can conclude, for now, that measuring LAV may prove to be a more straightforward preoperative tool. Should we refuse patients solely on the basis of LAV, or delayed-enhancement imaging? At the extremes, this seems reasonable. However, Hof did not see a correlation between LAV and improvement in AF burden. Similarly, Oakes reported that postablation, 84% of patients with AF recurrence responded well to AA drugs. Thus, markers of LA remodeling may prove best at allowing us to warn patients of a greater likelihood of needing either drug therapy postprocedure or a second ablation. In the future, it will be useful to determine whether LAV or more extensive delayed enhancement is a predictor of increased procedural complication rates, an issue that neither group addressed and could be used in preprocedural decision making.

In summary, noninvasive, preoperative markers of the extent of pathologic atrial tissue remodeling, such as scar burden and LAV, may become increasingly relevant tools in our management of patients with AF. The tissue is the issue; while the future holds promise for MRI, for now, LAV may be the most accessible glimpse at the state of the atrium. We should consider adding this measure to our registries and trial data sets.

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Chapter 6

Impact of catheter ablation of atrial fibrillation on the left atrium

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Abstract

The success of catheter ablation for atrial fibrillation (AF) has been proven but its impact on the left atrium (LA) itself remains uncertain. This article reviews the effects of catheter ablation of AF on the development of LA fibrosis, LA size and function, and the occurrence of LA tachycardias. Delayed enhancement magnetic resonance imaging has demonstrated that catheter ablation results in ablation induced fibrosis which, although necessary to obtain a successful outcome, may also have a negative effect on LA function. In addition, catheter ablation of AF affects LA size but it is undecided to what degree and in what manner since the literature regarding this subject is very conflicting. Less confusion exists in the literature regarding LA tachycardias post-ablation. Extensive ablation in the LA has shown to result in a higher incidence of post-ablation LA tachycardias compared to pulmonary vein isolation only.

Introduction

Catheter ablation with radiofrequency energy as a treatment for atrial fibrillation (AF) is commonly performed and is now performed worldwide [1]. It may involve solely pulmonary vein isolation or it may include more extensive ablation with additional ablation in the left atrium (LA). Its success in eliminating AF has been proven in many studies [2-6], however, the impact it has on the LA itself remains uncertain. Although several studies have looked into this subject by analyzing LA size and function, they report diverse results and are difficult to compare due to different applied methods (imaging techniques, ablation techniques, etc) [7, 8]. It is well known that AF causes remodeling of the atria on several levels [9, 10]. First, electrical remodeling takes place, which is characterized by changes in atrial refractoriness and atrial conduction due to changes in intracellular Ca^{2+} handling. Electrical remodeling is completely reversible once sinus rhythm is restored [11, 12]. Second, contractile remodeling occurs with loss in atrial contractility with thrombus formation and atrial dilatation, which is reversible as well after cessation of AF [13, 14]. And third, structural remodeling takes place, which involves myocyte cell loss with diffuse atrial fibrosis. Structural remodeling tends to persist after restoration of sinus rhythm [14, 15]. Two main factors may be responsible for the possible changes in hemodynamic parameters of the LA following catheter ablation of AF: remodeling, either by ongoing AF or reverse remodeling by restoration of sinus rhythm, and ablation induced LA fibrosis. However, it remains uncertain to what degree these factors may influence the LA.

The aim of this article is to review the literature on the effects of catheter ablation of AF on the LA with regard to the development of fibrosis, size, function, and the occurrence of post-ablation LA tachycardias. In addition, several parameters will be discussed which may influence LA size and function after ablation.

Impact of catheter ablation on the development of left atrial fibrosis

Catheter ablation of AF with radiofrequency energy results in thermal damage of the LA myocardium. It causes myocardial necrosis followed by inflammatory infiltrates that result in replacement or scarring fibrosis of the myocardial wall [16, 17].

Visualization of left atrial fibrosis

Delayed enhancement magnetic resonance imaging (MRI) is able to depict regions of scar or injured tissue in the myocardium due to altered washout kinetics of a contrast agent (a gadolinium based agent) [18, 19]. Gadolinium will accumulate in fibrotic myocardial tissue which will then appear as a bright signal on T1-weighted images. Although delayed enhancement MRI has been successfully used to identify scarring of the left ventricle, imaging of the LA has posed a greater challenge since the LA wall may be up to five times thinner than the left ventricular myocardium [20]. Nevertheless, in 2007 Peters et al published a study in which they reported their initial experience using delayed enhancement MRI to depict LA fibrosis after catheter ablation of AF [20]. They identified a partial to complete circumferential delayed enhancement pattern for the left inferior pulmonary vein (PV) in patients after PV antrum isolation. One year later, these results were confirmed by McGann et al who showed hyperenhancement of the LA wall in all patients post-ablation [21]. Evidence that these areas of LA fibrosis post-ablation are actually correlated to catheter ablation has been provided by Taclas et al [22]. They stated that 80% of their ablation sites on the Carto model corresponded with LA fibrosis detected with delayed enhancement MRI. Only 1% of LA fibrosis was present outside ablation areas marked by the Carto system. Additionally, Segerson et al described a highly significant correlation between the total LA radiofrequency delivery time and the percentage of LA fibrosis quantified by delayed enhancement MRI [23].

Impact of left atrial fibrosis on the left atrium

The abovementioned publications offer substantial proof that catheter ablation of AF results in fibrosis of the LA wall. However, does this ablation induced LA fibrosis have a possible unfavorable effect on LA function? Wylie et al performed delayed enhancement MRI to visualize LA fibrosis after ablation and they found a strong linear correlation between the decrease in LA ejection fraction and LA fibrosis volume after catheter ablation, suggesting that ablation induced fibrosis may have a detrimental effect on LA function [24]. However, further research concerning the influence of ablation induced fibrosis on LA function is lacking.

The positive side of ablation induced fibrosis is a favorable outcome. Several studies have shown that the amount of LA fibrosis post-ablation is related to the outcome of the ablation procedure [23, 25, 26]. For example, Segerson et al mentioned a significant relationship between the number of pulmonary veins (PVs) encircled by delayed enhancement and clinical success of catheter ablation of AF [23]. Their analysis revealed a relative reduction of 38% in AF recurrence rate for each PV that was encircled. In addition, progressive increases in post-ablation posterior LA wall fibrosis reduced AF recurrence rates with a hazard ratio of 0.65 in their statistical analysis. So although a certain amount of ablation induced LA fibrosis is necessary to have a successful outcome of the ablation procedure, it should be born in mind that this ablation induced fibrosis may potentially impair LA function.

Impact of catheter ablation on left atrial size

Methods to assess left atrial size

Several measures to determine LA size exist in the literature. A widely used measurement of LA size is the anteroposterior diameter derived from the parasternal long-axis view with echocardiography. Some clinical centers use this diameter to select AF patients for treatment with catheter ablation, since an increased diameter has been shown to correlate with a worse outcome [27-29]. However, this diameter inaccurately represents true LA size since the LA often has an asymmetrical shape and the enlargement, seen in patients with AF, does not occur in a uniform fashion [30, 31]. In addition, the American Society of Echocardiography has recommended quantification of LA size by a biplane method rather than using a one-dimensional measurement [32]. Biplane methods to assess LA size make fewer assumptions and are therefore more accurate, but still underestimate true LA size [33]. The most accurate method to assess LA size is LA volume calculated by Simpson's rule (Figure 1). This method involves manual tracing of LA area on each available slice and has been shown to correlate closely with true LA size obtained by post mortal assessment [34, 35]. Additionally, this method should be employed with either computed tomography (CT) or MRI, since echocardiography has shown to systematically underestimate LA volume compared to CT or MRI [36].

All the abovementioned imaging techniques and methods to assess LA size are used in the studies addressing the impact of catheter ablation of AF on LA size, and this

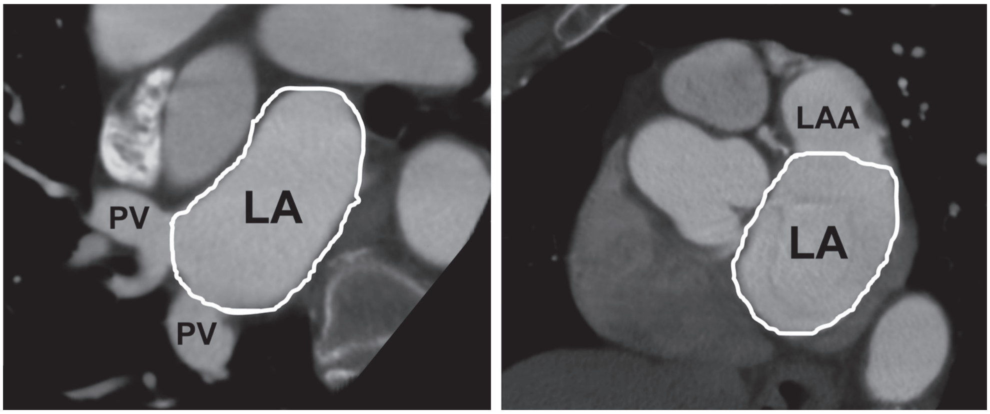

Figure 1. Simpson's rule demonstrated with computed tomographic images in oblique axial view of the left atrium. The white line demonstrates the manual tracings of left atrial area, excluding the pulmonary veins (left panel) and the left atrial appendage (right panel). LA = left atrium, LAA = left atrial appendage, PV = pulmonary vein.

partly accounts for the diversity in their results [8]. Consequently, it may be wise to particularly value the studies that have used the most precise method to estimate LA size (Simpson's rule by either CT or MRI) [37-42]. But even these studies report contradictory results. Lemola et al noticed a significant decrease in LA volume in patients with a successful outcome and no decrease in LA volume in patients with AF recurrences after catheter ablation [42]. A more recent study performed by Jahnke et al reported similar results [38]. However, research performed by our group revealed a significant decrease of LA volume in all patients regardless of outcome of catheter ablation [37], consistent with the study of Perea et al [41].

Catheter ablation technique

Catheter ablation as a treatment for AF has evolved rapidly, from a rather simple procedure targeting only the PVs to more complex procedures targeting multiple triggers and performing substrate modification. Not long after the PVs were identified as triggers that initiated AF, an ablation approach was introduced by Haissaguerre et al designed to electrically isolate the PVs [43, 44]. This segmental PV isolation involved delivery of radiofrequency energy very close to the PV ostia. The recognition of both PV stenosis as an important complication of segmental PV isolation and the PV antrum as an additional site of AF initiation, resulted in the development of PV antrum isolation. This involves wide continuous circumferential ablation surrounding left and right PVs in pairs [45, 46]. Furthermore, additive ablation strategies have been created to further improve outcome of catheter ablation of AF, especially in patients with (longstanding) persistent AF. These strategies include additional linear ablation in the LA mimicking the Cox Maze-III [47-49], for example the roof line and the mitral isthmus line, and ablation of areas with complex fractionated atrial electrograms (CFAEs) in both atria [50].

It can be assumed that segmental PV isolation would result in far less ablation induced fibrosis than PV antrum isolation with additional linear ablation and ablation of CFAEs in the LA. To the best of our knowledge, two studies exist in which only segmental PV isolation was performed and the change in LA volume after ablation was examined. Jayam et al noticed a significant reduction in LA volume in the total study population, regardless of clinical outcome [51]. However, Tsao et al reported opposing results [52]. They observed a borderline reduction of LA volume in the group with a successful outcome and an increase in LA volume in the group with AF recurrences. Nevertheless, as will be discussed in the next section, this may be influenced by the totally different time intervals used to measure LA volume. Jayam et al assessed LA volume approximately 2 months after ablation, while Tsao et al performed the post-ablation measurements at a mean of 21 months after ablation.

There are also conflicting results on what impact PV antrum isolation with additional linear ablation in the LA has on LA size [40-42, 53-59]. For instance, in the study by Tops et al PV antrum isolation was combined with a roof line and a mitral isthmus line and they reported a decrease of LA volume in patients with a successful outcome and an increase of LA volume in patients with AF recurrences [59]. Similar results were found in the study by Lemola et al [42]. Delgado et al and Perea et al performed PV antrum isolation and additional linear ablation in their study population, including a roof line, a mitral isthmus line and a posterior line, and noticed a decrease in LA volume in all patients [41, 55]. Finally, one study could be found in which they not only performed PV antrum isolation and additional linear ablation, but also performed ablation of CFAEs in the LA [39]. They reported a decrease of LA volume in the total study population but they did not perform a subanalysis with regard to LA volume and outcome of catheter ablation.

Timing of post-ablation left atrial size assessment

LA size after ablation of AF may vary because different ablation techniques are employed and different methods are used to assess it. Additionally, the timing of the post-ablation assessment of LA size is also of significant importance. As previously mentioned, the main factors influencing LA size after ablation are development of ablation induced fibrosis, reverse remodeling by restoration of sinus rhythm, or ongoing remodeling by AF. These factors may show a different progression over time. Badger et al performed delayed enhancement MRI in patients with AF who underwent catheter ablation to visualize ablation induced fibrosis [60]. The delayed enhancement MRI scans were made 24 hours, 3 months, 6 months, and 9 months after catheter ablation in order to examine the response of ablation induced fibrosis over time. They found that ablation induced fibrosis appears to have formed by 3 months post-ablation with no recovery or reduction of fibrosis after that time point.

The effect of the heart rhythm, either by restoration of sinus rhythm or relapse of AF, on the LA is rather an ongoing process. Restoration of sinus rhythm reverts the process of LA enlargement in patients with AF and therefore leads to a gradual decrease in LA size [61]. In contrast, persistence of AF may lead to further remodeling with dilatation of the LA [62, 63]. In the study of Suarez et al patients with lone AF were followed for 6 years and showed an increase in LA size compared to baseline measurements [63].

The studies by Donal et al and Jahnke et al only included successful cases (patients with a successful outcome after the ablation procedure) in the long-term follow-up [38, 53]. Both studies measured LA volume at 3 and 12 months after catheter ablation of AF and noticed a progressive decrease in LA volume in these successful

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cases, consistent with the information above concerning reverse remodeling of the LA by restoration of sinus rhythm. Interestingly enough, Rodrigues et al measured LA volume at one day and 8 months after ablation and did not see a decrease in LA volume at all, whether patients had recurrences of AF or not [64]. The study performed by Tsao et al has the longest time interval between catheter ablation of AF and post-ablation assessment of LA size [52]. They measured LA volume 21 months after ablation and reported a borderline reduction in the successful cases and a dilatation of the LA in the patients with AF recurrences.

Three articles exist that have very comparable methods [40-42]. They all performed PV antrum isolation with additional linear ablation, they measured LA volume using the Simpson's rule and MRI or CT, and they measured post-ablation LA volume at 4-6 months after catheter ablation. However, the results of these 3 articles could not be more different. Whereas Tsao et al reported no significant change in LA volume after ablation in the total study population [40], Perea et al noticed a significant decrease of LA volume in all patients, regardless of clinical outcome [41]. And finally, Lemola et al stated that LA volume decreased only in patients with a successful outcome of the ablation procedure [42].

Impact of catheter ablation on left atrial function

Methods to assess left atrial function

LA function is mainly determined by three phases during the cardiac cycle [65, 66]. First, during ventricular systole (or atrial diastole) the LA operates as a reservoir receiving blood from the PVs. Thereafter, during the early phase of atrial systole the LA functions as a conduit for passive transfer of blood to the left ventricle. Finally, during the second phase of atrial systole the LA actively pumps blood into the left ventricle. Most articles that analyze LA function before and after catheter ablation of AF employ the LA ejection fraction (LA EF) as a representative of LA function, which is calculated by LA EF = [(LAmax - LAmin)/LAmax] x 100. As the LA EF is comprised of both the passive and the active phase of the atrial systole, a more precise method divides the LA EF into the passive atrial emptying fraction, as an index of LA conduit function, and the active atrial emptying fraction, as an index of LA active contraction [67-69]. Other methods exist to determine LA function, for example peak transmitral A wave velocity [65]. However, because only 3 articles employed these different methods [53, 70, 71], and comparison is difficult because of the very different study protocols, this review will focus on articles that measure the LA EF.

Since LA EF and the active and passive atrial emptying fractions are derived from LA volume measurements, it is of significant importance to take into account which method and imaging technique has been used to obtain these volumes. As discussed previously, the most precise method to estimate LA volume is applying the Simpson's rule with either CT or MRI. One must consider, however, that CT imaging results in radiation exposure. Although CT protocols exist with a reduced amount of radiation, these protocols involve prospective gating and are therefore unsuitable for LA EF assessment. When examining the articles that have used the most precise method to calculate LA EF, we found the following results. Jahnke et al and Tsao et al reported similar results [38, 40]. They noted an increase in LA EF in patients with a successful outcome of catheter ablation and no change in LA EF in patients with AF recurrences. Perea et al, however, revealed no change in LA EF in patients with a successful outcome and a decrease in LA EF in patients with AF recurrences [41].

Few articles exist in which, in addition to LA EF, the passive and active atrial emptying fractions of the LA were calculated [24, 55, 72]. Delgado et al showed preservation of LA function in the total study population finding no change in LA EF or active atrial emptying fraction in all patients, regardless of clinical outcome [55]. In contrast, in the study by Marsan et al a deterioration of LA pump function was found in patients with AF recurrences [72]. They reported an increase in LA EF and active atrial emptying fraction in patients with a successful outcome and a decrease in LA EF and active atrial emptying fraction in patients with AF recurrences. And finally, Wylie et al noted a significant decrease of LA EF, passive and active atrial emptying fraction in the total study population [24].

Catheter ablation technique

As discussed previously, the extensiveness of the ablation procedure used in different studies is of importance, since it influences the degree of post-ablation induced fibrosis which can affect LA function. To our knowledge, in 5 studies only PV antrum isolation was performed with no additional ablation [24, 38, 64, 72, 73]. Two of these studies noticed an increase of LA EF after catheter ablation in patients with a successful outcome [38, 72], with a decrease of LA EF in patients with AF recurrences in one study [72] and no change in LA EF in patients with AF recurrences in the other study [38]. In the remaining 3 studies, no subanalysis was performed with regard to the effect of outcome of catheter ablation on LA function [24, 64, 73]. Interestingly, these studies again reported diverse results. Rodrigues et al and Wylie et al showed a decline in LA EF in the total study population [24, 64]. Additionally, Wylie et al performed delayed enhancement MRI to visualize LA fibrosis after ablation and they found a strong linear correlation between the decrease in EF and LA fibrosis volume after catheter ablation, suggesting that ablation induced fibrosis may have a detrimental effect on LA function [24]. However,

an improvement in LA EF in the total group was found in the study by Verma et al [73]. These last three studies used different imaging techniques, including echocardiography, MRI and CT, but the remaining part of their study protocol is rather comparable.
Analysis of the studies that performed PV antrum isolation with additional linear ablation in the LA does not provide much clarity either. Most studies reported no difference in LA function after ablation in patients with AF recurrences [40, 54, 55, 58]. But Perea et al, measuring LA EF by the most precise method, noticed a decrease in LA EF after ablation in patients with AF recurrences [41]. Results are more diverse when looking at LA EF after catheter ablation in patients with a successful outcome. Studies report either no change in LA EF in these successful cases [41, 55] or even an improvement in LA EF [40, 58]. Although not one of these studies has reported a decrease in LA EF in patients with a successful outcome after extensive ablation, it is still not clear whether LA function may not be impaired by catheter ablation. For example, Choi et al measured LA EF in patients with AF after cardioversion (ECV group) and in patients with AF after extensive ablation (ABL group) [54]. They noticed no change in LA function in the ABL group, but LA EF improved significantly in the ECV group.

Timing of post-ablation left atrial function assessment

In addition to LA size, LA function after catheter ablation is also influenced by the development of ablation induced fibrosis, reverse remodeling by restoration of sinus rhythm, or ongoing remodeling by AF. However, the recovery of LA function after restoration of sinus rhythm occurs at a faster rate than the reversion of LA enlargement. Depending on the duration of AF prior to conversion and the mode of conversion to sinus rhythm (pharmacological or electrical cardioversion), LA function improves between 1 week and 1 month [54, 74-76]. Van Gelder et al measured LA function in patients with chronic AF directly after cardioversion, and 1 week, 1 month and 6 months thereafter [76]. They already described an improvement of LA function at 1 week which remained unchanged thereafter.
As stated previously, according to Badger et al, ablation induced fibrosis appears to have formed by 3 months post-ablation with no recovery or reduction of fibrosis after that time point [60]. However, they did not perform additional delayed enhancement MRI between 24 hours and 3 months after ablation. Wylie et al already found a strong linear correlation between the decrease in LA EF and LA fibrosis using measurements between 30 and 60 days after catheter ablation [24]. This suggests that the effect of ablation induced fibrosis may be expected well before 3 months post-ablation.
A few studies reported results that agree with the information mentioned above regarding reverse remodeling. Jahnke et al mentioned a recovery of LA EF at one month post-ablation in the group with a successful outcome, which did not change at

3 months post-ablation [38]. The patients with AF recurrences did not show a recovery of LA EF during the total follow-up. In the study by Marsan et al, patients with a successful outcome showed no change in LA EF 3 days after catheter ablation, but they showed a significant improvement 3 months post-ablation [72]. In the same study, the patients with AF recurrences showed a decrease of LA EF at 3 months after ablation which was not seen at 3 days post-ablation. These studies confirmed that LA function can show a recovery between a few days and 1 month post-ablation if sinus rhythm is restored. However, articles exist that showed the opposite. The total study population in the study by Choi et al did not show any improvement in LA EF after ablation with a follow-up duration of 8 months [54]. And Perea et al described no change in LA EF at 4-6 months post-ablation in patients with a successful outcome and a decline in LA EF in patients with AF recurrences [41]. The results of these last mentioned studies may suggest that an effect of ablation induced fibrosis plays a role which may counteract the effect of reverse remodeling. An interesting detail that corresponds with this theory is that PV antrum isolation with additional ablation was performed in the last mentioned studies, while only PV antrum isolation was done in the study by Jahnke et al and Marsan et al who noticed an improvement in LA function [38, 41, 54, 72].

Impact of catheter ablation on the occurrence of left atrial tachycardias

In addition to the effect of catheter ablation of AF on the hemodynamic parameters LA size and function, catheter ablation may also give rise to post-ablation LA tachycardias. These post-ablation LA tachycardias are of significant importance since they tend to be incessant with a rapid ventricular response leading to unpleasant symptoms [77]. Two main mechanisms may be responsible for the occurrence of LA tachycardias following ablation. These tachycardias either have a focal origin within the PVs with reconnection to the LA, or they occur as a macro-reentrant or micro-reentrant tachycardia due to gaps in ablation lines [78, 79]. In agreement with these mechanisms, focal atrial tachycardias will occur mainly after segmental PV isolation, while macro-reentrant and micro-reentrant LA tachycardias are more likely to occur after extensive ablation, including linear ablation and ablation of CFAEs [77, 78]. In addition, it can be expected that increasing ablation in the LA would enhance the possibility of post-ablation atrial tachycardias. Gaps in circumferential ablation lesions or linear lines serve as the ideal substrate for atrial tachycardias.

The literature on this subject tends to be more homogenous compared to the literature regarding LA size and function after catheter ablation. When comparing studies with different ablation strategies for AF treatment, the reported incidence of post-ablation LA tachycardias was higher in studies with extensive ablation. In most studies, in which PV isolation was performed with additional linear ablation, incidences of post-ablation LA tachycardias ranged from 15 to 38% [6, 80-82]. Studies that included ablation of CFAEs on top of PV isolation with additional linear ablation reported similar incidences ranging from 19 to 43% [83-85]. Articles in which PV isolation was only combined with CFAE ablation tend to have a slightly lower incidence of post-ablation LA tachycardias (incidences between 8 and 18%), which may suggest that linear lesions are more pro-arrhythmic than CFAE ablation [50, 86, 87]. In contrast, articles that analyzed the incidence of LA tachycardias following only PV isolation found an incidence between 0 and 4% [78, 88-90]. However, once more exceptions exist in the literature. Oral et al performed PV antrum isolation with three additional linear lines in the LA and found post-ablation LA tachycardias in only 6% of their study population [91]. In addition, Karch et al performed PV antrum isolation with no additional ablation and 18% of their patients suffered from a post-ablation LA tachycardia [92].

Summary

Catheter ablation of AF may have several effects on the LA. First of all, it gives rise to ablation induced fibrosis which can be visualized by delayed enhancement MRI. Research has shown that at least a certain amount of ablation induced fibrosis is necessary in order to get a successful outcome, however, it may also have a negative effect on LA function post-ablation.

Second, catheter ablation of AF affects LA size but it is uncertain to what degree and in what manner. It is important to measure LA size using a precise method and to take into consideration what ablation technique is performed and at what time interval LA size is measured post-ablation. However, even after taking these parameters into account, the literature regarding LA size after ablation varies considerably. Additionally, the impact of catheter ablation on LA function, mainly expressed as LA EF, is still open for debate. Although not many studies reported a decrease of LA function after ablation in patients with a successful outcome, it is still unsure whether LA function may not be impaired by catheter ablation.

Other variables than those discussed in this article may have affected LA size and function after ablation and may have been responsible for the diversity in the literature, for example type of AF, presence of structural heart disease, and definition of outcome. However, analyzing the impact of these variables was outside the scope of this work.

Finally, catheter ablation of AF gives rise to post-ablation LA tachycardias. Less confusion exists in the literature regarding this topic. Extensive ablation in the LA, including PV antrum isolation with additional linear ablation and/or ablation of CFAEs, has shown to result in a higher incidence of post-ablation LA tachycardias compared to PV antrum isolation only.

In conclusion, although it has been proven that catheter ablation of AF results in ablation induced LA fibrosis and may give rise to post-ablation LA tachycardias, we are still relatively in the dark regarding the impact of catheter ablation of AF on LA size and function. More studies are needed that examine LA size and function after catheter ablation of AF with standardized methods, preferably measuring LA size and function by applying Simpson's rule with CT or MRI at multiple time intervals.

Table

Study	N	Imaging technique	Catheter ablation technique	Timing of post-ablation imaging	Subgroup analysis	Change in (max) LA size	Change in LA function*
Hof *et al* [37]	79	MRI	PVI	4 months	Success Failure	↓ ↓	n/a
Donal *et al* [53]	31	Echo	PVI + linear ablation	3 and 12 months	Success	↓	n/a
Jahnke *et al* [38]	41	MRI	PVI	1, 3, 6, and 12 months	Success Failure	↓ =	↑ =
Tsao *et al* [40]	48	CT	PVI + linear ablation	6 months	Success Failure	= =	↑ =
Nori *et al* [39]	29	MRI	PVI + linear ablation + CFAE ablation	3 months	Paroxysmal AF Persistent AF	↓ ↓	↓ ↑
Rodrigues *et al* [64]	33	Echo	PVI	1 day, 8 months	Success Failure	= =	↓
Choi *et al* [54]	33	Echo	PVI + linear ablation	1 week, 1 and 3 months	Total group	↓	=
Delgado *et al* [55]	34	Echo	PVI + linear ablation	6 months	Success Failure	= ↓	= =
Marsan *et al* [72]	57	Echo	PVI	3 days and 3 months	Success Failure	↓ =	↑ ↓
Muller *et al* [70]	91	Echo	Segmental PVI + linear ablation	6 months	Success Failure	↓ ↓	n/a
Perea *et al* [41]	55	MRI	PVI + linear ablation	4-6 months	Success Failure	↓ ↓	= ↓
Wylie *et al* [24]	33	MRI	PVI	30-60 days	Total group	↓	↓
Efremidis *et al* [56]	13	Echo	PVI + linear ablation	Not mentioned	Success Failure	↓ =	n/a

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Study	N	Imaging technique	Catheter ablation technique	Timing of post-ablation imaging	Subgroup analysis	Change in (max) LA size	Change in LA function*
Tops *et al*[59]	57	Echo	PVI + linear ablation	3 months	Success Failure	↓ ↑	n/a
Verma *et al*[73]	67	CT (n=26) Echo (n=41)	PVI	6 months	Total group	↓	↑
Beukema *et al*[57]	105	Echo	PVI + linear ablation	6 months	Success Failure	↓ ↑	n/a
Jayam *et al*[51]	51	MRI	Segmental PVI	6-8 weeks	Success Failure	↓ ↓	n/a
Lemola *et al*[93]	10	CT	PVI + linear ablation	5 months	Paroxysmal AF	↓	↓
Reant *et al*[58]	48	Echo	PVI + linear ablation	1, 3, 6, 9, and 12 months	Success Failure	↓ ↓	↑ =
Tsao *et al*[52]	45	MRI	Segmental PVI	21 months	Success Failure	↓ ↑	n/a
Lemola *et al*[42]	41	CT	PVI + linear ablation	4 months	Success Failure	↓ =	n/a
Pappone *et al*[71]	251	Echo	PVI	3 months	Success Failure	↓ =	n/a

Summary of the main studies that analyzed changes in left atrial size and function after catheter ablation of atrial fibrillation. *Only studies included in which the left atrial ejection fraction was calculated as a measure for left atrial function. "↓" = decrease in left atrial size or function; "↑" = increase in left atrial size or function; "=" = no change in left atrial size or function. AF = atrial fibrillation; CFAE = complex fractionated atrial electrograms; CT = computed tomography; LA = left atrial; MRI = magnetic resonance imaging; n/a = not applicable; PVI = pulmonary vein isolation.

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Chapter 7

Pulmonary vein antrum isolation in patients with atrial fibrillation leads to a significant decrease of left atrial size

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Abstract

Aim

Pulmonary vein antrum isolation (PVAI) is an effective treatment for atrial fibrillation (AF), however, its impact on left atrial (LA) size is unknown. This study evaluates the impact of PVAI on LA size, and whether LA size differs between patients with a successful outcome and patients with AF recurrences after PVAI.

Methods

Seventy-nine patients (76% male, mean age 56 ±8 years) with symptomatic, drug refractory AF (70% paroxysmal, 30% persistent/permanent) underwent radiofrequency PVAI. Ablation lesions were created encircling right and left pulmonary venous ostia in pairs. The endpoint was complete isolation of all pulmonary veins. Magnetic resonance imaging was performed before and 4 months after PVAI and LA volume was measured by manually tracing LA area. Clinical follow-up was at 1, 3, 6, 12, and 24 months. Rhythm status was determined by history, ECG, and 48 hours Holter monitoring.

Results

After a mean follow-up of 12±5 months, 62 patients (78%) were free of AF (72% without antiarrhythmic drugs). In the total group, LA volume decreased from 104±27 ml to 91±25 ml, p<0.001. Patients with a successful outcome showed a decrease in LA volume of 103±27 ml to 89±24 ml, p<0.001. Among patients with AF recurrences, LA volume decreased from 105±29 ml to 95±27 ml, p=0.012. No significant difference was seen between the change in LA volume in both subgroups, p=0.27.

Conclusion

PVAI in patients with AF resulted in a significant decrease of LA size. There was no relation between the decrease in LA size and the recurrence of AF after PVAI.

Introduction

During the past decade catheter ablation of atrial fibrillation (AF) has evolved rapidly and is now frequently performed in many clinical centers throughout the world. The most commonly employed ablation strategy nowadays is pulmonary vein antrum isolation (PVAI)[1]. This ablation strategy has proven to be effective in restoring sinus rhythm, however, its impact on the left atrium (LA), regarding LA volume, remains unclear. Several studies which examined the change in LA volume following catheter ablation revealed conflicting results. Some investigators reported a significant decrease in LA volume after catheter ablation in patients with a successful outcome[2-4], whereas others found a significant decrease in volume in all patients, regardless of clinical outcome[5-7]. In addition, these studies employed different imaging modalities and different methods to measure LA size, which makes it difficult to draw conclusions.
Both magnetic resonance imaging (MRI) and computed tomography are precise and reliable imaging modalities for depicting LA anatomy, with the advantage of no radiation with MRI[8]. In the present study we used MRI to measure LA volume by manually tracing LA area on every image slice to create a three-dimensional reconstruction. This technique takes into account that the LA is an asymmetrical shape and therefore provides an accurate assessment of LA volume[9-11]. In this study we used this technique to evaluate the impact of PVAI on LA volume. Additionally, we analyzed whether the change in LA volume differs between patients who remain in sinus rhythm after catheter ablation and patients with recurrences of AF.

Methods

Patient population

Patients admitted to our center for PVAI between January 2005 and September 2006 were considered possible candidates for this study. Inclusion criteria were patients with symptomatic AF refractory to at least two antiarrhythmic drugs (AAD), who underwent a cardiac MRI scan before and after catheter ablation for LA volume assessment. Additional inclusion criteria were an echocardiographic derived LA diameter in the parasternal long-axis view of ≤ 55 mm, and a minimum follow-up duration of 4 months to determine clinical outcome.

Magnetic resonance imaging

All patients underwent gadolinium-enhanced MRI to depict LA and pulmonary vein anatomy approximately 6 months prior to and 4 months after catheter ablation using a 1.5 Tesla MRI system (Philips Medical Systems, Best, The Netherlands). Imaging was performed with the patients in supine position with ECG gating. Gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Montville, New Jersey, USA) was administrated at a dose of 0.2 ml/kg and with an infusion rate of 1.5 ml/s. MR angiography (MRA) was obtained with single breath-hold three-dimensional fast spoiled gradient-echo imaging in coronal view. MRA acquisition was manually started after visualizing the contrast bolus in the left ventricle and giving a breath-hold command. The average acquisition time was approximately 20 s. Scan parameters were as follows: TR = 4 ms, TE = 1 ms, RF flip angle 35°, field-of-view 400 mm, matrix size 272x173, 3 mm slice thickness, and gap + slice 1.5 mm.

Left atrial volume assessment

LA volume was measured offline using commercially available software (Vitrea 2, Vital Images Inc, Minneapolis, Minnesota, USA) and the MRA images. Since the MRA represents the mean of the cardiac cycle, mean LA volume of the whole cardiac cycle was measured for each patient. The method to assess LA volume has been used in prior studies and has proven to be very closely related to true LA size as obtained by post mortal assessment [10-11]. First, the threshold level for defining the contour of the LA was set at 50% of the average contrast level in the center of the LA. Thereafter, LA area was manually traced on each image of the MRI scan in the coronal plane from the posterior side to the anterior side of the LA, as demonstrated in Figure 1, panel A.

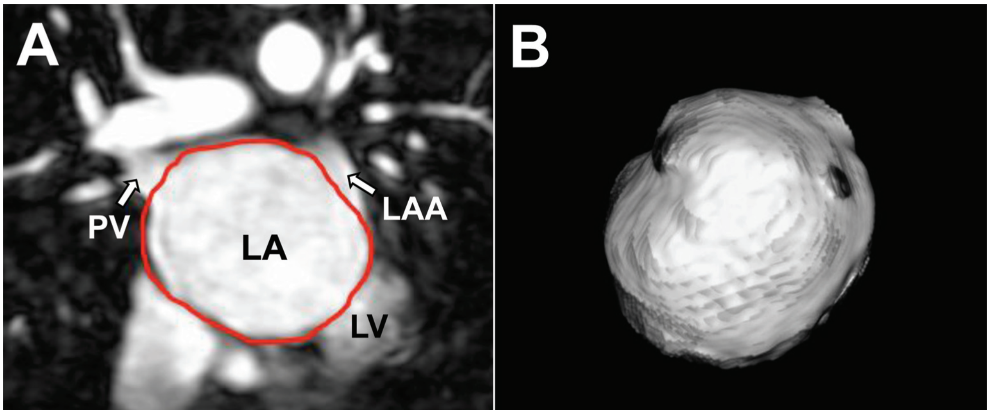

Figure 1. Panel A: Coronal plane of the left atrium in a patient after catheter ablation. The red line marks the manual tracing of left atrial area, excluding the pulmonary veins, the left atrial appendage, and the left ventricle. LA = left atrium, LAA = left atrial appendage, LV = left ventricle, PV = pulmonary vein. Panel B: Three-dimensional reconstruction of the left atrium in a posterior view.

The pulmonary veins were excluded at their ostia and the LA appendage was excluded at its base. The mitral annulus was considered to be the atrioventricular border, and therefore, the left ventricle was excluded at the point of insertion of the mitral valve leaflets. All the obtained LA areas formed a three-dimensional reconstruction as shown in Figure 1, panel B, with automatic calculation of LA volume. This reconstruction could be modified manually if too much tissue was included. All measurements were completed by a single investigator in a blinded fashion. Intraobserver variability was determined by performing blinded reassessments of LA volume in 30 randomly selected patients approximately 4 weeks after the first assessments by the same investigator. Interobserver variability was determined by performing blinded reassessments of LA volume in 30 randomly selected patients by a second investigator.

Pulmonary vein antrum isolation

AAD were discontinued at least five half-lives prior to the ablation procedure. Before catheter ablation a transesophageal echocardiogram was performed to exclude the presence of LA thrombus. Electrophysiologic study was performed in a fasting, non-sedated state. Catheters were introduced percutaneously through left and right femoral veins and positioned in the right atrium, right ventricle and the coronary sinus. After transseptal access, an initial intravenous bolus of 5,000 IU heparin was administered, followed by repeated doses of heparin to maintain an activated clotting time above 250 seconds. A three-dimensional reconstruction of the LA, including the pulmonary veins and the LA appendage, was obtained using a circular mapping catheter (Lasso®, Biosense Webster, Natick, Massachusetts, USA) and a navigation system (NavX™, St. Jude Medical, St. Paul, Minnesota, USA). Circumferential ablation lesions were created with an irrigated tip catheter (Thermocool®, Biosense Webster, Natick, Massachusetts, USA), widely encircling right and left pulmonary veins as ipsilateral pairs at their antrum, as demonstrated in Figure 2. Radiofrequency energy was delivered continuously with repositioning of the catheter tip every 20 to 30 seconds with a maximum electrode temperature of 43° Celsius and a maximum power of 35 Watt. The endpoint of the ablation procedure was electrical isolation of all pulmonary veins, as determined with a single circular mapping catheter.

After the ablation procedure, anticoagulation was restarted and patients received additional fragmin until a therapeutic INR was achieved. AAD were resumed on the second day after PVAI and subsequently patients were discharged.

Follow-up

All patients were seen at the outpatient clinic for follow-up at 1, 3, 6, 12, and 24 months following the ablation procedure. Follow-up data were also obtained by direct telephone

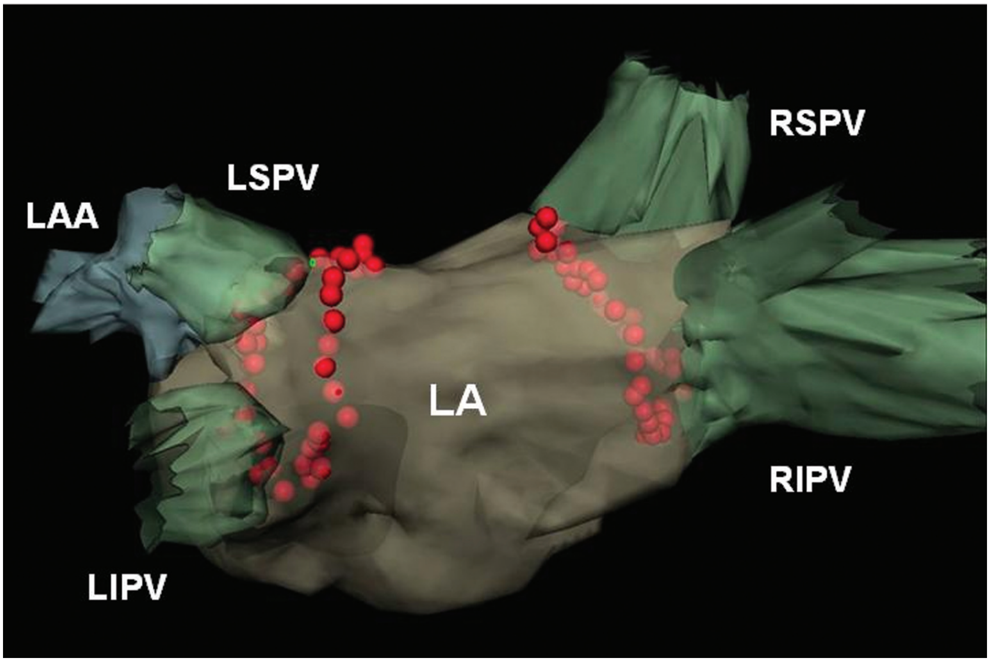

Figure 2. Pulmonary vein antrum isolation. Posterior view of the three-dimensional reconstruction of the left atrium, the red dots indicate the ablation lesions encircling right and left pulmonary veins in pairs. LA = left atrium, LAA = left atrial appendage, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, RIPV = right inferior pulmonary vein, RSPV = right superior pulmonary vein.

interview of patients. At each visit at the outpatient clinic the patient's rhythm status was determined using patient's history and ECG. At 3 months and 6 months, additional 48 hours Holter monitoring was performed. If the patient was free of recurrences of AF, AAD were discontinued at 3 months and anticoagulation was discontinued at 6 months after catheter ablation. Approximately 4 months following PVAI a second MRI scan using the same pre-ablation protocol was obtained to evaluate LA anatomy and possible pulmonary vein stenosis.
Because early recurrences of AF after catheter ablation may be transient, a blanking period of 3 months after the ablation procedure was applied [12]. A successful outcome of catheter ablation was therefore defined as freedom of AF, with or without AAD, after the blanking period.

Statistical Methods

Statistical analysis was performed using SPSS 16.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation, counts or percentages, as appropriate. Univariate analysis was performed to identify variables that may influence LA volume change after ablation. Continuous variables were compared with either a Student's t-test or a paired t-test. A chi square test was used to compare discrete variables. Intra- and interobserver variability were determined by calculating the mean difference between the first and the second measurement. A p-value below 0.05 was considered statistically significant.

Results

Baseline patient characteristics

The study population comprised 79 consecutive patients with symptomatic, drug refractory AF who underwent PVAI and who met the enrollment criteria for this study. The baseline patient characteristics are shown in Table 1. Most patients were male (n=60, 76%) and mean age was 56 ±8 years. Paroxysmal AF was present in 70% of patients, the remaining 30% had either persistent (25%) or permanent AF (5%). Structural heart disease was seen in a minority of the study population (n=7, 9%). Mean left atrial diameter, measured by echocardiography in the parasternal long-axis, was 43 ±6 mm.

Table Patient characteristics

N	79
Age (years)	56 ±8
Male	60 (76%)
Type of atrial fibrillation	
Paroxysmal	55 (70%)
Persistent	20 (25%)
Permanent	4 (5%)
Duration of AF (years)	8 ±6
Previous AAD	2.7 ±1.1
Hypertension	23 (29%)
Structural heart disease	
Hypertrophic cardiomyopathy	0
Dilated cardiomyopathy	0
Ischemic heart disease	6 (8%)
Valvular heart disease	1 (1%)
Echocardiographic left atrial diameter (mm)	43 ±6

Values are given as mean ± standard deviation or number (percent). AAD = antiarrhythmic drugs, AF = atrial fibrillation.

7

Clinical outcome

The ablation procedure was initially successful in all patients with complete electrical isolation of all pulmonary veins. The mean follow-up duration was 12 ±5 months. Nine patients (11%) underwent a repeat ablation procedure due to recurrences of AF. At the end of the follow-up period a successful outcome was achieved in 62 patients (78%), AAD could be discontinued in 57 patients (72%). According to our definition catheter ablation failed in 17 patients (22%). Success rates were similar in patients with paroxysmal AF and patients with persistent or permanent AF; 78% and 79% of patients were free of recurrences of AF, respectively.

A small number of complications took place within the study population. During one procedure a coronary air embolus with transient complaints occurred just after transseptal puncture. Moderate pulmonary vein stenosis, defined as a diameter reduction between 50 and 70%, was observed in 3 patients but was clinically asymptomatic in all [13].

Left atrial volume

Mean baseline LA volume in the total study population was 104 ±27 ml (range 50 - 188 ml). Patients with paroxysmal AF had a significantly smaller LA volume at baseline than patients with persistent or permanent AF, 97 ±22 ml versus 121 ±32 ml (p<0.001). Baseline LA volume was similar between patients with a successful outcome and patients with recurrences of AF (103 ±27 ml versus 105 ±29 ml, p=0.75).

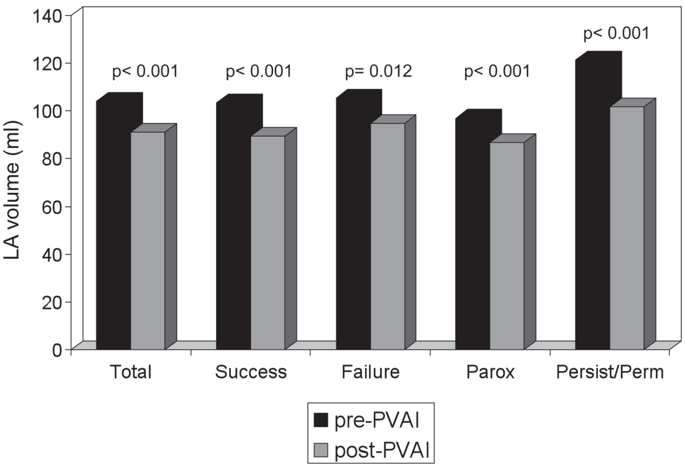

Figure 3. Pulmonary vein antrum isolation. Posterior view of the three-dimensional reconstruction of the left atrium, the red dots indicate the ablation lesions encircling right and left pulmonary veins in pairs. LA = left atrium, LAA = left atrial appendage, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, RIPV = right inferior pulmonary vein, RSPV = right superior pulmonary vein.

Mean LA volumes before and after PVAI (the first procedure in case repeat procedures were performed) in the total study population and in subgroups are shown in Figure 3. LA volume in the total study population decreased from 104 ±27 ml (range 50 – 188 ml) pre-ablation to 91 ±25 ml (range 49 – 162 ml) post-ablation, $p<0.001$. Patients with a successful outcome (N=62) showed a decrease in LA volume of 103 ±27 ml to 89 ±24 ml, $p<0.001$. Among patients with AF recurrences (N=17), LA volume decreased from 105 ±29 ml to 95 ±27 ml, p=0.012. The percentage change in LA volume in the group of patients with AF recurrences was not significantly different compared to the group with a successful outcome, p=0.27.
Both patients with paroxysmal AF and patients with persistent or permanent AF showed a significant reduction of LA volumes after PVAI. Comparison of the change in LA volume in both subgroups revealed again no significant difference, p=0.21.
In addition, change in LA volume after PVAI was not related to gender, age, duration of AF prior to catheter ablation, or the presence of hypertension or structural heart disease (p values ranging from 0.12 to 0.94).
Intraobserver and interobserver variability were calculated. For the intraobserver variability, mean difference between first and second assessments was 2 ±1.5 ml, for the interobserver variability, mean difference between assessments was 6 ±4.7 ml.

Discussion

The aim of the present study was to evaluate the impact of PVAI on LA volume using MRI images. In the total study population, PVAI led to a significant reduction of LA volume. Patients with a successful outcome and patients with AF recurrences showed a similar decrease in LA volume. In addition, both patients with paroxysmal AF and with persistent or permanent AF showed a decrease in LA volume following catheter ablation.
Various mechanisms can lead to a reduction of LA size following radiofrequency catheter ablation. Reverse remodeling due to a decreased AF burden and shrinking due to ablation induced fibrosis are the most likely causes [2-7,14].
Previous publications have found a reduction in LA size only in patients with a successful outcome [2-4,14]. These findings favor the theory that LA shrinking is caused by reverse remodeling due to elimination of the arrhythmia. Several factors can be suggested which may explain these conflicting results. The findings can be influenced by differences in imaging modalities and methods to determine LA size. We used MRI and the multiple slice method, which is an accurate method to determine LA volume, while Beukema and colleagues used the echocardiographic LA diameter in the

parasternal long-axis which has shown to be a rather inaccurate representative of actual LA size [2,15]. Even so, in the studies performed by Marsan et al. and Tops et al. LA size was also assessed by echocardiography and Tops and colleagues used a less accurate biplane method to estimate LA size [4,14]. Furthermore, differences in ablation techniques and follow-up strategies may be responsible for the discrepancies. For example, Lemola et al. as well as Perea et al. performed extensive LA ablation, including PVAI and additional linear ablation [3,16].

Other studies have reported a reduction of LA size in the total study population, consistent with our findings [5-7,17]. These studies support the hypothesis that the observed decrease in LA size may also be caused by fibrosis induced by the ablation procedure. Catheter ablation induced fibrosis in the LA has already been identified by Peters and colleagues, who were able to depict LA fibrosis with delayed enhancement MRI after PVAI [18]. Additional evidence for this hypothesis is provided by a study with canine histological specimens. This study showed that the creation of ablation lesions in the LA of dogs with and without AF resulted in a significant reduction of LA size in all dogs [19].

Another explanation for the observed reduction in LA size after catheter ablation may be an undetected decrease in AF burden in the recurrent AF group despite arrhythmia recurrence, thereby leading to reverse atrial remodeling.

Consequently, multiple factors can influence LA size after radiofrequency catheter ablation of AF. Since our study revealed a decrease in LA size in the whole study population, we think that, in addition to reverse remodeling, ablation induced fibrosis may play a role. Nevertheless, further research is required to confirm this theory.

Limitations

The present study had a few limitations. The MRA images included in the present study represented a mean of the cardiac cycle in each patient, regardless of the patients heart rhythm. Therefore, no diastolic or systolic volumes can be measured in patients with sinus rhythm during scanning and no influence of the cardiac rhythm during scanning on LA volume can be assessed. It is well known that the success rate of catheter ablation of AF is dependent on the screening protocol for AF recurrences. Asymptomatic AF recurrences, which were not recorded with ECG or 48 hours Holter monitoring, may be missed and patients could mistakenly be assumed to be free of AF. AF burden is therefore also difficult to determine. Longer periods of observation of the cardiac rhythm may be needed to determine outcome or true AF burden more accurately.

Furthermore, the small sample size of patients with AF recurrences may have limited the power of our results. An additional limitation of this study is that the post-ablation MRI was obtained after approximately 4 months, while the success of catheter ablation was determined after a mean follow-up of 12 months. To detect the influence of reverse remodeling due to reduced AF burden, it would be more accurate to perform additional MRI, for example at 12 months. However, Rodrigues and colleagues performed echocardiography 24 hours after ablation and at a mean of 8 months after ablation to measure LA volume[20]. They report that they did not see a change in LA volume 8 months after ablation compared to 24 hours after ablation. Therefore, it is not known yet whether several post-ablation MRI scans may change our statements noted above.

Conclusion

PVAI in patients with AF resulted in a significant decrease of LA volume. There was no relation between the decrease in LA volume and the recurrence of AF after PVAI. We hypothesize that, in addition to reverse remodeling, this decrease in LA volume may be caused by ablation induced fibrosis. However, further research is needed to confirm this hypothesis.

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Chapter 8

Impact of pulmonary vein antrum isolation on left atrial size and function in patients with atrial fibrillation

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Submitted.

Abstract

Aim

Although the success of pulmonary vein antrum isolation (PVAI) in eliminating atrial fibrillation (AF) has been proven, its impact on the left atrium (LA) remains uncertain. This study aimed to determine the impact of PVAI on LA size and function in patients with AF.

Methods

Consecutive patients with AF were included (n=206). Magnetic resonance imaging (MRI) was performed before and after PVAI in all patients. A subgroup (n=52) underwent delayed enhancement MRI. Maximal LA volume (LAVmax) and minimal LA volume (LAVmin) were assessed by Simpson's rule. LA function was determined by calculating LA ejection fraction (LA EF). LA fibrosis was manually encircled and summed in the region of interest.

Results

Single procedure success rate was 64%. LAVmax decreased post-ablation in all patients (125.1ml to 111.9ml, p<0.001). LAVmin only decreased in patients with a successful outcome post-ablation (65.6ml to 58.8ml, p<0.001). As a result, LA EF only showed a marked reduction in patients with AF recurrences (42.7% to 37.9%, p<0.001).

Post-ablation LA fibrosis could be visualized in 77% of patients who underwent delayed enhancement MRI (mean amount 1.4cm^3). LA fibrosis showed no correlation with the decrease in LAVmax or LA EF.

Conclusion

PVAI resulted in a reduction of LAVmax in all patients, indicating an effect of ablation induced fibrosis. LAVmin only decreased in patients with a successful outcome, indicating an effect of reverse atrial remodeling. As a result, LA function post-ablation was preserved in patients with a successful outcome and decreased in patients with AF recurrence.

Introduction

Catheter ablation as a treatment for atrial fibrillation (AF) is being performed more and more worldwide [1]. It may include pulmonary vein isolation only or it may involve extensive additional ablation in the left atrium (LA). Although the success of catheter ablation in eliminating AF has been proven in many studies [2-6], the impact it has on the LA remains uncertain. Pulmonary vein antrum isolation (PVAI) is the most frequently applied ablation technique and includes elimination of the trigger as well as modification of a part of the substrate of AF 1. Its success has been reported to be 70% or more [2], but since it involves a wide antrum ablation, it may have an impact on LA size and function. Several studies that have examined LA size and function after catheter ablation of AF report contradictory results [7, 8]. These studies are difficult to compare as they use different ablation techniques and also different imaging techniques and methods to assess LA size and function. Additionally, there is a great variation in timing of post-ablation assessment of LA size and function within these studies.
In the present study, we measured LA volume and function before and after PVAI in a large cohort of patients with AF. We used magnetic resonance imaging (MRI) and Simpson's rule in order to get the most accurate representative of true LA size. Additionally, in a subset of the study population, we performed delayed enhancement MRI (DE-MRI) to visualize ablation induced LA fibrosis before and after catheter ablation. With all these measurements, we aimed to determine the impact of PVAI on LA size and function in patients with AF.

Methods

Study population

Consecutive patients undergoing PVAI in our center between June 2007 and June 2011 were thought eligible for this prospective study. These patients had to fulfill the following inclusion criteria. They had to have symptomatic, drug refractory AF. A cardiac cine MRI had to be performed, including short axis images covering the complete LA, prior to and approximately 5 months following the ablation procedure. And finally, a minimum follow-up duration of 3 months had to be available in order to determine the clinical outcome of the ablation procedure. A random subset of these patients were selected to undergo an extended MRI with delayed enhancement imaging before and after catheter ablation. These patients provided informed consent according to a study protocol approved by the medical ethical committee of the University Medical Center Utrecht.

Magnetic resonance imaging

Patients underwent gadolinium-enhanced MRI scanning using a 1.5 Tesla MRI system (Philips Healthcare, Best, the Netherlands), as previously described, prior to and approximately 5 months after catheter ablation [9]. Imaging was performed with the patient in supine position and with ECG gating. A dedicated cardiac coil was used for signal reception.

First, a single slice steady-state free-precession cine MRI was performed in two-chamber and four-chamber orientations. Additionally, a breath-hold steady-state free-precession cine MRI was performed to cover the entire LA in the short axis view with on average 10-12 slices. Retrograde ECG gating was used to achieve 50 phases per R-R interval for the four-chamber and two-chamber views and 35 phases per R-R interval for the short axis view. Scan parameters were: TR = 3.1 ms, TE = 1.5 ms, flip angle 55°, Field-Of-View 350 x 277 mm, matrix size 192 x 150, slice thickness 8 mm, and gap + slice 8 mm.

Gadolinium (Gadovist®, Bayer Schering Pharma, Berlin, Germany) was administered intravenously at a dose of 0.2 ml/kg and with an infusion rate of 1.5 ml/s. Magnetic resonance angiography (MRA) was obtained with single breath-hold three-dimensional fast spoiled gradient-echo imaging in coronal view. MRA acquisition was manually started after visualizing the contrast bolus in the left ventricle and giving a breath-hold command. Scan parameters were: TR = 4 ms, TE = 1 ms, flip angle 35°, Field-Of-View 400 mm, matrix size 272 x 173, slice thickness 3 mm, interpolated to 1.5 mm.

Approximately 20 minutes after gadolinium injection, additional DE-MRI of the LA was acquired in a subgroup of patients. A three-dimensional phase-sensitive inversion recovery gradient echo sequence was performed with ECG-gating and respiratory compensation using navigator gating. Scan parameter were: TR = 6.4 ms, TE = 3.1 ms, flip angle 25°, Field-Of-View 350 mm, matrix size 256 x 196, slice thickness 1.5 mm.

Left atrial volume and function assessment

LA volume and function were assessed offline using commercial software (ViewForum, Philips Healthcare, Best, the Netherlands) [9]. LA volume and function were assessed before and after the first ablation procedure in case repeat ablation procedures were performed. These measurements were performed by a single investigator in a blinded fashion. Intraobserver variability was determined by performing at random selected reassessments. A second investigator performed at random measurements to determine interobserver variability.

The multiple short axis cine images covering the total LA were used for volume assessment. First, the following phases of the cardiac cycle were selected for LA

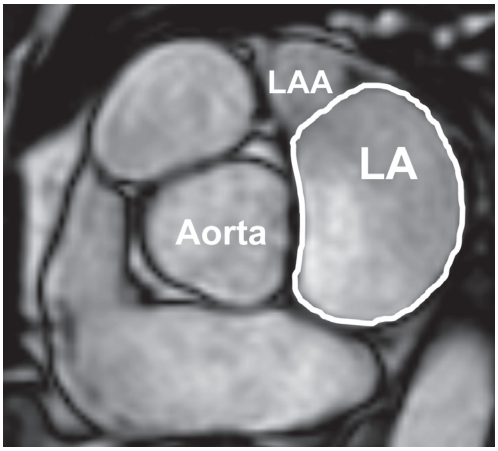

Figure 1. Illustration of the Simpson's rule in short axis view of the left atrium. The white line demonstrates the manual tracing of left atrial area, during the atrial end-diastolic phase, excluding the left atrial appendage. LA = left atrium, LAA = left atrial appendage.

volume measurement in patients with sinus rhythm during scanning: 1. The phase representing the atrial end-diastole, just before mitral valve opening, was selected for measurement of maximal LA volume (LAVmax) [10]. 2. The phase representing mid-diastole, just before atrial contraction, was chosen for measurement of mid LA volume (LAVmid). 3. The phase representing the atrial end-systole, at mitral valve closure, was selected for measurement of minimal LA volume (LAVmin) [10]. In patients with AF during scanning, only LAVmax was measured.

LA volume was measured by applying the Simpson's rule and manually encircling LA area on each image of the selected phase (Figure 1). This method is closely related to true LA size as has been shown by post mortal assessment [11, 12]. The left ventricle was excluded at the level of insertion of the mitral valve leaflets, the LA appendage was excluded at its base, and the pulmonary veins were excluded at their ostia [13]. LA volume was then automatically calculated from all the included slices.
Subsequently, LA function was derived from the LA volumes mentioned above in patients with sinus rhythm during scanning. LA ejection fraction (LA EF) was calculated with the following formula: LA EF = (LAVmax-LAVmin)/LAVmax. In addition, passive LA emptying fraction, which is considered an index of LA conduit function, was calculated as follows: LA passive EF = (LAVmax-LAVmid)/LAVmax. The active LA emptying fraction, which is considered an index of LA active contraction, was assessed with the formula: LA active EF = (LAVmid-LAVmin)/LAVmid.

Measurement of left atrial fibrosis

The delayed enhancement images of the LA were used for LA fibrosis assessment on commercially available software (ViewForum, Philips Healthcare, Best, the

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Netherlands). The measurements were performed by a radiologist with substantial experience in evaluating delayed enhancement images (EV). The main focus was the regions of interest where ablation lesions could be expected (Figure 2, panel A). These regions included the pulmonary venous ostia and the surrounding atrial tissue. Signal originating from (ablation induced) fibrosis was visually differentiated from healthy myocardium and blood by comparing the signal intensity with the signal intensity of the heart valves. Subsequently, areas with fibrosis in the region of interest were manually encircled on each delayed enhancement slice (Figure 2, panel B). Thereafter, the total fibrosis volume in the LA was summed automatically from all included slices.

Pulmonary vein antrum isolation

PVAI was performed in all patients as previously described [14]. Anti-arrhythmic medication was discontinued at least five half-lives prior to the ablation procedure. A transesophageal echocardiogram was obtained 1 to 4 days prior to catheter ablation to exclude the presence of a LA thrombus. Patients received oral anticoagulation to obtain an international normalized ratio (INR) above 2 for at least one month prior to the procedure. Anticoagulation was stopped one day before PVAI to attain an INR of approximately 2.

The ablation procedure was performed in a fasting state with conscious sedation using boluses of fentanyl. Venous access was obtained via the right and left femoral veins under local anesthesia. Diagnostic catheters were introduced and positioned

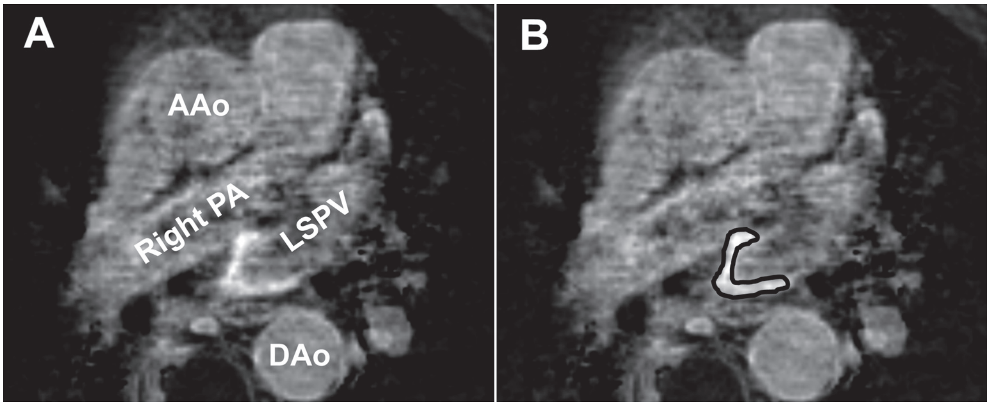

Figure 2. Delayed enhancement magnetic resonance imaging of the left atrium, in axial view, in a patient after pulmonary vein antrum isolation. A: an area of hyperenhancement is seen around the ostium of the left superior pulmonary vein. B: the area of hyperenhancement is manually encircled in order to calculate the amount of left atrial fibrosis. AAo= ascending aorta, DAo = descending aorta, LSPV = left superior pulmonary vein, Right PA = right pulmonary artery.

in the coronary sinus and the right ventricle, a screw catheter was placed in the right atrial septum as a reference for non-fluoroscopic catheter navigation. A transseptal puncture was performed to gain access to the LA. After transseptal access, an initial intravenous bolus of 5,000 IU heparin was administered, followed by repeated doses of heparin to maintain an activated clotting time above 250 seconds. A three-dimensional reconstruction of the LA, including the pulmonary veins and the LA appendage, was obtained using a circular mapping catheter (Lasso®, Biosense Webster, Diamond Bar, California, USA) and a navigation system (NavX™, St. Jude Medical, St. Paul, Minnesota, USA). Circumferential ablation lesions were created with an irrigated ablation catheter (Thermocool®, Biosense Webster, Diamond Bar, California, USA), widely encircling right and left pulmonary veins as ipsilateral pairs at their antrum. Saline irrigation was applied during ablation at a rate of 17 ml/min. Radiofrequency energy was delivered continuously with repositioning of the catheter tip every 20 to 30 seconds with a maximum electrode temperature of 43° Celsius and a maximum power of 40 Watt and 30 Watt to the anterior and posterior left atrium, respectively. The endpoint of the PVAI was electrical isolation of all pulmonary veins, as determined by using the circular mapping catheter.

In patients with additional documented right sided atrial flutter, cavotricuspid isthmus ablation was performed with a maximum electrode temperature of 43° Celsius and a maximum power of 40 Watt using the irrigated tip catheter. The endpoint was bidirectional isthmusblock confirmed by using a multipolar catheter (HALO XP®, Biosense Webster, Diamond Bar, California, USA).

In patients who underwent a second ablation procedure, re-isolation of the pulmonary veins could be supplemented with linear ablation across the roof of the LA or the mitral isthmus, and/or ablation of complex fractionated atrial electrograms.

After the ablation procedure, oral anticoagulation was restarted and patients received additional dalteparin until a therapeutic INR was achieved. Anti-arrhythmic medication was resumed on the second day after PVAI and subsequently patients were discharged.

Follow-up

Patients were seen at the outpatient clinic at 1, 3, 6, 12, and 24 months after the ablation procedure. Follow-up data were also obtained by direct telephone interview. Because early recurrences of AF after catheter ablation may be transient, a blanking period of 3 months after the ablation procedure was applied [15]. A successful outcome of catheter ablation was therefore defined as freedom of AF, with or without anti-arrhythmic medication, after the first 3 months. At each visit the patient's rhythm status was evaluated using patient's history and ECG recording. At 3 and 6 months, additional

48 hours Holter monitoring was performed. If the patient was free of AF recurrences, anti-arrhythmic medication was discontinued at 3 months and oral anticoagulation was discontinued at 6 months after catheter ablation. Approximately 5 months after PVAI a second MRI scan was obtained to evaluate LA anatomy, possible pulmonary vein stenosis, and fibrosis in the subgroup undergoing additional DE-MRI.

Statistical methods

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation, counts or percentages, as appropriate. Continuous variables were compared with either a independent samples T Test or a paired samples T Test. A Pearson correlation coefficient (r) was calculated to determine the correlation of the amount of LA fibrosis and possible changes in LA volume and function observed after ablation. Intra- and interobserver variability were determined by calculating the mean difference between first and second assessment and by calculating the intraclass correlation. A p-value below 0.05 was considered statistically significant.

Results

Baseline patient characteristics

The study population included 206 consecutive patients with AF who underwent PVAI and met the inclusion criteria. The baseline characteristics of these patients are described in Table 1. Of these patients, 52 patients gave informed consent to undergo DE-MRI before and after catheter ablation. Eighty percent of patients were male and mean age was 57 ±10 years. More than half of the patients had paroxysmal AF (55%), the remaining patients had either persistent (25%) or longstanding persistent AF (19%). Hypertension was present in 35% of the study population. Mean LA diameter at baseline, measured by echocardiography in the parasternal long-axis, was 44 ±6 mm.

Clinical outcome

PVAI was initially successful in all but one patient. In this patient the left sided pulmonary veins were not completely electrically isolated at the end of the procedure. In 46 patients, cavotricuspid isthmus ablation was performed in addition to PVAI. The mean procedure time was 259 ±69 minutes and mean total fluoroscopy time was 41 ±17 minutes. Four major complications occurred during PVAI within this study population, which involved cardiac tamponade requiring pericardiocentesis in all cases. Mean follow-up duration was 16 ±9 months. A successful outcome after a single ablation procedure was achieved in 131 patients (64%) of which 15 patients (7%) still used anti-arrhythmic medication. Fifty-four patients (26%) underwent a second ablation procedure due to AF recurrences, and 3 of these patients (1.5%) underwent a third procedure. At the end of the follow-up period, a successful outcome after multiple procedures was reached in 169 patients (82%), with 27 patients (13%) still on anti-arrhythmic drugs.

Left atrial volume

Of the 206 patients, 127 patients had sinus rhythm during both cardiac MRIs performed before and after catheter ablation. Mean LAVmax at baseline in the total study population was 125.1 ±32.9 ml with a range of 64.7 ml to 246.0 ml. Mean LAVmax in the total group decreased after PVAI from 125.1 ±32.9 ml to 111.9 ±31.1 ml, $p<0.001$. Patients with a successful outcome showed a decrease in LAVmax from 122.2 ±29.2 ml to 107.5 ±28.3 ml post-ablation, $p<0.001$ (Table 2 and Figure 3). In patients with AF recurrences after ablation, LAVmax decreased from 130.3 ±38.3 ml to 119.5 ±34.3 ml, $p<0.001$. When comparing the percentage of LAVmax reduction between both groups, patients with a successful outcome had a slightly larger decrease in LAVmax compared to patients with AF recurrences post-ablation, 11% decrease versus 7%

Table 1 Baseline patient characteristics

N	206
Male	165 (80%)
Age (years)	57 ±10
Body mass index	27 ±4
Type of atrial fibrillation	
Paroxysmal	114 (55%)
Persistent	52 (25%)
Longstanding persistent	40 (19%)
Duration of atrial fibrillation (years)	7 ±6
Hypertension	72 (35%)
Structural heart disease	
Hypertrophic cardiomyopathy	2 (1%)
Dilated cardiomyopathy	1 (0.5%)
Ischemic heart disease	20 (10%)
Valvular heart disease	6 (3%)
Echocardiographic left atrial diameter (mm)	44 ±6

Values are given as mean ± standard deviation or number (percent).

decrease respectively, p=0.03. In patients with sinus rhythm during both MRI scans (n=127), mean LAVmin decreased from 67.9 ±25.0 ml to 62.5 ±22.7 ml post-ablation, p<0.001. Subgroup analysis revealed that patients with a successful outcome showed a significant reduction in LAVmin (65.6 ±21.8 ml to 58.8 ±20.0 ml, p<0.001), and patients with AF recurrences after PVAI showed no change in LAVmin (72.0 ±29.7 ml to 69.4 ±25.7 ml, p=0.25), as shown in Table 2 and Figure 4.
Intraobserver and interobserver variability were calculated. For the intraobserver variability, mean difference between first and second assessments was 2.9 ±2.4 ml, and intraclass correlation was 0.995 (p<0.001). For the interobserver variability, mean difference between assessments of both investigators was 6.1 ±4.8 ml, and intraclass correlation was 0.968 (p<0.001).

Left atrial function

LA function could be evaluated in all patients with sinus rhythm during both MRI scans (n=127). Mean LA EF in these patients showed a small decrease from 43.8 ±9.3% to 41.2 ±9.6% after catheter ablation, p<0.001. Mean LA passive EF decreased from 22.0 ±7.4% to 21.2 ±7.4% (p=0.18), and mean LA active EF decreased from 27.9 ±9.5% to 25.4 ±9.5% (p=0.007). Subgroup analysis according to clinical outcome revealed the following results (Figure 5 and 6). Patients with a successful outcome showed a borderline significant reduction in LA EF following PVAI: 44.4 ±9.2% to 43.1 ±9.3%, p=0.04. Within these successful cases, LA passive EF and LA active EF showed no change after catheter ablation, as shown in Table 2.

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Table 2 Left atrial volume and function before and after catheter ablation in patients with a successful outcome and patients with recurrences of atrial fibrillation after catheter ablation.

	Successful outcome			AF recurrence		
	Pre	**Post**	**p-value**	**Pre**	**Post**	**p-value**
LAVmax (ml) n=206	122.2 ±29.2	107.5 ±28.3	**<0.001**	130.3 ±38.3	119.5 ±34.3	**<0.001**
LAVmin (ml) n=127	65.6 ±21.8	58.8 ±20.0	**<0.001**	72.0 ±29.7	69.4 ±25.7	0.25
LA EF (%) n=127	44.4 ±9.2	43.1 ±9.3	**0.04**	42.7 ±9.6	37.9 ±9.4	**<0.001**
LA passive EF (%) n=127	22.4 ±7.9	21.7 ±8.2	0.38	21.3 ±6.6	20.3 ±5.7	0.28
LA active EF (%) n=127	28.3 ±9.3	27.2 ±8.9	0.30	27.3 ±10.0	22.1 ±10.1	**0.003**

AF = atrial fibrillation, LA active = active left atrial emptying fraction, LA EF = left atrial ejection fraction, LA passive = passive left atrial emptying fraction, LAVmax = maximal left atrial volume, LAVmin = minimal left atrial volume

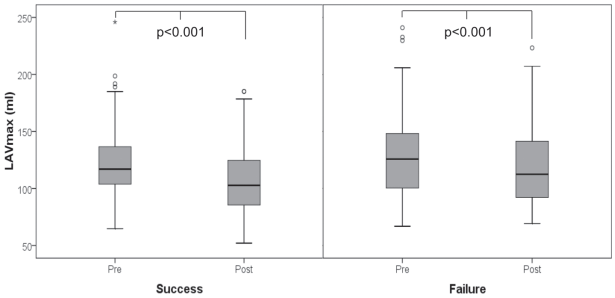

Figure 3. Change in maximal left atrial volume in patients with a successful outcome and patients with recurrences of atrial fibrillation post-ablation. LAVmax = maximal left atrial volume.

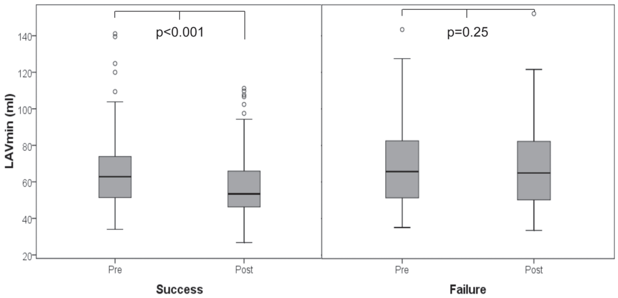

Figure 4. Change in minimal left atrial volume in patients with a successful outcome and patients with recurrences of atrial fibrillation post-ablation. LAVmin = minimal left atrial volume.

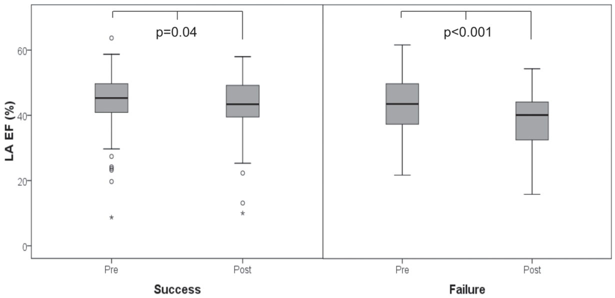

Figure 5. Change in left atrial ejection fraction in patients with a successful outcome and patients with recurrences of atrial fibrillation post-ablation. LA EF = left atrial ejection fraction.

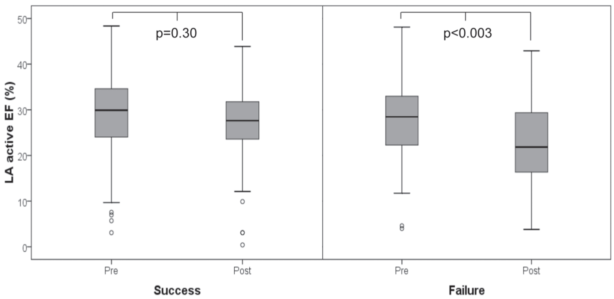

Figure 6. Change in active left atrial emptying fraction in patients with a successful outcome and patients with recurrences of atrial fibrillation post-ablation. LA active EF = active left atrial emptying fraction.

In patients with AF recurrences after PVAI, LA EF decreased from 42.7 ±9.6% to 37.9 ±9.4%, p<0.001. Within these patients, LA passive EF showed no change after ablation and LA active EF showed a significant reduction, as demonstrated in Table 2.

Left atrial fibrosis

Fifty-two patients underwent DE-MRI before and after catheter ablation. None of these patients had detectable LA fibrosis in the regions of interest (pulmonary venous ostia and surrounding atrial tissue) prior to catheter ablation. After catheter ablation, LA fibrosis could be visualized in 40 patients (77%). In the remaining patients (n=12, 23%), LA fibrosis could not be measured, due to incorrect timing of the DE-MRI (in 10 scans) or incomplete imaging of the LA (in 2 scans).

The mean amount of ablation induced LA fibrosis after catheter ablation was 1.4 ±0.9 cm3 with a range of 0.1 to 4.2 cm3. There was no correlation between the decrease in LAVmax and the amount of ablation induced LA fibrosis (r=-0.04, p=0.831). The correlation between LA EF and the amount of LA fibrosis could be calculated in 23 patients (patients with sinus rhythm during both MRI scans and accurate delayed enhancement images). No relation was found between the decrease in LA EF and the amount of ablation induced LA fibrosis (r=-0.10, p=0.663).

Discussion

8

The aim of the present study was to determine the impact of PVAI on LA size and function in patients with AF. Our results revealed a significant reduction of LAVmax post-ablation in the total study population. In contrast, LAVmin only decreased in patients with a successful outcome post-ablation. As a consequence, LA EF showed a slight and clinically irrelevant reduction in patients with a successful outcome and a clearly significant reduction in patients with AF recurrences after PVAI. The decrease in LA EF within these patients was the result of a decrease in LA active EF. Furthermore, ablation induced LA fibrosis could be visualized in 77% of patients who underwent DE-MRI. The observed changes in LAVmax and LA EF did not correlate with the amount of ablation induced LA fibrosis.

Two main factors may be responsible for changes in LA size and function following catheter ablation of AF: remodeling, either by ongoing AF or reverse remodeling by restoration of sinus rhythm; and ablation induced LA fibrosis. The literature concerning this subject reports conflicting results, making it impossible to draw conclusions [7, 8]. Some studies support the hypothesis that the observed changes in LA hemodynamic

parameters after ablation are due to remodeling. They report a decrease in LAVmax only in patients with a successful outcome and/or a decrease in LA EF in patients with AF recurrences post-ablation [16-21]. In contrast, other studies support the hypothesis that the LA is mainly influenced by ablation induced fibrosis with a reduction of LAVmax and/or a reduction of LA EF in the total study population [14, 22-27].
The discrepancies between these studies can be explained by the methodological differences, including different imaging techniques and different methods to assess LA size and function. Several studies used the LA diameter, assessed with echocardiography in the parasternal long axis, to measure LA size, which has shown to be an inaccurate representative of LA size and LA enlargement [20, 28, 29]. Other studies used a biplane method with either echocardiography, CT or MRI, which has shown to underestimate true LA size [26, 30, 31]. In addition, different ablation techniques were used, varying from segmental pulmonary vein isolation to PVAI with additional LA ablation [25, 27, 32]. Therefore, we performed a homogenous study with a large study population in which LA size and function were assessed with the most accurate method (Simpson's rule with MRI) and in which only PVAI was performed as ablation technique during the first procedure.

Our results suggest that reverse remodeling as well as ablation induced fibrosis affect LA size and function after catheter ablation of AF. With regard to LA size, a significant decrease in LAVmax after catheter ablation was observed in the total study population, both in patients with a successful outcome and in patients with AF recurrences. This implies that ablation induced fibrosis causes LA shrinking, since LAVmax also declines in patients with AF recurrences. A decrease in AF burden may also be partly responsible, but since we could not accurately assess the AF burden pre- and post-ablation, this remains inconclusive. Furthermore, the percentage of LAVmax reduction was slightly larger in patients with a successful outcome, which may indicate that reverse remodeling plays an additional role in the reduction of LA size post-ablation.
Interestingly, LAVmin only decreased in patients with a successful outcome post-ablation and showed no change in patients with AF recurrences. This suggests that the reduction in minimal LA size could be the result of reverse remodeling, since it only occurred in patients who maintained a stable sinus rhythm after ablation.
LA function can be divided into two phases [10, 33]. During the first phase the LA functions as a conduit for passive blood transfer to the left ventricle. Thereafter, during the second phase LA contraction occurs. In the present study, LA EF (which contains both phases) showed a slight and clinically irrelevant decrease in patients with a successful outcome. When dividing the LA EF into the LA passive EF (index of LA

conduit function) and the LA active EF (index of LA contraction), no change of these parameters was observed post-ablation in patients with a successful outcome. Regarding the subgroup of patients with AF recurrences post-ablation, LA EF significantly decreased after PVAI. Looking closely at both phases of the LA EF, LA passive EF showed no change whereas LA active EF significantly decreased after ablation within these patients. This decrease in LA contraction can be explained by a decrease in LAVmax observed in patients with AF recurrence, most likely due to ablation induced fibrosis, while LAVmin does not change, due to the absence of reverse remodeling.

Consequently, these data imply that both ablation induced fibrosis and reverse remodeling have impact on LA size and function after catheter ablation of AF. A decrease in LAVmax as observed in the total study population independent of outcome suggests ablation induced fibrosis as underlying substrate, while a decrease of LAVmin only in patients with a successful outcome implies reverse remodeling in this group. Therefore, reduction in LA EF is observed only in patients with AF recurrences because ablation induced fibrosis reduces LAVmax, while LAVmin remains unchanged due to lack of reverse remodeling post-ablation.

In a subpopulation, we performed DE-MRI of the LA with the aim to depict ablation induced fibrosis. We were able to visualize ablation induced LA fibrosis in 77% of patients who underwent DE-MRI. The presence of LA fibrosis in the areas of interest after catheter ablation suggests that ablation induced fibrosis may affect the LA. However, no correlation was found between the amount of LA fibrosis and the changes in LAVmax and LA EF. The lack of correlation could be explained by the method that was used for LA fibrosis quantification, which may have been less accurate and not sensitive enough. In addition, the subgroups of patients that were used for this analysis were rather small (40 patients for correlation of LAVmax and LA fibrosis, 23 patients for correlation of LA EF and LA fibrosis).

Study limitations

The post-ablation MRI scan was obtained only once, at approximately 5 months following PVAI. It would be interesting to perform additional MRI, for example at 12 months following PVAI, to analyze whether further changes in LA size and function may occur.

In the patients who underwent DE-MRI, we could not assess the amount of LA fibrosis in 23% (12 scans). However, other studies have experienced similar problems and reported a loss up to 20% of their study population [34, 35].

Regarding MRI analysis, the different phases of the cardiac cycle were defined by direct visualization of mitral valve opening and closure and atrial contraction, since no ECG recording was available during offline LA volume assessments.

Assessment of LA fibrosis with DE-MRI was based on visual differentiation of fibrosis from healthy myocardium by comparing the signal intensity with the signal intensity of the enhancing valvular structures. An automatic algorithm to assess the amount of LA fibrosis may have been more accurate, however, manually selecting areas of fibrosis enabled us to exclude obvious artifacts.

An additional limitation involves our screening protocol for AF recurrences. We performed ECG recordings and 48 hour Holter monitoring several times during follow-up, however, asymptomatic episodes of AF recurrences may be missed. The evaluation of clinical outcome may therefore be partly subjective. Additionally, it is also difficult to determine the exact AF burden of a patient pre- and post-ablation. This limitation can only be avoided with continuous electrocardiographic monitoring of the patient with e.g. an implantable recorder which was regarded an unethical approach for this study.

Clinical implications

The intention of this study was to analyze the impact of PVAI on the LA in order to determine to what extent ablation induced fibrosis and remodeling may influence the LA post-ablation. Our results demonstrated that ablation induced fibrosis does affect the LA, demonstrated by the reduced LA size observed in the total study population. This effect of LA fibrosis was not notable in patients with a successful outcome, since they experienced reverse atrial remodeling and, therefore, showed a preserved LA function. In patients with AF recurrences post-ablation, however, reverse remodeling was absent and a decrease in LA function was observed after catheter ablation. These results are of clinical importance because a preserved LA function in patients with a successful ablation procedure of AF may justify the discontinuation of anticoagulation at several months post-ablation. However, in the present study only PVAI was performed and further studies are necessary to evaluate the effects of more extensive catheter ablation in the LA on LA function and thrombo-embolic risks.

Conclusion

PVAI in patients with AF resulted in a significant reduction of maximal LA size in the total study population, indicating an effect of ablation induced fibrosis. Minimal LA size only decreased in patients with a successful outcome, suggesting an effect of reverse atrial remodeling. As a result, LA function post-ablation was preserved in patients with a successful outcome and showed a decrease in patients with AF recurrences.

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Summary

Nederlandse samenvatting

Acknowledgements

Curriculum Vitae

List of publications

Introduction

Catheter ablation of atrial fibrillation (AF) has evolved as an important treatment option for patients with symptomatic, drug refractory AF. Not long after the discovery that pulmonary veins could function as triggers initiating AF, an ablation approach was developed with the aim to electrically isolate these pulmonary veins. In the last decade, this ablation technique has evolved rapidly into a technique that involves wide continuous circumferential ablation in the left atrium (LA) surrounding left and right pulmonary veins in pairs, referred to as pulmonary vein antrum isolation (PVAI). Many studies have shown that PVAI is a successful treatment, especially in patients with paroxysmal AF, and it is performed worldwide nowadays. To further improve the success rate of catheter ablation of AF, particularly in patients with longstanding persistent AF, additional ablation strategies have been developed on top of PVAI, including linear ablation in the LA and ablation of areas with complex fractionated atrial electrograms. Since the LA is the target of these ablation strategies, it is important to assess whether catheter ablation of AF may cause significant damage to the LA. This may have important clinical implications, because if, for instance, LA function is impaired post-ablation, thrombo-embolic risk may be higher than anticipated and the post-ablation anticoagulation strategy may have to be modified. Several studies have looked into this subject and have analyzed changes in LA size and function following catheter ablation of AF. However, their results are conflicting in such a manner that it is impossible to draw conclusions. Consequently, until now, it remains unclear how the LA is influenced by catheter ablation of AF. Therefore, it was the aim of this thesis to analyze this topic in a structured and homogenous manner in order to provide more clarity concerning the impact of catheter ablation of AF on LA size and function.

One of the main factors responsible for the diversity in the literature concerns different methods to measure LA size and function that are applied. Therefore, **part 1** of this thesis focused on comparing different methods to assess LA size and evaluating their accuracy in patients with AF.

Part 2 of this thesis studied the clinical implications of the LA in patients with AF undergoing catheter ablation. First, the predictive value of LA size at baseline, in patients with AF undergoing catheter ablation, regarding clinical outcome was studied. And finally, the main topic of this thesis was addressed: the impact of catheter ablation of AF on LA size and function.

Part 1

Imaging of the left atrium in patients with atrial fibrillation

In order to be able to determine the impact of catheter ablation of AF on the LA, it is important to know the accuracy of the different imaging techniques and methods used to assess LA size and function before and after catheter ablation. **Part 1**, therefore, focused on comparing several methods used to measure LA size and function.

In **chapter 2**, the widely used and easy accessible LA diameter (LAD) measured by echocardiography in the parasternal long axis was compared to LA volume assessed by the Simpson's rule with computed tomography (CT). In previous publications, LAD by echocardiography has shown to predict clinical outcome after catheter ablation of AF. As a result, many clinical centers used this parameter as a selection criterion and excluded patients with a LAD of >5.0-5.5 cm for catheter ablation of AF. However, since the LAD only measures one dimension of the LA, it may not be an accurate representative of true LA size. We measured LAD by echocardiography and LA volume by CT in 50 patients with AF and found a poor correlation (r=0.49, p<0,001), suggesting that LAD does not correspond to LA size and LA enlargement. Of particular importance was the finding that patients with a LAD >5.0 cm, who might have been excluded for catheter ablation according to selection criteria in many centers, showed a wide range in LA volume.

The method used in **chapter 2** to measure LA volume, the Simpson's rule or multiple slice method, is considered to be the gold standard for LA size assessment. It involves manual tracings of LA area on each cross-sectional image of either magnetic resonance imaging (MRI) or CT scan. This method takes into account that the LA is an asymmetrical shape and it correlates closely with post mortal LA size assessment. However, the Simpson's rule is labor intensive and time consuming making it less suitable for clinical practice. Therefore, in **chapter 3** we validated a simpler estimation method of determining LA volume. According to this alternative technique, LA volume can be rapidly estimated by measuring 3 dimensions of the LA and employing a mathematical calculation. We measured LA volume by both techniques in 100 patients with AF and reported an excellent correlation of both methods (r=0.91, p<0.001). However, the alternative technique resulted in significantly smaller LA volumes with a mean underestimation of 17%. Although this estimation technique offers a good alternative based on an excellent correlation with the gold standard, it should be born in mind that it underestimates LA volume when applying this method in clinical practice.

In **chapter 4**, a different method for LA volume assessment was analyzed and compared to the gold standard. In this chapter it concerned the single plane area length method (ALM) originating from the echocardiography. Seventy-two MRI scans of patients with AF were used to assess maximal and minimal LA volume by both the ALM and the Simpson's rule. Additionally, LA function was determined by calculating LA ejection fraction. Measured by ALM, maximal and minimal LA volumes were significantly underestimated and LA ejection fraction was overestimated. However, a good and significant correlation of both methods was found (r=0.77 for maximal LA volume, p<0.001; r=0.85 for minimal LA volume, p<0.001). Even though the ALM underestimated LA volumes, it may offer a useful alternative because it correlated closely to the gold standard and this method is much easier to obtain (assessment time for the ALM approximately 1 minute and assessment time for the Simpson's rule 10 minutes). Additionally, LA volume by the Simpson's rule cannot always be obtained due to lack of multi-slice images of the LA.

Part 2

Clinical implications of the left atrium in patients with atrial fibrillation undergoing catheter ablation

The second part of this thesis focused on the clinical role of the LA in patients undergoing catheter ablation of AF. First, **chapter 5** concentrated on LA size at baseline in patients with AF undergoing catheter ablation. Several previous studies have shown that the baseline LAD by echocardiography in the parasternal long axis predicts clinical outcome after AF ablation. However, as we have shown in **chapter 2**, the LAD by echocardiography correlates poorly to LA volume assessed by CT. Therefore, we analyzed whether LA volume predicted success of catheter ablation of AF. In addition, we determined whether specific patterns of pulmonary venous (PV) anatomy were predictive of outcome. A total of 146 patients with AF who underwent CT prior to AF ablation were analyzed. LA volume was assessed with Simpson's rule and the number and distribution of PVs were recorded for each patient. The results revealed that LA volume was an independent predictor of AF recurrences after catheter ablation with an adjusted odds ratio of 1.14 for every 10 ml increase in volume (95% CI 1.00-1.29, p=0.047). In contrast, PV anatomy did not have any effect on the outcome of catheter ablation of AF. PV variations were equally distributed among patients with AF recurrence or no AF recurrence. These findings suggest that LA volume assessment may be incorporated into the pre-procedural evaluation of patients being considered for AF ablation in order to make an assumption regarding their prognosis.

Chapter 6 focused on the LA before and after ablation and reviewed the literature on the effects of catheter ablation of AF on the LA. This review provided an overview that demonstrated the great diversity that exists within the literature. What becomes clear is that catheter ablation of AF has several effects on the LA, but based on the existing articles, it was impossible to draw conclusions to what extent the LA may be affected. The first effect involves ablation induced LA fibrosis, which can be depicted with delayed enhancement MRI. A certain amount of ablation induced fibrosis may be necessary in order to achieve a successful outcome, however, its effect on LA function is not certain. Second, catheter ablation of AF influences LA size but the literature is disagreeing in what manner, since the results of the studies addressing this topic vary considerably. Additionally, the impact of catheter ablation on LA function is still open for debate. Although not many studies reported a decrease of LA function after ablation in patients with a successful outcome, it is still unclear whether LA function may not be impaired by catheter ablation. Finally, catheter ablation of AF gives rise to post-ablation LA tachycardias. Less confusion exists in the literature regarding this topic. Extensive ablation in the LA, including PVAI with additional LA ablation, has shown to result in a higher incidence of post-ablation LA tachycardias compared to PVAI only.

In **chapter 7**, our own initial experiences regarding changes in LA size after catheter ablation of AF are reported. We decided to measure LA volume by Simpson's rule with MRI before and after ablation in order to have the most accurate representative of LA size. Seventy-nine patients with symptomatic, drug refractory AF who underwent PVAI were included for this study. When analyzing the changes in LA volume, we noticed a decrease of LA volume in the total study population from 104 ml pre-ablation to 91 ml post-ablation, $p<0.001$. Subgroup analysis revealed that both patients with a successful outcome as well as patients with AF recurrences showed a significant reduction in LA volume post-ablation. Additionally, patients with paroxysmal AF at baseline and patients with persistent or longstanding persistent AF showed a significant reduction of LA volume after PVAI.

Various mechanisms can lead to a reduction of LA size following catheter ablation. Reverse remodeling due to a decreased or absent AF burden and shrinking due to ablation induced fibrosis are the most likely causes. Since our study revealed a decrease in LA size in the whole study population, we think that, in addition to reverse remodeling, ablation induced fibrosis plays a role.

However, more evidence was needed to determine the impact of catheter ablation of AF on the LA and, therefore, we decided to perform a homogenous study with a large study population. This study is discussed in **chapter 8** and involved 206 patients with

AF in which maximal and minimal LA volume and LA function were assessed with the most accurate method (Simpson's rule with MRI), and in which only PVAI was performed as ablation technique. In addition, a small subgroup of patients (n=52) underwent delayed enhancement MRI with the purpose to visualize ablation induced fibrosis in the LA. With all these measurements, we aimed to determine the impact of PVAI on LA size and function in patients with AF.

Our results revealed a significant reduction of maximal LA volume post-ablation in all patients, consistent with the results of **chapter 7** and indicating an effect of ablation induced fibrosis. In contrast, minimal LA volume solely decreased in patients with a successful outcome post-ablation, indicating an effect of reverse atrial remodeling. As a result, LA function showed a marked reduction only in patients with AF recurrences. Furthermore, ablation induced LA fibrosis could be visualized in 77% of patients who underwent DE-MRI. These results suggested that reverse remodeling as well as ablation induced fibrosis influence LA size and function after catheter ablation of AF. Only patients with AF recurrences post-ablation experienced a negative effect of catheter ablation, demonstrated as a decrease in LA function, since they lacked reverse remodeling. This is clinically important information, since a preserved LA function in patients with a successful ablation procedure of AF may justify the discontinuation of anticoagulation at several months post-ablation. However, in this study only PVAI was performed which made us unable to evaluate the risks of more extensive catheter ablation in the LA on LA function.

Conclusions and future perspectives

The literature regarding the impact of catheter ablation of AF on the LA shows a great diversity. Several reasons that may account for this diversity include different imaging techniques and methods to assess LA size and function, and different ablation techniques are applied. Therefore, the first part of this thesis focused on comparing different methods to assess LA size and evaluating their accuracy in patients with AF. The first method, the LAD by echocardiography is a rough and imprecise measurement and although this method is still often employed in clinical centers, we advise that it should not be used for accurate LA size assessment. The Simpson's rule with either CT or MRI is considered to be the gold standard for LA size assessment, since it takes into account that the LA is an asymmetrical shape. It is the method of choice for LA volume assessment in research settings in order to perform accurate and reliable analysis. However, for clinical practice this method may consume too much time and, therefore, alternative techniques exist that closely correlate to this gold standard and which are

much easier to obtain. Although these techniques have shown to underestimate true LA size, they may have enough precision for LA size assessment in clinical routine.
The impact of catheter ablation of AF on the LA is an important issue, since catheter ablation as a treatment for patients with AF is performed increasingly nowadays and ablation strategies may include extensive ablation in the LA. Due to the diversity in the existing literature, this thesis aimed to finally gain clarity to what extent the LA is influenced by catheter ablation of AF.
Two main factors may be responsible for changes in LA size and function following catheter ablation of AF: 1. remodeling, either by ongoing AF or reverse remodeling by restoration of sinus rhythm; 2. ablation induced LA fibrosis. This thesis has shown that the LA is influenced by both reverse atrial remodeling as well as ablation induced fibrosis. These results are of clinical importance since the LA function determines, to a certain extent, the thrombo-embolic risk of a patient. If LA function is impaired post-ablation, thrombo-embolic risk could be higher than anticipated from traditional risk factors assessment. However, we have shown that patients with a successful ablation procedure of AF had no change in their LA contraction post-ablation. Only patients with AF recurrences showed a decrease in LA contraction, since they lacked the positive effect of reverse remodeling. Based on these results, it can be stated that PVAI does not seriously impair the LA and that it may be defensible to discontinue the anticoagulation several months after ablation in patients free of AF recurrences. However, we must be careful here because we only examined the effect of PVAI on the LA and we did not look at other ablation techniques that involve extensive additional LA ablation. In addition, we did not analyze different anticoagulation strategies post-ablation. Further studies are necessary to evaluate the effects of more extensive catheter ablation in the LA on LA function and thrombo-embolic risks.

Introductie

Catheterablatie neemt een belangrijke plaats in bij de behandeling van patiënten met symptomatisch, therapieresistent atriumfibrilleren (AF). Niet lang na de ontdekking dat de longvenen verantwoordelijk zijn voor de initiatie van AF, werd er een ablatie techniek ontwikkeld die als doel had de longvenen electrisch te isoleren. In de laatste jaren heeft deze catheterablatie techniek een grote ontwikkeling doorgemaakt tot de techniek die nu het meest wordt toegepast, te weten pulmonaalvene antrum isolatie (PVAI). Deze techniek omvat aaneensluitende ablatie lesies in het linker atrium (LA) die in een wijde cirkel de linker en de rechter ipsilaterale longvenen omcirkelen. PVAI heeft in vele studies bewezen effectief te zijn in het bestrijden van AF, met name in patiënten met paroxysmaal AF, en wordt wereldwijd toegepast. Om het succespercentage van PVAI verder te verhogen, vooral bij patiënten met (langdurig) persisterend AF, zijn er ablatie technieken ontwikkeld die naast PVAI ook uitgebreide additionele ablatie in het LA omvatten. Deze additionele ablatie bestaat uit lineaire ablatie in het LA of ablatie van gebieden met complexe gefractioneerde atriale electrogrammen. Omdat het LA het doel is van deze ablatie technieken, is het belangrijk om te achterhalen of catheterablatie van AF het LA significant kan beschadigen. Hier komt namelijk een belangrijk klinisch aspect bij om de hoek kijken. Als de LA functie aanzienlijk afneemt na catheterablatie, is het risico op trombo-embolische complicaties zeer waarschijnlijk verhoogd en moet het beleid ten aanzien van antistolling aangepast worden. Verschillende studies hebben al naar dit onderwerp gekeken en hebben verandering in LA grootte en functie geanalyseerd na catheterablatie van AF. Echter, de resultaten van deze studies zijn dusdanig verschillend, dat het onmogelijk is om een conclusie te kunnen trekken. Derhalve is het tot nu toe nog steeds onduidelijk hoe het LA beïnvloed wordt door catheterablatie van AF. Om die reden heeft dit proefschrift als doel gesteld dit onderwerp verder te analyseren door gestructureerd en homogeen onderzoek uit te voeren en om op die manier uiteindelijk de invloed van catheterablatie van AF op het LA te bepalen.

Een van de voornaamste factoren verantwoordelijk voor de grote diversiteit in de literatuur behelst de methode die gebruikt is om LA grootte en functie te bepalen. Daarom is **deel 1** van dit proefschrift gericht op het vergelijken en valideren van verschillende methodes om LA grootte te meten in patiënten met AF.

In **deel 2** van dit proefschrift is gekeken naar het klinische belang van het LA in patiënten met AF die catheterablatie ondergaan. Als eerste werd de voorspellende waarde van de LA grootte voorafgaand aan catheterablatie van AF ten aanzien van het wel of niet slagen van de behandeling onderzocht. Daarna werd het belangrijkste onderdeel van dit proefschrift belicht: de invloed van catheterablatie van AF op LA grootte en functie.

Deel 1

Beeldvorming van het linker atrium in patiënten met atriumfibrilleren

Om in staat te zijn de invloed van catheterablatie op het LA te bepalen, is het belangrijk om de nauwkeurigheid van de verschillende methodes voor bepaling van LA grootte en functie te kennen. Het eerste deel van dit proefschrift is daarom toegespitst op het vergelijken van verschillende meetmethodes voor het LA.

In **hoofdstuk 2** werd de frequent toegepaste en makkelijk toegankelijke LA diameter (LAD), gemeten met echocardiografie in de parasternale lange as, vergeleken met LA volume gemeten met de Simpson's rule met computed tomography (CT). Eerdere publicaties hebben aangetoond dat de LAD voorspellende waarde heeft ten aanzien van de klinische uitkomst na catheterablatie van AF. Dit had als gevolg dat meerdere klinische centra's deze LAD als selectie criterium gebruikten en patiënten excludeerden voor catheterablatie van AF als ze een LAD >5.0-5.5 cm hadden. Echter, aangezien de LAD maar één dimensie van het LA betreft, is het zeer waarschijnlijk geen accurate weergave van de LA grootte. In 50 patiënten met AF werden de LAD met echocardiografie en LA volume met CT gemeten en de correlatie tussen beide methodes berekend. Uiteindelijk werd er een slechte correlatie gevonden (r=0.49, p<0,001), waardoor wij concludeerden dat de LAD niet correspondeert met LA grootte of LA dilatatie. Een belangrijke bevinding was dat patiënten met een LAD >5.0 cm, die in sommige centra op basis hiervan geen catheterablatie zouden krijgen, een grote variatie vertoonden in hun LA volumes.

De methode die in **hoofdstuk 2** gebruikt werd om LA volume te meten, de Simpson's rule, wordt gezien als de gouden standaard voor het bepalen van de LA grootte. Deze methode omvat het handmatig omcirkelen van het LA oppervlak op elke doorsnede van een CT of magnetic resonance imaging (MRI) scan en houdt er dus rekening mee dat het LA een asymmetrische vorm heeft. Hiernaast heeft deze methode aangetoond zeer goed te correleren met post-mortem LA grootte bepaling. Echter, het vergt aardig wat tijd en arbeid om met deze methode LA volume te meten, wat deze methode minder geschikt maakt voor de klinische praktijk. Daarom hebben we in **hoofdstuk 3** een simpelere alternatieve methode gevalideerd. Met deze alternatieve methode kan het LA volume berekend worden door 3 dimensies van het LA te meten en deze in te voegen in een wiskundige berekening. In 100 patiënten met AF zijn beide methodes gebruikt om het LA volume te meten, met CT, en de correlatie tussen de methodes te berekenen. We vonden een excellente correlatie (r=0.91, p<0.001), maar de alternatieve methode resulteerde in een significante onderschatting van de LA grootte van gemiddeld 17%. Gebaseerd op de excellente correlatie met de gouden standaard kan gezegd worden dat deze nieuwe techniek een goed alternatief is voor de klinische praktijk. Echter, men moet rekening houden dat de LA grootte onderschat wordt. In **hoofdstuk 4** werd een andere alternatieve methode onderzocht en vergeleken met de gouden standaard. In dit hoofdstuk ging het om de area-length methode (ALM), oorspronkelijk toegepast in de echocardiografie, waarbij het LA volume berekend wordt door het LA oppervlak en de lengte te meten op één doorsnede van het LA. Tweeënzeventig MRI scans van patiënten met AF werden gebruikt om maximale en minimale LA volumes te meten met de ALM en de Simpson's rule. Tevens werd de LA functie bepaald door met deze volumes de LA ejectiefractie te berekenen. LA volumes, gemeten met de ALM, waren significant lager dan de LA volumes gemeten met de Simpson's rule, wat zorgde voor een overschatting van de LA ejectiefractie gemeten met de ALM. Echter, een goede en significante correlatie tussen beide methodes werd gevonden ($r=0.77$ voor maximaal LA volume, $p<0.001$; $r=0.85$ voor minimaal LA volume, $p<0.001$). Ondanks deze onderschatting van de LA volumes, kan de ALM toch een goed alternatief zijn omdat het zeer makkelijk is toe te passen (duur van de meting 1 minuut tegenover 10 minuten bij de Simpson's rule) en toch goed correleert met de gouden standaard. Hiernaast kan de Simpson's rule niet altijd gebruikt worden, omdat daar meerdere doorsneden voor nodig zijn, in tegenstelling tot de ALM waar maar één doorsnede voor gebruikt wordt.

Deel 2

Het klinische belang van het linker atrium in patiënten met atriumfibrilleren die catheterablatie ondergaan

A

Het tweede deel van dit proefschrift richtte zich op de klinische rol van het LA in patiënten met AF die catheterablatie ondergaan. Als eerste werd er in **hoofdstuk 5** gekeken naar de LA grootte voorafgaand aan catheterablatie om te bepalen of dit de klinische uitkomst van de ablatie procedure kan voorspellen. Eerdere publicaties hebben al laten zien dat de LAD, gemeten met echocardiografie in de parasternale lange as, voorspellende waarde heeft ten aanzien van de klinische uitkomst na catheterablatie van AF. Niettemin, in **hoofdstuk 2** hebben we laten zien dat deze LAD slecht correleert met LA volume gemeten met de gouden standaard. Daarom hebben we geanalyseerd of het LA volume, gemeten met de Simpson's rule en CT, ook de klinische uitkomst van catheterablatie kan voorspellen. Daarnaast hebben we bepaald of variaties in de longvenen anatomie de klinische uitkomst kan voorspellen. In 146 patiënten met AF die catheterablatie ondergingen, werd voor ablatie het LA volume gemeten en de longvenen anatomie bepaald. De resultaten lieten zien dat LA volume, voorafgaand aan catheterablatie, een voorspellende waarde heeft ten aanzien van de klinische uitkomst met een odds ratio van 1.14 voor elke 10 ml verhoging in volume (95% CI 1.00-1.29, p=0.047). Daarentegen had de longvenen anatomie geen voorspellende waarde. De verschillende variaties in longvenen anatomie waren gelijk verdeeld tussen patiënten met een succesvolle uitkomst of zonder een succesvolle uitkomst. Deze resultaten suggereren dat het belangrijk is om de bepaling van LA volume voorafgaand aan de ablatie procedure toe te voegen aan de preprocedurele evaluatie van AF patiënten om een inschatting over diens prognose te kunnen maken.

Hoofdstuk 6 heeft zich gericht op het LA voor en na ablatie en heeft de literatuur ten aanzien van de invloed van catheterablatie van AF op het LA onder de loep genomen. Dit review artikel biedt een mooi overzicht van de grote diversiteit in de resultaten die gepubliceerd zijn ten aanzien van dit onderwerp. Wat duidelijk wordt door deze review is dat catheterablatie absoluut een effect heeft op het LA, echter, gebaseerd op de bestaande literatuur is het onmogelijk te bepalen op wat voor manier het LA beïnvloed wordt. Het eerste effect betreft ablatie geïnduceerde LA fibrose wat in beeld kan worden gebracht met delayed enhancement MRI. Een bepaalde hoeveelheid van ablatie geïnduceerde fibrose is waarschijnlijk nodig om een succesvolle PVAI te bereiken, echter, wat het effect van deze fibrose op de LA functie is, is onbekend. Ten tweede heeft catheterablatie een invloed op de LA grootte, maar het is nog niet bekend op wat voor manier, aangezien de literatuur hier totaal niet eenduidig over is. Tevens staat het effect van catheterablatie op de LA functie ter discussie. Ondanks dat er maar weinig artikelen zijn die een afname van de LA functie rapporteren na een succesvolle catheterablatie, is het nog onduidelijk of de LA functie toch niet aangetast wordt door ablatie. Minder verwarring bestaat er ten aanzien van het optreden van LA tachycardieën na catheterablatie. Uitgebreide ablatie in het LA, inclusief PVAI en additionele LA ablatie, resulteerde in een significant hogere incidentie van LA tachycardieën postablatie dan alleen PVAI.

In **hoofdstuk 7** worden onze eigen initiële resultaten gerapporteerd ten aanzien van de verandering in LA grootte na catheterablatie van AF. LA volume werd gemeten met de Simpson's rule en MRI plaatjes, voor en na ablatie, om de meest accurate weergave van LA grootte te hebben. Voor deze studie werden 79 patiënten met symptomatisch AF geïncludeerd die PVAI ondergingen. Bij de analyse van de veranderingen in LA volume na ablatie werd er een afname van LA volume gezien in de totale studiepopulatie, van 104 ml tot 91 ml, p<0.001. Subgroepanalyse liet zien dat zowel patiënten met een succesvolle uitkomst als patiënten met AF recidieven een significante afname in LA volume postablatie vertoonden. Tevens lieten zowel

patiënten met paroxysmaal AF als patiënten met (langdurig) persisterend AF een afname in LA grootte zien na ablatie.
Verschillende mechanismen kunnen verantwoordelijk zijn voor een afname in LA grootte na ablatie, waarvan atriale remodelering door herstel van sinusritme en ablatie geïnduceerde fibrose de twee meest belangrijke mechanismen zijn. Aangezien onze resultaten een afname in LA grootte lieten zien in de hele studiepopulatie, denken we dat ablatie geïnduceerde fibrose mede verantwoordelijk was.
Echter, meer bewijs was nodig om de invloed van catheterablatie van AF op het LA te bepalen en daarom is er een grotere studie opgezet met een uniforme methodiek en een grote studiepopulatie van patiënten met AF. Deze studie wordt beschreven in **hoofdstuk 8** en betrof een groep van 206 patiënten met AF waarbij minimale en maximale LA volumes en LA functie werd bepaald met de meest accurate methode (Simpson's rule met MRI) en waarbij PVAI als enige ablatie techniek werd uitgevoerd. Hiernaast onderging een kleine subgroep van deze patiënten (n=52) additionele delayed enhancement MRI voor en na ablatie met als doel de hoeveelheid ablatie geïnduceerde LA fibrose te bepalen. Met al deze gegevens zouden we in staat zijn de invloed van catheterablatie van AF op het LA te kunnen bepalen.
De resultaten van deze studie lieten een significante afname van maximaal LA volume zien in de hele studiepopulatie, in overeenstemming met het onderzoek uit **hoofdstuk 7**, passend bij een effect van ablatie geïnduceerde LA fibrose. In tegenstelling tot dit resultaat liet minimale LA volume alleen een afname zien in patiënten met een succesvolle uitkomst van de ablatie procedure, passend bij een effect van atriale remodelering. Dit had tot gevolg dat de LA functie alleen verminderde na ablatie in patiënten met AF recidieven. Hiernaast kon ablatie geïnduceerde LA fibrose in beeld worden gebracht bij 77% van de patiënten die delayed enhancement MRI ondergingen. Deze resultaten suggereren dat zowel atriale remodelering als ablatie geïnduceerde fibrose een invloed uitoefenen op LA grootte en functie postablatie. Alleen patiënten met AF recidieven na ablatie ondervonden een negatief effect van catheterablatie van AF, omdat ze geen atriale remodelering (door herstel van sinusritme) vertoonden. Dit is belangrijke informatie voor de klinische praktijk, aangezien een behouden LA functie in patiënten met een succesvolle uitkomst na catheterablatie kan rechtervaardigen dat de antistolling enkele maanden postablatie wordt gestopt. Echter, in deze studie is alleen het effect van PVAI onderzocht, waardoor we geen uitspraken kunnen doen over het effect van ablatie procedures die uitgebreidere ablatie in het LA omvatten.

Conclusies en toekomstperspectieven

De literatuur over de invloed van catheterablatie van AF op het LA vertoont zeer uiteenlopende resultaten. Meerdere factoren kunnen verantwoordelijk zijn voor deze diversiteit, waaronder de verschillende beeldvormende technieken en methodes die gebruikt worden om de LA grootte te bepalen en tevens verschillende ablatie technieken die gebruikt worden. Dat is de reden dat het eerste deel van dit proefschrift zich richt tot het vergelijken van verschillende methodes voor LA grootte bepaling en de precisie van deze methodes in patiënten met AF evalueert.
De eerste methode, de LAD gemeten met echocardiografie, is een ruwe en onnauwkeurige methode, en ook al wordt de LAD nog steeds veel gebruikt in de klinische praktijk, wij adviseren dat deze methode niet gebruikt moet worden voor accurate bepaling van de LA grootte. De Simpson's rule met CT of MRI wordt beschouwd als de gouden standaard voor LA grootte bepaling, aangezien het rekening houdt met de asymmetrische vorm van het LA. Het gebruik van de Simpson's rule heeft de voorkeur voor LA grootte bepaling in studieverband om vervolgens een accurate en betrouwbare analyse te kunnen uitvoeren. Echter, voor toepassing in de klinische praktijk neemt deze methode veel tijd in beslag en daarom zijn er alternatieve technieken beschikbaar die makkelijker toepasbaar zijn en die goed correleren met de Simpson's rule. Ook al zorgen deze alternatieve methodes voor een onderschatting van de LA grootte, mogelijk zijn ze toch goed genoeg voor LA grootte bepaling in de dagelijkse praktijk.

De invloed van catheterablatie van AF op het LA is een belangrijke kwestie, aangezien catheterablatie als behandeling van AF steeds frequenter wordt toegepast en ablatie technieken uitgebreide ablatie van het LA kunnen bevatten. Vanwege de grote diversiteit in de literatuur ten aanzien van dit onderwerp, was het doel van dit proefschrift om meer duidelijkheid te scheppen in het effect van catheterablatie van AF op het LA.
Twee factoren zijn hoofdzakelijk verantwoordelijk voor veranderingen in LA grootte en functie na ablatie: 1. atriale remodelering door herstel van sinusritme; 2. ablatie geïnduceerde LA fibrose. Dit proefschrift heeft laten zien dat het LA wordt beïnvloed door beide factoren, zowel atriale remodelering als ablatie geïnduceerde fibrose. Deze resultaten zijn van klinisch belang, aangezien de LA functie in zekere mate het trombo-embolische risico van een patiënt bepaalt. Als de LA functie na ablatie ernstig aangetast is, kan het trombo-embolische risico postablatie hoger zijn dan van tevoren was ingeschat met traditionele risicostratificatie. Echter, de bovengenoemde resultaten hebben laten zien dat de LA functie in patiënten met een succesvolle uitkomst na

catheterablatie van AF behouden blijft. Alleen patiënten met AF recidieven postablatie lieten een vermindering in de LA functie zien, omdat ze geen atriale remodelering vertoonden. Op basis van deze gegevens kan gesteld worden dat PVAI geen schadelijke gevolgen heeft op het LA in patiënten met een succesvolle uitkomst en dat het zeer waarschijnlijk gerechtvaardigd is om, in deze patiënten, de antistolling na enkele maanden te staken. Echter, men moet op zijn hoede blijven aangezien in dit proefschrift alleen het effect van PVAI op het LA is onderzocht en niet gekeken is naar het effect van meer uitgebreidere ablatie technieken. Tevens is niet gekeken naar het effect van verschillende antistolling strategieën postablatie. Meer studies zijn nodig om het effect van uitgebreide catheterablatie op het LA te bepalen en de consequenties voor het trombo-embolische risico van een patiënt na te gaan.

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Irene Hof was born on February 14, 1984 in Harderwijk, the Netherlands. In 2002, she graduated cum laude at grammar school in Harderwijk (Christelijk College Nassau-Veluwe). Thereafter, she started her medical school at the University of Utrecht. During a research internship in her fifth year she became acquainted with the wonders of the electrophysiology and started to collect her first data concerning the left atrium in patients with atrial fibrillation (supervisors: prof. dr. R.N.W. Hauer and dr. K.P. Loh). In her sixth year, she had the opportunity to perform research at the Johns Hopkins Hospital in Baltimore, USA, for six months (supervisor: prof. dr. H.G. Calkins). This research internship resulted in three articles which are incorporated in this thesis. After graduating from medical school in 2008, she started with her PhD project at the department of Cardiology/ Electrophysiology of the University Medical Center Utrecht (supervisors: prof. dr. R.N.W. Hauer, dr. K.P. Loh, and dr. B.K. Velthuis). During this project, she did not only perform research but she was also able to participate in the electrophysiology lab to gain experience in analyzing intracardiac ECGs and mechanisms of different cardiac arrhythmias. In October 2011, she started with clinical work at the Cardiology department of the University Medical Center Utrecht (educational head: dr. J.H. Kirkels).

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