Impact of left atrial fibrosis tissue before and induced scar tissue after pulmonary vein isolation on left atrial function detected using cardiac-MRI in patients with atrial fibrillation

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Diploma thesis

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List of abbreviation

AAD	-	Antiarrhythmic drug therapy
AC	-	Anticoagulants
ACE	-	Angiotensin-converting enzyme
ACh	-	Acetylcholine
AF	-	Atrial fibrillation
AP	-	Action potential
ASA	-	Acetylsalicylic acid
bpm	-	Beats per minute
CA	-	Catheter ablation
Ca^{2+}	-	Calcium
CAD	-	Coronary artery disease
cAMP	-	Cyclic adenosine monophosphate
CHA_2DS_2VASc score	-	Congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category
CHF	-	Congestive heart failure
COPD	-	Chronic obstructive pulmonary disease
CRT-D	-	Cardiac resynchronization therapy with a defibrillator
CRT-P	-	Cardiac resynchronization therapy with a pacemaker
CTA	-	Computed tomography angiography
DAD	-	Delayed afterdepolarization
df	-	Degree of freedom
ECG	-	Electrocardiogram
ECM	-	Extracellular matrix
EHRA	-	European Heart Rhythm Association
HAS-BLED	-	Hypertension, abnormal liver/ renal function, stroke history, bleeding history or predisposition, Labile INR, Elderly, Drug/ alcohol usage
HFpEF	-	Heart failure with preserved ejection fraction
HFrEF	-	Heart failure with reduced ejection fraction
HF	-	Heart failure
INR	-	International normalized ratio
I_{k1}	-	Inward rectifier K^+ current
iv	-	Intravenous
K^+	-	Kalium
LA	-	Left atrium
LAA	-	Left atrial appendage
LAEF	-	Left atrial ejection fraction
LAV_{max}	-	Maximal left atrial volume
LAV_{min}	-	Minimal left atrial volume
LVEF	-	Left ventricular ejection fraction
MI	-	Myocardial infarction
MRI	-	Magnetic resonance imaging
N	-	Number
NOAC	-	Non-vitamin K antagonist oral anticoagulants
PAH	-	Pulmonary arterial hypertension
PV	-	Pulmonary vein
PVI	-	Pulmonary vein isolation
RCT	-	Randomized controlled trials
RyR	-	Ryanodine receptors

SD	-	Standard deviation
TSH	-	Thyroid-stimulating hormone

1. INTRODUCTION

1.1. AF definition and classification

The most prevalent cardiac arrhythmia is atrial fibrillation (AF) (1,2,3). It is a supraventricular tachyarrhythmia characterized by inefficient atrial contraction as a result of disorganized atrial electrical activity. Representative electrocardiographic signs of AF comprise irregularly irregular R-R intervals, missing P waves and irregular atrial activation (4). The prevalence of developing acute AF increases with age. Around 50% of patients experience a spontaneous return to sinus rhythm within 24 to 48 hours, while many others will need treatments to regulate their heart rate or regain sinus rhythm (5).

The classification of AF includes various AF patterns. It includes the first diagnosed AF, which was not diagnosed until now, despite the possible presence of AF related symptoms (4). Paroxysmal AF occurs when recurrent AF spontaneously switches back to sinus rhythm within seven days (6). In certain cases, paroxysmal AF can even last longer (7). The episodes of paroxysmal AF can vary in length and frequency. As well as the difference of presence and intensity of symptoms (8). Another typical sign of paroxysmal AF is the spontaneous recurrence of AF at any time (1). In the circumstance of persistent AF, the episodes have been present for more than seven days. If it is accompanied by an accelerated and uncontrolled ventricular rate, it may cause dilated cardiomyopathy through electrical remodeling in cardiac myocytes (6). Another trait of persistent AF is that it does not terminate spontaneously (1). Long-standing persistent AF is characterized by continued AF for more than twelve months (6). This group does not seem to benefit from medical therapy for preserving sinus rhythm (9). Permanent AF is characterized by the decision that further treatment attempts have to be stopped due to the lack of maintaining or regaining sinus rhythm **(**6). Non-valvular AF is developing, as its name suggests, when there is no presence of rheumatic mitral valve disease, mitral valve repair, or prosthetic heart valve (1).

1.2. Epidemiology and etiology of AF

The incidence and prevalence of AF are rising, supporting the notion that it is a global pandemic. The increase in numbers can be attributed to a global trend of an aging population, coupled with improved overall survival rates among individuals with chronic conditions**.** Even over the last 50 years the probability of getting AF grew three-fold. Over 46.3 million people were expected to have AF globally in 2016, according to the Global Burden of disease research. Around 3 to 6 million Americans already have AF, and by 2050, it is estimated that this number will extend approximately 6 to 16 million (10). Additionally, women have a lower age-adjusted prevalence and incidence of AF than male do. Even when men experience greater age-adjusted

AF incidence and prevalence than women, women are older at the time of diagnosis and more likely to experience AF-related negative consequences, such as stroke (11).

Risk factors for AF can be summarized in cardiac and non-cardiac risk factors. An example for cardiac risk factor is the linkage of heart failure (HF) and AF. There can be a direct connection between the development and maintenance of both heart diseases (12). Furthermore, people with coronary heart disease are more likely to get new onset AF. Through altering reentry development, localized ectopic activity and neuronal remodeling, coronary heart disease can proactively accelerate AF (13). Additionally, cardiac valve diseases can also promote AF (14). In situations of rheumatic heart disease, AF can be a considerable consequence (15). The combination of AF and cardiomyopathy are also linked with poorer outcome (16). Another important cardiac risk factor is hypertension which is related to LA enlargement, poor ventricular filling, left ventricular hypertrophy and slowed atrial conduction velocity. These modifications to the heart structure enhance the progression to AF (17).

Non-cardiac risk factors include lung disease such as chronic obstructive pulmonary disease (COPD). One of the main characteristics of COPD is hypoxia, which can cause atrial remodeling and subsequently AF through increased vascular tone which is able to evoke pulmonary hypertension (18). Even 15% of patients with hyperthyroidism develop AF. It is the most prevalent cardiac complication of hyperthyroidism (19). As shown by the relationship between recent alcohol intake and AF episodes, a modifiable behavior may affect the likelihood that AF will occur (20). Pheochromocytoma can also be a reason for developing AF (21). Even severely ill patients with sepsis are at risk for developing cardiac dysrhythmias, most frequently AF (22). While ascribing causality to medication-associated AF is less common than it is with other drug-induced arrhythmias, such as torsades de pointes and sinus bradycardia, AF may still be provoked by administration of drugs. Drugs that can induce new-onset AF include medications such as corticosteroids, ondansetron, antineoplastic agents, or even cardiovascular drugs such as adenosine, dobutamine and milrinone (23). Last but not least, after performed heart surgery or even after non-cardiac thoracic surgery, AF can be a highly common issue (24). Occasionally, iatrogenic factors are responsible for the development of AF as well. All of these risk factors can be the cause of the occurrence of AF (4). The huge number of possible triggers indicate the big importance of keeping them in mind.

1.3. Pathophysiology of AF

As already mentioned, specific risk factors have been shown to result in architectural and electric alterations of atria (25). As a consequence of changes in ion channels and electrical

features, autonomic tone, Calcium (Ca^{2+}) handling and structural remodeling in the atria, the development of AF can occur (26).

Some causes for the structural remodeling and consequently developed AF are followed. The so called interstitial myofibroblasts are signs for atrial fibrosis which are correlated to AF (atrial fibrosis will be further discussed as a structural remodeler of the atrium in a separate subpoint). These cells are in charge for the pathological disconnection of cardiomyocyte bundles by the way of uncontrolled deposition of the extracellular matrix (ECM). Due to collagenous septum, which is a passive medium for propagation, we get an impulse conduction block and/or zigzag conduction, which again promotes arrhythmias (27).

The next mentioned point will be about the linkage between AF and mechanism of underlying ectopic firing. After repolarization, typical atrial cell action potential (AP) stay, due to high resting Kalium (K^+) permeability through the inward rectifier K^+ current (I_{k1}), at the resting potential. Atypical secondary cell membrane depolarizations can happen during repolarization phases and lead to early afterdepolarization. The primary reason for early afterdepolarization is AP duration lengthening which lead to L-type Ca^{2+} current being reactive and furthermore, triggers the inwards flow of Ca^{2+} ions that causes depolarization**.** The actual cause of delayed afterdepolarization is setting free Ca^{2+} from sarcoplasmic reticulum Ca^{2+} stores while diastole. Due to transmembrane Ca^{2+} reentry, the Ryanodine receptors (RyR) (sarcoplasmic reticulum Ca^{2+} channels) release Ca^{2+}. Typically, only when the RyRs are defective or the sarcoplasmic reticulum has too much Ca^{2+} the RyRs will open. Whereas physiologically RyRs are normally closed while diastole. The Na^+-Ca^{2+} exchanger swap one Ca^{2+} generated during diastole with three extracellular Na+ ions, resulting in a net depolarizing inward positive-ion flow (also known as transient inward current) that underpins delayed afterdepolarizations. This pathophysiology of atrial cell Ca^{2+} overload and delayed afterdepolarization is also seen in congestive heart failure (CHF) which is one of the most common causes of AF (28). In conclusion, AF has a big influence on atrial K^+ and Ca^{2+} currents influence on AP duration and AP duration rate adaptation (29). Consequently, it plays even an important role in perpetuation of AF and as a result of downregulation and changes in ion channels, we have a weakened contractility of the atrium (29, 30).

The triggering events are frequently represented by rapidly firing ectopic foci found inside one or more pulmonary veins (PV) and an aberrant atrial tissue substrate that is able to sustain the arrhythmia **(**2). Two mechanisms in connection with AF and PVs are suggested: 1. Nonreentrant (focal) and 2. Reentrant mechanisms. Specialized cells with spontaneous activity and smaller I_{k1} in PV cells are features that support nonreentrant processes. Reduced resting

potentials (which inactivate Na+ channels and delay conduction) and shorter AP duration, as well as rapid changes in fiber orientation that encourage unidirectional block and slow transmission, all favor reentrant PV activity (28). These aberrant impulses may result in bursts of atrial depolarization and is followed by the reentry pattern, in which the unusual impulse is continually passing through a circuit (26). The actual initiation of reentry starts with propagation of ectopic beats in certain directions that hits refractory tissue; yet, when propagating in the other direction, it might conduct in tissue that recovers more quickly ("unidirectional block") (31). Reentry can be considered either as spiral wave or leading circle. The determinant for ensuring continuous activity are adequate balance between refractory and excitability factors, additionally to atrium properties. The number of simultaneous reentry circuits that the atrium can handle increases with decreasing wavelength, vice versa the number of circuits decreases with growing wavelength. Thus, decreased conduction velocity and smaller refractory period induce reentrant AF, whereas inhibition of AF occurs for instance with drug-induced refractory period lengthening (28). The impulse needs to travel along the circuit slowly enough for all points to regain excitability in order for reentry to be sustained and conduction time must be longer than the circuit's longest refractory period. The refractory time regulates the return of excitability: The possibility that tissue will be ready for reactivation when the reentering stimulus passes through, is increased by short refractory times (31).

Also factors that affect the autonomic nerve system are crucial in the pathophysiology of AF. Vagal discharge stabilizes reentrant rotors, decreases APD and raises Acetylcholine (ACh)-dependent K^+ current. Via hyperphosphorylating RyR2a ß-adrenoceptor stimulation promotes diastolic Ca^{2+} leak and increases delayed afterdepolarization (DAD) related ectopic firing (28).

1.4. Signs and symptoms of AF

The symptoms of patients with AF varies from no symptoms at all to a dramatically impairment of the overall health status of individuals. Furthermore, the symptom intensity influences the decision of which treatment is chosen (4). The type of AF seems to play an important part in the severity of symptoms. Patients with paroxysmal AF tend to be more likely to be symptomatic than those with persistent/permanent AF (32). One of the most important symptoms include palpitations and dyspnea. In fewer cases they can experience chest pain, fatigue, dizziness and can be confronted with presyncope or even syncope. Around 69% of patients with AF experienced symptoms after the diagnosis of AF (32).

The symptoms of AF can be distinguished via the European Heart Rhythm Association (EHRA) symptom scale (33). It is important to clarify how symptoms (especially those that are vague, such shortness of breath, exhaustion, chest pain, etc.) relate to AF, because they might potentially be caused by unrecognized or inadequately managed concurrent cardiovascular risk factors or pathological illnesses (4). The EHRA symptom scale includes a score from 1-4 and shows how severe the symptoms of AF can be. When the patient has none symptoms while having an episode of AF, it is scored as 1. Score 2a is seen in patients that are not concerned by symptoms at their daily work. While in score 2b the patient has moderate symptoms that are not interfering with daily activity, nevertheless the patient feels discomfort through symptoms. Whereas in score 3 daily work is influenced by severe manifestation of AF, in score 4 the normal daily activity can´t be continued and has to be stopped (33).

1.5. Diagnostic of AF

Due to the fact that an increasingly number of people have AF and many patients are asymptomatic, the screening of AF is of great importance to prevent AF and possible consequences such as strokes (4). While performing anamnesis the focus should not only stay on symptoms but also on the beginning, course and end of AF (34). HF, myocardial infarction (MI), stroke or hemodynamic collapse can also be part of patient´s history and can correlate with AF (35). For detection of AF, pulse palpation has been suggested for detecting pulse irregularities as initial stage of screening (36). Additionally, a sometimes unused yet significant clinical sign in diagnosis of AF is pulse deficit (37). Blood pressure, heart rate, the detection of cardiac murmurs (such as mitral or aortic stenosis), and signs of HF should all be examined physically. Whenever AF is suspected based on a pulse rate evaluation, 12-lead electrocardiography should be used to confirm the diagnosis (35).

Typical findings in electrocardiogram (ECG) are “irregularly irregular” RR intervals without identifiable p-waves. Fibrillation waves are completely uncoordinated atrial depolarisations with variable morphology and amplitudes. Typical frequencies of fibrillation are between 350-500/min (38). In most of cases narrow QRS complexes are found (39). The typical ventricular rate varies from 80 and 180 beats per minute (6). Due to the fact that we have an irregular transition from atrium to the ventricle, we have an absolute arrhythmia (38). When an ECG was performed and it showed a normal sinus rhythm, it does not exclude the diagnosis AF. It is possible that a person with paroxysmal AF had sinus rhythm while the ECG was performed. In these cases, an event monitor (seven- to 30-day recording) or Holter monitor (24-hour recording) may be necessary when clinical suspicion of AF continues (35).

The following laboratory values are recommended in diagnostic to determine other causes related to AF. In new onset AF thyroid-stimulating hormone (TSH) should be tested due to the possible connection of subclinical hyperthyroidism and AF (40). Furthermore, there is a higher probability of occurring AF in electrolyte disturbances such as hypokalemia or hyponatremia. Consequently, checking electrolytes through laboratory tests is also crucial (41). Additionally, AF can be associated with infections, underscoring the utility of assessing inflammatory markers through laboratory tests (42). Depending on the patient´s medical history and present risk factors, further test can be required such as stress echocardiography, nuclear perfusion imaging or cardiac catheterization to look for any underlying ischemia or coronary artery disease (CAD) (35).

1.6. Therapy of AF

The overall comprehensive care of patients can be divided into three big parts that are all summarized in the AF better care (ABC) holistic pathway. ´A´ relates to the anticoagulation as a prevention for stroke. Whereas ´B´ stands for better symptom handling and ´C´ for cardiovascular and comorbidity optimization (4). These approaches are listed in the following section.

1.6.1. Anticoagulation

As already mentioned, AF can raise the risk of stroke five-fold. Typical risk factors of stroke include CHF, hypertension, age > 75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, and sex category (female). The sum of these signs is found in the CHA_2DS_2VASc score, which determines the risk of suffering stroke und consequently necessary prophylactic therapy (4). Whereas HF, hypertension, diabetes, peripheral vascular disease, f sex and age 65-74 are rated with one point, stroke or transient ischemic attack and age bigger than 75 are valued with two points (1). In the case of zero points in the CHA_2DS_2VASc score, there is no need for anticoagulation. With one point, it is optional to take anticoagulants (AC), while oral anticoagulation is recommended with more than 2 points (38). When antithrombotic therapy is suggested the possible risk of bleeding should always be considered. Therefore, it is understandable that one of the absolute contraindications of oral AC include active serious bleeding or previous bleeding such as intracranial hemorrhage. The best way of determining the bleeding risk is via HAS-BLED score.

One of the therapy options include Vitamin K antagonists (mainly Warfarin) which is used globally (4). Restrictions in the usage of Vitamin K antagonists include short therapeutic window, requiring regular monitoring of the international normalized ratio (INR) and dosage

adaptation (43). When adequate duration in therapeutic range is given, vitamin K antagonists are efficient and largely risk-free (44). Additional AC include non-vitamin K antagonist oral anticoagulations (NOAC) such as apixaban, dabigatran, edoxaban and rivaroxaban that presented non-inferiority to Warfarin in the purpose of impeding stroke. NOAC are even linked to decline overall mortality substantially by 10%. Some similarities of these mentioned AC include comparable features such as similar ischemic stroke risk reduction (4). Different advantages and disadvantages associated with each AC help to choose the best option for each individual. Other antithrombotic drugs such as clopidogrel in combination with aspirin were not as effective in prevention of vascular events in comparison to oral AC (45). The use of antiplatelet monotherapy is not only unsuccessful in protection against stroke development it can even be harmful (4). The combination of antiplatelet and AC is not promoted due to lack of evidence and little to no benefit in reducing stroke, MI, or mortality, but it significantly increases the risk of serious bleeding and intracranial hemorrhage (46).

For AF patients who are ineligible for long-term oral anticoagulation, left atrial appendage (LAA) occluder implantation is an alternative method for preventing stroke (47). Due to the fact that over 90% of atrial thrombosis develop in LAA in patients with nonvulvar AF, the approach to reduce the stroke probability via percutaneous LAA closure is comprehensible (48). But still the intervention of atrial appendage might contribute to major problems and even implantation related thrombosis can develop after procedure (4).

1.6.2. Symptom control

1.6.2.1. Rate control

The next important part of AF therapy includes rate control. The functional outcome of AF is dictated by ventricular rate and rhythm regularity. Rate control is just as effective in avoiding negative consequences compared to currently available rhythm control treatments (28).

Via the use of drugs such as beta-blockers, digoxin, diltiazem and verapamil rate control can be accomplished. Even some antiarrhythmic drugs such as amiodarone, dronedarone and sotalol showed rate guidance despite their primarily function as rhythm controllers (4). Beta-blockers are antiarrhythmic ß-blockers that basically reduce cyclic adenosine monophosphate (cAMP) and initiate a cascade that finally suppresses abnormal pacemaker (49). Due to the fact that beta blockers provide more powerful acute rate control compared to other drugs, they are frequently used as first-line rate-controlling medication. Whereas nonhyhdropyridine Ca^{2+} channel blockers, such as verapamil and diltiazem, have the benefit of controlling rate while

also improving AF-related symptoms (4). Digoxin is another option for controlling heart rate and restoring sinus rhythm (50). In spite of concerns about digoxin´s safety, it is still one of the most often prescribed drugs for AF around the world (50). When typical approaches are unsuccessful, amiodarone may be one of the last drugs that could be tried for heart rate regulation (51). This class III anti-arrhythmic drug can be used in supraventricular and ventricular arrhythmias, however severe and fatal side effects are possible (52). Due to its quick start of action and efficiency at high sympathetic tone, beta-blockers and diltiazem/verapamil are recommended over digoxin (4). The decision which rate control drug should be given, depends on many aspects such as preexisting comorbidities. For example, in patients with hypertension or heart failure with preserved ejection fraction (HFpEF) beta blockers or non-dihydropyridine Ca^{2+} channel blockers are recommended as first line treatment. In patients with severe COPD or Asthma beta-blockers are not the first treatment of choice. Instead, non-dyhydropyridine Ca^{2+} channel blockers are considered as primary medication.

If after reassessment patients still have not ideal rate control with a heart rate over 110 beats per minute (bpm) or even worsening of symptoms, a second line treatment with either a combination or changed drug should be prescribed. For instance, Digoxin and/or beta blocker and/or non-dyhydropyridine Ca^{2+} channel blockers are possible treatment options. If there is still no improvement, either a combination of three drugs should be considered or even an implanted cardiac resynchronization therapy with a pacemaker (CRT-P), cardiac resynchronization therapy with a defibrillator (CRT-D) or pacemaker and atrioventricular node ablation may be an alternative (4). As already mentioned, implanted pacemaker and atrioventricular node ablation can be advised for controlling ventricular rate when prescribed drugs are not helping with controlling rate anymore. Overall it has a low complication rate, it has a minimal risk of long-term mortality and its relative simplicity in procedure makes it to a recommended alternative to patients who are highly symptomatic and therapy-resistant to drugs (53).

1.6.2.2. Rhythm control

The goal of this therapy approach is to either restore or maintain sinus rhythm. It involves a variety of therapeutic approaches such as catheter ablation (CA), cardioversion and antiarrhythmic medication as well as accurate rate control and AC therapy. One of the main causes of rhythm management is to enhance quality of life by decreasing AF related symptoms (4).

One treatment option includes electrical cardioversion which is similar to electrical defibrillation. Contrary to defibrillation, which is used to patients experiencing cardiac arrest, cardioversion is employed for patients that are hemodynamically unstable but breathing. In synchronized cardioversion, a transthoracic electrical current is administered to the anterior chest to stop a potentially fatal or unstable tachycardic arrhythmia. In synchronized cardioversion, a shock is applied to the chest for regaining sinus rhythm (54). Normally it´s beginning with a dose of 100 J and should be increased in the case of ineffectiveness. If the conversion is still unsuccessful under high energy, either internal cardioversion with electrode catheter or administering Ibutilid can be an option for regaining sinus rhythm. Ibutilid increases the success rate of cardioversion by decreasing the necessary energy threshold for successful cardioversion (38). Potential side effects that should always be kept in mind are for instance ventricular fibrillation caused by general anesthesia or a deficiency of synchronization between the current shock and the QRS complex (55).

In patients with stable hemodynamics, pharmacological cardioversion may be indicated as an elective procedure. The real effectiveness of treatment is biased by the uncontrolled restoration of sinus rhythm within 48 hours. Consequently, it is more like a wait and watch strategy that may be considered in patients with recent onset AF as a non-inferior choice to immediate cardioversion (4). Already in patients with AF lasting for more than 48 hours, the success rate is visible decreasing (38). Typical drugs that can be used in pharmacological cardioversion include flecainide, ibutilide and amiodarone. One of the fastest cardioverting drug includes vernakalant which is more potent than flecainide or amiodarone **(**4).

1.6.2.2.1. CA and PVI

A common way of preventing recurrences of AF is via CA (4). An AF ablation is a minimally-invasive procedure that involves applying heat (radiofrequency) or cold (cryoablation) energy to cardiac tissue with the goal of producing scar tissue that blocks the malfunctioning electrical pathways that lead to AF (56). There is non-inferiority of cryoballoon versus radiofreuqent current ablation due to noticed significantly less all-cause rehospitalization, fewer repetitive ablations and during follow-ups less cardiovascular rehospitalization (57). With each approach, they recognized relatively equivalent sinus rhythm maintenance. Cryoballon ablation takes in general less time, but requires more fluoroscopy duration (4). Nevertheless, both have in common that they increase patients´ quality of life significantly (57).

CA is a good option for preserving sinus rhythm. Currently CA is advocated as a second-line treatment after class I or class III antiarrythmic drug failure (58). It is also noticeable that in the group of patients obtaining ablation therapy, both the improvement in quality of life and the consequent reduction in AF burden were significantly greater than compared to medical therapy (4). Nevertheless, in comparison to antiarrhythmic drug therapy (AAD), CA does not significantly lower primary composite outcome of death, limiting stroke events, major hemorrhage, or cardiac arrest. Until now the indication for CA has not been expanded beyond symptom relief, since no previous randomized controlled trials (RCT) could demonstrate decrease in mortality, stroke or severe bleedings (58). On the other hand, in patients that suffer from HF and/or reduced left ventricular ejection fraction (LVEF), a reduction in all-cause mortality and hospitalization after CA was seen (59). In patients with Heart failure with reduced ejection fraction (HFrEF) CA leads often, in comparison to antiarrhytmic drugs and rate control, to higher probabilities of preserved sinus rhythm, larger improvement in LVEF, better performance during exercise and better overall quality of life (58). It was recognized that important ectopic triggers of AF lie in PVs and electrical isolation of these PVs have the benefit of impede AF. Through this gained knowledge, a new non-pharmacological treatment opportunity for AF was discovered. Namely Pulmonary vein isolation (PVI) (60).

Before ablation a general evaluation and physical examination has to be done. It includes recognition of other existing medical illnesses that might affect the ablation results or raise the risk of problems during PVI. Furthermore, a very important part is the pre-procedural 3-dimensional cardiac imaging evaluation via either cardiac Computed tomography angiography (CTA) or cardiac magnetic resonance imaging (MRI). Latter is not only useful in giving anatomical information about heart function, it may also detect pre-existing fibrosis. Moreover, while PVI, 3D reconstructed LA images can be helpful in directing PVI catheter manipulation. As in all humans, anatomical variations can occur, we can also see differences in histology. In atrial myocardial fibers, we can recognize variations in length, direction and thickness. This plays a leading role in the differences of ablation outcomes in each patient (61).

Even when PVI nowadays is an important part in treating AF, it is challenging to preserve PV electrical isolation. Especially in cases of chronic and long-lasting persistent AF, more extensive ablation is needed. For instance, this can include the isolation of LAA, superior vena cava and lesions in the atria. Also, the type of AF determines the outcome of CA. Around 4-14% of patients that received ablation developed complications such as PV stenosis, persistent phrenic nerve palsy, any vascular complications or asymptomatic cerebral embolism. Around 2-3% of patients had life-threatening complications for instance periprocedural

thromboembolic event or cardiac tamponade or esophageal perforation/fistula (4). These complications should be kept in mind.

There is also the opportunity of performing surgical PVI called Maze-operation. In this procedure isolation of PV is performed by surgical intervention. Nowadays it´s mostly substituted by radiofrequent- and cryoablation. Even if surgery has good success rate with 80%, the intervention is connected with significant morbidity and mortality (38).

1.6.3. Emergency treatment

In the case of acute onset of AF with high ventricle frequencies, hypotension with hemodynamic instability, angina pectoris or pulmonary congestion emergency electrical cardioversion should be considered. Overstimulation is not indicated. The patient should receive anticoagulation with Heparin intravenous (iv) or alternatively Enoxaparin. In patients with good left ventricle function, the ventricle frequency should be managed with either beta-blocker, Ca^{2+} antagonist or diltiazem. Whereas in reduced left ventricle function digitalis is indicated (38).

1.7. Complications of AF

By far the most problematic complication is cardioembolic stroke. As a consequence of disorganized electrical impulses and lack of coordinated atrial contractions, an irregular blood flow develops in the LA and promotes thrombus development in the LAA. Further, endothelial dysfunction and other prothrombotic conditions facilitate thrombus development. If the thrombus moves, the probability to embolize into the cerebral or even more frequently into the peripheral artery beds is present. In comparison to patients that experience stroke unrelated to AF, patients that encounter an embolic stroke linked to AF have poorer outcomes, which is especially troubling (62). Additionally, for instance in rare situations AF related renal and splenic infarction can appear. Consequently, it is important to be aware of the probability that patients with high risk of thromboembolic events can even develop solid organ infarction (63). In the section “therapy of AF” is a detailed paragraph about available prophylactic treatment options that can impede thromboembolic development.

Another complication is HF that can either develop as a result of AF or can worsen under the influence of AF. Contrariwise the chance of developing AF can rise in patients that already suffer from HF. Both diseases frequently overlap and have a higher risk of morbidity and mortality together. Even more than if either illness existed by itself. But in the cases, when both diseases coexist, rhythm restoration can lead to hemodynamic and clinical benefits in

patients with HF. For instance, due to the advancement of CA, even in some patients, cardiac function can improve after ablation (64).

1.8. Prevention of AF

A prevention of AF is possible in patients that have no history of AF. Prior to the onset of atrial fibrosis and remodeling, the risk factors and the comorbidities that predispose to AF have to be identified and controlled as good as possible. The use of non-AADs as upstream therapy can stop the onset or recurrence of AF, via altering the atrial substance or targeting specific processes of AF (for instance structural changes such as fibrosis, hypertrophy and inflammation or influences on ion channel and gap junctions). HF and hypertension should also be managed properly due to the fact that it lowers atrial stretchiness and therefore prevents the development of AF. Additionally, suppression of the renin-angiotensin-aldosterone pathway can suppress electrical and mechanical remodeling of the heart and consequently have further protective function against AF (4).

1.9. Atrial structural remodeling – atrial fibrosis and induced scar tissue

As already mentioned a variety of pathological processes, such as amyloid deposition, collagen fiber buildup and fatty infiltration, take part in the development and maintenance of AF. These stated abnormalities are referred to as “atrial cardiomyopathy”. A significant factor in the development of atrial cardiomyopathy and consequently AF is atrial fibrosis (65). Even in non-AF patients atrial fibrotic remodeling is continuously rising in a dynamic manner (66).

ECM typically covers parenchymal cells and supports their migration, differentiation, proliferation, and normal activity, whereas in fibrosis excessive production and deposition of ECM is noticed. Fibrotic ECM severely impairs tissue homeostasis and as a result of remodeling of cardiac tissue and breakdown of the architectural integrity of heart tissue, organ dysfunction can be caused (65). The greater degree of LA remodeling in patients that developed AF can be either a sign of dynamic LA substrate or that AF speeds up the remodeling process of atrium (66). There are two distinct histopathological varieties of cardiac fibrosis namely ´replacement´/´reparative´ fibrosis and ´reactive´ fibrosis. A correlation between replacement/reparative fibrosis and cardiomyocyte death is seen after cardiac injury, where fibrotic scar tissue replaces necrotic myocardium regions. Whereas in ´reactive´ fibrosis replacement of injured or dead cardiomyocytes is missing and grown deposition of collagen and other ECM proteins in the interstitial space adjacent to cardiac cells and vessels are seen. This explains extension of ´reactive´ fibrosis (65). Fibrosis can be categorized into compact, diffuse, patchy or interstitial in association with the location of cardiac fibrosis and the size of

fibrotic region. This classification appears to have therapeutic consequences for the associated arrhythmogenesis, given that for instance compact fibrosis has been recognized as less proarrhythmic than the other types (67). The percentage of fibrosis in the LA can be classified into four Utah stages. Stage I includes 0-10% fibrosis, stage II 10-20% fibrosis, III 20-30% fibrosis and stage IV over 30% fibrosis (68). A connection between atrial fibrosis and thromboembolic illnesses was made. Even so, it is still unknown what´s the exact mechanism by which fibrosis causes thrombus formation, propensity to embolization and consequently higher probability of developing stroke (69).

Many new approaches for improving the result of CA by targeting fibrosis tissue were made. The DECAAF II trial assumed that, in patients with persistent AF, MRI-guided fibrosis ablation with PVI would reduce atrial arrhythmia recurrence in comparison to performed PVI without direct fibrotic tissue targeting. Due to the fact that no significant difference in AF recurrence was noted, the usage of MRI-guided fibrosis ablation is not recommended in patients with persistent AF (70).

After CA, scar tissue develops. The mechanical behaviors and electrical activity of the affected locations in the atrium are altered by ablation scars (71). Inadequate scar formation seems to be connected with recurrence of AF (72). Despite PVI being one of the best options for patients with paroxysmal AF, there is still some potential for improvement in the long-term success rate. One possible explanation for this limited success is the development of atrial function impairment after ablation (71)**.** While an average Left atrial ejection fraction (LAEF) value is not directly established until now, one study indicated that the approximate normal LAEF is around 55.94% (73). It would be interesting to have further inside into changes in LAEF in connection to the atrial remodeling.

2. OBJECTIVES

2.1. Aim of the study

The aim of this study is to determine the influence of atrial fibrosis before and induced scar tissue after PVI on the LA function in patients with paroxysmal AF.

2.2. Hypothesis

Atrial fibrosis before and induced scar tissue have an influence on LA function.

3. MATERIALS AND METHODS

3.1. Ethical Approval

This retrospective study received its approval by the IRB of the Medical School REGIOMED Coburg on Nov. 2022.

3.2. Study design

This retrospective, non-invasive and non-randomized study involved patients from the cardiology department of REGIOMED hospital Coburg, Germany. Patient data were collected between June 2021 and June 2022. A total of 30 patients met the inclusion criteria.

Inclusion criteria for the study encompassed high-quality MRI scans, sinus rhythm while pre-MRI and post-MRI and first ever ablation between the two MRIs.

Exclusion criteria consisted of bad MRI scans, no sinus rhythm in MRI and second or subsequently ablations.

During the analysis of descriptive data, the actual measured sample size for each variable was used. As some patients had missing information, the sample size had to be adjusted. For correlations we had to adjust the sample size to ensure a clear correlation among the accurate values. A sample reduction was also necessary in the examination of the association between EF and LA volume pre and post PVI.

3.3. Data collection

A random sample of 30 patients with paroxysmal AF was chosen within the time frame from June 2021 to June 2022. We selected the relevant data from the REGIOMED Hospital information system (Orbis). All these patients underwent their first PVI at REGIOMED Hospital Coburg and fulfilled the predefined inclusion criteria.

At first, details about prescribed drugs like angiotensin-converting enzyme (ACE)-inhibitors, beta-blockers, diuretics, NOAK, clopidogrel and ASS were collected. Moreover, demographic details such as gender, age and BMI were gathered. As well as previous MI and stroke, preexisting CAD, hypertension, diabetes, CHF, cardiomyopathy, pulmonary arterial hypertension (PAH), vasculitis, mitral regurgitation, history of smoking and hyperlipidemia. In addition, information about performed CABG, implanted devices and valve surgery were collected. Furthermore, cine sequences were analyzed to measure the LA function by using CVI 42. The next step was detecting the fibrotic tissue before PVI and observing the induced scar tissue 3 months after PVI by using MRI scans. In addition, the LA volume before and after PVI was analyzed. For this, the Merisight software was used. Afterwards, the discovered values were analyzed. All data of patients were anonymized and inserted into an electronic database

(Excel). The statistical analysis was performed anonymously. Traceability of patients was and is not possible.

3.3.1. Detecting LA function

As already mentioned, CVI 42 was used for the measurements of atrial function. The LA was manually encircled. The PVs were not included. The maximal left atrial volume (LAV_{max}) and the minimal left atrial volume (LAV_{min}) were the included parameters. The LA ejection fraction was calculated by $LAEF = (LAV_{max} - LAV_{min})/LAV_{max} \times 100\%$. The LAEF was calculated before and after PVI.

3.3.2. Fibrosis and induced scar tissue

By using Merisight image processing, quantification and segmentation of the LA fibrosis and induced scar tissue was possible. The LA fibrosis/induced scar tissue and LA volume was measured before and after PVI. In Figure 1 the pre-ablation imaging is seen with its green spots that indicate the structural tissue remodeling (fibrosis). Whereas in figure 2 we have the post-ablation imaging with red spots that illustrate the induced scar tissue.

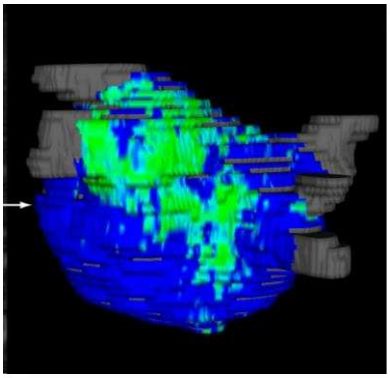

Figure 1 Pre-ablation imaging - diffuse structural tissue remodeling (fibrosis)
Special thanks to Dr. med. Christian Mahnkopf for permission of use.

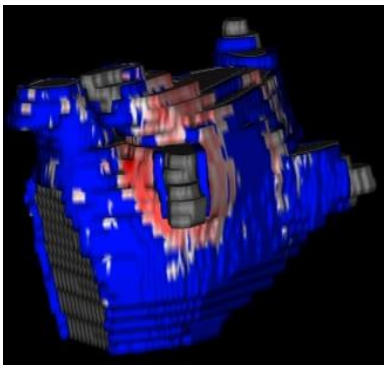

Figure 2 Post-ablation imaging – induced compact lesion (scar)
Special thanks to Dr. med. Christian Mahnkopf for permission of use.

3.4. Statistical analysis

For the statistical analysis JASP (version 0.17.2.0), a Computer software, Amsterdam, Netherlands, was utilized. Categorical data were expressed as number (N) and percentage (%). We collected data regarding the percentages of medication usage among our participants. Additionally, we documented the occurrence of previous events and comorbidities within our patient sample. For age and BMI, we calculated the mean, median and range. Descriptive data were presented as median, mean±standard deviation (SD), minimum and maximum values. In addition, we measured the skewness and kurtosis for each variable to assess their distribution. Based on our evaluation of normal distribution, we were able to make informed selections for our subsequent tests. For observing our correlation between our variables, we performed the Pearson´s correlation test. This test was chosen due to our approximate normal distribution of our data. Correlation coefficient and their corresponding p-values were analyzed. In the end, we used the paired-sample t-test to investigate the comparison between before and after PVI. We preferred the paired sample t-test over the Wilcoxon signed-rank test due to our approximate normal distribution. The paired sample t-test yielded the t-value, degree of freedom (df), and the corresponding p-value. The significance level was set to a P-value of <0.05.

4. RESULTS

4.1. Characteristics of patients

An overview of some medication taken by participants is presented in table 1. All patients were exclusively taking beta blockers. NOACs were included in the medication plan of 96.66% of patients, while ACE inhibitors were prescribed for 66.66%. On the other side, diuretics were prescribed to only 26.66% of patients, and clopidogrel to only 10%. None of the patients were taking aspirin (ASA).

Table 1. Taken medication

Taken medication	Total (N=30)
Beta-blocker n*(%)†	30(100)
NOAC[a]	29(96.66)
ACE-inhibitors[b]	20(66.66)
Diuretics	8(26.66)
Clopidogrel	3(10)
ASA[c]	0(0)

Data are presented as number and percentages
* Number of patients that take following medication
† Percentage of total number of patients, who take this medication
[a] Non-Vitamin K antagonist oral anticoagulants
[b] Angiotensin-converting enzyme-inhibitors
[c] Acetylsalicylic acid

Table 2 provides a detailed analysis of patient characteristics. In our research, the gender percentage was equally distributed, with exactly 50% women and 50% men (N=30). The average age of patients was 67, corresponding to a median value of 67 (range between 45-86). Additionally, in 26 out of 30 cases the BMI was measurable, with a mean BMI of 27.45kg/m^2 and a range spanning from 21.7kg/m^2 to 40.1kg/m^2. The average BMI was 28.27kg/m^2. Moreover, nearly all patients had hypertension (93.33%) and a substantial portion had hyperlipidemia (66.66%), mitral valve regurgitation (36.66%) and CAD (33.33%).

Table 2. Patient characteristics

Patient characteristics		Total (N=30)
Gender n*(%)†	female	15(50)
	male	15(50)
age	median	67
	range	45-86
	mean	67
BMI[a] n(kg/m^2)		(N=26)
	median	27.45
	range	21.7-40.1
	mean	28.27
Hypertension		28(93.33)
Hyperlipidemia		20(66.66)
Mitral valve regurgitation		11(36.66)
Coronary artery disease		10(33.33)
Diabetes mellitus		7(23.33)
Smoker		5(16.66)
Stroke		4(13.33)
Implanted device		2(6.67)
Cardiomyopathy		2(6.67)
Valve surgery		1(3.33)
CHF[b]		1(3.33)
Myocardial-infarction		0(0)
CABG[c]		0(0)
PAH[d]		0(0)
Vasculitis		0(0)

Data are presented as number and percentages
* Number of patients that have following characteristics
† Percentage of total number of patients, who have characteristic
[a] Body mass index
[b] Congestive heart failure
[c] Coronary artery bypass graft
[d] Pulmonary arterial hypertension

4.2. Descriptive data of LAEF before and after PVI, LA fibrosis and LA volume before and after PVI

In table 3, we have summarized the general descriptive data for LAEF, LA fibrosis, and LA volume before and after PVI. The average LAEF before PVI is 39.03% (±13.69%) and the median account to 40.00%, indicating an approximately normal distribution. The skewness value suggests relative symmetry (skewness=0.092), while the negative kurtosis suggests a flatter distribution (kurtosis=-0.988). Figure 3 shows the corresponding density graph and histogram. The majority of patients had their LAEF values concentrated between 20-30%, with the second highest frequency observed in the 40-50% range.

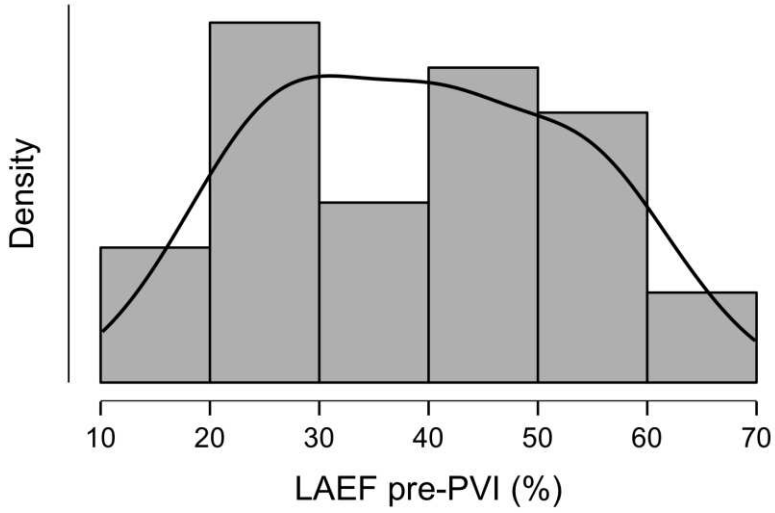

Figure 3. Distribution of LAEF pre-PVI (%)
Data are presented as histogram and density graph

As next variable, we examined the descriptive data of LAEF after PVI. The mean value was 40.43%, with a median of 40.00%, indicating a normal distribution. The skewness suggests a slight rightward (positive) skew in the distribution (skewness=0.228), while the kurtosis suggests a less peaked graph (kurtosis=-0.279). Figure 4 displays the corresponding histogram and density graph. The SD was slightly lower compared to the SD of LAEF before PVI (SD=12.99%). The minimum LAEF value is 18%, while the highest value is 70%.

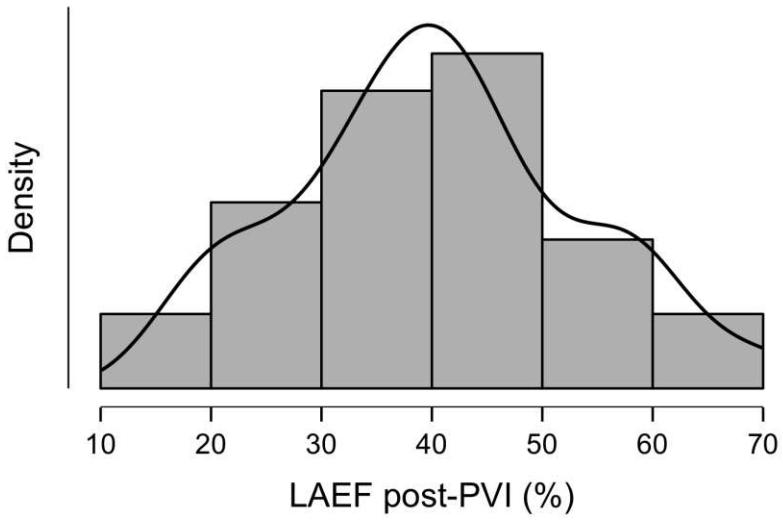

Figure 4. Distribution of LAEF post-PVI (%)
Data are presented as histogram and density graph

The LA-enhancement fibrosis has a mean of 17.62% and a median of 17.50%, which suggests a normal distribution. The skewness indicates a slight leftward screw (skewness=-0.292), and the negative kurtosis value illustrates a relatively flatter distribution (kurtosis=-0.683). Figure 5 displays the corresponding density graph and histogram.

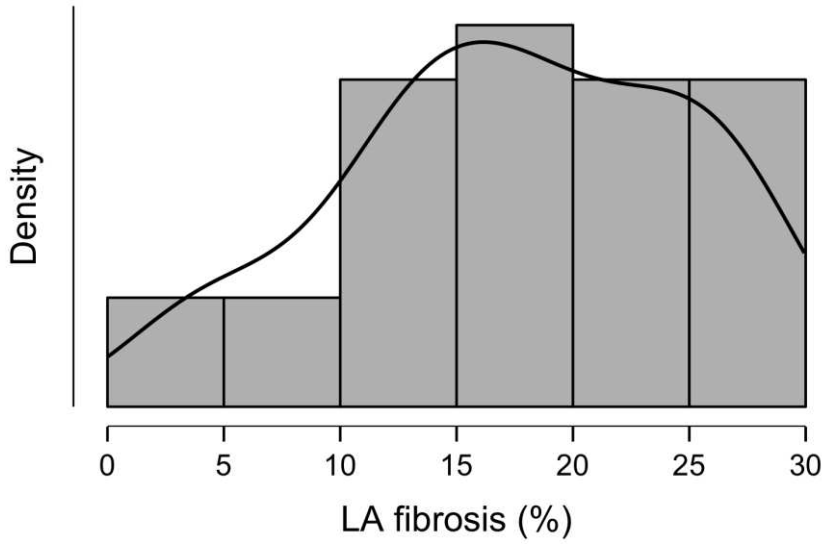

Figure 5. Distribution of LA fibrosis (%)
Data are presented as histogram and density graph

The LA volume pre-PVI had a mean of 106.2cm^3 and a median of 103.30cm^3. This difference is larger than in the previous three cases. Nevertheless, it most likely indicates a normal distribution. The SD is 24.35cm^3, and measured values ranged from 65.80cm^3 to 158.70cm^3. The skewness displays a slight rightward skew of 0.407, while the kurtosis again indicates a relatively flatter distribution with -0.524. This corresponds with the findings in histogram and density graph in figure 6. The bars of the histogram illustrate that most patients had a LA volume of 80-100cm^3, followed by 120-140cm^3.

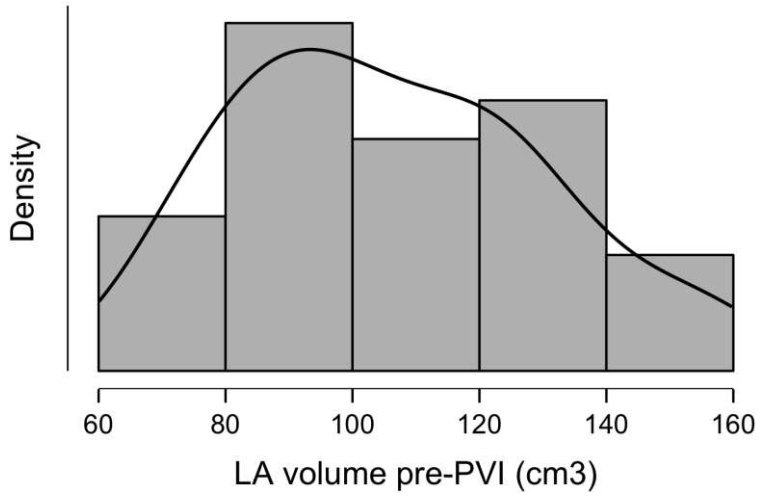

Figure 6. Distribution of LA volume pre-PVI (cm^3)
Data are presented as histogram and density graph

The average value in the case of distribution of LA volume post-PVI is 100.57cm^3 and its median is 95.40cm^3. This is the biggest difference observed between measured mean and median value. The skewness of 0.195 indicates a slight rightward skew, while the kurtosis of -0.479 again suggests less peaked graph. Figure 7 displays these findings. As seen in the histogram, most patients had a LA volume between 80-100cm^3.

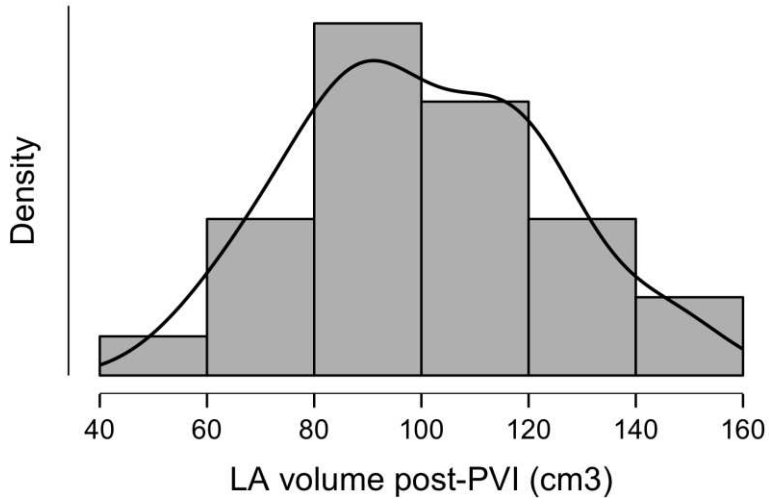

Figure 7. Distribution of LA volume post-PVI (cm^3)
Data are presented as histogram and density graph

Table 3. Descriptive data for LAEF, LA fibrosis, LA volume before and after PVI

	Mean	Median	SD[e]	Minimum	Maximum	Skewness	Kurtosis
LAEF[a] pre-PVI[b] (%) (N=30)	39.03	40.00	13.69	14.00	65.00	0.092	-0.988
LAEF post-PVI (%) (N=30)	40.43	40.00	12.99	18.00	70.00	0.228	-0.279
LA[c] fibrosis (%) (N=29)	17.62	17.50	7.37	3.30	29.20	-0.292	-0.683
LA volume pre-PVI (cm^3) (29)	106.21	103.30	24.35	65.80	158.70	0.407	-0.524
LA volume post-PVI (cm^3) (N=27)	100.57	95.40	23.13	57.60	147.60	0.195	-0.479

Descriptive data presented as mean, SD, minimum, maximum, skewness and kurtosis
[a] Left atrial ejection fraction
[b] Pulmonary vein isolation
[c] Left atrium
[d] Induced scar tissue
[e] Standard deviation

4.3. LA fibrosis before PVI and LAEF before and after PVI

Table 4 displays information from the Pearson correlation that relates LA fibrosis with measured LAEF, both before and after PVI. With a Pearson correlation coefficient of -0.252, it can be seen that there was a marginally weak negative relationship between LAEF pre-PVI, and LA fibrosis. Additionally, the LA fibrosis and LAEF after PVI had a weak negative link (Pearson´s correlation coefficient=-0.188). Both measured *P*-values are not statistically significant and substantiate the missing link. (*P*=0.187 and *P*=0.328). The data points in our study scatter randomly with no discernible pattern, as shown in figures 7 and 8. This is in line with recent findings.

Table 4. Correlation between LA fibrosis and LAEF before and after PVI

	r† **(N=29)**	***p****
LAEF[a] pre-PVI[b] (%) and LA[c] fibrosis (%)	-0.252	0.187
LAEF post-PVI (%) and LA fibrosis (%)	-0.188	0.328

data are presented as pearson´s correlation coefficient and associated p-value
***** Pearson´s correlation test
† Pearson´s correlation coefficient
[a] Left atrial ejection fraction
[b] Pulmonary vein isolation
[c] Left atrium

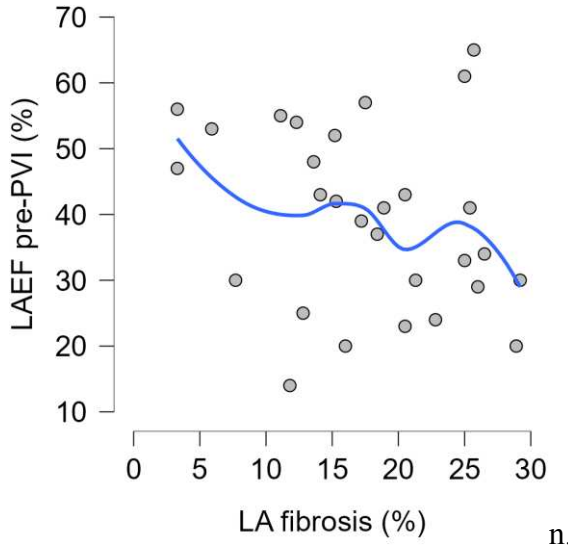

Figure 7. Correlation between LA fibrosis and LAEF pre-PVI
Data are presented as scatter plot
* not significant

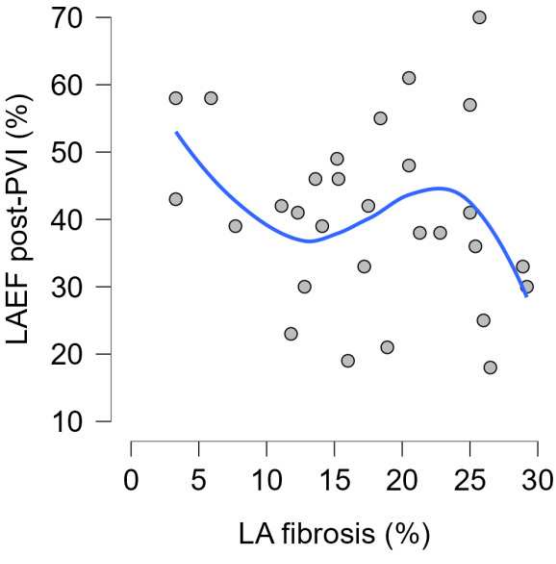

Figure 8. Correlation between LA fibrosis and LAEF post-PVI
Data are presented as scatter plot
* not significant

4.4. LA induced scar tissue and LAEF post-PVI

Table 5 shows the results of Pearson´s correlation that investigated a connection between the LA induced scar tissue and LAEF after PVI. The slight negative connection between LAEF after PVI and LA induced scar tissue showed a very weak relationship. The correlation indicated no statistically significance (*P*=0.706). Figure 9 supports the recent finding and illustrates that our measurements scatter randomly without clear pattern, supporting the recent finding.

Table 5. Correlation between LA induced scar tissue and LAEF post-PVI

	r† (N=27)	***p****
LAEF[a] Post-PVI[b] (%) and LA[c] induced scar tissue (%)	-0.090	0.655

Data are presented as pearson´s correlation coefficient and associated p-value
* Pearson´s correlation test
† Pearson´s correlation coefficient
[a] Left atrial ejection fraction
[b] Pulmonary vein isolation
[c] Left atrium

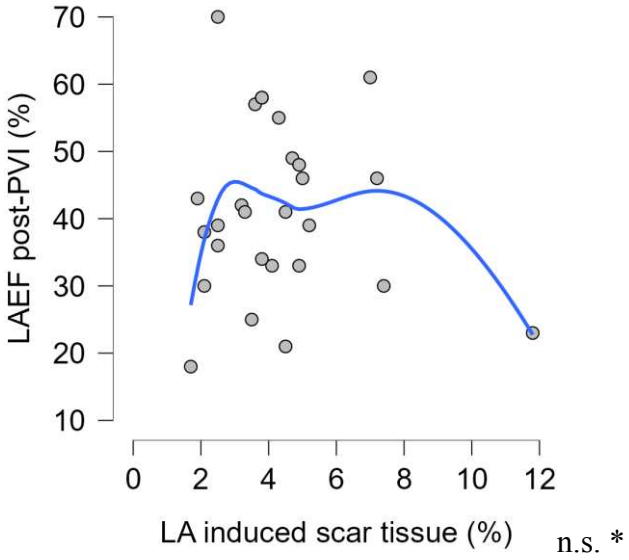

Figure 9. Correlation between LA induced scar tissue and LAEF post-PVI
Data are presented as scatter plot
*not significant

4.5. Association between LAEF and volume before and after PVI

In addition, we were interested in the association between LAEF and volume before and after PVI. In table 6 the association between these factors is illustrated. The measurements were implanted with the paired sample t-test for a comprehensive analysis of the results.

The t-value indicates that the observed change in LAEF is not significantly different to values that would be expected due to random variability. In addition, the p-value of 0.485 suggests no statistical significance. Based on these findings, there is no evidence that LAEF altered significantly after ablation.

Further on, the t-value of -2.721 shows a substantial decrease of LA volume after PVI. These findings are completed by the statistically significant change of LA volume before and after ablation (P=0.012). Consequently, we can say that the LA volume decreases significantly.

Table 6. Association between EF, volume and LA enhancement before and after PVI

	t†	**df‡**	***P****
LAEF[a] pre-PVI[b] (%) and LAEF post-PVI (%) (N=30)	0.708	29	0.485
LA[c] volume pre-PVI (cm^3) and LA volume post-PVI (cm^3) (N=26)	-2.721	25	0.012

Results presented as paired sample t-test and corresponding t-value, df and p-value
* paired-sampled t-test
† t-value
‡ degrees of freedom
[a] Left atrial ejection fraction
[b] pulmonary vein isolation
[c] left atrium
[d] degree of freedom

5. DISCUSSION

This retrospective study mainly aimed to investigate the influence of atrial fibrosis before and induced scar tissue after PVI on left atrial function in patients with AF. In the beginning, we checked patient´s characteristics. Many additional variables were analyzed, including LAEF before and after PVI, LA fibrosis, as well as the LA volume. Furthermore, we also demonstrated an association between LAEF and volume of LA, both before and after PVI. Due to the retrospective nature of our study, potential biases are possible. Firstly, we analyzed the proportion of patients taking certain medication. 100% of our sample were taking beta-blockers and 96.66% took NOACs, which is typically given in patients with AF. In addition, demographic information about our patients including gender, age, BMI, along with specific patient characteristics were collected. In our study we had an equal distribution between women and men. Especially a gender distribution is not good illustrated by a small sample size. No current study indicates that a clear gender has a predilection for AF, but apparently the sex difference seems to play a role in responsiveness to medical therapy and CA (74). The mean age was 67 years, aligning with the connection between general aging and cardiovascular aging, which is often associated with AF development (75). Our mean BMI accounts to 28.27, classifying as pre-obese. This result resonates with the known connection between overweight and many comorbidities (76). So, it`s not surprisingly that obesity and AF are connected as well (77). Further on, we note a few other patient characteristics. In our study 93.33% of patients had arterial hypertension, 66.66% had hyperlipidemia, 33.33% CAD and 23.33% diabetes mellitus. Whereas dyslipidemia can act as an amplifier or risk factor for AF, CAD, arterial hypertension and diabetes mellitus are major factors for the occurrence of AF (78). Most of our variables indicate a normal distribution. However, we should interpret these results with cautiously, considering the small sample size´s influence and potential presence of outliers. In certain cases, density graphs illustrate flatter trends, indicating broader spread of values. This broader distribution could signal increased variability of our results. Our mean LAEF before PVI measured approximately 39%. Since a standard LAEF isn´t available, we refer to a study that reported an average LAEF of around 56% (73). Our average was notably lower compared to this reference. This discrepancy could potentially be caused by generally poorer heart function of our patients compared to those in the reference study. The disparity might also be influenced by the small sample size and the limitations associated with manual imaging of the LA borders. Limitations will be discussed in further detail later on. We did not find a correlation between LA fibrosis and LAEF before and after PVI. The relatively high p-values (P=0.187 and P=0.328) indicated that our measurements were not statistically significant. Therefore, the observed connection might have arisen by chance. Nevertheless, the Pearson´s correlation

coefficient indicated a likelihood that higher LA fibrosis corresponds to lower LAEF and vice versa. At a pathophysiological level, it would make sense that atrial function would decrease with increased atrial structural remodeling. The atrium´s pumping capacity would decrease, consequently resulting in a lower LAEF. Further studies could investigate whether this connection is statistically significant or a chance occurrence. A more extensive study with a larger sample size could potentially uncover a significant association. One study discovered that increased LA enhancement might lead to a decrease in the efficiency of pumping (79). This difference in results could be attributed to the limitations of our study, which will be further discussed later on. More comprehensive research that offers insights into the connection between atrial remodeling and function could be relevant for future therapeutic strategies. For further studies, we recommend larger and diverse sample sizes to achieve clearer results and improve statistical power. Moreover, further research could also evaluate control groups without any known cardiac conditions to establish a baseline for LA fibrosis and LAEF correlation. We furthermore investigated, if there is a correlation between LA induced scar tissue after PVI and LAEF post PVI. We could not find a direct correlation between those factors. The Pearson´s correlation coefficient even suggested a weaker association between the variables compared to our earlier case**.** Therefore, our results suggest that with increasing or decreasing LA induced scar tissue the LAEF develops relatively independently. On the contrary, another study explored a direct link between LA function and induced scar tissue (80). This variation in findings may be caused by the potential limitation of manual imaging, which will be discussed as a limitation later on. Besides the already mentioned aspects that could be improved in following studies, exploring additional links between those factors and clinical outcomes like cardiovascular events, morbidity, mortality would be informative. As next point we examined the association between LAEF and volume of LA before and after PVI. Regarding changes in LAEF before and after we could not find any significance. Other researches were occupied by the same question. Some reported a significant 14% LAEF decrease after PVI (80). Whereas others discovered preserved contractile function, even after several CAs (81). And again, increasing the sample size in future studies could enhance the likelihood of obtaining more conclusive results. Apparently, also the type of AF may play an influence on the LAEF trend. Another study demonstrated that even years after successful ablation, contractility and compliance showed to be significantly reduced in patients with persistent AF (82). Additionally, we also investigated the association between LA volume before and after PVI, which resulted into a statistically significant decrease of LA volume after PVI, consistent with previous research (80). This may indicate an improvement of LA anatomy after PVI. Other

studies also documented significant reductions in LA volume post-PVI (83). From a pathophysiological perspective, the decrease in LA volume after PVI seems to make sense. Firstly, due to the fact that PVI improves the atrium´s efficiency, minimizing the need for excessive stretching. Secondly, the reduced strain on the atrium leads to a decrease in its volume, resulting in the observed outcome. In the end, we will discuss our limitations. Our retrospective study introduces selection bias, as the included patients are not representing the entire population. In addition, the retrospective study design lacks the ability to control the exposure and intervention, making it challenging to establish causality or determine the direction of observed relationships. This can lead to misleading associations between our measured variables. Furthermore, varying accuracy and completeness of medical records could affect the reliability and validity of our findings. We also have to consider the impact of our sample size (N=30) on the accuracy of our results. Specifically, our small sample size is not presentative for the whole population, lowering our statistical power and making significant connections between our measurements more challenging to detect. Moreover, manual imaging of the LA borders might introduce inter-observer variability that could alter the accuracy and precision of our measurements.

6. CONCLUSION

In conclusion, this retrospective study primarily focused on exploring the correlation between atrial fibrosis/atrial induced scar tissue and atrial function. Our findings revealed no significant correlation between these factors. Consequently, our hypothesis suggesting an influence of atrial fibrosis and atrial induced scar tissue on left atrial function can be rejected. Furthermore, the analysis of the association between LAEF before and after PVI indicated no statistically significance. However, the association between LA volume before and after PVI demonstrated a significant reduction of volume, which may indicate an improvement of LA anatomy after PVI.

7. REFERENCES

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8. SUMMARY

Objectives: The aim of this study is to determine the influence of atrial fibrosis before and induced scar tissue after PVI on the left atrial function in patients with paroxysmal AF.

Materials and methods: 30 patients from the cardiology department of REGIOMED Hospital in Coburg, Germany, were included in this retrospective, non-invasive and non-randomized study, using data collected between June 2021 and June 2022. Inclusion criteria comprised high-quality MRI scans, sinus rhythm during both pre-MRI and post-MRI, and initial ablation between both MRI scans. At first, we analyzed patient characteristics. For age and BMI, we calculated the mean, median and range. Furthermore, we looked at the cine sequences and measured the LA function by using CVI 42. The next step was detecting the LA fibrosis before PVI and observing the LA induced scar tissue 3 months after PVI by analyzing MRI scans. In addition, the LA volume before and after PVI was analyzed. For this, the Merisight software was used. The collected data was analyzed with JASP (Version 0.17.2.0). The distribution was measured with mean, median, skewness and kurtosis. Afterwards we correlated our measured LA fibrosis/induced scar tissue with LAEF with the Pearson´s correlation test. We measured the association between LAEF and volume, both pre- and post-PVI, with the paired sample t-test. The significance level was set to a P-value of <0.05.

Results: All of our variables had an approximate normal distribution. There was no correlation observed between LAEF pre-PVI and LA fibrosis (*P*=0.187), nor between LAEF post-PVI and LA fibrosis (*P*=0.328). However, the Pearson´s correlation coefficient did suggest that larger LA fibrosis could correspond to lower LAEF and vice versa. In addition, no correlation between LAEF post PVI and LA induced scar tissue was observed (*P*=0.655). Furthermore, no association between EF before and after PVI was found (*P*=0.485). In contrast, a significant connection between LA volume (*P*=0.012) before and after PVI was noticed. It showed a significant decrease of volume after PVI, which may indicate an improvement of LA anatomy after PVI.

Conclusions: In conclusion, this retrospective study primarily focused on exploring the correlation between atrial fibrosis/atrial induced scar tissue and atrial function. Our findings revealed no significant correlation between these factors. Consequently, our hypothesis suggesting an influence of atrial fibrosis and atrial induced scar tissue on left atrial function can be rejected. Furthermore, the analysis of the association between LAEF before and after PVI

indicated no statistically significance. However, the association between LA volume before and after PVI demonstrated a significant reduction of volume, which may indicate an improvement of LA anatomy after PVI.

9. CROATIAN SUMMARY

Ciljevi: Cilj ove studije je utvrditi utjecaj atrijalne fibroze prije i inducirane ožiljne tkivu nakon PVI na funkciju lijevog atrija kod bolesnika s paroksizmalnom fibrilacijom atrija.

Materijali i metode: U ovoj retrospektivnoj, neinvazivnoj i ne-randomiziranoj studiji uključeno je 30 pacijenata iz kardiološkog odjela REGIOMED bolnice u Coburgu, Njemačka, koristeći podatke prikupljene između lipnja 2021. i lipnja 2022. Kriteriji za uključivanje obuhvaćali su visokokvalitetne MRI snimke, sinusni ritam tijekom obje pre-MRI i post-MRI faze te početnu ablacija između obje MRI snimke. Prvo smo analizirali karakteristike pacijenata. Za dob i indeks tjelesne mase (BMI) izračunali smo srednju vrijednost, medijanu i raspon. Nadalje, analizirali smo filmske sekvence i mjerili funkciju lijevog atrija koristeći CVI 42. Sljedeći korak bio je detektiranje fibroze lijevog atrija prije PVI i promatranje induciranog ožiljnog tkiva 3 mjeseca nakon PVI analizom MRI snimaka. Dodatno, volumen lijevog atrija prije i poslije PVI-a je analiziran. Za to smo koristili Merisight softver. Prikupljeni podaci analizirani su uz pomoć JASP-a (verzija 0.17.2.0). Distribucija je izmjerena pomoću srednje vrijednosti, mediane, asimetrije i ekscesa. Zatim smo korelirali našu izmjerenu fibrozu lijevog atrija/inducirano ožiljno tkivo s LAEF pomoću Pearsonovog koeficijenta korelacije. Mjerili smo povezanost između LAEF i volumena, i prije i poslije PVI, pomoću uparenog uzorka t-testa. Razina značajnosti postavljena je na P-vrijednost <0,05.

Rezultati: Svi naši varijable imali su približno normalnu distribuciju. Nije uočena korelacija između LAEF prije PVI i fibroze lijevog atrija (P=0,187), niti između LAEF nakon PVI i fibroze lijevog atrija (P=0,328). Međutim, Pearsonov koeficijent korelacije sugerira da veća fibroza lijevog atrija može odgovarati nižem LAEF i obrnuto. Nadalje, nije uočena korelacija između LAEF nakon PVI i induciranog ožiljnog tkiva lijevog atrija (P=0,655). Nadalje, nije pronađena povezanost između EF prije i nakon PVI (P=0,485). Nasuprot tome, primijećena je značajna veza između volumena lijevog atrija (P=0,012) prije i nakon PVI. Pokazano je značajno smanjenje volumena nakon PVI, što može ukazivati na poboljšanje anatomije lijevog atrija nakon PVI.

Zaključak: U zaključku, ova retrospektivna studija prvenstveno je istraživala korelaciju između atrijalne fibroze/induciranog ožiljnog tkiva i funkcije atrija. Naši rezultati nisu pokazali

značajnu korelaciju između ovih faktora. Stoga se može odbaciti naša hipoteza koja sugerira utjecaj atrijalne fibroze i induciranog ožiljnog tkiva na funkciju lijevog atrija. Nadalje, analiza povezanosti između LAEF prije i nakon PVI nije ukazala na statističku značajnost. Međutim, povezanost između volumena lijevog atrija prije i nakon PVI pokazala je značajno smanjenje volumena, što može ukazivati na poboljšanje anatomije lijevog atrija nakon PVI.