Factors associated with left atrial myopathy in patients with sinus rhythm

Jakob, Eva-Maria Gertrud

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Eva-Maria Jakob

FACTORS ASSOCIATED WITH LEFT ATRIAL MYOPATHY IN PATIENTS WITH SINUS RHYTHM

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Dr. med. Christian Mahnkopf, PhD

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LIST OF ABBREVIATIONS

ACE-inhibitors – angiotensin-converting enzyme inhibitors

AF – atrial fibrillation

AVN – atrioventricular node

ASA – acetylsalicylic acid

Bpm – beats per minute

BMI – body mass index

Cx – connexin

ECG – electrocardiogram

ECM – extracellular matrix

Gd – gadolinium based media

HCN – hyperpolarization-activated cyclic nucleotide-gated

HF – heart failure

LA – left atrium

LAM – left atrial myopathy

LGE – late gadolinium enhancement

LV – left ventricle

MI – myocardial infarction

MRI – magnetic resonance imaging

NOAC – new oral anticoagulant

PTFV1 – P wave terminal force in lead V1

ROS – reactive oxygen species

S – seconds

SAN – sinoatrial node

SGLT2-inhibitors – sodium glucose transporter 2 inhibitors

STE – speckle tracking echocardiography

TEE – transesophageal echocardiography

TDI – tissue doppler imaging

TGF beta 1 - transforming growth factor beta 1

TTE – transthoracic echocardiography

1. INTRODUCTION

1.1. Introductory words

The expression “atrial myopathy” was introduced by Zipes in 1997, suggesting that atrial fibrillation (AF) might induce a pathologic remodeling process in the atrial myocytes. During the last twenty years, our understanding of atrial myopathy has significantly evolved (1).

The left atrium is crucial for the normal rhythm of the heart due to hosting pacemaker cells (2). It also is responsible for filling of the left ventricle by serving as a storage, passive channel, an active pump and regulator of the blood pressure by secreting A-type natriuretic peptide when mechanically stretched (3).

Left atrial myopathy (LAM) stands out as a key non-left-ventricular factor contributing to disease progression in cardiac patients (4). The structural changes may initiate a vicious circle that precipitates AF, which in turn exacerbates the condition of atrial myopathy. The pathogenesis of atrial myopathy is multifactorial with several contributing factors (5).
With AF being the most common arrhythmia worldwide (6), most of the studies focused on patients with LAM and AF. However, it is of interest to know whether and which factors are associated with LAM in patients with sinus rhythm.

Thus, we decided to evaluate the factors associated with left atrial myopathy in patients with sinus rhythm.

1.2. Left atrial myopathy

The following section focuses on the left atrium and LAM in general, its anatomy, histology, etiology and pathophysiology. The effects of LAM on the cardiovascular system including the heart and its rhythm will be described to provide an overview of the importance of further investigations on this topic.

1.2.1. Definition of atrial myopathy

Atrial myopathy describes any changes in structure, contraction and function of the atria with the possibility of leading to manifestations important to clinical practice, including aberrant contractility, fibrotic and dilated myocardium, pressure overload and autonomic derangement (2,5,7).

1.2.2. Structure and function of the heart

The focus in the following sections is on the heart in general, its anatomy, histology and the cardiac conduction system.

1.2.2.1. Anatomy of the heart

The heart is positioned in the middle mediastinum between the lungs and consists out of left and right atria and ventricles. The four chambers of the heart are organized into two parts, the left and the right pumping unit. The right atrium receives the deoxygenated blood from the body via the superior and inferior vena cava and deoxygenated blood from the heart muscle via the coronary sinus. The blood is transported via the tricuspid valve into the right ventricle from where it is pumped through the pulmonary valve into the pulmonary artery and the lungs for gas exchange. The oxygenated blood from the lungs drains via the four pulmonary veins into the left atrium. The left ventricle (LV) receives the oxygenated blood from the left atria via the mitral valve. It pumps the blood through the aortic valve into the systemic circulation (8).

The left atrium is oriented towards the left and posteriorly to the right atrium. Left atrial arrangement is characterized by pulmonary veins, a lateral appendage and an inferior vestibular component surrounding the mitral orifice. The structure is smooth except for the appendage being more rough with pectinate muscles (9).

1.2.2.2. Histology of the heart

The heart compromises three main layers: the inner endocardium; the middle myocardium; and the outer epicardium.

The endocardium includes endothelium, smooth muscle fibers and connective tissue and the subendocardial layer consisting out of connective tissue and branches of the impulse conducting system. The myocardium which is the thickest layer, is mainly out of cardiac muscle with spirally arranged fibers and also contains modified cardiac muscle cells from the conduction system of the heart. The epicardium, a simple squamous mesothelium, is supported by loose connective tissue with blood vessels and nerves (10). The cardiac extracellular matrix (ECM) not only consists out of collagen type I and type III, it also contains glycoproteins, glycosaminoglycans and proteoglycans. All of these can be activated following an injury to promote repair (11). Next to the cardiomyocytes and endothelial cells also fibroblasts play an important role in regulating the structural integrity of the heart (11).

1.2.2.3. Cardiac conduction system

The heart as a pump creates pressure to sustain the circulation (12). Rhythmic contractions of atria and ventricles are mandatory to function properly. All myocytes within the heart possess the ability to conduct cardiac impulses. A specialized group of myocytes generate the cardiac impulse and direct it from atrial to ventricular chambers (13). This conduction system of the heart accounts for the electrical control and the regulation of correct contraction timing which leads to a unidirectional pathway of excitation. It sends electrical stimuli to the heart muscles to initiate and coordinate contraction.

The conduction system can be divided into four parts. The sinoatrial node (SAN) which generates the electrical impulse. It is isolated functionally from adjacent atrial myocardium with exception of specific conduction pathways and is positioned at the border of the superior vena cava and right atrium. The electrical impulse from the SAN travels to the atrioventricular node (AVN), which is localized at the base of the interatrial septum and is important for a slow propagation of the impulse. The next station of the cardiac conduction system compromises the atrioventricular-bundle with right and left bundle branches in the interventricular septum. Finally, the impulse reaches the subendocardial plexus of conduction cells (Purkinje fibers) (8,12,14).

1.2.3. Pathophysiology

Fibrosis represents a frequently encountered pathway leading to damage and dysfunction in multiple organs (5). After explaining the general anatomy and function of the heart this section will focus on the pathophysiology of atrial myopathy.

1.2.3.1. Development of fibrosis

The heart of an adult human comprises approximately 4-5 billion cardiomyocytes and 6% of healthy myocardium consist out of extracellular matrix (ECM) to support the contractile function (15). The ECM is a three-dimensional system out of elastic collagen fibers and different glycoproteins, glycosaminoglycans and proteoglycans (11). The network incorporates cardiomyocytes, blood vessels, cardiac fibroblasts, immune cells and represents the skeleton of the heart (16).

As a permanent tissue, the heart consists out of terminally differentiated nonproliferative cells. Due to the limited endogenous regenerative capability of the myocardium, substantial loss of cardiac muscle results in fibrotic scar formation (15,17).

Fibrosis is characterized by the additional installation of extracellular matrix components including collagen (18). It is the final result of a chronic inflammatory process that leads to the activation and proliferation of the key mediators: fibroblasts and myofibroblasts, which are modulated fibroblasts accumulating in sites of injury (18).

There are four main stages in the process of fibrosis finally leading to progressive remodeling and destruction of normal myocardial architecture: the onset of body's reaction to the initial injury or persistent irritant, proliferation of effector cells, expansion of extracellular matrix (ECM) and progression towards fibrosis and organ failure resulting from excess matrix deposition (18).

Two pathogenic mechanisms can lead to fibrosis as illustrated in figure 1: "reparative" fibrosis repairing areas of myocardial cell death unable to regenerate and "reactive" fibrosis reacting on various stimuli and mediators for example pressure overload, chronic inflammation, aging and growth factors. These growth factors are typically produced by epithelial cells and macrophages near the site of damage. Several cytokines and growth factors such as transforming growth factor beta 1 (TGF beta 1), endothelin 1, angiotensin 2 and interleukin-1 bind to ECM proteins and activate signaling pathways inducing changes in gene expression. This causes proliferation of fibroblasts and myofibroblasts (5,11,17).

Cardiac fibroblasts also contribute to fibrosis themselves while sensing mechanical stress through their receptors (11). Correspondingly, atrial fibrosis is primarily composed of disorganized myocytes and collagen, resulting in an expanded extracellular space when compared to healthy myocardium as seen in figure 1 (19).

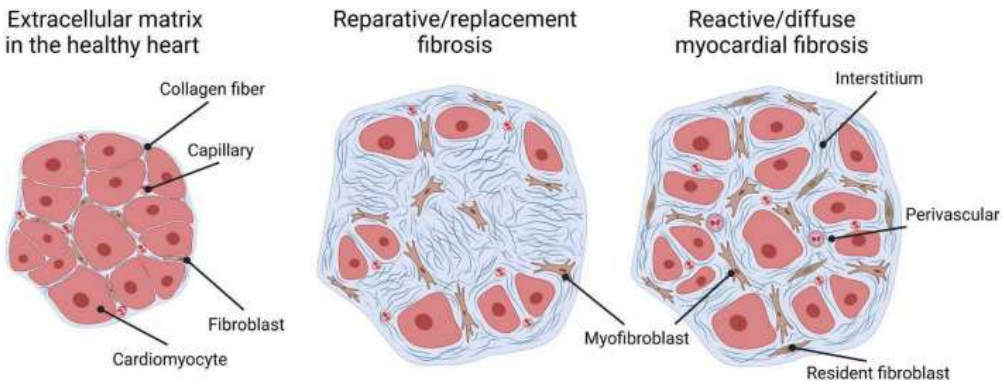

Figure 1. Types of cardiac fibrosis

Source: Schimmel K, Ichimura K, Reddy S, Haddad F, Spiekerkoetter E. Cardiac fibrosis in the pressure overloaded left and right ventricle as a therapeutic target. Front Cardiovasc Med. 2022;9:886553.

1.2.3.2. Electrophysiological remodeling

Atrial myopathy is a significant contributor creating the basis for electrophysiological remodeling due to changes in ion channels, excitation-contraction coupling and gap junctions (1,5,20).

Excessive and uncontrolled production of ECM by myofibroblasts can lead to reduced myocardial compliance, impeding ventricular filling and disruption of electrical coupling predisposing to rhythm disturbances (17). The presence of collagenous septa, which serve passively as medium for signal transmission, the blockage of impulse conduction and the heterogenous propagation are risk factors for arrhythmias and create a condition leading to re-entry (21). These changes are responsible for differences in conduction velocity, action potential duration and refractory period.

Two main gap junction proteins connexin (Cx) 40 and Cx43 are identified mediating electrical coupling between cardiomyocytes. Irregular distribution of Cx40 and Cx43 as seen in atrial myopathy often later will be related to atrial fibrillation (1).

Oxidative stress linked to atrial myopathy induces rapid atrial myocyte depolarization which leads to intracellular calcium overload, activating immune responses and apoptosis which in turn triggers atrial fibrosis (1).

In addition to atrial dilation, mitochondrial reactive oxygen species (ROS) and activation of inflammatory and pro fibrotic mediators result in fibrosis of the interstitium, hypertrophy of cardiac myocytes and remodeling of ion channels. In summary all these factors lead to progression from sinus rhythm to atrial fibrillation and present a vicious cycle in which arrhythmias generate arrhythmias (1).

1.2.4. Etiology

A wide range of different possible conditions that contribute to the development of left atrial fibrosis are known.

Reparative, also called replacement fibrosis, most often results from a healing process after cardiomyocyte death due to myocardial infarction (MI) (16).

Reactive fibrosis is an adaption to support the higher workload of the heart caused by chronic cardiac conditions such as chronic heart failure (HF) with pressure overload, hypertension or aortic stenosis (16).

There is a pathophysiologic heterogeneity of myocardial diseases and many different possible risk factors for atrial myopathy including: age, inflammatory reactions, oxidative stress and volume overload of the atria (20).

Cardiomyopathy affecting the heart in general also contributes to the ECM deposition. It can be divided into primary and secondary categories. These may result in different phenotypes including dilated, hypertrophic and restrictive patterns (22).

In primary cardiomyopathies the disease process is limited to the heart. This can be genetic, acquired or mixed in relation to its etiology (22).

In secondary cardiomyopathy, many systemic conditions lead to structural changes of the cardiac muscle. Secondary causes can be autoimmune such as sarcoidosis, rheumatoid arthritis, psoriasis or inflammatory bowel disease (23). A wide range of metabolic diseases characterized by adipose tissue inflammation may also lead to LAM. These include metabolic syndrome, type 2 diabetes mellitus and non-alcoholic liver disease (23).

Infectious diseases, infiltrative conditions such as amyloidosis, neuromuscular disorders, nutritional deficiencies or toxic states like alcoholism, can be found underlying to cardiomyopathy (22). For example, in amyloidosis, in which besides the left ventricle also the left atrial myocardium becomes replaced with amyloid, the increased LA pressure leads to akinetic and stiff atrium (24).

The genetic X-linked disorder Fabry disease which leads to the intracellular accumulation of glycosphingolipids in different tissues including the heart may also be a cause for atrial myopathy (25).

1.2.5. Clinical evaluation

Atrial myopathy can macroscopically be seen as non-AF atrial arrhythmias, reduced atrial systole, dilated atrium or pathologic cardiac imaging findings (1,26). Electrocardiogram (ECG) and imaging methods such as echocardiography and cardiac magnetic resonance imaging (MRI) are diagnostic techniques for atrial myopathy that will be presented in the following (5,26).

1.2.5.1. Electrocardiogram

The electrocardiogram (ECG) is a well-established and one of the most diagnostic tools utilized in clinical settings. It shows a graphical representation of the myocardial electrical activity recorded from surface electrodes (27).

For patients with sinus rhythm it represents a diagnostic procedure to check for developing atrial myopathy and AF (5).

The P wave terminal force in lead V1 (PTFV1) throughout sinus rhythm in a standard 12-lead ECG is associated with abnormalities in the left atrium. A large cohort study showed that PTFV1 > 0.06 mm/s was related to a higher risk for the development of cardioembolic stroke independently of AF. The study also presented that in contrast to a PTFV1 ≥ 0.04 mm/s that is commonly found in a 12-lead ECG of middle-aged subjects a PTFV1 ≥ 0.06 mm/s is associated with an increased risk for atrial fibrillation and death in the general population (5,28). Atrial arrhythmias except AF, for example atrial premature beats or paroxysmal atrial tachycardia, could suggest pathological atrial alterations and a susceptibility to AF which is also often associated with atrial myopathy (1).

1.2.5.2. Echocardiography

Echocardiography is a diagnostic ultrasound technique used for screening and follow up of patients with diseases involving the morphology and function of the atrium. Due to its functions such as strain Doppler, speckle tracking echocardiography (STE) or 3D echocardiography, it is possible to recognize an early atrial dysfunction before clinical symptoms may become apparent (9,29).

Echocardiography is a cheap and minimally invasive easily available procedure in the hospital setting and it provides significant information about the left atrium or the heart's function in general (30).

The most frequently used variants are transthoracic echocardiography (TTE), stress echocardiography and transesophageal echocardiography (TEE) (30).

Initially, Tissue Doppler imaging (TDI) was the echocardiographic procedure of choice to evaluate function of the atria but it shows certain limitations such as low reproducibility, angle dependence and single artifacts (31,32).

STE using two-dimensional echocardiography can overcome these limits. It is a non-Doppler technique that provides objective measurement of atrial shape from standard two-dimensional images, allowing analysis of strain and longitudinal strain rate of LA segments based on their shape relative to their original length. The longitudinal deformity of LA is a good parameter for the assessment of its function (31,32).

During sinus rhythm, when using STE, you can identify a positive peak strain relating to the reservoir phase during LV systole and a negative peak corresponding to the contraction of the atria (32). Echocardiographic parameters vary according to gender, body habitus, ethnicity, fitness level and age (31,32).

At the end-ventricular systole when the LA chamber is at its greatest width, the measurement of the LA size is accomplished. The anterior-posterior diameter is measured in the long-axis view and the longitudinal and transverse diameters are measured in 4-chamber view. An abnormal size of the LA can be related to adverse cardiovascular outcomes and impaired function of the LV. There is a potential correlation between an increase in size of the LA and the incidence of AF and stroke (9).

Not only the dimensions but also the LA volumes are measured by echocardiography. These include the left atrial active emptying volume, the left atrial filling volume and the left atrial passive emptying volume (9).

The pulsed Doppler examination giving information about the transmitral flow and the pulmonary venous flow in the left atrium. During beginning of atrial systole, LA systolic function relies on pressure and contraction of the LA. These values can vary in relation to aging and pathological changes (9).

1.2.5.3. Cardiac magnetic resonance imaging

Nowadays the gold standard for examination of structure and function of the heart's chambers is the cardiac magnetic resonance imaging (MRI). It is among the leading diagnostic procedures for the evaluation of morphological, functional and phenotypic cardiomyopathies. Apart from associated costs, acquiring accurate images necessitates a high level of expertise and substantial time for processing. Late gadolinium enhancement (LGE) is an innovative step for assessment of cardiomyopathies especially myocardial fibrosis. (1,33).

Delayed enhancement MRI is a successful modality to recognize fibrotic nonviable ventricular myocardium (34).

The percentage of fibrosis in the LA can be classified into four Utah stages as seen in figure 2. Stage 1 includes 0-10% fibrosis, stage II 10-20% fibrosis, III 20-30% fibrosis and stage IV more than 30% fibrosis (35).

Gadolinium-based media (Gd) as extracellular contrast agents, spreads in the interstitial space after being injected into peripheral veins. In healthy myocardium, Gd stays only for a few minutes before leaving through venules and the lymphatics. Late gadolinium enhancement (LGE) may be caused due to an increased interstitial space or a slower exit out of it (33).
As already discussed, fibrosis results from a remodeling process including excessive ECM deposition, which may lead to an increase of interstitial space. In every patient with suspicion of cardiomyopathy LGE technique should be accomplished (18).

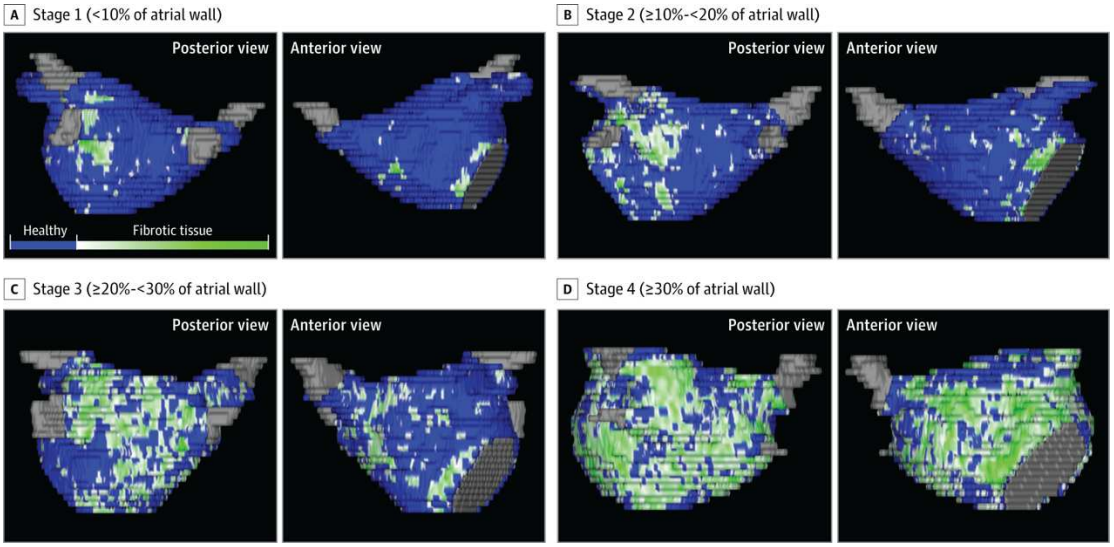

Figure 2. Four Stages of Left Atrial Tissue Fibrosis Based on 3D Delayed Enhancement. Magnetic Resonance Imaging Scans Representative example from 4 different patients of each stage of left atrial tissue fibrosis. Normal left atrial wall is displayed in blue; fibrotic changes are in green and white. Stages 1 through 4 show increasing amounts of fibrosis as a percentage of the total left atrial wall volume. The pulmonary veins and mitral valve are shown in gray.

Source: Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311:498-506.

1.2.6. Effects of left atrial myopathy

Animal models and human studies demonstrated that AF results in fibrosis of the atria (34,36,37). LAM may initiate a vicious cycle in which it leads to atrial fibrillation or stroke. As seen in figure 3 atrial myopathy caused by different factors and mediators such as inflammation or oxidative injury leads to endothelial damage. The blood stasis provides a prothrombotic environment. The electrophysiological alterations and the fibrotic composition contribute to rhythmical changes including atrial fibrillation. This interplay between thrombosis and atrial fibrillation leads to a deterioration of the prothrombotic state also reinforced by multiple cytokines and molecules (1).

There is a hypothesize stating that persistent atrial tachycardia leads to increased TGF-beta 1 levels which in turn promote atrial fibrosis as described above (1,5). Left atrial fibrosis is significant in patients with AF. It is associated with bad clinical outcomes and negative effects on AF catheter ablation (34).

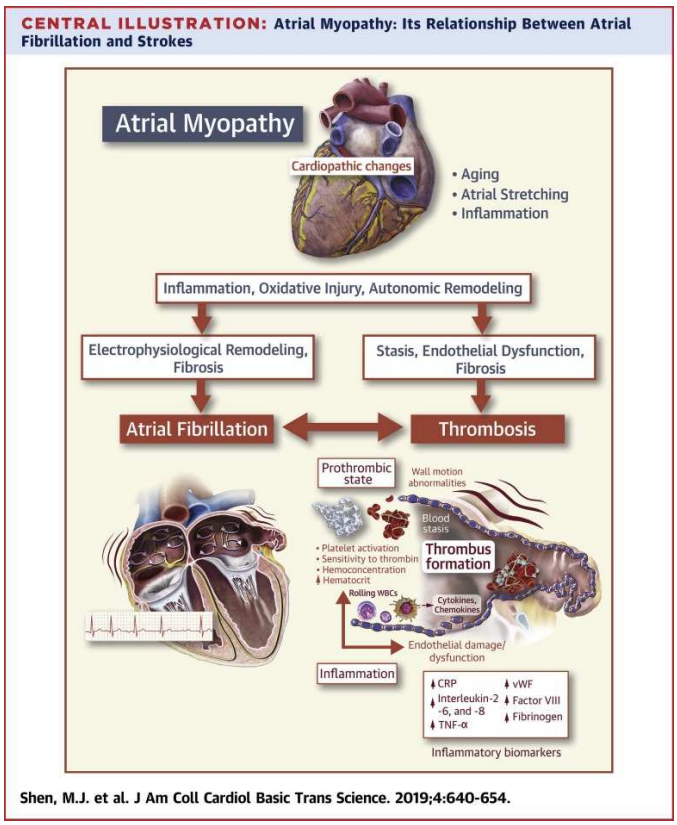

Figure 3. Atrial myopathy: Its Relationship between atrial fibrillation and strokes

Source: Shen MJ, Arora R, Jalife J. Atrial myopathy. JACC Basic Transl Sci. 2019;4:640-54.

1.3. Sinus rhythm

In the following we will focus on the sinus rhythm in general, how it is generated via the SAN and how it is defined.

1.3.1. Definition

Sinus rhythm refers to the normal cardiac rhythm that is initiated by the sinoatrial node and transmitted to the AV node, bundle of His, bundle branches and Purkinje fibers as described above. It describes a regular rhythm with a pacemaker activity of 60 to 100 beats per minute (bpm) (38). On the representative ECG the atrial depolarization is represented by the P wave with a duration < 0.12 seconds (s) and an amplitude < 0.25 mV before every QRS complex. Sinus P waves are generally oriented upright in leads I and II, inverted in lead aVR and biphasic in V1 due to the direction of the depolarization that is directed inferiorly and to the left. The P wave is best seen in leads II and V1 (39).

1.3.2. Physiology of sinoatrial node

The SAN pacemaker cells initiate the heart rhythm. This happens due to a complicated but organized interplay of numerous ion currents (40). The diastolic depolarization that is initiated immediately after repolarization of preceding action potentials is generated by several currents: hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels also called funny current, L- and T- type Ca2+ currents, slowly activating delayed rectifier K+ currents and Na/Ca exchange current (41). There is a division of SAN action potential into three phases: Phase 4 is described as spontaneous depolarization which is started once the membrane potential reaches a threshold at about -60mV. The funny channels open and lead to slow inward Na+ currents which is followed by slow depolarization. After the inward sodium current opened and the membrane potential rises to a threshold at around -50mV, the voltage-gated-T-type Ca2+ channels contribute to the depolarization in phase 4. At around -40mV the L-type Ca2+ channels open and also contribute to Phase 4. The action potential threshold is reached. Phase 0 is caused by increased L-type Ca2+ channels that began to open at the end of Phase 4 while other channels being closed. The repolarization in Phase 3 is mediated by slowly activating delayed rectifier K+ currents which lead to hyperpolarization. Subsequently, the cycle is repeated. In the SAN there is no phase 1 and no plateau phase (42,43).

The autonomic nervous system regulates the activity of the sinus node to start cardiac cycles and thereby influencing the heart rate with the aim to meet the metabolic needs.
The sympathetic and parasympathetic system controls the heart rate. Acetylcholine provokes hyperpolarization and decreases diastolic depolarization which leads to a slower sinus rate. Catecholamines lead to tachycardia by accelerating the diastolic depolarization (41).

1.4. Therapeutic strategies

The regeneration of adult cardiac muscle is highly limited due to low regenerative capacity. Recent studies showing different anti fibrotic strategies for myofibroblasts but more research is needed (44). Routine monitoring for atrial fibrillation and focus on stroke prevention should be conducted on these patients.

2. OBJECTIVES

2.1. Aim of study

This study's main aim was to identify factors that are associated with the development of left atrial myopathy in patients without atrial fibrillation.

2.2. Hypothesis

The hypothesis states that left atrial myopathy can be detected in patients without atrial fibrillation and it is correlated to comorbidities.

3. MATERIALS AND METHODS

3.1. Ethical approval

This study received its approval by the Institutional Review Board (IRB) of the Medical School REGIOMED Coburg on the 6th of March 2024.

3.2. Study design

In this retrospective, non-invasive study, we enrolled sixty-five consecutive patients (57.65 ±13.6 years old; 40 men and 25 women) with sinus rhythm and without a history of AF that underwent LGE-MRI to assess for LA-Fibrosis.

Each LGE-MRI was divided into segments by isolation of the LA wall and quantified for the relative degree of fibrotic reorganization using the Corview software (Marrek Inc.). The comorbidities were documented and their correlation with the degree of left atrial fibrosis was investigated through the implementation of univariate and multivariate analyses.

Inclusion criteria for the study comprised high-quality MRI scans and patients with SR while exclusion criteria being AF.

This study was conducted in the period between March 2021 and February 2023 in the department of cardiology in the REGIOMED hospital in Coburg.

3.3. Data collection

A random sample of 65 patients with sinus rhythm that underwent LGE-MRI to assess for LA fibrosis was selected within the period from March 2021 and February 2023. We choose all relevant data from REGIOMED hospital information system (Orbis).

The basic demographic information included the hospital identification number of the patient, gender, age and body mass index (BMI).

Each LGE-MRI was segmented by isolating the LA wall and quantified for the relative extent of fibrotic remodeling using the Corview software (Marrek Inc.). The data in relation to left atrial fibrosis was composed of LA volume, fibrosis in percentage and the Utah classification. By utilization of Merisight image processing, segmentation and quantification of LA fibrosis and classification according to Utah was possible.

Details based on comorbidities included myocardial infarction (MI), coronary artery disease, coronary artery bypass graft (CABG), implanted device, valve surgery, smoking, hypertension, Diabetes mellitus, congestive heart failure (HF), cardiomyopathy, mitral valve regurgitation, stroke, hyperlipidemia, pulmonary arterial hypertension (PAH) and vasculitis.

In addition, information about regularly taken drugs including angiotensin-converting-enzyme inhibitors (ACE-inhibitors), beta-blocker, diuretics, new oral anticoagulants (NOAC), clopidogrel, Acetylsalicylic acid (ASA) and sodium glucose transporter 2 inhibitors (SGLT2-inhibitors) were gathered.

Information about participants was collected in an electronic database (Excel). The statistical analysis was performed anonymously. Traceability of patients is not possible.

3.4. Statistical analysis

For the statistical analysis the statistical program R Version 4.3.0 was used. The categorical data were expressed as number (n) and percentage (%).

We collected data observing the percentages of atrial fibrosis and the occurrence of previous events and comorbidities within our sample. Additionally, we documented if the previously listed drugs were taken by our patients.

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. Each variable's effect on the outcome is represented by an effect size, standard error, and p-value. To identify significant comorbidities, we will focus on variables with p-values < 0.05.

4. RESULTS

4.1. Characteristics of the patients

Sixty-five consecutive patients with normal sinus rhythm and without a history of AF underwent LGE-MRI to assess for LA-Fibrosis. The mean age of all patients was 57.65 ±13.6 years old with 40 of them being male and 25 being female. The mean BMI of all patients was 27.67 ± 4.57. Six patients have experienced MI and twelve patients already have a known coronary artery disease. 16 out of 65 patients were smokers. Diabetes was manifested in 10 patients and hypertension in 35 patients. Four out of 65 patients presented with congestive heart failure and five participants with a medical history of cardiomyopathy. Mitral valve regurgitation was present in one patient while six participants previously had experienced a stroke. Hyperlipidemia was present in 32 patients. No participant underwent coronary artery bypass graft surgery, cardiac device implantation or heart valve surgery. There were no patients with a previous medical history of pulmonary arterial hypertension or vasculitis.

In regard to regularly taken medication, 32 participants had ACE-inhibitor as well as beta-blockers included in their medication plan. Diuretics were prescribed in 13 patients and NOAC in five participants. 10 people took clopidogrel and 19 ASA. Two out of 65 participants had SGLT2-inhibitors in their regular medication.

The complete collected baseline information about participating patients are presented below in table 1.

Table 1. Baseline characteristics of enrolled patients

Comorbidities	Total n=65
Female sex	25 (38.5%)
Age – years mean (SD)	57.65 ± 13.6
BMI[a] – mean (SD)	27.67 ± 4.57
MI[b]	6 (9.2%)
Coronary artery disease	12 (18.5%)
CABG[c]	0 (0%)
Implanted device	0 (0%)
Valve surgery	0 (0%)
Smoker	16 (24.6%)
Hypertension	35 (53.8%)
Diabetes	10 (15.4%)
Congestive HF[d]	4 (6.2%)
Cardiomyopathy	5 (7.7%)
Mitral valve regurgitation	1 (1.5%)
Stroke	6 (9.2%)
Hyperlipidemia	32 (49.2%)
PAH[e]	0 (0%)
Vasculitis	0 (0%)
ACE[f]-inhibitor	32 (49.2%)
Beta-blocker	32 (49.2%)
Diuretics	13 (20%)
NOAC[g]	5 (7.7%)
Clopidogrel	10 (15.4%)
ASA[h]	19 (29.2%)
SGLT2[i] inhibitors	2 (3.1%)

Data are presented as mean±standard deviation (SD) or as number (%)
[a] Body mass index
[b] Myocardial infarction
[c] Coronary artery bypass graft
[d] Heart failure
[e] Pulmonary arterial hypertension
[f] Angiotensin converting enzyme
[g] New oral anticoagulants
[h] Acetylsalicylic acid
[i] Sodium-Glucose Transport Protein 2

The mean degree of LA fibrosis among individuals without AF was 13.52 ± 7.7 percent. The prevalence of LA-Fibrosis among the participants ranged from 2.6% to 34.7%. The mean LA volume among patients was 76.13 cm^3 ± 28.02 cm^3.

4.2. Univariate analysis

In the univariate analysis, the following parameters were all statistically significant associated with left atrial fibrosis: age ($p=0.022$), mitral valve regurgitation ($p=0.007$), congestive heart failure ($p=0.026$), LA volume ($p<0.001$), weight ($p=0.010$), cardiomyopathy ($p=0.032$) and ASA ($p=0.011$). Marginal significance was found in patients with Diabetes ($p=0.051$).

Non-significant findings were associated with gender ($p=0.730$), higher BMI ($p=0.064$), myocardial infarction ($p=0.174$), coronary artery disease ($p=0.156$), smoking ($p=0.679$), hypertension ($p=0.370$), stroke ($p=0.171$), hyperlipidemia ($p=0.146$), ACE inhibitors ($p=0.226$), beta blockers ($p=0.461$), diuretics (0.299), NOAC (0.937), clopidogrel ($p=0.235$) and SGLT2-inhibitors ($p=0.227$).

In table 2 the comorbidities are listed along with its associated p-value, standard error (SE) and effect sizes.

Table 2. Univariate analysis of comorbidities

Comorbidity	Effect	SE[h]	p-value
Gender	0.681	1.964	0.730
Age	0.159	0.068	0.022
LA volume	0.135	0.030	<0.001
Height (meter)	13.985	11.961	0.247
Weight (kilogram)	0.185	0.070	0.010
BMI[a]	0.0387	0.205	0.064
MI[b]	4.473	3.256	0.174
Coronary artery disease	3.487	2.426	0.156
Smoker	0.923	2.218	0.679
Hypertension	1.720	1.907	0.370
Diabetes	5.125	2.571	0.051
Congestive HF[c]	8.740	3.825	0.026
Cardiomyopathy	7.602	3.460	0.032
Mitral valve regurgitation	20.289	7.340	0.007
Stroke	4.510	3.255	0.171
Hyperlipidemia	2.768	1.881	0.146
ACE[d] inhibitor	2.312	1.891	0.226
Beta blocker	1.413	1.905	0.461
Diuretics	2.481	2.371	0.299
NOAC[e]	-0.285	3.590	0.937
Clopidogrel	3.140	2.622	0.235
ASA[f]	5.255	1.996	0.011
SGLT2[g] inhibitors	6.683	5.475	0.227

[a] Body mass index
[b] Myocardial infarction
[c] Heart failure
[d] Angiotensin converting enzyme
[e] New oral anticoagulants
[f] Acetylsalicylic acid
[g] Sodium-Glucose Transport Protein 2
[h] Standard error

4.3. Multivariate analysis

The significance of LA volume (p=0.012) is maintained in multivariable analysis.

4.4. Distribution of LA volume

The box plot below (Figure 4) shows a comparison between the LA volume in cm^3 and Utah stages of patients. The Utah score classifies the percentage of fibrosis in the LA into four Utah stages as described above. The distribution of LA volume for patients in stages 1 and 2 is shown by the red box plot. The blue box plot represents the distribution for patients with Utah stages 3 and 4. In comparison the LA volume tends to be higher in patients with a higher percentage of left atrial fibrosis, meaning higher Utah stages. There is a statistically significant difference in LA volumes between patients in Utah stages 1 and 2 and in participants with Utah stages 3 and 4 ($p<0.001$).

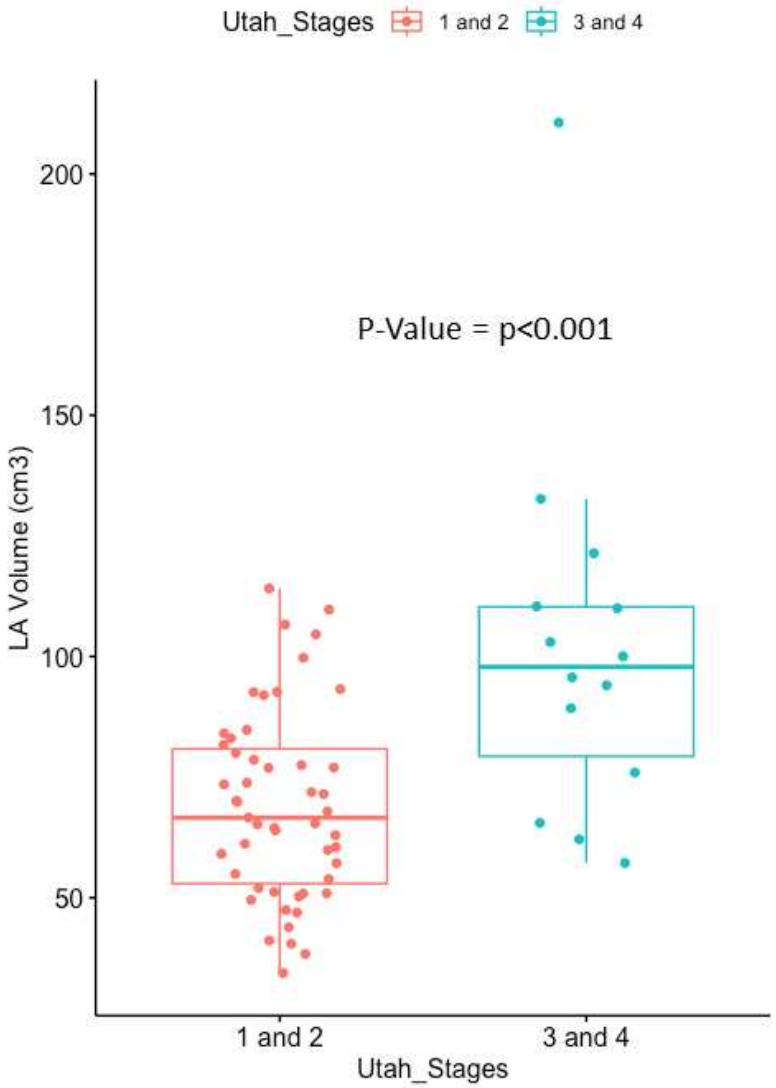

Figure 4. Left atrial (LA) volume (cm^3) in relation to Utah stages

The scatter plot beneath (Figure 5) illustrates the relationship between LA volume (cm^3) and LA fibrosis (%). The correlation coefficient R=0.49 indicating a moderate positive correlation between LA volume and LA fibrosis. The p-value (<0.001) represents a statistically significant correlation between LA volume and LA fibrosis.

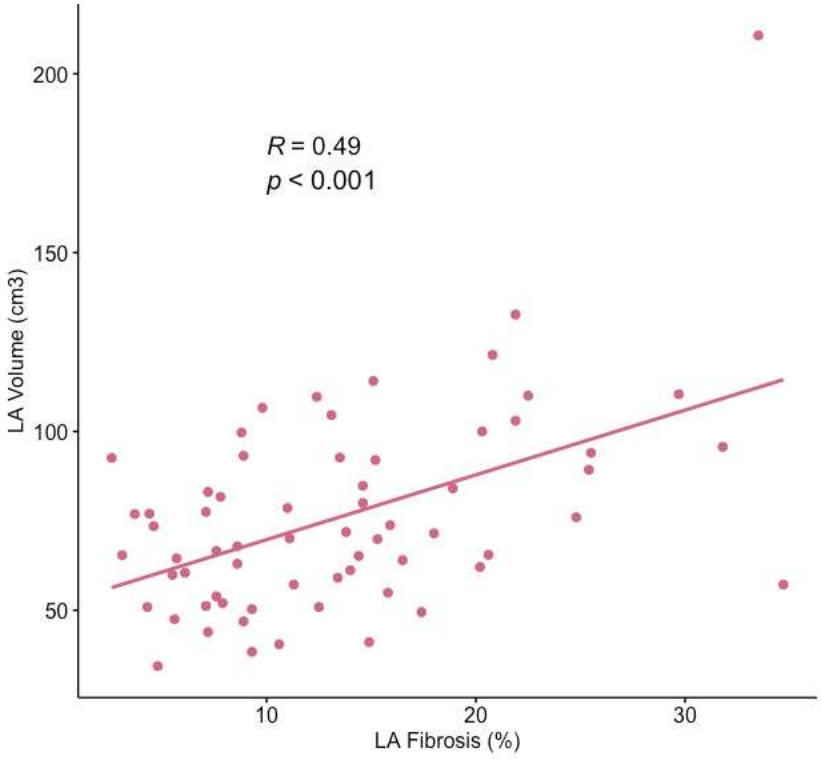

Figure 5. Left atrial (LA) volume (cm^3) compared to left atrial (LA) fibrosis (%)

5. DISCUSSION

This retrospective study mainly aimed to identify factors that are associated with the development of left atrial myopathy in patients with sinus rhythm. We compared 65 patients with left atrial myopathy with sinus rhythm in relation to their comorbidities. These included general personal data, atrial fibrosis characteristics, cardiovascular risk factors, past medical history and medications.

Our analysis identified several factors as statistically significant data. Our data suggests that age ($p=0.022$), LA volume ($p<0.001$), congestive HF ($p=0.026$), cardiomyopathy ($p=0.032$), mitral valve regurgitation ($p=0.007$), weight ($p=0.010$) and ASA ($p=0.011$) are comorbidities associated with the development of atrial myopathy in patients with sinus rhythm.

The data supports the theory that an older age ($p=0.022$) is related to the development of left atrial myopathy in patients with sinus rhythm which confirms the information from literature about atrial myopathy in patients with and without atrial fibrillation (20). The mean age of 57.65 ±13.6 years old suggests that the study population is predominantly middle-aged to older adults. This age group is characteristic for cardiac diseases in general, which are more prevalent in older generations (45).

Our retrospective analysis suggests that congestive HF ($p=0.026$) is connected to the development of left atrial fibrosis in patients with sinus rhythm which matches our found data about etiology of atrial fibrosis in general. This is clinically relevant as LA fibrosis can exacerbate HF symptoms (11,16).

The evaluation of previous cardiac diseases revealed that cardiomyopathy is one comorbidity related to atrial fibrosis in patients with sinus rhythm which also is a supported knowledge for patients with atrial fibrosis with atrial fibrillation (23).

Our analysis supports the theory that ASA significantly influences the progress of atrial fibrosis in patients with sinus rhythm. This association suggests potential area for future research since we could not find comparable studies.

Furthermore, the analysis also identifies mitral valve regurgitation and a larger LA volume as key factors in the development of atrial fibrosis in patients with sinus rhythm. These findings equal the results from literature research about the general etiology of atrial fibrosis which highlights volume and pressure overload as a possible source for the development of fibrosis in the atrium (20).

Our analysis detects weight (p=0.010) as a comorbidity associated with atrial fibrosis in patients with sinus rhythm. Given the significant result, weight may be an important factor to consider in the clinical setting. Interventions targeting weight management could potentially have a significant impact on the outcome. Despite the low p value given, there might be some limitations in weight as a significant comorbidity. BMI is body weight divided by body height^2. In our study the result for BMI is non-significant (p=0.064). The significant result for weight but not for BMI highlights the complexity of assessing body composition and its impact on health outcomes. Future research should focus on more precise measures of body composition and control for potential confounding variables to better recognize these relationships.

According to the box plot which is seen in figure 4, our results show a highly significant (p=0.00053) difference in LA volumes between the two Utah groups. The median LA volume (indicated by the line within each box) is higher for stages 3 and 4 compared to stages 1 and 2. The significant increase in LA volumes with higher Utah stages of fibrosis might indicate progressive structural remodeling of the atrium as fibrosis advances. This indicates that patients with increased LA volume may require more intensive monitoring and management to address the higher Utah stages of atrial fibrosis and to diminish potential effects of atrial fibrosis including rhythm disorders and blood stasis which potentially might lead to stroke (1).

The scatter plot shown in figure 5 represents a significant relationship between LA volume (cm^3) and LA fibrosis (%) ($p<0.001$). It shows a moderate positive correlation between the LA volume and LA fibrosis (R=0.49). As LA fibrosis increases, there is tendency for LA volume to increase as well. The low p-value provides strong evidence. This finding might suggest that patients with higher levels of fibrosis are at risk of atrial enlargement, which is a known risk factor for various cardiac conditions, including atrial fibrillation (1). Understanding the relationship between LA fibrosis and volume could help in risk stratification and management of patients with cardiac conditions. This correlation emphasizes the importance of monitoring both fibrosis and volume in patients for better prognostic evaluation and potential therapeutic interventions. In relation to its limitations it is important to recognize that the scatter plot also shows variability in the data, indicating that other factors might influence LA volume and should be considered in comprehensive analysis.

Despite significant findings, several limitations should be acknowledged. Our study includes 65 patients, which is a relatively small sample size. This limitation can affect the generalizability of findings and reduce the statistical power of the study. Exclusion of certain patient groups for example those with incomplete records may skew the sample, reducing its representativeness.

The retrospective design makes it prone to biases due to variations in data accuracy and completeness. Future research should involve larger, prospective studies to improve generalizability and control for biases.

6. CONCLUSION

This study concludes that a substantial proportion of individuals may have structural fibrotic alterations prior to the onset of atrial fibrillation, as evidenced by the high prevalence of atrial fibrosis among non-AF patients. There appears to be an association between the development of atrial cardiomyopathy and age, weight, congestive heart failure, cardiomyopathy, mitral valve regurgitation, ASA and LA volume according to our research. As a result, routine monitoring for atrial fibrillation and stroke prevention should be conducted on these patients.

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8. SUMMARY

Objectives: This study's main aim was to identify factors that are associated with the development of left atrial myopathy in patients without atrial fibrillation. The hypothesis states that left atrial myopathy can be detected in patients without atrial fibrillation and it is correlated to comorbidities.

Materials and methods: Sixty-five consecutive patients (40 male, 57.65 ±13.6 years old) with normal sinus rhythm (SR) and without a history of atrial fibrillation (AF) underwent late gadolinium enhancement – magnetic resonance imaging (LGE-MRI) to assess for fibrosis in the left atrium (LA). Each LGE-MRI was segmented by isolation of the LA wall and quantified for the relative extent of fibrotic remodeling using the Corview software (Marrek Inc.). The comorbidities were documented and their correlation with the degree of left atrial fibrosis was investigated through the implementation of univariate and multivariate analyses. Data collection included demographic information, comorbidities and regularly taken medication. The information was collected anonymously in Excel for statistical analysis with R Version 4.3.0, focusing on variables with p-values <0.05 to identify significant comorbidities.

Results: In a study of 65 patients (40 male, 57.65 ±13.6 years old) with normal sinus rhythm and no atrial fibrillation, the mean degree of left atrial (LA) fibrosis was 13.52 ± 7.7 percent, with LA volume of 76.13 ± 28.02cm^3. The prevalence of LA-fibrosis varies between 2.6% and 34.7%. In the univariate analysis, age (p=0.022), mitral valve regurgitation (p=0.007), congestive heart failure (p=0.026), LA volume (p<0.001), weight (p=0.010), acetylsalicylic acid (p=0.011) and cardiomyopathy (p=0.032) were all significantly associated with the extent of left atrial fibrosis. The significance of LA volume (p<0.001) is maintained in multivariable analysis.

Conclusion: This study concludes that a substantial proportion of individuals may have structural fibrotic alterations prior to the onset of atrial fibrillation, as evidenced by the high prevalence of atrial fibrosis among non-AF patients. There appears to be an association between the development of atrial cardiomyopathy and a range of cardiac and non-cardiac comorbidities, according to our research. As a result, routine monitoring for atrial fibrillation should be conducted on these patients.

9. CROATIAN SUMMARY

Naslov: Čimbenici povezani s mijopatijom lijeve pretklijetke kod pacijenata sa sinusnim ritmom

Ciljevi: Glavni cilj ove studije bio je identificirati čimbenike povezane s razvojem miopatije lijeve pretklijetke kod pacijenata bez atrijske fibrilacije. Hipoteza navodi da se miopatija lijeve pretklijetke može otkriti kod pacijenata bez atrijske fibrilacije i da je povezana s komorbiditetima.

Materijali i metode: Šezdeset i pet uzastopnih pacijenata (40 muškaraca, 57,65 ± 13,6 godina) sa sinusnim ritmom (SR) i bez povijesti atrijske fibrilacije (AF) podvrgnuto je magnetskoj rezonanci s pojačanjem gadolinija (LGE-MRI) kako bi se procijenila fibroza u lijevoj pretklijetki (LA). Svaka LGE-MRI segmentirana je izolacijom zida LA i kvantificirana za relativni opseg fibrotičkog preuređenja pomoću softvera Corview (Marrek Inc.). Dokumentirani su komorbiditeti i istražena je njihova korelacija s stupnjem fibroze lijeve pretklijetke kroz primjenu univarijantnih i multivarijantnih analiza. Prikupljeni su podaci uključivali demografske informacije, komorbiditete i redovno uzimane lijekove. Informacije su anonimno prikupljene u Excelu za statističku analizu s R verzijom 4.3.0, fokusirajući se na varijable s p-vrijednostima <0,05 kako bi se identificirali značajni komorbiditeti.

Rezultati: U studiji od 65 pacijenata (40 muškaraca, 57,65 ± 13,6 godina) sa normalnim sinusnim ritmom i bez atrijske fibrilacije, prosječni stupanj fibroze lijeve pretklijetke (LA) bio je 13,52 ± 7,7 posto, s volumenom LA od 76,13 ± 28,02 cm^3. Prevalencija fibroze LA varira između 2,6% i 34,7%. U univarijantnoj analizi, dob (p=0,022), regurgitacija mitralnog zaliska (p=0,007), kongestivno zatajenje srca (p=0,026), volumen LA (p<0,001), težina (p=0,010), acetilsalicilna kiselina (p=0,011) i kardiomiopatija (p=0,032) bili su značajno povezani s opsegom fibroze lijeve pretklijetke. Značaj volumena LA (p<0,001) zadržan je u multivarijantnoj analizi.

Zaključak: Ova studija zaključuje da značajan dio pojedinaca može imati strukturne fibrotičke promjene prije pojave atrijske fibrilacije, što potvrđuje visoka prevalencija atrijske fibroze među pacijentima bez AF. Prema našem istraživanju, čini se da postoji povezanost između razvoja atrijske kardiomiopatije i niza srčanih i nesrčanih komorbiditeta. Kao rezultat toga, rutinsko praćenje na atrijsku fibrilaciju trebalo bi se provoditi kod ovih pacijenata.