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Jarašūnas

Analysis of the Link Between Various Cardiovascular Factors and Atrial Fibrillation

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VILNIAUS UNIVERSITETAS

Jonas
Jarašūnas

Kardiovaskulinės sistemos rodiklių sąsajos su prieširdžių virpėjimu tyrimas

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CONTENTS

ABBREVIATIONS

ABP – arterial blood pressure

AF – atrial fibrillation

BMI – body mass index

BPM – beats per minute

BSA – body surface area

CRP – C reactive protein

DD – diastolic dysfunction

ECG – electrocardiogram

EDd – end diastolic diameter

EF – ejection fraction

HR – heart rate

IVS – interventricular septum

LA – left atrial

LV – left ventricular

MI – mass index

NT pro BNP – N-terminal prohormone of brain natriuretic peptide

PAH – primary arterial hypertension

PTD – percent time dropped

PTE – percent time elevated

PWd – posterior wall diameter

RAAS – renin-angiotensin-aldosterone system

TSH – Thyroid-Stimulating Hormone

1. INTRODUCTION

1.1 The Problem and Relevance of the Study

Atrial fibrillation (AF) is the most common long-standing form of atrial tachyarrhythmia, the prevalence of which is ever-increasing [1–4]. In a meta-analysis published in 2014, it was estimated that there are 33.5 million patients in the world suffering from this form of arrhythmia [2]. Having in mind the growth of the global population and the increasing prevalence of AF, it is likely that this number is even larger by now and will double in the coming 50 years [5]. AF increases the risk of heart failure, embolic complications, and cardiovascular mortality [6]. Patients with this arrhythmia have not only an increased risk of a stroke but also worse results of treatment and a larger residual neurologic deficiency [7]. The most effective way to prevent embolic complications is the use of anticoagulants. Anticoagulants are proven to reduce the risk of stroke by approximately two thirds regardless of the baseline risk [8, 9]. In order to prevent AF complications, it is vital to diagnose the arrhythmia in time, which is sometimes difficult with paroxysmal AF. Approximately a third of patients with paroxysmal AF are either asymptomatic or have nonspecific complaints [10]. When AF episodes are short-lasting, the ECG, and even a 24-hour ambulatory ECG monitoring, are sometimes not able to detect the arrhythmia and lead to the correct diagnosis [11]. Devices that can monitor a patient's ECG for at least 7 days in an ambulatory setting can increase the probability of detecting AF [11], but their availability is limited. In order to use these devices with maximum efficiency, it is essential to identify patients with the largest risk of AF and its complications. Though primary arterial hypertension (PAH) increases the risk of AF by a mere 1.42–1.9 fold [12, 13], it is the high prevalence of the disease that makes PAH the leading cause of AF in the general population [6, 12]. A study is needed to determine the cardiovascular factors linked to the increased risk of paroxysmal AF in a group of

patients with PAH. By selecting patients with an increased risk of arrhythmia, it would be possible to employ diagnostic methods that last longer but are more effective in establishing the correct diagnosis, such as 7-day ambulatory ECG monitoring. By treating these patients with anticoagulants, we could prevent embolic complications. There is data showing that renin-angiotensin-aldosterone system (RAAS) blockers are effective not only in secondary but also in the primary prevention of AF. The positive effect is more pronounced in the group of patients with PAH [14]. By identifying patients with an increased risk of AF, we could prevent it with RAAS blockers.

There are many articles published that prove both AF and PAH to worsen quality of life [15–18], but in the majority of the studies patients with these pathologies were compared to a healthy population. The absolute majority of data on life quality in patients with AF are derived from randomized interventional trials, and that is why the data might be biased toward picking out patients that are the most symptomatic and have the worse quality of life [19]. A study is needed to define what influence on quality of life, anxiety, and depression does paroxysmal AF caused by PAH have by comparing these patients to the general PAH population in the absence of other comorbidities.

1.2 Research Hypothesis

Patients with paroxysmal AF can be identified by a specific blood biomarker, a heart ultrasound, a 24-hour ambulatory ECG and arterial blood pressure (ABP) monitoring changes within the population of patients with PAH.

Paroxysmal AF is related to a worse quality of life as well as increased levels of anxiety and depression in patients with PAH.

1.3 Research Objectives

1. To define the cardiovascular factors and their changes that would allow to identify patients with paroxysmal atrial fibrillation or an increased risk of the arrhythmia in the population of patients with primary arterial hypertension.
2. To define the influence of paroxysmal atrial fibrillation on quality of life, anxiety, and depression in patients with primary arterial hypertension.

1.4 Research Tasks

1. To define the blood biomarkers and their changes that are linked to paroxysmal atrial fibrillation in patients with primary arterial hypertension.
2. To define the heart ultrasound parameters and their changes that are linked to paroxysmal atrial fibrillation in patients with primary arterial hypertension.
3. To define the 24-hour ambulatory ECG and ABP monitoring parameters and their changes that are linked to paroxysmal atrial fibrillation in patients with primary arterial hypertension.
4. To define the cardiovascular parameters with the best performance in identifying patients with paroxysmal atrial fibrillation and ability to predict the risk of the arrhythmia in patients with primary arterial hypertension.
5. To examine the differences in the parameters of the Short Form 36 quality of life questionnaire (SF-36) and Hospital Anxiety and Depression Scale (HADS) linked to paroxysmal atrial fibrillation in the population of patients with primary arterial hypertension.

1.5 Statements to be Defended

1. Paroxysmal atrial fibrillation is linked to increased concentrations of NT pro BNP and troponin I in patients with primary arterial hypertension.
2. Paroxysmal atrial fibrillation is linked to a decreased left atrial reservoir strain, reservoir strain rate, and ejection fraction values in patients with primary arterial hypertension.
3. Paroxysmal atrial fibrillation is linked to an increased number of short-run (<30 s) atrial tachyarrhythmia episodes during 24-hour ambulatory ECG monitoring in patients with primary arterial hypertension.
4. In the population of patients with primary arterial hypertension, heart ultrasound parameters of the left atrium (reservoir strain, reservoir strain rate, and ejection fraction) and the number of short-run atrial tachyarrhythmia episodes during 24-hour ambulatory ECG monitoring are able to predict paroxysmal atrial fibrillation.
5. Paroxysmal atrial fibrillation leads to a worse quality of life in patients with primary arterial hypertension.

1.6 Novelty of the Study

Even though it is agreed upon that patients with AF have a lower quality of life, the majority of data we have is derived from interventional randomized trials; that is why there might be a bias toward more symptomatic and therefore lower quality of life patients [19]. Quality of life research regarding AF in general and especially AF caused by primary arterial hypertension is lacking. It is difficult to clarify paroxysmal AF's contribution to the reduction of life quality, as the arrhythmia is often associated with other cardiovascular disease also leading to a worse quality of life. By excluding patients with other cardiovascular pathologies except for PAH and comparing AF patients not with healthy ones but with those that have PAH, we could clearly

evaluate the influence of paroxysmal AF on quality of life, anxiety, and depression.

In the literature regarding AF, the greatest attention is paid to predicting the risk of complications and not the arrhythmia itself. Nevertheless, there are some schemes to evaluate the risk of atrial fibrillation [20], the most important being FHS [21], ARIC [22], WHS [23], and CHARGE-AF [24]. These models are able to predict the risk of AF in the general population, but they include mostly clinical factors without paying enough attention to novel ultrasound methods used to assess LA function, such as 2D speckle tracking. There is data showing that LA strain and the strain rate are linked to the risk of AF recurrence after pulmonary vein isolation [25, 26], cardioversion success or failure [27], embolic complications [27–30], and LA appendage function in patients after stroke [31]. To our knowledge, there are no studies including the LA strain and strain rate parameters with their cut-off values in the models defining the risk of paroxysmal AF among patients with primary arterial hypertension. As the LA strain and strain rate parameters can be easily determined during a routine ultrasound of the heart, they can be used in predicting the risk of AF. A study is needed to define their performance in predicting the risk of arrhythmia. Another important aspect of novelty is the population of the study. A lone AF is a rare pathology that has a prevalence of 1.6%–30%, depending on the definition used [32–34]. The most common cardiovascular pathology causing AF in the general population is PAH [35]. Though the association of AF and PAH is the most common, there is a lack of studies in this numerous population. At the start of our study there were no published studies comparing AF caused by PAH patients with the ones with PAH. In August 2019, a study by I. Petre et al. was published that compared these two populations. Though very similar in design, the study had a lower number of included patients, and the group with AF was significantly older, which made the results questionable [36]. Matching subjects by age and gender allowed us to determine the influence of solely

paroxysmal AF on the studied cardiovascular factors in this abundant though little-studied population of patients with PAH.

2. METHODOLOGY

2.1 Overview

The study was conducted in Klaipėda Seamen's Hospital. An approval by the Lithuanian Bioethics Committee was obtained before starting the study (No. L-16-05/1). All the patients signed an informed consent form. A prospective case-control study was conducted over the period July 20, 2016 to December 31, 2018, which enrolled patients with paroxysmal atrial fibrillation and primary arterial hypertension. The patients filled out a dedicated study questionnaire, and instrumental tests were performed. Data without any possibility of identifying the patients were saved in a dedicated study database.

The protocol of the study was created by Prof. Audrius Aidietis and the author of this work, Jonas Jarašūnas. Patient screening, enrollment, questioning, and all the instrumental tests were performed by Jonas Jarašūnas. The overview of the study design is given in Figure 1.

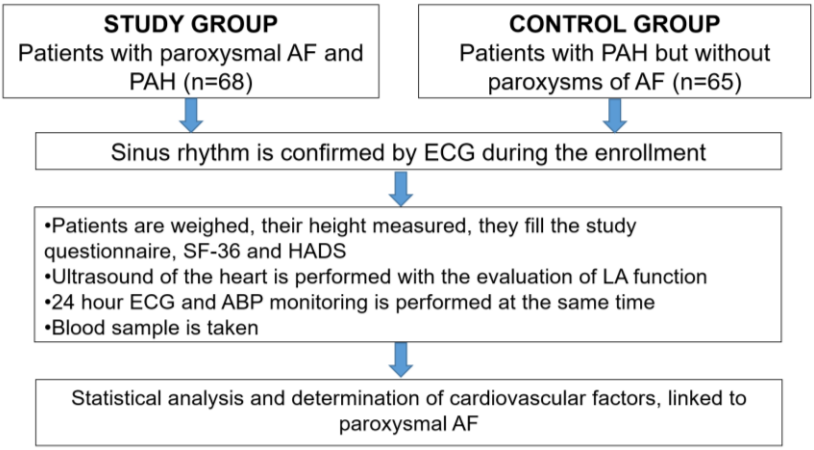

Figure 1. Overview of the study design.

The patients were divided into two groups:

- Study group – patients with PAH and at least one ECG documented AF episode within one year prior to inclusion in the study.
- Control group – patients with PAH but without any AF symptoms or ECG with the arrhythmia.

To enroll only the patients with PAH as the most likely reason for AF, we excluded patients with any other pathology known to cause AF.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria to the study group:

1. Established diagnosis of PAH for more than a year prior to enrollment;
2. Paroxysmal AF in the anamnesis according to the definition given in the 2016 ESC guidelines (AF is considered paroxysmal if the duration of the episode is less than 7 days) [6];
3. At least one ECG-documented episode of AF during one year prior to enrollment;
4. ECG-confirmed sinus rhythm at the moment of enrollment;
5. 18–80 years of age;
6. Agreement to participate in the study;
7. Ability to read, understand, and fill out the questionnaires.

Inclusion criteria for the control group had only one difference – only the patients without any symptoms of arrhythmia were included in this group. Inclusion criteria to the control group:

1. Established diagnosis of PAH for more than a year prior to enrollment;
2. No symptoms and documented ECG of AF;
3. ECG-confirmed sinus rhythm at the moment of enrollment;
4. 18–80 years of age;
5. Agreement to participate in the study;

6. Ability to read, understand, and fill out the questionnaires.

Exclusion criteria to both the study and control groups:

1. Verified coronary heart disease or its symptoms;
2. Heart surgery;
3. Heart failure signs or symptoms;
4. Left ventricular (LV) ejection fraction (EF) <55 %;
5. Glomerular filtration rate calculated using MDRD formula <60 ml/min/1,73 m^2;
6. Clinically relevant valvular heart disease or congenital heart disease;
7. TSH concentration outside normal range;
8. Chronic obstructive pulmonary disease;
9. Resistant hypertension according to the definition given in the 2013 ESC hypertension guidelines (when the combination of a diuretic and two other antihypertensive class agents fail to reduce blood pressure to <140/90 mm Hg) [37].

2.3 Study Questionnaire, HADS, and SF-36

All the patients completed a questionnaire that was specifically designed for the study and included the following information:

- Age;
- Gender;
- Education;
- Level of physical activity during the last month in minutes per week;
- Alcohol and tobacco consumption, other addictions;
- Medications taken regularly during the last month;
- Factors provoking AF;
- Number of AF episodes during the last year;
- Known duration of PAH in years;
- CHA_2DS_2-VASc score.

All the patients filled out the Hospital Anxiety and Depression Scale (HADS), which had been translated and adapted to the Lithuanian language [38]. The HADS consists of 14 questions. Seven of those are dedicated to the evaluation of depression, and the other 7 – to the evaluation of anxiety. The patients were instructed to choose the answer that is the closest to how they were feeling during the last week and to provide the answers that are the first to come to their mind and are the most intuitive ones rather than ones appearing after careful consideration. The levels of depression and anxiety are calculated in scores from 0 to 21. Scores from 0 to 7 represent normal levels of anxiety and depression, from 8 to 10 – light depression or anxiety, 11 to 14 – moderate, and 15 to 21 – severe levels of depression or anxiety.

All the patients completed the Short Form 36 quality of life questionnaire (SF-36), which was translated and adapted to the Lithuanian language [39]. The questions in the SF-36 represent eight sections of health: energy/fatigue, physical functioning, pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and emotional well-being. These eight sections are combined into two categories of health: mental and physical. Mental health is represented by energy/fatigue, social role functioning, emotional role functioning, and emotional well-being. Physical health is represented by physical functioning, bodily pain, general health perceptions, and physical role functioning. There is also one separate section dedicated to the perception of health change. Using a special algorithm, each of the section was estimated in scores from 0 to 100. Higher scores indicate a better quality of life.

Twelve derivation ECGs were recorded in the supine position. The weight and height of the patients were recorded using dedicated calibrated devices.

2.4 Laboratory Tests

Venous blood samples were taken from all the patients, and concentrations of the following substances and cells were measured in

a certified laboratory of the Klaipėda Seamen's Hospital: hemoglobin (g/l), leukocyte count (10^9/l), K^+ (mmol/l), Na^+ (mmol/l), Cl^-(mmol/l), Mg^{2+} (mmol/l), Ca^{2+} (mmol/l), creatinine (μmol/l), C reactive protein (CRP) (mg/l), troponin I (ng/l), N-terminal prohormone of brain natriuretic peptide (NT pro BNP) (pg/ml), and Thyroid-Stimulating Hormone (TSH) (mlU/l).

2.5 Ultrasound of the Heart

All the patients underwent ultrasound testing of the heart, which was carried out by Jonas Jarašūnas using the GE Vivid E9 (*General Electrical-Vingmed Ultrasound AS*, Horten, Norway) ultrasound system with a M5S-D (*General Electrical-Vingmed Ultrasound AS*, Horten, Norway) probe. Only patients with views of acceptable quality were included in the final analysis. During the ultrasound of the heart, patients were in the supine position on the left side, with the left hand placed under the head. All the limb leads of the ECG were recorded during the test, but only the one with the best distinguishable P waves and QRS complexes were used for analysis. The views were saved for further analysis. Ultrasounds of the heart and standard measurements were carried out according to the recommendations of the 2005 American Society of Echocardiography and the European Association of Cardiovascular Imaging and their 2015 update [40–42].

The diameter of the ascending aorta and aortic sinuses, LA diameter, interventricular septum diameter (IVSd), LV posterior wall diameter (PWd), end diastolic (ED), and end systolic (ES) LV diameters were measured from the parasternal long LV axis ultrasound views.

LV myocardial mass (MM) was calculated using Cube's formula, which is recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [41]:

$$\text{LV MM} = 1{,}04\,[(\text{IVSd}+\text{PWd}+\text{LV EDd})^3 - \text{LV EDd}^3] \times 0{,}8 + 0{,}6$$

LV myocardial mass index (LVMMI) (g/m^2) was calculated using the following formula:

LVMMI = MM/body surface area (BSA)

BSA (m^2) was calculated using the *Du Bois* formula:

$BSA = 0{,}007184 \times weight^{0{,}425} \times height^{0{,}725}$

LV volume at the end of systole before the opening of the mitral valve (MV) and at the end of diastole before the closure of the mitral valve (minimal and maximal LV volume (ml), accordingly) was calculated using Simpson's method of discs from two and four chamber apical views. The LV ejection fraction (EF) (%) was calculated using the following formula:

LV EF = (LV max. vol. – LV min. vol.)/ LV max. vol. × 100

LA volume (ml) was also calculated using Simpson's method of discs from two and four chamber apical views. The following volumes of LA were measured: minimal, taken at the end of LV diastole before the closure of MV, maximal, at the end of LV systole before the opening of MV, and LA volume before the P wave on the ECG. LA EF (%) was calculated using the following formula:

LA EF = (LA max. vol. – LA min. vol.)/ LA max. vol. × 100

LA volume index (VI) was calculated using the following formula:

LA VI = LA max. vol. / BSA

MV inflow and MV annular velocity were analyzed using a pulse wave Doppler and tissue Doppler from four chamber apical views. A pulse wave Doppler was used to measure the MV inflow velocities: E – maximal early LV filling velocity through MV (m/s); A – maximal LV filling velocity through MV during the contraction of the LA (m/s); EdecT – the duration of the deceleration of the E wave (ms). A tissue Doppler was used to measure the medial and lateral MV annular velocities: e' – velocity during early LV diastolic filling (cm/s), and a'

– velocity during late LV diastolic filling. Mean medial and lateral e‘ and a‘ velocities were calculated.

In the presence of a tricuspid regurgitation, a continuous wave Doppler was used to measure the peak velocity of the regurgitant jet (m/s).

The LV diastolic function was evaluated using the 2016 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [43]. The following factors of LV diastolic dysfunction (DD) were evaluated:

- MV annular velocity – e‘ medial <7 cm/s or e‘ lateral <10 cm/s);
- E/e‘ ratio >14. Parameter was calculated using the average of e‘ medial and e‘ lateral;
- LA VI >34 ml/m^2;
- Peak regurgitant jet velocity through tricuspid valve >2.8 m/s.

In order to evaluate the link between the LV DD factors and the LA strain and strain rate parameters the patients were grouped by the number of LV DD factors present. LA strain and strain rate parameters were compared between the groups of patients with a different number of factors showing LV DD.

2.5.1 Left Atrial Strain and Strain Rate

The LA strain and LA strain rate were evaluated using a 2D speckle tracking technology and the GE EchoPAC (version 112) software. Views used for the analysis were saved according to the expert recommendations published in the *European Journal of Echocardiography* [44]. The LA strain and strain rate were calculated from two and four chamber apical views, carefully avoiding foreshortening. In order to achieve the best quality, the focus was set to the middle of LA, while the width and depth were adjusted to achieve > 80 frames per second. The patients were asked to hold their

breath, and three consecutive heart cycles were recorded. The walls of the LA were marked manually. The software then automatically picked speckles and tracked them throughout the heart cycle. The walls of the LA were automatically divided into 6 segments, and the tracking quality of each segment was shown. If the tracking quality was not satisfying, the walls were adjusted to achieve better quality. The starting point of the analysis in the ECG was then changed manually from preset, which was the peak of the QRS complex to the start of the P wave. The software then generated separate curves for all the 6 segments, and one averaged, representing the global longitudinal strain of the LA that was used for further analysis. Three deformation points were identified in each curve, which represented different functions of the LA (%):

- First negative deflection peak at maximal contraction of the LA corresponding to the contractile function of the LA – the contractile strain.
- First positive deflection peak at MV opening corresponding to conduit function of the LA – the conduit strain.
- The difference between the first two peaks corresponding to the reservoir function of the LA – the reservoir strain.

LA 2D global longitudinal strain curve with certain points corresponding to the contractile, conduit, and reservoir strains is given in Figure 2. Identical calculations were performed for two and four chamber apical views, and the mean was used for final analysis.

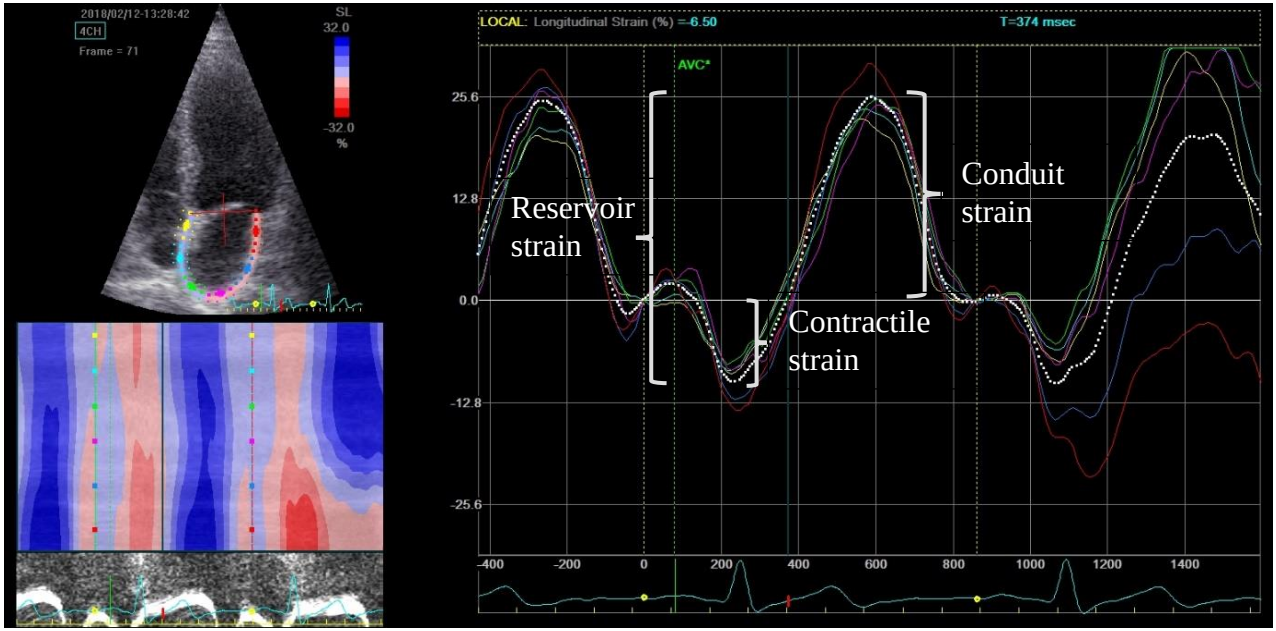

Figure 2. Contractile, conduit, and reservoir strain determination using a four chamber apical view and using the P wave as a starting point in the ECG.

After the strain values were calculated using the same settings and views, the strain rate measurement setting was selected. The software automatically generated 6 strain rate curves for each segment of the LA wall and one averaged global longitudinal strain rate curve, which was used for further analysis. Three deformation points were identified in each curve, which represented the different functions of the LA (1/s):

- First negative peak in the curve representing the rate of the LA contractile strain – the contractile strain rate.
- Second negative peak in the curve representing the rate of the LA conduit strain – the conduit strain rate.
- First positive peak in the curve representing the rate of the LA reservoir strain – the reservoir strain rate.

The 2D global longitudinal strain rate curve, together with certain points corresponding to the contractile, conduit, and reservoir strain rates, is given in Figure 3. Identical calculations were performed using two and four chamber apical views, and the mean was used for the final analysis.

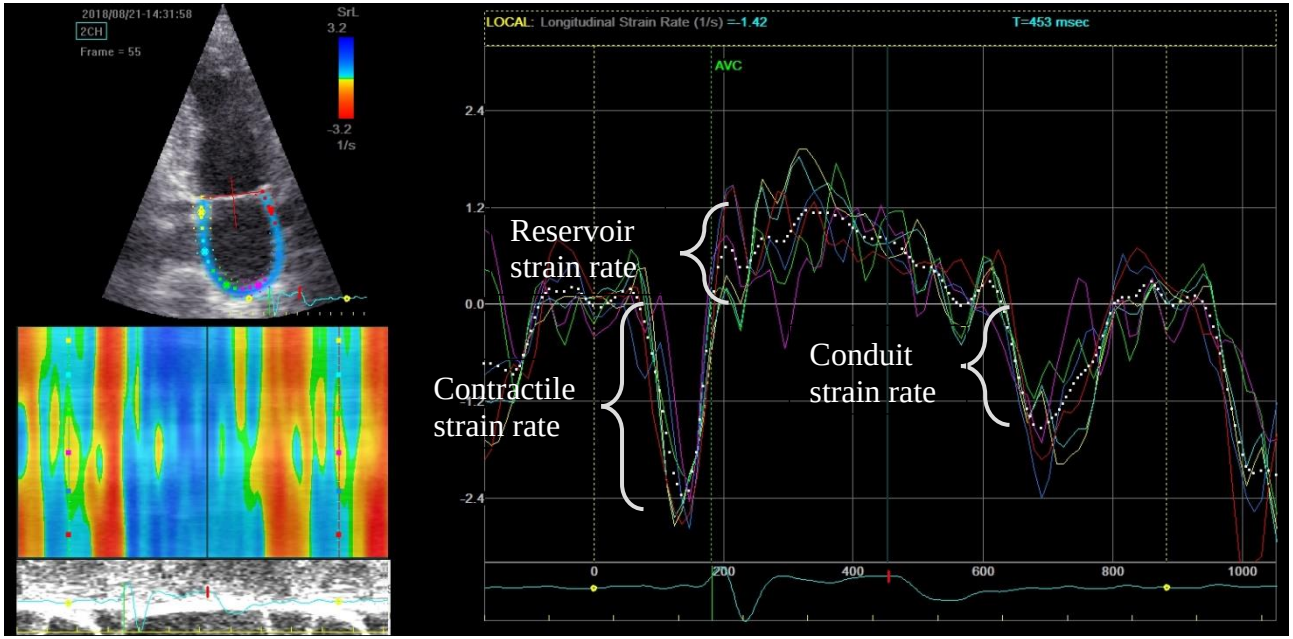

Figure 3. Contractile, conduit, and reservoir strain rate determination using a two chamber apical view using the P wave as a starting point in the ECG.

2.5.2 Reproducibility of Left Atrial Strain Parameters

The intra- and interobserver variability of contractile, conduit, and reservoir LA strains was assessed in 20 randomly selected patients. Intraobserver variability was performed by the same echocardiographer, blind to the previous measurements, and interobserver variability was performed by a second experienced echocardiographer also blind to the previous measurements.

2.6 24-Hour Ambulatory ECG and Arterial Blood Pressure Monitoring

The 24-hour ambulatory ECG and ABP monitoring was done at the same time for all the patients using the *Meditech card(X)plore* device (Meditech Ltd., Budapest, Hungary). The device recorded 3 independent bipolar channels of electrograms and measured ABP at a predefined intervals using the upper arm cuff (oscillometric tonometry method, stepwise deflation). The analysis of the data was carried out using the CardioVisions version 1.23.0 software.

A 24-hour ambulatory ABP monitoring was performed according to the recommendations of the European Society of Hypertension [45]. Target time for ABP monitoring was 24 hours. The patients with a monitoring time of less than 22 hours had to repeat the test until more than 22 hours of consecutive monitoring was achieved. When programming the device, the patients were asked to specify the approximate time of when they go to sleep and wake up – this information was used for setting daytime and nighttime modes. During the daytime, ABP was measured at 20-minute intervals, while during the nighttime – 40-minute intervals. Measurements were repeated in case a failed attempt was activated. The cuff was put on the right upper arm, aiming for the level of the right atrium, and the device itself was attached to the waist with the help of a special belt. The patients were instructed to live their normal daily lives but to temporarily stop physical activity during the measurements. The monitoring was

stopped the next day at the same time. The data were transferred to the computer for further analysis.

The minimal requirements for 24-hour ABP monitoring were:

- ≥70 % successful measurements;
- ≥ 20 successful measurements during daytime;
- ≥ 7 successful measurements during nighttime.

The monitoring was repeated if these requirements were not met.

For the calculation of the mean ABP parameters, a weighted average was used, which was done automatically using the software.

ABP parameters assessed:

- 24-hour systolic ABP mean (mm Hg);
- 24-hour systolic ABP mean standard deviation (SD);
- 24-hour diastolic ABP mean (mm Hg);
- 24-hour diastolic ABP mean SD;
- Daytime systolic ABP mean (mm Hg);
- Daytime systolic ABP mean SD;
- Daytime diastolic ABP mean (mm Hg);
- Daytime diastolic ABP mean SD;
- Nighttime systolic ABP mean (mm Hg);
- Nighttime systolic ABP mean SD;
- Nighttime diastolic ABP mean (mm Hg);
- Nighttime diastolic ABP mean SD;
- Systolic ABP drop during the night (%);
- Diastolic ABP drop during the night (%).
- Morning surge – the difference between the mean systolic ABP during the 2 hours after waking and rising minus the mean systolic ABP of the lowest blood pressure during sleep and its nearby neighbors (3 values). The software interpreted the last night measurement as the time of waking.

- Systolic ABP Percent Time Elevation (PTE) – percent of the total analyzed time the sABP was above cut-off lines (%).
- Diastolic ABP PTE – percent of the total analyzed time the sABP was above cut-off lines (%).
- Systolic ABP Percent Time Drop (PTD) – percent of the total analyzed time the sABP was below cut-off lines (%). Hypotensive PTE.
- Diastolic ABP PTD – percent of the total analyzed time the sABP was below cut-off lines (%). Hypotensive PTE.

A 24-hour ECG monitoring was performed at the same time as the ABP monitoring. At the sites recommended by the manufacturer, 7 electrode stickers were applied and connected to the device itself via provided cables. After the end of monitoring, the data were transferred to the computer, analyzed by the software, and verified by the author of this dissertation. In case of inaccuracies, the data were adjusted manually. The following parameters were assessed:

- 24-hour mean heart rate (HR) in beats per minute (bpm);
- Minimal HR (lowest mean HR for a 30 s time interval) (bmp);
- Maximal HR (highest mean HR for a 30 s time interval) (bmp);
- Ventricular premature beats (calculated as percentage in all QRS complexes) (%);
- Atrial premature beats (calculated as percentage in all QRS complexes) (%);
- Short-run atrial tachyarrhythmia (AT) episodes (calculated during the monitoring period of 24 hours). The episode was diagnosed if all the following criteria were present: more than 3 consecutive premature beats with a narrow QRS, RR intervals of > 600 ms, and a duration of less than 30 s. An example of the episode is given in the Figure 3. All the episodes were inspected and verified manually by the author of this dissertation.

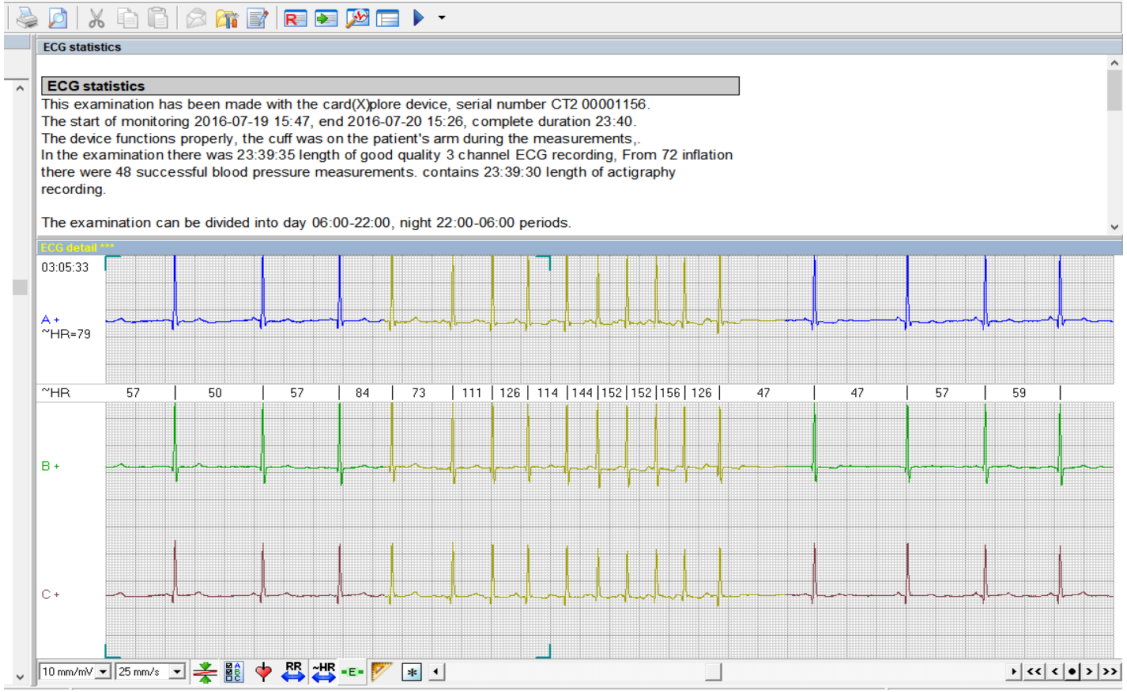

Figure 3. An example of a short-run atrial tachyarrhythmia of a duration less than 30 s.

2.7 Statistical Analysis

Statistical analysis of the data was performed using the IBM SPSS Statistics 23 (IBM, Armonk, New York, United States of America) software. First of all, mean values of the analyzed parameters were calculated, and the numbers were compared between the groups. Mean values are given together with a standard deviation. The normality of the data distribution was checked using the Shapiro-Wilk test. If the data were distributed normally, the means were compared using Student's t-test; the Mann Whitney U test was used otherwise. Nonparametric data were compared using the Chi square. The equality of variances between the groups was compared using Levene's test. The difference was considered statistically significant when the p value was <0.05. When the parameters with a statistically significant difference between the groups were identified, a binary logistic regression analysis method was applied to determine the factors that are independently linked to paroxysmal AF. Age, gender, and body mass index were also included in the regression analysis. The results are given as an odds ratio with 95% confidence intervals and a p value. To characterize the regression model and its performance, R^2 was calculated using the Cox and Snell as well as Nagelkerke formulas. Sensitivity, specificity, and positive and negative prognostic values, together with an ROC curve and calculated area under the curve values, are given. A binary logistic regression analysis was repeated including just the factors that were statistically significant in the primary analysis. The same parameters characterizing the first model are given for the second one. In order to determine a decision-making algorithm, the most important parameters, and their cut-off values in predicting paroxysmal AF, a logistic regression tree analysis was performed. The parameters of the tree were: growing method CRT (Classification and Regression Tree), depth ≤ 5 levels, and a minimum number of cases for child node – 10. The importance of the parameters in the model is shown graphically. In order to characterize the tree and its performance, a classification table, specificity, sensitivity, and

positive and negative prognostic values, together with an ROC curve and a calculated area under the curve's values were all given.

To compare the LA strain parameter values between the groups of patients with different number of LV DD factors, an ANOVA analysis with an LSD post hoc test were used. Box and whisker charts are used to show the differences between the groups graphically. The difference was considered significant when the p value was <0.05.

To evaluate the reproducibility of the LA strain, measurements of the intraclass correlation coefficient, together with the absolute difference (divided by the mean of two measurements and given as a percentage), were calculated for both intra- and interobserver variability.

3. RESULTS

3.1 Overview of the Study and Control Group Patients

The final analysis included 133 patients – 68 patients in the study group (with PAH and paroxysmal AF) and 65 patients in the control group (with PAH but without paroxysmal AF). The general characteristics of the patients are given in Table 1.

Table 1. General characteristics of the study and control groups.

Parameter	Study group (n=68)	Control group (n=65)	P value
Age (±SD)	62.9 (11.61)	59.15 (11.77)	0.067
Male %	44.11	43.07	0.862
Higher education %	**35.29**	**61.54**	**0.012**
Body mass index (±SD)	29.58 (4.27)	29.03 (4.79)	0.484
Diabetes %	7.35	7.69	1
24-hour sABP mean (±SD)	129.4 (10.58)	133.57 (14.67)	0.053
24-hour dABP mean (±SD)	**74.4 (8.59)**	**77.89 (8.44)**	**0.015**
Physical activity level (min./week) (±SD)	**58.75 (105.21)**	**118.77 (199.17)**	**0.015**
Number of antihypertensives taken daily (±SD)	1.59 (1.14)	1.59 (1.24)	0.986
ACEI %	**55.88**	**32.81**	**0.009**
ARB %	16.2	26.56	0.201
CCB %	26.47	34.38	0.349
β-blockers %	29.41	32.81	0.71
Diuretics %	17.65	21.88	0.662
α-blockers %	1.47	0	1
Centally acting agents %	4.41	9.36	0.314
Spironolactone %	7.35	3.12	0.442

SD – standard deviation; sABP – systolic arterial blood pressure; dABP – diastolic arterial blood pressure; ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin II receptor blockers; CCB – calcium channel blockers.

3.2 Quality of Life, Anxiety, and Depression Comparison Between the Study Groups

A comparison between scores of anxiety and depression evaluated by the HADS, together with the SF-36 evaluated scores of life quality sections, are given in Table 2.

Table 2. HADS and SF-36 data comparison between the groups.

Parameter	Study group (±SD)	Control group (±SN)	Difference of means	P value
HADS				
Anxiety	7.57 (±4.43)	6.35 (±3.75)	1.22	0.126
Depression	5.06 (±3.59)	3.91 (±2.58)	1.15	0.104
SF-36				
Physical functioning	**68.31 (±22.92)**	**78.77 (±18.71)**	**-10.46**	**0.004**
Physical role functioning	**39.71 (±42.59)**	**60 (±41.41)**	**-20.29**	**0.007**
Emotional role functioning	60.29 (±42.85)	68.71 (±40.38)	-8.42	0.343
Energy/fatigue	56.47 (±18.73)	61.85 (±18.64)	-5.38	0.138
Emotional well-being	65.77 (±17.83)	67.02 (±14.44)	-1.25	0.805
Social role functioning	69.37 (±21.94)	73.86 (±23.27)	-4.49	0.237
Pain	65.91 (±24)	67.32 (±25.46)	-1.41	0.838
General health	**46.03 (±18.92)**	**53.92 (±17.33)**	**-7.89**	**0.016**
Health change	36.03 (±28.45)	39.23 (±23.37)	-3.2	0.466

SD – standard deviation; HADS – hospital anxiety and depression scale; SF-36 – short form 36.

Patients with paroxysmal AF had limited physical functioning, physical role functioning, and estimated their general health as worse compared to the control group.

3.3 Laboratory Tests

Mean values of laboratory tests are given in Table 3.

Table 3. Mean values of laboratory tests compared between the groups.

Parameter	Study group (±SD)	Control group (±SD)	Difference of means	P value
Hemoglobin(g/l)	141.34 (±13.59)	142.87 (±13.5)	-1.53	0.53
Leukocyte count (10^9/l)	6.2 (±1.28)	6.72 (±2.1)	-0.52	0.451
K^+(mmol/l)	4.52 (±0.39)	4.63 (±0.36)	-0.08	0.091
Na^+ (mmol/l)	141.45 (±1.84)	139.92 (±3.29)	1.53	0.06
Cl^- (mmol/l)	105.73 (±2.96)	104.63 (±3.57)	1.1	0.126
Mg^{2+} (mmol/l)	0.87 (±0.076)	0.89 (±0.08)	-0.02	0.248
Ca^{2+}(mmol/l)	2.38 (±0.1)	2.41 (±0.14)	-0.03	0.136
Creatinine (µmol/l)	77.87 (±17.18)	74.5 (±17.26)	3.37	0.22
CRP (mg/l)	1.87 (±2.26)	2.76 (±3.1)	-0.89	0.087
Troponin I (ng/l)	**4.16 (±4.8)**	**2.66 (±2.7)**	**1.5**	**0.045**
NT pro BNP (pg/ml)	**287.68 (±325.59)**	**124.54 (±105.11)**	**163.14**	**<0.001**
TSH (mlU/l)	**1.68 (±1.05)**	**1.07 (±0.46)**	**0.61**	**<0.001**

SD – standard deviation; CRP – C reactive protein; NT pro BNP – N-terminal prohormone of brain natriuretic; TSH – Thyroid-Stimulating Hormone.

Patients with paroxysmal AF had higher values of NT pro BNP, troponin I and TSH. Though the difference of TSH concentrations between the groups was statistically significant, according to the

exclusion criteria, none of the test values were outside the normal range.

3.4 Ultrasound of the Heart

General ultrasound of the heart parameters are given in Table 4.

Table 4. Mean values of ultrasound parameters compared between the groups.

Parameter	Study group (±SD)	Control group (±SD)	Difference of means	P value
Ascending aorta diameter (cm)	3.44 (±0.48)	3.5 (±0.46)	-0.06	0.455
Aortic sinus diameter (cm)	3.46 (±0.4)	3.44 (±0.43)	0.22	0.764
IVSd (cm)	1.06 (±0.13)	1.09 (±0.12)	-0.03	0.186
LV EDd (cm)	5.07 (±0.5)	4.95 (±0.43)	0.12	0.171
LV PWd (cm)	0.91 (±0.1)	0.89 (±0.12)	0.02	0.347
LV MI (g/m^2)	92.46 (±19.21)	90.25 (±16)	2.21	0.473
LV EF (%)	61.43 (±4.94)	61.25 (±5.05)	0.18	0.835
E (m/s)	0.74 (±0.16)	0.73 (±0.16)	0.01	0.723
A (m/s)	**0.72 (±0.19)**	**0.81 (±0.16)**	**-0.09**	**0.004**
LAd (cm)	4.09 (±0.62)	4.14 (±0.44)	-0.57	0.549
LA VI (ml/m^2)	35.81 (±9.48)	33.55 (±6.98)	2.26	0.119
LA max. volume (ml)	71.09 (±19.52)	66.05 (±15.64)	5.04	0.104
LA pre P volume (ml)	53.68 (±14.77)	50.52 (±11.47)	3.16	0.178
LA min volume (ml)	**38.09 (±13.87)**	**31.35 (±9.11)**	**6.74**	**0.002**
LA EF (%)	**46.95 (±9.76)**	**53.72 (±8.53)**	**-6.77**	**<0.001**
e'lat. (m/s)	0.099 (±0.029)	0.101 (±0.029)	-0.002	0.698
e'med. (m/s)	0.079 (±0.022)	0.078 (±0.017)	0.001	0.745

e' mean (m/s)	0.089 (±0.023)	0.09 (±0.02)	-0.001	0.926
E/e' mean	8.72 (±2.83)	8.4 (±2.35)	0.32	0.476
E deceleration time (ms)	226.7 (±55.1)	237.5 (±61.7)	-10.8	0.3

SD – standard deviation; IVSd – interventricular septum diameter; LV – left ventricular; EDd – end diastolic diameter; PWd – posterior wall diameter; MI – mass index; EF – ejection fraction; LA – left atrium; VI – volume index;

Patients with paroxysmal AF had a significantly lower A wave velocity, a higher minimal volume of LA, and a lower LA EF.

All the patients were grouped according to the number of LV DD factors present and compared between the study and control groups. The numbers are given in Table 5.

Table 5. Comparison of LV DD factors between the groups. P=0.362.

LV DD factors present	Study group	Control group
0 factors	17	24
1 factor	26	23
2 factors	23	15
3 factors	2	3
4 factors	0	0

LV DD – left ventricular diastolic dysfunction.

There was no statistically significant difference between the groups.

3.5 Left Atrial Strain and Strain Rate

The LA strain and strain rate parameters are compared between the groups in Table 6.

Table 6. Mean values of the LA strain and strain rate compared between the groups.

Parameter	Study group (±SD)	Control group (±SD)	Difference of means	P value
Contractile strain (%)	**14.25 (±3.92)**	**15.51 (±3.05)**	**-1.26**	**0.041**
Conduit strain (%)	15.48 (±4.22)	16.42 (±3.97)	-0.94	0.192
Reservoir strain (%)	**29.74 (±6.6)**	**31.93 (±5.41)**	**-2.19**	**0.038**
Contractile strain rate (1/s)	1.72 (±0.63)	1.87 (±0.49)	-0.15	0.121
Conduit strain rate (1/s)	1.17 (±0.42)	1.25 (±0.37)	-0.08	0.266
Reservoir strain rate (1/s)	**1.04 (±0.29)**	**1.23 (±0.27)**	**-0.19**	**<0.001**

SD – standard deviation.

Patients with paroxysmal AF had significantly lower values of contractile strain, reservoir strain, and reservoir strain rate.

3.6 Reproducibility of Left Atrial Strain Measurements

Intraclass correlation coefficients (95 % CI) for intraobserver variability of the LA contractile, conduit and reservoir strains were 0.91 (0.79—0.96), 0.92 (0.81—0.97) and 0.94 (0.86—0.98) respectively. The absolute difference divided by the mean of two measurements for intraobserver variability of the LA contractile, conduit, and reservoir strains was 5.7 %, 5.5 %, and 4.9 % respectively. Intraclass correlation coefficients (9 5% CI) for interobserver variability of the LA contractile, conduit, and reservoir strains were 0.89 (0.75—0.96), 0.91 (0.79—0.96), and 0.93 (0.82—0.97), respectively. The absolute difference divided by the mean of two measurements for interobserver variability of the LA contractile, conduit, and reservoir strains was 8.6%, 6.0%, and 5.5%, respectively.

3.7 The Link Between Left Atrial Strain/Strain Rate Parameters and the Left Ventricular Diastolic Dysfunction Factors

All patients of the study and control groups were regrouped according to the number of LV DD factors present, and the LA strain and strain rate mean values were compared between the groups. The data are shown in Table 7.

Table 7. LA strain and strain rate comparison between the groups of patients with different number of LV DD factors present.

Parameter		Mean (±SD)	P value for difference between groups (ANOVA)
Contractile strain (%)	0 LV DD factors	16.52 (3.37)	0.001
	1 LV DD factor	14.55 (2.77)	
	2 LV DD factors	13.63 (4.11)	
Conduit strain (%)	0 LV DD factors	17.9 (4.11)	<0.001
	1 LV DD factor	15.96 (3.84)	
	2 LV DD factors	13.94 (3.29)	
Reservoir strain (%)	0 LV DD factors	34.42 (5.63)	<0.001
	1 LV DD factor	30.51 (4.76)	
	2 LV DD factors	27.56 (6.02)	
Contractile strain rate (1/s)	0 LV DD factors	2.14 (0.52)	<0.001
	1 LV DD factor	1.71 (0.55)	
	2 LV DD factors	1.57 (0.5)	
Conduit strain rate (1/s)	0 LV DD factors	1.45 (0.36)	<0.001
	1 LV DD factor	1.23 (0.39)	
	2 LV DD factors	0.94 (0.27)	
Reservoir strain rate (1/s)	0 LV DD factors	1.34 (0.3)	<0.001
	1 LV DD factor	1.12 (0.25)	
	2 LV DD factors	0.95 (0.21)	

SD – standard deviation; LV DD – left ventricular diastolic dysfunction.

All the parameters of the LA strain and strain rate had statistically significant differences between the groups of patients with a different number of LV DD factors present. With the increasing number of LV DD factors, there was a statistically significant drop in all LA strain and strain rate values. LA reservoir strain and strain rate differences are shown in Figures 3 and 4, the LA conduit strain and strain rate –

Figures 5 and 6, and the LA contractile strain and strain rate – Figures 7 and 8.

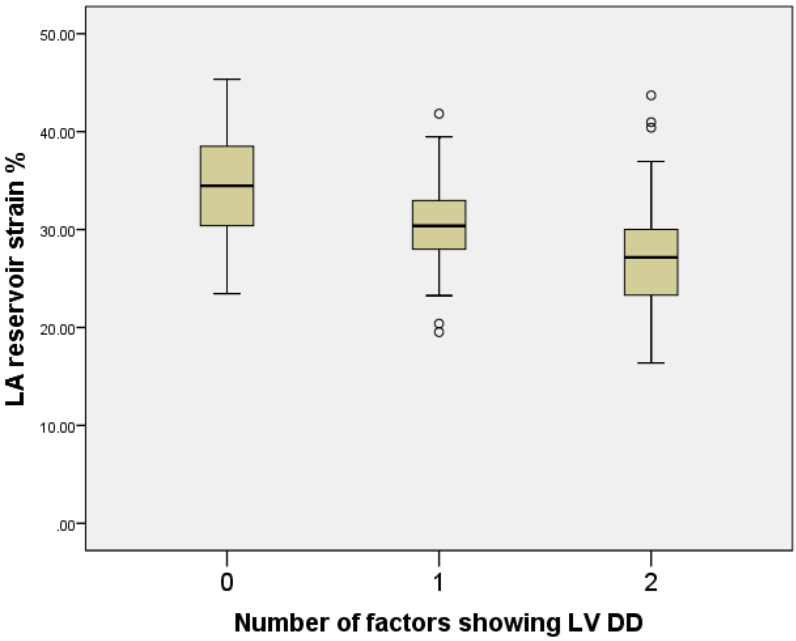

Figure 3. LA reservoir strain values between the groups of patients with a different number of factors showing LV DD. P<0.05 between all the groups.

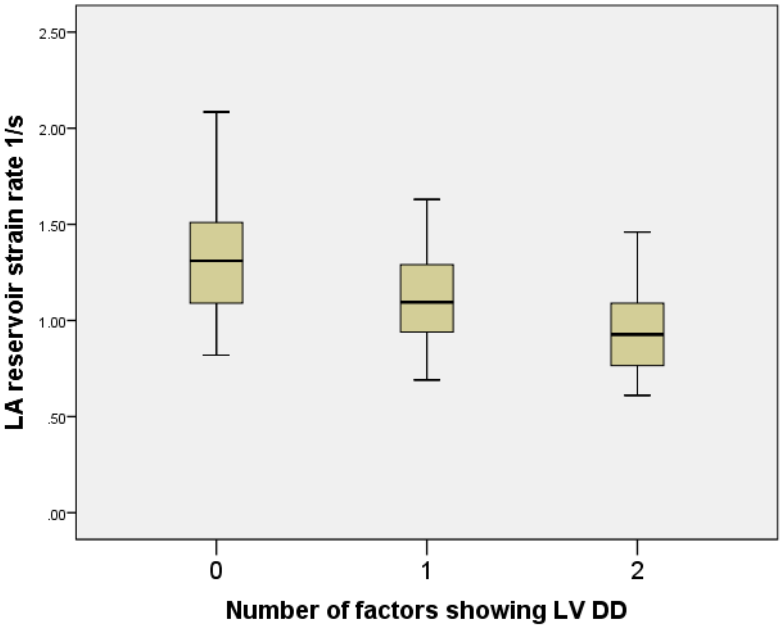

Figure 4. LA reservoir strain rate values between the groups of patients with a different number of factors showing LV DD. P<0.05 between all the groups.

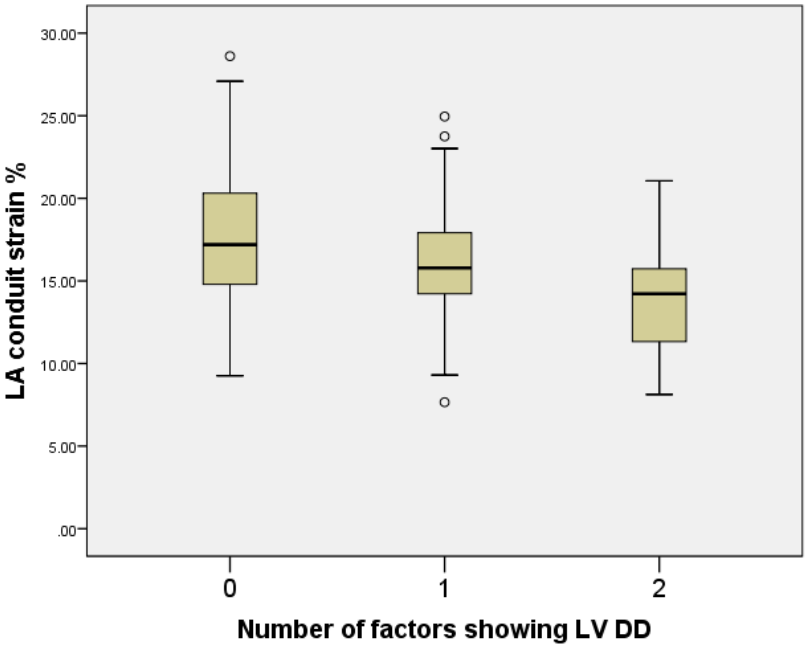

Figure 5. LA conduit strain values between the groups of patients with a different number of factors showing LV DD. P<0.05 between all the groups.

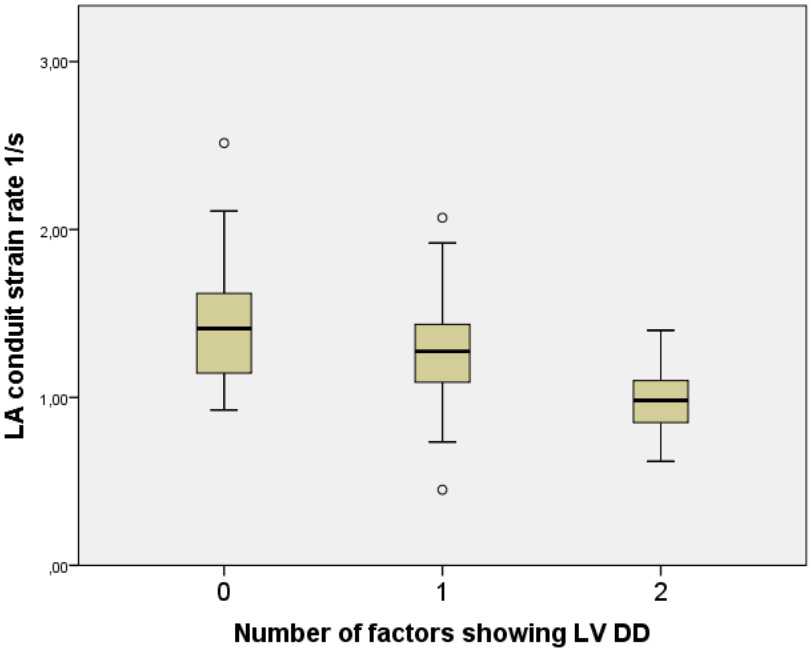

Figure 6. LA conduit strain rate values between the groups of patients with a different number of factors showing LV DD. P<0.05 between all the groups.

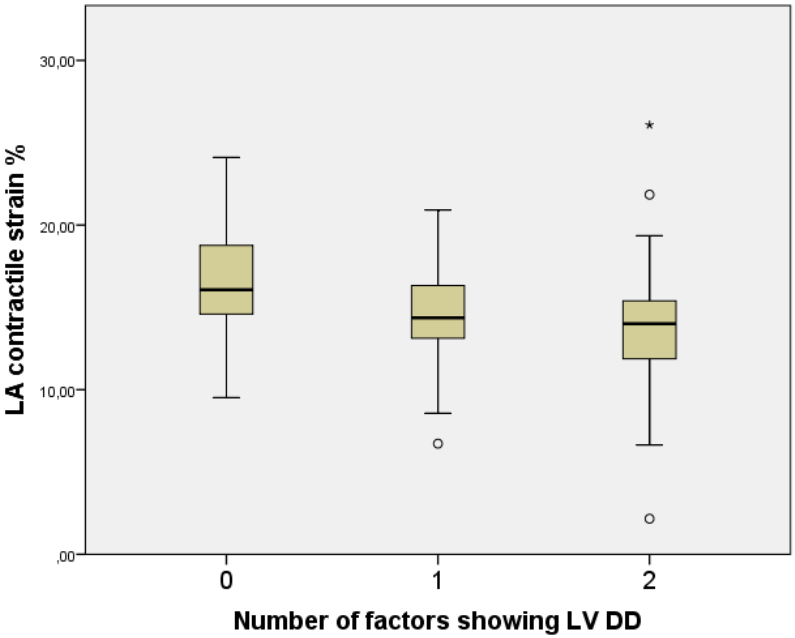

Figure 7. LA contractile strain values between the groups of patients with a different number of factors showing LV DD. The difference between the groups of 1 and 2 LV DD factors is not statistically significant ($p=0.212$); other differences are statistically significant ($p<0.05$).

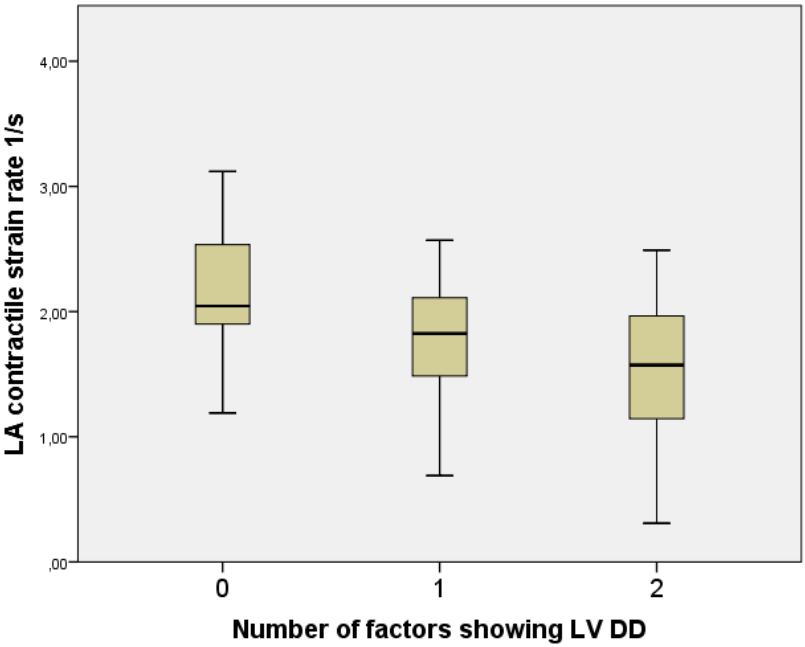

Figure 8. LA contractile strain rate values between the groups of patients with a different number of factors showing LV DD. The difference between the groups of 1 and 2 LV DD factors is not statistically significant ($p=0.202$); other differences are statistically significant ($p<0.05$).

LA reservoir strain and strain rate association with E/e' rate is graphically displayed in Figures 9 and 10.

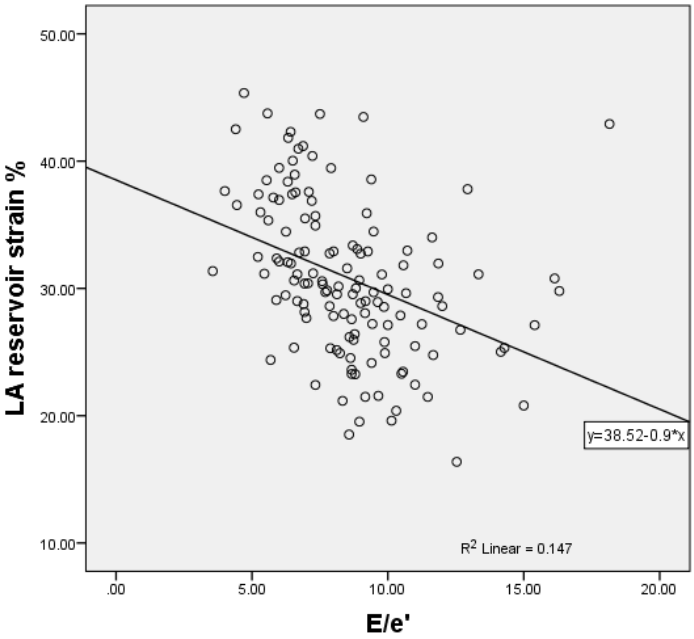

Figure 9. LA reservoir strain and E/e' association. Correlation coefficient -0.459, $p<0.001$.

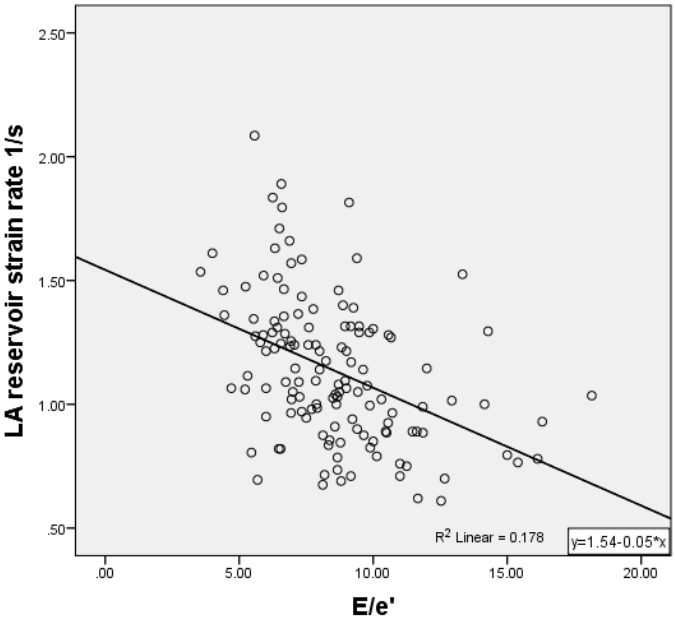

Figure 10. LA reservoir strain rate and E/e' association. Correlation coefficient -0.451, $p < 0.001$.

3.8 24-Hour Ambulatory Arterial Blood Pressure Monitoring

A comparison of 24-hour ambulatory ABP monitoring parameters is shown in Table 8.

Table 8. 24-hour ambulatory ABP monitoring parameters compared between the groups.

Parameter	Study group (±SD)	Control group (±SD)	Difference of means	P value
24-hour systolic ABP mean (mm Hg)	129.63 (±10.67)	133.57 (±14.67)	-3.94	0.08
24-hour systolic ABP mean SN	14.97 (±3.24)	16.17 (±4.11)	-1.2	0.065
24-hour diastolic ABP mean (mm Hg)	**74.4 (±8.56)**	**77.9 (±8.44)**	**-3.5**	**0.026**
24-hour diastolic ABP mean SD	11.04 (±2.96)	11.91 (±3.63)	-0.87	0.135
Daytime systolic ABP mean (mm Hg)	133.75 (±10.76)	138.15 (±14.48)	-4.4	0.05
Daytime systolic ABP mean SD	14.11 (±3.51)	15.37 (±3.86)	-1.26	0.052
Daytime diastolic ABP mean (mm Hg)	**77.88 (±8.58)**	**81.89 (±8.65)**	**-4.01**	**0.008**
Daytime diastolic ABP mean SD	10.54 (±3.42)	11.15 (±3.68)	-0.61	0.323
Nighttime systolic ABP mean (mm Hg)	121.41 (±13.12)	125.12 (±17.3)	-3.71	0.165
Nighttime systolic ABP mean SD	12.35 (±8.42)	12.88 (±5.56)	-0.53	0.674
Nighttime diastolic ABP mean (mm Hg)	67.91 (±9.43)	70.95 (±10.28)	-3.04	0.077
Nighttime diastolic ABP mean SD	**7.79 (±2.76)**	**8.97 (±3.34)**	**-1.18**	**0.029**

Systolic ABP drop during the night (%)	9.3 (±7.34)	9.45 (±7.76)	-0.15	0.917
Diastolic ABP drop during the night (%)	12.68 (±8.3)	13.22 (±10.06)	-0.54	0.736
Morning surge (%)	18.15 (±12)	19.43 (±12.62)	-1.28	0.549
systolic ABP PTE (%)	47.03 (±26.94)	53.35 (±29.97)	-6.32	0.174
diastolic ABP PTE (%)	**30.94 (±25.91)**	**42.12 (±26.95)**	**-11.18**	**0.013**
systolic ABP PTD (%)	0.79 (±1.84)	1.4 (±2.57)	-0.61	0.103
diastolic ABP PTD (%)	15.22 (±18.3)	10.65 (±13.34)	4.57	0.297

SD – standard deviation; ABP – arterial blood pressure; PTE – percent time elevation; PTD – percent time drop.

Patients with paroxysmal AF had significantly lower values of the 24-hour diastolic ABP mean, daytime diastolic ABP mean, nighttime diastolic ABP mean SD, and diastolic ABP PTE. Even though the difference was statistically significant, we cannot reject the influence of medication on the ABP parameters. Patients in the study group were more frequently on ACEI as compared to the control group, which could have contributed to lower diastolic blood pressure. We therefore did not include the blood pressure parameters in the further analysis.

The percentage of dippers (nighttime drop >10%) and non-dippers (nighttime drop <10%) was compared between the groups. There were no statistically significant differences. The results are shown in Tables 9 and 10.

Table 9. Systolic ABP drop comparison between the groups. P=0.853.

Systolic ABP drop during the night	Study group	Control group
>10 %	37	33
0-10 %	24	26
<0	7	6

Table 10. Diastolic ABP drop comparison between the groups. P=0.927.

Diastolic ABP drop during the night	Study group	Control group
>10 %	42	42
0-10 %	22	19
<0	4	4

ABP – arterial blood pressure.

3.9 24-Hour Ambulatory ECG Monitoring

The parameters of the 24-hour ambulatory ECG monitoring are compared in Table 11.

Table 11. 24-hour ambulatory ECG monitoring parameters compared between the groups.

Parameter	Study group (±SN)	Control group (±SN)	Difference of means	P value
24-hour mean HR (bpm)	**64.73 (9.96)**	**69.12 (8.85)**	**-4.39**	**0.008**
Minimal HR (bpm)	**48.21 (5.75)**	**50.48 (8.02)**	**-2.27**	**0.063**
Maximal HR (bpm)	110.25 (23.68)	113.23 (17.52)	-2.98	0.26
Ventricular premature beats (%)	0.3 (0.87)	0.32 (0.95)	-0.02	0.918
Atrial premature beats (%)	**1.23 (3.36)**	**0.52 (2.16)**	**0.71**	**<0.001**
Short-run atrial tachyarrhythmia episodes	**23 (77.25)**	**1 (2.07)**	**22**	**<0.001**

SD – standard deviation; HR – heart rate; bpm – beats per minute.

Patients with atrial fibrillation had a significantly lower 24-hour mean HR, minimal HR, a higher percentage of atrial premature beats, and a higher number of short-run atrial tachyarrhythmia episodes. In order

to exclude the influence of taken medications, we repeated the analysis, excluding the patients that were on antiarrhythmics in both groups. The results are shown in Table 12.

Table 12. 24-hour ambulatory ECG monitoring parameters compared between the groups. Patients on antiarrhythmics excluded.

Parameter	Study group (±SD) (n = 39)	Control group (±SD) (n = 43)	Difference of means	P value
24-hour mean HR (bpm)	67.74 (9.94)	69.02 (7.73)	-1.28	0.515
Minimal HR (bpm)	49.23 (5.75)	48.67 (7.5)	0.56	0.705
Maximal HR (bpm)	116.9 (23.97)	116.42 (18.21)	0.48	0.919
Ventricular premature beats (%)	0.41 (1.12)	0.29 (1.03)	0.12	0.638
Atrial premature beats (%)	1.12 (2.83)	0.56 (2.51)	0.56	0.345
Short-run atrial tachyarrhythmia episodes	**11.55 (25.52)**	**0.93 (2.04)**	**10.62**	**0.015**

SD – standard deviation; HR – heart rate; bpm – beats per minute.

When the influence of antiarrhythmics was excluded, only one statistically significant parameter remained: the number of short-run atrial tachyarrhythmia episodes.

3.10 Binary Logistic Regression Analysis

After identifying the potentially useful parameters in predicting paroxysmal AF, we performed a binary logistic regression analysis.

Parameters included in the analysis were age, gender, BMI, NT pro BNP, troponin I, A wave velocity, LA EF, reservoir strain, and reservoir strain rate. Although we found differences in minimal LA volume and the contractile strain, these parameters were excluded from the regression analysis because of their close connection with already included parameters: the LA EF and reservoir strain. Data of the model are shown in Tables 13, 14, and 15.

Table 13. Results of a binary logistic regression analysis with potentially useful parameters in predicting paroxysmal AF.

Parameter	Odds ratio Exp(B)	95% confidence interval		P value
Age	0.983	0.924	1.046	0.591
BMI	0.923	0.809	1.053	0.232
Gender	0.759	0.247	2.332	0.63
NT pro BNP	1.002	0.998	1.006	0.255
Troponin I	0.984	0.84	1.154	0.844
A wave velocity	0.047	0.002	1.182	0.063
LA EF	**0.925**	**0.864**	**0.990**	**0.025**
Reservoir strain	**1.184**	**1.042**	**1.346**	**0.01**
Reservoir strain rate	**0.003**	**0**	**0.079**	**<0.001**
Short-run atrial tachyarrhythmia episodes	**1.268**	**1.051**	**1.53**	**0.013**

BMI – body mass index; LA EF – left atrial ejection fraction.

Table 14. R^2 values.

Cox and Snell R^2	Nagelkerke R^2
0.415	0.556

Model characteristics: sensitivity 79.7%, specificity 73.6%, positive prognostic value 78.5%, negative prognostic value 75%. The ROC curve, together with its characteristics, is shown in Figure 11 and Table 15.

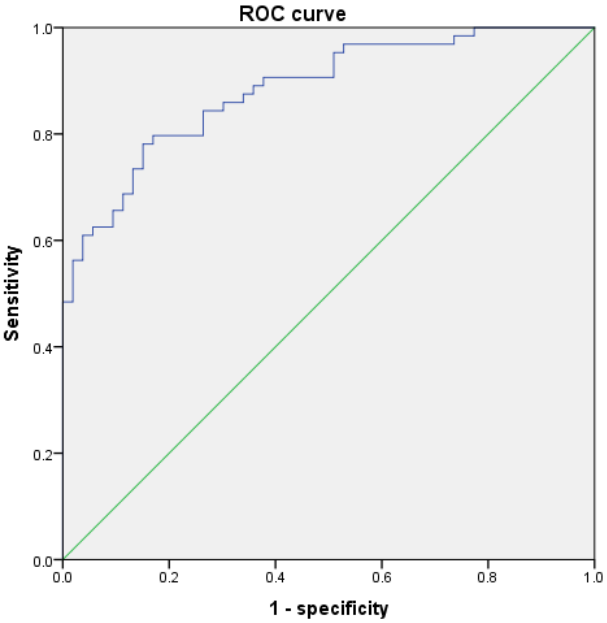

Figure 11. ROC curve for binary logistic regression model.

Table 15. Characteristics of the ROC curve.

Area under the curve	Standard error	P value	95% confidence intervals	
0.884	0.03	<0.001	0.826	0.942

The binary logistic regression analysis showed that independent and statistically significant parameters linked to paroxysmal AF are the LA EF, LA reservoir strain, LA reservoir strain rate, and short-run atrial tachyarrhythmia episodes during a 24-hour ambulatory ECG monitoring cycle. A new model of binary logistic regression was formed including only the parameters that were statistically significant in the previous one. The results are shown in Tables 16 and 17.

Table 16. Results of the binary logistic regression analysis with the parameters that were statistically significant in the previous model.

Parameter	Odds ratio Exp(B)	95% confidence interval		P value
LA EF	**0.922**	**0.872**	**0.975**	**0.005**
Reservoir strain	**1.164**	**1.037**	**1.307**	**0.01**
Reservoir strain rate	**0.013**	**0.001**	**0.133**	**<0.001**
short-run atrial tachyarrhythmia episodes	**1.217**	**1.037**	**1.429**	**0.016**

LA EF – left atrial ejection fraction.

Table 17. R^2 values.

Cox and Snell R^2	Nagelkerke R^2
0.328	0.438

Model characteristics: sensitivity 78.8%, specificity 70.4%, positive prognostic value 76.5%, negative prognostic value 73.1%. The ROC curve and its characteristics are shown in Figure 12 and Table 18.

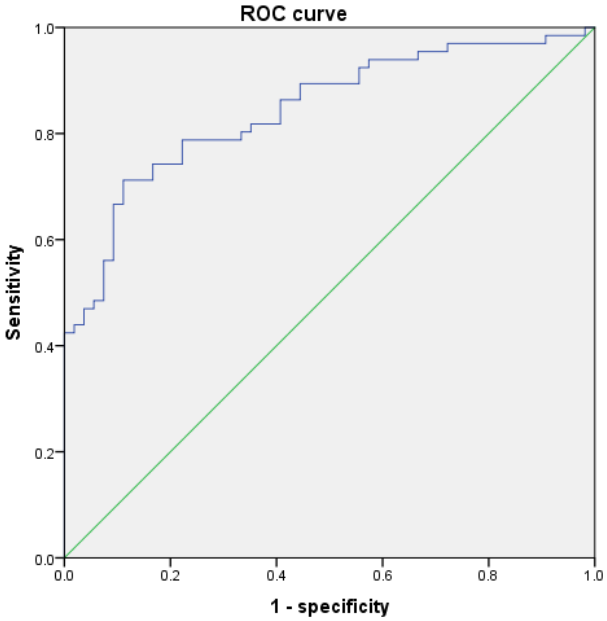

Figure 12. ROC curve for the binary logistic regression model.

Table 18. Characteristics of the ROC curve.

Area under the curve	Standard error	P value	95% confidence intervals	
0.845	0.035	<0.001	0.775	0.914

3.11 Classification and Regression Tree

A classification and regression tree analysis was carried out to identify the most useful parameters, their cut-off values, and the decision algorithm for predicting paroxysmal AF. The following factors were included in the analysis: NT pro BNP, troponin I, LA EF, LA reservoir strain, LA reservoir strain rate, and short-run atrial tachyarrhythmia episodes. The classification and regression tree is shown in Figure 13.

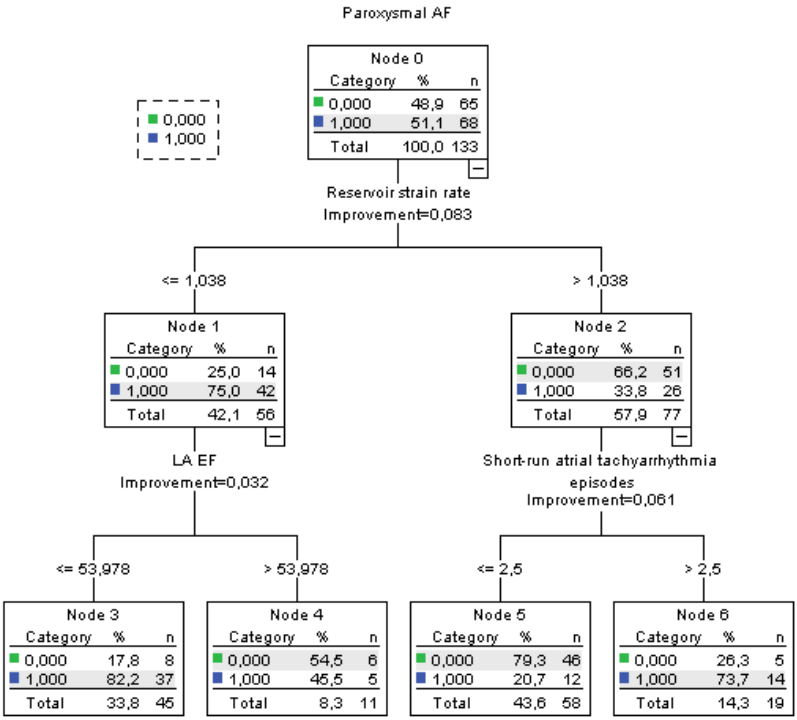

Figure 13. Classification and regression tree. The green color represents the control group (without AF), and blue – the study group patients (with paroxysmal AF).

The normalized importance of the variables is shown in Figure 14.

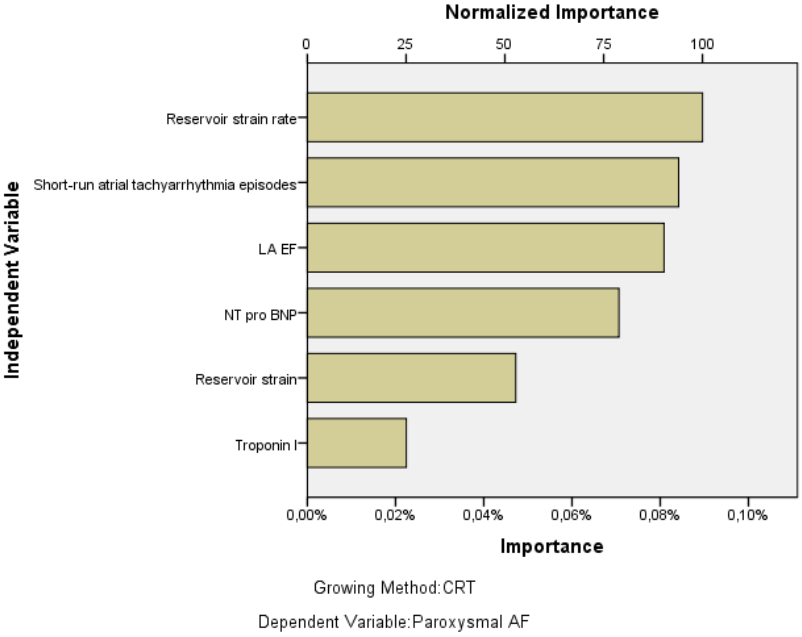

Figure 14. Normalized importance of the independent variables in the model for predicting paroxysmal AF in patients with PAH.

A classification and regression tree revealed that the most important cardiovascular factors in predicting paroxysmal AF are the LA reservoir strain rate, short-run atrial tachyarrhythmia episodes during a 24-hour ambulatory blood pressure monitoring, and LA EF. Cut-off values of the variables were also determined: 1.038 for the LA reservoir strain rate, 2.5 for the short-run atrial tachyarrhythmia episodes during a 24-hour ambulatory blood pressure monitoring, and 53.978 % for the LA EF.

The classification table of the model is shown in Table 19.

Table 19. Classification table of the classification and regression tree model.

Observed		Predicted		
		Paroxysmal AF		Correct %
		Yes	No	
Paroxysmal AF	No	52	13	80
	Yes	17	51	75
Total %				77,4

AF – atrial fibrillation.

Characteristics of the model: sensitivity 75%, specificity 80%, positive prognostic value 79.7%, negative prognostic value 75.4%.

The ROC curve and its characteristics are shown Figure 15 and Table 20.

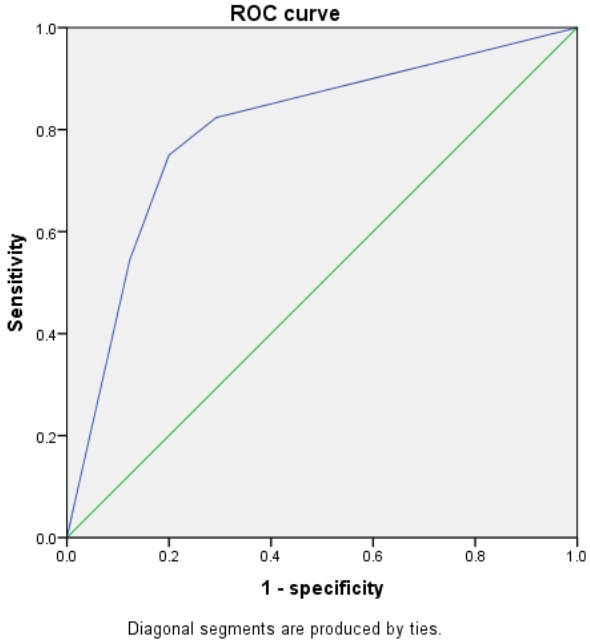

Figure 15. ROC curve for the classification and regression tree model.

Table 20. Characteristics of the ROC curve for the classification and regression tree model.

Area under the curve	Standard error	P value	95% confidence intervals	
0.801	0.04	<0.001	0.723	0.879

4. DISCUSSION

4.1 General Characteristics of Study and Control Group Patients

Before discussing the results, it is of paramount importance to describe the characteristics of the patients included in the study. The patients included in both groups were mostly middle-aged (the mean age of the study and control groups is 62.9±11.61 and 59.15±11.77, respectively) and a little overweight (the mean BMI of the study and control group is 29.58±4.27 and 29.03±4.79, respectively). Type II diabetes was not an exclusion criteria, but there was the same number of patients with this pathology in both groups (5 patients in each group), so we do not expect this to influence the results in any way. Gender-wise, the groups were almost identical (44 % and 43 % males in the study and control groups, accordingly). All in all, the patients were well-matched, as there were no statistically significant differences in the general chracteristics of the patients.

The patients in the study mostly had stage I or II hypertension, which was well-controlled by taking on average just 1.59 antihypertensive medications. This number was identical between the groups. To diminish the possibility of secondary hypertension, the ones with resistant PAH were excluded. The fact that hypertension was well-controlled is proved by the 24-hour ambulatory ABP monitoring: systolic ABP values were 129.4±10.58 and 133.57±14.67 mm Hg, and the diastolic values were 74.4±8.59 and 77.89±8.44 in the study and control group patients, respectively. Although a small one (3.49 mm Hg), the difference of diastolic blood pressure values between the groups was statistically significant (p=0,015). We think that this might be due to the differences of the antihypertensive medications taken: the patients with AF were significantly more frequently on ACEI as compared to the control group. There were no other significant differences of the medications taken. As the majority of the patients were on ACEI, ARB, CCB, β-blockers, and diuretics, we can conclude

that the patients were mostly treated according to the valid ESC guidelines.

4.2 Quality of Life, Anxiety and Depression

We have not found any studies of life quality, anxiety, and depression on patients with paroxysmal AF caused by PAH comparing them with hypertensive patients. Most of the studies in the field are interventional, aimed to find the effect of treatment on quality of life in patients with AF. The fact that paroxysmal AF reduces quality of life in the general population is somehow taken for granted without much strong evidence. Our study allowed us to exclusively evaluate the influence of paroxysmal AF on quality of life, anxiety, and depression, as we excluded all other pathologies. Paroxysmal AF was the single factor differentiating the study and control groups.

Though the difference of anxiety and depression levels between the groups did not meet the cutoff for statistical significance, patients with AF had higher levels of both. The level of anxiety in the study group was higher by 19.2 %, and the level of depression – by 29 %. In our opinion, the cutoff for statistical significance was not met because of the low number of patients included in the study. It is worth mentioning that patients with AF and PAH had anxiety levels above the cutoff where an anxiety disorder can be suspected. In comparing our results with similar studies, one aspect must be highlighted: there is more evidence about the increased level of anxiety and not depression in patients with AF. A study published in 2018 found that patients with AF had higher levels of anxiety than those of depression (HADS values 8.9 and 5.8, respectively). These levels of anxiety were also significantly higher in patients with AF as compared to the control group, which was not the case with depression [17]. Other studies also highlight increased levels of anxiety and not depression in patients with AF [46]. Our results support the fact that patients with paroxysmal AF have high levels of anxiety.

Patients with AF had worse quality of life in all sections evaluated by SF-36, but statistical significance was reached in sections corresponding to physical health. Patients with paroxysmal AF had lower levels of physical functioning, physical role functioning, and general health. We used the SF-36 questionnaire to evaluate quality of life, and this allowed us to compare the results with other studies, as it is the most popular tool. Other studies, which did not have perfectly matched groups, show similar results [19, 47, 48]. Paroxysmal AF caused by PAH, with the influence of other pathologies set aside, leads to a worse quality of life, mostly limiting physical functioning. The results are further validated by our questionnaire of physical activity, which revealed that patients with paroxysmal AF were indeed less physically active if compared with the control group.

Discussing quality of life questions cannot be done without taking into consideration the age of the patients. Perret-Guillaume et al. published a study in 2010 that evaluated the quality of life in elderly patients with AF. The mean age in both groups was approximately 72 years. The study proved that in elderly patients, AF primarily alters the mental quality of life [49]. Having in mind these data, we can deduce that the influence that AF has on quality of life is dependent on the age of the patients: physical health is affected more in younger patients, while the older ones tend to suffer more from a decline in mental health. All in all, we can undoubtedly say that paroxysmal AF leads to a worse quality of life in patients with hypertension.

4.3 Blood Biomarkers

Comparing the means of laboratory parameters revealed significant differences of three biomarkers: troponin I, NT pro BNP, and TSH. We decided not to include TSH into further analysis because of two things. First, we had excluded all the patients having TSH concentration outside the normal range, therefore creating a biased population regarding this aspect. Second, large scale prospective Framingham population studies revealed no influence of increased

TSH on AF [50], whereas decreased TSH was clearly linked to arrhythmia [51].

Though there was not a single patient with troponin I concentrations outside the normal range, the study group patients had significantly higher concentrations of this biomarker. From the perspective of coronary heart disease diagnostics, the values of troponin I were very little (in the study and control groups – 4.16±4.8 and 2.66±2.7 ng/l, respectively), but the difference revealed the potential usefulness of the biomarker in predicting paroxysmal AF. Other studies also show that troponin I might be linked with AF even when the concentrations are low [52]. The mechanism of troponin I release during the episodes of paroxysmal AF is proved in animal studies. At high frequency pacing of the heart, conditions similar to AF were created, and this led to increased concentrations of troponin I [53].

The values of NT pro BNP had a substantial difference between the groups. Patients with paroxysmal AF had a 2.3-fold increased concentrations of NT pro BNP (287.68±325.59 in the study group and 124.54 ±105.11 pg/ml in the control group). Though the patients with heart failure symptoms and LV EF < 55% were excluded, NT pro BNP values were surprisingly high in the paroxysmal AF group. At the moment, the cutoff value of NT pro BNP in diagnosing heart failure is 125 pg/ml [54]. Our results show not only the fact that increased concentrations of NT pro BNP are linked with paroxysmal AF, but also raise the question of the cutoff for diagnosing heart failure in patients with AF. Other studies revealing high concentrations of NT pro BNP in patients with AF also discussed the valid cutoff values. [55].

The facts that NT pro BNP is linked with early LV DD, LA stretch, and remodeling, as well as fibrosis, confirm the close link between this biomarker and paroxysmal AF in patients with PAH.

Although higher concentrations of troponin I and NT pro BNP should raise suspicion of paroxysmal AF in certain situations, a binary logistic regression analysis revealed that the studied biomarkers were not among the best AF predicting factors.

Our study revealed that paroxysmal AF is particularly related to the parameters of LA function. Of all the routine ultrasound parameters, a significant difference was obtained in three: A wave velocity, minimal LA volume, and LA EF. These variables surpassed LA volume index, the E/e' ratio, and mitral annular velocity. Our findings unequivocally answer the question of the importance of LA size or function parameter in the early detection of paroxysmal AF. The LA function is far more sensitive than size in predicting paroxysmal AF. Mean LA volume index values were on the cutoff of being increased in both groups (34 ml/m^2) with a minor and not statistically significant difference. This shows that patients with PAH can have increased LA size, but it is the function that can answer the question whether the patient has paroxysms of AF or not. A logistic regression showed that LA EF, differently from A wave velocity and minimal LA volume, remained an independent and significant prognostic factor of paroxysmal AF. This did not surprise us, as LA EF corresponds to the reservoir function of LA and, subsequently, LA fibrosis [56, 57].

Among the LA strain and strain rate parameters, a significant difference was obtained in mean LA contractile and reservoir strains as well as the reservoir strain rate. A regression analysis showed that the best independent predictors were the LA reservoir strain and reservoir strain rate. All in all, we can conclude that the reservoir function of the LA is essential in predicting the risk of paroxysmal AF in patients with PAH.

4.5 Left Atrial Strain – An Early Marker of Left Ventricular Diastolic Dysfunction

Though it is well-defined that the decline in the LA reservoir function is linked with the remodeling of LV, there is also data showing that the changes in the LA cannot be explained solely by LV DD [58]. The remodeling of the LV and LA is possibly occurring in parallel with

each other, and this brings up the idea that the parameters of the LA function can be early markers of LV DD. When we grouped the patients according to the number of traditional ultrasound variables present showing LV DD, the groups had significantly different values of the LA strain and strain rate parameters. That means that we could group the patients into the same groups without using the traditional parameters of LV DD. This leads us to two conclusions. First, the LA strain and strain rate are undoubtedly related with LV DD. This proves the fact that LA and LV diastolic functions are closely related with each other. Second, our results show that LA remodeling occurs very early in the course of the disease. The LA strain and strain rate variables are among the earliest markers of LV DD, certainly preceding traditional ones. The results of other studies also prove this hypothesis. In 2016 a study published by A. Brecht et al., ultrasound data of 473 patients was analyzed. Of them, 153 had LV DD according to the traditional parameters recommended by the guidelines. All the patients were asymptomatic, which means the disease was in its early stages, when the changes are subtle and hard to find. When the LA strain parameters were compared among different LV DD grade patients, the LV reservoir and conduit strains appeared to be the most sensitive and specific markers of the disease surpassing LA VI [59]. This topic is also discussed in the 2019 publication by L. Thomas et al. in *JACC* [60]. Studies analyzing the link between different LA ultrasound parameters and LV DD are reviewed. The conclusions of the publication are on par with the ones of our study. First, the parameters of the LA reservoir function are important in diagnosing and grading LV DD as well as evaluating the effect of treatment. Second, parameters of LA size are not sensitive enough in the early stages of the disease. Increased LA size is already a late consequence of ongoing processes in the LA and LV. This is also proved in our study.

4.6 24-Hour Ambulatory Blood Pressure Monitoring

All the statistically significant differences between the groups are in the values of diastolic blood pressure. The patients with paroxysmal AF had mildly though significantly lower values of 24-hour mean and daytime diastolic blood pressure, a higher variability of nighttime diastolic blood pressure, and their diastolic blood pressure exceeded the nighttime cutoff value less often as compared with the control group. This all leads to a conclusion that the patients with paroxysmal AF were treated better by prescribing ACEI. The reason that there were statistically significant differences in the antihypertensive medication profile between the groups made us refrain from any further analysis of these differences.

4.7 24-Hour Ambulatory ECG Monitoring

There were statistically significant differences in 24-hour mean and minimal HR, atrial premature beat percentage, and short-run atrial tachyarrhythmia episodes between the groups. The fact that a substantial part of the patients in both groups were on antiarrhythmic drugs made us repeat the analysis, including only those that were not on antiarrhythmic medications. This revealed a single relevant variable: short-run atrial tachyarrhythmia episodes. A regression analysis confirmed that this factor is independent and one of the most important in predicting the risk of paroxysmal AF. According to the ESC guidelines, we can diagnose AF when the episode without apparent P waves and irregular RR intervals on the ECG is longer than 30 s [6]. However, the duration of 30 s is not proven by any trials, and the results of ours as well as others' studies raise questions regarding its validity. This is taken further by a 2017 publication in *Stroke*, which analyzed the risk of stroke in patients with short-run atrial tachyarrhythmia episodes. The results revealed that these episodes, as well as atrial premature beats, were related to an increased risk of stroke [61]. The most important question regarding short-run atrial tachyarrhythmia episodes is whether we can reduce the risk of stroke

in these patients with anticoagulation. Although we are not aware of any published studies dealing with this question, if this was proven, the 30 s cutoff for the diagnosis of AF would be compromised.

4.8 Limitations of the Study

Firstly, the study is limited by a rather small number of patients in both groups. This possibly did not allow us to reach statistical significance when the changes were subtle. Ideally, the patients should have been divided into two groups and, after the useful variables were identified in one part of the patients, their performance in predicting AF should have been tested in another part of the patients. The small number of patients did not allow us to perform such an analysis. Another limitation is the design of the study. In order to fully answer the question, a prospective longitudinal study design would have been a better choice, when the patients are included with hypertension only and observed until they develop paroxysmal AF. However, this would have required huge resources and a very long observation period, as the annual percentage of patients with PAH developing AF is not that high and would have probably not exceeded a few percent a year.

5. CONCLUSIONS

1. Paroxysmal atrial fibrillation is linked to increased concentrations of NT pro BNP and troponin I in patients with primary arterial hypertension.
2. Paroxysmal atrial fibrillation is linked to a decreased left atrial reservoir strain, reservoir strain rate, and ejection fraction values in patients with primary arterial hypertension.
3. Paroxysmal atrial fibrillation is linked to an increased number of short-run (<30 s) atrial tachyarrhythmia episodes during 24-hour ambulatory ECG monitoring in patients with primary arterial hypertension.
4. In the population of patients with primary arterial hypertension, heart ultrasound parameters of the left atrium (reservoir strain, reservoir strain rate, and ejection fraction) and the number of short-run atrial tachyarrhythmia episodes during 24-hour ambulatory ECG monitoring are able to predict paroxysmal atrial fibrillation.
5. Paroxysmal atrial fibrillation leads to a worse quality of life in patients with primary arterial hypertension.

6. RECOMMENDATIONS FOR CLINICAL PRACTICE

1. In order to differentiate the risk of paroxysmal AF among patients with primary arterial hypertension, it is useful to perform laboratory tests of NT pro BNP and troponin I, a 24-hour ambulatory ECG monitoring searching for short-run atrial tachyarrhythmia episodes, and an ultrasound of the heart determining the parameters of the LA function.
2. The most important variables in predicting paroxysmal atrial fibrillation in patients with primary arterial hypertension are the LA strain rate, LA EF, and the number of short-run atrial tachyarrhythmia episodes during 24-hour ambulatory ECG monitoring.
3. The parameters of the LA function are better than the ones of LA size in predicting the risk of paroxysmal atrial fibrillation in patients with primary arterial hypertension.
4. LA strain and strain rate parameters are useful in detecting and grading the left ventricular diastolic dysfunction in patients with primary arterial hypertension.

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8. ANNEXES

8.1 Authorization Provided by the Lithuanian Bioethics Committee

PATVIRTINTA
Lietuvos bioetikos komiteto direktoriaus
2016 m. birželio 10 d. įsakymu Nr. V-14

LIETUVOS BIOETIKOS KOMITETAS

Biudžetinė įstaiga, Vilniaus g. 16, LT-01402 Vilnius, tel. (8 5) 212 4565,
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LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2016-07-26 Nr.: L-16-05/1

Vilnius

Tyrimo pavadinimas: **„Arterinio kraujospūdžio bei kitų kardiovaskulinių veiksnių įtaka prieširdžių virpėjimo išsivystymui pacientams, sergantiems pirmine arterine hipertenzija“**	
Protokolo Nr.:	**AKS-PV-1**
Versija:	**02**
Data:	**2016 m. liepos 17 d.**
Tiriamiesiems skirti dokumentai: Asmens informavimo ir informuoto asmens sutikimo forma (lietuvių kalba) : Versija: **02** Data: **2016 m. balandžio 18 d.**	
Pagrindinis tyrėjas:	**Gyd., med. m. dr., prof. Audrius Aidetis**
Tyrimo centro pavadinimas:	**Vilniaus universiteto ligoninės Santariškių klinikos**
Adresas:	**Santariškių g. 2, 08661, Vilnius**

Leidimas atlikti biomedicininį tyrimą išduotas Lietuvos bioetikos komiteto Biomedicininių tyrimų ekspertų grupės posėdžio, įvykusio **2016 m. liepos 19 d.**, sprendimu.

Direktorius Eugenijus Gefenas

LIETUVOS RESPUBLIKA Lietuvos bioetikos komitetas VILNIUS

8.2 The List of Publications

1. **Jarasunas J**, Aidietis A, Aidietiene S. Left atrial strain – an early marker of left ventricular diastolic dysfunction in patients with hypertension and paroxysmal atrial fibrillation. *Cardiovasc Ultrasound*. 2018 Oct 31;16(1):29. DOI: 10.1186/s12947-018-0147-6.
2. Berukstis A, **Jarasunas J**, Daskeviciute A, Ryliskyte L, Baranauskas A, Steponeniene R, Laucevicius A. How to interpret 24-h arterial stiffness markers: comparison of 24-h ambulatory Mobil-O-Graph with SphygmoCor office values. *Blood Press Monit*. 2019 Apr;24(2):93–98. DOI: 10.1097/MBP.0000000000000369.

8.3 The List of Presentations

1. **Jarasunas J**, Berukstis A, Daskeviciute A, Misonis N, Ryliskyte L, Laucevicius A. Evaluation and comparison of ambulatory Mobil-O-Graph 24-hour mean arterial stiffness parameter values with Sphygmocor office values in high cardiovascular risk patients. Cardiology Update Conference 17, February 11–15, 2017, Davos, Switzerland.
2. **Jarasunas J**, Jakovlevaitė G, Aidietis A. Anxiety and depression in patients with paroxysmal atrial fibrillation. The 4th International Conference "Evolutionary Medicine: Health and Diseases in a Changing Environment," June 5–10, 2018, Vilnius University, Vilnius, Lithuania.
3. **Jarasunas J**, Aidietis A. LA function assessed by 2D speckle tracking in patients with hypertension and paroxysmal atrial fibrillation. The IX International Congress "Cardiology at the Crossroads of Sciences," May 23–25, 2018, Tyumen, Russia.

8.4 Curriculum Vitae

Name	**Jonas Jarašūnas**
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Address	23 Tvenkinio Str., Kvecių k., Kretingos raj., Lithuania
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Education

2017.09–2017.12	Electrophysiology fellowship in IKEM, Prague (Prof. J. Kautzner)
2015–now	Vilnius University, Faculty of Medicine, PhD studies
2010–2014	Vilnius University, Faculty of Medicine, residency in cardiology
2004–2010	Vilnius University, Faculty of Medicine, medical doctor
1992–2004	Klaipėda Vytautas Didysis Gymnasium

Work experience

2014.08–present	Klaipeda Seamen's Hospital, (45 Liepojos Str., LT-92288, Klaipėda), interventional electrophysiologist
2010.09–2014.06	Vilnius University Hospital Santariškių klinikos (2 Santariškių Str., 08661, Vilnius), resident in cardiology
2011.01–2014.08	Vilnius University Hospital Santariškių klinikos (2 Santariškių Str., 08661, Vilnius), Cardiac Intensive Care Unit, doctor assistant

8.5 Summary of the Doctoral Dissertation in Lithuanian

Įvadas

Prieširdžių virpėjimu (PV) serga 5,5 % populiacijos > 55 metų, tai labiausiai paplitusi ilgos trukmės prieširdinė aritmija. PV susijęs su didele embolinių komplikacijų rizika, kurią galima ženkliai sumažinti skiriant antikoaguliantus. Pirminė arterinė hipertenzija – dažniausia PV sukelianti patologija bendroje populiacijoje. Kadangi esant paroksizminiam PV aritmijos epizodai gali būti retesni arba asimptomiai, ligą nustatyti dažnai nėra lengva. Tikslinga išaiškinti lengvai nustatomus rodiklius, kurie leistų identifikuoti didelę PV riziką turinčius pacientus, bei jiems taikyti ilgesnę ambulatorinę EKG stebėseną, siekiant diagnozuoti PV bei paskirti gydymą. Taip pat yra duomenų, jog renino-angiotenzino-aldosterono sistemos blokatoriai efektyvūs tiek pirminėje, tiek antrinėje PV prevencijoje. Nustačius didelę PV riziką būtų tikslingas gydymas šiais medikamentais.
Nors visuotinai sutariama, jog PV sergančių pacientų gyvenimo kokybė yra prastesnė, absoliuti dauguma duomenų šioje srityje gauti iš randomizuotų intervencinių PV gydymo tyrimų, todėl galimai į tyrimą įtraukti tik labiausiai simptomus jaučiantys, o tuo pačiu metu ir prasčiausią gyvenimo kokybę turintys pacientai. Gyvenimo kokybės tyrimų bendroje PV, o ypač PV nulemto pirminės arterinės hipertenzijos, populiacijoje yra nepakankamai.

Tyrimo hipotezė

Paroksizminiu PV ir pirmine arterine hipertenzija sergantys pacientai turi būdingų kraujo biožymenų, širdies ultragarsinio tyrimo, 24 val. EKG ir arterinio kraujo spaudimo (AKS) stebėsenos rodiklių pokyčių, kurie leidžia identifikuoti paroksizminiu PV sergančius pacientus tarp pirmine arterine hipertenzija sergančių pacientų.
PV susijęs su blogesne pacientų, sergančių pirmine arterine hipertenzija, gyvenimo kokybe, didesniu nerimo ir depresijos lygiu.

Tyrimo tikslas

1. Nustatyti kardiovaskulinės sistemos rodiklius ir jų pokyčius, kurie leistų identifikuoti paroksizminiu prieširdžių virpėjimu sergančius ir didesnę aritmijos riziką turinčius pacientus tarp pirmine arterine hipertenzija sergančių pacientų.

2. Nustatyti, kokį poveikį paroksizminis prieširdžių virpėjimas turi pacientų, sergančių pirmine arterine hipertenzija, gyvenimo kokybei, nerimo ir depresijos lygiui.

Tyrimo uždaviniai

1. Nustatyti su paroksizminiu prieširdžių virpėjimu susijusius kraujo biožymenis, tiriant pacientus, sergančius pirmine arterine hipertenzija.

2. Nustatyti su paroksizminiu prieširdžių virpėjimu susijusius širdies ultragarsinio tyrimo rodiklius, tiriant pacientus, sergančius pirmine arterine hipertenzija.

3. Nustatyti su paroksizminiu prieširdžių virpėjimu susijusius 24 val. EKG ir AKS stebėsenos rodiklius, tiriant pacientus, sergančius pirmine arterine hipertenzija.

4. Nustatyti kardiovaskulinės sistemos rodiklius, kurie labiausiai susiję su paroksizminiu prieširdžių virpėjimu ir geriausiai leidžia prognozuoti, ar pacientas turi šios aritmijos paroksizmų, tiriant pacientus, sergančius pirmine arterine hipertenzija.

5. Nustatyti pagal gyvenimo kokybės klausimyną (SF-36) ir ligoninės nerimo ir depresijos skalę (HADS) vertinamų pacientų, sergančių pirmine arterine hipertenzija, gyvenimo kokybės, nerimo ir depresijos rodiklių skirtumus, susijusius su paroksizminiu prieširdžių virpėjimu.

Tyrimo naujumas

Šiuo metu literatūroje aprašyti PV rizikos vertinimo modeliai geba nusakyti prieširdžių virpėjimo riziką bendroje populiacijoje, tačiau į juos daugiausia įtraukti klinikiniai faktoriai, neskiriant pakankamo dėmesio naujiems kairiojo prieširdžio (KP) funkcijos vertinimo metodams, tokiems kaip ultragarsinis deformacijos bei deformacijos

greičio matavimas. Yra nemažai duomenų, jog KP deformacijos rodikliai susiję su PV rizika po plaučių venų izoliacijos procedūros, kardioversijos sėkme arba nesėkme, tromboembolinėmis komplikacijomis bei insultą patyrusių pacientų KP ausytės funkcija. Tyrimų, įtraukiančių KP deformacijos bei deformacijos greičio rodiklius į PV riziką nusakančias schemas tarp pirmine arterine hipertenzija sergančių pacientų bei nustatančių šių parametrų ribines vertes nėra publikuota. Kitas svarbus tyrimo naujumo aspektas yra tiriamoji populiacija. Nesusijęs su kita kardiovaskuline patologija PV yra reta liga, kurios paplitimas įvairių tyrimų duomenimis priklausomai nuo naudojamo apibrėžimo svyruoja nuo 1,6 % iki 30 %. Dažniausia kardiovaskulinė patologija, nulemianti PV išsivystymą bendroje populiacijoje yra pirminė arterinė hipertenzija. Nors šių dviejų patologijų sąsaja pasitaiko dažniausiai, tačiau tyrimų šioje pacientų grupėje yra nepakankamai.

Kadangi PV dažniausiai susijęs su kita gyvenimo kokybę bloginančia kardiovaskuline patologija, išskirti vien PV įtaką gyvenimo kokybei sudėtinga. Neįtraukdami pacientų, turinčių kitų reikšmingų patologijų, išskyrus hipertenziją, ir lygindami ne su sveikais, o hipertenzija sergančiais pacientais, mes galėjome įvertinti, kaip (ar) PV prisideda prie gyvenimo kokybės bloginimo bei didesnio nerimo ir depresijos lygio.

Metodika

Į tyrimą iš viso įtraukti 133 pacientai, sergantys pirmine arterine hipertenzija. Jie suskirstyti į 2 grupes. Tiriamąją grupę (n = 68) sudarė pacientai, sergantys paroksizminiu PV, o kontrolinę grupę (n = 65) pacientai, niekada neturėję PV paroksizmų. Siekiant įtraukti tik pirminės arterinės hipertenzijos nulemtus paroksizminio PV atvejus, į tyrimą neįtraukti pacientai, sergantys kitomis aritmiją galinčiomis sukelti ligomis: koronarine širdies liga, vožtuvine širdies liga, širdies nepakankamumu, inkstų nepakankamumu, lėtine obstrukcine plaučių liga, turintys skydliaukės patologiją bei patyrę širdies operaciją.

Ištyrimas:

- gyvenimo kokybės klausimynas SF-36, HADS
- širdies ultragarsinis tyrimas su išplėstiniu KS diastolinės funkcijos vertinimu
- ultragarsinis KP rezervuarinės, konduitinės bei kontraktilinės funkcijos vertinimas taikant 2D taškelių žymėjimo metodiką
- 24 val. EKG stebėsena
- 24 val. AKS stebėsena
- laboratoriniai tyrimai (troponinas I, NT pro BNP, TSH, CRB, elektrolitų konc.)

Rezultatai

Tiriamąją ir kontrolinę grupę sudarė panašių charakteristikų pacientai: vidutinis amžius buvo atitinkamai 62,9 ± 11,61 ir 59,15 ± 11,77, vyrai sudarė 44,11 ir 43,07 %, kūno masės indeksas 29,58 ± 4,27 ir 29,03 ± 4,79, pacientai vartojo vidutiniškai po 1,59 antihipertenzinio medikamento abiejose grupėse.
Lyginant gyvenimo kokybės parametrus, paroksizminiu PV sergantys pacientai statistiškai patikimai ($p < 0,05$) blogiau vertino savo bendrą sveikatą, fizinį aktyvumą bei veiklos apribojimą dėl fizinių problemų (įvertinimai tiriamosios bei kontrolinės grupės atitinkamai 46,03 ± 18,92 ir 53,92 ± 17,33, 68,31 ± 22,92 ir 78,77 ± 18,71, 39,71 ± 42,59 ir 60 ± 41,41). Nors paroksizminiu PV sirgę pacientai pasižymėjo didesniu nerimo bei depresijos lygiu (įvertinimai atitinkamai 7,57 ir 6,35, 5,06 ir 3,91), statistinis reikšmingumas nebuvo pasiektas (atitinkamai $p = 0,126$ bei 0,104).

Lyginant tiriamąją ir kontrolinę grupes reikšmingiausi skirtumai rasti tarp šių rodiklių:

Rodiklis	Tiriamoji grupė n = 68 (±SN)	Kontrolinė grupė n = 65 (±SN)	Vidurkių skirtumas	P reikšmė
Troponino I koncentracija (ng/l)	4,16 (±4,8)	2,66 (±2,7)	1,5	0,045
NT pro BNP koncentracija (pg/ml)	287,68 (±325,59)	124,54 (±105,11)	163,14	<0,001

KP išstūmio frakcija (%)	46,95 (±9,76)	53,72 (±8,53)	-6,77	<0,001
Rezervuarinė deformacija (%)	29,74 (±6,6)	31,93 (±5,41)	-2,19	0,038
Rezervuarinės deformacijos greitis (1/s)	1,04 (±0,29)	1,23 (±0,27)	-0,19	<0,001
< 30 s trukmės prieširdinės tachiaritmijos epizodų skaičius	23 (77,25)	1 (2,07)	22	<0,001

Taikant binarinės logistinės regresijos analizę nustatyti nepriklausomai su paroksizminiu PV susiję rodikliai: KP IF (p = 0,025), rezervuarinė deformacija (p = 0,001), rezervuarinės deformacijos greitis (p < 0,001), < 30 s trukmės prieširdinės tachiaritmijos epizodų skaičius (p = 0,013). Modelio jautrumas 78,8 %, specifiškumas 70,4 %, teigiama prognostinė vertė 76,5 %, neigiama prognostinė vertė 73,1 %, plotas po ROC kreive 0,845.
Siekiant nustatyti didžiausią prognostinę vertę turinčius rodiklius bei jų ribines vertes, sudarytas klasifikacijos ir regresijos medis. Jame didžiausia verte pasižymėjo rezervuarinės deformacijos greitis (ribinė vertė 1,038), KP IF (ribinė vertė 53,98) bei < 30 s trukmės prieširdinės tachiaritmijos epizodai (ribinė vertė 2,5). Sudaryto prognozavimo modelio jautrumas 75 %, specifiškumas 80 %, teigiama prognostinė vertė 79,7 %, neigiama prognostinė vertė 75,4 %, plotas po ROC kreive 0,801.

Išvados

1. Paroksizminis prieširdžių virpėjimas susijęs su padidėjusia NT pro BNP bei troponino I koncentracija kraujyje tarp pacientų, sergančių pirmine arterine hipertenzija.

2. Paroksizminis prieširdžių virpėjimas susijęs su širdies ultragarsinio tyrimo metu nustatytomis mažesnėmis kairiojo prieširdžio rezervuarinės deformacijos, rezervuarinės deformacijos

greičio ir kairiojo prieširdžio išstūmio frakcijos reikšmėmis tarp pacientų, sergančių pirmine arterine hipertenzija.

3. Paroksizminis prieširdžių virpėjimas susijęs su didesniu < 30 s trukmės prieširdinės tachiaritmijos epizodų kiekiu 24 val. EKG stebėsenos metu tarp pacientų, sergančių pirmine arterine hipertenzija.

4. Pirmine arterine hipertenzija sergančių pacientų grupėje ultragarsiniai kairiojo prieširdžio funkcijos rodikliai (rezervuarinė deformacija, rezervuarinės deformacijos greitis ir išstūmio frakcija) bei < 30 s trukmės prieširdinės tachiaritmijos epizodų kiekis 24 val. EKG stebėsenos metu leidžia prognozuoti, ar pacientas serga paroksizminiu prieširdžių virpėjimu.

5. Paroksizminis prieširdžių virpėjimas susijęs su blogesne pacientų, sergančių pirmine arterine hipertenzija, gyvenimo kokybe.

NOTES

NOTES

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