

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

**Prediction and risk stratification of atrial and ventricular
arrhythmias in systemic sclerosis**

by Veronika Sebestyén MD

Supervisor:

Zoltán Szabó MD, PhD, DSc



UNIVERSITY OF DEBRECEN

DOCTORAL SCHOOL OF HEALTH SCIENCES

2025.

PREDICTION AND RISK STRATIFICATION OF ATRIAL AND VENTRICULAR ARRHYTHMIAS IN SYSTEMIC SCLEROSIS

by Veronika Sebestyén MD

Supervisor: Zoltán Szabó MD, PhD, DSc

Drawn up within the framework of the Doctoral School of Health Sciences,
University of Debrecen

The Doctoral Examination Committee:

Chair: Prof. Dr. Margit Balázs PhD, DSc

Members: Dr. Éva Varga PhD

Dr. Marcell Clemens PhD

Time and venue of doctoral examination: University of Debrecen, Faculty of
Medicine, library of the Department of Emergency Care and Oxyology, 10:00 on the
22nd of Oct 2025.

Reviewers of the dissertation:

Dr. Judit Barta PhD

Prof. Dr. László Márk PhD

The Dissertation Review Committee:

Chair: Prof. Dr. Margit Balázs PhD, DSc

Members: Dr. Judit Barta PhD

Prof. Dr. László Márk PhD

Dr. Éva Varga PhD

Dr. Marcell Clemens PhD

Time and venue of the defence of the dissertation: University of Debrecen, Faculty of
Medicine, lecture hall of the Department of Emergency Care and Oxyology. 14:00 on
the 22nd of Oct 2025.

1. INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by diffuse damage of the microvasculature, endothelial dysfunction, and fibrotic transformation of the skin and internal organs.

Primary cardiac involvement is observed in 15% of SSc patients, while secondary cardiac involvement may develop in another 20% of them. Mortality due to cardiac factors accounts for 20-30% of the overall mortality of SSc patients, of which 6% is the result of some arrhythmia event. Based on these data, it can be stated that clinically manifested cardiac involvement is an important prognostic factor of scleroderma and significantly worsens survival.

Beyond fibrosis, persistent inflammation and autonomic dysfunction can lead to cardiovascular complications, including cardiac arrhythmias, even in the early stage of the disease. The most common arrhythmia events in SSc patients are atrial fibrillation, supraventricular tachycardia, ventricular premature beats and ventricular tachycardia. Sudden cardiac death occurs in 1-3.3% of SSc patients.

Cardiological follow-up of scleroderma patients is essential due to the unfavorable mortality rates of these patients because of cardiac involvement. The follow-up involves electrocardiography, echocardiography and laboratory tests in addition to high-resolution CT and cardiac MRI examinations.

Further development of protocols used in cardiovascular and arrhythmia risk assessment in SSc patients and finding novel biomarkers, which correlate well with electrocardiographic and echocardiographic parameters, may be useful in the early identification of high-risk patients.

Our aim was to determine atrial and ventricular arrhythmia risk markers in SSc patients and to examine their associations with various inflammatory and lipid parameters.

2. REVIEW OF THE LITERATURE

2.1. SCLERODERMA HEART INVOLVEMENT (SHI)

The incidence of SSc varies greatly worldwide, with an incidence of 0.2–300 cases/million people/year. It typically occurs between the ages of 45 and 65 and is more common among women. Two main subtypes of systemic sclerosis can be distinguished: diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). In the case of dcSSc we can detect more severe symptoms, more extensive visceral involvement, and higher mortality than in the lcSSc form.

Scleroderma heart involvement can occur even in the early phase of the disease as a result of myocardial fibrosis, ongoing autoimmune inflammation and vasculopathy. It can manifest as asymptomatic focal fibrosis of the myocardium but can also be seen as myocarditis, pericarditis, endocarditis, heart failure, heart conduction disorders, arrhythmias, and sudden cardiac death. Occurrence of cardiovascular events has a two-fold risk in SSc patients compared to healthy controls. Furthermore, in 65% of cases, the cause of death in SSc patients is a pulmonary or cardiac manifestation of the disease.

2.2. SYSTEMIC SCLEROSIS (SSC) AND ARRHYTHMIAS

In scleroderma patients patchy fibrosis develops in the myocardium, as part of the autoimmune inflammatory process, which leads to secondary electrical instability, so-called anisotropy, due to the structural inhomogeneity of the myocardium, and thus increases the likelihood of developing cardiac impulse generation and conduction disorders. Structural changes of the heart secondary to pulmonary arterial hypertension (PAH) (e.g. atrial and ventricular dilation, ventricular wall thickening, newly appearing valvular insufficiency, etc.), which occur as part of the disease, ischemic damage due to coronary vasoconstriction, and circulating anti- β -adrenergic receptor autoantibodies can also contribute to the increased risk of arrhythmias in SSc patients.

In a study examining clinical data from a Swedish scleroderma population, the incidence of arrhythmias was 255/10,000 person annually. Arrhythmia episodes can develop even in the early phase of the disease and their presence is associated with increased mortality (2.2x risk). Some supraventricular arrhythmias can be detected in 32-66% of scleroderma patients, of which supraventricular premature beats occur most frequently (2.6-90%). Atrial fibrillation (AF) develops in 1.8-36.7% of scleroderma patients. Previous studies show that ventricular tachycardia may develop in 7 to 13% of SSc patients even 1-2 years after the recognition of the autoimmune disease. A meta-analysis using data from 13,609 scleroderma patients found that the annual incidence of sudden cardiac death (1-3.3%) was ten times higher than in the control population. Compared to the results of healthy subjects, the incidence of non-sustained monomorphic ventricular tachycardia (NSVT) was 13.3 times higher, while the incidence of ventricular premature beats was 10.5 times higher in patients with scleroderma.

2.3. ELECTROCARDIOGRAPHIC (ECG) DIAGNOSTICS OF ATRIAL AND VENTRICULAR ARRHYTHMIAS IN SSC PATIENTS

On ECG recordings, the depolarization of the atrial myocardium is represented by the P wave. Changes in the morphology and duration of the P wave therefore indicate electrical abnormalities of the atrial myocardium and can help in the prediction and recognition of several pathological conditions.

Previous studies have shown that the P wave interval (P int) is proportional to the atrial conduction time. It is therefore not surprising that P int and a derived electrocardiographic parameter, the so-called P wave dispersion (Pd), have proven to be suitable markers for predicting atrial arrhythmias, since the lengthening of P int indicates the prolongation of atrial conduction time. When determining P int, the starting point of the P wave is the first electrical activity following the T or U wave, and its endpoint is the intersection of the descending part of the P wave and the isoelectric line.

During the determination of the P wave interval for a given lead, the length of 5 consecutive, clearly visible P waves is measured and the average of these values is calculated. Pd can be defined as the difference between the longest and shortest P waves observed in the 12 leads of an individual's surface ECG, which refers to the spatial electrical inhomogeneity of the atrial myocardium.

Prolongation of the maximal P wave interval (P max) and P wave dispersion (Pd), which characterizes the spatial inhomogeneity of the atrial myocardium were described in scleroderma patients. Furthermore, it was also observed that the P wave amplitude measured in standard lead II of the surface ECG was positively correlated with the mean pulmonary arterial pressure detected during right heart catheterization.

The QT interval (QT int), which characterizes the repolarization of the ventricular myocardium, represents the plateau phase and the descending part of the ventricular monophasic action potential. If the duration of the action potential increases, or its duration is not uniform within the ventricular myocardium, a so-called transmural electrical inhomogeneity develops, which results in increased ventricular arrhythmia susceptibility. On the surface ECG, this phenomenon can appear as the prolongation of the QT interval, which can help in identifying patients with an increased risk of ventricular arrhythmia. The QT int extends from the starting point of the Q wave to the intersection point formed by the descending part of the T wave and the isoelectric line. The length of the QT interval is significantly influenced by the heart rate, therefore use of the heart rate-corrected QT interval (QTc) is also widespread in the clinical practice. The spatial inhomogeneity of the ventricular myocardium can be described by the QT interval dispersion (QTd), which is the difference between the longest and shortest QT intervals observed between the 12 leads on the surface ECG. The QT interval variability is a beat-to-beat variability of the QT interval in the given lead using at least fifty consecutive QT intervals. It describes the temporal variability of the ventricular repolarization. The lengthening of another ventricular arrhythmia marker, the T wave peak-to-end interval (Tpe), may also indicate increased vulnerability to ventricular

arrhythmia. It can be described as the distance between the highest point of the T wave and the point of intersection of the descending part of the T wave and the isoelectric line. The arrhythmogeneity index (AIX), defined as the ratio of Tpe and the maximum QT interval (QT max) in a given lead, and can be a good predictor of the occurrence of sudden cardiac death and the development of torsades de pointes tachycardia.

The above-mentioned markers of ventricular repolarizational inhomogeneity, which can be determined from the 12-lead surface electrocardiogram, can also be used in the risk assessment of ventricular arrhythmia events in scleroderma patients. Previous research has shown that QTc and QTd are prolonged in SSc patients compared to healthy controls. It has also been described that the QT variability index, which can be formed from the ratio of the means and logarithms of QT variability and heart rate variability, is significantly higher in patients with scleroderma than in healthy individuals. Furthermore, it is known that Tpe and AIX values are also increased in the scleroderma group compared to controls.

2.4. ECHOCARDIOGRAPHY IN THE ASSESSMENT OF SHI

One of the cornerstones of the early diagnosis and monitoring of scleroderma heart involvement is the annual transthoracic echocardiography. Nowadays, this can also be supplemented using 2D or 3D speckle tracking echocardiography (STE) techniques. It is known that 69% of the scleroderma patients show some abnormalities during the cardiac ultrasound examination. The systolic function of the left ventricle is typically not impaired in the initial stage of SSc, however, an increase in right ventricular systolic pressure (RVP), a small decrease in the tricuspid annular plane systolic excursion (TAPSE), and an increase in left ventricular filling pressure (E/e') can already be observed at this stage, which indicates early diastolic function changes, i.e. diastolic dysfunction. In addition, a reduced mitral E/A value, a significant increase in the diameter of the inferior vena cava, pericardial effusion, and valvular insufficiency are also common. Typically, left atrial volume and left atrial area are larger in SSc

patients compared to controls, and left atrial ejection fraction as well as left atrial strain parameters are reduced. In addition, we can detect reduced right ventricular strain parameters and decreased right atrial reservoir and conduit strain values in SSc patients without the presence of PAH.

2.5. FEASIBLE LABORATORY MARKERS IN THE CARDIOVASCULAR RISK ASSESSMENT OF SSc PATIENTS

2.5.1. CLASSICAL LABORATORY MARKERS

In scleroderma patients the “gold standard” for detecting cardiac involvement is the determination of NT-proBNP level, but hsTnT and CK levels, which correlate with muscle damage, are also routinely monitored. Furthermore, an increase in CRP levels can be observed in myocardial fibrosis confirmed by cardiac MRI. Based on the 2017 recommendation of the UK Systemic Sclerosis Study Group, annual control of HgbA1c and lipid profile is also recommended for SSc patients.

2.5.2. ADHESION MOLECULES

Intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) can cause the retention of myeloid cells in the skin of scleroderma patients, which contributes to the fibrotic degeneration of the skin. It is known that serum levels of VCAM-1 and ICAM-1 also correlate with disease severity. In scleroderma patients, as part of the autoimmune inflammatory process, serum level of tumor necrosis factor alpha (TNF- α) is also elevated, which exacerbates endothelial injury through the induction of ICAM-1 and VCAM-1 adhesion molecules.

2.5.3. PROGRANULIN

Previous investigations have shown that the organokine-like progranulin (PGRN), which influences the activity of the TNF- α signaling pathway, may play a protective role in several autoimmune diseases. In addition, it has been described in

animal models that PGRN may have a cardioprotective role through its anti-inflammatory, anti-atherogenic, and antioxidant properties. The presence of autoantibodies against progranulin has also been detected in SSc patients. It has been assumed that these autoantibodies block the anti-TNF- α effect of PGRN, thereby enhancing the progression of fibrotic processes. The cardioprotective effects of PGRN is well-documented, however, in the case of fibroblasts obtained from the skin of scleroderma patients, overproduction of PGRN has been observed, so hyperprogranulinemia may also be associated with increased fibrosis of the skin.

2.5.4. LIPID PARAMETERS

The presence of dyslipidemia also contributes to the development of increased vascular risk in SSc patients. Previous studies have reported elevated total cholesterol (TC) and Lp(a), and reduced LDL-C, HDL-C and Apo A-I levels in patients with scleroderma. The so-called lipid paradox was described in several autoimmune diseases, according to which serum levels of TC and LDL-C were lower in untreated inflammatory diseases. This was interpreted as the lipid-lowering effect of systemic inflammation.

Oxidized LDL (oxLDL) is an important risk factor for the development of atherosclerotic plaques. OxLDL colocalizes with immunoreactive lymphocytes, thus presumably playing a role in immune processes in the vascular wall.

Leptin is involved in the modulation of inflammatory processes, among other things, as it can up-regulate the production of pro-inflammatory cytokines (e.g. IL-6, IL-12, TNF- α) and results in the activation of certain immune cells (NK, Th1, macrophage cells). Based on previous investigations, leptin levels are significantly lower during the acute phases of systemic sclerosis compared to the remission state, thus serum leptin levels show a correlation with disease activity.

3. AIMS

In connection with the cardiac involvement present in scleroderma patients, an increased risk of atrial and ventricular arrhythmias and an increased risk of sudden cardiac death can be observed, so their cardiological follow-up is essential. However, there is no accepted international protocol regarding the examinations included in this procedure, so the definition of additional suitable markers may be necessary.

In our research, we aimed to determine the following electrocardiographic risk markers of atrial and ventricular arrhythmias in SSc patients and in our control group:

- P wave interval
- maximal P wave interval
- P wave dispersion
- QT interval and corrected QT interval
- QT interval dispersion
- QT interval variability
- T wave peak-to-end interval
- arrhythmogeneity index

We also aimed to examine the echocardiographic parameters of the scleroderma group and the control group to assess the function and systolic pressure values of the right heart side, and systolic and diastolic dysfunction of the left ventricle.

We also aimed to examine the differences in serum concentrations of the following laboratory parameters, potentially indicating arrhythmia risk, between the SSc patient group and the control group:

- sVCAM-1
- sICAM-1

- PGRN
- leptin
- HDL and LDL subfractions
- oxLDL

In addition, we would like to examine the correlations of atrial and ventricular arrhythmia ECG risk markers and echocardiographic parameters with various inflammatory and lipid parameters.

4. PATIENTS AND METHODS

4.1. STUDY POPULATION

The study population was made up of 26 SSc patients and 36 healthy controls, who were between 18 and 70 years of age. Patients with any type of diabetes mellitus, structural heart diseases, atrial fibrillation or the history of any other kind of arrhythmia events were excluded from the study. Patients with hypothyroidism could enter the study if they were in a stable euthyroid state. In the studied SSc group, 12 patients had limited cutaneous, and 14 patients had diffuse cutaneous SSc and received treatment accordingly. The average time elapsed from the diagnosis was 4.1 ± 1.8 years, while 6.5 ± 2.1 years passed before the detection of the first clinical symptoms on average.

Written informed consent was obtained from all participants before study entry. The Medical Research Council and the Hungarian Ministry of Human Resources (Deputy State Secretary for National Chief Medical Officer, Department of Health Administration) approved our study protocol (number of approvals: 21325-2-1/2017/EKU, 11920-2/2017/EUIG and 19927-1/2018/EKU). We performed our investigations according to the Declaration of Helsinki.

4.2. ELECTROCARDIOGRAPHIC MEASUREMENTS

We gained a standard 12-lead surface electrocardiogram (ECG) and a digital ECG from every patient. Digital ECG recordings were obtained and analyzed with the use of CardioSys Plus ECG analyzing hardware and software (MDE GmbH, Walldorf, Germany).

During the ECG analysis, we determined the P wave interval (P int), maximal P wave interval (P max) and P wave dispersion (Pd) with the help of CardioSys software (CardioSys CA-12, Logirex Kft., Budapest, Hungary). The program calculates the P wave interval as an average of five consecutive P waves in every lead. The maximal P wave interval is determined as the longest P wave in the given lead. Furthermore, P wave dispersion has been calculated as the difference between the longest and the shortest P wave intervals in the 12 leads of the electrocardiogram.

During the ECG analysis, the following ventricular arrhythmia markers were determined with the help of CardioSys software: QRS interval, QT interval (QT int), maximal QT interval (QT max), corrected QT interval (QTc), QT dispersion (QTd), T wave peak-to-end interval (Tpe), arrhythmogeneity index (AIX), and QT interval variability (QTv). The CardioSys program calculated the average QRS interval per lead by considering 5 QRS complexes. Similarly, the software defined the QT interval as the average of five consecutive, well-identifiable QT intervals measured in one lead. If an error was detected by visual inspection of the analysis, the location of the beginning of the Q wave and the end point of the T wave could be manually altered, or a repeated analysis could be requested based on another, more suitable ECG part. The QT interval corrected for the ventricular frequency was calculated by the software using the Bazett's formula ($QTc = QT / \sqrt{RR}$). In addition, the QT dispersion value was determined by subtracting the shortest QT interval value from the longest QT interval value measured in the 12 leads of the digital ECG record. For the determination of Tpe, the program applied the so-called threshold method to define the end of the T wave. In this case, the end of the T wave is exactly the point where the descending part of the T wave intersects the isoelectric line. AIX can be calculated as the ratio of the Tpe and QT max values

measured in the given lead. The QT interval variability (QTv) can be calculated from the beat-to-beat differences in the QT intervals registered in a lead (beat-to-beat variability) using at least fifty consecutive QT intervals.

Moreover, 24-h Holter ECG monitoring was performed with three-channel CardioMera ECG-Holter monitors (MediTech Kft, Budapest, Hungary) using CardioVisions software (CardioVisions 1.30.2, MediTech Kft, Budapest, Hungary), where average heart rate, average RR cycle length, time- and frequency-based heart rate variability, arrhythmia events and conduction disorders were evaluated.

4.3. ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed by using a Philips HDI ATL 5000 imaging system (Philips ATL ULTRASOUND INC., Washington, DC, USA) and a 3.5 MHz transducer (Acuson Sequoia C 256 Mountain View, Siemens Medical Solutions USA, Mountain View, CA, USA). During our examinations, we used 2D, M-mode, pulsatile and continuous wave Doppler techniques to determine the parameters describing the systolic and diastolic function of the right and left sides of the heart. In addition to the left atrial diameter, we measured the value of the left atrial area, the diameter of the inferior vena cava, the right ventricular systolic pressure, the TAPSE indicating the right ventricular systolic function and the mitral E/A and the left ventricular filling pressure (E/e') by means of the tissue Doppler technique.

4.4. BLOOD SAMPLING AND DETERMINATION OF LABORATORY PARAMETERS

Blood sampling was performed in the triage rooms of the Department of Emergency Medicine at the University of Debrecen, during which a total of 12 ml of blood was collected into native and anticoagulant containing blood collection tubes. Routine laboratory parameters were determined at the Institute of Laboratory Medicine at the University of Debrecen from the submitted blood samples in accordance with international standards. A Cobas 6000 analyzer (Roche Diagnostics, Mannheim,

Germany) was used for the measurements, and the reagents used had the same lot number. In addition to serum electrolyte levels, the scleroderma autoantibody profile, cardiac troponin, CK, and NT-proBNP levels, as well as parameters describing thyroid function, renal function, lipid panel, iron panel, CRP, and blood cell counts were also determined.

Serum PGRN, soluble VCAM-1 (sVCAM-1), soluble ICAM-1 (sICAM-1), oxLDL and leptin levels were determined by ELISA method at the Research Laboratory of the Division of Metabolism, Department of Internal Medicine at the University of Debrecen (PGRN kit: catalog number: RMEE103R, BioVendor, Brno, Czech Republic; human sVCAM-1, sICAM-1 and leptin kits: catalog numbers: DVC00, DCD540 and DLP00, R&D Systems Europe Ltd., Abington, United Kingdom, oxLDL: catalog number: 10-1143-01, Mercodia AB, Uppsala, Sweden).

4.5. DETERMINATION OF LDL AND HDL SUBFRACTIONS

The separation of lipoprotein subfractions was performed using the Lipoprint system using polyacrylamide gel electrophoresis at the Research Laboratory of the Division of Metabolism, Department of Internal Medicine at the University of Debrecen. Lipoprint allows the separation of lipoprotein subfractions according to size, and LDL and HDL subfractions are separated with different tests (LDL test cat. no.: 48-7002, HDL test cat. no.: 48-9002, Quantimetrix Corp., Redondo Beach, California, United States). Twenty-five µl of serum sample was weighed onto the top of the glass tube containing polyacrylamide, then mixed with an acrylamide solution containing Sudan black dye. After thirty minutes of photopolymerization, the lipoprotein subfractions were separated in an electrophoresis bath at a current of 3 mA/tube. After scanning the tubes, the data were evaluated using Lipoware software (Quantimetrix Corp., Redondo Beach, California, United States).

During electrophoresis, the distribution of the ten HDL and seven LDL subfractions, as well as the three IDL subfractions (IDL-A, -B, and -C) and the

percentage of VLDL were also determined. The small LDL percentage (small LDL) was calculated from the average of the ratios of LDL 3-7 subfractions, while the large LDL percentage (large LDL) was calculated from the average of the ratios of LDL 1-2 subfractions. In addition, three main groups were formed from the HDL subfractions. The large HDL group was formed from the HDL 1-3 subfractions, the intermediate HDL group from the HDL 4-7 subfractions, and the small HDL group from the average of HDL 8-10 subfractions. Using the TC and HDL-C values determined from the blood samples, the absolute values of these parameters were also calculated using Lipoware software. The mean LDL size was also determined using Lipoware software (Quantimetrix Corp., Redondo Beach, California, United States).

4.6. STATISTICAL ANALYSIS

Statistical analysis was performed with the use of GraphPad Prism software (version 10.4.1. (627), GraphPad Software, San Diego, CA, USA). Descriptive statistics from the variables (arithmetic mean, median, 90 and 95 % confidence intervals, and quartile values) were determined. Ordinary one-way ANOVA (analysis of variance) was used to determine statistically significant differences between the means of the investigated parameters. Pairwise comparisons were carried out using t-test in the case of normal, and Mann-Whitney test in the case of non-normal distribution. When difference between variances were observed, Welch correction was applied. The difference between categorical variables was calculated with the Chi-squared test. Correlations between the variables were analyzed using Pearson's test in the case of normal distribution and Spearman's rank test in the case of non-normally distributed data. To examine if there are any independent predictors of the serum progranulin, sVCAM-1 and sICAM-1 level among the investigated parameters, we performed a multiple regression analysis based on a backward stepwise method (STATISTICA software, ver. 13.0 StatSoft Inc., Tulsa, OK, USA). $P < 0.05$ was considered as the level of significance.

5. RESULTS

5.1. CLINICAL DATA OF THE STUDY POPULATION

The mean age of the 26 scleroderma patients in our study group was 56.82 ± 2.27 years, while that of the control group was 53.21 ± 6.31 years. The compared groups did not differ significantly in terms of BMI or gender distribution. The modified Rodnan score (mRSS) can be calculated based on the thickness of the skin of scleroderma patients on different body regions, and it also helps in assessing the general condition of the patients. Furthermore, it shows a correlation with the primary and secondary endpoints of different studies. In our population, the mean mRSS was 8.62 ± 3.05 at the time of our study. In terms of blood pressure medication, the SSc group did not take significantly more ACE inhibitors, ARBs, NDHP-type Ca-channel blockers, or β -blockers than the control group, but significantly more SSc patients took DHP-type Ca-channel blockers. We did not observe any significant difference in the use of statins and diuretics between the two study subpopulations. In terms of comorbidities, the incidence of hypertension, GERD, and hypothyroidism was similar in the two subpopulations. The most frequent autoantibody positivities, found in our SSc population, were antinuclear antibodies (ANA), metaphase chromosome, anti-topoisomerase-I (Scl-70), and anti-Ku autoantibodies. Among the observed scleroderma organ involvements, the most common were interstitial lung disease (16/26), diastolic dysfunction (21/26), and esophageal dysmotility (12/26) in the studied population.

5.2. ECG AND ECHOCARDIOGRAPHY RESULTS

Regarding electrocardiographic parameters, we found that both the P wave interval (P int) and the maximal P wave interval (P max) were prolonged in SSc patients compared to controls (69.1 ± 13.4 msec vs. 92.9 ± 18.2 msec, $p < 0.0001$; 102.8 ± 15.3 msec vs. 113.5 ± 20.9 msec, $p < 0.05$, respectively). However, no significant difference was found between these two populations in the P wave dispersion (Pd), which characterizes

the spatial inhomogeneity of atrial depolarization (43.1 ± 9.6 msec vs. 44.1 ± 10 msec, $p=0.71$).

Furthermore, among the ECG markers describing ventricular repolarization, we observed lengthening of the QT interval, the corrected QT interval (QTc), the QT dispersion (QTd) and the QT variability (QTv) (399.4 ± 36.6 msec vs. 461.7 ± 43.3 msec, $p<0.0001$; 421.8 ± 28.9 msec vs. 485.6 ± 36.9 , $p<0.0001$; 58.7 ± 23.8 msec vs. 87.7 ± 28.3 , $p<0.0001$; 7.4 ± 2.7 msec vs. 17 ± 4.5 msec, $p<0.0001$, respectively). In addition, we also observed an increase in the T wave peak-to-end interval (Tpe) and the arrhythmogeneity index, which can be calculated as the ratio of Tpe and QT max (Tpe: 92.68 ± 17.38 msec vs. 129.7 ± 32.57 msec, $p<0.0001$; AIX: 0.23 ± 0.03 vs. 0.27 ± 0.05 $p<0.001$).

In our study, 24-hour Holter ECG examinations were also performed. There was no significant difference in the ratio of ventricular and atrial premature beats between the study groups (logarithmic values: SVPB ratio: -2.76 ± 0.57 vs. -2.69 ± 0.69 , $p=0.68$ VPB ratio: -3.13 ± 0.66 vs. -3.06 ± 0.69 , $p=0.72$), however, the overall incidence of arrhythmias was significantly higher in the SSc group. On the contrary, sinus tachycardia episodes and frequent ventricular premature beats (589 VPB/24 hours) were registered in the control group. However, paroxysmal atrial fibrillation was recorded in 4 patients, AV nodal reentry tachycardia (AVNRT) episodes in 2 patients, ventricular bigemina in 6 patients, and ventricular trigeminal episodes in 4 patients among SSc patients. Furthermore, frequent ventricular premature beats (more than 2000 VPB/24 hours) were confirmed in case of one patient and ventricular runs consisting of 3-5 consecutive beats were observed in the recordings of four SSc patients. In one SSc patient, a non-sustained monomorphic ventricular tachycardia (NSVT) episode lasting 4.2 seconds was also recorded.

In scleroderma patients, time-based heart rate variability was significantly lower compared to the control group (30.35 ± 7.73 vs. 25.33 ± 7.9 , $p<0.05$). Furthermore,

frequency-based heart rate variability was also lower, although this did not reach the level of statistical significance (3.15 ± 1.5 vs. 2.52 ± 1.2 , $p=0.1$).

Regarding echocardiographic parameters, no significant difference was found in the left atrial diameter (37.2 ± 3.8 mm vs. 39.1 ± 4.5 mm, $p=0.08$), while the left atrial area was significantly larger in SSc patients (13.2 ± 2.9 cm² vs. 16.1 ± 4.6 cm², $p<0.01$). The ejection fraction, which refers to the systolic function of the left ventricle, did not differ significantly between the scleroderma and control groups (58.5 ± 5.69 % vs. 56 ± 6.08 %, $p=0.13$). E/e' , which is used to estimate left ventricular filling pressure, and calculated right ventricular systolic pressure were higher, while TAPSE was lower in scleroderma patients compared to the control group (8.88 ± 1.9 vs. 12.39 ± 3.9 , $p<0.00001$; 16.7 ± 4.38 mmHg vs. 19.8 ± 7 mmHg, $p<0.05$; 30 ± 3.8 mm vs. 26 ± 5.38 mmHg, $p<0.001$, respectively).

In our study, we observed some correlations between ECG and echocardiographic parameters. The left atrial diameter showed a positive correlation with the P int value ($r=0.47$, $p<0.05$). The left ventricular mass and the left ventricular mass index also showed a significant positive correlation with QT interval variability ($r=0.48$, $p<0.05$; $r=0.481$, $p<0.05$). Interestingly, among the examined electrocardiographic markers, Tpe, AIX and QTv showed a significant positive correlation with the diameter of the inferior vena cava ($r=0.42$, $p<0.05$; $r=0.49$, $p<0.05$; $r=0.55$, $p<0.01$, respectively).

5.3. ALTERATIONS OF LABORATORY PARAMETERS

Regarding serum biomarkers, NT-proBNP and cTnT levels were significantly higher in scleroderma patients compared to the control group (43 ($17 - 70$) ng/l vs. 120 ($80 - 374$) ng/l, $p<0.0001$; 8 ($5 - 10$) ng/l vs. 17.8 ($9.5 - 27.8$) ng/l, $p<0.01$). We also saw an elevation in CRP levels, which have been associated with increased cardiovascular risk in previous studies, in the SSc group (2.69 ± 0.96 mg/l vs. 5.04 ± 1.07 mg/l, $p<0.05$). Serum soluble ICAM-1 and VCAM-1 levels were also significantly

higher in our scleroderma patients, while serum PGRN levels did not differ significantly between the two studied groups (186.4 ± 32 ng/ml vs. 230.2 ± 76 ng/ml, $p < 0.01$; 586.2 ± 98.1 ng/ml vs. 655.7 ± 109.1 ng/ml, $p < 0.05$; 36.3 ± 6.3 ng/ml vs. 37 ± 9.1 ng/ml, $p = 0.73$). The TC, LDL-C and Apo A-I values of scleroderma patients were lower than those of the control group (5.59 ± 1.07 mol/l vs. 4.86 ± 0.95 mmol/l, $p < 0.01$; 3.43 ± 0.8 mmol/l vs. 2.99 ± 0.6 mmol/l, $p < 0.05$; 1.5 ± 0.2 g/l vs. 1.4 ± 0.2 g/l, $p < 0.05$), however, no significant differences were found in Apo B and Lp(a) levels between the two study groups (1.06 ± 0.25 g/l vs. 0.99 ± 0.25 g/l, $p = 0.19$; 65 (35-138) mg/l vs. 64.5 (32.3-112.3) mg/l, $p = 0.39$). The oxidized LDL levels of our scleroderma patients were slightly lower than those of the control group, but this difference was not significant (74.5 ± 18.1 U/l vs. 67.3 ± 18.7 U/l, $p = 0.28$).

Lipoprotein subfraction analyses performed with the Lipoprint system showed that the percentage of IDL was significantly higher in SSc patients compared to controls, while no significant difference was observed in VLDL % ($19.4 \pm 3.3\%$ vs. $24.3 \pm 3.8\%$, $p < 0.0001$; $20 \pm 3.6\%$ vs. 18.8 ± 2.9 , $p = 0.14$). The percentage of large LDL subfraction was significantly lower in scleroderma patients ($31.9 \pm 4.5\%$ vs. 28.3 ± 5.4 , $p < 0.01$). In case of small LDL subfractions, significantly higher values were observed in scleroderma patients compared to controls ($0.25 \pm 0.4\%$ vs. $1.9 \pm 2.2\%$, $p < 0.0001$).

The percentage of large HDL was higher, but the percentage of intermediate and small HDL was lower in SSc patients compared to the control group. However, only the difference in the levels of intermediate HDL was significant ($50.54 \pm 3.87\%$ vs. $48.56 \pm 4\%$; $p < 0.05$).

In our study, the mean LDL size did not differ significantly between the SSc and control groups, but this value was smaller in the control group (27.04 ± 0.03 vs. 26.81 ± 0.05 nm, $p = 0.06$).

5.4. CORRELATIONS BETWEEN ECG AND LABORATORY MARKERS

Among the laboratory parameters, NT-proBNP, CRP and LDL-C levels showed significant positive correlations with the P wave interval ($r=0.24$, $p<0.05$; $r=0.36$, $p<0.05$; $r=0.49$, $p<0.01$, respectively) among SSc patients. Regarding other examined parameters characterizing inflammatory activity, serum PGRN level was not significantly correlated with the P int value ($r=-0.003$, $p=0.99$), while serum levels of sICAM-1 and sVCAM-1 showed a significant positive correlation with P int ($r=0.78$, $p<0.001$; $r=0.17$, $p<0.01$). In addition, oxLDL levels, which indicate increased atherosclerosis risk, showed a positive correlation with Pd values, which refers to increased atrial arrhythmia risk ($r=0.26$, $p<0.05$). Serum leptin levels also showed a significant positive correlation with P max ($r=0.62$, $p<0.001$).

We also investigated the potential associations between ECG parameters and lipid subfractions. The P wave interval showed a significant negative correlation with the small HDL percentage, while it was correlated positively with the large HDL % ($r=-0.41$, $p<0.05$; $r=0.39$, $p<0.05$). Interestingly, P int also showed a positive correlation with the Apo A-I level ($r=0.54$, $p<0.01$).

Regarding ventricular arrhythmia markers, the QRS interval ($r=0.45$; $p<0.05$), the QTc ($r=0.63$; $p<0.001$) and the Tpe ($r=0.42$; $p<0.05$) showed a positive correlation with serum CRP levels. In addition, LDL-cholesterol levels were found to be higher in the control group compared to the scleroderma group, but it only showed a positive correlation with QRS interval and QT interval in the SSc population ($r=0.46$, $p<0.05$; $r=0.38$, $p<0.05$). Furthermore, sICAM-1, sVCAM-1 and serum PGRN levels showed a significant positive correlation with QT interval in scleroderma patients ($r=0.44$, $p<0.001$; $r=0.04$, $p<0.01$; $r=0.54$; $p<0.01$). Moreover, AIX also had a significant positive correlation with sVCAM-1 and PGRN levels ($r=0.3$, $p<0.05$; $r=0.36$, $p<0.05$).

Interestingly, sICAM-1 and PGRN levels ($r=0.33$, $p<0.001$) and sVCAM-1 and PGRN levels ($r=0.31$, $p<0.05$) were also significantly positively correlated with each other. Furthermore, we also showed that sVCAM-1 and serum PGRN values, which

indicate increased cardiovascular risk, showed a significant negative correlation with large HDL% ($r = -0.41$, $p < 0.05$; $r = -0.35$, $p < 0.05$, respectively). Small HDL%, on the other hand, was positively correlated with PGRN levels ($r = 0.42$, $p < 0.05$).

The above-mentioned correlations were not observed during the analysis of the data of the control group, they were found only in our SSc study group.

Based on the multiple regression analysis, we could not determine any independent predictor of serum progranulin, sVCAM-1, or sICAM-1 levels, although this could be the result of the limited study population.

5.5. SUMMARY OF THE NEW FINDINGS

1. In scleroderma patients, IDL % was significantly higher compared to the control group, while no significant difference was observed in VLDL %.
2. Large LDL % was significantly lower, while small LDL % was significantly higher in scleroderma patients compared to the control group.
3. Large HDL % was higher, but intermediate and small HDL % were lower in SSc patients compared to the control group.
4. Serum levels of sVCAM-1, sICAM-1 and LDL-C showed a significant positive correlation with the P wave interval in SSc patients.
5. P wave interval showed a significant negative correlation with small HDL percentage, while large HDL percentage and Apo A-I level showed a significant positive correlation with it.
6. Pd showed a positive correlation with VLDL percentage, and IDL percentage was negatively correlated with P wave interval.
7. In SSc patients and control subjects the values of lipid parameter correlate differently with atrial arrhythmia risk markers.

8. QRS interval, QTc and Tpe values were positively correlated with serum CRP level in SSc patients, but similar differences were not observed in the control group.

9. LDL-C levels were positively correlated with QRS interval and QT interval in SSc patients.

10. sICAM-1, sVCAM-1, and PGRN were significantly positively correlated with QT interval in the SSc group.

6. DISCUSSION

In systemic sclerosis, microangiopathy, tissue fibrosis, autonomic dysfunction, and secondary myocardial edema increase the probability of the development of atrial and ventricular arrhythmias. In SSc, the incidence of sudden cardiac death is 21–54%, which mainly results from ventricular tachycardia and prevalently affects patients with dcSSc.

In SSc patients, abnormalities were found on the surface electrocardiogram in 25–75% of the cases. When analyzing the digital ECG records of our patients, we found prolonged P wave interval and P wave dispersion, and in 77% of our 26 scleroderma patients, we experienced QTc prolongation, and in 73% of them, we registered an abnormally longer Tpe. Previous studies have also described that 56% of SSc patients have alterations on the Holter ECG record, and 24% of them have frequent ventricular premature beats, which correlate with reduced left ventricular function and increased serum hsTnT levels. Frequent ventricular premature beats (>2000 VES/24 hours) were detected in 30.76% of our SSc patients. We observed episodes of ventricular bigeminia in six patients, ventricular trigeminia in four patients, and short ventricular runs consisting of 3–5 beats in four patients. During the examination of one patient, we recorded an episode of monomorphic ventricular tachycardia lasting 4.2 seconds. In addition, we recorded frequent sinus tachycardia events (15 episodes/person on average), as well as AVNRT (2.6 arrhythmia events/person on average) and atrial

fibrillation episodes (3.2 arrhythmia events/person on average), even though no previous arrhythmia event was recorded in the medical history of our patients. In contrast, we found frequent ventricular premature beats in only one patient, and sinus tachycardia episodes in 6 patients in the control group. Our observations confirm the increased risk of atrial and ventricular arrhythmias in the examined scleroderma patients.

In accordance with the literature data, our echocardiographic results showed that left ventricular ejection fraction was not reduced in SSc patients, however, there was an increase in right ventricular systolic pressure (RVP), E/e' , left atrial area, and a small decrease in TAPSE, which may refer to diastolic dysfunction. However, contrary to the literature, we did not observe a significantly reduced mitral E/A value or a significant increase in the diameter of the inferior vena cava in scleroderma patients, which could be explained with the quite small size of the study population.

Examining the relationships between ECG and echocardiographic parameters, we found that the left atrial diameter was positively correlated with the P wave interval, and our results confirmed that in the SSc group, the diameter of the inferior vena cava was positively correlated with the T wave peak-to-end interval, the arrhythmogenicity index, and the QT interval variability.

Serum cTnT and NT-proBNP levels correlate with the degree of cardiac involvement in scleroderma patients. In our study, we also observed an increase in serum troponin and NT-proBNP levels in scleroderma patients.

Elevated CRP levels exacerbate the process of atherosclerosis, thus the risk of the development of cardiovascular diseases. Serum CRP levels were increased in scleroderma patients compared to healthy controls, which was also confirmed in the present study. Based on our results, we highlight that serum CRP levels in scleroderma patients showed a significant positive correlation with QRS interval, QTc and Tpe values, which indicate an increased risk of ventricular arrhythmia. We also observed a

positive correlation between CRP level and P wave interval, which highlights the unfavorable effect of the autoimmune inflammatory process on atrial arrhythmia susceptibility.

Elevated serum sVCAM-1 and sICAM-1 levels are thought to have a negative cardiovascular effect, mainly due to their role in endothelial dysfunction and exacerbation of pulmonary involvement. It has been previously shown that elevated sVCAM-1 and sICAM-1 levels are not specific for the development of PAH in SSc patients, but the relationship of these biomarkers with cardiac manifestations has not been investigated. Among our results, we highlight that elevated sICAM-1 and sVCAM-1 levels observed in our scleroderma patients showed a positive correlation with the P wave and QT intervals of the surface ECG, suggesting that elevated serum levels of adhesion molecules indicate an increased risk of atrial and ventricular arrhythmias.

Serum PGRN level can be elevated in several pathological conditions including hypoxia, acidosis, aging, obesity, acute renal failure, or neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, frontotemporal dementia, or amyotrophic lateral sclerosis. In patients with reperfusion therapy due to ischemic heart disease and after myocardial infarction, PGRN was demonstrated to have a cardioprotective role due to its anti-inflammatory, anti-atherogenic, and antioxidant effect associated with increased nitrogen monoxide synthesis. Previous studies have reported that dermal fibroblasts in lcSSc patients overexpress PGRN. We found positive correlations between serum PGRN levels, QT interval, and AIX, which suggests that elevated PGRN level may rather promote fibrotic processes and might be associated with increased cardiovascular and arrhythmia risk in scleroderma patients. This may also explain the finding that serum levels of PGRN positively correlated with adhesion molecules such as sVCAM-1 and sICAM-1 in the SSc group.

In connection with the so-called lipid paradox, which often exists in autoimmune diseases, the LDL-C level of our scleroderma patients was lower than that of the control subjects. This may be partly due to the lipid-lowering effect of the ongoing inflammation, and partly due to the health-conscious lifestyle maintained by the patient due to the awareness of the disease. Interestingly, the decreased LDL-C level is associated with the development of atrial fibrillation in the general population, which is also supported by the clinical observation that the use of statins does not reduce the likelihood of the development of atrial fibrillation in this population; in contrast with its' effects observed in patients suffering from ischemic heart disease and structural heart diseases. In our study, we observed that the LDL-C level of the control group showed a negative correlation with the value of the P wave interval. However, in our scleroderma patients, LDL-C had a significant positive correlation with the P interval. This may indicate that the autoimmune inflammatory process influences the effect of lipids on arrhythmia risk, and it also suggests that lipid-lowering treatment and achieving a favorable lipid profile may be of particular importance in SSc patients in terms of reducing the risk of atrial arrhythmias. It is possible that cholesterol, including LDL-C, may also cause changes in the membrane fluidity of atrial myocardial cells, thus it contributes to the increased risk of atrial arrhythmias. In a study, isolated atrial myocardium from sheep with atrial fibrillation was examined and found to have decreased membrane fluidity compared to samples from non-atrial fibrillation animals.

Our research group previously found that LDL-C, TG and Apo B levels showed a positive correlation with the QTd, which indicates increased ventricular arrhythmia risk. Consequently, dyslipidemia may increase the ventricular arrhythmia risk presumably due to its effect on the cell membrane function and composition. In our study, we also found that serum LDL cholesterol levels showed a positive correlation with QRS and QT intervals in scleroderma patients.

Moreover, we found that large LDL% and intermediate HDL% were significantly lower in scleroderma patients compared to the control patients. This

difference in the lipid profile can play a role in the occurrence of arrhythmia events, since the P wave interval showed a negative correlation with the small HDL percentage, while it correlated positively with the large HDL percentage. In comparison with healthy subjects, Gaál et al. found decreased concentrations of all HDL subfractions in patients with systemic lupus erythematosus. This highlights that our observation does not apply to each autoimmune disease. Although the background of this has not clearly elucidated yet, thus further investigations are needed.

In our study, lower Apo-A-I levels were detected in the scleroderma group compared to the control, where Apo-A-I levels appeared normal. In a previous study, low Apo-A-I levels showed a significant correlation with the QTc interval in SSc patients, showing an increased risk for ventricular arrhythmia susceptibility. Previous studies demonstrated that low Apo-A-I levels increased the risk for atrial fibrillation in those individuals who did not take statins regularly. On the contrary, we found that the ratio of large HDL and the Apo-A-I level showed a significant positive correlation with the P wave interval, suggesting that Apo-A-I and large HDL levels may also be associated with an increased risk for atrial arrhythmias in this population. Apo A-I is one of the most important structural proteins of the HDL molecule, from which small HDL particles usually contain 2 molecules, while the larger HDL particles may contain as many as 5–7 molecules, so the large HDL has a higher Apo A-I content. Previous studies showed significant differences in the quality and quantity of further HDL-associated proteins between the HDL subfractions. The human paraoxonase 1 and 3, with known antioxidant activity, and the antiatherogenic apolipoprotein M and sphingosine-1-phosphate can be detected mainly on the small HDL particles, while the proatherogenic apolipoprotein B and α -2 macroglobulin are bound to the large HDL particles. These differences in the protein composition between the subfractions may explain our observation according to which the large HDL subfractions and the Apo A-I correlate positively with arrhythmia markers.

The level of one triglyceride-rich lipoprotein, the IDL, was significantly higher in scleroderma patients compared to the control group. In another autoimmune disease, multiple sclerosis patients, elevated IDL levels have been shown to increase cardiovascular risk, and IDL-C levels have been positively correlated with elevated systolic blood pressure. Elevated IDL levels have also been shown to exacerbate atherogenesis in the carotid arteries.

In the early stages of rheumatoid arthritis, a smaller mean LDL size was described in comparison with the control group. In our SSc population, the mean LDL size was also smaller compared to the control group, although the difference was not significant.

Our study also showed that the serum leptin level, which influences lipid metabolism, was not significantly higher in SSc patients compared to that of the control group, which is in agreement with previous literature data. Of note, the serum leptin level of SSc patients showed a significant positive correlation with the maximal P wave interval of SSc patients, which may be related to the pro-inflammatory effect of leptin. Based on these findings, we can assume that leptin has an arrhythmogenic rather than cardioprotective role regarding the development of atrial arrhythmias in SSc patients.

Examining the relationships between biomarkers describing inflammatory processes and lipid parameters, we also showed that sVCAM-1 and serum PGRN values, which indicate increased cardiovascular risk, also showed a significant negative correlation with large HDL %. On the other hand, small HDL % was positively correlated with PGRN level. Nádró et al. also observed a positive correlation between small HDL% and PGRN levels, while a negative correlation was found between large HDL% and PGRN in patients with familial hypercholesterolemia. In their work, they hypothesized that PGRN exerts its anti-atherogenic effect probably through influencing the composition of HDL.

7. MAIN CONCLUSIONS

1. Significant differences in the composition of LDL and HDL subfractions were observed in scleroderma patients, as IDL% and small LDL% were significantly higher, while large LDL% and intermediate HDL% were significantly lower compared to the values of the control group, which presumably contributes to the increased cardiovascular risk of SSc patients.
2. Serum levels of sVCAM-1, sICAM-1 and LDL-C showed a significant positive correlation with the P wave interval among SSc patients. Serum leptin was positively correlated with the P max value. These parameters are presumed to play a role in the increased arrhythmia susceptibility of scleroderma patients.
3. The P wave interval showed a significant negative correlation with the small HDL percentage, while a significant positive correlation was observed between the large HDL percentage and the Apo A-I level. This may highlight the atrial arrhythmogenicity increasing effect of large HDL subfractions and Apo A-I.
4. In SSc patients and control subjects, lipid parameters correlated differently with atrial arrhythmia risk markers, which may indicate that the presence of autoimmune inflammatory processes influences the atrial arrhythmia risk-modifying effects of lipids.
5. QRS interval, QTc and Tpe values were positively correlated with serum CRP levels in SSc patients, but similar differences were not observed in the control group. Based on this, ECG markers of ventricular arrhythmia risk may be useful in predicting increased arrhythmogenicity caused by systemic inflammation.
6. LDL-C levels showed a positive correlation with QRS interval and QT interval length in SSc patients, but a similar relationship was not observed in the control group. Based on this, inflammatory processes in SSc patients may also influence the ventricular arrhythmia risk-modifying effects of lipids.
7. sICAM-1, sVCAM-1, and PGRN were significantly positively correlated with the QT interval in the SSc group, so the determination of these parameters may be suitable

for predicting potentially life-threatening ventricular arrhythmias during the cardiological follow-up of scleroderma patients.

8. SUMMARY

Arrhythmias occur more frequently in SSc patients than in the general population, and unfavorable mortality rates can be observed due to scleroderma heart involvement, therefore it is important to recognize patients at increased risk, for which the most commonly used examinations are electrocardiography and echocardiography.

In our study, the P wave interval, P wave dispersion, QT interval and QT dispersion determined from the 12-lead surface ECG were all prolonged in the scleroderma patient group compared to the data of the control group. Furthermore, based on our results, it can be stated that in the case of SSc patients, the determination of CRP, sICAM-1, sVCAM-1, PGRN, leptin, LDL-C and oxLDL levels, as well as the examination of LDL and HDL subfractions can also provide valuable information regarding atrial and ventricular arrhythmia risk.

Our data also draws attention to the fact that the lipid composition of scleroderma patients, which is different from that of the control group, correlates differently with ECG parameters refers to increased atrial and ventricular arrhythmia risk compared to the control group. This observation suggests that autoimmune inflammation in scleroderma patients may influence the effects of lipids on atrial arrhythmia susceptibility. Further studies are needed to clarify this.

Inflammatory biomarkers such as PGRN, sVCAM-1 and sICAM-1 showed a significant positive correlation with atrial and ventricular arrhythmia risk markers, thus their increased levels may indicate an increased vulnerability to arrhythmia.

In addition to serum cTnT and NT-proBNP levels, the determination of CRP level and lipid panel should also be routinely included in the assessment of cardiovascular risk in patients with scleroderma. Determination of serum biomarkers

such as sVCAM-1, sICAM-1, and PGRN may also be useful in cardiological diagnostics, as our studies show a correlation with certain electrocardiographic parameters.

ACKNOWLEDEMENTS

I am very grateful to my supervisor, Professor Dr. Zoltán Szabó, who introduced me to the possibilities of preventing atrial and ventricular arrhythmias when I was a resident physician. He devotedly guided our studies in the interdisciplinary field of cardiology and immunology during my PhD training, greatly assisted in my scientific work, thereby contributing to the development of my medical approach, our joint results and the preparation of my dissertation.

I am grateful to Professor Dr. Gabriella Szűcs, who provided significant assistance with her professional knowledge and experience in the planning and implementation of the immunological studies.

I would like to thank Professor Dr. Mariann Harangi and scientific associate Dr. Hajnalka Lőrincz for their helpful contribution in answering questions related to the field of lipidology and for their professional guidance.

I would like to express my gratitude to the co-authors of my scientific publications, Assistant Professor Dr. Dóra Ujvárosy, Associate Professor Dr. Sándor Somodi and Assistant Professor Dr. Balázs Ratku.

I am grateful to all the staff of the Department of Emergency Medicine, Faculty of General Medicine, University of Debrecen, and the Emergency Clinic of the Clinical Center, as well as to the staff of the Building “A” of the Institute of Internal Medicine A” for their support in the success of my research work. I am especially grateful to Kálmánné Tömpe, László Zelei, Róza Csák Feketéné, Zsanett Molnár, Sára Csiha and Piroska Szikszai Jámborné for their indispensable help in collecting samples and organizing and carrying out the examinations.

I would also like to thank my family for their patience and unwavering support, without which my dissertation would not have been possible.

PUBLICATION LIST



UNIVERSITY of
DEBRECEN

UNIVERSITY AND NATIONAL LIBRARY

UNIVERSITY OF DEBRECEN

H-4002 Egyetem tér 1, Debrecen

Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number:
Subject:

DEENK/409/2025.PL
PhD Publication List

Candidate: Veronika Borbásné Sebestyén

Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. Borbásné Sebestyén, V., Ujvárosy, D., Ratku, B., Lőrincz, H., Csiha, S., Tari, D., Majai, G., Somodi, S., Szűcs, G., Harangi, M., Szabó, Z.: Inflammatory Biomarkers and Lipid Parameters May Predict an Increased Risk for Atrial Arrhythmias in Patients with Systemic Sclerosis. *Biomedicines*. 13 (1), 1-15, 2025.
DOI: <http://dx.doi.org/10.3390/biomedicines13010220>
IF: 3.9 (2024)
2. Borbásné Sebestyén, V., Ratku, B., Ujvárosy, D., Lőrincz, H., Tari, D., Végh, L., Majai, G., Somodi, S., Páll, D., Szűcs, G., Harangi, M., Szabó, Z.: Progranulin, sICAM-1, and sVCAM-1 May Predict an Increased Risk for Ventricular Arrhythmias in Patients with Systemic Sclerosis. *Int. J. Mol. Sci.* 25 (13), 1-13, 2024.
DOI: <http://dx.doi.org/10.3390/ijms25137380>
IF: 4.9
3. Borbásné Sebestyén, V., Szűcs, G., Páll, D., Ujvárosy, D., Ötvös, T., Csige, I., Pataki, T., Lőrincz, I., Szabó, Z.: Electrocardiographic markers for the prediction of ventricular arrhythmias in patients with systemic sclerosis. *RHEUMATOLOGY*. 59 (3), 478-486, 2020.
DOI: <http://dx.doi.org/10.1093/rheumatology/kez644>
IF: 7.58





List of other publications

4. Ratku, B., Lőrincz, H., Csiha, S., Borbásné Sebestyén, V., Berta, E., Bodor, M., Nagy, E. V., Szabó, Z., Harangi, M., Somodi, S.: Serum afamin and its implications in adult growth hormone deficiency: a prospective GH-withdrawal study.
Front Endocrinol (Lausanne). 15, 1-13, 2024.
DOI: <http://dx.doi.org/10.3389/fendo.2024.1348046>
IF: 4.6
5. Ratku, B., Borbásné Sebestyén, V., Szelesné Árokszállási, A., Erdei, A., Berta, E., Szabó, Z., Bodor, M., Nagy, E. V., Somodi, S.: A felnőttkori növekedési hormon-hiány szív- és érrendszeri szövődésményei.
Orv. hetil. 164 (41), 1616-1627, 2023.
DOI: <http://dx.doi.org/10.1556/650.2023.32890>
IF: 0.8
6. Ratku, B., Borbásné Sebestyén, V., Erdei, A., Nagy, E. V., Szabó, Z., Somodi, S.: Effects of adult growth hormone deficiency and replacement therapy on the cardiometabolic risk profile.
Pituitary. 25 (2), 211-228, 2022.
DOI: <http://dx.doi.org/10.1007/s11102-022-01207-1>
IF: 3.8
7. Borbásné Sebestyén, V., Nagy, É., Mocsár, G., Volkó, J., Szilágyi, O., Kenesei, Á., Panyi, G., Tóth, K. Á., Hajdu, P., Vámosi, G.: Role of C-Terminal Domain and Membrane Potential in the Mobility of Kv1.3 Channels in Immune Synapse Forming T Cells.
Int. J. Mol. Sci. 23 (6), 1-16, 2022.
DOI: <http://dx.doi.org/10.3390/ijms23063313>
IF: 5.6
8. Ujvárosy, D., Borbásné Sebestyén, V., Ötvös, T., Ratku, B., Lőrincz, I., Szűk, T., Csanádi, Z., Berényi, E., Szabó, Z.: Cardiopulmonary Resuscitation With Mechanical Chest Compression Device During Percutaneous Coronary Intervention: a case report.
Front. Cardiovasc. Med. 8, 1-6, 2021.
DOI: <http://dx.doi.org/10.3389/fcvm.2021.614493>
IF: 5.846
9. Szabó, Z., Ujvárosy, D., Ötvös, T., Borbásné Sebestyén, V., Nánási, P. P.: Handling of ventricular fibrillation in the emergency setting.
Front. Pharmacol. 10, 1640, 2020.
DOI: <http://dx.doi.org/10.3389/fphar.2019.01640>
IF: 5.81





10. Ujvárosy, D., Borbásné Sebestyén, V., Pataki, T., Ötvös, T., Lőrincz, I., Paragh, G., Szabó, Z.: Cardiovascular risk factors differently affect the survival of patients undergoing manual or mechanical resuscitation.
BMC Cardiovasc Disord. 18 (1), 1-7, 2018.
DOI: <http://dx.doi.org/10.1186/s12872-018-0962-6>
IF: 1.947
11. Pál, L., Bujdosó, O., Szűcs, S., Baranyi, G., Borbásné Sebestyén, V., Vámosi, G., Rácz, G., Ádány, R., McKee, M., Árnas, E.: How do methanol and higher alcohols found in alcoholic beverages affect membrane fluidity and migration of granulocytes?
J. Food Biochem. 42 (5), 1-8, 2018.
DOI: <http://dx.doi.org/10.1111/jfbc.12593>
IF: 1.358
12. Nagy, É., Mocsár, G., Borbásné Sebestyén, V., Volkó, J., Papp, F., Tóth, K., Damjanovich, S., Panyi, G., Waldmann, T. A., Dóczy-Bodnár, A., Vámosi, G.: Membrane Potential Distinctly Modulates Mobility and Signaling of IL-2 and IL-15 Receptors in T Cells.
Biophys. J. 114 (10), 2473-2482, 2018.
DOI: <http://dx.doi.org/10.1016/j.bpj.2018.04.038>
IF: 3.665
13. Szabó, Z., Borbásné Sebestyén, V., Ujvárosy, D., Ötvös, T., Végh, L., Lőrincz, I.: A pitvarfibrilláció sürgősségi diagnosztikája és kezelése az újabb adatok tükrében.
Magyar Mentésügy. 31 (1), 24-33, 2017.
14. Páll, A., Borbásné Sebestyén, V., Czifra, Á., Becs, G., Anupam, A., Zarjou, A., Paragh, G., Lőrincz, I., Balla, J., Szabó, Z.: The disparate effect of hemodialysis and hemodiafiltration on T-wave-peak-to-end interval (Tpe) and Tpe/QT ratio of the surface electrocardiogram.
Trauma Emerg. Care. 2 (4), 1-6, 2017.
DOI: <http://dx.doi.org/10.15761/TEC.1000142>
15. Páll, A., Czifra, Á., Borbásné Sebestyén, V., Becs, G., Kun, C., Balla, J., Paragh, G., Lőrincz, I., Páll, D., Padra, J. T., Agarwal, A., Zarjou, A., Szabó, Z.: Hemodiafiltration and hemodialysis differently affect P wave duration and dispersion on the surface electrocardiogram.
Int. Urol. Nephrol. 48 (2), 271-277, 2016.
DOI: <http://dx.doi.org/10.1007/s11255-015-1144-4>
IF: 1.564
16. Borbásné Sebestyén, V., Szabó, Z.: The role of electrocardiographic markers in the prevention of atrial and ventricular arrhythmias.
In: *Echocardiography in Heart Failure and Cardiac Electrophysiology*. Ed.: Umashankar Lakshmanadoss, InTech, [s.n.], 13-34, 2016.





17. Borbásné Sebestyén, V., Szabó, Z.: The Value of P Wave Interval and Dispersion in the Prediction of Atrial Fibrillation in the Emergency Setting.
Austin Emerg. Med. 2 (9), 1-2, 2016.
18. Czifra, Á., Páll, A., Borbásné Sebestyén, V., Barta, K., Lőrincz, I., Balla, J., Paragh, G., Szabó, Z.: Végstádiumú vesebetegség és kamrai szívritmuszavarok: a hemodialízis és a hemodiafiltráció a kamrai repolarizációt eltérően befolyásolja.
Orv. Hetil. 156 (12), 463-471, 2015.
IF: 0.291

Total IF of journals (all publications): 51,661

Total IF of journals (publications related to the dissertation): 16,38

The Candidate's publication data submitted to the Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

18 June, 2025

