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IMPACT OF ATRIAL FIBRILLATION ON BLOOD FLOW IN THE POSTERIOR SEGMENT OF THE EYE

Mateusz Nowak* Department Of Cardiology, District Hospital In Chrzanów, Poland Opthalmology Centre, Libiąż, Poland *Corresponding Author

Piotr Nowak Department Of Cardiology, District Hospital In Chrzanów, Poland

Piotr Puc Department Of Cardiology, 5th Military Hospital With Polyclinic In Cracow, Poland

Piotr Piejko Department Of Cardiology, 5th Military Hospital With Polyclinic In Cracow, Poland

Aleksander Siniarski Department Of Coronary Artery Disease And Heart Failure, Institute Of Cardiology, Faculty Of Medicine, Jagiellonian University Medical College, Cracow, Poland; St. John Paul Ii Hospital, Cracow, Poland

Piotr Chaniecki Department Of Ophthalmology, 5th Military Hospital With Polyclinic In Cracow, Poland

ABSTRACT

Background: Retinal microvascular perfusion (RMVP) is analyzed by angio-OCT. There is little data on the impact of atrial fibrillation (AF) on the changes in RMVP. **Aims:** The aim of the study is to analyze the impact of atrial fibrillation (AF) on blood flow (blood perfusion) in the posterior segment of the eye in patients treated with direct oral anticoagulants (DOACs), using a new technology based on optical coherence tomography angiography (OCTA). The study focuses on the blood perfusion relationship in patients treated with DOACs. **Method:** This case-control study included 20 patients diagnosed with permanent atrial fibrillation (AF) and heart failure (HF), which were compared with 20 healthy volunteers. To assess blood perfusion, a series of central retinal measurements were performed in each patient, assessing blood perfusion parameters using the Zeiss AngioPlex OCT Cirrus 5000 angiography platform with the FastTrac™ function. **Results:** In patients with AF and HF, the vessel density in both eyes was significantly lower than in healthy people (without AF). In healthy controls, vessel density was significantly higher than in patients treated with dabigatran. Interestingly, vascular density was similar in patients treated with rivaroxaban compared to healthy controls. **Conclusions:** Patients with stable HF and permanent AF had lower vessel density in the superficial retinal vascular plexus compared to the healthy control group. Furthermore, rivaroxaban had a beneficial effect on the vessels of the superficial retinal vascular plexus, reducing vascular damage in patients with AF. The detailed mechanism of this positive effect requires further investigation in larger clinical cohorts.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Its incidence is increasing due to the aging of the population. In Poland, in patients aged ≥ 65 years, the AF occurs in almost 20% of population, so therefore affects approximately 1.5 million people.[1]

AF is the most common supraventricular tachyarrhythmia, characterized by rapid, uncoordinated depolarization of the atria, leading to the loss of the hemodynamic effectiveness of their contraction, resulting in significant impairment of mechanical activity, and irregular ventricular rhythm.[1]

AF is associated with an increased risk of cardiovascular (CV) events including CV deaths or strokes,[2] but also and incidents of peripheral embolism, including blindness caused by retinal artery embolism.[3-5]

Atrial fibrillation treatment should not be underestimated. In patients not treated with anticoagulants, ischemic stroke or retinal artery embolism and permanent disability occur. Studies show that 25–30% of all strokes in the age group of 80–89 are caused by atrial fibrillation.[6] Stroke is one of the leading causes of death in the world. In developed countries, heart disease and cancer are associated with higher mortality. In poorer countries, strokes cause 85% of all deaths. The mortality rate in their course is 10–30%. In Poland, on the other hand, approximately 60,000 people suffer from stroke every year. Although the morbidity rate is similar to that in developed European countries, the mortality rate in the course of stroke is 2–3 times higher in our country compared to Western Europe or the United States.[7]

The treatment uses: old anticoagulants – VKA (vitamin K antagonist) – warfarin and acenocoumarol, as well as new NOAC drugs (non-vitamin K antagonist oral anticoagulant) – anticoagulants that are not vitamin K antagonists. Traditional anticoagulants include oral vitamin K antagonists, while new-generation drugs include direct thrombin inhibitors – dabigatran and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). An interesting issue is the influence of pleiotropic mechanisms of action of NOAC drugs via PAR-1 and PAR-2 receptors located on platelets and many other cells on the modification of the course of atherosclerosis.

The introduction of OCT angiography (OCTA) in autumn 2014 was considered to be another milestone in ophthalmological diagnostics. OCTA is the latest method that allows visualization of blood flow in the retinal vessels and choriocapillaries without the use of a contrast agent.[8-11] The basis of OCTA is split spectrum amplitude decorrelation angiography (SSADA) technology, which identifies retinal vessels by detecting and measuring the movement of blood cells in the vessels, which allows to distinguish solid tissue from blood flow.[8-11] OCTA enables the assessment of the histological vascular structure of the retina. Angio-OCT is part of a routine OCT examination performed using AngioRetina scans (to assess flow in the macula) or AngioDisc (to assess flow through the optic disc), and the image acquisition time during the examination is a few seconds. Thanks to the use of angio-OCT, three-dimensional images are obtained, which is not possible with fluorescein angiography.

Objectives

The study focused on observing changes in blood perfusion depending on the type of anticoagulant drug used comparing

the results to the microcirculation of healthy people. The following research question was asked: how does atrial fibrillation, depending on the anticoagulant treatment used, affect perfusion density and vessel density. Patients with atrial fibrillation are best treated with anticoagulants by selecting a drug with a pleiotropic effect.

To date, single studies demonstrating the pleiotropism of rivaroxaban have been published - they concern animal and "in vitro" models.[12] We wanted to confirm above-mentioned observations in our follow-up study.

METHODS

Study Population

Case control study with a comparison group of AF vs. healthy included, 20 patients with AF and chronic HF treated with DOAC. The control group consisted of 20 apparently healthy people, with no diagnosed concomitant diseases and without any prior treatment. Inclusion criteria: general health and mental condition enabling participation in the study, informed consent of the patient to the examination, translucency of optical centers enabling proper performance of the examination using the AngioPlex OCT Cirrus 5000 device from Zeiss with the FastTrac™ function, retinal evaluation scan showing a signal strength score greater than 6 (normal image strength to allow for correct quantification), patient's motivation to perform detailed retina diagnostics. The exclusion criteria in the process of selecting the study group include lack of patient's consent to perform tests: mental illnesses that make it impossible to carry out research, age-related macular degeneration (AMD), lack of transparency of optical media, central serous retinopathy (CSR), retinal detachment, hole/scar in the macula, diabetes, circulatory failure NYHA III–IV, acute coronary syndrome, decompensated hypertension, mitral valve stenosis, aortic valve stenosis, narrowing of the cephalic arteries (over 70%). All ophthalmology assessment was performed in the Clinical Department of Ophthalmology of the 5th Military Clinical Hospital in Krakow, Poland, between April 2019 and December 2019.

All cardiology assessment was performed in the Clinical Department of Cardiology of the 5th Military Clinical Hospital in Krakow, Poland.

Consent was obtained from the Bioethics Committee at the District Medical Chamber in Cracow, no. 242/KBL/OIL/2018 of December 11, 2018. All data are contained in the manuscript.

Optical Coherence Tomography Angiography (OCTA)

AngioPlex OCT Cirrus 5000 device from Zeiss. Equipment enabling anatomical and functional assessment of the retina (examination with this device is non-invasive, does not pose a threat to the health and safety of the examined persons - it does not violate the continuity of eye tissues).

Then, each patient underwent a series of measurements of the central part of the retina, assessing perfusion and thickness parameters, using the AngioPlex OCT Cirrus 5000 device from Zeiss with the FastTrac™ function. An angiography scan was considered normal when the signal strength was at least 6. During each assessment of the posterior segment of the eye, central retinal thickness (macula thickness/macular cube) was measured in the ILM-RPE 200 × 200 view, density and perfusion in 3 × 3 mm, 6 × 6 mm scans. The superficial capillary plexus (SCP) was recorded and captured by personalized segmentation between the internal limiting membrane (ILM) and the internal plexiform layer (IPL). All scans were automatically analyzed using the macular density algorithm (v 10.0.1) developed by Zeiss Algorithm Development - macular grain density and FAZ dead zones. Perfusion density and vessel density of the superficial capillary plexus were measured in two zones: central and full. Perfusion density is defined as the total area of the perfused vascular system per unit area in the measurement area. Thus, unitless scores range from 0 (no perfusion) to 1 (fully perfused). Vascular density refers to the total length of vascularization per unit area within the measurement area in inverse millimeter units. Vessel perfusion and density were analyzed in two relevant areas: including the central 1 mm and 3 mm ETDRS ring (hereafter referred to as inner 3 mm) and the entire 3 mm × 3 mm scanning area (henceforth referred to as 3 × 3 mm).

Transthoracic Echocardiography (TTE)

Transthoracic echocardiography (TTE) was performed in the Echocardiography Laboratory of the Cardiology Clinic of the 5th Military Clinical Hospital in Krakow, Poland. The examination monitored: the size of the left atrium, left ventricle, right ventricle in cm, the volume of the right atrium in cm2, the degree of mitral valve regurgitation (range of the regurgitant wave), described as grade I, II, III, IV or no wave - 0, ejection fraction of the left ventricle calculated as a percentage, thickness of the heart chambers in cm (interventricular septum and posterior wall), width of the pulmonary trunk and width of the ascending aorta in cm, systolic pressure in the right ventricle (RVSP) calculated as 4 ×V2 + RAP (pressure in the right atrium of the heart) in mmHg and the width of the inferior vena cava (VCI) in cm. All ophthalmology assessment was performed in the Clinical Department of Ophthalmology of the 5th Military Clinical Hospital in Krakow, Poland. The patient's general condition was determined based on the subjective and objective interview. The patients participating in the study underwent additional tests: blood count, INR, glucose level and anti-HCV and HBsAg antibodies. Routine care laboratory evaluation in all groups (Table 1).

Statistical Analysis

The GLM (general linear models) methodology was used for the analysis. Due to the existence of 20 explanatory variables, the best model was selected for each explained variable using the Cp information criterion, which is one of the methods indicating the best model fit. More precisely, for each explained variable, all possible linear models were checked using explanatory variables and the Cp index was calculated for each such model. Optimal models are reflected by the smallest Cp index. Then, ANCOVA test of the significance of explanatory variables was performed for the previously selected model. When the p-value is less than 0.05, the explanatory variable has a significant impact on the explained variable; the smaller the p-value, the greater the significance. Regression coefficients in the linear model were also calculated - both for the original and standardized variables. 95% confidence intervals for beta coefficients (i.e. coefficients of standardized variables) were also determined. It should be noted that wherever the MP variable was calculated as significant (patients differ significantly from healthy people), an additional test was performed (Dunnett's post hoc test). Dunnett's test was used to check whether each subgroup differed significantly from the control group, i.e. healthy people.

DISCUSSION

The most important conclusions from the analysis of the statistical calculations presented in our work are listed below:

1. In people with atrial fibrillation, the density of vessels in both eyes is significantly lower than in healthy people (without AF).
2. In healthy people, vascular density is significantly higher than in patients taking dabigatran (the exception is rivaroxaban).
3. Patients taking dabigatran have significantly lower vessel density levels than healthy people. Patients taking rivaroxaban do not have significantly lower vessel density levels than healthy people. This suggests that rivaroxaban stands out in favor.

One of the three main goals of atrial fibrillation treatment (in addition to symptom control and prevention of thrombotic complications) is to avoid the development of tachyarrhythmic cardiomyopathy. From a clinical point of view, the possibility of complete resolution of HF symptoms by controlling the ventricular rate or restoring sinus rhythm is important from a clinical point of view.[13]

In clinical practice, regardless of the development of de novo cardiomyopathy, arrhythmia may exacerbate the symptoms of existing HF. The loss of atrioventricular synchrony, responsible for approximately 30% of cardiac output, may significantly worsen the symptoms of HF with preserved systolic function, especially in the elderly.[14]

An attack of MP also promotes circulatory decompensation in patients with hypertensive left ventricular hypertrophy, hypertrophic and restrictive cardiomyopathy, as well as in clinically significant stenosis of the left venous outlet.[15]

The rapid rhythm of the ventricular response and the variability of the force of contraction depending on its duration are also responsible for the severity of HF symptoms.

Studies have shown that an attack of AF impairs the flow through coronary vessels, causing their spasm, dependent on sympathetic activation, which may intensify the symptoms of ischemic HF.[16]

According to the classic results of the Framingham Heart Study, MP is an independent risk factor for death in cardiovascular diseases.[17]

Regardless of the form of HF (with preserved or reduced LV ejection fraction), HF worsens the prognosis and increases mortality in this group of patients.[18]

Apart from the obvious impact of HF on the occurrence of AF, it is also crucial for the prognosis in the context of thromboembolic complications and is an important factor in the occurrence of stroke. Therefore, anticoagulant treatment is the only therapy with proven prognostically beneficial significance in patients with AF and HF.[19]

The presented research results prove that the more damaged the heart muscle is and the older the patient is, the more damaged the superficial retinal vascular plexus is (the lower the vessel density).

The study proved the positive effect of rivaroxaban on the condition of the vessels of the superficial vascular plexus of the retina (reduction of blood vessel damage).

Vascular density in patients taking rivaroxaban is similar to that in healthy people. This phenomenon was not observed in the group of people treated with dabigatran.

Limitations

The limitations of the method are the same as standard OCT: opaque optical media, lack of fixation, lack of cooperation, too narrow a pupil, nystagmus. In addition, this method does not allow for an accurate assessment of the retinal periphery. Currently, scans of 3 × 3 mm, 6 × 6 mm, and 8 × 8 mm can be used, which provides a detailed assessment of the posterior pole. With good patient cooperation and proper fixation, the average perimeter of the retina can be assessed. Other limitations include diseases affecting retinal microcirculation, such as diabetes, glaucoma, and age-related macular degeneration, which constituted exclusion criteria.

RESULTS

The statistical analysis confirmed the hypothesis formulated before the work was performed that cardiac arrhythmias in the form of atrial fibrillation result in a reduction in retinal microcirculation parameters, such as vessel density (in patients with atrial fibrillation, the vessel density in both eyes is significantly lower than in healthy people).

Statistical analysis excluded the influence of cardiac arrhythmias in the form of atrial fibrillation on perfusion density.

3.1. Statistical Analysis Of Vessel Density In The Right Eye

Vessel density in mm/mm2 – central part of the retina of the right eye. The results of regression using the best subset method - Cp criterion are presented in Table 2.

It was checked whether the types of drugs differed from each other. In the above model, MP was replaced by drug. Dunnett's test was performed for comparison with the control group (NA) Figure 1.

In patients with atrial fibrillation, the vessel density mm/mm2 of the central right eye is significantly lower than in healthy people (in healthy people +1.184 standard deviations, in patients -1.184 standard deviations). In women, the vessel density mm/mm2 central of the right eye is significantly lower than in men (in men +0.335 standard deviation, in women -0.335 standard deviation). An increase in the right atrium cm2 variable by 1 standard deviation causes a significant increase in the vessel density mm/mm2 central of the right eye by 0.368 standard deviations. An increase in the variable pulmonary trunk AcT ms by 1 standard deviation causes a significant increase in vessel density mm/mm2 central of the right eye by 0.845 standard deviation. An increase in the variable left ventricle cm by 1 standard deviation causes a significant decrease in the vessel density mm/mm2 central of the right eye by 0.367 standard deviations. An increase in the RVSP mmHg variable by 1 standard deviation causes a non-significant decrease in the vessel density mm/mm2 central of the right eye by 0.217 standard deviations.

In healthy people, the central vessel density mm/mm2 of the right eye is significantly higher than in patients taking dabigatran.

3.2. Statistical Analysis Of Vessel Density In The Left Eye

Vessel density in mm/mm2 – central part of the retina of the left eye. The results of regression using the best subset method - Cp criterion are presented in Table 3.

It was checked whether the types of drugs differed from each other. In the above model, MP was replaced by drug. Dunnett's test was performed for comparison with the control group (NA) Figure 2.

In patients with atrial fibrillation, the vessel density mm/mm2 central area of the left eye is significantly lower than in healthy people. An increase in the variable right atrium cm2 by 1 standard deviation causes a significant increase in vessel density mm/mm2 central of the left eye. An increase in the variable pulmonary trunk AcT ms by 1 standard deviation causes a significant increase in vessel density mm/mm2 central of the left eye. An increase in the left atrium cm variable by 1 standard deviation causes a non-significant decrease in the vessel density mm/mm2 central of the left eye by 0.275 standard deviations.

In healthy subjects, the central vessel density mm/mm2 of the left eye is significantly higher than in patients taking dabigatran.

3.3. Statistical analysis of vascular perfusion in the right eye

Vascular perfusion – central part of the retina of the right eye. The results of regression using the best subset method - Cp criterion are presented in Table 4.

In this model, the influence of MP on the central perfusion density % of the right eye is insignificant.

3.4. Statistical Analysis Of Vascular Perfusion In The Left Eye.

Vascular perfusion – central part of the retina of the left eye. The results of regression using the best subset method - Cp criterion are presented in Table 5. Vascular perfusion – central part of the retina of the left eye. In this model, the effect of MP on the central perfusion density % of the left eye is insignificant.

List of values of measured parameters in patients with symptomatic atrial fibrillation and list of values of measured parameters in healthy patients (Table 6,7).

Data sharing is not applicable to this article as all data are already in the manuscript.

What's New: There are scarce data on the retinal microvascular changes in heart diseases (innovative study). The presented research results prove that the more damaged the heart muscle and the older the patient is, the more damaged the superficial retinal vascular plexus. Patients with atrial fibrillation and heart failure have a lower density of vessels in the superficial capillary plexus compared to the control group without AF. Changes in vascular perfusion of the superficial retinal plexus depend on the presence of atrial fibrillation and on the anticoagulant drug used. The study confirmed the results of studies conducted in animal models or in vitro on the pleiotropic effect of rivaroxaban, an anticoagulant from the NOAC group, and a factor Xa inhibitor.[17]

Table 1. Routine Care Laboratory Evaluation In All Groups

Variable	Results	Reference range
Leukocytes, x10^3/ul	4.69	4.23 - 9.07
Neutrophils, x10^3/ul	2.74	1.5 – 7.7
Lymphocytes, x10^3/ul	1.29	1.1 – 4.5
Monocytes, x10^3/ul	0.51	0.1 – 0.9
Eosinophils, x10^3/ul	0.11	0.02 – 0.5
Basophils, %	0.03	0 – 0.2
Neutrophils, %	58.5	34 – 67.9
Lymphocytes, %	27.5	21.8 – 53.1
Monocytes, %	10.9	5.3 – 12.2
Eosinophils, %	2.3	0.8 – 7
Basophils, %	0.6	0.2 – 1.2
IG, %	0.20	0 – 0.5
NRBC, x10^3/ul	0.000	0 – 0.03
Erythrocytes, x10^6/ul	4.82	4.63 – 6.08
Hemoglobin, g/dl	14.7	13.7 – 17.5
Hematocrit, %	43.9	40.1 – 51
MCV, fl	91.1	79 – 92.2
MCH, pg	30.5	25.7 – 32.2
MCHC, g/dl	33.5	32.3 – 36.5
RDW-SD, fl	42.6	35.1 – 43.9
RDW-CV, %	13.0	11.6 – 14.4
Platelets, x10^3/ul	159	150 – 400
PDW, fl	14.4	9.8 – 16.1
MPV, fl	11.3	9.4 – 12.6
P-LCR, %	37.7	19.2 – 47
PCT, %	0.18	0.16 – 0.35
Potassium, mmol/L	3.89	3.5 – 5.1
Sodium, mmol/L	141.9	136 – 145
Chlorides, mmol/L	105.4	98 - 107
Ferritin, ng/ml	43.32	21.9 – 274.7
Glucose, mg/dl	99	74 - 99

Numbers are shown as median (IQR) or mean (SD) with ANOVA test used respectively

Table 2. Regression using the best subset method (Cp criterion). Applies to: vascular density – central part of the retina of the right eye

Effect	Level effect	p-value	Factor regression b	Factor beta regression	95% interval confidence for beta	
		0.018	12.200			
Left ventricle [cm]		0.001	−2.374	−0.367	−0.587	−0.147
Right atrium [cm2]		0.011	0.409	0.368	0.088	0.649
Pulmonary trunk – AcT [ms]		0.009	0.065	0.845	0.224	1.466
RVSP [mmHg]		0.084	−0.126	−0.217	−0.463	0.030
MP	0	0.001	5.175	1.184	0.493	1.874
Gender	M	0.004	1.485	0.335	0.114	0.556

AcT – blood acceleration time in the pulmonary trunk, RVSP – systolic pressure in the right ventricle, MP – atrial fibrillation

Figure 1.

Medicine	p-value
Rivaroxaban	0.335
Dabigatran	0.006
Control group (NA)	

Figure 1. Expected marginal means across groups for different drugs with 95% confidence intervals. Applies to: vascular density – central part of the retina of the right eye

Table 3. Regression using the best subset method (Cp criterion). Vessel density – central part of the retina of the left eye

Effect	Level effect	p-valuć	Factor regression b	Factor beta regression	95% interval confidence for beta	
		0.329	4.563			
Left ventricle [cm]		0.091	−1.697	−0.275	−0.594	0.045
Right atrium [cm2]		0.025	0.410	0.407	0.053	0.761
Pulmonary trunk – AcT [ms]		0.001	0.083	1.182	0.475	1.888
MP	0	0.000	5.836	1.472	0.714	2.230

AcT – blood acceleration time in the pulmonary trunk, MP – atrial fibrillation

Figure 2.

Medicine	p-value
Rywaroksaban	0.991
Dabigatran	0.012
Control group (NA)	

Figure 2. Expected marginal means across groups for different drugs with 95% confidence intervals. Vessel density – central part of the retina of the left eye

Table 4. Regression using the best subset method (Cp criterion). Vascular perfusion – central part of the retina of the right eye

Effect	Level effect	p-valueć	Factor regression b	Factor beta regression	95% interval confidence for beta	
		0.000	51.360			
Age		0.130	−0.092	−0.167	−0.385	0.051
Left ventricle [cm]		0.004	−4.068	−0.338	−0.560	−0.115

RVSP [mmHg]		0.006	−0.332	−0.307	−0.520	−0.094
Gender	M	0.000	3.582	0.434	0.212	0.655

RVSP – systolic pressure in the right ventricle of the heart.

Table 5. Regression using the best subset method (Cp criterion). Vascular perfusion – central part of the retina of the left eye

Effect	Level effect	p-value	Factor regression b	Factor beta regression	95% interval confidence for beta	
		0.000	37.049			
Left ventricle [cm]		0.004	−4.321	−0.370	−0.616	−0.123
Gender	M	0.018	2.283	0.301	0.054	0.547

Table 6. List of values of measured parameters in patients with symptomatic atrial fibrillation.

Patient/gender		Drug	Age	Left ventricle cm	Right ventricle cm	Ascending aorta cm	Left atrium cm	Right atrium cm2	Posterior heart wall cm	IVS cm	Pulmonary trunk -ACT ms	AV-Vmax m/s	E/A	TAPSE mm	IVC cm	RVSP mmHg	IM	IT	IA	EF %	Vessel density m/m2 central OD	Vessel density m/m2 full OD	Vessel density m/m2 central OS	Vessel density m/m2 full OS	Perfusion density % central OD	Perfusion density % full OD	Perfusion density % central OS	Perfusion density % full OS
1	F	dabigatran	77	5.00	4.00	3.50	5.00	20	1.00	1.20	110	1.4	0.9	23	1.8	38	III st	II st	I st	60	5.4	14.9	7.9	15.4	11	31.2	17	34
2	M	dabigatran	79	6.20	2.60	2.60	4.50	22	1.30	1.30	100	1.5	0.8	22	0.2	30	I st	I st	I st	45	9	15	6.3	15.8	14.7	34.4	12	32
3	F	dabigatran	92	5.00	3.50	3.10	5.00	24	1.30	1.40	115	1.37	2.38	20	2	20	IIII st	II st	0	45	5.1	16	5.1	16	12.4	35.2	11.3	39.6
4	M	dabigatran	76	5.6	3.3	3.2	4.9	23	1.4	1.2	87	1.7	0.9	18	2.1	30	II st	I st	I st	45	0.4	13	3.6	13.5	0.8	30.5	7.4	32.5
5	F	dabigatran	66	5.6	2.6	3.4	5.7	30	1.3	1.3	100	1.5	1.1	24	2	30	II st	III st	0	60	11.2	21.2	9.9	20.9	21	40.3	18.5	37.8
6	M	rivaroksaban	54	5.5	3.1	3	4.5	20	1.7	1.7	125	1.3	0.8	22	2.5	20	I st	I st	I st	60	13.7	19.2	10.1	18.1	31.3	47.5	22.5	43.6
7	M	rivaroksaban	62	5.70	3.40	3.90	5.00	20	1.10	1.40	146	1.15	X	20	1.3	25	I st	I st	0	60	11.5	20.7	10.1	19.4	19.4	37.6	17.8	36.1
8	F	rivaroksaban	67	4.40	2.90	2.70	3.70	22	1.20	1.20	100	1.3	1.1	20	2.5	20	0	I st	I st	60	8.1	17	12.8	19.2	17.4	41.6	28.3	47.4
9	M	rivaroksaban	86	4.90	3.00	2.90	4.80	20	1.30	1.20	100	1.5	2	22	2.5	15	II st	I st	I st	60	5.5	15.1	8.2	16.1	11.7	37.6	18.1	39.6
10	F	rivaroksaban	65	3.9	2.9	3	5.2	25	1	1.1	110	1.3	1.5	22	1	20	I st	I st	0	55	13.2	22.7	13.9	22.1	23.7	40.6	24.4	38.4
11	M	rivaroksaban	70	5.7	3.8	3.3	4.4	28	1.2	1.3	126	0.86	0.8	22	0	25	I st	I st	0	55	5.4	16.7	11.7	18.8	13.5	36.7	24.2	38.6
12	M	rivaroksaban	80	5.6	3.9	3	4.5	24	1.2	1.2	120	1.7	3	18	2.2	40	II st	III st	II st	50	7.5	12.3	11.5	17.4	18	36.5	26	43.7
13	F	rivaroksaban	89	5.4	3.6	3.5	5.8	23	1.3	1.2	90	1.3	2	18	1.8	30	III st	III st	0	45	2	12.9	4.7	12	3.6	30.9	9.8	28.8
14	F	rivaroksaban	75	3.9	3.7	2.6	5.2	32	1	0.9	110	1.2	2	20	2	45	I st	III st	0	60	14.3	22	13.1	33.7	13.1	33.7	11.4	30
15	M	rivaroksaban	80	4.9	2.6	2.6	4.7	20	1.4	1.4	155	1.5	0.8	23	2	20	II st	I st	0	60	18.9	19.9	17.2	18.1	33.1	37.2	21.7	35.4
16	F	rivaroksaban	90	5.5	2.6	2.6	4.4	20	1.4	1.4	79	1.6	0.8	20	2	20	II st	I st	0	55	1.9	7.9	2.8	9.7	1.7	23	5.2	18.5
17	M	rivaroksaban	60	5.20	3.70	3.20	4.60	20	1.10	1.10	114	1	0.7	18	1.6	20	II st	I st	0	50	10	22.9	8.6	20	17.1	40.2	14.2	35.3

18	M	rivaroksaban	69	5.6	3.2	2.6	5.3	20	1.3	1.3	155	1.5	2	20	1.8	20	II st	I st	I st	50	13.4	20	12.1	19.4	24.7	37.9	22.8	36.5
19	M	rivaroksaban	91	4.5	3.1	2.5	4.5	18	1.2	1.3	115	1.3	2.35	23	2.5	20	I st	I st	I st	40	10.3	18.3	15.4	18.4	23.1	44.9	35.8	46.4
20	F	rivaroksaban	86	4.6	2.5	2.7	4.4	22	1.3	1.3	125	1.6	3	20	1.8	25	II st	I st	I st	45	14.7	18.9	15.2	18.1	34	46.4	36.2	45.8

Abbreviations: F – female; M – male; IVS - interventricular septum; AcT – acceleration time (acceleration); AV – aortic valve; Vmax – maximum velocity of blood flow through the AV; E/A – mitral flow; TAPSE – amplitude of tricuspid ring movement - a marker of the systolic performance of the right ventricle; IVC – width of the inferior vena cava; RVSP – systolic pressure in the right ventricle of the heart; IM – mitral valve regurgitation; IT – tricuspid valve regurgitation; IA – aortic valve regurgitation; EF – left ventricular fraction

Table 7. List of values of measured parameters in healthy patients

Patient/gender		Age	Left ventricle cm	Right ventricle cm	Ascending aorta cm	Left atrium cm	Right atrium cm2	Posterior heart wall cm	IVS cm	Pulmonary trunk -ACT ms	AV-Vmax m/s	E/A	TAPSE mm	IVC cm	RVSP mmHg	IM	IT	IA	EF %	Vessel density m/m2 central OD	Vessel density m/m2 full OD	Vessel density m/m2 central OS	Vessel density m/m2 full OS	Perfusion density % central OD	Perfusion density % full OD	Perfusion density % central OS	Perfusion density % full OS
1	F	71	4.7	2.9	2.8	4.2	20	1.3	1.3	2	1.6	0.8	22	2.5	25	II st	I st	II st	60	6.2	16.1	6.3	17.8	10.0	29.3	10.1	32.1
2	F	69	4.7	3.2	3.3	4.2	20	1.3	1.3	2.3	1.8	0.8	24	2.2	25	I st	I st	0	55	15.6	22.1	16.1	22.8	23.4	39.6	28.4	40.3
3	F	68	3.5	2.3	2.5	3.2	20	0.9	0.9	1.8	1.3	0.63	20	1.8	20	II st	I st	0	65	11.1	19.7	13.7	21.3	19.5	36.0	24.6	39.3
4	F	25	4.3	2.6	2.6	3.4	18	1	1	2	1.5	1.3	28	1	20	0	0	0	60	11.5	22.8	10.0	21.3	19.6	40.0	18.5	36.8
5	F	55	5.5	4.1	3.4	4.2	20	1	1.1	2	1.6	0.85	22	1.6	24	I st	I st	0	60	4.4	14.0	13.0	20.2	7.3	26.6	22.5	36.5
6	F	69	4.6	2.6	2.6	3.9	16	1.2	1.2	2	1.5	0.9	22	1.8	20	0	0	0	60	9.0	18.5	8.5	16.7	18.3	36.8	18.5	34.2
7	F	68	4.5	2.6	2.7	4	20	1.1	1.2	2	1.4	0.98	24	1.4	27	II st	I st	I st	60	6.8	18.6	7.0	18.9	12.1	34.6	13.8	38.1
8	F	59	4.7	3.1	3.4	3.9	18	1.2	1.2	2	1.3	0.9	28	2.5	15	II st	I st	I st	60	8.1	20.0	8.3	19.5	14.6	36.9	13.5	34.7
9	F	65	4.6	2.6	2.6	3.9	18	1.2	1.2	2	1.5	0.9	22	0	20	0	I st	0	60	10.1	20.6	10.0	21.6	16.8	36.6	10.0	21.6
10	F	66	5.1	2.6	3.9	2.6	12	1.2	1.2	2	1.5	1.3	22	2	20	0	I st	0	60	9.1	20.0	7.7	19.3	17.7	37.4	13.9	34.4
11	M	83	5.2	3.7	2.7	4	18	1.2	1.2	1.8	1.7	0.46	22	1.8	18	II st	I st	I st	50	9.2	21.2	10.7	20.6	17.4	38.4	17.7	37.3
12	M	63	5.9	3	2.6	5.2	20	1.2	1.2	2	1.5	0.9	22	1.4	22	I st	I st	0	55	11.9	21.6	9.6	20.3	21.8	39.1	16.2	35.9
13	M	55	4.6	3.2	3.2	4.2	18	1.4	1.4	1.8	1.6	0.9	22	1,4	30	II st	II st	I st	55	15.8	22,2	17.2	23.6	27.2	38.1	30.1	40.7
14	M	38	3.9	3.1	3.3	3.7	16	1	1.1	2	1.3	1.35	28	2.5	20	I st	I st	0	60	14.0	20.1	13.0	19.5	25.6	35.6	22.9	35.2
15	M	43	4.7	3.1	3.3	4.3	20	1.3	1.3	2	1.3	1.35	26	2.5	20	II st	I st	I st	60	8.2	19.3	7.7	17.6	14.9	35.5	13.1	32.6
16	M	58	4.5	3.1	3.1	4.1	18	1.3	1.3	2	1.3	0.9	26	2.5	20	0	I st	I st	65	9.6	21.5	6.1	17.8	17.9	39.7	10.3	31.4
17	M	71	4.7	3.2	2.4	4.2	20	1.4	1.4	2	1.5	1.3	22	1.8	20	0	I st	0	60	11.0	21.9	10.3	20.5	19.7	40.0	17.9	38.6
18	M	52	5.6	2.6	2.6	4.8	22	1.6	1.6	2	1.5	0.9	20	1.4	20	I st	I st	0	60	12.4	22.6	10.9	20.9	21.0	39.5	17.1	36.3
19	M	59	4.3	3	2.7	4.2	20	1	1	2.2	1.7	1.3	24	1.6	20	I st	I st	0	65	13.5	20.4	12.9	20.8	24.0	38.2	17.0	29.6
20	M	49	4.5	2.4	3.3	4.3	22	1.2	1.3	2.3	1.6	0.8	24	1.9	15	I st	I st	0	55	14.9	22.1	14.5	22.4	27.4	40.6	26.5	40.6

Abbreviations: F – female; M – male; IVS - interventricular septum; AcT – acceleration time (acceleration); AV – aortic valve; Vmax – maximum velocity of blood flow through the AV; E/A – mitral flow; TAPSE – amplitude of tricuspid ring movement - a marker of the systolic performance of the right ventricle; IVC – width of the inferior vena cava; RVSP – systolic pressure in the right ventricle of the heart; IM – mitral valve regurgitation; IT – tricuspid valve regurgitation; IA – aortic valve regurgitation; EF – left ventricular fraction

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