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nr **3**/tom **15**/**2020**

ISSN 2353–7752

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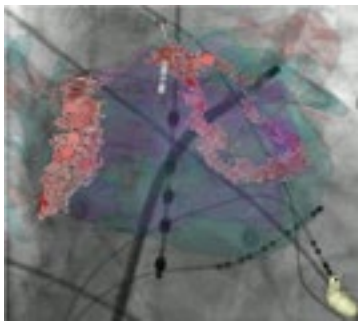

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Folia Cardiologica, ISSN 2353–7752 (pod wcześniejszym tytułem *Folia Cardiologica Excerpta*, ISSN 1896–2475) jest czasopismem wydawanym 6 razy w roku przez wydawnictwo VM Media sp. z o.o. VM Group sp.k., ul. Świętokrzyska 73, 80–180 Gdańsk, tel. 58 320 94 94, faks 58 320 94 60, www.journals.viamedica.pl/folia_cardiologica

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Folia Cardiologica 2020
tom 15, nr 3
DOI: 10.5603/FC.2020.0045

ISSN 2353–7752

Od Redaktora

Szanowni Państwo,
Drodzy Czytelnicy,

kolejny numer czasopisma *Folia Cardiologica* trafia do Państwa w czasie epidemii, okresie trudnym dla nas wszystkich, czasie, w którym system ochrony zdrowia w naszym kraju poddany jest ciężkiej próbie, a my — przystosowujący się do nowych i zmieniających się stale warunków — podlegamy obciążeniom i stresom na niepotykaną dotychczas skalę. Niemniej jestem przekonana, że również teraz, a może zwłaszcza teraz, wartościowa lektura poza walorem poznawczym niesie za sobą możliwość „oderwania się" od trudnej rzeczywistości i uspokojenia emocji, jakim codziennie ulegamy.

Prace oryginalne zamieszczone w bieżącym numerze pochodzą ze znakomitych ośrodków kardiologicznych w kraju. Autorzy pracy „Morphometry of peripheral arteries in the assessment of the cardiovascular risk" dr n. med. Dariusz Sławek i prof. Jarosław D. Kasprzak z Wojewódzkiego Szpitala Specjalistycznego im. Władysława Biegańskiego w Łodzi, po ocenie ultrasonograficznej i analizie, pozytywnie zweryfikowali hipotezę, że zwiększenie średnicy tętnic szyjnych wspólnych i tętnicy ramiennej dominującej kończyny stanowi marker zwiększonego ryzyka wystąpienia choroby wieńcowej. Doktor n. med. Krzysztof Myrda i wsp. ze Śląskiego Centrum Chorób Serca w Zabrzu w pracy „Radiation exposure reduction during atrial fibrillation ablation in real-life population using fluoroscopy and 3D mapping system integration" potwierdzili, że wykorzystanie nowego systemu elektroanatomicznego 3D zintegrowanego z klasyczną fluoroskopią pozwala na zmniejszenie ekspozycji na promieniowanie jonizujące podczas zabiegów ablacji migotania przedsionków. Praca została opracowana na podstawie danych 96 pacjentów poddawanych zabiegowi ablacji podłoża migotania przedsionków. Z kolei artykuł „Assessment of adherence to physician recommendations among patients with diagnosed diabetes mellitus type 2" Aurelii Grzywacz i dr. n. med. Daniela Śliża z III Kliniki Chorób Wewnętrznych i Kardiologii Warszawskiego Uniwersytetu Medycznego zawiera ocenę przestrzegania zaleceń lekarskich przez pacjentów ze zdiagnozowaną cukrzycą typu 2 i postulat konieczności współpracy zespołów wielospecjalistycznych.

Zwracam również uwagę Państwa na niezwykle interesujące w ocenie redakcji prace poglądowe, spośród których artykuł dr. n. med. Michała Marchela i wsp. z Warszawskiego Uniwersytetu Medycznego, poświęcony diagnostyce i terapii pacjentów z chorobami nerwowo-mięśniowymi, został opatrzony równie zajmującym komentarzem dr. hab. n. med. Piotra Bieniasa. Ponadto zapraszam do lektury opisów przypadków oraz bardzo przydatnej w tej chwili, omawiającej aspekty prawne trwającej pandemii, pracy pt. „Coronavirus — some legal aspects concerning physician's dilemmas". Redaktor działu „Kardiologia i prawo" dr n. prawnych Kamila Kocańda zaprosiła do współautorstwa artykułu dyrektora jednej z największych jednostek medycznych w kraju. Uzyskano dzięki temu tego ciekawe spojrzenie na problem nie tylko z punktu widzenia prawnika, ale i menadżera w ochronie zdrowia.

Mając nadzieję na spotkanie *on-line* w trakcie V Konferencji Czasopisma *Folia Cardiologica*, życzę Państwu odporności, zdrowia i miłej lektury

Redaktor Naczelna

B. Wożakowska-Kapłon

prof. dr hab. n. med. Beata Wożakowska-Kapłon

Folia Cardiologica 2020
tom 15, nr 3, strony 193–202
DOI: 10.5603/FC.a2018.0091

ISSN 2353–7752

Morphometry of peripheral arteries in the assessment of the cardiovascular risk

Parametry morfologiczne tętnic obwodowych w ocenie ryzyka sercowo-naczyniowego

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Abstract

Introduction. The aim of the study was to test the hypothesis that ultrasound measurements of common carotid artery (CCAd) and brachial artery (BAd) diameters represent markers of higher coronary artery disease risk (CAD, defined as ≥ 50% reduction in diameter of at least one large coronary artery segment).

Materials and methods. Seventy-one patients (pts) evaluated for suspected stable CAD (23.9% women, age 61.5 ± 7.5) underwent ultrasound measurements of averaged diameters of both common carotid arteries and the brachial artery diameter of dominant arm. Clinical protocol included also: standard medical examination, assessment of biochemical parameters, resting electrocardiography, treadmill exercise test and transthoracic echocardiography. Diagnosis was established using quantitative coronary angiography measurements and calculation of Gensini Score (GS).

Results. Angiographic CAD was present in 43 (60.5%) patients. Average CCAd was larger in CAD group (7.97 ± 0.96 mm vs. 7.37 ± 0.67 mm, p = 0.0052), similar to BAd (5.06 ± 0.65 vs. 4.68 ± 0.75, p = 0.03), respectively. The peripheral arterial diameters correlated with values of GS index, more pronounced for CCAd (ρ = 0.35, p = 0.0023) than for BAd (ρ = 0.24, p = 0.0368). CCAd significantly more positively correlated with the distal coronary artery segments values of the GS index (ρ = 0.35, p = 0.0024), whereas the diameter of BA with the proximal segments values of GS index (ρ = 0.239, p = 0.045). CCA and BD diameters indexed to body surface area (BSA) showed a strong trend toward larger average diameters in CAD patients: CCAd/BSA index: 4.06 ± 0.46 mm/m^2 vs. 3.85 ± 0.56 mm/m^2, p = 0.087, BAd/BSA index: 2.57 ± 0.29 mm/m^2 vs. 2.42 ± 0.35 mm/m^2, p = 0.057. Gensini score significantly correlated with CCAd/BSA index (ρ = 0.24, p = 0.043) with a strong trend of positive correlation between GS index and BAd/BSA index (ρ = 0.21, p = 0.076).

Conclusions. The diameters of common carotid arteries and the brachial artery of dominant arm are greater in CAD pts. Peripheral arteries ultrasound may complement classic diagnostic pathway of stable coronary artery disease.

Key words: coronary artery disease, peripheral arteries ultrasound

Folia Cardiologica 2020; 15, 3: 193–202

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Introduction

Coronary disease is a manifestation of atherosclerotic process which can be present in multiple arterial beds. Therefore imaging of peripheral arteries with ultrasound may complement the understanding of advanced atherosclerotic disease.

Detection of endothelial dysfunction and evaluation of atherosclerotic lesions in peripheral arteries is a useful marker of arterial disease severity and extent.

Non-invasive methods based on ultrasonography the most commonly used techniques for assessing peripheral arterial walls include: assessment of the thickness of the intima media (IMT, intima–media thickness) and evaluation of the flow-dependent expansion of the brachial artery (FMD, flow-mediated dilatation) [1, 2]. Some studies indicated the importance of ultrasound measurement of peripheral arterial diameter at rest, without further evaluation of their vasodilatory reactivity. This concept is based on the theory of vascular remodeling, which is a consequence of exposure to adverse factors leading to damage to the wall of the arteries. The result of this process is a gradual increase in arteries diameters, including both coronary and peripheral circulation. Thanks to advances in the development of high resolution ultrasonography, it has become possible to evaluate vascular remodeling within periphery arteries in vivo, usually using to measure the brachial artery and carotid arteries, which lie superficially and are easy to evaluate by ultrasound [3–5].

The aim of the present study was to evaluate the measurements of brachial artery diameter of dominant arm and both common carotid arteries diameters as markers correlated with the presence of coronary disease.

Material and methods

The study group consisted of 54 men (76.1%) and 17 women (23.9%), average age of 61.5 ± 7.5 years, without symptomatic atherosclerosis of carotid or extremity arteries referred to the tertiary cardiology center for the diagnostics of coronary artery disease. Prior to inclusion, each participant signed informed consent to participate in the study. The study protocol was approved by the Bioethics Committee of the Medical University of Lodz.

The studied group was divided into two subgroups: patients with angiographic confirmation of significant angiographic coronary stenoses [coronary artery disease group (+) — CAD (+)] and a group of patients, without the presence of significant stenoses in the coronary arteries [coronary artery disease group (–) — CAD (–)], defined as ≥ 50% diameter reduction of at least one segment of the large coronary artery (LMCA, LAD, LCx, RCA) or one of their larger primary branches. Based on the results of the coronarography presence of significant stenoses within the coronary arteries was found in 43 (60.6%) patients. Demographic data, prevalence of specific risk factors for coronary artery disease, and coronary angiography details are presented in Table 1.

Table 1. Patients characteristics

Parameter	Mean	Range
Age	61.5 ± 7.5	54–70
Men	54	76.1%
Body mass	81.3 ± 13.7	70.2–90.0
Body mass index [kg/m^2]	27.8 ± 3.6	24.9–31.0
Obesity	22	31%
Smoking	23	32.4%
Diabetes mellitus	20	28.2%
Hypertension	61	85.9%
Chronic kidney disease	3	4.2%
Peripheral artery disease	9	12.7%
Myocardial infarction in past	12	16.9%
1-vessel disease	21	30%
2-vessel disease	11	15.5%
3-vessel disease	11	15.5%
Gensini Score index	27 ± 31.2	0–52.6

The study protocol included clinical examination, resting electrocardiography (ECG), assessment of biochemical markers, transthoracic echocardiography, ECG stress test according to Bruce protocol, and ultrasound measurements of averaged diameters of both common carotid arteries (CCAd) and the brachial artery diameter (BAd) of dominant arm.

Ultrasound measurement of peripheral vascular diameters: common carotid arteries and brachial artery of dominant arm

The bilateral ultrasound examination of common carotid arteries and the brachial artery of dominant arm was made in a B-mode presentation, using ultrasound Logiq400 Pro GE (General Electric) and ultrasound Sonoace PICO (Medison Sonoace), with a linear probe 7.5–9 MHz. The diameter of the vessel was evaluated in end diastolic phase by measuring the distance between the proximal and distal "M" line, which is a boundary between the intima media and the adventitia [6, 7]. All examinations were performed by one ultrasonographer.

During measuring of the common carotid arteries diameters, the subjects were in a supine position with a head arranged in a deviation of approximately 45° with respect to the sagittal plane of the body and in the opposite direction to the examined vessel. Visualization of vessels was performed in their longitudinal projection. The study was performed at approximately 10 mm proximal to the

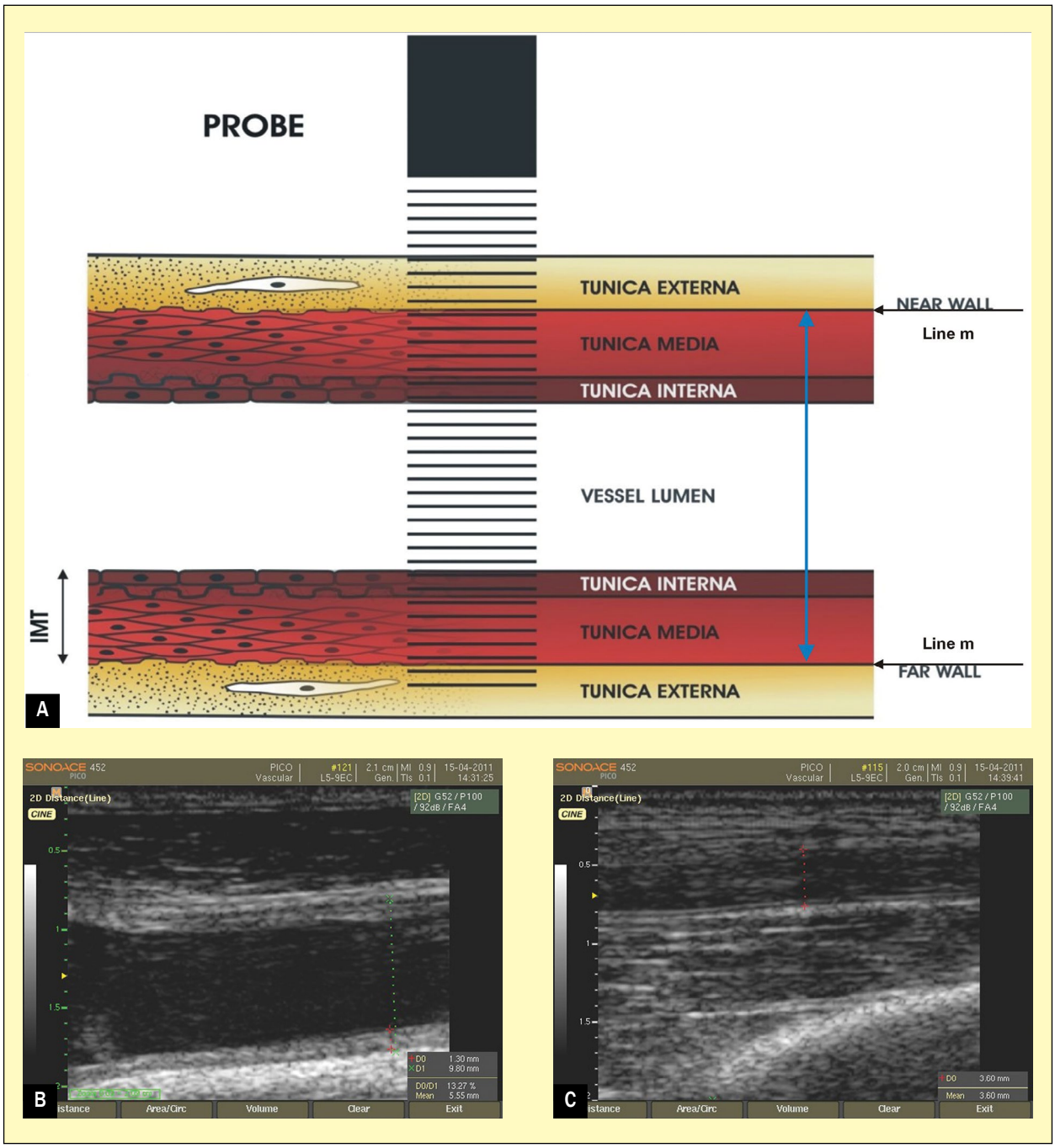

Figure 1A–C. The principle of measuring the diameter of examined peripheral arteries and sample measurements of common carotid artery diameter and measurement of brachial artery diameter

carotid bulb. With regard to the evaluation of brachial artery diameter of dominant arm measurement was taken at 5–10 cm above the bottom of the elbow. The diameter of the examined vessel was determined by averaging 5 heart cycles — Figure 1.

Coronarography

The study was performed in the Hemodynamics Laboratory of the Chair and Department of Cardiology of the Medical University of Lodz on the Innova 2000 angiography (GE Health Care) from radial or femoral access by the Seldinger method. The degree of coronary artery stenosis was assessed visually using quantitative analysis in doubtful cases. Semi-quantitative analysis of atherosclerotic lesions was performed, using Gensini Score, which is the sum of the points assigned to the individual coronary arteries associated with particular segments of the coronary arteries depending on the location of the degree of lumen reduction.

Vascular segments were divided into proximal (proximal Gensini Score) including respectively — LM, p-LAD, LCx-p, p-RCA and distal sections (distal Gensini Score) [8].

Statistical analysis

All quantitative variables were pre-tested for compatibility with the normal distribution in Kolmogorov-Smirnov test. In the presentation of quantitative variables in the case where the variable had normal distribution, the values were expressed as mean ± standard deviation (M ± SD).

In the case of rejecting the normal distribution hypothesis, the median and the interquartile range were used to characterize the variable. Qualitative variables were presented as numbers (n) and percentage participants in the study group. For the comparison of the test and control groups in the situation of positive verification of the hypothesis of normal distribution, the *t*-Student test was used. For more variables, ANOVA variance analysis was used. For non-normal distributions, the Mann-Whitney U test for two variables or the Kruskal-Wallis test for more variables was used.

To assess the strength of relationship between the variables in the study population, the linear correlation coefficients were calculated. For variables with a parametric distribution was used Pearson correlation coefficient (r); for nonparametrically distributed variables — Spearman's rank correlation coefficient (ρ). In order to determine the optimal values of the investigated parameters which might indicate the presence of significant myocardial ischemia, an analysis was performed using ROC (receiver operating curve).

In statistical analysis licensed copy of a computer program MedCalc® (MedCalc Software, Frank Schoonjans 1993-2012, Belgium) version 12.2.1 was used.

Results

Ultrasound characteristics of peripheral arteries, and demographic data

Examined ultrasonographic parameters differed significantly between the genders — in the group of female the mean brachial artery diameter was 4.20 ± 0.66 mm and in the male group it was 5.10 ± 0.59 mm, $p < 0.0001$. The mean value of common carotid arteries on the right side in the female group was 7.42 ± 0.80 mm, and in men it was 7.88 ± 1.0 mm, $p = 0.093$; on the left side it was 7.31 ± 81 mm and 7.83 ± 0.91 mm, respectively, $p = 0.039$; and after averaging the values on both sides, in the female group it was 7.36 ± 0.74 mm, and in men 7.85 ± 0.92 mm, $p = 0.046$.

Analysis of subsequently collected ultrasound data showed that peripheral arterial diameters were different between smokers and non-smokers. The mean value of common carotid arteries diameters in non-smokers was 7.54 ± 0.70 mm and in smokers 8.14 ± 0.84 mm, $p = 0.007$, and brachial diameters were 4.78 ± 0.72 mm and 5.18 ± 0.61 mm, respectively, $p = 0.027$.

Correlation analysis of examined ultrasonographic parameters with body surface index (BSA) showed their association, especially with regard to brachial artery diameter ($r = 0.52$, $p < 0.0001$). Similar correlations were observed in the analysis of patients' growth. These differences may explain the dissimilarities observed between male and female patients. The collected data are presented in Table 2.

In the analysis of ultrasonographic parameters indexed to the body surface area, a significantly greater carotid artery diameter was found in women compared to men ($p = 0.02$), which was not observed with respect to the brachial artery — Table 3.

Measurement of peripheral arterial diameters, and the results of echocardiography

Carotid and brachial artery dimensions correlated with echocardiographic parameters — Table 4. The left atrial size correlated with the diameter of common carotid artery and brachial artery ($r = 0.26$, $p = 0.028$, $r = 0.42$, $p = 0.0002$). The thickness of the end-systolic interventricular septum correlated with the diameter of the brachial artery ($r = 0.24$, $p = 0.04$). The thickness of the end-diastolic interventricular septum correlated with the diameter of the common carotid artery and the brachial artery ($\rho = 0.24$, $p = 0.04$, $\rho = 0.3$, $p = 0.009$). The thickness of the posterior myocardial wall correlated with brachial artery diameter ($\rho = 0.33$, $p = 0.004$). The thickness of the end-diastolic posterior wall, correlated both with common carotid arteries ($\rho = 0.27$, $p = 0.02$) and brachial artery diameter ($\rho = 0.31$, $p = 0.008$). A parameter strongly associated with the larger arterial diameters was also the left ventricular myocardial mass.

The dimensions of the arteries and the results of coronary angiography

Analysis of collected data from coronary angiography and peripheral vascular ultrasonography revealed that the diameters of the peripheral arteries examined in groups with confirmed or absent angiographic CAD differed significantly. On average, the diameter of the common carotid artery was 7.97 ± 0.96 mm in patients with significant angiographic lesions and 7.37 ± 0.67 mm in the group without coronary artery disease, $p = 0.005$. Brachial artery diameters were 5.06 ± 0.65 mm and 4.68 ± 0.75 mm, respectively, $p = 0.03$. A strong trend for larger diameters of the arteries in patients with coronary artery disease remained after BSA indexation — Table 5.

Table 6 and Figure 2 show descriptive analysis of the examined ultrasonographic parameters in subgroups of patients differing in the number of narrowed major epicardial coronary arteries. Unindexed diameters of common carotid arteries in patients with one-vessel disease and three-vessel disease were significantly larger than in those without CAD.

Table 2. Analysis of the relationship between ultrasound parameters and demographic data

Variable	Mean ØCCA [mm]	Mean ØCCA [mm]/BSA	ØBA [mm]	ØBA [mm]/BSA
CCS class	ρ = 0.188	**ρ = 0.23**	ρ = 0.06	ρ = 0.12
	p = 0.11	**p = 0.047**	p = 0.58	p = 0.29
NYHA class	**ρ = 0.297**	ρ = 0.14	ρ = 0.05	ρ = –0.05
	p = 0.011	p = 0.23	p = 0.67	p = 0.68
Age	r = 0.2	**r = 0.37**	r = –0.13	r = 0.02
	p = 0.08	**p = 0.001**	p = 0.25	p = 0.85
Diabetes mellitus	p = 0.09*	p = 0.14*	p = 0.3*	p = 0.26*
Hypertension	p = 0.72*	p = 0.49*	p = 0.91*	p = 0.68*
Smoking	**p = 0.007***	**p = 0.047***	**p = 0.0268***	**p = 0.039***
Peripheral artery disease	p = 0.61*	p = 0.86*	p = 0.33*	p = 0.54*
BMI [kg/m^2]	r = 0.19	**r = –0.31**	r = 0.18	**r = –0.28**
	p = 0.1	**p = 0.006**	p = 0.12	**p = 0.01**
BSA [m^2]	**r = 0.29**	–	**r = 0.52**	–
	p = 0.01		**p < 0.0001**	
Height [cm]	**r = 0.257**	**r = –0.34**	**r = 0.49**	r = –0.003
	p = 0.03	**p = 0.003**	**p < 0.0001**	p = 0.98
Sex	**p = 0.046***		**p < 0.0001***	

In the table are compiled the Pearson r correlation coefficients and the Spearman correlation coefficients. The value of "p" calculated using the t test for independent samples*; p — level of statistical significance; ØCCA mean — arithmetic mean of carotid artery diameter; ØBA — diameter of the brachial artery of dominant arm; CCS — Canadian Cardiovascular Society; NYHA — New York Heart Association; BMI — body mass index; BSA — body surface area

Table 3. Analysis of the index values — the diameter of brachial artery diameter and common carotid arteries to body surface area (BSA) according to gender

Parameter	Men n = 54	Female n = 17	p
ØRCCA/BSA	3.91 ± 0.55	4.26 ± 0.51	**0.026**
ØLCCA/BSA	3.89 ± 0.49	4.19 ± 0.46	**0.03**
Mean ØCCA/BSA	3.9 ± 0.51	4.2 ± 0.44	**0.02**
Mean ØBA/BSA	2.54 ± 0.31	2.42 ± 0.35	0.19

The value of "p" calculated using the t-test for independent samples; p — level of statistical significance; ØCCA mean — arithmetic mean of carotid artery diameter; ØBA — diameter of the brachial artery of dominant arm; BSA — body surface index

Arterial diameters were correlated with Gensini Score more significantly for the common carotid artery (ρ = 0.35, p = 0.0023) than the brachial artery (ρ = 0.24, p = 0.0368). The mean diameter of common carotid arteries significantly correlated with the Gensini Score index of the distal coronary arteries segments (ρ = 0.35, p = 0.0024), while the brachial artery diameter with the Gensini Score index of the proximal segments (ρ = 0.239, p = 0.045). After indexation to BSA, only dimension of common arteries significantly correlated with the values of Gensini Score index — Table 7 and Figure 3.

The presence of angiographically significant CAD was predicted by common carotid artery diameter > 7.6 mm with a sensitivity of 62.8% and a specificity of 75.0% (area under ROC curve — 0.697; 95% CI: 0.577–0.801), positive and negative predictive values were 79.4% and 56.7% respectively, and accuracy was 67.6%. Analysis of the ROC curve for brachial artery diameter > 4.9 mm showed a prognostic value for the presence of significant coronary stenoses with a sensitivity of 69.8% and a specificity of 60.7% (area under ROC curve — 0.653, 95% CI: 0.53–0.762), positive and negative predictive values were 73.2% and 56.7%, respectively, accuracy of 66.2%.

Table 4. Correlation analysis of selected parameters of echocardiography with peripheral vascular ultrasonography

Variables	Mean ØCCA [mm]	Mean ØCCA [mm]/BSA	ØBA [mm]	Mean ØBA [mm]/BSA
LV systolic diameter [mm]	r = 0.13	r = –0.11	r = –0.02	r = –0.06
	p = 0.28	p = 0.35	p = 0.88	p = 0.58
LV diastolic diameter [mm]	r = 0.17	r = 0.7	r = 0.19	r = –0.025
	p = 0.16	p = 0.54	p = 0.11	p = 0.83
Left atrium diameter [mm]	**r = 0.26**	**r = –0.24**	**r = 0.43**	r = 0.02
	p = 0.028	**p = 0.04**	**p = 0.0002**	p = 0.84
Aortic diameter [mm]	r = –0.006	**r = –0.25**	r = 0.2	r = –0.03
	p = 0.95	**p = 0.03**	p = 0.09	p = 0.80
Right ventricular diameter [mm]	r = –0.08	**r = –0.25**	r = 0.04	r = –0.12
	p = 0.5	**p = 0.029**	p = 0.7	p = 0.29
Septal thickness systolic diameter [mm]	r = 0.14	r = –0.0002	**r = 0.24**	r = 0.09
	p = 0.24	p = 0.99	**p = 0.04**	p = 0.43
Septal thickness diastolic diameter [mm]	**ρ = 0.24**	r = –0.038	**ρ = 0.3**	r = 0.04
	p = 0.04	p = 0.75	**p = 0.009**	p = 0.7
Posterior wall thickness systolic diameter [mm]	ρ = 0.12	r = 0.1	**ρ = 0.33**	r = 0.18
	p = 0.3	p = 0.4	**p = 0.004**	p = 0.11
Posterior wall thickness diastolic diameter [mm]	**ρ = 0.27**	r = –0.027	**ρ = 0.31**	r = 0.19
	p = 0.02	p = 0.82	**p = 0.008**	p = 0.1
Ejection fraction [%]	r = –0.1	r =–0.17	r = –0.16	**r = –0.27**
	p = 0.37	p = 0.16	p = 0.16	**p = 0.02**
LV mass [g]	r = 0.32	r =–0.01	**r = 0.3**	r = 0.05
	p = 0.057	ρ = 0.92	**p = 0.009**	ρ = 0.67
LV mass index [g/m^2]	r = 0.13	r = 0.06	r = 0.18	r = 0.14
	p = 0.27	p = 0.62	p = 0.12	p = 0.23

The table summarizes the Pearson r correlation coefficients and the Spearman correlation coefficients. p — level of statistical significance; LV — left ventricle

Table 5. Analysis of brachial artery diameter and carotid artery diameter

Parameter	CAD (+) n = 43	CAD (–) n = 28	p
ØRCCA [mm]	8.05 ± 0.99	7.33 ± 0.75	**0.002**
ØRCCA/BSA	4.1 ± 0.5	3.83 ± 0.61	**0.049**
ØLCCA [mm]	7.9 ± 0.98	7.42 ± 0.70	**0.03**
ØLCCA/BSA	4.02 ± 0.45	3.87 ± 0.55	0.21
Mean ØCCA [mm]	7.97 ± 0.96	7.37 ± 0.67	**0.005**
Mean ØCCA/BSA	4.06 ± 0.46	3.85 ± 0.56	0.087
ØBA [mm]	5.06 ± 0.65	4.68 ± 0.75	**0.03**
ØBA/BSA	2.57 ± 0.29	2.42 ± 0.35	0.057

ØRCCA — diameter of the right common carotid artery; ØLCCA — diameter of the left common carotid artery; ØCCA mean-arithmetic mean of carotid arteries diameters; ØBA — diameter of the brachial artery of dominant arm; BSA — body surface area; CAD (+) — group with coronary artery disease; CAD (–) — group without coronary artery disease

Table 6. Results of measurements of brachial arterial diameter and carotid arteries diameters before and after indexing to the body surface area according to the number of significant stenoses in the main epicardial arteries

Parameter	Without CAD n = 28	1-vessel disease n = 21	2-vessel disease n = 11	3-vessel disease n = 11	p
ØRCCA [mm]	7.33 ± 0.75	8.02 ± 1.05	7.65 ± 0.88	8.5 ± 0.89	**0.002**
ØLCCA [mm]	7.42 ± 0.70	7.9 ± 1.0	7.48 ± 0.66	8.3 ± 1.1	**0.025**
Mean ØCCC [mm]	7.37 ± 0.67	7.96 ± 0.99	7.57 ± 0.75	8.4 ± 0.97	**0.005**
ØBA [mm]	4.68 ± 0.75	4.96 ± 0.6	5.1 ± 0.59	5.2 ± 0.81	0.139
ØRCCA/BSA	3.83 ± 0.61	4.13 ± 55	3.92 ± 0.47	4.24 ± 0.41	0.12
ØLCCA/BSA	3.87 ± 0.55	4.0 ± 0.5	3.83 ± 0.39	4.12 ± 0.4	0.29
Mean ØCCA/BSA	3.85 ± 0.56	4.1 ± 0.51	3.88 ± 0.42	4.18 ± 0.37	0.19
ØBA/BSA	2.42 ± 0.35	2.55 ± 0.28	2.6 ± 0.29	2.58 ± 0.32	0.28

The "p" value calculated using the ANOVA variance test; p — level of statistical significance; ØRCCA — diameter of the right common carotid artery; ØLCCA — diameter of the left common carotid artery; ØCCA mean — arithmetic mean of carotid arteries diameters; ØBA — diameter of the brachial artery of dominant arm

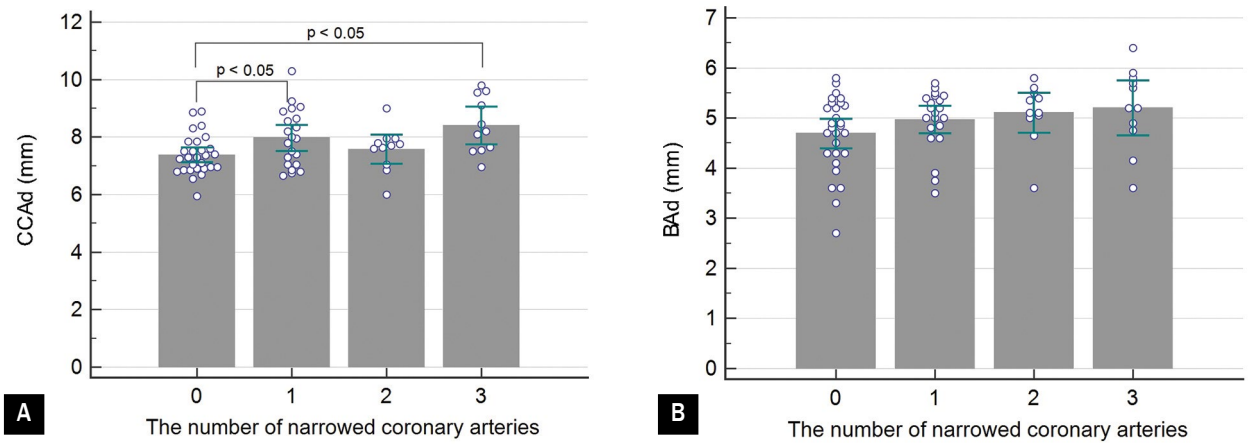

Figure 2. Comparison of the average diameters of common carotid arteries (CCA; **A**) and the brachial artery diameter (BA; **B**) depending on the number of coronary arteries with angiographically significant stenoses

Discussion

The results of the present study indicate that remodeling and dilatation of large arteries may be related to coronary atherosclerotic process.

Initial prospective experimental studies assessing the diameters of the peripheral arteries were conducted on animal models in which an inadequate increase in the diameters of arteries in response to an atherogenic diet rich in saturated fatty acids was observed. One of the first researchers who described this relationship in humans were Glagov and Zarins, evaluating autopsy correlations between arterial diameter and degree of atherosclerotic lesions within coronary arteries [9, 10]. Vascular remodeling has been demonstrated as a compensatory arterial response to progression of atherosclerosis to maintain adequate vascular flow. Further experiments have shown that progression and maintenance of this process is possible to a certain level, after which it comes to the predominance of "vasoconstrictive" atherosclerotic plaques, which may result in both gradual vasoconstriction and sudden rupture of existing atherosclerotic plaques.

It has been proven that both too small and excessive shear forces acting on the vessel wall contribute to abnormal cellular reaction of the intima, resulting in their hypertrophy and pathological vascular remodeling.

The results of the studies demonstrate the interdependence of observed vascular changes, with risk factors for atherosclerosis [11–13]. Previous publications suggested the predictive value of measurements of resting brachial artery diameter is similar to flow-mediated dilation (FMD) examination with regard to the risk of coronary disease. Importantly, measuring arterial diameter is easier and less time consuming. It was confirmed by work published by Yeboah at al. [14]. It has been demonstrated that, after taking into account additional risk factors such as gender, age, type 2 diabetes, hypertension, nicotine addiction, larger brachial artery diameter positively correlated with

Table 7. Analysis of the correlation between the values of the diameters of the examined arteries, and values of the Gensini Score index

Variable	Gensini Score	Proximal Gensini Score	Distal Gensini Score
ØRCCA [mm]	**ρ = 0.4**	ρ = 0.24	**ρ = 0.38**
	p = 0.0006	**p = 0.04**	**p = 0.0009**
ØLCCA [mm]	**ρ = 0.26**	ρ = 0.11	**ρ = 0.29**
	p = 0.025	p = 0.33	**p = 0.013**
Mean ØCCA [mm]	**ρ = 0.35**	ρ = 0.2	**ρ = 0.35**
	p = 0.0023	p = 0.082	**p = 0.0024**
ØBA [mm]	**ρ = 0.24**	**ρ = 0.239**	ρ = 0.18
	p = 0.0368	**p = 0.045**	p = 0.118
Mean ØCCA/BSA	**ρ = 0.24**	ρ = 0.13	ρ = 0.2
	p = 0.043	p= 0.27	p= 0.09
ØBA/BSA	ρ = 0.21	ρ = 0.19	ρ = 0.12
	p = 0.076	p = 0.09	p = 0.29

ØRCCA — diameter of the right common carotid artery; ØLCCA — diameter of the left common carotid artery; ØCCA mean — arithmetic mean diameter of the carotid arteries; ØBA — diameter of the brachial artery of dominant arm

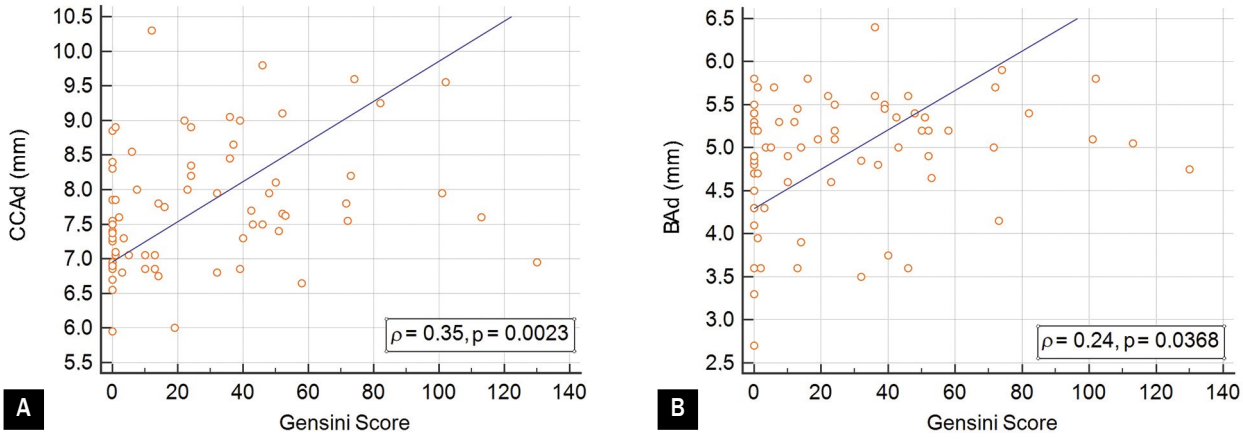

Figure 3A, B. Correlations of carotid artery diameters and brachial artery diameter with Gensini Score index

cardiovascular events. The median diameter of this vessel at rest was 5.1 mm for men and 4.06 mm for women. With an increase in diameter of the brachial artery above 1 mm in average, the risk of cardiovascular events increased by approximately 1.12 times (1.02 to 1.28) [14].

Another study that demonstrated diagnostic usefulness of the assessment of brachial artery diameter at rest was work carried out by Holubkov et al. [15]. This study conducted on a group of 376 women confirmed that the increase in artery diameter at rest positively correlated with the degree of coronary atherosclerosis assessed in coronarography. After adjusting for age, body weight and other risk factors of coronary artery disease, it was demonstrated that the probability of significant atherosclerotic lesions in the coronary arteries (> 50% stenosis in ≥ 1 vessels) was approximately 3.6 times greater in women with brachial artery diameter greater than 4.1 mm than in women with brachial artery diameter at rest below 3.6 mm [15]. In another study, Montalcini et al. [16] evaluated correlations of IMT values and the presence of atherosclerotic plaques in carotid arteries with resting brachial artery diameters in diastole. The study was conducted on 166 postmenopausal women. The presence of significant atherosclerotic lesions in carotid arteries was associated with a significantly larger diameter of both of these vessels as well as the brachial artery. The mean diameter in the control group was 6.86 mm and 6.75 mm for the right and left carotid artery and in the group with the presence of significant atherosclerosis it was 7.3 mm and 7.06 mm, respectively. For brachial arteries these values were 3.57 mm and 3.82 mm, respectively [16]. A similar correlation was observed in the analysis by Steinke et al. which also demonstrated a significant correlation between

the presence of atherosclerotic plaques and carotid artery enlargement [4]. Additionally, some data suggest prognostic implications of larger arterial diameter.

Our study reproduces these finding in the Polish population. Among the analyzed echocardiographic data, larger diameters of examined peripheral arteries correlated also with left ventricular mass and left atrial size. The association between the thickness of the ventricular septum and the posterior wall of the left ventricle with larger diameters of the arteries was also present.

Regarding the average values of the diameters of common carotid arteries and the brachial artery in patients with significant coronary atherosclerotic lesions, they were significantly higher; however, after indexing of the examined parameters to body surface area, the relationships decreased to the trend level. Similar significant correlations were observed after the use of semi-quantitative analysis of atherosclerotic lesions in coronary arteries expressed as Gensini Score index. After indexation by BSA, significant correlation was found only with respect to the common carotid artery — $\rho = 0.24$, $p = 0.043$. These results correspond to the results reported by Mirek where larger carotid arteries and femoral artery were observed with more advanced coronary atherosclerotic lesions assessed both quantitatively and with Gensini Score index [17].

The abovementioned publications and observations based on ongoing analysis indicate that the diameter of the examined vessel also should be taken into account in the ultrasound assessment of peripheral vascular morphology. Ultrasonographic evaluation of peripheral vascular morphology can, indirectly, also provide information of coronary artery status, allowing, in combination with classical coronary artery disease risk factors and the results of other studies, improved classification of patients for more advanced diagnostics methods and consequently proper treatment.

Conclusions

The results of the current study confirm that ultrasound assessment of peripheral arterial diameter may contribute to atherosclerotic risk assessment. Optimal presentation of these parameters including indexation is subject to future research.

Conflict of interest

The authors declare that there is no conflict of interest

Streszczenie

Wstęp. Celem badania była weryfikacja hipotezy, czy ultrasonograficzny pomiar średnic tętnic szyjnych wspólnych (CCAd) i tętnicy ramiennej (BAd) może stanowić marker zwiększonego ryzyka wystąpienia choroby wieńcowej (CAD), definiowanej jako zwężenie większe lub równe 50% średnicy co najmniej jednego segmentu dużej tętnicy wieńcowej.

Materiały i metody. Diagnozowanych w kierunku choroby wieńcowej 71 pacjentów (23,9% kobiet, średni wiek 61,5 ± 7,5) poddano ultrasonograficznej ocenie średnic obu tętnic szyjnych wspólnych i tętnicy ramiennej dominującej kończyny górnej. Protokół badania obejmował również ocenę kliniczną, ocenę wskaźników biochemicznych, spoczynkowy zapis elektrokardiograficzny, elektrokardiograficzny test wysiłkowy, przezklatkowe badanie echokardiograficzne, z weryfikacją wyników w koronarografii i oceną zmian w naczyniach wieńcowych metodą cyfrowej angiografii ilościowej i wyliczeniem wskaźnika Gensiniego (GS).

Wyniki. Obecność istotnych zwężeń w koronarografii stwierdzono u 43 (60,5%) pacjentów. Średnia wartość CCAd była większa u pacjentów z CAD (7,97 ± 0,96 mm *vs.* 7,37 ± 0,67 mm; p = 0,0052), podobnie jak wartość BAd (5,06 ± 0,65 *vs.* 4,68 ± 0,75; p = 0,03). Wartości średnic tętnic obwodowych korelowały ze wskaźnikiem GS bardziej wyraźnie w przypadku CCAd ($\rho = 0,35$; p = 0,0023) niż dla BAd ($\rho = 0,24$; p = 0,0368). Wartości CCAd znacząco wyraźniej dodatnio korelowały z dystalnymi segmentami ($\rho = 0,35$; p = 0,0024), natomiast średnica BA — z proksymalnymi segmentami tętnic wieńcowych ocenianych według GS ($\rho = 0,239$; p = 0,045). Po zastosowaniu metody indeksacji do pola powierzchni ciała (BSA) stwierdzono obecność silnego trendu w kierunku wyższych wartości średnic badanych tętnic obwodowych wśród pacjentów z chorobą wieńcową — wskaźnik CCAd/BSA: 4,06 ± 0,46 mm/m^2 *vs.* 3,85 ± 0,56 mm/m^2, p = 0,087, wskaźnik BAd/BSA: 2,57 ± 0,29 mm/m^2 *vs.* 2,42 ± 0,35 mm/m^2, p = 0,057. Wskaźnik Gensiniego znacząco korelował z indeksem CCAd/BSA ($\rho = 0,24$; p = 0,043) oraz wykazano dodatni trend w korelacji między wskaźnikiem GS i indeksem BAd/BSA ($\rho = 0,21$; p = 0,076).

Wnioski. Średnice tętnic szyjnych wspólnych i średnicy ramiennej dominującej kończyny górnej są większe u pacjentów z CAD. Ultrasonografia tętnic obwodowych może stanowić uzupełniającą metodę w diagnostyce CAD.

Słowa kluczowe: choroba wieńcowa, ultrasonografia tętnic obwodowych

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Folia Cardiologica 2020
tom 15, nr 3, strony 203–209
DOI: 10.5603/FC.a2018.0099

ISSN 2353–7752

Radiation exposure reduction during atrial fibrillation ablation in real-life population using fluoroscopy and 3D mapping system integration

Redukcja ekspozycji na promieniowanie podczas ablacji migotania przedsionków z wykorzystaniem systemu elektroanatomicznego 3D zintegrowanego z fluoroskopią w codziennej praktyce klinicznej

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Abstract

Introduction. Fluoroscopy integration with three dimensional (3D) electroanatomical mapping system may allow dose reduction while invasive electrophysiological procedures. In this retrospective study we present real-population experience with integrated model.

Material and methods. Ninety-six patients with paroxysmal atrial fibrillation (AF) after radiofrequency pulmonary vein isolation have been analyzed. In 48 patients, 3D mapping system integrated with fluoroscopy (Carto 3 UniVu) has been used. Clinical and peri-procedural data, inclusive, fluoroscopy time and dose, in-hospital complications and efficacy rate at 6 months have been compared.

Results. Patients treated with classic 3D mapping system were significantly older ($p = 0.036$). Both fluoroscopy mean time (11.6 ± 4.3 vs. 6.7 ± 2.9 minutes, $p < 0.05$) and a median of the fluoroscopy dose [460.0 (IQR: 288.0–785.5) vs. 271.0 (IQR 145.0–535.0) mGy, $p < 0.05$] have been significantly reduced by using Carto3 UniVu. Total procedure time was comparable between groups. Periprocedural complications and recurrence of clinical arrhythmia rate in 6-month follow-up were comparable.

Conclusions. Utilization of novel 3D mapping systems with classic fluoroscopy integration supports the radiation time and the dose reduction during AF ablation procedure, without any adverse impact on the total procedure time, complication or success rate. This real-life population results corresponds with previously presented prospective studies.

Key words: atrial fibrillation, fluoroscopy, radiofrequency catheter ablation, radiation protection, medical imaging

Folia Cardiologica 2020; 15, 3: 203–209

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Introduction

The ablation of atrial fibrillation (AF) with the usage of the radiofrequency energy (RF) is a well-established and widely performed procedure in electrophysiology (EP) laboratories [1]. However, high radiation doses during a single procedure, a repetitive exposure of the electrophysiology lab personnel as well as possible genetic consequences [2] gave rise to the persistent search for the new ways of radiation exposure reduction.

Implementation of electroanatomical systems in a daily clinical practice has significantly reduced the applied doses in a single procedure [1, 3, 4]. The current studies focusing on the complex left atrial ablation undermine the necessity of X-ray radiation in such procedures [5]. Therefore, further investigation to optimize the navigation and to reduce the radiation exposure is needed. One of the possible ways is the integration of classical fluoroscopy and the 3D model created with electroanatomical system [6, 7].

This work is aimed to demonstrate the clinical experience in radiofrequency ablation of atrial fibrillation using the integrated module in real-life population.

Material and methods

Study objectives

To show the possible improvement in efficacy and safety as well as fluoroscopy time reduction during AF ablation with integrated mapping module (Carto 3 UniVu™), the clinical, peri-procedure data, in-hospital complications and efficacy at 6th month after the ablation with classic 3D mapping system have been compared.

Technology description

UniVu™ is the Carto 3 module that allows integrating entirely the classic fluoroscopy image with electroanatomical maps (EAM). In order to obtain an integrated image, two additional components are needed: a registration plate — mounted on the location pad — and the software component. A complete localizing calibration during each consecutive procedure — "registration" — is achieved through the capture of the disc marker located on the Registration plate. After the "registration", prerecorded single X-ray images, fluoroscopy video loops or left atrium (LA) angiographies could be transferred to mapping system and combined with EAM. Such approach allows to project the catheters on those images in real-time and repeated utilization of fluoroscopy is not necessary. Two different views can be used simultaneously. Other technical details of this module have previously been described [6, 7].

Population

The population study consists of 96 patients with the symptomatic, documented, drug-resistant paroxysmal AF, who have undergone pulmonary vein isolation between May 2014 and May 2015. The patients were included into analysis, if were > 18 years old. The exclusion criteria were: prior AF ablations, significant enlargement of left atrium in transthoracic echocardiography (TTE) — defined as LA > 55 mm in TTE long axis view — or the need for LA substrate modification with the additional ablations lines.

Pre-ablation procedure

Prior to the admission the computer tomography (CT) for 3D cardiac imaging was performed. On admission to hospital all patients underwent clinical examination, laboratory check and transesophageal echocardiography (TEE) for the recognition of the intra-cardiac thrombi. If thrombus was found, the patient was not qualified to the procedure, and the ablation was postponed. Medication with vitamin K antagonists (VKA) and novel anticoagulant drugs (NOAC) was interrupted one day prior admission and withdrawn during hospitalization. In patient with INR < 2.0 or in patients on NOAC, the additional low molecular weight heparin (LMWH) was administered.

Anti-arrhythmic medication was continued during the hospital stay and modified if needed.

Catheter ablation procedure

All procedures were performed by two experienced operators (> 5 years of experience in EP studies and AF ablations). The procedures were performed, after written informed consent, under general anesthesia using sevoflurane and/or propofol with boluses of midazolam and fentanyl. During the whole procedure time the patients stayed under anesthetist control. For invasive blood pressure monitoring, routinely radial approach was used. The intraesophageal temperature feedback during the ablation was achieved by the usage of a temperature probe (SensiTherm, St. Jude Medical). After veins punctures, decapolar steerable coronary sinus catheter and quadric-polar non-steerable right ventricular apex catheter were placed under fluoroscopy guidance. A single transseptal puncture (TSP) was performed directly with the use of steerable sheath — Agilis, St. Jude Medical, St Paul, MN). After TSP, heparin was administrated and added to achieve ACT level of 300–350 s. In the case of AF ablation with UniVu™ Module after positioning of the diagnostic catheters and fluoroscopy guided TSP, localizations reference for UniVu™ Module were registered. Thereafter, routinely right anterior oblique (RAO), left anterior oblique (LAO) and posterior-anterior (PA) cine loops were captured (Figure 1). The electroanatomical map of LA was created and merged with reconstructed CT scans. In patients ablated with UniVu™ Module obtained additional fluoroscopy information (cine loops) were used to facilitate the CT merging. For LA mapping and ablation, pre-recorded cine loops were used predominantly. The level of temperature probe in the esophagus in reference

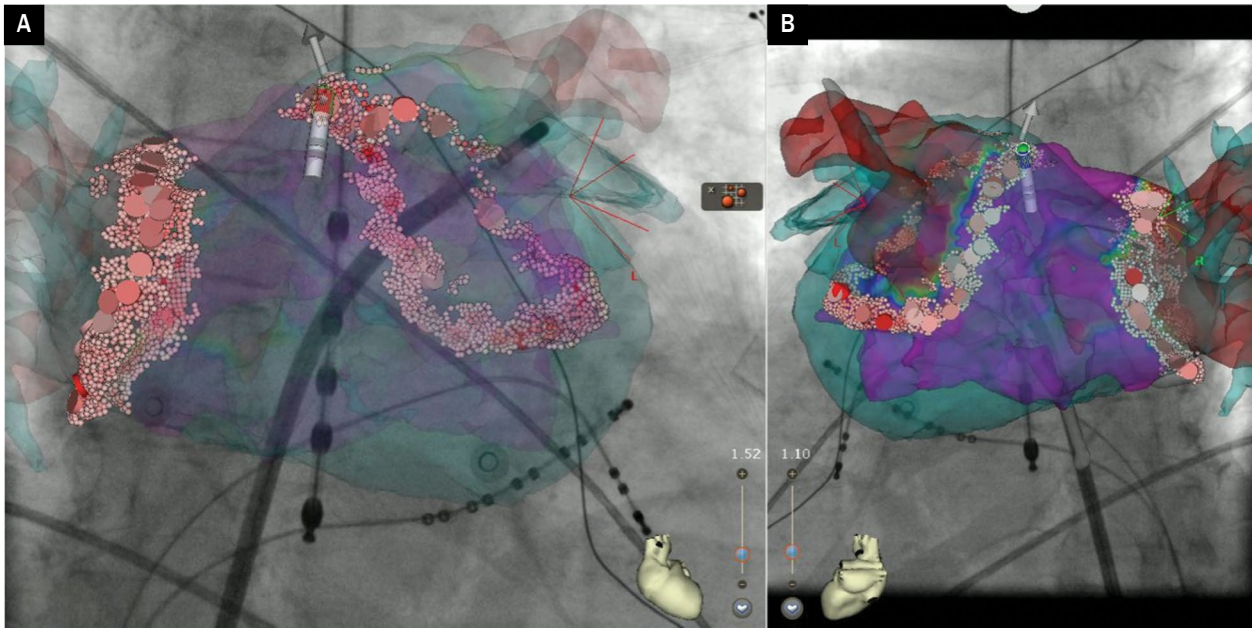

Figure 1A, B. Standard right anterior oblique (RAO) 30 and posterior-anterior (PA) position captured with integrated fluoroscopy

to ablation catheter was controlled using fluoroscopy. All mapping and RF ablation were performed with the same ablations catheter: F or D-type, irrigated tip, Thermocool® SmartTouch™ Catheter (Biosence Webster, Inc., Diamond Bar, CA) which allowed for the measurements of catheter contact force. For ablation, a maximum power of 35 Watts, upper temperature limit of 43°C and flow rate of 30 mL/min were set. Maximal power delivered at posterior wall and near esophagus was reduced and adapted according to the intraesophageal temperature. To avoid the atrio-esophageal fistula, intraesophageal temperature was limited to 41°C [8]. In all cases, the circumferential ablation around the pulmonary veins (PV) was performed. The acute success of the procedure was defined as the bidirectional conduction block for PV isolations lesions after 20 minutes from the last application proven by both: pacing along ablation line with mapping catheter (MAP), thereafter with a multipolar spiral mapping catheter (Lasso® eco NAV catheter, Biosense Webster) introduced via Agillis after MAP removal. After ablation and removal of the Agilis sheath from LA, protamine was administered to the reverse heparin. If the activated clot time was lower than 200 seconds, the femoral sheaths were removed. LMWH was continued 6 hours after the procedure (after exclusion of groin complications and pericardial effusion in TTE). We recommend continuing previous anticoagulation therapy after the procedure.

Between May and November 2014 only the Carto 3 electroanatomical mapping system was used (Carto 3 group). UniVu™ Module was not available. Thereafter, during consecutive 6 months, we performed AF ablations only with Carto UniVu™ support (UniVu group).

Analyzed parameters

Demographics data and body mass measurements were collected on the day of admission. For the calculation of the stroke risk and bleeding risk, CHA_2DS_2-VASc score and HAS-BLED score were used. LA diameter was measured in a TTE parasternal long-axis view and the LA area was measured in an apical four-chamber view. The total procedure time was measured from the first femoral puncture to the removal of all sheaths. All patients have been controlled and undergone 7-days Holter electrocardiogram monitoring in our outpatient clinic after 3 and 6 months form hospital discharge.

Statistical analysis

Continuous parameters with normal distribution were presented as an arithmetic mean ± standard deviation, while qualitative parameters were presented as percentages. The parameters the distribution of which was found to be different than normal were presented as a median with an interquartile range (IQR). The differences regarding clinical and periprocedural parameters were compared with *t*-Student, λ^2 test or U-Mann Whitney respectively. Statistical significance was considered by $p \leq 0.05$ bilateral. All analyses were conducted using Statistica 10.0.

Results

Study population, efficacy and safety endpoints

We analyzed 96 patients with paroxysmal atrial fibrillation, who have undergone PV isolation with 3D electroanatomical

Table 1. Baseline characteristics

	All (n = 96)	Carto 3 group (n = 48)	UniVu group (n = 48)	p
Demographics date				
Age [years]	58 ± 10	60 ± 11	56 ± 9	**0.036**
Male [%]	63.5	66.7	60.4	0.53
Weight [kg]	79 ± 17	90 ± 14	89 ± 17	0.78
BMI [kg/m^2]	29.4	29.2	30.1	0.73
	[25.7–33.1]	[27.1–31.6]	[25.3–33.4]	
Hypertension [%]	71.2	72.9	70.8	0.82
Diabetes [%]	25.0	18.8	31.3	0.16
CHA_2DS_2-VASc	1.0	2.0	1.0	0.13
	[1.0–3.0]	[1.0–3.0]	[1.0–2.0]	
HAS-BLED	1.0	1.0	1.0	0.28
	[1.0–1.0]	[0.0–2.0]	[0.0–1.0]	
Echocardiographic parameters				
LVEF [%]	55 ± 7	55 ± 5	55 ± 8	0.98
LA diameter [mm]	42.0 ± 4.5	42.2 ± 4.6	41.0 ± 4.6	0.21
LA diameter ≥ 40 mm [%]	64.6	70.8	58.3	0.25
LA area [cm^2]	21 ± 4.8	21.6 ± 3.3	20.9 ± 5.6	0.64

BMI — body mass index; LVEF — left ventricular ejection fraction; LA — left atrium

mapping system. We included 48 consecutive patients both in Carto 3 group and UniVu group. Patients treated with the support of UniVu™ Module were younger (p = 0.036). No further statistical differences in demographic and echocardiographic data were observed (Table 1). Furthermore, neither total procedure time (140 ± 27 vs. 149 ± 24 minutes, p = NS) nor the acute success rate (100% vs. 100%, p = 1.0) were significantly different. The rate of complications and in-hospital AF episodes after the ablation were comparable in both groups. During the hospital stay there were noted complications such as: two hematomas and one femoral bleeding that needed blood transfusion. After 6 months of follow-up 78.2% of the patients of the whole study population were free from arrhythmia. There were no statistically significant differences between two compared groups (Table 2).

Fluoroscopy

In the UniVu group, a significant reduction in the mean total fluoroscopy time (11.6 ± 4.3 vs. 6.7 ± 2.9 minutes, p < 0.05) was observed. The decrease corresponded to a reduction of the median total fluoroscopy dose [460.0 (IQR: 288.0–785.5) vs. 271.0 (IQR: 145.0–535.0) mGy, p < 0.05]. The results of the radiation exposure are presented in the Table 2.

Learning curve

Out of 48 patients ablated with an integrated module, a radiation exposure data of the first 10 patients and the next 38 patients were compared. The growing operators' work experience with the integrated module allowed a significant reduction in the total fluoroscopy time (8.3 ± 3.0 vs. 6.3 ± ± 2.8 min, p = 0.044).

Discussion

In our study we found that the usage of an integrated model of classic fluoroscopy and 3D mapping system is a feasible and effective technology for the interventional AF ablation. The usage of it shows the same acute success rate in the same procedure time with a lower use of the total fluoroscopic time and dose. These results correspond with data obtained from prospective studies [6, 7].

The usage of 3D mapping systems as a clinical routine in an interventional electrophysiology was correlated with the reduction of the total fluoroscopy time and dose. Estner et al. [9] in a prospective randomized study demonstrated a significant reduction in the total fluoroscopy exposure time (p < 0.01) and dose (p = 0.03) in patients who underwent catheter ablation for drug refractory AF using 3D system. The same group from Italy [10] compared clinical

Table 2. Periprocedural and outcome data depending on the used 3D mapping system

	All (n = 96)	Carto 3 group (n = 48)	UniVu group (n = 48)	p
Periprocedural data				
Total procedure time [min]	144 ± 26	140 ± 27	149 ± 24	0.07
Total fluoroscopy dose [mGy]	345.5 [221.3–682.3]	460.0 [288.0–785.5]	271.0 [145.0–535.0]	**0.001**
Total fluoroscopy time [min]	9.2 ± 4.4	11.6 ± 4.3	6.7 ± 2.9	**< 0.001**
Total RF application time [s]	3092 ± 1131	3161 ± 1212	3010 ± 1037	0.54
Efficacy and safety endpoints				
Periprocedural efficacy [%]	100.0	100.0	100.0	1.0
AF recurrence during hospital stay [%]	8.3	10.4	6.3	0.16
In-hospital complications [%]	3.1	4.2	2.1	0.14
6-month efficacy [%]	78.2	75.0	81.3	0.31

RF — radiofrequency; AF — atrial fibrillation

data of patients with atrial fibrillation who had undergone circumferential PV isolation with use of 3D Carto 3 or Carto XP system. The acute success rate was the same in both groups. In the same time of the procedure duration (157 ± 67 vs. 159 ± 65 min, p = 0.8), the use of Carto 3 system was associated with the reduction in fluoroscopy time (15.9 ± 12.3 vs. 26.0 ± 15.1 min, p < 0.001). The reduction of fluoroscopy time in Carto 3 group was greater in patients with paroxysmal AF (14.2 ± 12.7 vs. 26.3 ± ± 15.2 min, p < 0.001).

Our results are comparable with data form prospective studies analyzing results of utilization Carto 3 with UniVu™ Module during AF ablation [6, 7, 11]. The use of fluoroscopy integrated with EAM was studied in the group of 295 patients with a wide spectrum of cardiac arrhythmias. Using the UniVu™ Module has significantly contributed to the reduction in the fluoroscopy time and dose without a prolongation in the total procedure time [median ablation procedure time 135 (IQR: 113–170) min] [11]. In AF group, using UniVu™ has reduced the radiation exposure by 60% of the time (p < 0.001) and 49% of the dose (p < 0.001). In the prospective, randomized study, 80 patients with paroxysmal AF will also have benefitted from the UniVu™ Module use. The implementation of the integrated fluoroscopy with 3D system resulted in 84% of fluoroscopy time reduction [1.75 (IQR: 1.08–1.37) vs. 10.7 (IQR: 8.8–12.8), p < 0.001] and 73% of fluoroscopy dose reduction during the AF ablation [12]. Similar results were published in the study by Akbulak et al. [7]. In observation of 60 patients with paroxysmal AF both were reduced: the dose (476.5 ± 282.0 vs. 882.9 ± 550.4 cGycm^2, p = 0.001) and the radiation exposure time (7.4 ± 2.6 vs. 11.9 ± 2.1 min, p = 0.0006).

What draws the attention in a closer analysis of data is the comparable efficacy of the procedures 6 months after the experience in both groups (75.0% vs. 81.3%, p = NS) and in the whole population (78.2%). The results correlate with those published by the Akbular et al. after 125.7 ± ± 45.6 days of observation with the attested 81.7% patients free from any AF episodes, similarly to the Huo et al. with 5.9 ± 1.3 months of observation and 76.3% patients without AF [12].

Conclusions

The AF catheter ablation using an integrated model of classic fluoroscopy and 3D mapping system is safe and has resulted in a significant reduction of fluoroscopy time and dose. The same success rate after a follow-up was achieved without a prolongation of the procedure time and an increase in the rate of complications. This real-life population results corresponds with previously presented prospective studies.

Study limitations

The study we present is, a retrospective observational analysis from the single center. Secondly, only patients who suffered from paroxysmal AF were recruited in the present study. Moreover, compared group has not been homogenous. As mentioned previously patients from UniVu™ Module group were younger (p = 0.036). Due to retrospective nature of this study a limited number of parameters were a subject to our analysis with the measurements of the entire dose and time of fluoroscopy, without any emphasis put to the state after TSP. One should

also remember about that additional dose of radiation exposure during pre-procedural CT scan, not analyzed in our study. Lastly, since this study was designed to investigate whether a novel non-fluoroscopic imaging system reduces the procedure and fluoroscopy times of catheter ablation in real-life population, we limited data only to the mid-term clinical outcomes, without any information on long-term outcomes.

Conflict of interest

All authors declare no conflict of interest.

Streszczenie

Wstęp. Integracja obrazu fluoroskopowego z systemem obrazowania elektroanatomicznego 3D może zmniejszać ekspozycję na promieniowanie jonizujące podczas zabiegów elektrofizjologicznych. W tym retrospektywnym badaniu zaprezentowano wyniki stosowania zintegrowanego systemu elektroanatomicznego u pacjentów poddawanych ablacji migotania przedsionków w codziennej praktyce.

Materiał i metody. Przeanalizowano 96 pacjentów z napadowym migotaniem przedsionków poddanych zabiegowi izolacji żył płucnych prądem o częstotliwości radiowej. U 48 z nich wykorzystano system elektroanatomiczny 3D zintegrowany z fluoroskopią (Carto 3 UniVu). U pozostałych zastosowano klasyczny system elektroanatomiczny 3D (Carto 3). Analizie poddano dane kliniczne, a także okołozabiegowe, w szczególności dawkę i czas skopii, a także częstość powikłań i nawrotu arytmii w okresie 6 miesięcy.

Wyniki. Pacjenci leczeni z użyciem klasycznego systemu 3D byli istotnie starsi (p = 0,036). We wszystkich przypadkach uzyskano całkowitą izolację żył płucnych. Zarówno średni czas skopii (11,6 ± 4,3 *vs.* 6,7 ± 2,9 min; p < 0,05), jak i mediana dawki (460,0 [IQR 288,0–785,5] *vs.* 271,0 [IQR 145,0–535,0] mGy; p < 0,05) były istotnie mniejsze u pacjentów w grupie, w której stosowano Carto 3 UniVu. Całkowity czas zabiegu w obu grupach był porównywalny. Częstości powikłań okołozabiegowych oraz nawrotu klinicznej arytmii były porównywalne w obu grupach.

Wnioski. Wykorzystanie nowego systemu elektroanatomicznego 3D zintegrowanego z klasyczną fluoroskopią pozwala na zmniejszenie ekspozycji na promieniowanie jonizujące podczas zabiegów ablacji migotania przedsionków, nie wpływając jednocześnie negatywnie na czasu zabiegu, ryzyko komplikacji czy skuteczność. Dane te, uzyskane w toku codziennej praktyki, korespondują z wcześniejszymi dowodami uzyskanymi z badań klinicznych.

Słowa kluczowe: migotanie przedsionków, ablacja przezskórna, obrazowanie diagnostyczne, ochrona radiologiczna

Folia Cardiologica 2020; 15, 3: 203–209

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Folia Cardiologica 2020
tom 15, nr 3, strony 210–218
DOI: 10.5603/FC.2020.0029

ISSN 2353–7752

Assessment of adherence to physician recommendations among patients with diagnosed diabetes mellitus type 2

Ocena przestrzegania zaleceń lekarskich przez pacjentów ze zdiagnozowaną cukrzycą typu 2

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Abstract

Introduction. Adherence to physician recommendations and the principles of healthy lifestyle is the key to avoid diabetic complications. Daily physical activity, a healthy diet and adherence to drug therapy can delay the development of the disease and its complications, leading to an increased life expectancy.

The aim of the study was to evaluate the adherence to physician recommendations among patients with diagnosed diabetes mellitus type 2 (DM2).

Material and methods. We studied 57 patients, including 27 women (47.4%) and 30 men (52.6%) diagnosed with DM2. The patients were hospitalized in the Department of Diabetology and Internal Diseases at the Independent Public Central Clinical Hospital in Warsaw in April–August 2019. The average age was 57 years in women and 58 years in men. We analyzed the answers obtained from the respondents in response to the original questionnaire developed by the authors.

Results. We found that 70% of respondents did not follow dietary recommendations, 52% regularly consumed fast foods, 82% consumed sweets, 15% consumed the recommended amount of vegetables, 92% consumed meat at least once a day, and 39% were physically inactive. Among those declaring any physical activity, the most commonly reported type of activity was walking (32 patients or 56%).

Conclusions. The adherence to physician recommendations in patients with diagnosed DM2 is unsatisfactory. The available solutions lack cooperation within multi-specialist teams.

Key words: diabetes mellitus type 2, adherence, compliance

Folia Cardiologica 2020; 15, 3: 210–218

Introduction

Diabetes mellitus type 2 (DM2) has been the first non-infectious disease to reach the epidemic proportions. It has been estimated that more than 3 million individuals suffer from diabetes in Poland, and this number will increase to about 4 million by 2040 [1]. If untreated or inappropriately treated, diabetes leads to serious complications such as neuropathy, retinopathy and vascular complications. The mainstay of the management involves normalization of

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blood glucose levels with lifestyle intervention and drug therapy. Diabetes is characterized by a progressive course, eventually leading to the need for insulin therapy [2]. Studies showed a cardioprotective effect of metformin which is the most popular glucose-lowering drug [3]. Specific guidelines on nutrition [4] and physical activity [5] have been published. Lifestyle changes are most important in this type of diabetes, and they should always be the mainstay of the treatment. These mostly include adherence to a diabetic diet, appropriate physical activity, and avoiding stimulants.

Material and methods

We studied 57 patients including 27 women (47.4%) and 30 men (52.6%) with diagnosed DM2. The mean age was 57 years in women and 58 years in men. Data were analyzed using the Statistica 13 software. The study group included diabetic patients hospitalized in the Department of Diabetology and Internal Diseases at the Independent Public Central Clinical Hospital (Klinika Diabetologii i Chorób Wewnętrznych, Samodzielny Publiczny Centralny Szpital Kliniczny) in Warsaw in April–August 2019. Most patients were residents of a large city and had secondary (42%) or higher (33%) education. Twenty-two respondents were professionally active, and 34 were pensioners, social security benefit recipients, or unemployment allowance recipients. More than half of patients judged their economic status as "average". The respondents filled a questionnaire under supervision using a computer, with automatic answer storage in a Google Forms document. The inclusion criterion was the diagnosis of DM2. The exclusion criteria included diabetes mellitus type 1 and gestational diabetes.

The questionnaire items were related to the patients' diet, physical activity and habits. The first part of the questionnaire dealt with the diet and adherence to dietary recommendations. The next group of questions focused on so called "recreational" foods. The respondents were asked about the frequency of consuming such products. Next parts of the questionnaire dealt with physical activity and sources of knowledge about diabetes. The results were entered into a database which was subjected to statistical analysis.

The aim of the study was to evaluate the adherence to physician recommendations among patients with diagnosed DM2.

Results

The study included 57 patients with diagnosed DM2, including 27 women and 30 men. The mean age was 57 ± 16.8 years in women and 58 ± 11.2 years in men. Most patients were residents of a large city (47.7%). Higher education was reported by 19 (33.3%) patients, secondary education by 24 (42.1%) patients, vocational education by 13 (22.8%) patients, and primary education by one (1.8%) patient (Table 1).

The diets most commonly adhered to by the patients were the "diabetic" diet and low glycaemic index diet,

Table 1. Age, gender, place of residence and education profile of the study group

Age (years)	Men	**58.8 ± 11.2**	
	Women	**57 ± 16.8**	
		Number (n = 57)	**Percentage [%]**
Gender	Men	30	52.6
	Women	27	47.4
Place of residence	City > 250,000 inhabitants	27	47.7
	City < 250,000 inhabitants	4	7.0
	Town < 100,000 inhabitants	5	8.8
	Town < 50,000 inhabitants	4	7.0
	Town < 25,000 inhabitants	8	14.0
	Rural area	9	15.8
Education	Higher	19	33.3
	Secondary	24	42.1
	Vocational	13	22.8
	Primary	1	1.8

Table 2. Patients' adherence to dietary recommendations

Are you using any diet?		
	Number	**Percentage**
Gluten-free	1	1.80%
Lactose-free	1	1.80%
Low glycaemic index	15	26.30%
"Diabetic"	30	52.60%
Low-carb	3	5.30%
Paleo	1	1.80%
No specific diet	20	35.10%
How many meals do you consume daily?		
5 or more	20	35.10%
4	23	40.40%
3	13	22.80%
2	1	1.80%

indicated by 30 (52.6%) and 15 (26.3%) patients, respectively. No adherence to any specific diet was reported by 20 (35.1%) patients. Twenty-three (40.4%) respondents reported having 4 meals daily, 20 (35.1%) reported 5 or more meals, 13 (22.8%) reported 3 meals, and one (1.8%) patient reported 2 meals daily (Table 2).

Despite declaring adherence to the diabetic or low glycaemic index diet, many respondents [18 (31.6%) and 16 (28%) patients, respectively] consumed the recommended vegetable portions only 1–2 times a day. Only 5 (8.77%) patients consumed vegetables with every meal. A similar trend was noted for fruits, with 31 (54.4%) patients reporting consuming one portion of fruits daily, and 7 (12.3%) reporting no fruit consumption at all. A large proportion of patients (42 or 73.7%) consumed dairy products once daily. The most commonly chosen products were white cheese and milk. A dairy-free diet was reported by 6 patients (10.53%). Most respondents declared consuming meat once daily (25 patients or 43.86%), and 16 patients (28.07%) reported consuming meat twice daily. A vegetarian diet was reported by 4 respondents (7%). Fish was consumed once a week by 36 patients (63.16%), while as many as 17 patients (29.82%) reported no seafood consumption at all. Many respondents reported limiting consumption of cereal products to 2 or 3 meals [13 (22.81%) and 21 (36.84%) patients, respectively]. Two patients (3.51%) reported consuming no cereal products. Many respondents declared consumption of liquid fat in the everyday det. Most respondents (36 patients or 63.16%) reported consuming these products once daily, while 6 patients (10.53%) reported not consuming liquid plant fat at all. Regarding consumption of nuts and seeds, 29 patients (50.88%) reported no consumption of these products and 20 respondents (35.09%) consumed them once daily (Table 3).

Table 3. Consumption of selected food groups.

How many portions of the following products do you consume daily?			
	No. of meals	**No. of patients**	**Percentage**
Vegetables (80–100 g)	5 or more	5	8.77%
	4	4	7.02%
	3	13	22.81%
	2	16	28.07%
	1	18	31.58%
	0	1	1.75%
Fruits (80–100 g)	5	1	1.8%
	4	2	3.5%
	3	4	7.0%
	2	12	21.1%
	1	31	54.4%
	0	7	12.3%
Dairy products	5	0	0%
	4	0	0%
	3	1	1.75%
	2	8	14.04%
	1	42	73.68%
	0	6	10.53%
Meat	5	1	1.75%
	4	2	3.51%
	3	9	15.79%
	2	16	28.07%
	1	25	43.86%
	0	4	7.02%
Fish (weekly)	5	0	0.00%
	4	0	0.00%
	3	1	1.75%
	2	3	5.26%
	1	36	63.16%
	0	17	29.82%
Cereal products	5	2	3.51%
	4	9	15.79%
	3	21	36.84%
	2	13	22.81%
	1	10	17.54%
	0	2	3.51%
Liquid fat	5	0	0.00%
	4	1	1.75%
	3	1	1.75%
	2	13	22.81%
	1	36	63.16%
	0	6	10.53%
Nuts/seeds	5	0	0.00%
	4	0	0.00%
	3	4	7.02%
	2	4	7.02%
	1	20	35.09%
	0	29	50.88%

Table 4. Consumption of "recreational foods"

How often do you consume the following products?			
	No. of meals	**No. of patients**	**Percentage**
Fast-food	Daily	0	0.00%
	Several times a week	0	0.00%
	Once a week	0	0.00%
	Several times a month	1	1.75%
	Once a month	7	12.28%
	Several times a year	19	33.33%
	Once a year	3	5.26%
	Never	27	47.37%
Candy bars, pastries, candies	Daily	1	1.75%
	Several times a week	10	17.54%
	Once a week	3	5.26%
	Several times a month	18	31.58%
	Once a month	3	5.26%
	Several times a year	11	19.30%
	Once a year	1	1.75%
	Never	10	17.54%
Cakes	Daily	0	0.00%
	Several times a week	3	5.26%
	Once a week	3	5.26%
	Several times a month	11	19.30%
	Once a month	4	7.02%
	Several times a year	19	33.33%
	Once a year	0	0.00%
	Never	17	29.82%
Salty snacks	Daily	1	1.75%
	Several times a week	1	1.75%
	Once a week	1	1.75%
	Several times a month	9	15.79%
	Once a month	7	12.28%
	Several times a year	11	19.30%
	Once a year	2	3.51%
	Never	25	43.86%

A large proportion (27 patients or 47.37%) reported no consumption of fast-food at all, while 19 (33.33%) patients declared their consumption several times a year. Regarding consumption of confectionery, 10 patients (17.54%) reported consuming such products several times a week, 18 (31.58%) consumed them several times a month and 10 (17.54%) reported no consumption. The most commonly consumed sweets included candy bars, pastries, and candies. Cakes were consumed several times a month by 11 (19.3%) patients, several times a year by 19 (33.33%) patients, and not consumed at all by 17 (29.82%) patients. Salty snacks were occasionally consumed by 11 (19.3%) respondents, while 25 (43.86%) reported no consumption of such products.

Any leisure physical activity was reported by 35 patients (61.4%). The most commonly reported type of activity was walking (32 respondents). No physical activity was reported by 22 patients (Table 5).

Table 5. Physical activity

	Question to respondents	Number of patients	Percentage
Do you undertake any physical activity?	Yes	35	61.40%
	No	22	38.60%
What type of activity do you engage in?	Walking	32	56.10%
	Cycling	8	14%
	Gym exercises	2	3.50%
	Swimming pool	2	3.50%
	Nordic walking	4	7%
	Home exercises	3	5.30%
	Cardio (running, cross-trainer)	1	1.80%
	None	21	37.20%

Table 6. Interest in visits to a diabetes educator

Would you be interested in visits to a diabetes educator?		
	Number of patients	**Percentage**
Yes	7	12.30%
Yes if covered by the National Health Fund	27	47.40%
No	23	40.40%

Table 7. Reasons for not adhering to physician recommendations

What is the reason for not adhering to physician recommendations?		
	Number of patients	**Percentage**
Lack of time	10	18.20%
Lack of money	8	14.50%
Lack of motivation to fight the disease	17	30.90%
Belief that lifestyle changes would not improve the patient's health status	22	40%
Health status not allowing to engage in physical activity	18	32.70%
Lack of strong will	1	1.80%
Unforeseen events outside home	1	1.80%
I do adhere to all recommendations	5	9.10%

When asked whether they would be interested in visits to a diabetes educator and education regarding the diet, physical activity, and lifestyle in diabetes, the respondents mostly answered they would be willing to use such a service if covered by the National Health Fund (27 respondents or 47.4%), while 7 patients (12.3%) would be willing to pay out-of-pocket for such a service (Table 6).

When asked about the reason for not adhering to physician recommendations, the patients indicated that they did not believe that lifestyle changes would improve their health status (22 answers, 40%), that their health status would not allow engaging in physical activity (18 answers, 32.7%), or that they lacked motivation to fight the disease (17 answers, 31%), lacked time (10 answers, 18.2%), or lacked money (8 answers, 14.5%). Only 5 patients adhered in their opinion to all physician recommendations (Table 7).

Discussion

Diabetes is an interdisciplinary condition requiring patient support at various levels to increase therapeutic adherence and health literacy. The major goals in diabetes are not only to maintain normal blood glucose levels but

also to reduce and maintain normal body weight. Patient self-management is thus required to achieve these goals, including home monitoring of blood glucose levels using a glucose meter, monitoring haemoglobin A_{1c} (HbA_{1c}) level, and adherence to physician recommendations regarding diet, physical activity, and taking prescribed medications.

Dietary recommendations in DM2 include elimination of highly processed foods including meat, and foods containing simple carbohydrates. A special focus should be given to providing necessary vitamins and microelements. According to the most recent recommendations, carbohydrate intake should be limited to 40–50% of the total caloric intake and should be based on low or medium glycaemic index (GI) products. GI is the most precise system for classification of foods in regard to their postprandial digestion rate and carbohydrate absorption. It allows precise prediction of changes in blood glucose level at 2 hours after carbohydrate intake. The reference is glucose which has the GI of 100 [6]. Based on GI, the carbohydrate-containing products which should be chosen by patients with DM2 include coarse-grained groats, unrefined cereals, unrefined rice, and rolled oats. In our study, only 15 patients reported adhering to a low GI diet. The "diabetic" diet, adhered to by 30 respondents, is not consistent with the recommendations for diabetic patients, as it allows consumption of high GI products such as millet groats or bread made from white flour. No adherence to any specific diet was reported by 20 study participants.

Vegetables may be consumed without limitations due to their low GI and calorie content. They contain necessary vitamins, microelements, antioxidants, and soluble fiber which has a beneficial effect on weight reduction and stabilization of cholesterol levels. According to the World Health Organization (WHO) dietary guidelines and the food pyramid by the Polish National Food and Nutrition Institute, consumption of 5 portions of vegetables daily is suggested (with one portion defined as 100 g) [6, 7]. In our study, only 5 patients reported consuming the recommended daily amount of vegetables, while 18 and 16 respondents, respectively, reported consuming one or two portions of vegetables daily, mostly at the second or third meal during the day. When asked about the reasons for non-adherence to the recommendations, the respondents indicated a prohibitively high cost of fresh vegetables but did not mention their seasonal availability.

The amount of fruits consumed by diabetic patients should be limited to 200–300 g daily due to high GI of some fruits. Berry fruits are recommended due to their low GI, always as an addition to a meal and not as a standalone meal or snack [6]. In our study, 31 patients reported consuming fruits once daily, and 7 reported consuming no fruits at all. Many patients with DM2 are afraid of excessive postprandial blood glucose levels following fruit consumption and thus limit fruits or eliminate them completely from their diet.

A study by Hidayat et al. showed that the presence of milk proteins in the diet results in a reduction of postprandial lipaemia in patients with DM2. Consumption of dairy products may lead to lipoprotein synthesis by the enzyme lipase [8]. The most commonly recommended products are low-fat white cheese, low-fat milk, and natural yoghurt without addition of sugar or powdered milk. In our study, 42 respondents reported consuming dairy products once daily. The most commonly chosen product was white cheese, consumed at breakfast.

In a study by Toumpanakis et al. [9], use of a plant-based diet was shown to have a positive effect on HbA_{1c} level. The difference between HbA_{1c} levels at baseline and at the end of the study was 0.55%, compared to 0.19% in the control group [9]. In our study, 25 respondents reported consuming meat once daily, and 16 reported consuming meat twice daily. Vegetarian diet was used by only 4 patients. Fish and other seafoods are particularly recommended as a source of essential unsaturated fatty acids and polyunsaturated fatty acids. Consuming marine fish at least twice weekly has been recommended [10]. In our study, consumption of one fish portion per week was reported by 36 patients, while 17 respondents did not consume fish or other seafoods.

Potatoes as the most commonly chosen addition to the main meal have become less popular compared to groats, rice, and pasta. Since 2005, potato consumption has fallen by about 25 kg per person. Consumption of complex carbohydrates has also fallen, from 145 kg per person in 1960 to 108 kg per person in 2010–2014 [10]. This group of food products was reported to be consumed three times per day by 21 patients and twice daily by 13 patients. The most commonly chosen sources of carbohydrates are bread, buckwheat and rice. Patient often choose so-called "GI bread" which, in contrast to what its name suggests, is not suitable for persons with impaired carbohydrate metabolism as it contains white flour and addition of sugar. For this reason, its GI and glycaemic load are high. Another frequently chosen product is white rice which also has a high GI of 70 [11].

Nuts are a valuable source of protein, fatty acids, vitamins, antioxidants, and microelements. Almonds contain L-arginine and are particularly recommended in the diet of diabetic persons. In addition to a vasodilating effect (resulting in smooth muscle relaxation and blood pressure reduction), L-arginine may stimulate insulin release [12]. Other studies showed that consumption of cashew nuts (10% of the total caloric intake) reduced the homeostatic model assessment for insulin resistance (HOMA-IR) index compared to the control group with no cashew nut

consumption [13]. In our study, only 35% of the respondents consumed nuts once daily, mostly as a snack, while more than 50% of the respondents reported no consumption of nuts.

Development of diabetes is strongly associated with consumption of so-called "recreational foods", *i.e.*, fast-food products, sweets, and highly processed foods. Consumption of "recreational foods" increases absorption of saturated and trans fats [14]. Studies showed the more frequent were visits to fast-food restaurants, the higher was the risk of developing DM2 [10]. In other studies, consumption of processed meats such as fried smoked bacon and frankfurters was also associated with a higher risk of incident DM2 [15]. A similar effect was associated with consumption of sweet and salty snacks [15]. Most patients avoid fast-food products, sweets, and salty snacks but some individuals continue to consume such products despite being aware of their harmful effects. In some cases, these products are consumed daily or several times a week.

Physical activity should be an inherent element of a healthy lifestyle in all individuals. WHO recommends moderate physical activity for about 150 minutes per week or intense activity for about 75 minutes per week [5]. One should also consider non-exercise activity thermogenesis (NEAT) which describes the amount of calorie expenditure related to daily non-exercise activity [16]. In our study, 22 patients reported being physically inactive. This has been mostly related to a poor health status precluding any activity. These are often patients after limb amputation due to diabetic neuropathy and diabetic foot. Any activity was declared by 35 respondents in our study. The most commonly chosen types of exercise were walking (56%) and cycling (14%).

A high level of health literacy is strongly associated with adherence to physician recommendations. Studies by Al Sayah et al. [17] and Dahal and Hosseinzadeh [18] showed an association between better knowledge about diabetes and adherence to a diet, physical activity, use of medications, or appropriate diabetic foot care. In our study, 25 patients did not expand their knowledge, as they believed that their current level of knowledge about diabetes was sufficient.

The study by Atmaca et al. [19] showed that the knowledge about the disease was erroneous or insufficient. This is related to the level of health literacy, patient education, and socioeconomic factors [19]. The Diabetes Attitudes, Wishes and Needs Second Study (DAWN2) highlighted a poor alignment of the healthcare system with the needs related to diabetes treatment, including lack of prevention and education, and inadequate communication with physicians and diabetic nurses [1]. There are no diabetes educators in Poland, which does not benefit the patients who do not know what diet they should adhere to and what physical activity would be best for them considering their current health status. In our study, 34 respondents were willing to use the services of a diabetes educator to support them in their fight against the disease.

Non-adherence to physician recommendations may have various forms and reasons. The WHO report listed reasons related to the patient, condition, therapy, healthcare system, and social and economic reasons [20]. The study by Kardas et al. [21] showed that adherence to physician recommendations was mostly affected by interpersonal relationships involving the family and friends. Socioeconomic factors such as the ability to fill prescriptions and access to healthcare are also important [21]. In our study, the reasons for non-adherence to physician recommendations listed by respondents included a belief that lifestyle changes would not improve the patient's health status (40%), health status not allowing to engage in physical activity (32.7%), and lack of motivation to fight the disease or lack of support (30.9%).

Conclusions

The level of adherence to physician recommendations in patients with diabetes type 2 is low, and their knowledge about the disease is unsatisfactory. Non-adherence to therapeutic recommendations has a negative effect on the patient's health and may lead to serious complications. In addition, it generates increased healthcare costs. Cooperation within multidisciplinary teams of physicians, nurses, physical therapists, dieticians, and educators is necessary to improve the current situation in this regard.

Conflict of interests

The authors report no conflicts of interests.

Streszczenie

Wstęp. Przestrzeganie zaleceń lekarskich i założeń zdrowego stylu życia jest kluczem do uniknięcia powikłań cukrzycowych. Codzienna aktywność fizyczna, zdrowa dieta oraz stosowanie się do farmakoterapii mogą opóźnić rozwój choroby oraz pojawiania się powikłań, a także wydłużyć spodziewaną długość życia.

Celem pracy była ocena poziomu przestrzegania zaleceń lekarskich przez pacjentów obciążonych cukrzycą typu 2 (DM2).

Materiał i metody. Badaniem objęto 57 osób: 27 kobiet (47,4%) oraz 30 mężczyzn (52,6%) ze zdiagnozowaną DM2. Pacjenci przebywali w Klinice Diabetologii i Chorób Wewnętrznych Samodzielnego Publicznego Centralnego Szpitala Klinicznego w Warszawie od kwietnia do sierpnia 2019 roku. Średni wiek kobiet wynosił 57 lat, a mężczyzn 58 lat. Materiał do analizy stanowiły odpowiedzi uzyskane od respondentów w badaniu przeprowadzonym za pomocą autorskiej ankiety.

Wyniki. Zaleceń odnoszących się do diety nie przestrzega 70% respondentów. Spośród ankietowanych 52% spożywa regularnie *fastfood*, 82% — słodycze, 15% — zalecaną ilość warzyw, a 92% osób — mięso przynajmniej raz dziennie, 39% respondentów jest nieaktywna fizycznie, natomiast Ci, którzy deklarują jakąkolwiek aktywność fizyczną, najczęściej wybierają spacery (32 pacjentów, tj. 56%).

Wnioski. Stopień przestrzegania zaleceń lekarskich przez pacjentów ze zdiagnozowaną DM2 nie jest zadowalający. W dostępnych rozwiązaniach brakuje współpracy zespołów wielospecjalistycznych.

Słowa kluczowe: cukrzyca typu 2, przestrzeganie zaleceń, *adherence*

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Folia Cardiologica 2020
tom 15, nr 3, strony 219–226
DOI: 10.5603/FC.2020.0017

ISSN 2353–7752

Interpretation of cardiac troponin levels regarding the fourth universal definition of myocardial infarction published in 2018

Interpretacja stężeń troponin sercowych w świetle czwartej uniwersalnej definicji zawału serca z 2018 roku

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Abstract

Cardiac troponin (cTn) is a laboratory test routinely used in patients with suspected acute coronary syndrome (ACS). Unfortunately, wide variety of laboratory assays and different cut-off values regarding gender may result in difficulties with diagnosis and delay the treatment. Troponin I and less specific troponin T are used to diagnose ACS. Dynamic changes in cTn concentration are required to confirm the diagnosis of myocardial infarction (MI). The fourth universal definition of myocardial infarction defines five major types of MI — atherosclerotic plaque disruption, imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, cardiac death with symptoms suggestive of myocardial ischaemia and new ischaemic electrocardiographic changes, MI connected with percutaneous coronary intervention or coronary bypass grafting. Considering this definition, increased cTn concentrations are not always related to abnormal findings in coronary angiography and can be associated with many conditions. Increased high sensitivity cTn values in healthy individuals can be induced by intense physical activity, which is confirmed by studies performed in marathoners. While elevated cTn levels are observed in 20–60% of patients with acute ischemic stroke and are associated with an increased long-term mortality, acute MI is diagnosed only in 3,5% of patients. Elevated cTn levels often accompany chronic kidney disease, however changes in serial testing are obligatory for acute MI diagnosis. Deterioration of kidney function is more connected with elevated TnT rather than TnI levels. Regardless of the reason, increased cTn concentration is a negative predictive factor. Patients with elevated cTn levels need further diagnosis, risk stratification and a long-term follow-up.

Key words: troponin, myocardial infarction, acute coronary syndrome

Folia Cardiologica 2020; 15, 3: 219–226

Introduction

Cardiac troponins (cTn) were first described in 1963 [1], and at the end of the 1970s and 1980s they were considered to be indicators of myocardial injury. In 1999, it was suggested that the cTn level should be determined and used to diagnose ACS; one year later, they were recognised as the biomarkers of choice in the diagnosis of myocardial infarction [2, 3]. Due to the difficulties in the interpretation of troponin concentration for the purposes of diagnosing

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ACS, the European Society of Cardiology proposed to differentiate myocardial injury from myocardial infarction (MI) in the document on the fourth universal definition of myocardial infarction, published in 2018.

Myocardial injury is defined as the state in which cTn concentration in the blood is above the 99th percentile upper reference limit (URL). It is considered acute if there is an increase and/or decrease in cTn values.

Myocardial infarction is myocardial injury diagnosed based on the abnormal cTn values in a clinical situation in which the symptoms of acute myocardial ischaemia are observed [4] (Table 1). It is therefore necessary to relate cTn results to the clinical picture and to be aware of the difficulties in the interpretation of the elevated cTn level. The article presents available data on the interpretation and significance of cardiac troponin results.

Biochemical characteristics

The sarcomere is the basic contractile unit of the heart that is composed of thick filaments (myosins) and thin filaments (actins). The thin filament is a helix composed of two filamentous actins (F-actins), which are polymers of globular actin subunits (G-actin). The F-actin helix groove contains tropomyosin to which troponin is attached. Myofibrillar contraction is activated by the depolarisation and then modulated by the interaction of calcium ions (Ca^{2+}) with specific regulatory sites on the contractile apparatus of striated muscles of the heart [5]. These sites are troponin complexes immobilised on the thin filament, which acts in an allosteric manner to regulate the Ca2+-dependent interaction between filaments of actin and myosin [6]. Cardiac troponin I (cTnI) and troponin T (cTnT) are part of the contractile apparatus of myocardial cells and they are expressed almost exclusively in the heart [7, 8]. No increases in the cTnI level were observed after an injury to tissues other than the striated muscle of the heart.

In case of cTnT, the situation is more complex. Skeletal muscles express proteins which are detected by the assay used to determine the cTnT level. For this reason, skeletal muscles may be the source of increased cTnT values [9]. New data indicate that the frequency of elevated cTn values without ischaemic heart disease may be higher than initially thought [10, 11]. The preferred biomarkers used to evaluate myocardial injury are cTnI and cTnT, high-sensitive cardiac troponins (hs-cTn) are recommended to be used in [12] clinical practice [7].

Positive values

The 99th percentile URL was adopted as the cut-off point for myocardial injury. This point must be specified precisely

Table 1. Types of myocardial infarction (MI) (source [4])

Myocardial infarction	Definition	Comments
Type 1	The term "acute myocardial infarction" should be used in the case of acute myocardial injury with clinical symptoms of acute myocardial ischaemia if there is an increase and/or decrease in the cTn level in the blood with at least one value above the 99th percentile URL and at least one of the following criteria is met: • development of symptoms of myocardial ischaemia • presence of new ischaemic changes in ECG • development of pathological Q waves in ECG • imaging of a new loss of viable myocardium or new regional systolic dysfunction the location of which corresponds to the ischaemic aetiology • detection of a thrombus in the coronary artery during coronary angiography or autopsy (not applicable to type 2 and 3 MI)	Post-mortem identification of acute coronary atherothrombosis in the artery supplying the infarcted area of the myocardium meets the criteria for type 1 MI
Type 2	Identification of an imbalance between myocardial oxygen supply and demand that is not related to the acute coronary atherothrombosis	
Type 3	Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumably new ischaemic changes in ECG before the cTn level is determined or before it becomes abnormal	
Type 4a	Myocardial infarction related to percutaneous coronary intervention (PCI)	
Type 4b	Myocardial infarction caused by stent thrombosis	
Type 4c	Myocardial infarction caused by in-stent restenosis	
Type 5	Myocardial infarction related to coronary artery bypass grafting (CABG)	

cTn — cardiac troponin; URL — upper reference limit; ECG — electrocardiography

for each assay [13]. However, for all cTn assays, including high-sensitivity cTn assays, there is still no expert opinion on the criteria for how to define the 99th percentile URL [14]. It is therefore necessary to rely on changes in the values obtained during serial cTn testing. Significantly lower cTn values are observed in women than in men, which is why sex-specific 99th percentile URL values are recommended for high-sensitivity cTn assays [13, 14].

cTn evaluation time

The cardiac troponin level should be determined during the first assessment of the patient's condition and repeated during evaluation. According to the recent NSTE-ACS guidelines using 0 h/1 h algorithm (best option) is recommended to rule in/out MI. 0 h/2 h algorithm (second best option) is recommended alternatively, if an hs-cTn test with a validated 0 h/2 h algorithm is available. Time — 0 h, 1 h or 2 h — refers to blood sampling [15]. To diagnose acute MI, an increase and/or decrease with at least one value above the 99th percentile URL in the cTn level has to be observed, combined with a high likelihood of myocardial ischaemia based on the clinical assessment and/or ECG test. High-sensitivity cTn methods shorten the time to diagnose myocardial infarction in many patients to less than 3 hours from the onset of symptoms. However, there are still patients in whom MI is diagnosed late, after 6 hours. In patients with suspected acute MI who are assessed more than 12–18 hours after the onset of symptoms, it may take longer to detect the changing cTn level due to the downward phase of the cTn-concentration curve [16]. As a result of the implementation of hs-cTn assays, there is an increase in the frequency of diagnosing NSTEMI and a decrease in the frequency of diagnosing unstable angina [17].

Types of myocardial infarction

Table 1 shows the types of myocardial infarction and their definitions according to the current fourth universal definition of myocardial infarction.

Table 2. Clinical conditions increasing the cardiac troponin level other than MI (source [5])

Direct myocardial cell injury	**Infiltrative cardiac diseases** — direct compression of cardiomyocytes, regional loss of myocardium
	Chemotherapy — cardiotoxicity
Excessive myocardial strain	**Chronic heart failure** — myocardial wall stress
	Systemic hypertension — increased LV afterload (pressure overload)
	Aortic stenosis — increased LV afterload (pressure overload)
	Pulmonary hypertension — increased RV afterload (pressure overload)
	Valvular regurgitation — increased preload (volume overload)
	Chronic kidney disease and end-stage renal failure — chronic activation of the RAA system, excessive activation of the sympathetic nervous system (volume and pressure overload)
Myocardial ischaemia (reduced oxygen supply)	**Chronic heart failure and adverse cardiac remodelling:** • impaired coronary reserve • subendocardial ischaemia
	Coronary artery disease: • endothelial dysfunction and atherosclerosis • clinically silent microinfarctions
	Hypotension — reduced perfusion pressure
	Hypovolaemia — reduced filling pressure, output
	Anaemia — reduced oxygen supply
	Diabetes mellitus — vascular complications (endothelial dysfunction and coronary artery disease)
Increased oxygen demand	**Chronic heart failure and cardiac remodelling:** • reduced myocardial compliance during diastole and contractile dysfunction (collagen deposition, focal fibrosis) • subendocardial ischaemia
	Atrial fibrillation — increased myocardial oxygen consumption
	Chronic kidney disease — excessive sympathetic activity and release of catecholamines
	Stroke — excessive sympathetic activity and release of catecholamines

Positive cTn values — a variety of causes

Cardiac troponin is a biomarker that is "organ-specific", not "disease-specific" [5]. Therefore, an elevated cTn level indicates myocardial cell injury, but it does not determine its mechanism. The term "myocardial injury" better describes elevated cTn levels in patients without ACS and those with no imbalance between myocardial oxygen supply and demand. The cTn level may increase as a result of mechanical stretch caused by a preload or physiological stresses on a healthy heart [4]. The effect of repeated periods of increased preload on myocyte loss may be significant, and it may lead to cell hypertrophy and myocardial dysfunction in the absence of ischaemia. Histological symptoms of myocardial injury can be detected in clinical conditions with a non-ischaemic aetiology [2, 18].

The coexistence of various causes of elevated cardiac troponin values is often observed in everyday clinical practice (Table 2). Particular attention should be paid to the interpretation of elevated cTn values in athletes, ischaemic stroke (IS) and chronic kidney disease (CKD).

Elevated cardiac troponin values in athletes

According to the analysis of the results of the studies conducted from 2008 to 2013 (as many as 10 studies were analysed, the total number of subjects was 392), hs-cTn values above the 99th percentile were observed in about 70% of marathon runners after the end of the run (the values were determined within 0–6 hours after the end of the run). The hs-cTnT level was assessed in the majority of runners, and the hs-cTnI level in a much smaller group [19]. In the study involving the Brighton marathon participants, higher hs-cTnT values were observed in relation to greater exercise intensity [20]. In another study on the participants of this marathon, there were no differences in the hs-cTnT level between the control group, the group with diagnosed heart diseases, and runners who collapsed after the run [21].

An elevated exercise-induced hs-cTn level results from the prolonged stress on the cell membrane of cardiomyocytes, the release of reactive oxygen species and decreased pH [22]. Initially, it was believed that small-degree necrosis occurred, but there is no evidence to confirm this theory — no late gadolinium enhancement (LGE) areas were found in cardiac magnetic resonance and there is still a lack of histopathological examinations.

The clinical significance of positive exercise-induced hs-cTn values remains unclear. Most data indicate that an increase in the hs-cTn level after intensive exercise is physiological and does not affect the short-term prognosis. However, there is still no evidence of the effect of increased exercise-induced hs-cTn values on long-term prognosis [19, 21].

Significance and interpretation of positive cardiac troponin values in acute ischaemic stroke

Elevated cTn values in patients with acute ischaemic stroke (AIS) are usually of little clinical significance even

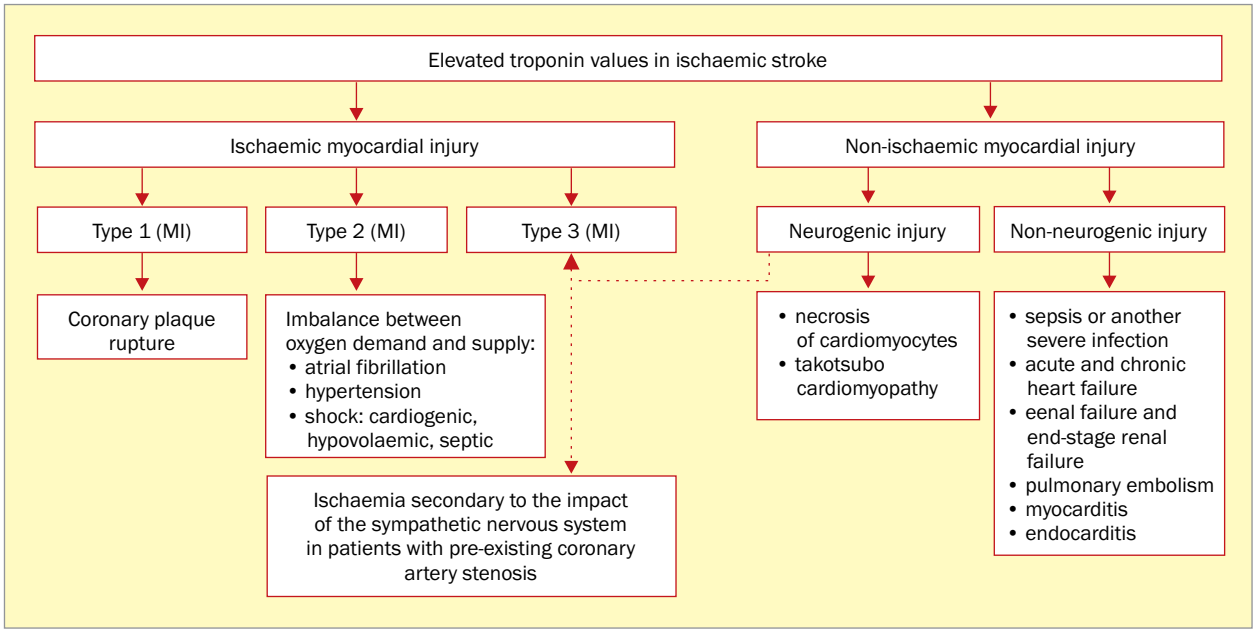

Figure 1. Possible mechanisms leading to an increase in the cTn level in ischaemic stroke; MI — myocardial infarction (source [26])

though they are observed in 20–60% of these patients [23–25].

An increase in the cTn level during a stroke may be associated with ischaemic or non-ischaemic myocardial injury (Figure 1) [26]. These processes are not mutually exclusive. Neurocardiogenic mechanisms may contribute to myocardial ischaemia or sudden cardiac death.

In a clinical trial involving almost 2,000 patients with ischaemic stroke, elevated cTn values were observed in as many as 353 individuals. Acute myocardial infarction was diagnosed in 16% of patients with ischaemic stroke and elevated cTn values, who represented 3.5% of all patients with AIS. However, it was shown that elevated cTn levels are associated with long-term mortality rates that are twice as high as those in patients with ischaemic stroke and normal cTn values. Acute ischaemic stroke may act as a kind of indirect stress test for underlying coronary artery disease. This type of stress test is closely associated with the 30-day mortality rate. Despite the clinically mild nature of stroke in the analysed population, as many as 60% of patients with ischaemic stroke and positive cTn values died within 3 years [27]. Importantly, the TRELAS (Troponin Elevation in Acute Ischaemic Stroke) study showed that only 24% of 29 patients with AIS and positive cTn values had significant changes in coronary angiography [28].

Recent reports also indicate that positive troponin results are primarily associated with cardioembolic ischaemic stroke. In other types of strokes, positive cTn values are observed much less frequently [29]. Therefore, patients with AIS require special attention, risk stratification and detailed cardiological evaluation.

Significance and interpretation of positive cardiac troponin values in chronic kidney disease (CKD)

Persistently elevated cardiac troponin levels are often observed in patients with CKD. This can be caused by the myocardium through increased release, as well as by the kidneys through reduced clearance of cTn [30]. This especially applies to hs-cTnT, the level of which is elevated more often than that of hs-cTnI [31, 32].

It was found that hs-cTnT demonstrates a 24-hour variation — its level decreases during the day, and then increases at night until it reaches the highest value again in the morning. The deterioration of renal function is more strongly associated with elevated cTnT levels than cTnI levels, which may suggest that renal function plays a role in the 24-hour clearance of cTn [33].

In recent studies it was shown that impaired renal clearance may be important in case of a significantly elevated cTn level in response to acute episodes of myocardial injury [34]. The injury mechanisms include increased ventricular pressure, impaired patency of small coronary vessels, anaemia, hypotension and possibly direct toxic effects on the myocardium associated with the uraemic state [35]. An elevated cTn level is therefore frequent; it has a high prognostic value in long-term observation due to the fact that it reflects myocardial injury [31]. Diagnosing MI in patients with CKD and elevated cTn values may be difficult if there are no clinical symptoms or changes in ECG indicating myocardial ischaemia. However, the study results suggest that changes in the cTn level based on serial measurements make it possible to diagnose MI in patients with CKD as effectively as in individuals with normal renal function [36, 37].

Impaired renal clearance is therefore not the main cause of persistently elevated TnT values and it is important to have comprehensive tests carried out in all patients with elevated cTn levels, regardless of their eGFR [30].

Prognostic significance of elevated cTn values

In the recent study conducted by Chapman et al. [38] on more than 2,000 patients with an elevated TnI level, it was shown that approximately two thirds of patients with type 2 MI or myocardial injury died within 5 years. However, most of the deaths were from non-cardiovascular causes. The prevalence of nonfatal myocardial infarction or cardiovascular death in patients with type 2 MI and myocardial injury was similar to that in patients with type 1 myocardial infarction. Major adverse cardiac events (MACE) occurred in one third of patients with elevated cardiac troponin levels, regardless of whether myocardial cell necrosis was spontaneous or secondary to another acute disease. The risk of MACE in patients with type 1 myocardial infarction was highest, but there was no difference in its level between patients with type 2 MI and patients with myocardial injury. Patients with type 2 MI or myocardial injury with diagnosed coronary artery disease were at the highest risk of cardiovascular events [38].

In another study conducted by the same author, the TnI value of 5 ng/L (Abbott Architect STAT assay) was considered as a cut-off point for risk stratification in patients admitted with suspected acute coronary syndrome. The hs-cTnI value below 5 ng/L on admission identified patients with low risk of myocardial infarction or cardiac death within 30 days [38].

Furthermore, the HiSTORIC study carried out on a group of more than 30,000 patients showed that it is possible to exclude myocardial infarction on the basis of only one hs-cTnI result below 5 ng/L (Abbot Architect STAT assay), measured on admission to the emergency department. Such a strategy showed 99.5% accuracy in excluding MI during the 30-day observation. In patients with hs-cTn levels from 5 ng/L to the 99th percentile, hs-cTnI was measured again

after 6 hours, whereas those with values above the 99th percentile in the first hs-cTnI measurement were admitted to the hospital. While applying this diagnostic scheme a low risk of cardiovascular events was observed during the 12-month period. Additionally, the number of patients discharged from the emergency department increased by 57% (from 53% to 74%) [40].

Conclusion

To sum up, elevated cardiac troponin values may result not only from coronary artery disease, but also from many different conditions that are often comorbid conditions. The prognostic significance of elevated hs-cTn values induced by intensive exercise remains unclear. However, it should be kept in mind that poor long-term prognosis and high mortality rates are common in the majority of patients with elevated cTn values, even without clinical or ECG markers of myocardial infarction. It is necessary perform detailed diagnostics of these patients for coronary artery disease and comorbidities, and to take preventive and therapeutic measures to improve their prognoses.

Conflict of interest

Authors do not declare the conflict of interest.

Streszczenie

Stężenia troponin sercowych (cTn) oznacza się rutynowo w diagnostyce ostrego zespołu wieńcowego (ACS). Rozpoznanie ACS mogą jednak utrudniać różne rodzaje testów laboratoryjnych oraz inne punkty odcięcia wartości patologicznych u kobiet i mężczyzn. W diagnostyce ACS znajdują zastosowanie troponina I (TnI) oraz mniej specyficzna troponina T (TnT). Do potwierdzenia zawału serca (MI) konieczne jest stwierdzenie dynamicznych zmian stężenia cTn. W czwartej uniwersalnej definicji zawału serca wyróżnia się pięć głównych typów MI w zależności od patomechanizmu: związany z pęknięciem blaszki miażdżycowej, związany z dysproporcją między podażą a zapotrzebowaniem mięśnia sercowego na tlen, zgon sercowy u pacjentów z objawami sugerującymi niedokrwienie mięśnia sercowego i nowymi zmianami niedokrwiennymi w elektrokardiografii oraz MI towarzyszący angioplastyce wieńcowej i pomostowaniu aortalno-wieńcowemu. Zgodnie z tą definicją podwyższone stężenie cTn nie zawsze wynika z obecności istotnych zwężeń w tętnicach wieńcowych i może towarzyszyć wielu stanom. Wzrost wartości cTn oznaczanej metodą wysokoczułą u zdrowych osób może być indukowany intensywnym wysiłkiem fizycznym, co potwierdzają badania maratończyków. Podwyższone stężenie cTn występuje u 20–60% pacjentów z udarem niedokrwiennym mózgu i wiąże się z wyższą śmiertelnością odległą, jednak ostry MI w tej grupie chorych diagnozuje się jedynie u 3,5% osób. Podwyższone stężenie troponin sercowych często towarzyszy przewlekłej chorobie nerek, jednak w przypadku podejrzenia ACS znaczenie ma dynamika seryjnych pomiarów. Pogorszenie funkcji nerek ma większy wpływ na wzrost stężenia cTnT niż cTnI. Niezależnie od przyczyny podwyższone wartości cTn stanowią niekorzystny czynnik rokowniczy. Pacjenci, u których stwierdzono wzrost wartości cTn, wymagają rozszerzenia diagnostyki, stratyfikacji ryzyka i długoterminowej obserwacji.

Słowa kluczowe: troponiny, zawał serca, ostry zespół wieńcowy

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Folia Cardiologica 2020
tom 15, nr 3, strony 227–235
DOI: 10.5603/FC.2020.0030

ISSN 2353–7752

The role of limiting sodium intake in the diet — from theory to practice

Rola ograniczenia spożycia sodu w diecie — od teorii do praktyki

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Abstract

Sodium is the main extracellular cation. In recent years, many mechanisms that have been involved in the regulation of sodium metabolism have been described, such as interstitial tissue and glycosaminoglycans, Th17 lymphocytes and interleukin 17, epithelial sodium channel, glycocalyx and proprotein converting enzyme subtilisin/kexin type 6. Complexity of homeostasis mechanisms sodium makes it an interest in modern pharmacology. The described mechanisms somewhat explain the sodium sensitivity phenomenon occurring in a significant proportion of patients with arterial hypertension.

Processed foods are the main source of salt in the diet. The food processing process is associated with a significant increase in the salt content of these products. Excessive salt intake in the diet is observed in most countries of the world. The relationship between excessive salt intake in the diet and the occurrence of diseases such as hypertension, stroke, stomach cancer, left ventricular hypertrophy, urolithiasis and others has been the subject of numerous studies. Numerous benefits of reducing salt in the diet have been demonstrated.

Key words: sodium, salt, cardiovascular disease

Folia Cardiologica 2020; 15, 3: 227–235

Sodium metabolism in the human body

Sodium is the main extracellular cation in the human body. Its total body content is approx. 4200 mmol (60 mmol/kg body weight). As much as 91% of total sodium in the human body is found in the extracellular space, where it reaches a concentration of 135–145 mmol/L. The intracellular space contains 9% of total sodium in the human body, and its concentration is 10–20 mmol/L [1, 2]. Nearly 1/3 of total sodium in the body (approx. 20 mmol/kg body weight) is poorly exchangeable or not exchangeable, and it is mostly located in the bones. The remaining amount of sodium (approx. 40 mmol/kg body weight) is mainly located in the extracellular space, and it is well exchangeable [1–3].

Sodium supplied with food is mostly absorbed in the middle and further part of the small intestine. In case of preserved sodium homeostasis, as much as 95% of sodium ingested with food is excreted through the kidneys, 4.5% through the digestive tract and 0.5% through the skin [2]. A number of mechanisms are involved in the regulation of sodium metabolism. The most important ones include: renin–angiotensin–aldosterone system, reduction of sodium charge reaching the macula densa in the distal convoluted tubule of the nephron, natriuretic peptide system, pressure natriuresis as well as hypercalcaemia and hypokalaemia [4].

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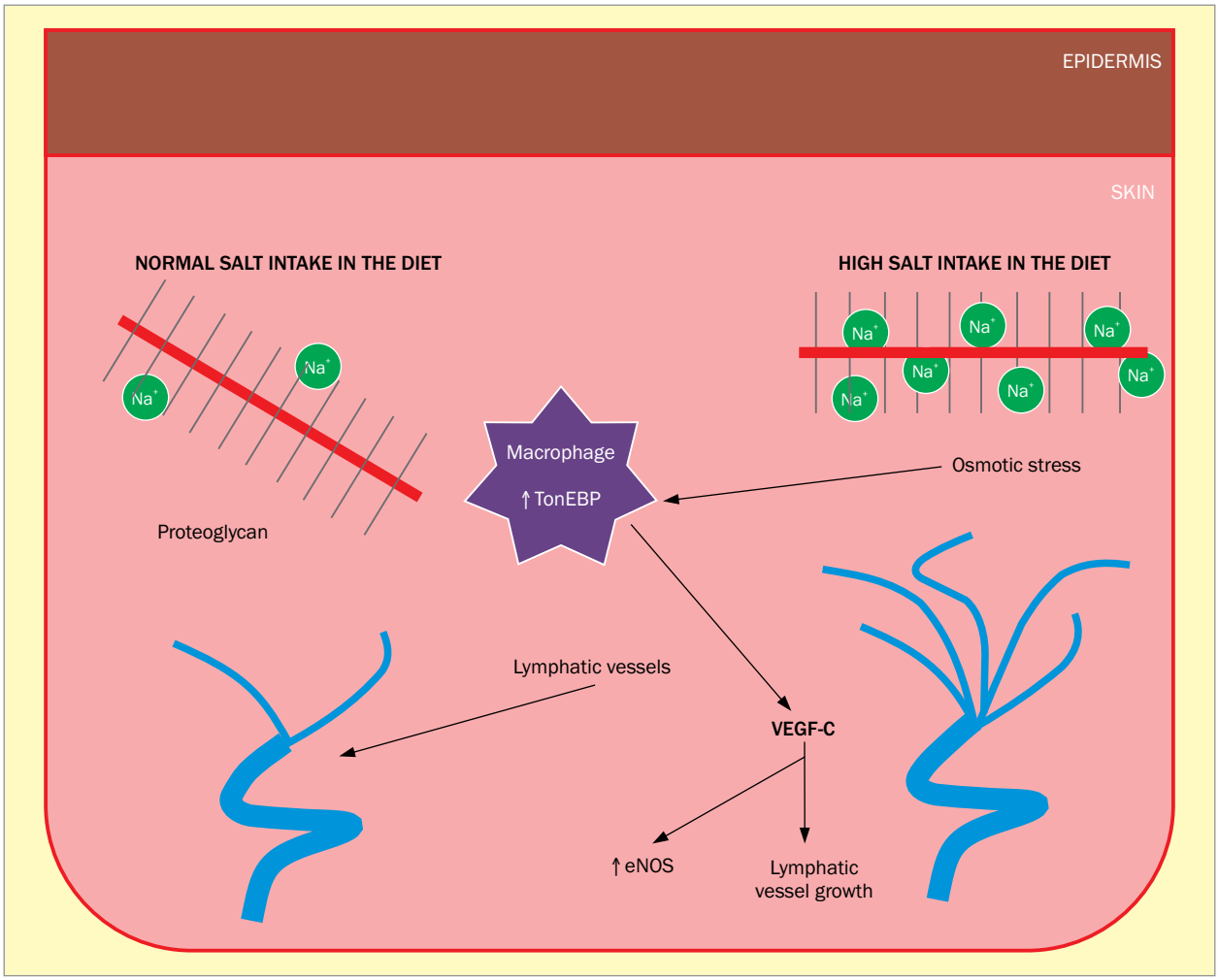

Figure 1. Involvement of the interstitial tissue in the regulation of sodium metabolism (based on [10]); TonEBP — tonicity enhancer binding protein; VEGF-C — vascular endothelial growth factor C; eNOS — endothelial nitric oxide synthase

Regulation of sodium metabolism — selected mechanisms

Subcutaneous connective tissue — glycosaminoglycans

For many years it has been believed that the sodium concentration in the extracellular extravascular fluid compartment (*i.e.* interstitial fluid compartment) does not differ much from the sodium concentration in the plasma. Small differences in the sodium concentration between these compartments were explained by significantly higher concentrations of proteins in the blood plasma than in the interstitial fluid compartment, which was justified in the Gibbs-Donnan effect [5].

An important role of subcutaneous tissue in the regulation of sodium metabolism has been described in recent years [6]. In the interstitial fluid compartment, especially in the subcutaneous tissue, there are a lot of glycosaminoglycans (GAGs) forming proteoglycans of the connective tissue. GAGs are involved in the storage of sodium in the subcutaneous tissue (Figure 1) [6,7]. Sodium accumulated in the interstitial tissue is inactive osmotically, as a result of which it does not affect the water retention by the kidneys [7].

An increased sodium concentration in the interstitial tissue stimulates the inflow of macrophages (MPS, mononuclear phagocyte phagocyte system cells) into this space. Under the influence of local hypernatraemia, these cells activate the expression of the tonicity enhancer binding protein (*TonEBP*) gene, which is a transcription factor [7, 8]. The protein stimulates the expression of the vascular endothelial growth factor C gene (*VEGF-C*) and increases its secretion by MPSs. The main effects of VEGF-C are: activation of lymphangiogenesis, angiogenesis, sodium clearance from the interstitial tissue through the stimulation of sodium bonding by GAGs and generation of nitric oxide. The VEGF-C gene performs these functions through two membrane receptors. The activation of

vascular endothelial growth factor receptor 3 (VEGFR-3) leads to the above-mentioned lymphangiogenesis and angiogenesis and to GAGs being transported with lymph. The activation of the vascular endothelial growth factor receptor 2 (VEGFR-2 receptor) stimulates vascular endothelial cells to the above-mentioned synthesis of nitric oxide (the VEGF-C gene activates the endothelial nitric oxide synthase). The bonding between sodium and GAGs leads to their osmotic immobilisation [6, 9, 10]. It was demonstrated that during a diet rich in sodium hypertension was more common in animals in which macrophages were destroyed as a result of the administration of liposomes with clodronate [9].

The above-mentioned phenomena related to the accumulation of sodium ions by GAGs in the subcutaneous tissue and the involvement of the immune system in this process were also demonstrated in humans. Selvarajah et al. [11] showed that the skin can buffer sodium provided in the diet, reducing the haemodynamic effects of an increased sodium content in the body. This effect was more visible in men, which indicates that gender affects the ability of the subcutaneous tissue to immobilise sodium [11]. The method used to locate osmotically inactive sodium is $^{23}Na^{+}$-MRI [12].

Taking the above-mentioned data into account, it can be concluded that sodium can be accumulated not only in the osmotically active form, increasing the volume of extracellular fluid (according to the Guyton's hypothesis), but also in the osmotically inactive form associated with GAGs. Moreover, the immune system also has a significant effect on the regulation of sodium metabolism through the formation of new lymphatic vessels, thanks to which GAGs are extracted from the skin along with sodium [10].

It is also worth noting that the above mechanisms that form the signalling pathway TonEBP-VEGF-C-VEGFC--R-NO-lymphangiogenesis and angiogenesis may explain different levels of sensitivity to sodium supplied with diet, expressed by changes in blood pressure (sodium sensitivity). Sodium sensitivity is defined as a change in blood pressure of at least 10 mm Hg in response to a 4-hour infusion of 2,000 mL of NaCl compared to the blood pressure measured after following a low-sodium diet (10–20 mmol NaCl/day) for several days [13]. Sodium sensitivity occurs in 30–50% of patients with hypertension and 20–30% of patients with normal blood pressure, which indicates that it is a significant clinical problem [14]. In conclusion, it can be stated that sodium-dependent blood pressure (sodium-dependent hypertension) may result from reduced interstitial volume in the scope of the osmotic inactivation of sodium (as well as an impaired normal immobilisation of sodium in the interstitium), whereas sodium-independent hypertension may be the result of increased volume in the scope of the inactivation of sodium ions by the interstitial tissue [10].

There is also another practical conclusion to be drawn from this discussion. It is not possible to predict an increase in natraemia in patients with hyponatraemia during corrective treatment based on the knowledge of the size of fluid compartments in the body. In such patients, the ability of the interstitial tissue to immobilise sodium may vary. Therefore, to avoid the phenomenon of overcorrection, the most severe complication of which is pontine demyelination syndrome, it is necessary to determine natraemia as often as possible during corrective treatment [3].

Th17 lymphocytes and interleukin 17

The results of some tests on animals indicate that Th17 lymphocytes, which produce interleukin 17 (IL-17), are attracted to the interstitial tissue by GAGs combined with sodium ions. Interleukin 17 has hypertensive properties by increasing the stiffness of the vascular endothelium [15, 16].

Increased salt intake in the diet leads to an increase in the number of Th17 lymphocytes and reduces the number of *Lactobacillus murinus* in the human gut microbiota. Based on the studies, it was demonstrated that the administration of probiotics with *Lactobacillus murinus* reduces the occurrence of sodium-dependent increase in blood pressure and in the number of Th17 lymphocytes [17]. An excessive amount of salt leads to a reduction in the number of *Lactobacillus murinus*, as a result of which the amount of indole compounds decreases. A reduced concentration of these compounds leads to the stimulation of the differentiation of T lymphocytes into Th17 lymphocytes. These lymphocytes secrete the above-mentioned IL-17, which, on the one hand, intensifies the reabsorption of sodium from the intestines and, on the other hand, damages the vascular endothelium (impaired vasodilatory properties). Both mechanisms increase blood pressure [18]. It was shown that an increased amount of salt in the diet can also increase the number of Th17 lymphocytes by activating the antigen-presenting cells (*APC*). As a result of the stimulation of APC, IL-23, IL-6 and IL-1 are secreted, which stimulate T lymphocytes to secrete IL-17 and other proinflammatory cytokines. The above-mentioned phenomena lead to the inflammation of the kidneys and blood vessels, which in turn contributes to the development of hypertension [19].

The study results indicate that Th17 lymphocytes, interleukin 17 and gut microbiota, the composition of which depends on the diet, has a significant impact on the regulation of sodium metabolism [20].

Epithelial sodium channel (ENaC) and glycocalyx

Increased sodium intake in the diet leads to the activation of the sympathetic nervous system, which results, for instance, in the activation of the renin–angiotensin–aldosterone system [21]. By affecting the mineralocorticoid

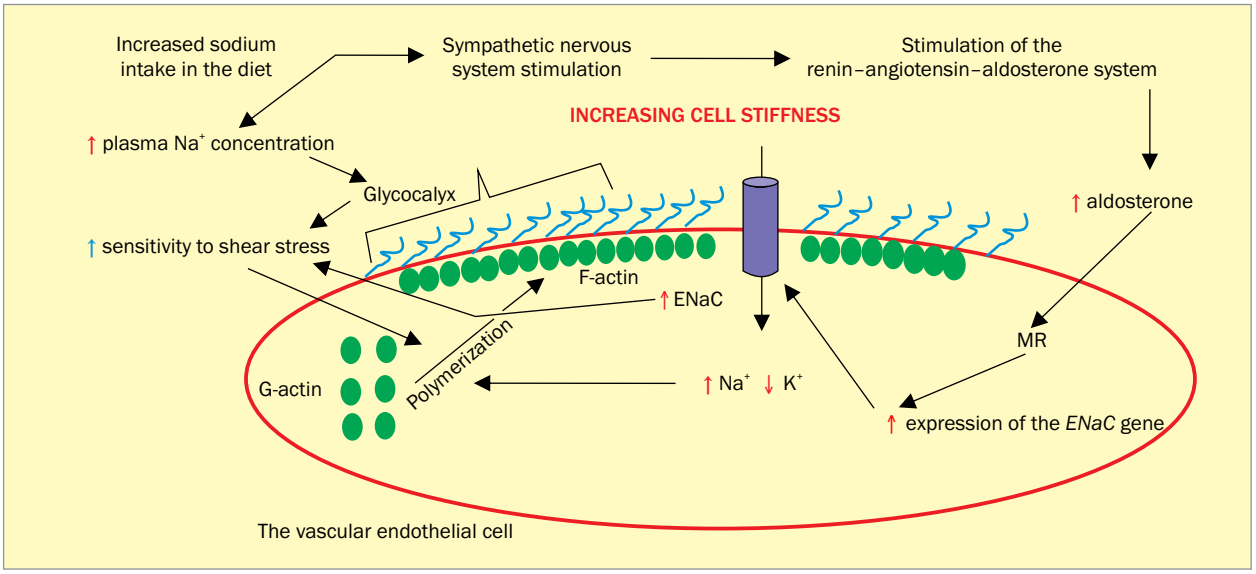

Figure 2. Effects of increased sodium intake in the diet on vascular endothelial cells; Na^+ — sodium; ENaC — epithelial sodium channel; K^+ — potassium; MR — mineralocorticoid receptor

receptor (MR), aldosterone increases the gene expression for the epithelial sodium channel (*ENaC*) [22]. Increased sodium intake in the diet can also increase the MR activity by increasing the activity of protein Rac1 (MR activity modulator). It has been demonstrated that an increased activity of Rac1 may lead to the development of sodium-dependent hypertension [23]. An increase in the amount of ENaC on the surface of vascular endothelial cells increases the sensitivity of these cells to shear stress exerted by bloodstream. The ENaC channel combines with globular actin (G-actin) leading to its polymerisation and the creation of filamentous actin (F-actin). Filamentous actin increases the stiffness of the shell of vascular endothelial cells, resulting in an increase in the total peripheral resistance (*TPR*), which is an important determinant of blood pressure (Figure 2) [24].

The more ENaC is found in the membrane of vascular endothelial cells, the more sensitive to shear stress and the stiffer these cells are. An additional factor stimulating the change in actin conformation is the change in glycocalyx conformation (decrease in its height and increase in the stiffness) of vascular endothelial cells. The factors changing the glycocalyx conformation are *shear stress* and direct toxic effects of sodium (already in the concentration found in the plasma > 139 mmol/L, *i.e.* within the normal range) [25, 26]. Glycocalyx and ENaC are therefore shear stress sensors (Figure 2). Moreover, an increase in the intracellular concentration of sodium ions with a simultaneous decrease in the concentration of potassium ions is another factor activating the polymerisation of G actin into F actin (this is an important mechanism because in Poland people consume an excessive amount of salt and a low amount of potassium in their diet) (Figure 2). An increased stiffness of the shell of endothelial cells reduces the activity of nitric oxide synthase and reduces the sensitivity of these cells to NO [27]. In contrast to sodium, an increased serum concentration of potassium reduces the stiffness of endothelial cells and increases the release of NO [28, 29]. According to Oberleithner et al. [24]: 1) there is a negative correlation between the "stiffness" of vascular endothelial cells and the activity of endothelial nitric oxide synthase; 2) an increase in the concentration of sodium in the plasma significantly increases the stiffness of vascular endothelial cells (in the presence of aldosterone and ENaC); 3) an increase in potassium in the plasma reduces the stiffness of vascular endothelial cells and increases the activity of endothelial nitric oxide synthase only in the case of low sodium concentrations in the plasma.

In conclusion, it can be stated that an increased sodium intake in the diet has a negative effect on the vascular endothelial function by stimulating the sympathetic nervous system and the renin–angiotensin–aldosterone system, and by changing the glycocalyx conformation. All these processes lead to an increased stiffness of vascular endothelial cells, which directly results in increased blood pressure. It should be emphasised that increased sodium intake directly impairs normal endothelial function, which in turn results in increased blood pressure in the mechanism independent of the volume status.

Proprotein convertase subtilisin/kexin type 6 (PCSK6)

Proprotein convertase subtilisin/kexin type 6 (PCSK6) is a serine protease involved in the activation of corrin. Corrin

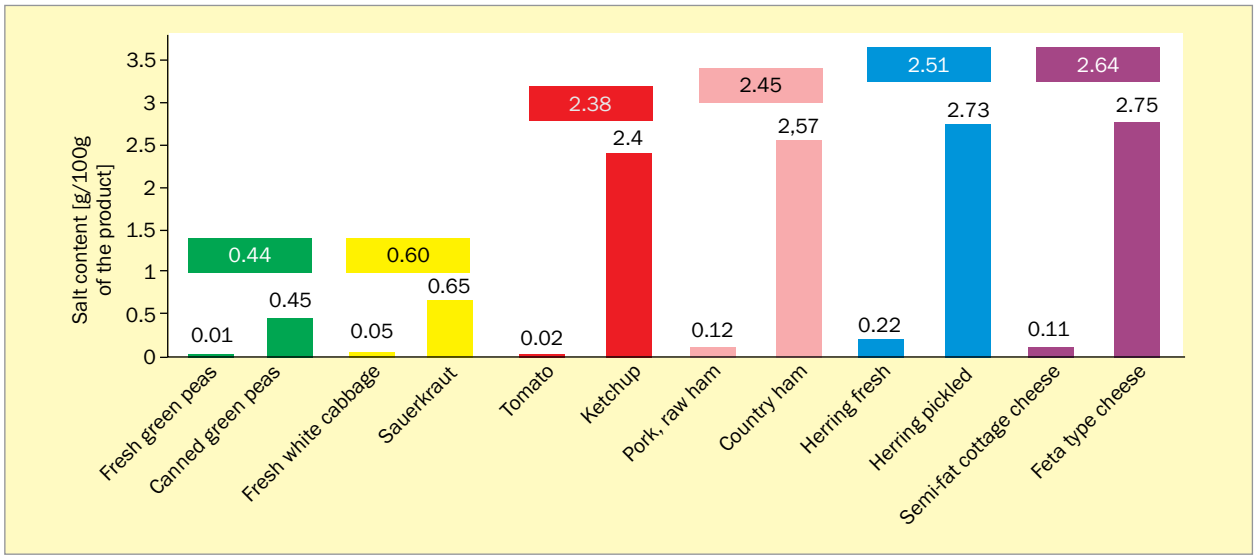

Figure 3. Salt content in selected fresh and processed products. The difference in salt content in products (g/100g of the product) is given in rectangles (based on [31, 33])

is an enzyme necessary for the formation of a biologically active atrial natriuretic peptide (ANP). The *PCSK6* gene mutation leads to sodium-dependent hypertension. Experimental studies have shown that the use of benzamidine (serine protease inhibitor) led to the inhibition of corrin activation. The *PCSK6* gene mutation leads to a decrease in the secretion of ANP, which in consequence impairs the excretion of excessive sodium from the body and increases natraemia. Increased natraemia in turn leads to an increase in the volume status and blood pressure [30].

The above-mentioned mechanisms regulating sodium metabolism, which have been described relatively recently, show us the complexity of sodium homeostasis. It can be expected that the above-mentioned elements of the regulation of sodium metabolism will be the subject of further experimental and clinical studies and that they may become be a new possible target for drug therapy of hypertension and other cardiovascular diseases in the future.

Sources of sodium in the diet

Sodium is a natural ingredient of food of animal and plant origin. It is used in the form of table salt (NaCl) during seasoning and adding salt to meals. Moreover, it is an important ingredient added to processed food to extend its shelf-life [31].

According to the European Society of Cardiology (ESC), the sources of salt in everyday diet include processed products (72%), salt added during cooking (20%) and salt contained in water and drugs (8%) [32]. It is worth noting that we may directly affect only 20% of all salt sources in our diet [32].

According to other authors, processed food products are the source of not 72% but 85% of the daily amount of salt in the diet [31, 33].

A high salt content is typical of fast-food products. A typical fast-food lunch set consisting of a hamburger, chips and sauce (usually ketchup) contains 4.5 g of salt, which is as much as 90% of the daily recommended intake (*DRI*). Kebab, which is another popular fast-food product, contains about 4.0 to 8.4 g of salt, while pizza 7.0 to 12.8 g of NaCl. It is also worth mentioning the so-called instant soups which contain even up to 4.1 g of salt [34–37]. One slice of white or wholegrain bread contains about 0.5 g of NaCl [38].

The Institute of Food and Nutrition in Warsaw has prepared a report comparing salt content in fresh products and their processed equivalents (Figure 3).

As can be seen in Figure 3, The processing of food involves a significant increase in its salt content [31, 33].

Salt consumption in Poland and Europe

Studies carried out by Eaton and Konner have shown that the ancestors of man consumed food with a salt content not exceeding 1 g/day. These observations indicate that man is evolutionarily adapted to a diet considered now to be low sodium [39, 40].

Currently, the average consumption of sodium in the world is about 3.95 g/day, *i.e.* about 10 g of NaCl (1 g of NaCl contains 0.4 g of sodium). Salt consumption varies in European countries (Figure 4) [41].

As far as the consumption of salt in Poland, especially by men, is concerned, our country ranks high compared to other EU countries [41].

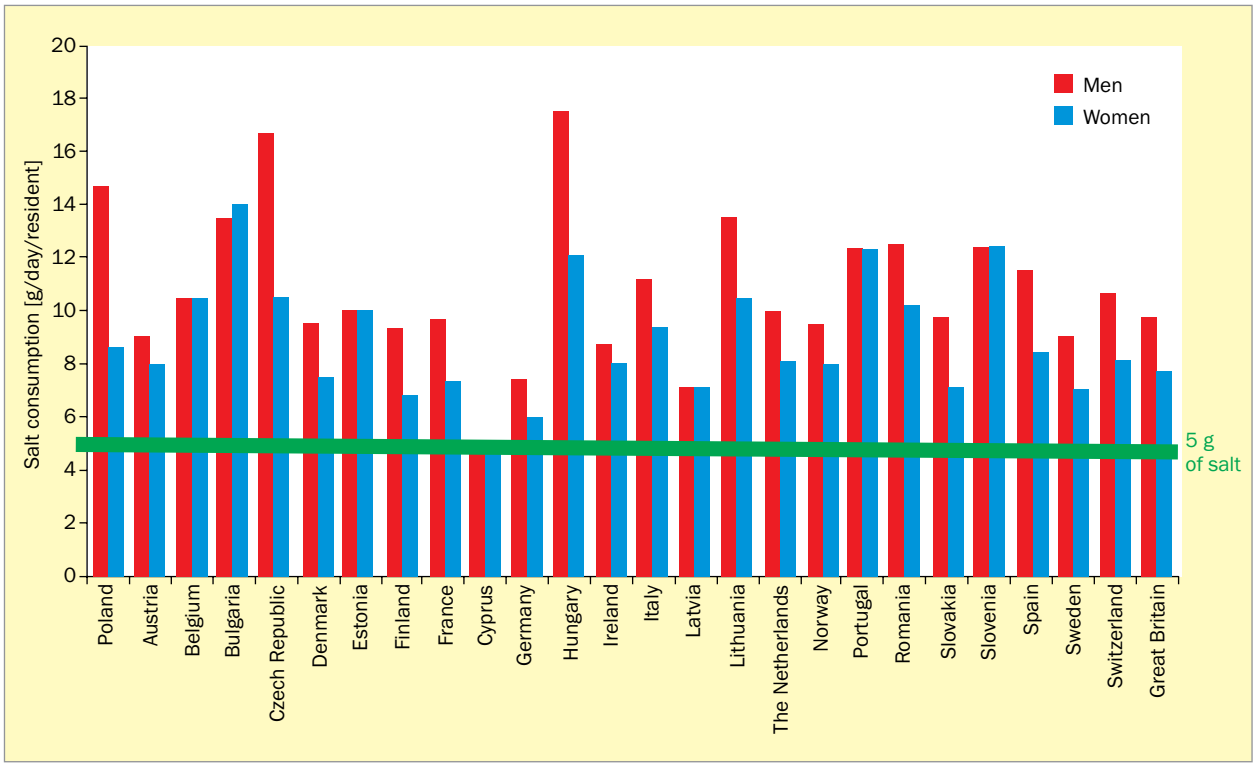

Figure 4. Average salt consumption in Poland and in Europe (g/day/resident) (based on [41])

In Central and Eastern Asia and Western Europe, the average sodium intake is > 4.2 g/day (> 10.5 g NaCl/day). In North America, Western Europe as well as Australia and New Zealand, the average sodium intake varies between 3.4 to 3.8 g/day (8.5 to 9.5 g NaCl/day), whereas in Sub-Saharan Africa and Central America, it is < 3.3 g/day (< 8.25 g NaCl/day) [42].

Salt consumption and cardiovascular diseases

According to Mozzaffarian et al., 1.65 million deaths from cardiovascular diseases per year all over the world are associated with excessive sodium consumption: 61.9% of these deaths occurred in men and 38.1% in women. These deaths represented almost 1 in 10 deaths from cardiovascular diseases (9.5%) [43].

Arterial hypertension

The risk of cardiovascular disease increases with an increase in blood pressure. Evidence derived from many different studies confirms a direct correlation between salt consumption and blood pressure. The INTERSALT Study (International Study of Electrolyte Excretion and Blood Pressure) was one of the first observational studies on salt intake and blood pressure. The study included 10,074 women and men from 32 countries. Sodium excretion was measured based on the 24-hour urine collection. A clear correlation was observed between daily sodium intake and systolic blood pressure [44]. Taking the above results into account, it was decided to check whether limited sodium intake in the diet would result in the decrease in blood pressure. The DASH-Sodium Study (Dietary Approaches to Stop Hypertension - Sodium Study), conducted in the United States on a group of 412 patients with prehypertension or stage-1 hypertension, was the flagship study evaluating this phenomenon. The subjects were randomly assigned to follow the DASH diet, *i.e.* the so-called healthy diet (low in salt), and the typical American diet (rich in salt). It was observed that the systolic blood pressure in patients with both prehypertension and stage-1 hypertension decreased by 11.5 mm Hg on average, which corresponds to the administration of one antihypertensive drug [45].

The meta-analysis of 126 intervention studies with the participation of patients with hypertension, carried out by Graudal et al. [46] showed that limited salt intake in the diet leads to a decrease in systolic and diastolic blood pressure. It should be mentioned that the race of the subjects did not affect the observed effect [46]. It is also worth pointing out that limited salt intake in the diet may help to control resistant hypertension [47]. The TONE (Trial of Nonpharmacologic Interventions in the Elderly) study assessed the effect of limiting the dietary sodium intake (< 80 mmol/day) in hypertensive patients treated with a single antihypertensive drug. After 3 months an attempt was made to stop antihypertensive treatment. The attempt was successful for 30% of the patients [48].

In conclusion, it should be stated that any limitation of table salt intake in the diet has a beneficial effect on both the risk of developing, and the treatment of, hypertension.

Other cardiovascular diseases

An increase of 5 g/day in salt intake involves a 17-percent higher risk of cardiovascular disease and a 23-percent higher risk of stroke. Finland has been striving to reduce the intake of salt in the diet since the 1970s. For more than 30 years of taking preventive action, Finland has managed to reduce its salt intake by one third (6 g/day). Systolic blood pressure decreased by over 10 mm Hg on average and mortality from stroke and ischaemic heart disease fell by 75–80%, whereas life expectancy increased by 5–6 years [49, 50]. Similar preventive measures have also been taken in Japan. Over the decade, salt intake in this country has fallen from 13.5 g/day to 12.1 g/day. It was associated with a significant decrease in stroke mortality [49, 50].

Left ventricular hypertrophy is an important risk factor for premature failure of this organ. Regardless of blood pressure, salt intake is a risk factor for left ventricular hypertrophy. It has been shown that limited salt intake in the diet leads to the regression of left ventricular hypertrophy [51]. Moreover, limited dietary salt intake seems to normalise glomerular hyperfiltration, which often precedes the development of hypertension, observed in sodium-sensitive individuals [52].

Excessive salt intake is also a risk factor for other diseases (Table 1).

Table 1. Impact of excessive salt intake in the diet on human health (based on [50])

Clinical situation/disease	Reliability of evidence*
Arterial hypertension	++++
Stroke	+++
Cardiovascular diseases	+++
Left ventricular hypertrophy	+++
Glomerular hyperfiltration	+++
Kidney stone	+++
Calcium excretion	++++
Bone demineralization	++
Bone fractures	+
Stomach cancer	++
Liquid retention in the body	++++
Cataract	+
Bronchial asthma	+
Meniere's disease	+

*Based on the arbitrarily adopted Cappuccio's scale

Recommendations for limiting salt intake in the diet

In the guidelines published in 2018, the Polish Society of Hypertension recommends to limit the intake of table salt from the usual amount of 9–12 g of NaCl to less than 5 g of NaCl (2 g Na)/day. This recommendation concerns both patients with hypertension and those who want to lead a healthy lifestyle [53]. It is worth mentioning that 5 g of table salt is the equivalent of one teaspoon. Salt intake in Poland and Europe significantly exceeds the recommended amount of 5 g/day (Figure 4 — green line) [41].

The Institute of Food and Nutrition in Warsaw symbolically crosses out the salt shaker on the Pyramid of Healthy Nutrition and Physical Activity and proposes several ways to reduce the intake of salt in the diet, such as: limiting the amount of salt added during meal preparation or, if necessary, adding salt at the end of cooking, using fresh or dried herbs instead of salt, using potassium sodium salt (a mixture of KCl and NaCl) and choosing products with a lower salt content (DRI, daily recommended intake — %) [54].

A study carried out on the veterans living in Taiwan (2.5-year observation) showed that a 17% reduction in the use of NaCl along with a 76% increase in the intake of KCl in the diet reduced the risk of death from cardiovascular diseases by 40% [55].

Conclusion

The article presents the elements of the regulation of sodium metabolism that have been discovered only recently and that are of interest to modern pharmacology; they show how complex maintaining the homeostasis of this ion in the body is. These mechanisms also explain, in a way, the phenomenon of sodium sensitivity occurring in a considerable number of people. As shown by the research, eating habits associated with the consumption of table salt lead to the development of hypertension, cardiovascular and many other diseases resulting in many premature deaths. The consumption of salt in Poland still significantly exceeds 5 g recommended by the Polish Society of Hypertension. Most of salt in an average diet comes from processed foods (72–85%). The Institute of Food and Nutrition in Warsaw recommends several ways that will help people limit the intake of salt in the diet. Special attention is drawn to the use of potassium sodium salt.

Conflict of interest

Authors do not declare the conflict of interest.

Streszczenie

Sód jest głównym kationem zewnątrzkomórkowym. W ostatnich latach opisano wiele mechanizmów biorących udział w regulacji gospodarki sodowej, takich jak: tkanka śródmiąższowa i glikozaminoglikany, limfocyty Th17 i interleukina 17, nabłonkowy kanał sodowy, glikokaliks oraz proproteinowa konwertaza subtyliziny/kexiny typu 6. Złożoność mechanizmów homeostazy gospodarki sodowej sprawia, że budzi ona zainteresowanie nowoczesnej farmakologii. Opisane mechanizmy poniekąd tłumaczą zjawisko sodowrażliwości występujące u znacznej części chorych z nadciśnieniem tętniczym.

Głównym źródłem soli w diecie są pokarmy przetworzone. Proces przetwarzania pokarmów wiąże się z znacznym wzrostem zawartości soli w tych produktach. Nadmierne spożycie soli w diecie obserwuje się w większości krajów świata. Związek między nadmiernym spożyciem soli w diecie a występowaniem chorób, takich jak nadciśnienie tętnicze, udar mózgu, rak żołądka, przerost lewej komory serca, kamica moczowa i inne, był przedmiotem licznych badań. Wykazano liczne korzyści płynące z ograniczenia soli w diecie.

Słowa kluczowe: sód, sól, choroby układu krążenia

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Folia Cardiologica 2020
tom 15, nr 3, strony 236–242
DOI: 10.5603/FC.a2020.0031

ISSN 2353–7752

Impedance techniques in medical practice

Techniki impedancyjne w praktyce lekarskiej

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Abstract

Hemodynamics monitoring provides important information about the performance of the heart, including preload, afterload, contractility, and pump efficiency. The most popular techniques used to be based on invasive methods, such as the Fick's formula, thermodilution, and invasive intravascular pressure monitoring, and noninvasive ultrasound-based methods such as echocardiography, transesophageal Doppler monitoring of stroke volume, and peripheral arterial tonometry. Impedance methods combined with opportunities provided by telemedicine could bring new quality to the medical practice.

Key words: impedance cardiography, rebreathing, hemodynamics, telemedicine

Folia Cardiologica 2020; 15, 3: 236–242

Introduction

Conventional, gold standard methods to evaluate haemodynamic parameters including measurements of stroke volume and blood pressures in the vascular bed are associated with risks typical for invasive procedures and are limited to the hospital settings. A search continues for non-invasive methods which could be used in the outpatient settings, with automated analysis of the collected data. A widely available and established method is echocardiography. However, it is characterized be a long learning curve and requires expensive equipment. The ideal method would be reproducible, characterized by a short learning curve, feasible in the outpatient settings, and relatively inexpensive.

Current efforts focus on several areas. One approach is to use techniques based on the evaluation of respiratory gases. These measurements may allow evaluation of the respiratory function and indirect calculation of haemodynamic parameters. Based on multiple studies, methods of estimating cardiac output based on changes in respiratory gas parameters have been introduced to the clinical practice. The technique of estimating stroke volume based in on changes in carbon dioxide in breathing air is described by the Gedeon-Capek equation [1, 2]. It has been introduced to the clinical practice, *e.g.*, in the intensive care unit of the OLVG hospital in Amsterdam [3].

An extension of this technique is the inert gas rebreathing device, the Innocor® CO (Cosmed, Italy) [4]. This device is filled with a breathing gas mixture containing oxygen, 0.5% nitrous oxide (N_2O) and 0.1% sulfur hexafluoride (SF_6). Measurement of differences in gas concentrations during breathing allows calculation of the effective blood flow through the pulmonary vascular bed. This stroke volume measurement method was employed, among others, in the Columbia space shuttle. The technique was used to study pulmonary blood flow in patients with lung fibrosis [5]. Comparison with cardiac output measurements by magnetic resonance imaging showed good concordance in both lung disease patients and healthy individuals [6].

Carbon dioxide measurements in breathing air were also used in studies on the effect of posture on haemodynamic parameters [7].

Another approach to evaluate the cardiopulmonary system using breathing air gas measurements is the cardiopulmonary exercise test. Assessment of the composition of the exhaled air during exercise allows calculation of

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numerous body function parameters. The cardiopulmonary exercise test allows evaluation of exercise tolerance and provides information regarding the overall body response, including pulmonary, cardiovascular, and skeletal muscle response to exercise. The obtained metabolic and ventilation parameters correlate with increasing symptoms of exercise intolerance (dyspnoea, acid-base balance abnormalities, and exhaustion) [8–10].

In the 20th century, a method based on measurements of impedance changes, with the chest being considered a volume conductor of an electric current, was used for the first time in studies on the cardiovascular system. During application of a 25–100 kHz current, electrical impedance changes occurring with changes in blood volume during the cardiac cycle are measured. This non-invasive method is called impedance cardiography (ICG) or reocardiography.

Physical basis of ICG

The human body is a biological material. The behaviour of biological objects in the electric field has specific features. Electric current flow through a biological material, a human body, generates resistive and capacitive impedance. The net effect is called mutual impedance. Each tissue has specific characteristics of these impedance components during alternating current application, and the frequency spectrum of these impedance components allows tissue differentiation. These tissues include the circulating blood and air within the chest. The mutual relation between these two components is called chest impedance.

The parameters used in impedance techniques include complex permittivity (describing storage and loss properties of biological materials when placed in an electric field), conductivity, and relative electrical permittivity. Biological materials have variable characteristics depending on electric current frequency, as shown in Figure 1 [11].

Chest impedance includes a component related to changes in the circulating blood volume. Blood volume changes during the cardiac cycle lead to changes in chest electrical impedance. Blood is an inhomogeneous suspension. Electrical properties and orientation of erythrocytes result in changing blood electrical conductivity during circulation phases. During current flow with alpha dispersion in the frequency range of 10–100 kHz, erythrocytes generally do not conduct an electric current. Brownian motion results in their random orientation at rest. An electric current running along the vessel must be conducted around the erythrocytes, which results in low electrical conductivity. Blood flow results in parallel erythrocyte orientation. In these settings, an electrical current runs against a lower erythrocyte surface, with a resulting increase in conductivity [12]. Electrical impedance was found to be related to the haematocrit. Impedance cardiography was used in practice before its theoretical physical basis was established. The theoretical basis

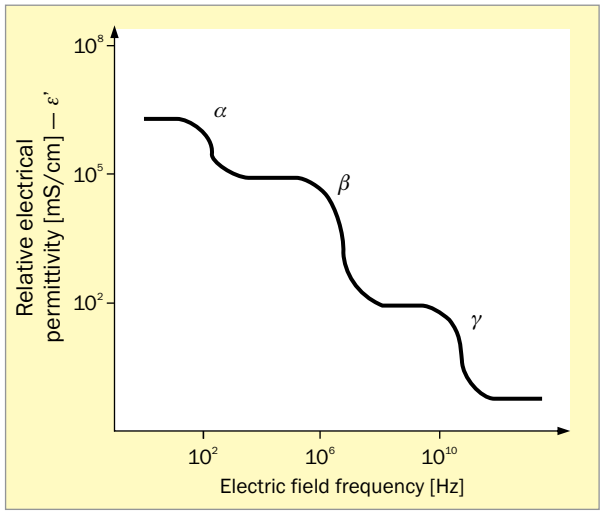

Figure 1. Relative electrical permittivity ε' [mS/cm] of a striated muscle in relation to the electric field frequency [Hz] (adapted from [11])

of impedance changes resulting from conductivity changes in a given location was developed by Geselowitz [13] and Lehr [14], and 8 years later expanded by Moratrelli [15]. The recording of changes in chest impedance during the cardiac cycle was called impedance cardiography or reocardiography. In classical bioimpedance models, the chest was modeled as a cylinder or a truncated cone.

The difference between the classical measurement algorithm by Kubiček (chest as a cylinder) and the Šramek-Brenstein algorithm (chest as a truncated cone) lies in considering a different geometrical solid as an approximation of the chest shape.

The Kubiček formula (chest as a cylinder) is as follows:

$$SV = \rho \frac{L^2 \times dz/dt\ max \times T}{Zo^2}$$

SV — stroke volume; ρ — blood specific electrical resistance factor/determined individually based on haematocrit; L — distance between electrodes in centimeters; dz/dt max — maximum amplitude of the first derivative of impedance (in [Ω/s]); Zo — baseline impedance (in [Ω]); T — left ventricular ejection time (in [s])

The Šramek-Brenstein formula (chest as a truncated cone) is as follows:

$$SV = \rho \frac{L^3 \times dz/dt\ max \times T}{4.25\ Zo}$$

SV — stroke volume; ρ — blood specific electrical resistance factor/determined individually based on haematocrit; L — chess length; dz/dt max — maximum amplitude of the first derivative of impedance (in [Ω/s]); Zo — baseline impedance (in [Ω]); T — left ventricular ejection time (in [s])

The basic Kubiček formula was modified, yielding the Šramek-Brenstein formula [16].

Practical applications of ICG

The bioimpedance technique was used to monitor cardiac performance and cardiovascular haemodynamics in the astronauts of the Apollo space program [17]. After numerous modification, ICG is still used for research purposes [18, 19]. It was employed in studies in patients with heart failure, hypertension [20, 21], children with congenital heart disease [22], and individuals with sleep apnea [23, 24], chronic obstructive pulmonary disease (COPD) [25, 26], and pulmonary hypertension [27, 28]. Despite significant limitations of ICG [29], the method has been approved by the US Food and Drug Administration. The clinical uses of ICG covered under the Medicare program (CMS Coverage Issues Manual {50–54}, 2005 Federal Register) include:

- monitoring of fluid balance in heart failure;
- management of drug-resistant hypertension;
- adjustment of pacemaker settings;
- evaluation of patients receiving inotropic drugs;
- evaluation of patients after cardiac transplantation or myocardial biopsy;
- differentiating between cardiac and pulmonary causes of acute dyspnoea.

In Poland, ICG was approved by the National Health Fund on Jan 1, 2010 as a useful technique (TISS-28 scoring) for monitoring haemodynamic changes in intensive care units. Measurements of changes on electrical chest impedance were performed during high frequency alternating current application using the four electrode configuration. For example, the Niccomo™ device (Medis, Germany) used four dual application/sensing electrodes to apply 1.0–4.0 mA current at 25–75 kHz. The receiving electrodes recorded the electrocardiogram and changes in electrical impedance.

In the analyses of the results, the following parameters were used:

- preload — thoracic fluid content (TFC);
- stroke volume (SV);
- cardiac output — CO = SV × HR;
- systolic, diastolic, mean pressure;
- afterload as described by systemic vascular resistance (SVR).

The above parameters were automatically indexed for the body surface area of the studied individual.

Cardiac contractility was described using the following parameters:

- Heather index (the ratio of peak ventricular ejection flow [dz/dt max] to the period of increasing first derivative of impedance with respect to time [electromechanical time interval, or time from the onset of ventricular depolarization to dz/dt max]);
- preejection period (PEP);
- left ventricular ejection time (LVET);
- PEP/LVET ratio (Weissler index).

The results were correlated with echocardiographic and clinical evaluation.

The PhysioFlow Q-Link device used a different electrode configuration (Figure 3 [30]).

Dyspnoea is one of the most common symptoms of heart failure. However, differentiating between various

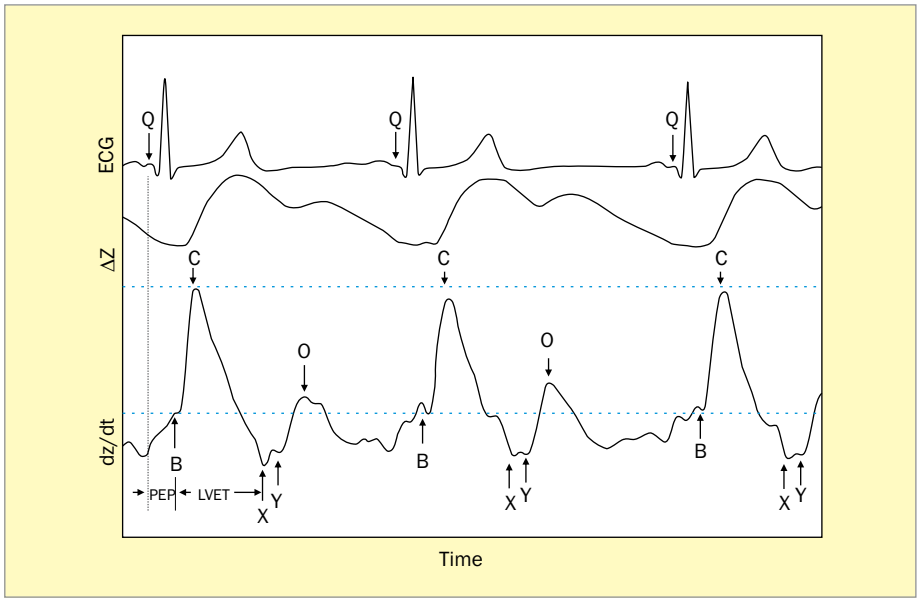

Figure 2. Impedance cardiogram and electrocardiogram. Temporal and amplitude relations; B — aortic and pulmonary valve opening; C (dz/dt max) — peak blood flow through the aortic valve; ECG — electrocardiography; LVET — left ventricular ejection time; O dz/dt — is the effect of limited ventricular ability to accommodate venous inflow during early diastole; PEP — preejection period; Q — onset of ventricular depolarization; X — aortic valve closure; Y — pulmonary valve closure (adapted from [11])

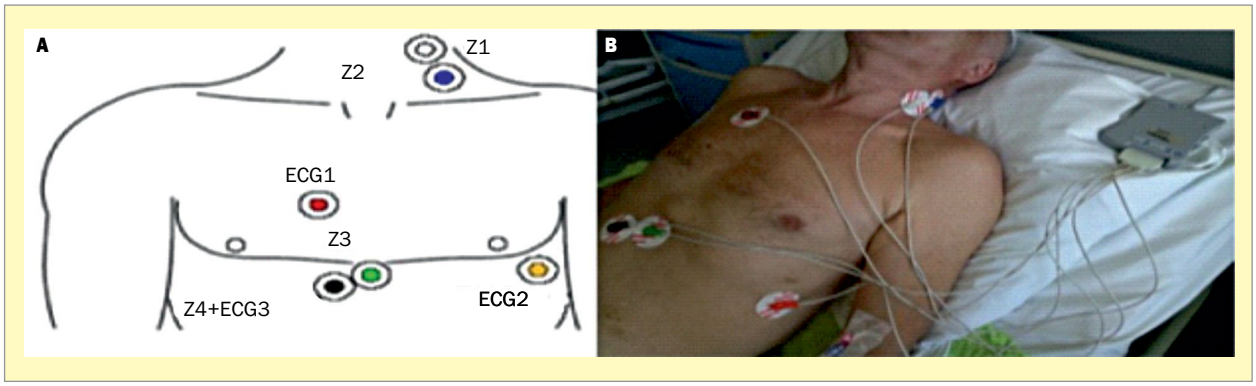

Figure 3A, B. Chest electrode configuration for the measurements of chest impedance changes using the PhysioFlow Q-Link device (Manatec Biomedical, Paris, France). The scheme and photography from the author's own research; Z1, Z4 — current electrodes; Z2, Z3 — voltage electrodes; ECG — electrocardiography (adapted from [30])

causes of dyspnoea continues to be a major challenge in the clinical practice. Dyspnoea is the most common symptom in patients presenting to emergency departments. Early accurate diagnosis may be of a major importance for selecting appropriate treatment. ICG as a non-invasive modality for the evaluation of the cardiovascular system was studied as a tool to support diagnostic and therapeutic decisions.

In the Impact of Impedance Cardiography on Diagnosis and Therapy of Emergent Dyspnea (ED-IMPACT) trial, the utility of ICG for differentiating between various causes of dyspnoea in the emergency department was evaluated [31]. ICG was performed in two academic centres in 89 subjects above 65 years of age who presented with dyspnoea. A complete clinical examination was performed, and haemodynamic parameters obtained from ICG in the emergency department were analyzed. ICG had been performed before laboratory test and chest X-ray results were available. The number of changes in diagnoses and treatment modifications following unblinding of ICG haemodynamic data was evaluated. A comparison of haemodynamic parameters showed significant differences between the group with predominant heart failure and the groups with COPD and other conditions ($p < 0.02$). Thoracic fluid content was highest in the group with heart failure (38.5 ± 12.3 vs. 30.0 ± 6.17 vs. 30.4 ± 5.6 $kOhm^{-1}$, respectively). SVR was highest in the group with heart failure (1772 ± 565 vs. 1361 ± 407 vs. 1789 ± 638 dyn × sec × cm^{-5}, respectively).

The cardiac index (CI) was highest in the group with COPD (2.39 ± 0.56 vs. 3.08 ± 0.57 vs. 2.48 ± 0.65 L/ /min/m^2, respectively).

Patients with heart failure had higher SVR, TFC, and lower CI, while patients with COPD had low TFC, SVR, and higher CI. Exacerbated heart failure and COPD were the final diagnoses in 43 (48%) and 20 (22%) patients, respectively. Data from ICG changed the diagnosis in 12 patients [13%; 95% confidence interval (CI) 7% to 22%] and the therapy in 35 patients (39%; 95% CI 29% to 50%). The authors noted that this simple test clearly supported diagnostics and therapeutic decisions.

Another randomized IMPEDANCE-HF trial evaluated whether lung impedance monitoring would reduce hospitalizations in patients with acute exacerbated heart failure. This blinded study was performed in two centres [32]. The study included 256 patients with chronic heart failure and, reduced left ventricular ejection fraction (≤ 35%) and New York Heart Association (NYHA) class II–IV symptoms. All patients were hospitalized due to acute exacerbated heart failure during the previous 12 months. They were randomized to the impedance monitoring group or the usual care group. Telemedical thoracic fluid content monitoring was performed using the electrode configuration shown in Figure 4.

The primary endpoint was hospitalization due to exacerbation of the primary condition. Secondary endpoints were hospitalizations due to other causes and deaths. Significantly fewer patients were readmitted in the monitoring group (67 vs. 158, $p < 0.001$), with lower cardiac and overall mortality. These results suggest that the impedance monitoring is useful in the outpatient setting.

Other authors used a four-electrode configuration to study changes in thoracic fluid content, particularly in lungs. Two electrodes (current and voltage) are placed below the right scapular angle, and two more below the right clavicle in the right parasternal line. Changes in electrical impedance compared to the measurement at the optimal clinical status of the patient indicate an increase or reduction of thoracic fluid content [33]. An increase in thoracic fluid content results in an impedance drop compared to baseline, while a decrease in thoracic fluid content will be reflected by an increase in impedance. In the study, a telemetric system to monitor changes in

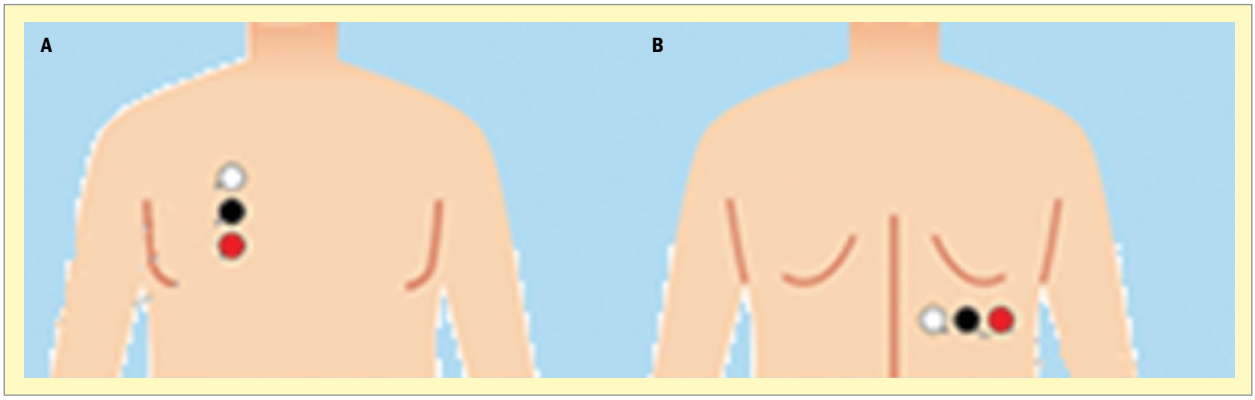

Figure 4A, B. Electrode configuration for measurements of changes in thoracic fluid content based on chest impedance measurements (adapted from [32])

lung fluid content was used. Data obtained during 90-day monitoring in patients discharged after heart failure decompensation were compared to a similar period without monitoring. A reduction in the hospitalization rate by 87% in men and 79% in women was found in the monitoring group. The authors concluded that telemetric lung fluid content monitoring had a significant diagnostic potential to reduce the rate of recurrent admissions for acute decompensated heart failure.

Another group of authors evaluated the utility of telemedical chest impedance measurements to detect fluid accumulation. The recorded data were automatically sent via a cellular phone to the monitoring center. The monitoring was undertaken in 106 patients for 45 days, followed by a follow-up of 75 days. The algorithm used was found to be 87% sensitive and 70% specific. As highlighted by the authors, the study subjects transmitted data on thoracic fluid content changes daily without any significant technical issues [34].

Use of telemetric systems has been a subject of studies undertaken by The National Centre for Research and Development in Poland. ICG was used to monitor cardiac performance in patients with ischaemic stroke in the PBS2/A3/17/2013 project "Internet platform for data integration and cooperation of medical research teams for the purposes of stroke units". Currently, the STRATEGMED3/305274/8/NCBR/2017 project is underway under the AMULET acronym [35], "A new model of medical care using modern techniques of noninvasive clinical evaluation and telemedicine in patients with heart failure". Impedance methods were used to monitor therapy in patients with heart failure. In this randomized study, the effect of ICG monitoring on cardiovascular mortality and recurrent hospitalizations due to acute decompensated heart failure compared to usual care is being evaluated in nine centers in Poland. The primary combined endpoint includes cardiovascular deaths and/or hospitalizations due to exacerbation of the primary condition.

Studies on the use of noninvasive techniques to monitor haemodynamic changes during the exercise test were carried out in several centres. A major problem is the selection of the measurement technique for practical studies. For this purpose, four techniques were compared simultaneously:

- conventional Fick technique;
- ICG using the PhysioFlow device;
- pulse contour analysis;
- measurements of changes in breathing gas composition (Innocor – rebreathing).

Values obtained using the Innocor device were lower, and those obtained by ICG were higher compared to other techniques. The authors concluded that the precision of cardiac output measurements depended on the technique used [36]. Other authors simultaneously used ICG and the indocyanine green dye dilution method (CO_{DD}) during the exercise test in patients with COPD. A strong correlation between measurements using these two techniques was noted in 50 patients [37].

Intrathoracic impedance measurement in patients with a cardiac pacemaker

In 2003, encouraging results regarding the use of an ICG device incorporated into a cardiac pacemaker were published by the research group of Patterson and Wang. These authors hypothesized that a device measuring impedance between the pacemaker casing and the pacemaker lead would provide information on the changes in water content in the lung tissue [38]. A computer software automatically calculates a specific impedance curve in an individual patient, providing a measure of water content called the fluid index. Exceedance of the critical level of thoracic water content is signaled by the peripheral device. Studies showed that intrathoracic impedance measurements in patients with heart failure and an implantable cardioverter-defibrillator allowed early detection of acute decompensated

heart failure. The devices to monitor thoracic fluid content incorporated into implantable cardiac devices continue to be modified [39, 40].

Summary

Noninvasive methods, including the impedance techniques, continue to be developed. The impedance techniques have been introduced in the outpatient settings for the monitoring of haemodynamic changes as the indices of cardiac performance.

Funding

The study was performed under the STRATEGMED3/305274/8/NCBR/2017 project.

Streszczenie

Monitorowanie hemodynamiczne dostarcza istotnych informacji o wydolności serca — obciążeniu wstępnym, następczym, kurczliwości serca, wydajności „pompy sercowej". Najbardziej popularne techniki obejmowały pomiary metodami inwazyjnymi — Ficka, termodylucji i pomiary inwazyjnych ciśnień w łożysku sercowo-naczyniowym oraz metodami nieinwazyjnymi opartymi na technikach ultradźwiękowych — echokardiografii, przezprzełykowym doplerowskm monitorowaniu przepływu przez aortę wstępującą oraz tonometrii aplanacyjnej. Połączenie metod impedancynych z możliwością analizy telemedycznej wyników może stworzyć nową wartość w praktyce lekarskiej.

Słowa kluczowe: kardiografia impedancyjna, *rebreathing*, hemodynamika, telemedycyna

Folia Cardiologica 2020; 15, 3: 236–242

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Folia Cardiologica 2020
tom 15, nr 1, strony 243–249
DOI: 10.5603/FC.2020.0035

ISSN 2353–7752

Cardiac evaluation in patients with neuromuscular diseases

Diagnostyka kardiologiczna u chorych z chorobami nerwowo-mięśniowymi

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Abstract

Cardiac involvement in neuromuscular disease most often manifests with cardiomyopathy, atrioventricular conduction disturbances, and supraventricular and ventricular tachyarrhythmias, accompanied by heart failure in some patients. The phenotype of cardiac involvement, and to a large extent also the symptoms and the timing of their occurrence, depend on the genetic background of the neurological disease, hence the importance of genetic testing. Knowledge of the proper neurological diagnosis supported by genetic testing results allows for targeted cardiological investigations. Non-invasive imaging modalities (echocardiography, cardiac magnetic resonance) and cardiac rhythm monitoring using electrocardiography allow the assessment of myocardial involvement progression and implementation of appropriate treatment. In addition, they enable identification of asymptomatic patients at an early disease stage and prevention of future sudden cardiac death.

Key words: muscular dystrophy, cardiomyopathies, conduction disorders, dystrophinopathies, laminopathies, myotonic dystrophy

Folia Cardiologica 2020; 15, 3: 243–249

Introduction

Neuromuscular diseases (NMD) are a wide group of disorders with varying clinical phenotypes. Peripheral muscle dysfunction is often accompanied by abnormal myocardial structure and function, particularly in patients with various types of muscular dystrophy. In the recent decades, our knowledge on the genetic defect underlying most muscular dystrophies has expanded significantly. Of interest, the same mutations may be associated with various phenotypes, including isolated cardiomyopathies without peripheral muscular symptoms [1]. In most muscular dystrophies, cardiac involvement manifests as various types of cardiomyopathy, with or without symptomatic heart failure, atrioventricular conduction disturbances, and atrial and ventricular tachyarrhythmias (Table 1). Cardiac involvement manifesting during childhood or in the first three decades of life is typical for many NMD. However, cardiac symptoms may also develop much later, or precede the diagnosis of NMD in some relatively low-symptomatic neurological syndromes. Some NMD are associated with a high risk of sudden cardiac death (SCD). Others, despite evidence of advanced cardiac involvement, are not associated with an increased SCD risk, and the cause of death is usually respiratory failure or other organ damage. In addition to appropriate neurological phenotypic characterization, an attempt to make the genetic diagnosis is of key importance in NMD. Early detection of mutations predisposing to the development of cardiomyopathy or conduction disturbances should prompt appropriate investigations and prevention of life-threatening arrhythmia. Of note, with non-invasive modalities to evaluate myocardial function, such

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Table 1. Most common types of neuromuscular disease and associated cardiac complications

NMD type	Molecular defect	Mode of inheritance	Cardiac involvement		
			Cardiomyopathy	AV conduction disturbances	Arrhythmia
DMD	Dystrophin	XR	DCM	Rare	Common mild
BMD	Dystrophin	XR	DCM	Rare	Common
EDMD 1	Emerin	XR	CM	Common	Common
EDMD 2	Lamin A/C	AD	DCM	Common	Common
DM 1	Protein kinase	AD	Rarely HCM/DCM	Common	Common
LGMD 1B	Lamin A/C	AD	DCM	Common	Common
LGMD 2E	B-sarcoglycan	AR	DCM	Common	Common
FA	Frataxin	AR	HCM	Rare	Common

NMD — neuromuscular disease; DMD — Duchenne muscular dystrophy; BMD — Becker muscular dystrophy; EDMD — Emery-Dreifuss muscular dystrophy; DM — myotonic dystrophy; LGMD — limb-girdle muscular dystrophy; FA — Friedreich ataxia; CM — cardiomyopathy; DCM — dilated cardiomyopathy; HCM — hypertrophic cardiomyopathy; XR — X-linked; AD — autosomal dominant; AR — autosomal recessive; AV — atrioventricular

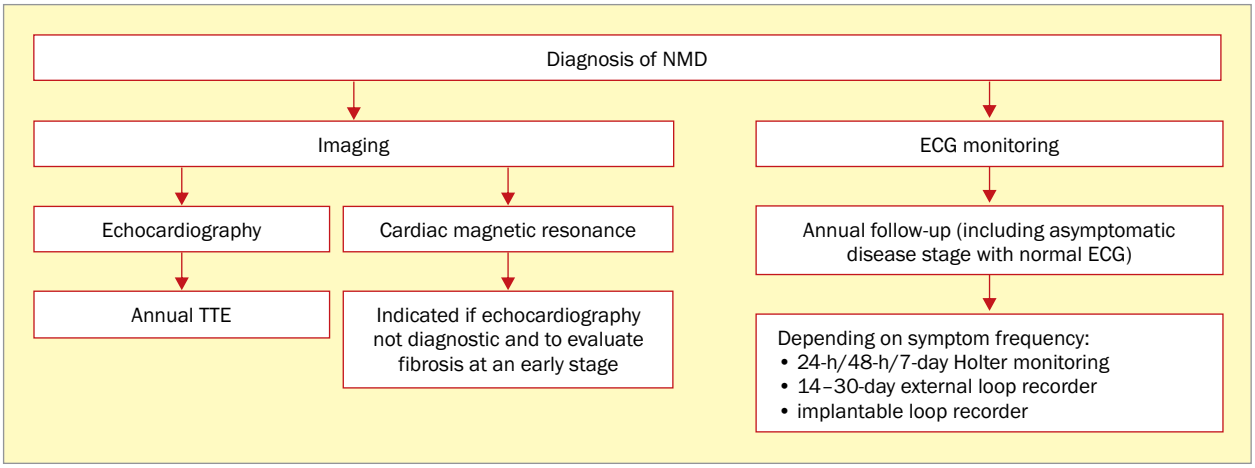

Figure 1. Suggested cardiac evaluation following the diagnosis of neuromuscular disease (NMD); TTE — transthoracic echocardiography; ECG — electrocardiogram

as echocardiography, cardiac magnetic resonance (CMR) and electrocardiography (ECG), it is possible to identify cardiac dysfunction prior to any cardiovascular symptoms [2] (Figure 1). In the present review, we focused on selected issues related to cardiac involvement in dystrophinopathies, laminopathies, and myotonic dystrophy (DM).

Dystrophinopathies

Duchenne muscular dystrophy (DMD) is the most common NMD. It is an X-linked disorder with the incidence of 1:3600–1:9300 births among males. The genetic defect usually involves deletion of multiple exons of the dystrophin gene on chromosome X. Due to frame shift, dystrophin is virtually absent. In Becker muscular dystrophy (BMD), dystrophin gene mutation usually does not lead to frame shift and the gene is translated, leading to a partially functional protein, although present in lesser amounts. This results in a much milder clinical course of muscular dystrophy, and usually much later onset of cardiomyopathy. The incidence of BMD is also much lower (1:18,000).

DMD

Myocardial involvement in DMD manifests with dilated cardiomyopathy (DCM). The mean age at the onset of systolic dysfunction is about 14 years [3], and development of heart failure symptoms is usually delayed, which may be explained by limited activity of the patients. Cardiac investigations should be initiated at the time of the diagnosis of DMD [4] and should also target mutation carriers, *i.e.*, mothers and sisters of DMD patients, as systolic dysfunction and evidence of myocardial fibrosis can usually be identified in them in the fifth decade of life [5]. Despite severe systolic

dysfunction present in DMD, ventricular arrhythmia is less frequent than might be expected, which may be partially explained by lower sympathetic tone in these patients. Atrioventricular conduction disturbances, typical for some NMD, are also very rare in this disorder.

BMD

In most patients with BMD, initial manifestations of cardiac involvement develop after 20 years of age but they are present in 70% of patients by the age of 40 [6]. The clinical phenotype is of DCM with varying severity of heart failure symptoms. The clinical course of BMD is much less predictable compared to DMD. There is no simple correlation between the severity of DCM and peripheral muscle involvement. In addition, the risk of SCD seems higher in BMD compared to DMD, which may only be partially explained by earlier development of respiratory failure in DMD, potentially leading to earlier death. As a result, patients with BMD-related cardiomyopathy are much more often referred for implantation of a cardioverter-defibrillator (ICD).

Laminopathies

Emery-Dreifuss muscular dystrophy (EDMD) is a rare form of NMD (incidence about 1:100,000 births) characterized by an early presence of joint contractures, slowly progressing muscle weakness and associated atrioventricular conduction disturbances. The underlying genetic defect may involve various proteins of the nuclear envelope. Several subtypes have been defined, and the most common ones are EDMD 1 due to emerinopathies (caused by mutations in the *EMD* gene) and laminopathies (caused by mutations in the *LMNA* gene).

EDMD 1

EDMD 1 is an X-linked disorder. The clinical course is initially mild. Sometimes the correct neurological diagnosis is only made after an advanced atrioventricular block develops in a young man without conventional cardiovascular risk factors. Atrioventricular conduction disturbances are usually accompanied by junctional escape rhythm and atrial standstill, often preceded by low-amplitude atrial fibrillation (AF) [7]. In the early disease phase (usually second to third decade of life), patients require cardiac pacing without a defibrillator, as the risk of malignant ventricular arrhythmia is initially not high [6]. With disease progression, fibrosis may progress and involve not only atria but also ventricles, ultimately leading to the typical DCM phenotype. At that stage, the risk of ventricular arrhythmia is high enough to warrant consideration of ICD implantation. The disease is associated with significant atrial enlargement, predisposing to supraventricular arrhythmia. As a result, the risk of thromboembolic complications including ischaemic stroke is significantly increased [8].

EDMD 2

This type of dystrophy is usually characterized by an autosomal dominant mode of inheritance. A defect in the lamin *A/C* gen may also lead to a phenotype of isolated DCM with particularly poor prognosis resulting from a high rate of SCD. A similar genetic defect was identified in one type of limb-girdle muscular dystrophy (LGMD 1B) [9]. The neurological phenotype is the same in both most common forms of EDMD, while the cardiac presentation varies. EDMD 2 is usually characterized by DCM with a relatively modest left ventricular chamber enlargement despite severe systolic dysfunction, accompanied by atrioventricular conduction disturbances. This type of EDMD is associated with a high risk of tachyarrhythmia-related SCD, usually due to ventricular fibrillation (VF) [6]. In all patients with this type of muscular dystrophy, SCD risk should be evaluated using available tools including dedicated calculators [10, 11] (Table 2).

Myotonic dystrophy

Myotonic dystrophy is one of the most common (incidence 1:8,000 births) muscular dystrophies, most typically manifesting with myotonia, or impaired muscle relaxation, which accompanies muscle weakness and atrophy, and symptoms from other organ systems (glaucoma, frontal hair loss, hormonal disturbances). The mode of inheritance is autosomal dominant. The risk of cardiac complications depends on the type of DM.

DM 1

In the more common type 1, the defect involves the *DMPK* gene coding for a protein kinase, and it is characterized by trinucleotide triplet expansion. Genetic anticipation can be seen, with increasing symptom severity in successive generations due to prolongation of repeated sequences. In this type of DM, cardiac involvement is seen in about 80% of patients. Atrioventricular and intraventricular conduction disturbances are most commonly accompanied by supraventricular and ventricular tachyarrhythmias [12] (Table 1). Cardiomyopathy, usually of the DCM phenotype, is relatively rare.

DM 2

In this type, the defect involves the *CNBP* gene which encodes a zinc finger protein. Trinucleotide triplet expansion is also present but without evident genetic anticipation. The clinical presentation is more heterogeneous compared

Table 2. Evaluation of the risk of life-threatening tachyarrhythmia in laminopathies (from [10])

Parameter	Evaluation
Gender [M/F]	Higher risk in men
Non-missense *LMNA* gene mutation [yes/no]	Insertions, deletions, truncation mutations, abnormal splicing
AVB [no/1st degree AVB/advanced AVB]	The highest degree of AVB should be taken into account. First-degree AVB is defined as PR interval ≥ 0.2 s, and advanced AVB is defined as second-degree Mobitz II AVB or third-degree AVB (but not second-degree Mobitz I AVB)
nsVT [yes/no]	≥ 3 ventricular beats ≥ 120/min and duration < 30 s during Holter ECG monitoring for a minimum of 24 h
LVEF [%]	Echocardiographic measurement

M — male; F — female; AVB — atrioventricular block; nsVT — nonsustained ventricular tachycardia; LVEF — left ventricular ejection fraction; ECG — electrocardiography

to type 1 but usually milder, with a lower risk of cardiac involvement which is seen in up to 10–20% cases. Typical cardiac manifestations include first-degree atrioventricular block and bundle branch blocks [13].

Cardiac tests in patients with NMD

Imaging is necessary to identify myocardial involvement, assess its progression, and select patients for implantation of cardiac devices. Echocardiography or CMR is recommended upon the diagnosis of NMD due to the possibility of an low-symptomatic course of cardiac involvement. If no abnormalities are found, imaging should be repeated anually or ever 1–5 years [4, 14]. Due to concomitant chest deformities and poor acoustic windows, mostly in DMD, echocardiography is often not fully diagnostic and CMR is warranted. The latter modality is also dedicated for patients with identified mutations but no abnormalities found on echocardiography. To detect supraventricular or ventricular arrythmia that may be associated with a risk of SCD, follow-up ECG monitoring should be performed annually since the diagnosis of NMD [4, 15]. Depending on the frequency of symptoms suggesting arrhythmia which was not recorded in conventional ECG, options include 24-hour, 48-hour, or 7-day Holter ECG monitoring, 14- to 30-day monitoring with an external loop recorder, or an implantable loop recorder [15] (Table 3).

Drug therapy in patients with cardiac involvement in NMD

Few data are available to support the use of typical drug therapy recommended in heart failure or asymptomatic left ventricular systolic dysfunction in patients with NMD-related cardiomyopathies. There is some evidence indicating that angiotensin-converting enzyme (ACE) inhibitors and corticosteroids (used to improve muscle strength and prevent cardiomyopathy) are warranted in patients with DMD. However, most recommendations are based on extrapolating data from the general population of patients with heart failure of various aetiology to the NMD populations. Currently, ACE inhibitors are recommended in all patients with NMD and reduced left ventricular ejection fraction (LVEF) and should be considered in boys above 10 years of age with DMD for the primary prevention of DCM [4].

There is a consensus that beta-blockers should be used in patients with NMD and existing systolic dysfunction, and in patients with cardiac arrhythmia to relieve symptoms related to tachyarrythmias. However, beta-blockers are generally not recommended solely for the prevention of systolic dysfunction or symptomatic heart failure in patients without existing left ventricular systolic dysfunction.

Based on promising data on the effectiveness of combined aldosterone antagonist and ACE inhibitor treatment in patients with DMD and concomitant left ventricular systolic dysfunction, such a combination should be considered in patients with DMD/BMD who fulfil the above criterion. It may also be considered in those with preserved systolic function and myocardial fibrosis identified in CMD [4]. Of note, the above recommendations apply only to patients with dystrophinopathies.

Similarly, glucocorticosteroids may be considered to delay progression of cardiac involvement in a limited population of patients with DMD.

Based on the current recommendations, anticoagulation in NMD should be limited to patients with established indications for such treatment (*e.g.*, presence of an intracardiac thrombus), and may be considered in patients with documented AF. The role of commonly used scoring systems for the risk of thromboembolic complication, and of novel oral anticoagulants has not been established in the NMD population. In the clinical practice, patients above 30 years of age with EDMD and concomitant AF, atrial flutter or atrial standstill receive anticoagulation due to markedly increased stroke risk regardless of the risk estimation using the CHA_2DS_2-VASc score (Table 4).

Table 3. The 2005 European Society of Cardiology (ESC) recommendations of arrhythmia treatment in patients with neuromuscular disease (from [15])

Recommendation	Class of recommendations	Level of evidence
Annual follow-up is recommended in patients with muscular dystrophies, even in the concealed phase of the disease when patients are asymptomatic and the ECG is normal	I	B
It is recommended that patients with NMD who have ventricular arrhythmia are treated in the same way as patients without NMD	I	C
Permanent pacemaker implantation is recommended in patients with NMD diseases and third--degree or advanced second-degree AVB at any anatomical level	I	B
Permanent pacemaker implantation may be considered in patients with DM type 1 (Steinert disease), Kearns–Sayre syndrome or LGMD with any degree of AVB (including first-degree) in consideration of the risk of rapid progression	IIb	B
The use of an ICD may be considered in DM type 1 (Steinert disease), EDMD and LGMD type 1B when there is an indication for pacing and evidence of ventricular arrhythmias	IIb	B

ECG — electrocardiography; NMD — neuromuscular disease; AVB — atrioventricular block; DM — myotonic dystrophy; LGMD — limb-girdle muscular dystrophy; EDMD — Emery-Dreifuss muscular dystrophy

Table 4. Indications for cardiac treatment in patients with neuromuscular disease

Type of therapy		Indicated	May be considered	Not recommended
Drug therapy	ACEI	LVEF ≤ 35% DMD > 10 years of age		
	MRA	DMD/BMD + LV systolic dysfunction (in combination with ACEI)	DMD/BMD + preserved LV systolic function when fibrosis present on CMR	
	BB	Systolic dysfunction, symptomatic tachyarrhythmia		Prevention of systolic dysfunction, symptomatic HF without systolic dysfunction
	GCS		DMD + to delay progression of cardiac involvement	
	AC	Depending on the risk of thromboembolic complications; documented intracardiac thrombus; documented AF or atrial flutter	EDMD + AF, atrial flutter, atrial standstill > 30 years of age	
Conventional pacing		Symptomatic bradyarrhythmia, AV conduction disturbances (absolute indications: asymptomatic third degree or second degree Mobitz II AV block)	DM 1, LGMD, EDMD + symptomatic second degree Mobitz I or first degree AV block	
Cardiac device	ICD	Symptomatic HF with NYHA class II–III symptoms, LV systolic dysfunction, LVEF ≤ 35%, high SCD risk		
	CRT	QRS ≥ 130 ms + LBBB (in SR) particularly in EDMD, BMD, DM 1	QRS ≥ 130 ms without LBBB (in SR) or with AF	
Ventricular assist device			Destination therapy in selected situations in DMD	
Cardiac transplantation		Mild changes in peripheral muscle, preserved respiratory function		

ACEI — angiotensin-converting enzyme inhibitors; LVEF — left ventricular ejection fraction; DMD — Duchenne muscular dystrophy; MRA — mineralocorticoid receptor antagonists; BMD — Becker muscular dystrophy; LV — left ventricle; CMR — cardiac magnetic resonance; BB — beta-blockers; HF — heart failure; GCS — glucocorticosteroids; AC — anticoagulants; AV — atrioventricular; DM — myotonic dystrophy; LGMD — limb-girdle muscular dystrophy; EDMD — Emery-Dreifuss muscular dystrophy; AF — atrial fibrillation; ICD — implantable cardioverter-defibrillator; NYHA — New York Heart Association; SCD — sudden cardiac death; CRT — cardiac resynchronization therapy; LBBB — left bundle branch block; SR — sinus rhythm

Conventional pacing

Candidates for permanent cardiac pacing include patients with symptomatic bradycardia due to sinus node disease or atrioventricular block [15]. In the population with NMD, atrioventricular conduction disturbances are more common in patients with EDMD, DM and LGMD, and cardiac pacing should be considered at the initial manifestation (usually below 30 years of age). It should be remembered, however, that pacemaker implantation in patients with EDMD does not protect from stroke due to the occurrence of AF or atrial standstill. In patients with bradycardia and AF, rate adaptive ventricular pacing should be preferred over dual-chamber pacing.

Implantable cardiac devices (cardioverter defibrillator, cardiac resynchronization therapy)

Typical indications for ICD implantation for primary prevention of SCD are present in optimally managed patients with symptomatic heart failure with New York Heart Association (NYHA) class II–III symptoms and left ventricular systolic dysfunction with LVEF ≤ 35% [16]. In general, the same indications apply to the NMD population. The final decision, however, should also take into account specific circumstances in these patients, including life expectancy, potentially futile care in end-stage disease, risk of procedural complications, and the risk of inappropriate ICD interventions. The neurological diagnosis, genetic defect, or even mutation type in a given patient should also be considered, as these may indicate a particularly high SCD risk. In summary, ICD implantation should be considered in selected patients with DMD, BMD, EDMD 2, LGMD 1B, DM 1, and Friedreich ataxia, taking into account the above risk factors. Cardiac resynchronization therapy (CRT) may be considered in patients with indications for permanent pacing, systolic dysfunction, and predicted high percentage of pacing, particularly in EDMD, BMD, and DM 1.

Other options

In some patients, particularly with EDMD 2, LGMD 1B and BMD, cardiac transplantation may be considered if peripheral muscle changes are not advanced and respiratory function is preserved. There are also single reports of the use of ventricular assist devices as destination therapy in patients with DMD. Integrated palliative care is recommended in end-stage heart failure.

Summary

Most patients with NMD are at risk of cardiac involvement. Precise neurological diagnosis is vital for early determination of this risk and implementation of appropriate treatment, including therapies to delay the development of cardiomyopathy. Early imaging using echocardiography or CMR and systematic monitoring of the progression of myocardial involvement are necessary to guide decisions regarding initiation of drug treatment and therapies to prevent SCD. The risk of cardiac complications, and thus management may vary significantly depending on the underlying genetic defect despite similar or even identical phenotypic presentation. Both effective drug therapy and invasive procedures that modify outcomes in many NMD are currently available. Neurological units involved in the diagnosis and management of NMD should cooperate with adequately prepared cardiologists experienced in managing NMD patients.

Conflict of interest(s)

The authors declare no conflicts of interests.

Streszczenie

Zajęcie mięśnia sercowego w przebiegu chorób nerwowo-mięśniowych najczęściej objawia się pod postacią kardiomiopatii, zaburzeń przewodnictwa przedsionkowo-komorowego oraz tachyarytmii nadkomorowych i komorowych, przebiegających niekiedy z niewydolnością serca. Fenotyp zajęcia serca, a w dużej mierze również objawy i czas ich wystąpienia, zależą od podłoża genetycznego choroby neurologicznej, dlatego należy podkreślić istotę badań genetycznych. Znajomość właściwego rozpoznania neurologicznego popartego wynikiem badań genetycznych pozwala na ukierunkowaną diagnostykę kardiologiczną. Nieinwazyjne badania obrazowe (echokardiografia, rezonans magnetyczny serca) oraz monitorowanie rytmu serca za pomocą elektrokardiografii pozwalają na ocenę progresji zajęcia mięśnia sercowego i wdrożenie odpowiedniego leczenia. Co więcej, umożliwiają wychwycenie pacjentów bezobjawowych na wczesnym etapie choroby i prewencję wystąpienia nagłego zgonu sercowego w przyszłości.

Słowa kluczowe: dystrofia mięśniowa, kardiomiopatie, zaburzenia przewodnictwa, dystrofinopatie, laminopatie, dystrofia miotoniczna

Folia Cardiologica 2020; 15, 3: 243–249

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Commentary

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The article "Cardiac evaluation in patients with neuromuscular diseases" deals with an important issue in specialist cardiology practice. Individuals with neuromuscular diseases are a heterogeneous group of patients with various clinical presentation in terms of both neurological symptoms and potential cardiovascular complications.

While the knowledge on specific neuromuscular disorders is well established among the neurologists, in the cardiology practice these patients may be collectively referred to as "patients with dystrophy", without detailed differentiation between different types. Obviously, this may be sometimes justified and explained by the organization of health care, as the duration of the diagnostic workup from the suspicion of neuromuscular disease to the genetic diagnosis is usually long. The authors briefly present the most important aspects of cardiac investigations and therapeutic possibilities in the most important and most common neuromuscular diseases, including Duchenne and Becker muscular dystrophies, Emery-Dreifuss muscular dystrophy, and myotonic dystrophy type 1 (Steinert disease) and type 2.

Cardiac involvement in myotonic dystrophies deserves a more detailed discussion. Indeed, the most dangerous consequences of cardiac involvement in myotonic dystrophy type 1 include advanced atrioventricular conduction disturbances, with or without prior first degree atrioventricular block present for many years. It should be stressed that sudden cardiac death in patients with myotonic dystrophy type 1 is most commonly associated with advanced or complete atrioventricular block. In contrast, tachyarrhythmias are less frequent in Steinert disease but may also contribute to poor prognosis. Established risk factors for sudden cardiac death in this population should be borne in mine, *i.e.*, non-sinus rhythm (particularly atrial fibrillation), PR interval prolongation > 240 ms, QRS duration > 120 ms, intermittent second- and third-degree atrioventricular block, and corrected QT interval > 450 ms. A history of bradycardia-induced ventricular fibrillation is also considered an indication for prompt cardioverter-defibrillator implantation in some countries, especially in patients with left ventricular systolic dysfunction.

As indicated by the authors, the risk of cardiac involvement in myotonic dystrophy type 2 is lower compared to type 1. Our experience indicates that atrioventricular and interventricular conduction disturbances are much less common, while supraventricular and ventricular arrhythmia is significantly more common in type 2 (except for atrial fibrillation which often accompanies myotonic dystrophy type 1, as also reported by others). For a proper understanding of cardiovascular complications of myotonic dystrophy type 2, it should be remembered that this disorder often manifests later in life. Hence, cardiac involvement related to the underlying neuromuscular disorder may coexist with pathologies resulting from normal aging and concomitant conditions such as diabetes type 2 which is typical for this type of dystrophy, thyroid disorders, or hypertension which is ubiquitous in later years of life.

The value of the article also stems from the discussion of the practical aspects of the proposed cardiac investigation, and a figure that clearly presents suggested cardiac investigations following the diagnosis of neuromuscular disease. It should be noted that a patient with neuromuscular disorder should have a good quality 12-lead electrocardiogram (ECG) recorded during each follow-up visit, with careful evaluation of all necessary parameters including corrected QT interval. Unfortunately, obtaining a good quality tracing is not always easy, and some patients are reluctant to undergo ECG recording due to their limited mobility. Patients with neuromuscular disorders are usually regularly followed-up by neurologists, while cardiac evaluation is usually performed after the genetic diagnosis is established, and only occasionally afterwards. It is thus important, as also highlighted in the commented article, that these patients should also undergo regular cardiological controls, optimally in specialized tertiary care centres cooperating with neurology experts.

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Folia Cardiologica 2020
tom 15, nr 3, strony 251–254
DOI: 10.5603/FC.2020.0016

ISSN 2353–7752

Will 3D echocardiography replace computed tomography in the diagnostics of myocardial perforation in patients with implanted electrical devices?

Czy echokardiografia 3D zastąpi tomografię komputerową w diagnostyce perforacji mięśnia sercowego u pacjentów z implantowanymi urządzeniami elektrycznymi?

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Abstract

We present two cases of patients who have had myocardial perforation due to implantation of the cardiac stimulating system. The first is an 81-year-old woman with a history of tachy-brady syndrome, in whom despite the suspicion of perforation in 2D echocardiographic (ECHO) imaging, computed tomography did not confirm the problem, and eventually after a few years clinical symptoms associated with perforation were revealed, which was clearly confirmed in the ECHO 3D study. In the second case, in a 62-year-old man with a pacemaker implanted because of atrioventricular block, 3D ECHO allowed for an evident diagnosis. The presented cases aim to draw attention to the potential value of 3D ECHO in the diagnosis of this type of complication.

Key words: echocardiography, pacemaker, perforation

Folia Cardiologica 2020; 15, 3: 251–254

Introduction

Perforation of the right ventricle (RV) of the heart constitutes one of relatively rare, though potentially lethal complications of the implantation of electric cardiac devices, both pacemakers (PM) and implantable cardioverter defibrillators (ICD). It occurs with a frequency ranging from 0.3% to 1.2% of the total number of implantations [1]. The ever-increasing number of these procedures inevitably leads to an increase in the number of such complications, which may either manifest in symptoms or remain entirely asymptomatic; it does not, however mean that the patient is not at risk [2]. Diagnosing cardiac perforation may be a challenge, especially when it does not lead to cardiac tamponade. Standard echocardiographic (ECHO) examination with the use of the 2D method often does not suffice to properly visualise electrode displacement, and computed tomography (CT) has been so far considered to be a reference method enabling formal diagnosis. Below are 2 cases from the Department of Cardiology and Electrotherapy at the Medical University in Gdansk, the aim of which is to demonstrate the potential role of the 3D ECHO in the diagnostics of these significant complications.

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Case report

The first case is an 81-year-old woman with a history of tachycardia-bradycardia syndrome, and a DDD-R cardiac pacemaker. After the implantation of the pacemaker, the patient did not complain of any discomfort, and PM check showed no abnormalities. After a 2D ECHO examination, performed after the implantation, physicians suspected so-called dry perforation — the tip of the electrode passed through the entire RV wall, protruding beyond it by about 2 mm; in this area, there was a discrete effusion in the pericardial sac and a small layer of fibrin. However, CT of the chest did not confirm the diagnosis. The patient was discharged and referred to further outpatient follow-ups. A similar image was visualised in the ECHO examination performed one year later, while the image of a 3D reconstruction, performed additionally, clearly showed passing of the electrode through the myocardium and rising of the pericardium during systole just above the electrode (Figure 1), which made perforation diagnosis obvious. In addition, the patient began to complain of stinging in the vicinity of the heart, which had been occurring for three months. She was finally qualified for the removal of the perforating electrode and an implantation of a new one, after which both the above changes in echocardiography and clinical ailments subsided.

The second case concerns a 62-year-old man with a history of an atrioventricular block and a DDD-R cardiac pacemaker. In the first 72 hours after the procedure, the patient reported acute chest pain; electrocardiography (ECG) showed, previously absent, elevations of the ST segment and lowering of the PR segment in leads I, II, aVL, aVF and V3–V6 (Figure 2). In addition, the level of C-reactive protein concentration was elevated to 180 mg/L. No abnormalities in the operating parameters of the implanted device were observed. X-ray of chest showed no signs of emphysema or pathological displacement of pacemaker electrodes. After 2D echocardiography physicians suspected perforation - the tip of the electrode was located deep in the RV wall; in addition, a small layer of fibrin and fluid in the pericardial sac were present. 3D imaging show the electrode protruding beyond the free RV wall for the length of approximately 8 mm (Figure 3), which made the diagnosis of perforation obvious, and it was decided that CT was unnecessary.

After the removal of the perforating electrode and the implantation of a new one, the ailments subsided and the above-described abnormalities were quickly resolved.

Discussion

Myocardial perforation is a potentially lethal complication which leads to sudden death through the mechanism of pericardial tamponade. Regrettably, it is not always easy to diagnose this dangerous complication. Clinical symptoms accompanying myocardial perforation with the electrode of the implanted device may vary to a large extent. The ones which occur most frequently are chest pain, dyspnea, palpitations; it should be noted, however, that patients may show no symptoms at all [3]. Apart from clinical symptoms, perforation diagnosis may be facilitated by chest X-ray, ECG imaging, a check of the implanted device showing abnormalities in its operation, 2D ECHO. So far, CT examination has been the basis for formal diagnosis. The above cases show how diverse clinical manifestations in patients with perforation can be — varying from entirely asymptomatic

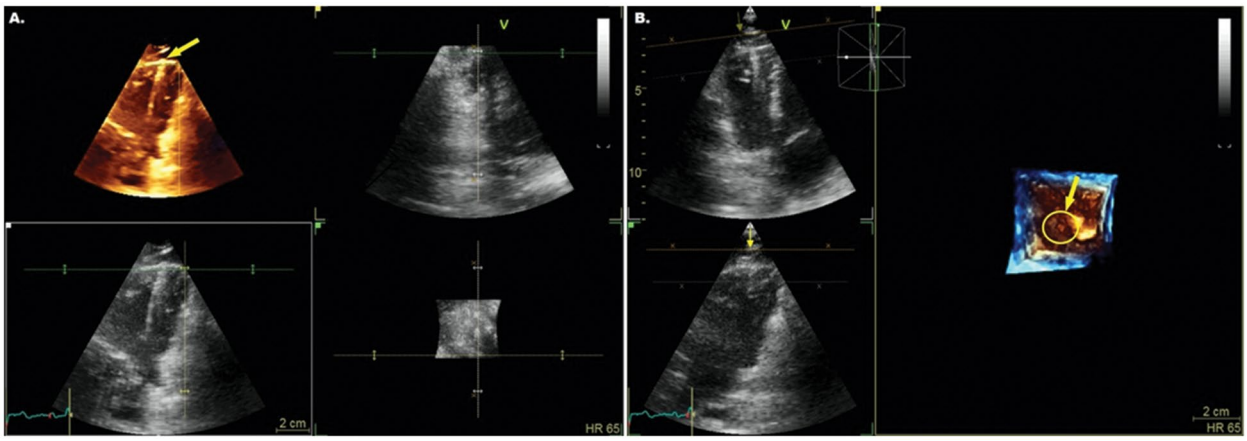

Figure 1. 3D (full volume) imaging with the use of the flexi-slice function (GE Vivid 9, 4V head). The yellow arrow indicates the site of electrode passage through the muscle of the RV and the rising of the pericardium: **A.** Visualisation of the right vetricular long axis; **B.** Visualisation of the right vetricular short axis at the level of the apex

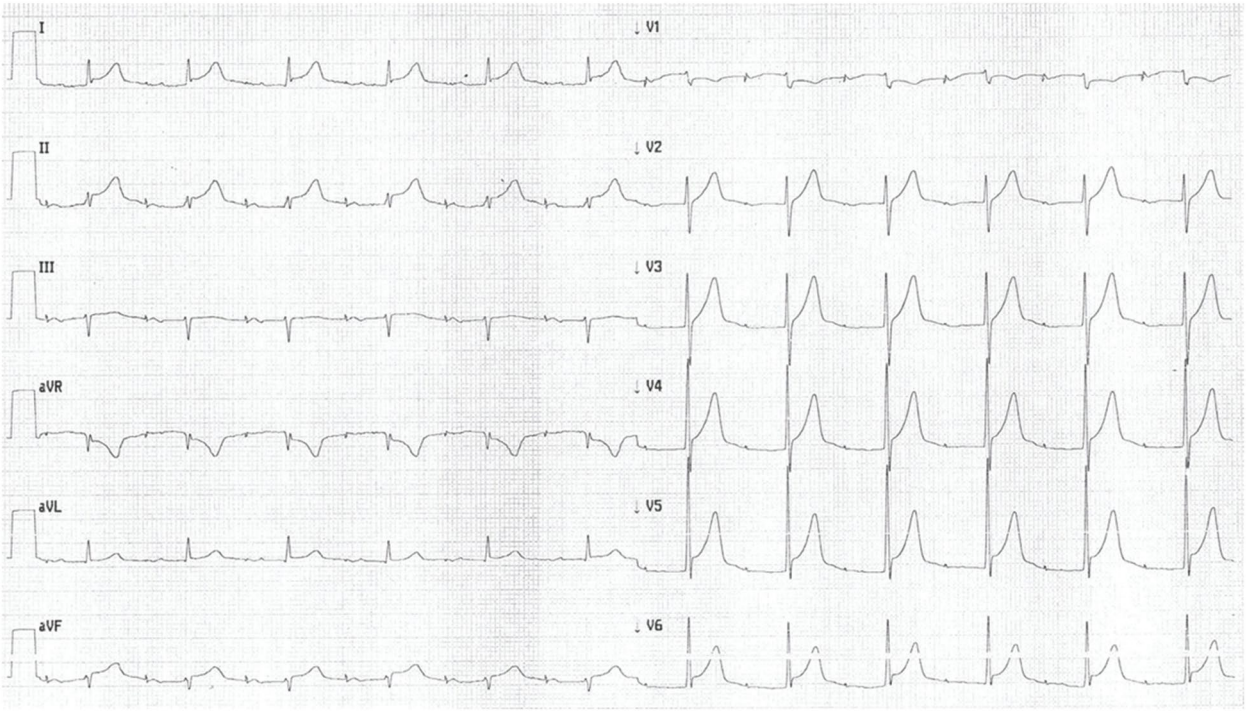

Figure 2. Electrocardiography of a 62-year-old patient, performed during the period of the occurrence of the symptoms reported by him. Atrial stimulation, 72/min, normogram, ST segment elevation and lowering of the PR segment in leads I, II, aVL, aVF and V3–V6

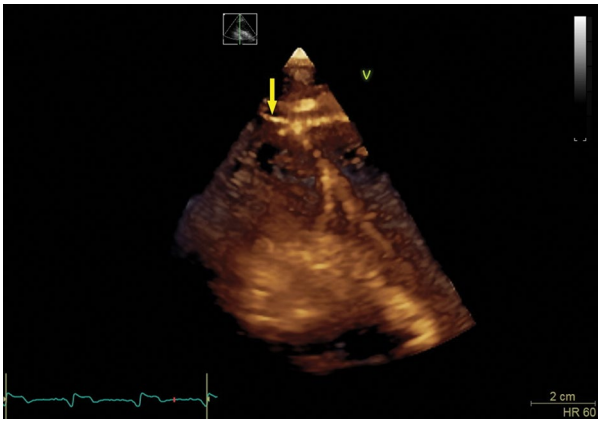

Figure 3. 3D full volume imaging (GE Vivid 9, 4V head). The yellow arrow indicates the site of the electrode passage through the muscle of the right ventricle

to symptoms raising many doubts. Additionally, the performed examinations were not always helpful either. In the second case described, no abnormalities in operating parameters of the PM were revealed, despite its protrusion for the length of approximately 8 mm, which could be misleading for the clinician. In both presented patients it was the modern ECHO technique, based on 3D imaging, that proved to be the most important examination confirming the diagnosis of a dangerous complication that perforation is. Due to the non-invasive nature of the examination as well as its increasing availability in hospital units, it should be expected that the method will significantly decrease the number of CT examinations, or perhaps even replace them in formal diagnoses of myocardial perforation as a result of electric device implantation.

Conclusions

3D echcardiography should be considered the be a method which is very promising for diagnosing myocardial perforation by electrodes of implantable devices, which may contribute to decreasing the need to perform CT examinations, or become the sle diagnostic method for this type of perforation in some cases. As a result, proper diagnosis could be made faster and physicians could avoid exposing patients to X-rays. In addition, the costs of hospitalising such patients would be decreased, which is quite significant in the era of modern medicine.

Conflict of interest

The authors confirm that there is no conflict of interest involving the published work.

Streszczenie

Przedstawiono dwa przypadki pacjentów, u których doszło do perforacji mięśnia sercowego po implantacji układu stymulującego serce. Pierwszym jest 81-letnia kobieta z zespołem tachy-brady w wywiadzie, u której mimo podejrzenia perforacji w echokardiograficznym obrazowaniu 2D tomografia komputerowa nie potwierdziła problemu, a ostatecznie po kilku latach doszło do ujawnienia się objawów klinicznych związanych z perforacją, którą ostatecznie potwierdzono w badaniu echokardiograficznym (ECHO) 3D. W drugim przypadku, u 62-letniego mężczyzny z implantowanym z powodu bloku przedsionkowo-komorowego stymulatorem serca, ECHO 3D pozwoliło na ewidentne postawienie diagnozy. Celem przedstawienia przypadków jest zwrócenie uwagi na potencjalną wartość ECHO 3D w diagnostyce tego typu powikłań.

Słowa kluczowe: echokardiografia, rozrusznik serca, perforacja

Folia Cardiologica 2020; 15, 3: 251–254

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Folia Cardiologica 2020
tom 15, nr 3, strony 255–257
DOI: 10.5603/FC.2020.0032

ISSN 2353–7752

Left atrium tumor imitating the clinical image of acute pulmonary embolism

Guz lewego przedsionka imitujący obraz kliniczny ostrej zatorowości płucnej

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Abstract

We present a case of left atrium tumor in computed tomography angiography images that imitated acute pulmonary embolism in the clinical picture.

Key words: left atrium tumor, acute pulmonary embolism, computed tomography angiography

Folia Cardiologica 2020; 15, 3: 255–257

We present a case of left atrium tumor in computed tomography angiography (CTA) images that imitated acute pulmonary embolism in the clinical picture.

A 31-year-old man without significant medical history reported to the hospital emergency department due to shortness of breath, cough, chest pain and a hemoptysis episode that occurred within the last 24 hours.

Electrocardiography conducted in the hospital emergency department showed regular sinus rhythm, 62 bpm, without signs of acute myocardial ischemia. In laboratory tests, a negative determination of high-sensitive troponin and increased concentration of d-dimers were found. Due to the clinical picture suggesting acute pulmonary embolism, a decision was made to supplement the diagnostics with pulmonary artery CTA.

In the CTA performed in the algorithm for assessing pulmonary embolism, defects in the lumen contrast enhancement of the pulmonary arterial vessels with the nature of embolic material were not visualized. The main pulmonary arteries were not widened: the diameter of the main pulmonary artery was 3.0 cm, the right pulmonary artery 2.0 cm, the left pulmonary artery 1.9 cm. CTA image enabled negative verification of the suspected clinical pulmonary embolism (Figure 1A).

The CTA made it possible to detect cardiac tumor. In the left atrium a polycyclic, slightly heterogeneous, soft-tissue structure with dimensions up to about 6.0 × 4.5 cm in cross-sections (Figure 1B) and about 7.5 cm in the cranio-caudal dimension (Figure 1C), remaining in communication with the posterior-upper-left-sided wall of the atrium, penetrating towards the left atrioventricular ostium, not exceeding the mitral valve plane, including the ostium of the pulmonary veins on the left, was observed. Features of contrast enhancement of the left pulmonary vein ostium to the left atrium, or contrast enhancement of the main venous trunks of the left lung in the CTA study protocol carried out in such a manner were not demonstrated (Figure 1D). In addition, soft tissue thickening of tissue surrounding the vessels of the left lung hilum was noteworthy. Irregular thickening of the atrial septum to a thickness of about 0.8 cm was also seen (Figure 1E). Changes in CTA of the pulmonary arteries corresponded to the radiologic image of the left atrial

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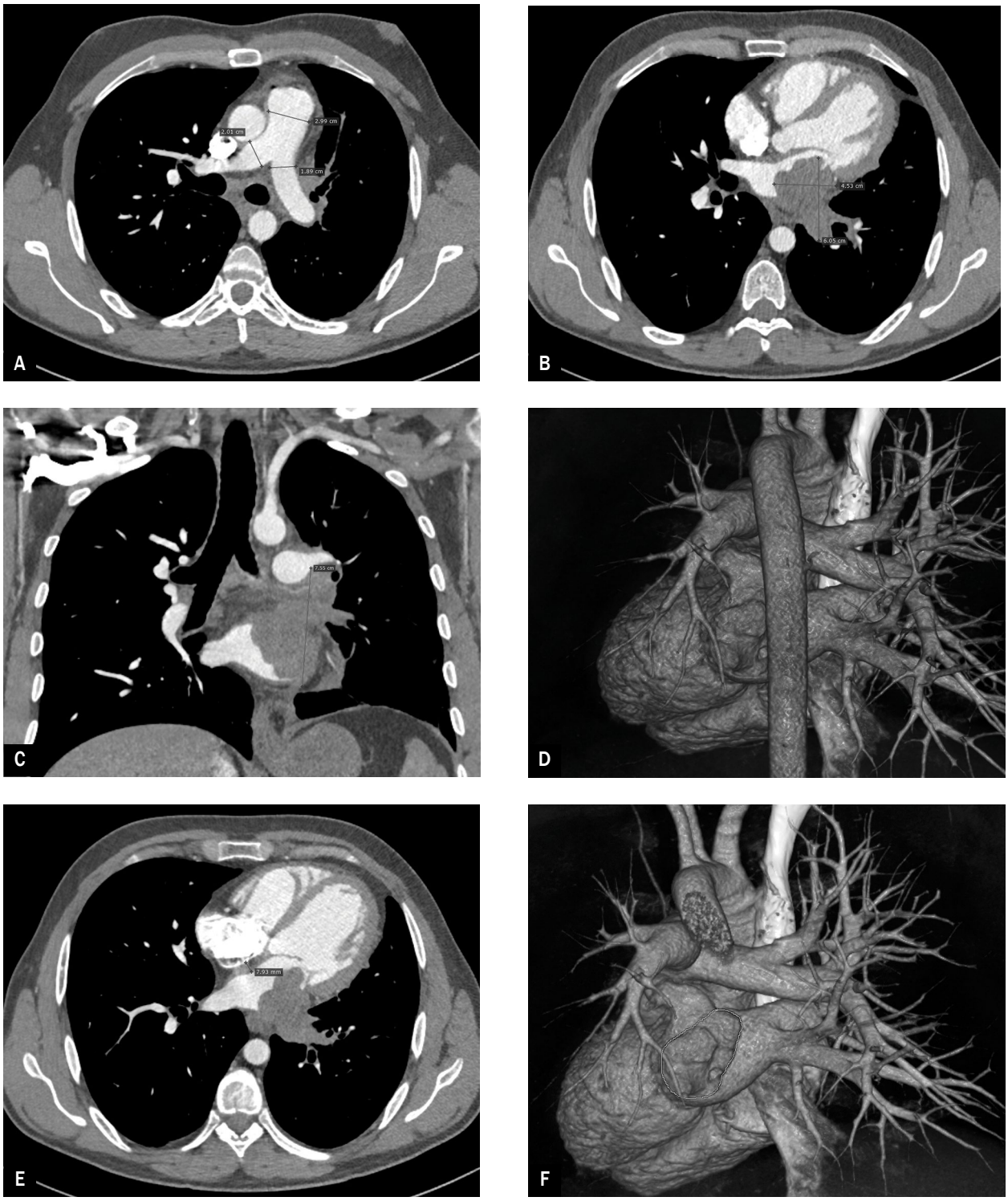

Figure 1. Left atrial tumor in computed tomography angiography images of pulmonary arteries: **A.** Axial reconstruction. Contrasted, non-expanded main pulmonary arteries; **B.** Axial reconstruction. The tumor in the left atrium with transverse dimensions of approx. 6.0 × 4.5 cm; **C.** Frontal multiplanar reformation (MPR) reconstruction. A tumor in the left atrium with a cranial-caudal dimension of about 7.5 cm; **D.** Volume rendering technique (VRT) reconstruction. There is no contrast enhancement in the main venous trunks of the left lung; **E.** Axial reconstruction. Irregular thickening of the atrial septum; **F.** VRT reconstruction with removal of the descending aorta. Loss of left atrial lumen contrast enhancement and left pulmonary veins due to tumor mass

tumor (Figure 1F). In differentiating the type of the tumor, lymphoma, sarcoma and myxoma have been suggested.

Pulmonary embolism is a common diagnosis. Its incidence is 100–200 cases per 100,000 people [1]. In recent years, the number of cases of pulmonary embolism has increased, which is explained by the increasing average life expectancy, but also by the improvement of diagnostic methods [2]. Primary cardiac tumors are rare. Among them, benign lesions dominate, which constitute about 75% of this type of pathology. Sarcomas are the most common of primary malignant cardiac tumors with poor prognosis [3]. Symptoms of cardiac tumors depend on the location; they are asymptomatic for a long time. Cardiac tumors become symptomatic when heart failure occurs. Therefore, they can imitate other more common causes of heart failure [4].

Summarizing, in the differential diagnosis of clinical suspicion of acute pulmonary embolism, one should remember about cardiac tumors.

Funding

None

Conflict of interest

None declared

Streszczenie

Przedstawiono przypadek guza lewego przedsionka w obrazach angiografii tomografii komputerowej, który klinicznie imitował ostrą zatorowość płucną.

Słowa kluczowe: guz lewego przedsionka, ostra zatorowość płucna, angiografia tomografii komputerowej

Folia Cardiologica 2020; 15, 3: 255–257

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Folia Cardiologica 2020
tom 15, nr 3, strony 258–264
DOI: 10.5603/FC.2020.0033

ISSN 2353–7752

Application of the Dutch Lipid Clinic Network Scale in the diagnosis of familial hypercholesterolemia and further clinical implications in the era of PCSK9 inhibitors

Zastosowanie skali *the Dutch Lipid Clinic Network* w diagnostyce hipercholesterolemii rodzinnej i dalsze implikacje kliniczne w erze inhibitorów PCSK9

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Abstract

The article presents a case of 64-year-old patient with years-long history of coronary artery disease, after several coronary events and percutaneous coronary intervention, with a late diagnosis of familial hypercholesterolemia (FH). Based on the clinical case, the authors presented the current diagnostic possibilities and the importance of early FH diagnosis as well as modern lipid-lowering treatment with the use of PCSK9 inhibitors.

Key words: familial hypocholesterolemia, PCSK9 inhibitors, the Dutch Lipid Clinic Network Scale

Folia Cardiologica 2020; 15, 3: 258–264

Introduction

Since 2003–2005 (the WOBASZ study), hyperlipidemia has invariably been one of the most common risk factors of cardiovascular diseases in Poland [1]. Genetically determined forms of the disease, such as familial hypercholesterolemia (FH), are observed among hyperlipidemias. The disease is still rarely diagnosed, *i.a.* due to the fact that until the present, the assessment of the lipidogram has only been routinely conducted in men over 40, post-menopausal women or women over 50 [2], which makes early detection of severe FH cases diffuclt. The newest guidelines of the European Society of Cardiology (ESC) [3] recommend tests for FH, including the assessment of the lipidogram in children aged 5 or less if there is a suspicion of a homozygotic variant of the disease (class I recommendations, data credibility level: C).

Other factors which have an impact on the unsatisfactory level of lipid disorders detection is the failure to conduct clinical assessment of patients according to the Dutch Lipid Clinic Network Scale (DLCNS) (Table 1), or the lack of genetic testing, despite their availability for tests reimbursed by the National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*). Patients bearing at least one of the listed elements should be referred for such tests [2]:

- total cholesterol (TC) concentration in serum ≥ 310 mg/dL (≥ 8 mmol/L) in an adult patient or their family member;
- premature coronary artery disease (CAD) in a patient or their family member (men < 55 years of age, women < 60 years of age);
- tendon xanthelasmas in a patient or their family member;
- sudden cardiac death of a family member at a young age.

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Table 1. Criteria of *the Dutch Lipid Clinic Network Scale* (prepared on the basis of [2, 3])

Clinical interview	Number of points
Premature cardiovascular disease in the patient (men < 55 years of age, women < 60 years of age)	2
Premature cerebrovascular or peripheral vascular disease in the patient (men < 55 years of age women < 60 years of age)	1
Family history	
First-degree relatives diagnosed with premature coronary artery disease (men < 55 years of age women < 60 years of age)	1
OR	
First-degree relatives with LDL-C concentration > 95th percentile for the age and sex in a given country [> 190 mg/dL (> 4,9 mmol/L)]	1
First-degree relatives with tendon xanthelasmas and/or Corneal limbi in a patient < 45 years of age	2
OR	
Children and adolescents < 18 years of age with LDL-C concentration > 95th percentile for age and sex in a given country (> 155 mg/dL [> 4 mmol/L])	2
Physical examination	
Tendon xanthelasmas	6
Corneal limbi	4
LDL-C concentration (without treatment)	
≥ 325 mg/dL (≥ 8.5 mmol/L)	8
251–325 mg/dL (6.5–8.4 mmol/L)	5
191–250 mg/dL (5.0–6.4 mmol/L)	3
155–190 mg/dL (4.0–4.9 mmol/L)	1
Genetic testing	
Confirmed mutation of LDL, ApoB or PCSK9 receptor gene	8
Diagnosis of familial hypocholesterolemia	
Certain	> 8
Likely	6–8
Possible	3–5
Unconfirmed	< 3

LDL-C — low-density lipoprotein cholesterol; ApoB — apolipoprotein B; PCSK9 — proprotein convertase subtilisin/kexin 9

Hereditary forms of lipid disorders, especially homo- (HoFH) and heterozygotic familial hypercholesterolemia (HeFH), constitute a particular challenge in clinical practice.

The Third Declaration of Sopot [2] recommends the following treatment goals in terms of the concentration of low-density lipoprotein cholesterol (LDL-C):

- below 1.8 mmol/L (< 70 mg/dL) in the group of high-risk patients;
- below 1.4 mmol/L (< 55 mg/dL) in the group of patients bearing very high risk;
- below 0.9 mmol/L (< 35 mg/dL) in the group of patients bearing extremely high risk;

This document distinguishes a group of patients bearing extremely high cardiovascular risk, which is partially based on the recommendations of American endocrinological societies [2]. The LDL-C goal in this group of patients, *i.e.* concentration below 0.9 mmol/L, was determined on the basis of prospective clinical studies on proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9), which demonstrated cardiovascular benefits in secondary prevention [2].

On the other hand, the most recent guidelines of the ESC Guidelines [3] do not include the group of patients with extremely high cardiovascular risk, while compared to the previous recommendations, treatment goals for particular risk groups have been changed. They are presented in Table 2.

On the basis of the clinical case in question, we are presenting the current state of knowledge concerning the possibilities of effective treatment of patients with HeFH in the era of PCSK9 inhibitors.

Case report

In 2017, a man of 64, with 13-year-long history of cardiac disease, was admitted to a cardiac unit due to unstable angina. The patient had controlled hypertension, hyperlipidemia (TC 9.58 mmol/L, LDL-C 6.98 mmol/L and increased concentration of triglycerides (TG) — 2.88 mmol/L; Table 3), hyperuricemia (uric acid concentration 477 μmol/L) as well as level I obesity — body mass index (BMI) of 33.9 kg/m^2.

Echocardiography showed segmental disorders of systolic function of the left ventricle with preserved global systolic function [ejection fraction (EF) 58%]. Coronary angiography showed restenosis in the stent implanted in the left descending artery (LAD) with lumen stenosis of 70%, the right coronary artery (RCA) obstructed from segment 2, and without atherosclerotic lesions in the left circumflex (LCx) and intermediate branch (IM). Percutaneous coronary intervention (PCI) of RCA was performed with an implantation of 3 stents releasing the medication: 3.0 × 13 mm, 2.5 × × 40 mm and, proximally, 3.5 × 20 mm with integrilin infusion. The procedure was completed without complications.

The patient was diagnosed with coronary artery disease in 2004 when he suffered an infarction of the anterior and inferior wall, and was treated by means of PCI in LAD

Table 2. Allocation of patients to particular cardiovascular risk groups (prepared on the basis of [2, 3])

Levels of cardiovascular risk	The Third Declaration of Sopot [2]	ESC Guidelines [3]
High	• ≥ 2 risk factors and risk of 10–20% on the Pol-SCORE scale • DM or CKD in 3rd–4th stage without other risk factors **Secondary treatment goal:** • non-HDL-C < 2.6 mmol/L (< 100 mg/dL)	• TC > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL) or BP ≥ 180/110 mm Hg • FH without significant risk factors • DM duration ≥ 10 years, or with another co-existing risk factor, but without organ complications • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2) • Risk on the SCORE scale ≥ 5% and < 10% for a ten-year risk or critical CVD **Treatment goals:** • primary: LDL-C < 1.8 mmol/L (< 70 mg/dL) • secondary: non-HDL-C < 2.6 mmol/L (< 100 mg/dL) Apo-B < 80 mg/dL
Very high	• ASCVD in patients in whom LDL-C < 70 mg/dL (< 1.8 mmol/L) was achieved and continuously maintained • Diagnosed ACS, coronary, carotid or peripheral artery disease • Status post-revascularisation • Risk on the Pol-SCORE scale > 20% • DM or CKD in 3rd–4th stage and ≥ 1 risk factor • FH • History of premature ASCVD (men < 55 years of age, women < 65 years of age) • Patients with DM or CKD at 3rd–4th stage diagnosed with CVD **Secondary treatment goal:** • non-HDL-C < 2.2 mmol/L (< 85 mg/dL)	• Clinically documented ASCVD after ACS (MI or UA), SA, post-revascularisation (PCI, CABG or other procedures), stroke or TIA and peripheral artery disease • ASCVD documented in diagnostic imaging through the detection of substantial atherosclerotic plaque during angiography of coronary arteries or CT (polyvascular coronary artery disease with > 50% stenosis of the lumen of 2 main arteries), or in the ultrasound of carotid arteries • DM with organ complications or with ≥ 3 main risk factors or with early onset of long-term (> 20 years) T1DM • Acute CKD (eGFR < 30 mL/min/1.73 m^2) • Risk in the SCORE scale < 10% for 10-year-long risk or critical CVD • FH with coexisting ASCVD or another risk factor **Treatment goals:** • primary: LDL-C < 1.4 mmol/L (< 55 mg/dL) • secondary: non-HDL-C < 2.2 mmol/L (< 85 mg/dL) Apo-B < 65 mg/dL)
Extremely high	• History of numerous cardiovascular events and/or revascularisation • PCI of the main left coronary artery trunk and/or polyvascular coronary artert disease with complex angioplasty • Generalised atherosclerosis of multiple vascular beds with additional risk factors • Progression of ASCVD in patients in whom LDL-C < 55 mg/dL (< 1.4 mmol/L) was achieved and continuously maintained **Secondary treatment goal:** • non-HDL-C < 1.7 mmol/L (< 65 mg/dL)	

ACS — acute coronary syndrome; ApoB — apolipoprotein B; ASCVD — atherosclerotic cardiovascular disease; BP — blood pressure; CABG — coronary artery bypass graft surgery; CKD — chronic kidney disease; CT — computed tomography; CVD — cardiovascular disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; ESC — European Society of Cardiology; FH — familial hypercholesterolemia; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; MI — myocardial infarction; PCI — percutaneous coronary intervention; SA — stable angina; SCORE — Systematic COronary Risk Estimation; T1DM — type 1 DM; TIA — transient ischemic attack; UA — unstable angina; USG — ultrasonography

with the implantation of a medication-releasing stent as well as PCI in RCA and IM with the implantation of metal stents. In the following years, the patient underwent the following PCIs with simultaneous implantation of medication-releasing stents: LAD in 2007, RCA in 2014 and LCx in 2016. The patient had 9 stents altogether implanted into coronary arteries.

Moreover, patient's father and brother suffered from premature CAD:

— the brother suffered an infarction at the age of 45 and died of infarction at the age of 57;
— the father suffered an infarction at the age of 48 and died of another infarction at the age of 67.

Based on patient's history and physical examination, he was assessed in accordance with the DLCNS and diagnosed with probable FH — with a score of 8 points.

— premature CAD — 2 points;
— premature CAD in first-degree relatives — 1 point;
— LDL-C concentration of 6.98 mmol/L — 5 points.

In addition, a DNA analysis in search for the most common mutations in Poland, *i.e.* p.G592E of the *LDRL* gene and p.R3500Q of the *APOB* gene, was conducted to confirm clinically diagnosed FH. The mutations were not detected. Further molecular tests in search for other mutations of the *LDLR* and *MTHFR* genes were planned, and presence of mutation c.415G>C in exone 4 of *LDLR* gene, which confirms the diagnosis of HeFH form, was documented. The patient was informed about the necessity to conduct genetic tests in his first-degree relatives.

In March 2019, due to short-term coronary-related symptoms in stressful situations, the patient underwent angiography computed tomography (angio-CT), which showed progression of CAD — signs of restenosis in the stent implanted in LAD causing narrowing of the lumen to 50% as well as a narrowing to 60–70% in the artery behind the stent, narrowing of the IM ostium to 50% and narrowing in the first segment of RCA to 50–60%; the coronary artery calcium score was 369 j.A. The patient was qualified for the assessment of the functional extent of myocardial ischaemia with the use of the single-photon emission computed tomography (SPECT).

Resting perfusion scintigraphy of the heart showed established perfusion disorders encompassing the apex, anterior-septal wall and the parabasal section of the inferior wall (25–30%), worsening during the physical test in the area of parabasal and central segment of the inferior wall and adjacent segments of the inferior-lateral wall (Figure 1) which constituted 10%. In accordance with the current ESC guidelines for chronic coronary syndromes [4], the patient was referred for follow-up coronary angiography which showed a 50–70% stenosis of the central part of the intermediate artery, atherosclerotic plaque in the proximal segment of RCA with a narrowing to 50% as well as peripheral 90% stenosis of the right posterior-lateral (diameter < 1.5 mm) branch of RCA. The results of the implantation of stents in LAD and LCx were also good. The patient was referred to further conservative treatment.

Since the most recent PCI in 2017, the patient has been receiving acetylsalicylic acid in the dose of 75 mg, 25 mg of metoprolol, 5 mg of ramipril, 20 mg/day of pantoprazole and trimethazidine in the dose of 35 mg/twice a day as well as intensive lipid-lowering treatment — 80 mg of atorvastatin + 10 mg of ezetimib once a day. Eight months and one year after the implementation of lipid-lowering treatment the lipidogram was performed again. The results of the examination are presented in Table 3.

The application of combined therapy did not contribute to the achievement of treatment goals neither in relation to LDL-C, nor non-HDL-C, both according to the ESC guidelines concerning high cardiovascular risk and the Third Declaration of Sopot concerning patients with extremely high risk.

New options for the treatment of lipid disorders

Lifestyle modification, particularly with regard to diet and physical activity, lies at the basis of the pyramid of lipid interventions. It is followed by statin treatment, intensive statin therapy and combined lipid-lowering treatment [2]. A new group of medications — PCSK9 inhibitors — has been for the first time included in the newest ESC guidelines for the treatment of lipid disorders [2]. So far, researchers have studied and documented benefits related to lowered risk of cardiovascular death, infarction, stroke, hospitalisation due to unstable angina (UA) or coronary artery revascularisation — hazard ratio (HR) [95% confidence interval (CI)] compared to placebo 0.85 (0.79–0.92) for evolocumab [5] and HR (95% CI) compared to placebo 0.85 (0.78–0.93) for alirocumab [6].

Proprotein subtilisin/kexine type 9 convertase is a protein which participates in the metabolism of LDL receptors (LDLR) through binding with them and stimulation of endocytosis of the LDLR-PCSK9 complex and degradation of LDLR in lysosome. On the other hand, PCSK9 inhibitors are monoclonal antibodies for PCSK9, which lead to a decrease in LDLR degradation and cause a decrease in LDL-C concentration by 60% on average regardless of another lipid-lowering treatment conducted simultaneously [7].

The RUTHERFORD-2 (Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2) study teremined the effectiveness of evolocumab in lowering LDL-C concentration in HeFH patients by 59–68% [8]. In turn, the ODDYSEY FH I (Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately

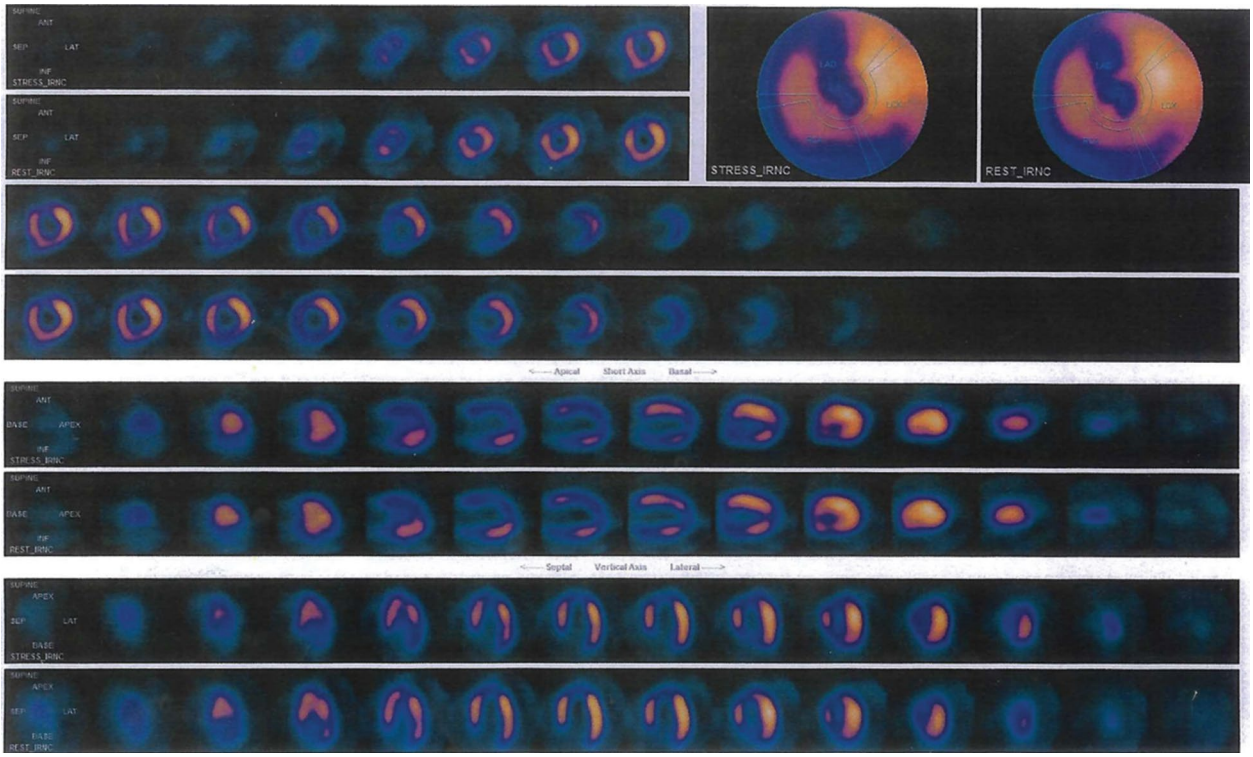

Figure 1. Result of perfusion scintigraphy of the heart conducted in 2019

Table 3. Comparison of lipidogram results before and after the implementation of intensive lipid-lowering treatment

Assessed parameter	October 3, 2017	November 2, 2017	2018
TC concentration [mmol/L]	9.58	5.87	4.53
LDL-C concentration [mmol/L]	6.98	3.69	2.61
HDL-C concentration [mmol/L]	1.29	1.11	1.11
TG concentration [mmol/L]	2.88	2.34	1.54
Non-HDL concentration [mmol/L]	8.29	4.76	3.42
AlAT activity [U/L]	48	–	40

TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; AlAT — alanine aminotransferase

Controlled With Their Lipid-Modifying Therapy) study established that the effectiveness of alirocumab ranged from 51–58% in the same group of patients [9]. It is also worth noting that PCSK9 inhibitors are well tolerated. Comparison of selected aspects of statin and PCSK9 inhibitor treatment is presented in Table 4.

There are two PCSK9 inhibitors available in the Polish market — alirocumab and evolocumab. They are administered subcutaneously; evolocumab usually in the dose of 140 mg every 2 weeks [10] and alirocumab usually in the dose of 75 or 150 mg every 2 weeks [10].

Discussion

The presented clinical case constitutes an example of the application of a scale of the World Health Organization — the Dutch Lipid Clinic Network, a useful tool in clinical practice which enables the diagnosis of FH. It is estimated that the incidence of FH in Europe amounts to 1/500–1/2,000 people, and in most countries the percentage of diagnosed patients is less than 1% [11]. The estimated number of people living with HeFH in Poland ranges from 76,860 to 192,150 people, however, due to the lack of a register of FH patients, it is impossible to determine the number of diagnosed patients. Due to the fact that outpatient assessment of the parameters which constitute an element of the WHO scale (the Dutch Lipid Clinic Network) is easy, it is possible to increase the number of people in whom FH is diagnosed. The 10% increase in the CAD risk in HeFH patients as well as the incidence of premature CAD, at the level of 50% in men and 25% in women without treatment [2], emphasises

Table 4. Comparison of selected aspects of treatment with statins and treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Medication	Effectiveness of monotherapy	Treatment of HeFH patients	Tolerance of treatment	Adverse effects of treatment [16]
Statin [14]	Lowering of LDL-C concentration by 30–50%	In 80% of patients the LDL-C concentration of < 100 mg/dL is not reached with the use of monotherapy	80–90% of patients	Muscle inflammation and rhabdomyolysis, liver dysfunction, myopathies, proteinuria, acute kidney damage, cognitive changes, development of diabetes
PCSK9 inhibitor [14, 15]	Lowering of LDL-C concentration by 46% (alirocumab) to 56.1% (evolocumab)	Lowering of LDL-C concentration by 60% (evolocumab)	96% of patients (evolocumab)	Gastrointestinal disorders, infections and infestations, musculoskeletal, cutaneous or subcutaneous tissue disorders (alirocumab) Nasopharyngitis, infections of the upper respiratory tract, flu-like symptoms and back pain (evolocumab)

HeFH — heterozygous familial hypercholesterolemia; LDL-C — low-density lipoprotein cholesterol

the significance of early diagnosis and implementation of treatment. Cascade diagnostics including the assessment of TC and LDL-C concentrations as well as genetic testing, conducted in the relatives of the identified proband, constitutes the most effective method of detecting new FH cases. The current ESC guidelines for FH diagnosis recommend the performance of genetic tests, if it is possible, to confirm the clinical diagnosis in accordance with the DLCNS, classifying it as class I recommendation with data reliability level C [3].

Due to the lack of diagnosis for FH, the patient in question had been treated with weak statins for many years, which did not bring the expected results — neither clinical nor in terms of LDL-C concentration. After the implementation of intensive lipid-lowering treatment (atorvastatin 80 mg + ezetimib 10 mg) it was observed that the patient tolerated it well, but the treatment goal for LDL-C remained unachieved. In addition, despite the co-existing metabolic and cardiovascular diseases, the patient was not subjected to multi-factor treatment. For years, despite the diagnosis of hyperurycemia, he did not take medication lowering the concentration of uric acid, nor was he diagnosed for obstructive night apnea, despite the symptoms indicating the existence of this clinical problem.

It stems from the above that there is a need for continuous education on cardiovascular risk factors and FH. There is an Association of Patients with Familial Hyperlipidemia in Gdańsk [12], the primary aims of which are effective prevention and health education leading to raising awareness of the disease in the society and its early diagnosis. The activities of the Organisation include not only actions such as annual meetings on the occasion of the Familial Hypercholesterolemia Awareness Day, but also provide constant access to information about the disease as well as the possibilities concerning prevention and treatment via its website, in order to provide patients with the best mental support in their struggles with the disease. The medication programme for HF patients which exists in Poland [13] contains restrictive criteria concerning the effectiveness of lowering of LDL-C concentration up to date — LDL-C above 160 mg/dL despite diet and:

- intensive treatment with statins in maximum doses, *i.e.* atrovastatin 80 mg or rosuvastatin 40 mg, and then atrovastatin 40–80 mg or rosuvastatin 20–40 mg in combination with ezetimib 10 mg, administered for 6 months in total, including combined treatment for at least one month;
- or very intensive treatment with statins at maximum-tolerated doses, and subsequently in combination with ezetimib 10 mg, administered for 6 months in total, including combined treatment for at least one month.

Despite the lack of effectiveness of the so-far administered combined treatment, the above-described patient cannot be treated with PCSK9 inhibitors due to the high cost of the treatment and the fact that he cannot be qualified for the programme as the criterion of LDL-C concentration is not met.

Conclusions

The Dutch Lipid Clinic Network Scale is an easy and effective tool in the estimation of FH probability. However, due to excessively narrow criteria of the programme and the high cost of the treatment when it is not reimbursed, the access to effective treatment of hypercholesterolemia with the use of PCSK9 inhibitors remains limited.

Conflict of interest

Authors do not declare the conflict of interest.

Streszczenie

W artykule opisano przypadek 64-letniego pacjenta z wieloletnim wywiadem choroby wieńcowej, po licznych incydentach wieńcowych i przezskórnej interwencji wieńcowej, u którego późno zdiagnozowano hipercholesterolemię rodzinną (FH). Na podstawie przypadku klinicznego przedstawiono aktualne możliwości diagnostyczne i istotność wczesnego rozpoznania FH oraz nowoczesną terapię hipolipemizującą z wykorzystaniem inhibitorów PCSK9.

Słowa kluczowe: hipercholesterolemia rodzinna, inhibitory PCSK9, skala *the Dutch Lipid Clinic Network*

Folia Cardiologica 2020; 15, 3: 258–264

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Folia Cardiologica 2020
tom 15, nr 3, strony 265–268
DOI: 10.5603/FC.a2020.0034

ISSN 2353–7752

Noninvasive hemodynamic evaluation of chronic obstructive pulmonary disease and heart failure patient

Nieinwazyjne badanie hemodynamiczne u pacjenta z niewydolnością serca i przewlekłą obturacyjną chorobą płuc

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Abstract

The noninvasive hemodynamic monitoring in patients with heart failure and chronic obstructive pulmonary disease was presented in this paper.

Key words: heart failure, COPD, impedance cardiography

Folia Cardiologica 2020; 15, 3: 265–268

Introduction

A common symptom reported by patients is dyspnea — a subjective feeling of lack of air, difficulty breathing or shortness of breath. The sensation of breathlessness can be experienced in many diseases. In an outpatient setting, differentiating between the causes of dyspnea can be a diagnostic challenge and is usually based on physical examination, laboratory tests and imaging tests available in primary healthcare settings. Outpatient non-invasive hemodynamic monitoring has the potential to predict exacerbation of heart failure. Impedance cardiography (ICG) [1–3] and impedance scale are used in monitoring primary health care patients, which helps to differentiate between the causes of dyspnea in patients with heart failure (HF) and chronic obstructive pulmonary disease (COPD) [4, 5]. The aim of this study was to present the use of non-invasive monitoring of hemodynamic parameters in patients with COPD and coexisting HF [6].

ICG was used to assess hemodynamic parameters. This method is based on a change in the volume of blood pumped during the heart's cycle, causing a change in electrical resistance. Hemodynamic indices are calculated from the changes in the chest resistance, heart rate and blood pressure. The following parameters were used for the study: thoracic fluid content (TFC) [1/kΩ], contractility index (HI, Heather index) [Ω × s^{-2}], heart rate (HR) [1/min], stroke volume (SV) [ml] and cardiac output (CO) [l/min]; systemic vascular resistance (SVR) [dyn × s/cm^5] was also calculated. The pre-ejection period (PEP) [ms] and the left ventricular ejection time (LVET) [ms] were determined from the curve, and the contractility index was calculated based on the PEP/LVET ratio — the so-called Weissler index [7].

Case report

A 64-year-old patient, diagnosed many years ago with COPD and HF, was treated on an outpatient basis due to increasing dyspnea, decreased exercise tolerance and worsening of well-being. He was included in the AMULET program ("A new model of medical care with use of modern methods of non-invasive clinical assessment and telemedicine in patients with heart failure") [8]. In the 6 months preceding the visit, he was hospitalized due to an exacerbation of HF.

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The functional status of the patient was assessed according to the modified Medical Research Council (mMRC) apnea scale at level 3, and heart failure was assessed according to the New York Heart Association (NYHA) at grade II–III. The medical history revealed COPD (cat. B), paroxysmal atrial fibrillation, mitral valve insufficiency, chronic kidney disease (stage G3b), arterial hypertension, type 2 diabetes, mixed hyperlipidemia, Mallory-Weiss syndrome. The patient underwent the following procedures: percutaneous coronary intervention (PCI) of the left posterolateral branch (LPL) from the circumflex artery (Cx) (coated stent), PCI of the left anterior descending (LAD) (coated stent) and implantation of a resynchronization pacemaker. The patient denied alcohol consumption; however, he had smoked a pack of cigarettes a day for 50 years (50 pack-years), but had not smoked for the last 6 months. Pharmacotherapy during stabilization state included: amiodarone, metoprolol, potassium chloride, metformin, rivaroxaban, torasemide, ramipril, budesonide, and iprathiopium bromide.

The physical examination at the first visit showed a body weight of 75 kg and a height of 169 cm. The waist circumference was 102 cm and the body mass index (BMI) was 26.3 g/m^2.

An electrocardiogram (ECG) showed a paced rhythm of 80/min, and an X-ray of the chest showed an enlargement of the heart and visible signs of stasis. Echocardiography showed an increased diastolic left ventricular-diameter of 73 mm, increased left atrial diameter of 59 mm and a left ventricular ejection fraction reduced to 23%.

The following results were obtained in laboratory tests: B-type natriuretic peptide (BNP) — 524 pg/mL, ferritin — 124 μg/L, iron — 37 μg/dL, thyroid-stimulating hormone (TSH) — 2 μg/L, white blood count (WBC) — 11 × 10^9/L, red blood count (RBC) — 3.3 × 10^{12}/L, hemoglobin (Hb) — 10 g/dL.

The patient underwent ICG three times at monthly intervals. This study compares the results obtained during all the examinations (Figures 1, 2).

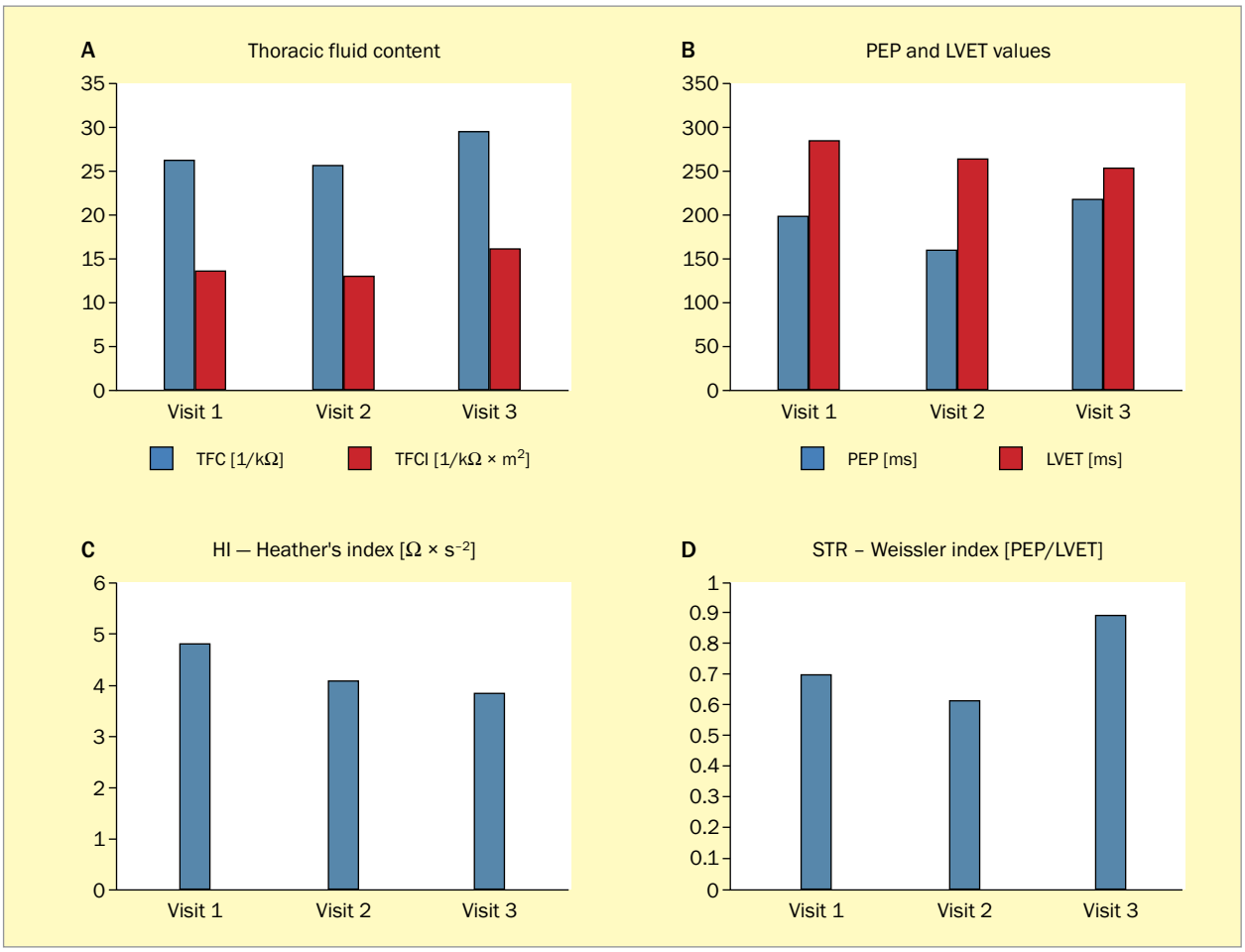

Figure 1A–D. Preload [thoracic fluid content (TFC)] and myocardial contractility in a patient with heart failure and chronic obstructive pulmonary disease; TFCI — thoracic fluid content index; PEP — pre-ejection period; LVET — left ventricle ejection time; STR (systolic times ratio) — contractility coefficient/Weissler index

The assessment of the cardiovascular system was based on the analysis of changes in preload, myocardial contractility, CO and afterload characterized by SVR. Thoracic fluid content decreased slightly on the second examination and increased significantly on the third visit. Relative preload changes were determined using the ΔTFC. Compared to the first examination, the result obtained in the third visit increased by 11.94%.

Cardiac contractility was assessed by HI and the PEP/LVET ratio. It was noticed that HI was 5 times lower than the lower limit of normal — it oscillated between 4.8 and 3.9. The relative decrease in contractility between Visit 1 and Visit 3 was 18.75%. The contractility abnormalities are also reflected in the increase in the Weissler index. According to Czaplicki et al. [7] the PEP/LVET ratio is a sensitive, classic indicator of myocardial contractility. There was a clear increase in the value of Weissler index during the third examination. The relative deterioration reflected in the increase of this index, was 27.14% [7]. Systemic vascular resistance was within normal limits.

The obtained picture of hemodynamic changes indicated that the cardiac pump function was preserved despite critical disturbances in contractility. Presumably, the preservation of cardiovascular function resulted from the change in preload, in accordance with the Frank-Starlig law. Studies suggest that a slight increase in preload may cause a breakdown in cardiac contractility and pump function [7]. Based on the telephone interview, information was obtained about the patient's death.

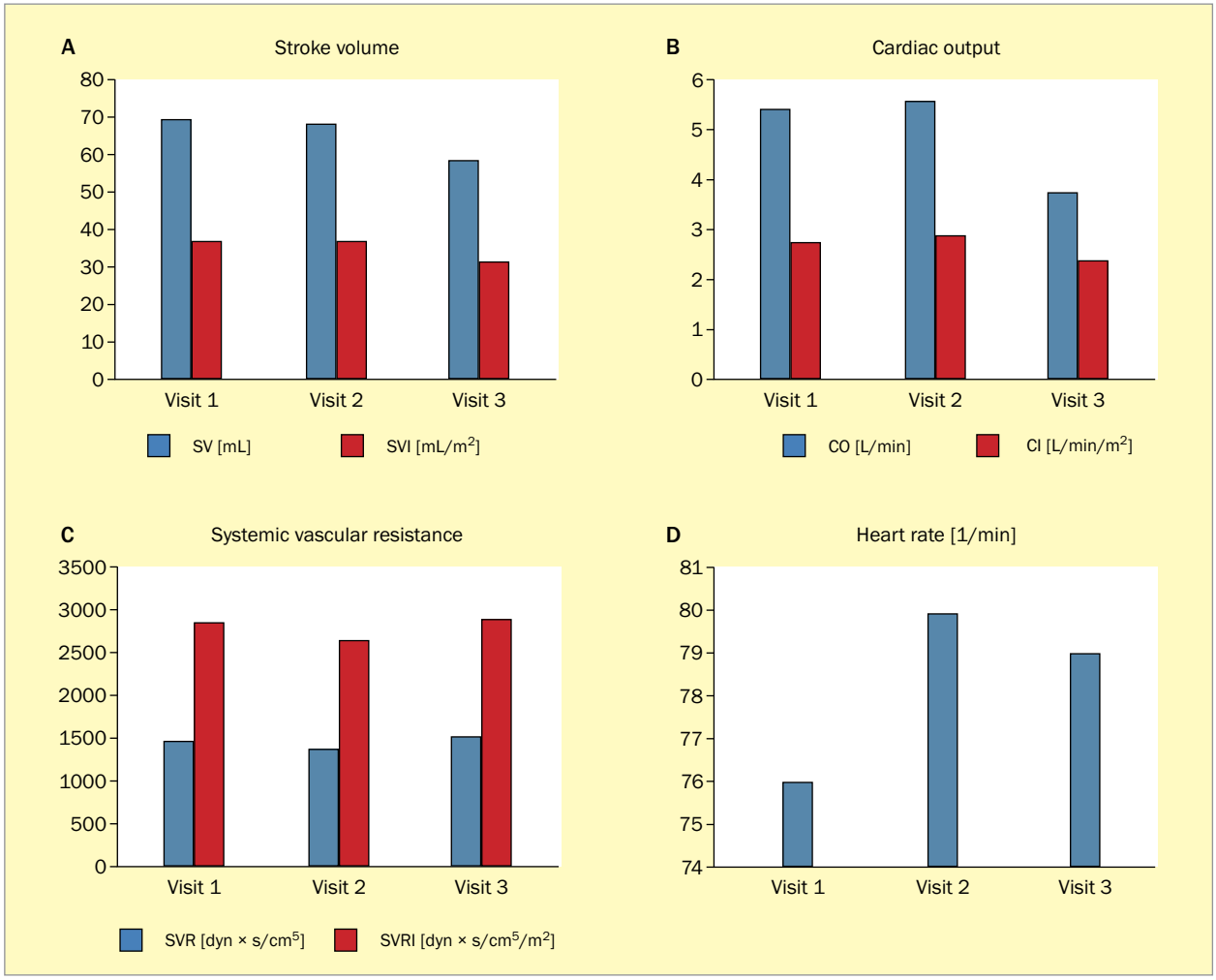

Figure 2A–D. Stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) in a patient with heart failure and chronic obstructive pulmonary disease; SVI — stroke volume index; CI — cardiac index; SVRI — systemic vascular resistance index

Summary

The analysis of the results presented above shows that the deterioration of the patient's condition was mainly due to hemodynamic disturbances, and not to exacerbation of COPD.

The presented application of non-invasive cardiovascular examination in patients with coexisting HF and COPD may provide information useful for differentiating between the causes of clinical deterioration. Examination with the use of ICG in an outpatient setting may be performed by mid-level medical staff.

Funding

The study was supported by: STRATEGMED3/305274/8/ /NCBR/2017.

Streszczenie

W pracy przedstawiono zastosowanie nieinwazyjnej oceny hemodynamicznej u chorego z niewydolnością serca i przewlekłą obturacyjną chorobą płuc.

Słowa kluczowe: niewydolność serca, POChP, kardiografia impedancyjna

Folia Cardiologica 2020; 15, 3: 265–268

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Folia Cardiologica 2020
tom 15, nr 3, strony 269–271
DOI: 10.5603/FC.2020.0036

ISSN 2353–7752

Coronavirus — some legal aspects concerning physician's dilemmas

Koronawirus — wybrane aspekty prawne dotyczące rozterek lekarzy

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Abstract

In the age of pandemic, health services face even more often tragic and irreconcilable dilemmas. A physician is obliged to provide medical procedure whenever a delay in providing it could cause a risk of loss of life, serious injury or health disorder, and in every other urgent case. However, each medical intervention, although necessary and urgent, may be risky for a patient in the age of pandemic, as a doctor may be potentially infected by SARS-CoV-2 (severe acute respiratory syndrome corona virus 2). While it is widely known medical staff is more likely to be exposed to become a source of infection, the risk related to each medical procedure becomes inevitable. The physicians face a serious dilemma as they are aware they might be infected, not having any symptoms or pending the test results while at the same time the necessity to perform medical procedure might occur live-saving. It seems a physician cannot prematurely resign from medical assistance with reference to a potential infection risk. However, the risk has to be reasonably estimated and responsibly reduced. If the risk of SARS-CoV-2 infection is high enough to exceed potential advantages of the medical intervention, this intervention might occur unjustified. It might not apply to super urgent lifesaving situations in which failure to provide treatment may lead to patient's death. It is necessary to minimize the risk to achievable level in order to avoid infection.

Key words: coronavirus, law, health services.

Folia Cardiologica 2019; 15, 3: 269–271

Introduction

In the age of pandemic, health services face even more often tragic and irreconcilable dilemmas. Common deficits of the healthcare system, such as the lack of medical staff, become more important when there are hundreds of patients who require immediate intervention.

Many of the physicians' choices which they have to make in everyday practice encompass choice of the lesser evil, as none of the solutions is cost-free [1]. Nevertheless, under conditions of common battle, such medical quandaries may have huge medical consequences and include legal motifs.

To risk medical treatment

Under the provisions of Polish law, a physician may bear liability both for action and abandonment [2]. The necessary conditions of a physician's liability include failure to act with due diligence or current medical knowledge [3]. Due diligence requires certain level of precision and precaution during medical activities [4]. A doctor acts with due diligence when he or she makes sufficient effort while medical process; however, no matter the result, as he, as a rule, is he or she, as a rule is not responsible for a certain result [5]. Current medical knowledge is a dynamic category which obliges physicians to perform medical practice with

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obligatory medical standards, in according to healthcare level which is legal and available for a certain physician [6].

A physician is obliged to provide medical procedure whenever a delay in providing it could cause a risk of loss of life, serious injury or health disorder, and in every other urgent case [7]. While performing medical activities on a legal basis, a physician is a guarantor who ensures the non-occurrence of a certain effect. Thus, he or she may bear criminal liability for abandonment of medical activities which are necessary for a patient in an urgent state [8].

However, each medical intervention, although necessary and urgent, may be risky for a patient in the age of pandemic, as a doctor may be potentially infected by COVID-19 (coronavirus disease 2019).

Medical services in the face of pandemic

In December 2019, rapidly spreading outbreaks of unspecified severe viral pneumonia appeared in Wuhan, China. The new etiological factor was the new Betacoronavirus, which transmission has not been reported in the human population. The World Health Organization has described the newly sequenced virus as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and the disease it causes as COVID-19 [9]. On March 11, 2020, the World Health Organization announced the COVID-19 pandemic. Epidemiological reports indicate that the epicenter of the pandemic is currently in Europe.

While it is widely known medical staff is more likely to be exposed to become a source of infection, the risk related to each medical procedure becomes inevitable. The physicians face a serious dilemma as they are aware they might be infected, not having any symptoms or pending the test results while at the same time the necessity to perform medical procedure might occur live-saving. The lack of medical staff in Poland is commonly known and constitutes a serious obstacle in peacetime. All the more becomes it a huge problem at the time when we face a pandemic crisis. Not only is it caused by the fact more patients need medical assistance, but apparently because the medical staff is more likely to infect themselves while providing health services.

To cure or not to cure

A physician, experienced in premature radiology, is the only specialist within a radius of hundreds of kilometers who is able to properly diagnose a patient for whom it can be considered as a lifesaving procedure. A physician is employed in a medical entity in which the risk of SARS-CoV-2 infection is statistically high while premature consultations take place on a contractual basis in a different medical unit.

A patient with heart attack is transported to a hospital in which SARS-CoV-2 has been just detected. He is in super urgent state of health which obligates to receive immediately as his transport to another medical unit may cause his imminent death. His admission to such a medical entity is necessary; however, the risk of SARS infection is at the same time inevitable. Many medical procedures are commonly being provided on an outpatient basis but at the same time they cannot be easily postponed, *i.e.* in the field of gynecologist or urgent stomatology cases. In Poland majority of the physicians practice their medical activity in many units, as the medical entities have to share medical staff to meet National Health Fund organizational requirements.

Some of the fields of their practice can be easily or cost-free reduced, while other guarantee consistency of essential health services. Employers in public medical sector have no legal means to prevent physicians from different forms of medical activity. At the same time, in the light of current legal order, medical staff is not restricted in other ways, thus a visit in a post office, gas station or a grocery may potentially expose one to an infection, even though the possibility of it is at the time less likely. Is it alternative to choose between protection not to infect but at the same time to deprive of necessary medical intervention which is urgent and life-saving?

Findings

It seems a physician cannot prematurely resign from medical assistance with reference to a potential infection risk. However, the risk has to be reasonably estimated and responsibly reduced. If the risk of SARS-CoV-2 infection is high enough to exceed potential advantages of the medical intervention, this intervention might occur unjustified. It might not apply to super urgent lifesaving situations in which failure to provide treatment may lead to patient's death. On one hand, it is necessary to minimize the risk to achievable level in order to avoid infection, and on the other hand, medical entities have to seek for available alternative in medical staff, provided that it is feasible. It therefore seems this situation basically does not differ from typical medical obligations discussed earlier. Namely, as for the SARS-CoV-2 infection prevention, it obliges to act in due diligence according to current epidemiological standards (medical knowledge) in order to provide necessary medical assistance for every patient who requires urgent help.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

W dobie pandemii lekarze częściej stają przed trudnymi dylematami, będąc zobowiązanymi do udzielania świadczeń zdrowotnych w stanach nagłych. Każda interwencja medyczna, choć uzasadniona i pilna, może być dla pacjenta o tyle dodatkowo ryzykowna, o ile lekarz może się okazać potencjalnie zakażony SARS-CoV-2 (*severe acute respiratory syndrome corona virus 2*). Ponieważ powszechnie wiadomo, że personel medyczny jest bardziej narażony na zakażenie, to ryzyko związane z każdą procedurą medyczną staje się wyższe i nieuniknione. Lekarze stają wówczas przed poważnym dylematem, ponieważ zdają sobie sprawę, że mogą zostać zarażeni, nie mając żadnych objawów ani nie otrzymując wyników badań, a jednocześnie może wystąpić konieczność wykonania pilnego zabiegu ratującego życie. Wydaje się, że lekarz nie może pochopnie zrezygnować z pomocy medycznej w związku z potencjalnym ryzykiem infekcji. Jednak ryzyko to należy rozsądnie oszacować i odpowiedzialnie obniżyć. Jeśli niebezpieczeństwo zakażenia SARS-CoV-2 jest na tyle wysokie, że może przekroczyć potencjalne korzyści z interwencji medycznej, to interwencja może się okazać nieuzasadniona. Powyższe wydaje się nie mieć jednak zastosowania w bardzo pilnych przypadkach ratujących życie, w których bierność lekarza jest dla pacjenta równoznaczna z wyrokiem, a pomocy medycznej nie można inaczej zapewnić.

Słowa kluczowe: koronawirus, prawo, świadczenie zdrowotne

Folia Cardiologica 2019; 15, 3: 269–271

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Folia Cardiologica 2020
tom 15, nr 3, strony 272–275
DOI: 10.5603/FC.2020.0037

ISSN 2353–7752

Results of clinical trials from the latest Congress of the European Society of Cardiology in Paris, 31st August–4th September 2019

Najnowsze wyniki badań klinicznych z Kongresu Europejskiego Towarzystwa Kardiologicznego w Paryżu, 31 sierpnia–4 września 2019

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Introduction

The last Congress of the European Society of Cardiology, the world's largest meeting for cardiologists, took place from 31st August to 4th September 2019, together with the World Congress of Cardiology. It was held in one of the most charming European capitals — Paris. Among the many interesting thematic lectures, the participants were most interested in hotline sessions, which presented the results of the latest, long-awaited clinical cardiology research, including innovative treatments using new drugs.

This congress abounded in breakthrough scientific reports which, in the near future, may change the pharmacotherapy standards of the most common diseases in cardiology — heart failure (HF) and coronary artery disease (CAD). Of the many relevant clinical trials, the most interesting ones that may have practical application are described below.

DAPA-HF — dapagliflozin as a new effective drug in HF?

One of the most important studies presented to cardiologists for the first time was **DAPA-HF** (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) [1], a study on the use of dapagliflozin — an inhibitor sodium-glucose co-transporter 2 (SGLT2) as a drug in HF. Researchers examined whether adding dapagliflozin 10 mg OD to standard pharmacotherapy would benefit patients with reduced left ventricular ejection fraction (LVEF), regardless of the type 2 diabetes mellitus (T2DM). The study included patients with HF symptoms in II, III, IV failure class according to the New York Heart Association (NYHA), LVEF not more than 40% and a minimum concentration of the N-terminal pro-B-type natriuretic peptide (NT-proBNP) higher than or equal to 600 pg/mL, as well as greater than or equal to 400 pg/mL, when they were hospitalised due to HF during last 12 months or at least 900 pg/mL for co-existing atrial fibrillation or flutter. Exclusion criteria were chronic kidney disease and estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, symptomatic arterial hypotension with systolic blood pressure (SBP) less than 95 mm Hg, or type 1 diabetes mellitus. During the 14-day initial assessment, researchers analysed the inclusion and exclusion criteria for patients from the study. After this period, patients were divided into groups receiving dapagliflozin or placebo. The further diagnostic evaluation followed 14 or 60 days after inclusion. Additional visits took place after 4 months, and then every 4 months (from February 15, 2017 to August 17, 2018). The primary endpoint was an exacerbation of HF symptoms associated with unplanned hospitalization or requiring intravenous diuretic therapy, as well as cardiovascular death. Of the initially evaluated 8,134 patients from 20 countries, 4,744 patients were randomised, including 2,373 patients treated with dapagliflozin. The study brought ground-breaking results; dapagliflozin, developed as a hypoglycaemic drug, has been

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shown to be suitable for the treatment of HF regardless of the diabetes coexistence. The primary endpoint was seen in fewer people treated with inhibitor SGLT2 (386/16.3%, including 215 patients with diagnosed T2DM) compared to 502/21.17% undergoing standard therapy (including 271 with T2DM), which means a 26% risk reduction [hazard ratio (HR) = 0.74, p = 0.00001]. Listed as one of the primary endpoints, unplanned hospitalisation was significantly less common in patients treated with dapagliflozin (231 patients required an additional hospital stay — 9.7%, vs. 318 patients — 13.4% from the control group; HR = 0.7, p = 0.00003). Weaker but also statistically significant results were obtained in the area of deaths from cardiovascular causes — 227 patients (9.6%) who received the SGLT2 inhibitor died compared to 273 (11.5%) patients undergoing standard treatment (HR = 0.82, p = 0.029). Total deaths were also compared, showing lower mortality in the dapagliflozin group (11.6% vs. 13.9% in the control group; HR = 0.83, p = 0.022). Researchers defined the secondary endpoint as hospitalisation for HF or death from cardiovascular causes. Also, in this regard, the results of the study showed the benefits of using dapagliflozin (HR = 0.75, p = 0.00002). The authors also considered the severity of HF symptoms in accordance with the Kansas City Cardiomyopathy Questionnaire (KCCQ) scale, demonstrating improvement in the clinical condition after 8 months (p < 0.001) in the case of inhibitor SGLT2 treatment. Dapagliflozin had a neutral effect on renal function with no signs reported of the adverse effects of the study drug. Importantly, the protective effect in HF did not depend on the use of ARNI — it was identically strong in patients treated with and without sacubitril/valsartan, suggesting a different mechanism of action. The DAPA-HF study has already shown that adding dapagliflozin to standard therapy reduces the risk of exacerbation of HF symptoms, as well as improves clinical status, which is associated with a reduced number of hospitalisations and reduced cardiovascular mortality in HF patients with reduced LVEF also without T2DM, which is a breakthrough observation and means the identification of a new drug that improves prognosis in HF.

PARAGON-HF — angiotensin receptor neprilysin inhibitor in HF with intermediate and preserved LVEF?

Another study on HF, the results of which had been expected, was PARAGON-HF (Efficacy and Safety of ARNI Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction) [2]. It compared the effects of treatment with angiotensin II receptor blocker (ARB) — valsartan 160 mg, and treatment with ARB and neprilisin inhibitor (ARNI) — sacubitril/valsartan (97/103 mg) for 35 months in a difficult-to-treat group of patients with HF with intermediate and preserved LVEF. The study included 4,822 patients aged 50 years and from 43 countries with persistent HF symptoms in NYHA and LVEF class II–IV not less than 45% and elevated NT-proBNP concentration. Individuals were excluded with acute, decompensated HF, LVEF below 40%, SBP values below 110 mm Hg or above 180 mm Hg, and SBP above 150 mm Hg if patients did not take more than 3 antihypertensive drugs. Researchers failed to reach the primary endpoint — only the benefit trend of the new therapy was obtained (reduction of hospitalisations and cardiovascular death by 13%, p = 0.059). Similarly, there was a trend to reduce the risk of hospitalisation in the key ARNI group (690 vs. 797 in the valsartan group; relative risk [RR] 0.85, p = 0.056). Among the secondary endpoints, there was a statistically significant improvement in clinical status in the ARNI-treated group compared to ARB-treated patients [odds ratio (OR) 1.35, p = 0.004], also confirmed on the KCCQ quality of life scale (OR = 1.3, p = 0.019). Protective effects on kidney function have also been observed [HR = 0.55; 95% confidence interval (CI) 0.33–0.77, p = 0.002]. In the group of patients undergoing complex therapy, a higher tendency to hypotonia (p < 0.0001) and angioedema was observed, with less frequent hypokalemia. Subgroup analysis suggested a better effect of the drug in patients with LVEF below 57%. Although the results of the PARAGON-HF study did not indicate the efficacy of ARNI in patients with HF and preserved left ventricular systolic function to improve survival, it improved clinical status, quality of life and kidney function when compared to patients receiving valsartan.

ISAR-REACT 5 — prasugrel versus ticagrelor in patients with acute coronary syndrome after coronaroplasty

ISAR-REACT 5 Study (The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) caused a real sensation [3]. Two antiplatelet drugs (prasugrel and ticagrelor) added to acetylsalicylic acid (ASA) were compared in patients after acute coronary syndrome (ACS) requiring an invasive treatment strategy after coronary angiography, 85% of whom had coronaroplasty. The patients with active bleeding, treated with anticoagulants, after a stroke or transient ischaemic attack (TIA), with renal failure requiring dialysis, with acute or moderate liver failure, and using CYP3A drugs were excluded in this non-commercial study. 4,018 people were included in the study; 2012 received ticagrelor and 2006 prasugrel. The authors determined for the first time in a head-to-head study the impact of these drugs on mortality, ST-segment elevation myocardial infarction (STEMI), haemorrhagic and ischaemic stroke during 12 months of therapy. To the surprise of the initiators of the study, there were significantly fewer (36%) adverse events in the prasugrel-treated group (6.9% vs. 9.3%, p = 0.006). When comparing each of the

primary endpoint components individually, benefits were also seen in patients treated with prasugrel in regard to stent thrombosis. In the group of patients treated with prasugrel, there were insignificantly less (12%) incidents of major bleeding (determined by the Bleeding Academic Research Consortium scale — 4.8% vs. 5.4%, p = 0.46) compared to those treated with ticagrelor. ISAR-REACT 5 demonstrated that treatment with prasugrel in patients with ACS reduces the risk of death, recurrent heart attack and stroke without increasing the risk of bleeding. These results come from study with a very well-planned protocol in which two antiplatelet drugs were compared for the first time in the context of percutaneous coronary intervention (PCI). The results of the ISAR-REACT 5 study emphasise the importance of solid evidence-based medicine, using direct, precise studies of relevant clinical groups, not stopping at indirect comparisons — using the results of separate trials with not necessarily identical characteristics.

THEMIS — dual antiplatelet therapy with ticagrelor versus ASA monotherapy in patients with stable CAD and T2DM

The attention of the participants was also focused on the **THEMIS** (The Effect of Ticagrelor on Health Outcomes in DiabEtes Mellitus Patients Intervention Study) study [4], which aimed to demonstrate the benefits of using ticagrelor (dual antiplatelet therapy with ASA) compared to a control group receiving only ASA in patients with T2DM treated for at least 6 months and stable CAD with no history of myocardial infarction. The primary endpoint was a risk of cardiovascular death, heart attack or stroke. 19,220 patients were enrolled in the study, of whom 9,619 received ticagrelor. The inclusion of ticagrelor significantly reduced the risk of a composite endpoint by 10% (HR = 0.9, p = 0.038). In the analysis of individual treatment goals, dual antiplatelet therapy reduced the number of myocardial infarction (HR = 0.84, p = 0.029) and strokes (HR = 0.8, p = 0.038). Acute limb ischaemia was also rarer (HR = 0.45, p = 0.017). However, the primary safety-related endpoint proved unfavourable for dual therapy, which more than doubled the number of bleeding complications and the increased the risk of intracranial haemorrhage by 71%. A group of patients **THEMIS-PCI** (THEMIS-Percutaneous Coronary Intervention) [5] treated with the PCI was prospectively separated from the group of patients included in the THEMIS study. This subgroup consisted of 5,558 patients who underwent dual antiplatelet therapy and 5,596 patients from the control group. In this subgroup, the inclusion of ticagrelor reduced the risk of a composite endpoint (cardiovascular death, myocardial infarction or stroke) by 15% (HR = 0.85, p = 0.013). In the analysis of individual treatment goals, dual antiplatelet therapy also reduced the number of heart attacks and strokes in the group of patients treated with PCI. When analysing each of the points, the risk of myocardial infarction was reduced by 20% (HR = 0.8, p = 0.027), STEMI by 68% (HR = 0.32, p < 0.0001) and stroke by 26% (HR = 0.74, p = 0.024). Comparing the composite endpoint including death, myocardial infarction, ischaemic stroke, fatal bleeding and intracranial haemorrhage, it was demonstrated that the inclusion of ticagrelor reduced the risk by 15% (HR = 0.85, p = 0.005). Pharmacotherapy with ticagrelor (initially at 2 × 90 mg, but in the later phase of the study reduced to 60 mg) in THEMIS in CAD and T2DM patients treated with prior PCI has also been shown to reduce the risk of cardiovascular death, MI and stroke despite the bleeding. The results of the study suggest that long-term, even lasting 3 years, ticagrelor therapy with ASA may become useful in patients with stable CAD and T2DM, especially those patients treated with percutaneous coronary angioplasty, with a high risk of thromboembolic events and a low risk of bleeding.

AFIRE — rivaroxaban monotherapy versus dual antiplatelet therapy in patients with CAD and atrial fibrillation

A recent study focused on the treatment of patients with CAD and co-existing atrial fibrillation. The aim of the Japanese **AFIRE** study [6] was to compare the effectiveness of rivaroxaban treatment alone or in combination with antiplatelet agents. The study included 2,200 patients with CAD and atrial fibrillation (with $CHADS_2 \geq 1$) one year after coronary angioplasty or coronary artery bypass grafting, and those not requiring intervention with vasoconstriction exceeding 50%. The study excluded patients with a history of stent thrombosis, concomitant active tumour, and poorly controlled hypertension. Patients received rivaroxaban monotherapy at a "Far-Eastern" typical dose of 10–15/day, which corresponded to typical dosing in Caucasian patients, or in combination with one of the antiplatelet agents (also in modified dosing — ASA 81–100 mg, clopidogrel in 50–75 mg or prasugrel 2.5–3.75 mg). Finally, 1,005 patients treated with rivaroxaban only and 968 undergoing dual antiplatelet therapy were randomised. Researchers assessed a composite endpoint including stroke, embolic complications, MI, unstable angina requiring revascularization, or death over a 23-month follow-up period. A 28% lower risk of composite endpoint was seen with rivaroxaban alone (HR = 0.72, p < 0.001), as well as a 41% less bleeding event (HR = 0.59, p = 0.01). Taking into account the occurrence of cardiovascular incidents and mortality, rivaroxaban monotherapy significantly better protects patients who underwent coronary revascularization a year ago or earlier, which is the first evidence of the risk of the chronic combination of new anticoagulants with antiplatelet agents.

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