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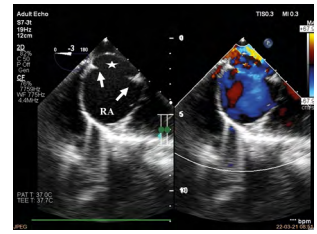

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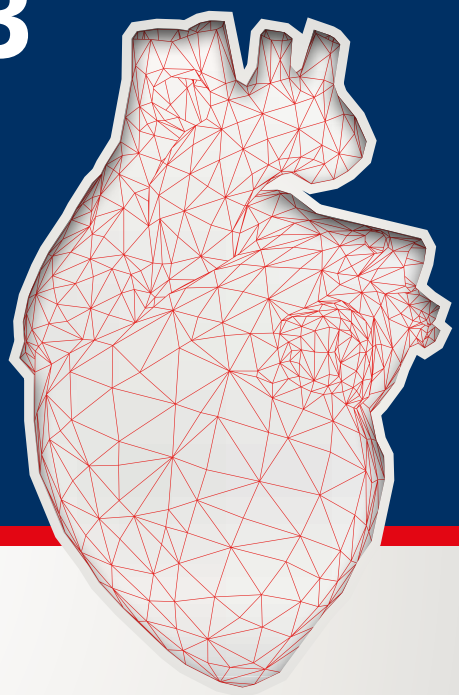

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Od Redaktora

Szanowni Czytelnicy,

otwieramy rok 2023 pierwszym numerem czasopisma *Folia Cardiologica*, a w nim prace oryginalne, poglądowe i kazuistyczne. Pierwszą kardiologiczno-ortopedyczną pracą jest praca oryginalna Anny Szałek-Goralewskiej i wsp. „Influence of training and half marathon run on the right ventricle in amateur runners" pochodząca z Uniwersytetu Medycznego w Poznaniu, dotyczy oceny przebudowy serca u osób uprawiających amatorsko biegi długodystansowe, co, jak wiemy, ostatnio stało się nawet swego rodzaju modą, a na pewno jednym z elementów aktywnego spędzania wolnego czasu. Kolejną pracę badawczą prezentują autorzy z Kliniki Kardiologii Uniwersytetu Medycznego w Łodzi — Carl Thaddäus Braun i wsp. w artykule „The assessment of right atrial function with the use of speckle tracking echocardiography" przedstawili wyniki oceny funkcji prawego przedsionka za pomocą echokardiograficznej metody śledzenia markerów akustycznych. Jak się okazuje, parametry deformacji prawego przedsionka słabo korelują ze wskaźnikami funkcji prawej komory, co nakazuje poszukiwanie innych wskaźników będących bezpośrednimi barometrami funkcji prawej komory.

Zachęcam Państwa również do lektury bardzo ważnego i cennego opracowania poglądowego „Iron deficiency, heart failure and cerebrovascular events: what is the connection?", w którym Phillip Kiełbowicz i wsp. z Uniwersytetu Medycznego w Łodzi w zwięzły i obrazowy sposób przedstawili związki niedoboru żelaza z różnymi patologiami w przebiegu niewydolności serca. Praca poglądowa „Coffee and lipid profile: from theory to everyday practice" Stanisława Surmy i wsp. afiliowanych w ośrodkach katowickim, szczecińskim i warszawskim, dotyczy nas wszystkich, bo przecież bez porannej kawy większość z nas nie wyobraża sobie rozpoczęcia dnia. Czy więc osoby z hipercholesterolemią powinny powstrzymać się od wypicia małej czarnej? Odpowiedź znajdziecie Państwo w artykule. Na koniec numeru cztery niezwykle interesujące prezentacje przypadków z ośrodków katowickich, białostockiego i łódzkiego.

Życząc miłej lektury, pozostawiam Państwa z pierwszym numerem *Folia Cardiologica* w 2023 roku.

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Influence of training and half marathon run on the right ventricle in amateur runners

Wpływ treningu i biegu półmaratońskiego na prawą komorę u biegaczy amatorów

Anna Szałek-Goralewska[1], Rafał Dankowski[1], Wioletta Sacharczuk[1], Stefan Ożegowski[1], Jędrzej Tschurl[2], Barbara Rabiega[1], Andrzej Szyszka[1]

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Abstract

Introduction. Endurance running may lead to heart remodelling. There are little data on the right ventricular (RV) changes in amateur athletes running shorter than marathon distances.

The study aimed to investigate whether training and running a half marathon affect the anatomy and function of the RV in amateur runners and whether these changes affect the athlete's competitive performance.

Material and methods. The study included 45 recreational runners with a mean age of 32.96 (5.12) years, 27 men. Echocardiography was performed before the ten-weeks training period and before and after the half marathon run. The morphological and functional parameters of the RV were analysed, including two-dimensional, Doppler and speckle-tracking echocardiography.

Results. In training period, the RV outflow tract (27.98 [5.46] vs. 30.07 [4.90]; p = 0.003) and the RV index of myocardial performance (0.36 [0.29; 0.45] vs. 0.39 [0.33; 0.52]; p = 0.017) increased significantly and no changes were found for E/e'. After the half marathon run, the absolute value of the RV free wall global longitudinal strain increased significantly (–25.89 [3.08] vs. –27.20 [3.42]; p = 0.008). Athletes who trained more intensively during the training period achieved significantly better half marathon results (r = –0.4; p ≤ 0.05).

Conclusions. More enhanced physiological RV remodelling under exercise in amateur athletes results in better half marathon finishing times. The preparation period and 21.0975 kilometres run do not affect the diastolic function of the RV in recreational runners. The RV systolic function improves immediately after the half marathon performance.

Key words: amateur athletes, echocardiography, global longitudinal strain, right ventricle, right ventricular strain

Folia Cardiologica 2023; 18, 1: 1–9

Introduction

Regular physical activity carries several health benefits [1]. Among its many forms, running is one of the most accessible forms of exercise. Over the last decades, a major increase in interest in long-distance running and competitions was observed. In the United States of America, the number of half marathon finishers increased from 612 thousand in 2004 to 2046.6 thousand in 2014 [2]. Many participants are amateurs whose training program is not always properly set and supervised. Moreover, amateur runners are not subject to obligatory medical examinations.

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This is a potential health threat, and recreational runners are not always aware of the risk [3].

Intensive endurance exercise may lead to myocardial remodelling [4]. There are numerous data concerning sport-related cardiovascular changes in professional runners [5–7], whereas the group of amateur athletes is studied less likely [8]. Moreover, previous studies have mainly assessed the influence of marathon distance running (42.195 kilometres) on cardiovascular function. While numerous studies have assessed several parameters of the left ventricular (LV) function in recreational long-distance running athletes [9], the influence of a half marathon run (21.0975 kilometres) on the right ventricular (RV) function remains unclear. Moreover, there is little data in the literature describing the influence of training on cardiovascular function in amateur runners.

Echocardiography is a well-established technique in the assessment of both the structure and function of the RV. Moreover, the recent introduction of RV global longitudinal strain (GLS) analysis expands the possibilities of echocardiographic evaluation of the RV [10]. Compared to magnetic resonance imaging, echocardiography requires less time and resources. Therefore, it is particularly useful in assessing larger groups of subjects and the parameters that change quickly over time. It is especially important in analysing post-exertional changes in amateur athletes.

This study aimed to evaluate the echocardiographic changes of the RV during the training period and after participating in the half marathon in amateur runners. It is hypothesized that amateur training affects the structure and function of the RV and that changes occurring during the training influence the result of the planned competition.

Material and methods

Study participants and inclusion criteria

We designed a prospective study that involved amateur runners preparing to participate in a half marathon run (21.0975 kilometres). The inclusion criteria were as follows: age of 18–40 years, both sexes, and a minimum of one previous start in a long-distance running competition (≥ 10 kilometres). The athletes diagnosed with chronic diseases — particularly cardiovascular conditions, such as coronary artery disease, hypertension, arrhythmia, heart failure, and valve abnormalities — were excluded from the study. Each person was in sinus rhythm, normotensive, and had no structural disease of the heart and no obstructive or restrictive lung diseases. All the participants gave written informed consent before enrolment.

Study protocol

Our study consisted of two stages and was conducted in 2019 and 2021 among amateur athletes preparing for the 12th PKO Poznan Half Marathon in April 2019 and for the 13th PKO Poznan Half Marathon in October 2021, respectively. Participants were recruited *via* the online application form posted on social media running forums.

Both recruitments were based on the same study protocol that involved three checkpoints. The first point (P1) was conducted 10 weeks before the run, the second point (P2) was carried out within 48 hours before the competition, and the third point (P3) was conducted within 48 hours after finishing the run.

At each checkpoint, blood samples were collected and a physical examination was performed, twelve-lead electrocardiogram and transthoracic echocardiography. No special diet was recommended before any of the three checkpoints of the study. Athletes were allowed to rehydrate as needed. At each checkpoint, participants were anthropometrically assessed — data on height, body mass, body mass index, arterial blood pressure and heart rate were collected. All participants were required to declare their regular training intensity, expressed in kilometres per week.

The study protocol was approved by the Bioethics Committee of the Poznan University of Medical Sciences, Poland (No. 19/21) and was consistent with the Declaration of Helsinki.

Echocardiographic assessment

We performed the transthoracic echocardiography using commercially available ultrasound systems: Vivid E9 and Vivid S70N (GE Healthcare). All measurements were made following the guidelines of the European Association of Cardiovascular Imaging [11] in the lateral decubitus position. Echocardiographic data were transferred and analysed offline using EchoPAC software (GE Healthcare, version 204).

We measured the proximal RV outflow tract (RVOT) in the parasternal long-axis view (PLAX). RV basal diameter and fractional area change (FAC) were assessed from an RV-focused apical four-chamber view.

Early (E) and late (A) tricuspid inflow velocities and E/A ratio are recorded using pulsed wave Doppler at the tricuspid leaflet tips. Using tissue Doppler imaging, RV lateral tricuspid annulus velocity parameters were assessed: s' wave and e' wave. E/e' ratio was calculated.

The RV index of myocardial performance (RIMP) was calculated based on time intervals measured with pulsed wave Doppler, obtained from the lateral tricuspid annulus. It was defined as the sum of the isovolumetric contraction time and isovolumetric relaxation, divided by the RV ejection time.

The GLS of the RV was measured from the RV-focused apical four-chamber view. The automated function imaging application was used for the calculations [12]. After selecting the optimal cardiac cycle, the operator selected the region of interest by placing three points: 1 — on the basal segment of the free wall of the RV; 2 — on the basal

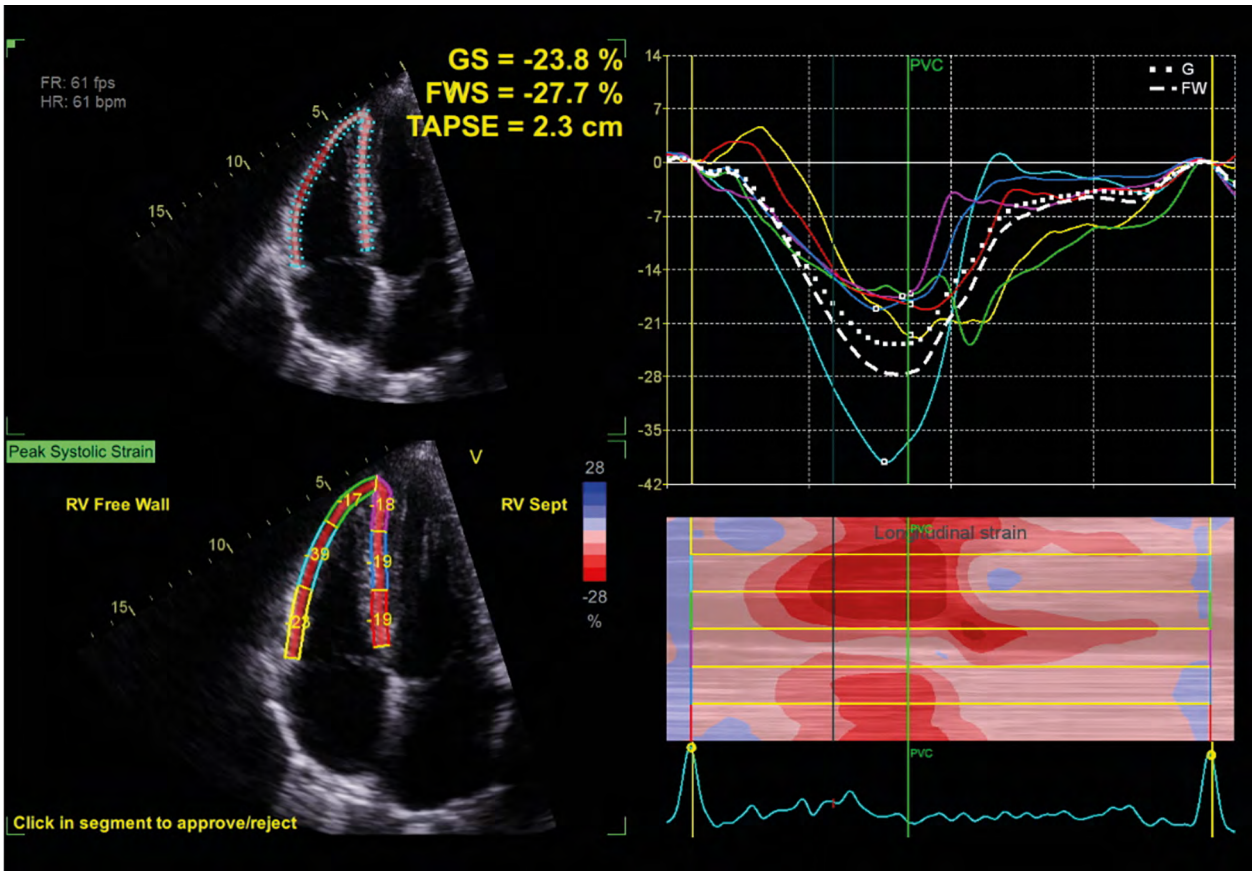

Figure 1. The right ventricular (RV) free wall global longitudinal strain (GLS). The RV-free wall was divided into three segments: basal, midventricular and apical. The peak negative value was chosen as the RV free wall GLS; GS — global strain; FWS — free wall strain; TAPSE — tricuspid annular plane systolic excursion

segment of the septum, and 3 — on the RV apex. The region of interest was selected with special attention to avoid the inclusion of RV epicardium. Then, the concordance between visually assessed RV contractility and the RV endocardial tracings was checked and corrected by the operator if needed. The RV was divided into 6 standard segments: basal, midventricular and apical for both — free and septal walls [13]. The RV GLS was calculated for all the segments. The peak negative curve was chosen as the RV GLS. The RV free wall GLS was measured analogously and included three free wall segments only (Figure 1).

Statistical analysis

Data analysis was conducted using the R package, version 4.0.5. Calculations are based on a significance level of 0.05. Data are presented as mean and standard deviation (SD) or median (quartile 1 [Q1]; quartile 3 [Q3]), depending on data normality. The normality of distribution was verified with the Shapiro–Wilk test, based on skewness, kurtosis level, and visual assessment of histograms. Comparison of parameters between time points (time point 1 vs. 0 and time point 2 vs. 1) was made with paired tests: t-test or Wilcoxon test, as appropriate. Additionally, the mean or median difference (MD) were calculated between time points, including a 95% confidence interval. Correlation between variables was verified using Pearson's or Spearman's correlation, as appropriate.

Results

Characteristics of the group

Characteristics of the study group are presented in Table 1. Of the 50 participants initially included, 45 runners started the half marathon (10% drop) (Figure 2). The study group consisted of 45 persons with a mean age of 32.96 (5.12) years, 18 (40%) were females, and 27 (60%) were males. Each subject had prior half marathon experience and a minimum of three years of regular running training history. All starting participants finished the run.

The athletes were non-smokers, men and women of normal weight (Table 1). The average weekly running distance during the training period was 35.89 (17.78)

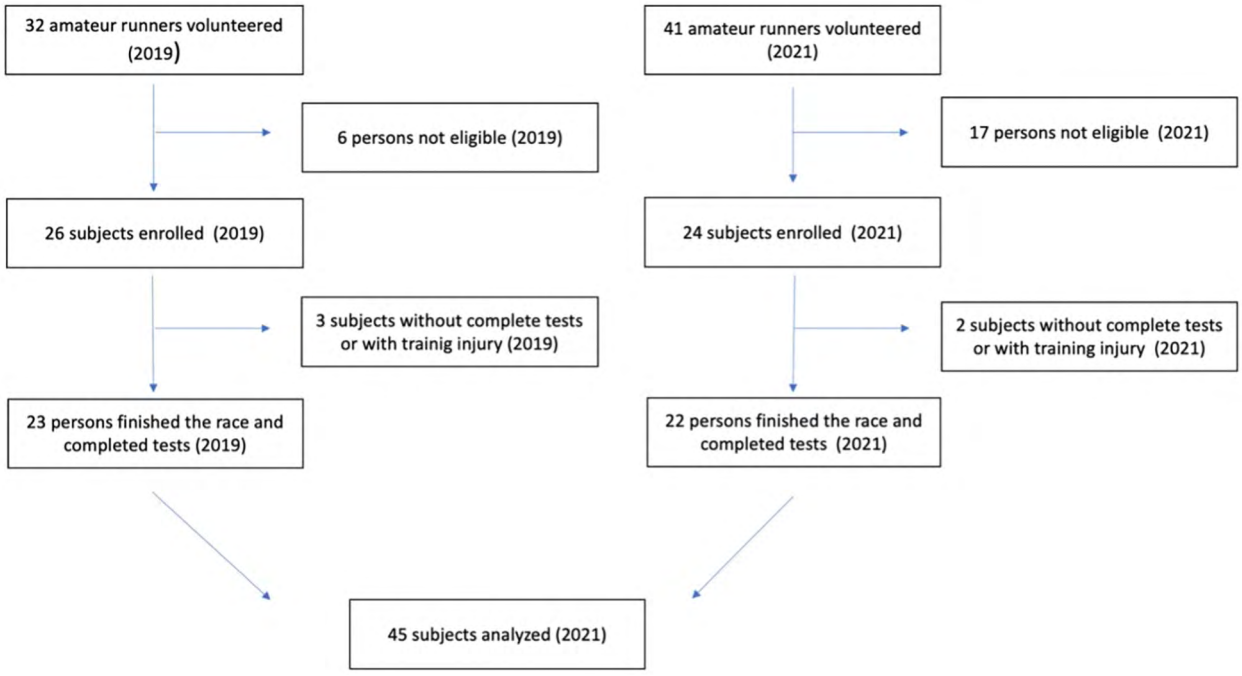

Figure 2. Study participation diagram

Table 1. Study group characteristics

Characteristic	Pre-training period (P1)	48 hours before the run (P2)	48 hours after the run (P3)
Body weight [kg]	72.15 (12.80)	71.37 (12.11)*	71.39 (12.26)
BMI [kg/m^2]	23.65 (2.92)	23.40 (2.74)*	23.41 (2.77)
Systolic blood pressure [mm Hg]	126.04 (16.57)	119.71 (12.74)*	117.67 (11.79)
Diastolic blood pressure [mm Hg]	68.96 (13.21)	68.58 (8.46)	68.00 (7.67)
Heart rate [bpm]	63.05 (7.61)	61.29 (10.31)	63.20 (12.32)
Training intensity [kilometres run/week]	–	35.89 (17.78)	–
Results of the Half Marathon, duration [min]		107.4 (15.75)	
LVEF [%]	59.96 (5.20)		
LA [mm]	31.87 (4.62)		
MV E/A ratio	1.60 (0.46)		

*$p < 0.05$; data presented as mean (SD); BMI – body mass index; LA – left atrium; LVEF – left ventricular ejection fraction; MV E/A ratio – transmitral E-wave/A-wave ratio

kilometres run per week. The average result of the half marathon runners was 107.4 (15.75) minutes (1 h 47 min). Dimensions of the LV, left atrium and LV systolic and diastolic function at baseline were in normal ranges. LV ejection fraction was normal.

Body weight and body mass index significantly decreased during the training period (P1 vs. P2). The systolic blood pressure decreased significantly during the training period (P1 vs. P2 and P1 vs. P3). Diastolic blood pressure and resting heart rate did not change during the study. The left atrium dimension increased significantly during the training period (P1 vs. P2). Mitral inflow velocities were normal and did not change throughout the study.

Correlation between the training intensity and the result of half marathon performance

Athletes who trained more intensively before the competition (according to the declared training intensity expressed in kilometres run per week) achieved significantly better half marathon results ($r = -0,4$; $p \leq 0.05$) (Figure 3).

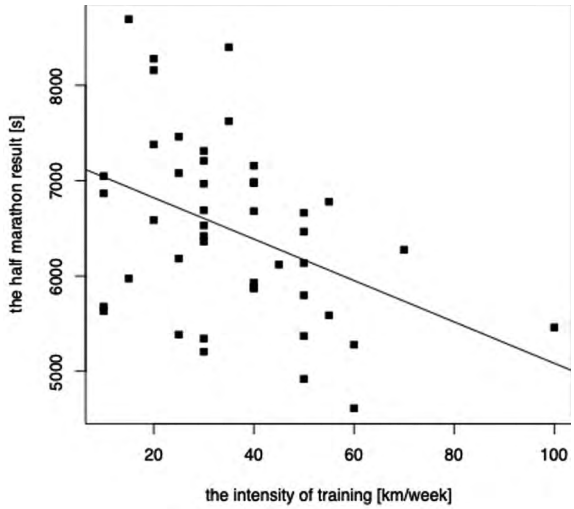

Figure 3. Correlation between the intensity of training before the half marathon run and the result of half marathon performance

Influence of training on echocardiographic parameters of the right ventricle

RVOT dimension increased significantly during the training period (Table 2). The training before the half marathon run did not significantly impact the RV basal diameter, RV wall thickness and RV FAC. No significant differences were found between pre-training and post-training measurements of the GLS for either the RV or the RV-free wall. The tricuspid annular systolic velocity and tricuspid annular plane systolic excursion did not change. The E/e' ratio remained constant during training for the run. A significant increase was observed in the RIMP after the training period.

Influence of half marathon run on echocardiographic parameters of the right ventricle

Running a half marathon had no significant impact on the RVOT and RV basal diameter (Table 3). The thickness of the RV wall remained unchanged immediately after the run (P2 vs. P3). A significant difference in RV FAC values after the run was not observed compared to 48 hours before the start. The RV GLS remained unchanged after the start, but the absolute value of the RV free wall GLS increased significantly. No significant changes in tricuspid annulus velocities immediately after the half marathon were observed. The RV index of myocardial performance remained constant.

Correlations between right ventricular echocardiographic parameters, the intensity of training before the half marathon and the result of half marathon performance

The more intensive the training, the higher the RVOT dimension after the training period and immediately after the half marathon run (at P2 and P3) (Table 4) ($r = 0.36$; $p = 0.02$ and $r = 0.3$; $p \leq 0.05$) In athletes who had larger RV basal diameter before the half marathon run (at P2) and after the run (at P3), the significantly better half marathon result was observed ($r = -0.3$; $p = 0.049$ and $r = -0.34$;

Table 2. Measurements of the right ventricle in the pre-training period (P1) and before the half marathon (P2)

Variable	Pre-training (P1)	48 hours before the run (P2)	MD (95% CI)	p-value
RVOT [mm]	27.98 (5.46)	30.07 (4.90)	2.09 (0.74; 3.44)	0.003*
RV basal diameter at end-diastole [mm]	36.71 (4.53)	35.67 (4.10)	–1.04 (–2.20; 0.11)	0.075
RV free wall thickness [cm]	0.43 (0.13)	0.42 (0.14)	–0.01 (–0.04; 0.02)	0.569
TV E-wave velocity [m/s]	0.63 (0.11)	0.62 (0.09)	0.01 (–0.02; 0.03)	0.756
TV A-wave velocity [m/s]	0.39 (0.30; 0.44)	0.36 (0.32; 0.40)	–0.03 (–0.05; 0.02)	0.388
TV E/A ratio	1.72 (0.39)	1.73 (0.34)	0.03 (–0.11; 0.17)	0.663
RV FAC [%]	46.80 (7.25)	44.53 (8.59)	–2.27 (–4.83; 0.30)	0.082
RV GLS [%]	–20.22 (2.15)	–19.76 (1.86)	0.47 (–0.12; 1.06)	0.118
RV free wall GLS [%]	–26.27 (3.58)	–25.89 (3.08)	0.38 (–0.88; 1.64)	0.548
TV s' [m/s]	0.16 (0.02)	0.15 (0.02)	–0.01 (–0.01; 0.003)	0.212
TAPSE [mm]	25.24 (3.73)	25.31 (3.23)	0.07 (–1.25; 1.38)	0.919
TV E/e'	4.66 (1.02)	4.47 (0.88)	–0.19 (–0.44; 0.06)	0.136
TV a' [m/s]	0.14 (0.04)	0.13 (0.05)	–0.004 (–0.02; 0.01)	0.606
RIMP	0.36 (0.29; 0.45)	0.39 (0.33; 0.52)	0.06 (0.01; 0.12)	0.017*

*$p < 0.05$; data presented as mean (SD) or median (Q1; Q3), depending on normality of distribution; MD — mean/median difference between time points with a 95% confidence interval (CI). Time points compared with paired t-test or Wilcoxon test; FAC — fractional area change; GLS — global longitudinal strain; RIMP — right ventricular index of myocardial performance; RV — right ventricular; RVOT — proximal right ventricular outflow tract; TAPSE — tricuspid annular plane systolic excursion; TV — tricuspid valvular; TV a' — tricuspid annular A-wave velocity; TV E/e' — tricuspid valvular E-wave velocity/tricuspid annular early diastolic velocity ratio; TV s' — myocardial systolic excursion velocity at the tricuspid annulus

Table 3. Measurements of the right ventricle before the half marathon (P2) and within 48 hours after finishing the run (P3)

Variable	48 hours before the run (P2)	48 hours after the run (P3)	MD (95% CI)	p-value
RVOT [mm]	30.07 (4.90)	29.71 (4.54)	–0.36 (–1.07; 0.36)	0.32
RV basal diameter at end-diastole [mm]	35.67 (4.10)	36.00 (4.56)	0.33 (–0.92; 1.59)	0.59
RV free wall thickness [cm]	0.42 (0.14)	0.44 (0.14)	0.02 (–0.02; 0.05)	0.41
TV E-wave velocity [m/s]	0.62 (0.09)	0.62 (0.10)	–0.01 (–0.04; 0.02)	0.50
TV A-wave velocity [m/s]	0.36 (0.32; 0.40)	0.35 (0.31; 0.41)	–0.01 (–0.03; 0.03)	0.78
TV E/A ratio	1.73 (0.34)	1.71 (0.39)	–0.03 (–0.18; 0.12)	0.66
RV FAC [%]	44.53 (8.59)	44.64 (8.74)	0.11 (–3.17; 3.39)	0.95
RV GLS [%]	–19.76 (1.86)	–20.09 (1.92)	–0.33 (–0.85; 0.18)	0.20
RV free wall GLS [%]	–25.89 (3.08)	–27.20 (3.42)	–1.31 (–2.26; –0.36)	0.008*
TV S' [m/s]	0.15 (0.02)	0.16 (0.02)	0.004 (–0.003; 0.01)	0.30
TAPSE [mm]	25.31 (3.23)	25.31 (3.65)	0.0 (–0.98; 0.98)	> 0.99
TV E/e'	4.47 (0.88)	4.50 (0.92)	0.03 (–0.17; 0.22)	0.776
TV annular A-wave velocity [m/s]	0.13 (0.05)	0.14 (0.04)	0.002 (–0.01; 0.01)	0.71
RIMP	0.39 (0.33; 0.52)	0.40 (0.33; 0.54)	–0.01 (–0.07; 0.04)	0.56

Data presented as mean (SD) or median (Q1; Q3), depending on the normality of distribution; MD — mean/median difference between time points with a 95% confidence interval (CI). Time points compared with paired t-test or Wilcoxon test; FAC — fractional area change; GLS — global longitudinal strain; RIMP — right ventricular index of myocardial performance; RV — right ventricular; RVOT — right ventricular outflow tract; TAPSE — tricuspid annular plane systolic excursion; TV — tricuspid valvular; TV E/e' — tricuspid valvular E-wave velocity/tricuspid annular early diastolic velocity ratio; TV S' — myocardial systolic excursion velocity at the tricuspid annulus

Table 4. Correlations between RV ECHO parameters, the intensity of training before the half marathon and the results of half marathon performance

RV ECHO parameters	Training intensity, kilometres run/week (r)	Results of the half marathon, duration (r)
RVOT (P2)	0.36*	–0.24
RVOT (P3)	0.3*	–0.26
RV basal diameter at end-diastole (P2)	0.24	–0.3*
RV basal diameter at end-diastole (P3)	0.39*	–0.34*
RV FAC (P3)	0.01	0.39*
TV E/e' ratio (P2)	0.16	–0.08
TV E/e' ratio (P3)	0.1	–0.05

*p < 0.05; r = correlation coefficient; FAC — fractional area change; RV — right ventricular; RVOT — right ventricular outflow tract; TV — tricuspid valvular

p = 0.02). Subjects who trained more intensively had significantly larger RV basal diameter dimensions immediately after the half marathon competition (r = 0.39; p = 0.008). Recreational runners with higher RV FAC immediately after the run achieved significantly worse half marathon results (r = 0.39; p = 0.008). No significant change in diastolic function of the RV based on the E/e' parameter was observed both after the training period and after the half marathon performance.

Discussion

This study investigated whether the training period and participation in half marathon distance run impacted the morphology and function of the RV of recreational runners. The major findings are as follows: (1) the amateur training affected both the anatomy and function of the RV of the amateur athletes; (2) opposite to the training, the half marathon run did not affect the anatomy of RV, but what was observed was the improvement of the GLS of the RV-free wall immediately after the run; (3) the results of this study indicate that amateur athletes with RV remodelling achieve significantly better results in completing a half marathon run.

Right ventricular function

D'Ascenzi et al. [7] analysed the cohort of 1009 professional athletes practising various sports disciplines and confirmed the most significant impact of endurance sport (such as long-distance running) on the RV remodelling, including significant enlargement of RVOT. The present study shows that amateur training with a mean weekly

distance of 35.89 (17.78) kilometres has a similar effect on the RV dimensions.

The enlargement of RVOT is one of the most characteristic echocardiographic changes occurring in the heart of endurance athletes [7]. However, heart pathology should be considered an alternative explanation for RVOT enlargement in amateur athletes. In the UK, 13% of sudden cardiac death in young athletes is attributed to arrhythmogenic RV cardiomyopathy (ARVC) [14]. In pre-screening before significant physical exertion such as a half marathon run, ARVC should be excluded. This can be done by using the Task Force Criteria (TFC) [15], which include the echocardiographic assessment of RV structure and function (RVOT enlargement, tricuspid annular plane systolic excursion reduction, RV FAC reduction, RV ejection fraction reduction), electrocardiogram repolarization abnormalities, MRI tissue characterization and family history. Qasem et al. [16] analysed 214 elite male athletes, of which 34 met the TFC and had an enlarged RVOT. These same individuals had significantly lower global RV strain compared to participants who did not meet the TFC. Among this study participants, RVOT enlargement after the training period (in P2) met the minor TFC. However, other necessary ARVC criteria were not met in any study subject.

The RIMP is useful in estimating pulmonary vascular resistance [17]; its increase indicates a global impairment of the systolic and diastolic function of the RV. Alsafi et al. [18] examined the group of 32 female elite athletes and compared them to a control group of 34 sedentary subjects, assessing the myocardial performance index for both — LV and RV. The study showed no significant difference in RIMP among athletes and the sedentary group; the myocardial performance index was significantly higher in LV compared to RV in both groups. Nevertheless, the present study showed a significant increase in RIMP after the preparation for the half marathon period (at P2), which indicates the impairment of global RV function under the influence of running training. It is consistent with the analysis made by Lewicka-Potocka et al. [19], who investigated that the two-week preparation for the marathon run period and marathon performance among 34 male amateur runners resulted in a significant increase in RIMP.

We did not observe a significant change in RV diastolic function expressed by the tricuspid valvular E/e' ratio after the training period and a half marathon run. The present results align with Teske et al. [20], who analysed 269 subjects among whom amateur, regular, and professional athletes were present. The endurance training did not result in RV diastolic function changes in any group. Simsek et al. [21] compared the group of 44 long-distance runners with 30 sedentary controls and involved them in a regular exercise program. They did not prove any diastolic alteration among athletes and controls.

The echocardiographic assessment of the RV ventricle is challenging because of its complex geometry and highly trabeculated inner wall contour [10]. The speckle-tracking echocardiography turns out to be a useful tool in this evaluation. According to recent studies, RV GLS is the more preferred echocardiographic method for clinical assessment of the RV function than the conventional 2D echocardiographic parameters [22]. Research shows that RV GLS is significantly higher among athletes practising low-intensity exercise compared to healthy sedentary subjects [23]. Yaman et al. [23] analysed the group of 84 sports practitioners (who practised static and dynamic exercise for three months) and compared them to 82 sedentary subjects. RV GLS was significantly higher in athletes, and the RV free wall GLS tended to be higher among the sportive population but was not statistically significant. The present analysis proves the significant increase of the RV free wall GLS absolute value and the non-statistically significant tendency to increase RV GLS immediately after the half marathon run. In the context of the results presented by Yaman et al. [23], the present study suggests that the half marathon distance does not induce acute RV dysfunction in amateur runners.

On the other hand, increased RV free wall GLS after a half marathon run may probably be caused by the physiological decrease of pulmonary vascular resistance occurring in exertion and described in the literature [24, 25]. However, the authors lack the direct data to prove this statement (such as the mean pulmonary artery pressure value) since invasive diagnostics with the right heart catheterization were not performed.

The correlations between the intensity of training, the results of the half marathon performance and the echocardiographic parameters

The more intensively the subjects of this study trained, the better finishing race time they achieved (Figure 3). It was demonstrated that the RV remodelling influenced by training for a half marathon distance run results in better finishing times. At the same time, the authors did not observe significant correlations between the systolic echocardiographic parameters such as RV s', tricuspid annular plane systolic excursion and RV GLS and the intensity of training and the run finishing time. It proves that among amateur runners, the RV remains a thin-walled, volumetric chamber that can not be provoked to contract better during the preparation for the half marathon run. Moreover, the paradoxical impairment of systolic function in better-trained and faster participants of this study, depicted by the significant higher RV FAC among these athletes who achieved worse finishing race results, probably comes from the fact that the RV in amateur runners remains the low-pressure chamber. Thus, it compensates for an increased inflow during exertion by

the rise of the end-diastolic volume without the rise of the systolic volume.

We did not observe any significant correlations between the RV diastolic function parameters, such as the E/e' ratio (dependent on the ventricular filling pressure) and the intensity of training or the result of the run. Therefore, it is concluded that the physical effort over the half marathon distance and preceding preparations do not affect the diastolic function of the RV of amateur runners.

Limitations

There are certain limitations of this analysis. This study included a relatively small group of athletes with varying training intensities. Since the participants of this study were recreational runners, their training period was not strictly planned and was difficult to control. Nevertheless, data on the weekly distance run was collected at baseline, confirmed and updated during the study period.

Recent echocardiographic European Association of Cardiovascular Imaging guidelines consider proximal RVOT in PLAX to be dependent on imaging plane position and less reproducible than distal RVOT in PLAX. There is a risk of underestimation or overestimation if the RV view is obliquely oriented concerning the RV outflow tract. Limited normative data on proximal RVOT in PLAX is available. However, a relatively young, non-obese study group resulted in good quality echocardiographic images allowing high reproducibility.

As RIMP presents the relation of the isovolumetric time to ejection time, it is useful for describing RV's systolic and diastolic function but has its limitations. It depends on elevated right atrial pressures and loading conditions [10, 26].

Conclusions

In summary, remodelling of the RV under amateur training for the half marathon run expressed as increased RVOT is related to a better finishing time. The effort in the training period and 21.0975 kilometres run itself does not improve or worsen the diastolic RV function in recreational runners. The RV systolic function expressed by the RV free wall GLS improves immediately after the half marathon run, probably due to a decrease in pulmonary vascular resistance in exertion.

Conflict of interest

None declared.

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Streszczenie

Wstęp. Biegi długodystansowe mogą prowadzić do przebudowy serca. Niewiele jest danych na temat zmian w prawej komorze u sportowców amatorów biegających na dystansach krótszych niż maratoński.

Celem pracy było wykazanie, czy trening i ukończenie półmaratonu wpływają na anatomię i funkcję prawej komory u biegaczy amatorów oraz czy zmiany te wpływają na osiągany przez sportowca wynik.

Materiał i metody. Badaniem objęto 45 biegaczy amatorów w średnim wieku 32,96 (5,12) lat, w tym 27 mężczyzn. Echokardiografię wykonano przed 10-tygodniowym okresem treningowym oraz przed i po biegu półmaratońskim. Analizie poddano parametry morfologiczne i czynnościowe prawej komory. Wykonano echokardiografię dwuwymiarową, dopplerowską i stosowano technikę śledzenia plamki akustycznej.

Wyniki. W okresie treningowym droga odpływu prawej komory (27,98 [5,46] *vs.* 30,07 [4,90]; p = 0,003) oraz wskaźnik sprawności prawej komory (0,36 [0,29; 0,45] *vs.* 0,39 [0,33; 0,52]; p = 0,017) wzrosły znacząco i nie stwierdzono zmian dla E/e'. Po półmaratonie wartość bezwzględna globalnego podłużnego odkształcenia wolnej ściany prawej komory istotnie wzrosła (–25,89 [3,08] *vs.* –27,20 [3,42]; p = 0,008). Sportowcy, którzy w okresie treningowym trenowali intensywniej, osiągnęli istotnie lepsze wyniki w półmaratonie (r = –0,4; p ≤ 0,05).

Wnioski. Silniejsza fizjologiczna przebudowa prawej komory serca pod wpływem ćwiczeń u sportowców amatorów skutkuje lepszym czasem ukończenia półmaratonu. Okres przygotowań i przebiegnięcie 21,0975 km nie wpływa na funkcję rozkurczową prawej komory u biegaczy rekreacyjnych. Funkcja skurczowa prawej komory poprawia się natychmiast po ukończeniu półmaratonu.

Słowa kluczowe: sportowcy amatorzy, echokardiografia, globalne odkształcenie podłużne, prawa komora, odkształcenie prawej komory

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The assessment of right atrial function with the use of speckle tracking echocardiography

Ocena funkcji prawego przedsionka za pomocą echokardiografii metodą śledzenia markerów akustycznych

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Abstract

Introduction. Speckle tracking echocardiography (STE) is a well-established tool to assess cardiac function parameters, however, the value of this tool in the assessment of right atrial (RA) function is still largely unknown. The aim of the study is to investigate the feasibility of RA function assessment by STE and the relationship between right ventricular (RV) deformation and the function of the RA.

Material and methods. 94 patients with various cardiovascular pathologies have been included in the study group. All patients underwent transthoracic echocardiography with subsequent off-line analysis using speckle tracking technique and measurement of numerous RA deformation parameters, including peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS), as well as established indices of RV function, such as tricuspid annular peak systolic excursion (TAPSE) and global longitudinal strain (GLS).

Results. RA function assessment by STE was feasible in all patients. A statistically significant correlation was observed between RA strain (PACS and PALS) and RV parameters. RV-GLS showed weak correlation with PALS ($r = -0.38$; $p = 0.0015$) and PACS ($r = -0.30$; $p = 0.013$). Similarly, TAPSE correlated with PALS and PACS ($r = 0.34$; $p = 0.02$) and ($r = 0.23$; $p = 0.04$) respectively.

Conclusion. RA function assessment by STE is feasible. The RA deformation parameters weakly correlate with RV function indices, indicating that other factors significantly influence RA function. Therefore, the RA function cannot be regarded as a direct barometer of the RV function.

Key words: right atrium, right ventricle, speckle tracking echocardiography

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Introduction

Speckle tracking echocardiography (STE) has become a widely recognized tool to assess cardiac function and gather both prognostic and predictive information [1]. The software used to evaluate echocardiographic images was initially designed to evaluate left ventricular function, but its use in assessing the function of other cardiac chambers has become increasingly more common and well-established [2].

From a physiologic point of view, the right atrial (RA) has proven to have an impact on overall right ventricle (RV) performance and *vice versa* [3]. In a single-centre study, RA strain has proven to be significantly impaired in patients with pulmonary arterial hypertension (PAH) [4] being independently associated with systolic pulmonary arterial pressure (SPAP) and showing high sensitivity and specificity in predicting an increased SPAP [5]. Moreover, peak atrial contraction strain (PACS) and peak atrial longitudinal strain (PALS) showed significant association with RV global longitudinal strain (GLS) of the free wall (RV GLS FW) [6]. Right atrium strain is also prognostic for hospitalizations and mortality [7–10]. In this study population, it was aimed to investigate the feasibility of RA function assessment by STE and the relationship between RV function and its impact on the RA parameters.

Materials and methods

Study population

The present retrospective study included 94 patients (60 male, mean age 61.9 ± 14.4 years) with good echocardiographic image quality and various cardiac pathologies: hypertension (12), ischaemic heart disease (37), and valvular heart disease (50). Patients suffering from atrial fibrillation were excluded.

Echocardiography

The patients underwent transthoracic echocardiography and the echocardiographic images were analysed offline using EchoPac Software (GE Healthcare, Chicago, IL, USA). Apical 4-chamber view images were used to estimate the RV end-systolic area (RV ESA) and the RV end-diastolic area in order to calculate RV fractional area change (RV FAC). The RV inflow tract was measured just below the tricuspid valve between RV free wall and interventricular septum. Tricuspid annular plane systolic excursion (TAPSE) was assessed using M-mode, measuring the distance of tricuspid annular movement between end-diastole and end-systole. Peak systolic annular excursion (S') was assessed by tissue Doppler imaging.

Speckle tracking echocardiography

For STE assessment was used the QRS method and the apical 4-chamber view. The region of interest (ROI) was defined as the area between the inner endocardial border (inner contour of RA/RV) wall and the outer epicardial border (outer contour of RA/RV) and if needed manually adjusted. If more than 1/3 of the ROI was missing the image was rejected [11]. Once the ROI was fully adjusted, the software generated longitudinal strain curves for each segment. RA strain was assessed using peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS). PALS was measured at the end of the RA reservoir phase. PACS was measured just before the start of the active contractile phase of the atrium [11]. Global PALS and PACS (Figure 1) are averages of all segments. In the RV was assessed global longitudinal strain (RV GLS) as the peak systolic strain of all tracked segments. Moreover, RV GLS FW was measured based on the 3 segments of the free wall. If image assessment was not possible due to image quality, affected images and measurements were excluded.

Statistical methods

Continuous variables were initially tested for normality of data distribution by the Kolmogorov-Smirnow test. Normally distributed variables are expressed as mean ± standard deviation. Categorical variables are presented as percentages (%). Regression and correlation analysis was used to assess the relationship between RA and RV parameters (MedCalc Software, Frank Schoonjans, Belgium).

Results

Table 1 summarises the mean values and standard deviations of echocardiographic parameters in the study group.

Tables 2 and 3 present the relationship between RA functional parameters (PALS and PACS) and right ventricular parameters, whereas Tables 4 and 5 presen t the relationship between PALS and RA size. PALS showed a negative correlation with RA size expressed as ESA ($r = -0.42$; 95% CI: –0.59/–0.22; $p = 0.0001$) and RA end-systolic volume ($r = -0.41$; 95% CI: –0.58/–0.22; $p = 0.0001$). Also, PACS correlated with RA size expressed as ESA ($r = -0.32$; 95% CI: –0.51/–0.11; $p = 0.004$) and RA end-systolic volume ($r = -0.35$; 95% CI: –0.53/–0.14; $p = 0.002$).

We also found significant, yet weak, correlations between RA functional parameters (PALS and PACS, respectively) and RV parameters. PALS correlated with RV GLS ($r = -0.38$; 95% CI: –0.57/–0.15; $p = 0.0015$), TAPSE ($r = 0.34$; 95% CI: 0.13/0.52; $p = 0.002$) and RV GLS FW ($r = -0.35$; 95% CI: –0.56/–0.09; $p = 0.0095$).

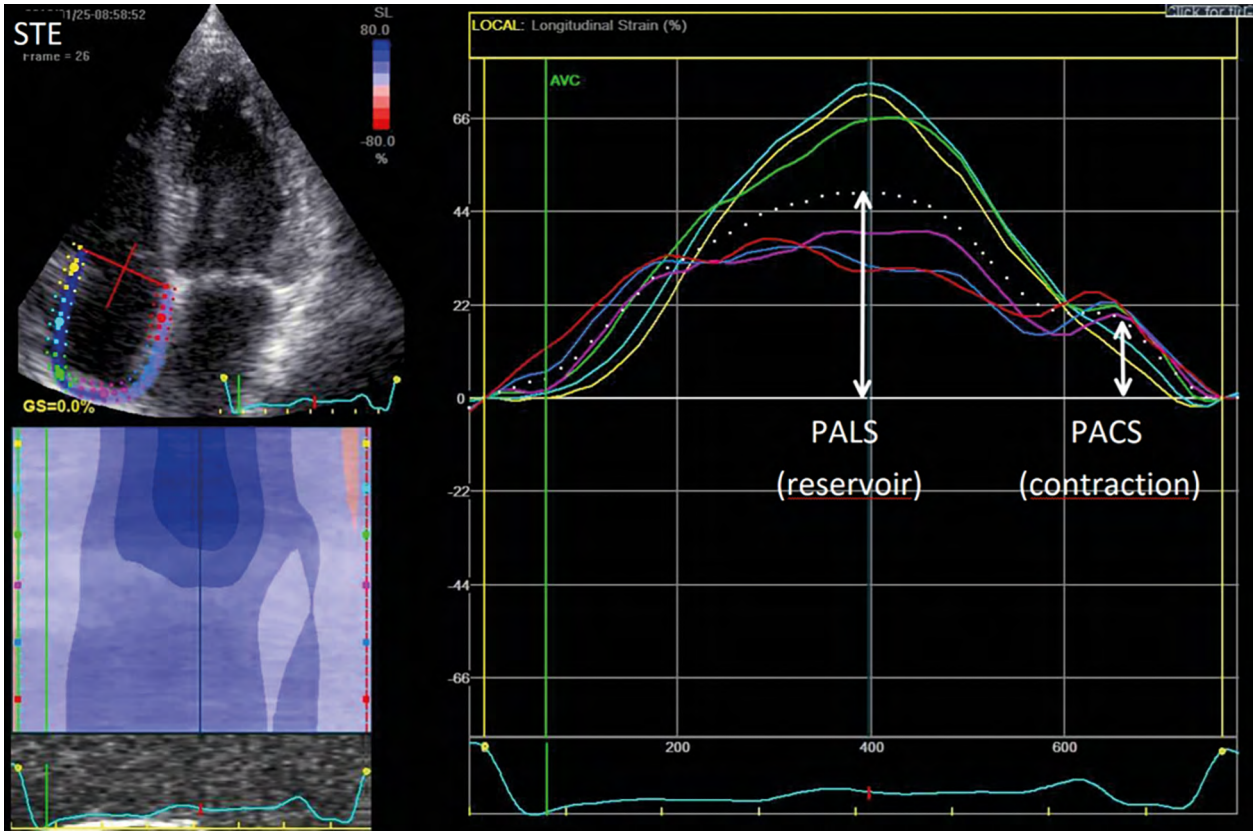

Figure 1. Speckle tracking assessment of the right atrium with measurement of PALS and PACS; PACS — peak atrial contraction strain; PALS — peak atrial longitudinal strain; STE — speckle tracking echocardiography

Table 1. The mean values and standard deviations of measured echocardiographic parameters

Parameter	Mean	SD
PALS (%)	30.8	12.7
PACS (%)	14.8	6.9
RA Ø (cm)	3.5	0.6
RA ESV (mL)	34.5	20.4
GLS (%)	–17.8	6
TAPSE (cm)	21.7	4.9
RVITD (cm)	3.5	0.6
S' (m/s)	11.4	2.7

ESV — right atrial end-systolic volume; GLS — global longitudinal strain; PACS — peak atrial contraction strain; PALS — peak atrial longitudinal strain; RA Ø — right atrial diameter; RVITD — right ventricular inflow tract diameter; S' — peak systolic annular velocity; SD — standard deviation; TAPSE — tricuspid annular plane systolic excursion

Table 2. Correlation coefficients between peak atrial longitudinal strain and RV parameters

Parameter	R	95% CI	p
RV GLS	–0.38	–0.57/–0.15	0.0015
RV FAC	0.21	–0.2/0.43	0.08
TAPSE	0.34	0.13/0.52	0.002
S'	0.08	–0.15/0.31	0.46
RV GLS FW	–0.35	–0.56/0.09	0.0095
RVITD	0.08	–0.15/0.31	0.48

CI — confidence interval; FAC — functional area change; FW — free wall; GLS — global longitudinal strain; RV — right ventricular; RVITD — right ventricular inflow tract diameter; S' — peak systolic annular velocity; TAPSE — tricuspid annular plane systolic excursion

PACS significantly correlated with RV GLS (r = –0.3; 95% CI: –0.51/–0.07; p = 0.013) and TAPSE (r = 0.34; 95% CI: –0.01/0.4; p = 0.04). Neither PALS nor PACS showed significant associations with RV size (r = –0.03; 95% CI: –0.21/0.27; p = 0.78) and (r = –0.005; 95% CI: –0.24/0.23; p = 0.96), respectively.

The analysis of subgroups disclosed a mean PALS of 37.25 ± 11.01% for healthy individuals and 29.92 ± ± 12.69% for patients suffering from cardiovascular pathologies. Stronger correlations between PALS and RV GLS were noted in the patients' group (r = –0,37; 95% CI: –0.57/–0.12); p = 0.005; n = 68) than in the healthy subjects group (r = –0.3; 95% CI: –0.78/0.4; p = 0.39; n = 10). However, this may be a result of a small subgroup of healthy subjects. Independent sample t-test yielded

Table 3. Correlation coefficients between peak atrial contraction strain and RV parameters

Parameter	r	95% CI	p
RV GLS	–0.3	–0.51/–0.07	0.013
RV GLS FW	–0.26	–0.5/0.01	0.059
RV FAC	0.21	–0.1/0.37	0.26
TAPSE	0.34	0.01/0.4	0.04
S'	0.08	–0.22/0.25	0.91

CI — confidence interval; FAC — functional area change; FW — free wall; GLS — global longitudinal strain; RV — right ventricular; S' — peak systolic annular velocity; TAPSE — tricuspid annular plane systolic excursion

Table 4. Correlation coefficients between peak atrial longitudinal strain with RA size

Parameter	r	95% CI	p
RA area	–0.42	–0.59/–0.22	0.0001
RA ESV	–0.41	–0.58/–0.22	0.0001
RA TD	–0.31	–0.50/–0.09	0.005

CI — confidence interval; ESV — end-systolic volume; RA — right atrial; TD — transverse diameter

Table 5. Correlation coefficients between peak atrial contraction strain with RA size

Parameter	R	95% CI	P
RA area	–0.32	–0.51/–0.11	0.004
RA ESV	–0.35	–0.53/–0.14	0.002
RA TD	–0.27	–0.46/–0.05	0.016

CI — confidence interval; ESV — end-systolic volume; RA — right atrial; TD — transverse diameter

a non-significant difference in PALS between healthy and diseased subjects (p = 0.08).

Discussion

The main finding of this study is that in patients with good image quality RA function analysis by STE is feasible and the RA deformation parameters correlate weakly with RV function indices, indicating that other factors significantly influence RA function. Therefore, the RA function cannot be regarded as a direct barometer of the RV function.

We used the QRS method (measuring the strain using two consecutive QRS complexes as intervals) [12] during the analysis of the strain of RA. This method was utilised by Padeletti et al. [13] to determine reference values of normal RA strain yielding feasible results. In the present study, the PALS of the study's healthy volunteers (PALS = 37.25%) yielded similar results to the reference values suggested by Padeletti et. al. (PALS = 49 ± 13%). In comparison, the strain measured in the study's patient population was uniformly lower (PALS = 29.92%). However, due to the small sample size, the difference was not statistically significant.

Numerous studies have demonstrated a profound impact of right ventricular stress, represented by increased right ventricular end-systolic pressure, on the haemodynamic properties of the right atrium [3, 14]. An adequate atrial response to an increased RV end-systolic pressure consists of an increase in reservoir function and a decrease in conduit-to-reservoir ratio, which in turn is inversely related to cardiac output [3]. It is being proposed that a "flexible atrium" stores elastic energy during systole and hence, atrial compliance plays a crucial role. The correlation between PALS and markers of RV function in this study population can be, at least partially, attributed to the underlying effects of this hypothesis.

No correlation was found between PALS and RA size in healthy volunteers, nevertheless, in patients suffering from cardiac pathology, there is a significant correlation between RA size and PALS, hinting at common underlying factors. Querejeta Roca et al. [16] pointed out that in patients suffering from PAH, RA reservoir and passive conduit function are impaired independently of RA size and greater dysfunction was associated with RV dysfunction and overload. PALS and PACS both showed significant correspondence to right ventricular parameters, namely: RV GLS (as a prognostic marker in right heart disease [2] and a correlate to RVEF [16, 17]) both with and without IV septum segment. Even though the cardiovascular pathologies of the patients in this study vary, patients with diminished atrial compliance (represented by decreased PALS), were also more likely to show diminished mechanical deformation of the RV (measured by RV GLS and RV FW GLS). Wright et al. [6] pointed out, the RA has a tethering effect on the free wall of the ventricle as other cohorts influence RV deformation as well, and therefore the association should not be overestimated.

Limitations

This was a single-centre study with a small group of subjects. It should also be kept in mind that the Echopac software was originally programmed for the left ventricle, warranting further adjustment of the ROI to measure the much thinner RA wall correctly.

Conclusion

RA function assessment by STE is feasible. The RA deformation parameters weakly correlate with RV function indices, indicating that other factors significantly influence RA function. Therefore, the RA function cannot be regarded as a direct barometer of the RV function.

Streszczenie

Wstęp. Echokardiografia metodą śledzenia markerów akustycznych (STE) jest uznanym narzędziem oceny parametrów czynności serca, jednak wartość tego narzędzia w ocenie czynności prawego przedsionka (RA) jest nadal w dużej mierze nieznana. Celem pracy jest zbadanie możliwości oceny funkcji RA za pomocą STE oraz związku między deformacją prawej komory (RV) a funkcją RA.

Materiał i metody. Do badanej grupy włączono 94 osoby z różnymi patologiami sercowo-naczyniowymi. U wszystkich pacjentów wykonano echokardiografię przezklatkową z późniejszą analizą off-line z wykorzystaniem techniki śledzenia markerów akustycznych i pomiarem licznych parametrów deformacji RA, w tym szczytowe odkształcenie podłużne przedsionków (PALS) i szczytowe napięcie skurczowe przedsionków (PACS), a także ustalonych wskaźników funkcji RV, takich jak: wychylenie skurczowe pierścienia trójdzielnego (TAPSE) i globalne odkształcenie podłużne (GLS).

Wyniki. Ocena funkcji RA za pomocą echokardiografii śladowej plamki była możliwa u wszystkich pacjentów. Zaobserwowano statystycznie istotną korelację między odkształceniem prawej komory (PACS i PALS) a parametrami RV. RV-GLS wykazało słabą korelację z PALS ($r = -0{,}38$; $p = 0{,}0015$) i PACS ($r = -0{,}30$; $p = 0{,}013$). Podobnie TAPSE korelowało z PALS i PACS ($r = 0{,}34$; $p = 0{,}02$) i ($r = 0{,}23$; $p = 0{,}04$).

Wnioski. Ocena funkcji RA za pomocą echokardiografii metodą śledzenia markerów akustycznych jest możliwa. Parametry deformacji RA słabo korelują ze wskaźnikami funkcji RV, co wskazuje, że inne czynniki mają istotny wpływ na funkcję RA. Dlatego funkcja RA nie może być traktowana jako bezpośredni barometr funkcji RV.

Słowa kluczowe: prawy przedsionek, prawa komora, echokardiografia metodą śledzenia markerów akustycznych

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Iron deficiency, heart failure and cerebrovascular events: what is the connection?

Niedobór żelaza, niewydolność serca, incydenty mózgowo-naczyniowe — jaki jest związek?

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Abstract

Heart failure (HF) is the leading cause of hospitalization among patients aged 65 years and older. One of the most common comorbidities in HF is iron deficiency (ID), being present in about 50% of all HF patients. ID in HF has been shown to reduce exercise capacity, increase the risk of cerebrovascular events, and increase patient morbidity and mortality. The association between heart failure with reduced ejection fraction (HFrEF) and ID has already been proven to lead to an increased risk of cardiovascular events, and some research is establishing a similar relation between heart failure with preserved ejection fraction (HFpEF) and ID. ID can lead to hypercoagulability, which in HF may be associated with an increased risk of stroke/TIA (transient ischemic attack).

Although current HF treatment guidelines recognize ID as a significant problem, ID is still rarely recognized and undertreated.

Key words: iron deficiency, heart failure, stroke, transient ischemic attack, cerebrovascular events

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Introduction

Iron deficiency (ID) is currently one of the most prominent nutrient deficiencies worldwide [1]. There are many possible causes of ID, such as increased demand and loss of iron, decreased absorption and inadequate dietary intake, and impaired iron release [2, 3]. According to current ESC guidelines, ID in HF patients is defined as either a serum ferritin concentration < 100 µg/mL or as 100–299 µg/mL with transferrin saturation (TSAT) < 20% [4].

However, ID still continues to be undertreated and underdiagnosed in the clinical setting [5]. Concurrent ID and HF can have profound negative effects on the patient's condition leading to a decreased exercise capacity and quality of life (QoL), higher morbidity, and mortality [4, 6, 7]. ID may also cause a wide range of hematological complications within patients, such as predisposing the patient to thromboembolic events [8].

The aim of this paper is to emphasize connections made through the most current literature on the issue of cerebrovascular events connected with ID in HF patients and to indicate the most needed directions of further research.

Iron deficiency

Iron is an essential mineral for the body and is vital for a multitude of different functions, such as oxygen transport, metabolism and storage, cardiac and skeletal

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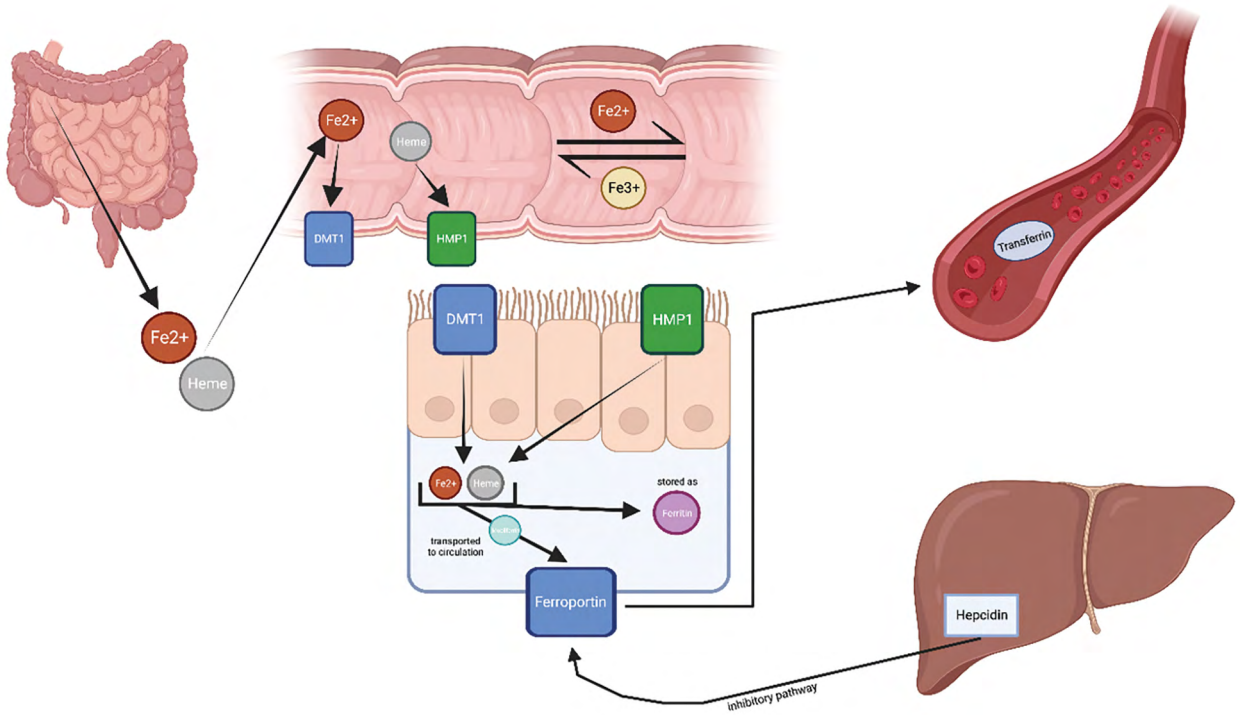

Figure 1. Iron metabolism in the body; DMT1 — divalent-metal-transporter-1; Fe2+ — ferrous iron form; Fe 3+ — ferric iron form; HMP1 — heme-carrier-protein-1

muscle metabolism, erythropoiesis, mitochondrial preservation and function, a cofactor for various enzymes or cellular metabolism [5, 7, 9]. Iron exists either in the ferrous form (Fe^{2+}), during absorption in the small intestine, or bound intracellularly to ferritin or as the ferric form (Fe^{3+}) coupled to the transport protein transferrin during circulation [5].

Iron homeostasis is solely regulated by absorption, as no means of iron excretion exists [9]. In the physiological state, only about 5–10% of the dietary iron is absorbed.

Iron absorption, taking place mainly in the duodenum and upper jejunum [5], can occur in three pathways according to the chemical form of iron present. Those pathways are shown in Figure 1. Free ferrous ions are absorbed *via* the divalent-metal-transporter-1 pathway, whereas heme-bound iron is absorbed *via* the heme-carrier-protein-1 pathway. In the enterocyte, iron can be stored bounded by ferritin or it can be transported directly to the basolateral side by mobilferrin to release iron to the circulation *via* the intramembranous channel ferroportin. Hepcidin, produced in the liver, is the main regulator of iron absorption as it binds to ferroportin to decrease its expression as well as by inhibiting the mobilization of stored iron in macrophages of the reticuloendothelial system [10].

Iron deficiency anemia (IDA) is a consequence of prolonged ID where the ID is severe enough to reduce erythropoiesis in the bone marrow [11]. The prevalence of iron deficiency has been extensively studied and well summarized by Savarese et al. [12], about one in every two persons with HF has ID. It seems that regardless of anemia, ID is present in about 50% of patients with HF [12]. On the contrary, ID and anemia in HF coexist rarely [13]. Moreover, anemia does not influence mitochondrial functions, and its treatment relieved HF symptoms, but at the same time increased thromboembolic events' risk [13]. IDA leads to structural and functional alterations in tissues with a high mitotic index and oxygen demand, such as neoplastic, immune and cardiac cells, which are especially sensitive to anemia [5]. It has a significant impact on HF pathology and is an established predictor of a worse prognosis [10]. Previous studies have shown accelerated left ventricular (LV) remodeling, mitochondrial damage, and low iron content in cardiomyocytes in HF patients, possibly explaining reduced peak oxygen consumption and LV dysfunction associated with HF [7]. Furthermore, skeletal muscle dysfunction can ultimately lead to inspiratory muscle weakness, dramatically lowering the QoL of HF patients [5]. Impaired exercise capacity is the result of crucial patient characteristics and multisystem dysfunction, including aging, impaired pulmonary reserve, peripheral and respiratory skeletal muscle dysfunction as well as ID [14, 15].

Despite the significant prevalence of ID in HF, the etiology is often unrecognized [3]. The main suggested mechanisms include reduced iron intake and absorption,

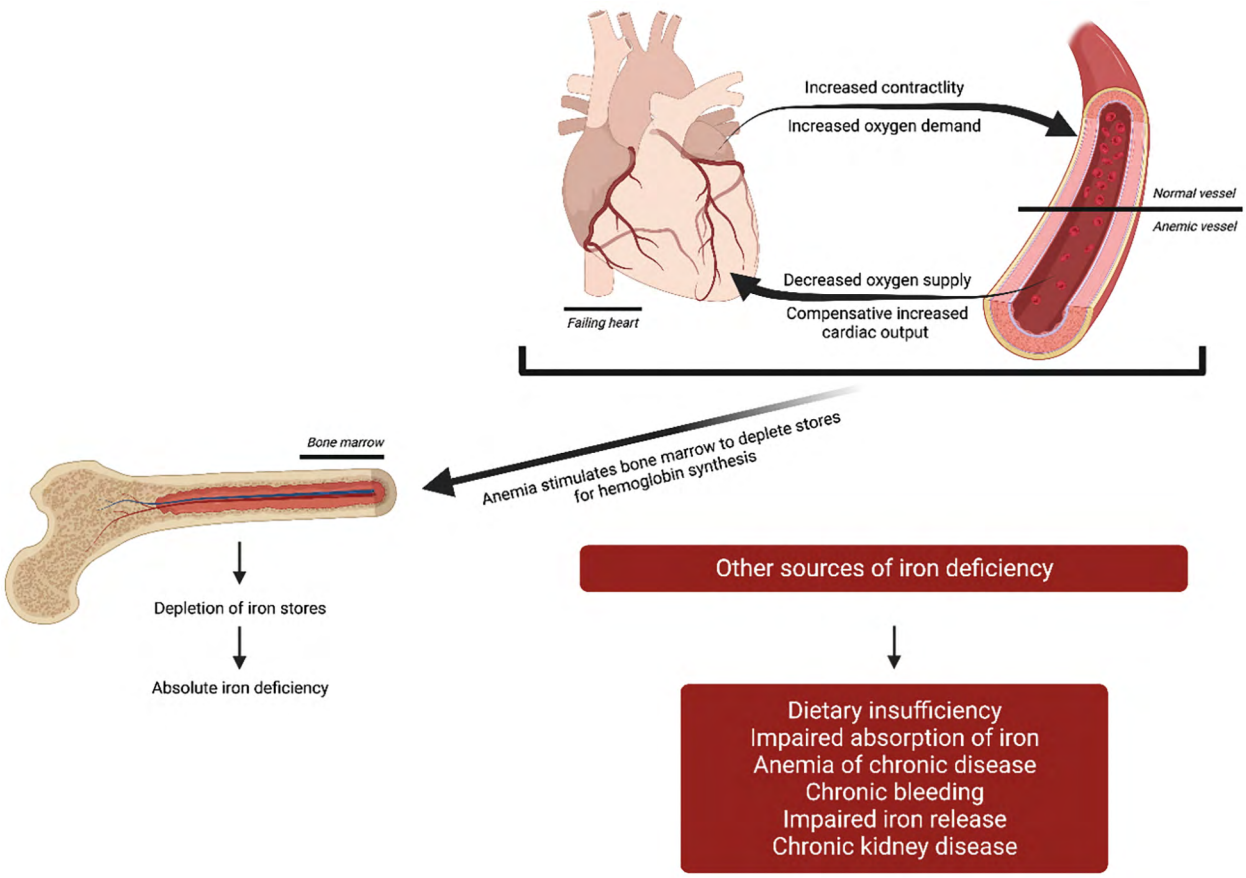

Figure 2. Iron deficiency etiology in heart failure

increased iron loss, and impaired iron release [2]. The summary of the possible etiologies of ID in HF is seen in Figure 2.

Reduced iron intake

Iron requirements and thus recommended iron intake depend mainly on sex, age and pregnancy status. In a large international HF cohort, Van Der Wal et al. [3] showed that a poor nutritional status with low serum albumin level might bean etiological pathway for ID in HF. As iron intake was not studied itself, and the underlying reason for the poor nutritional status is not clear yet, further studies need to be done. A cross-sectional study from Christina Andreae [16] identified a significant prevalence of loss of appetite with a high risk of weight loss in patients with HF. It needs to be emphasized that increasing the intake of iron such as in oral iron therapy is not effective and due to excessive polypharmacy and possible side effects is not recommended [5].

Reduced iron absorption

Venous congestion leads to gastrointestinal wall edema, which might reduce the absorption of nutrients such as iron [3]. Other factors like concomitant diseases such as inflammatory bowel disease or the high prevalence of proton pump inhibitor usage in HF patients, might also play an etiological role in ID in HF [3]. Furthermore, recent studies showed that hepcidin levels are decreased in HF patients, suggesting that the iron concentration is a dominating factor over the inflammatory state to determine the rate of hepcidin synthesis [3, 5, 10]. In conclusion, ID is more likely caused by an absolute decrease in iron availability than by a metabolic mechanism induced by a chronic inflammatory state [5].

Increased iron loss

Increased iron loss is another factor that contributes ID in HF. Firstly, as a recent study by Meijers et al. [17] identified HF as a novel risk for incident cancer, blood loss, and as a consequence, iron loss in HF might therefore be due to malignancies or gastrointestinal diseases such as gastritis or peptic ulcers [2]. Secondly, patients with ID have a higher prevalence of antiplatelet use [3]. Thus, iron loss in these patients might be due to an increased tendency for bleeding.

Table 1. A review of current literature regarding heart failure and iron deficiency and its correlation with cerebrovascular events

Author	Year	Type of study	N	Results/conclusions
Gillum et al. [24]	1995	Follow-up of a national cohort	5033	There is a significant U-shaped association of transferrin saturation with risk of incident stroke
Dubyk et al. [26]	2012	Prospective, cohort	94	IDA as a risk factor in elderly patients at hospital admission for TIA or first stroke
Shovlin et al. [27]	2014	Prospective, cohort	497	Iron deficient patients with pulmonary malformations at a higher risk of ischemic stroke
Potaczek et al. [28]	2016	Prospective, cohort	229	ID may represent a riskfactor for thrombosis recurrence
Adelborg et al. [19]	2017	General population cohort	1 446 765	HF is an important risk factor for all types of stroke.
Gill et al. [29]	2018	Mendelian randomized	48 972	Higher iron status is associated with increased stroke risk
Tang et al. [30]	2020	Prospective, cohort	795	ID and CC are risk factors for thromboembolic diseases
Szulc-Bagrowska et al. [31]	2022	Retrospective, observational	150	ID in HF is associated with ahigher risk of stroke/TIA
Doehner et al. [32]	2022	Prospective, observational	746	ID and anemia significantly lower functional capacity after acute stroke

CC — contraceptives; ID — iron deficiency; IDA — iron deficiency anemia; HF — heart failure; TIA — transient ischemic attack

All in all, the etiology of ID in HF is highly complex, multifactorial, and not well understood. Further research on the etiopathogenesis of ID in HF needs to be conducted to establish recognized causal factors which can help in finding sufficient treatment of ID in HF, as a predictor of a worse prognosis [7].

Stroke and ID in heart failure

The etiology of HF varies depending on the phenotype. HFrEF results as a consequence of the necrosis of cardiomyocytes, due to myocardial ischemia, myocarditis, or cardiotoxins, and it has the predisposition to affect males more [18]. HFpEF occurs most often in patients suffering non-cardiac comorbidities such as hypertension, pulmonary disease, diabetes mellitus, sleep apnea or obesity and it has the predisposition to affect females more often [18]. It is known that HF, even in its earliest stage, is a risk factor for stroke [19, 20]. Among stroke patients, 9% had HF as the cause of the event [20]. Furthermore, 10–24% of stroke patients also have HF [20]. The Framingham Heart Study emphasized that patients with HF are two to 3 times more likely to suffer from a stroke than those without HF [21]. On the other hand, one of the pathomechanisms of HF is chronic inflammation which may either be a consequence of HF or it may precede and be one of the causative factors which led to HF. In consequence, chronic inflammation leads to hypercoagulability. Finally, endothelial damage is also responsible for the pathogenesis of HF, which may be caused by various different vasculopathies [20, 21]. The above-mentioned factors form the Virchow's Triad, which are at the same time the most important elements for the formation of thrombosis [22]. That makes HF a disease of a higher risk of thromboembolism forming.

Aside from the already proven fact that ID in HF patients leads to a decreased QoL and exercise tolerance, as well as to increased patient mortality and morbidity [4], it should also be The combination of both these diseases may prove deleterious consequences in patients ultimately leading to an increased probability of stroke occurring. Kandinata et al. [23] presented a case of a 34-year-old patient with ID who suffered from a stroke. It implies that ID may be a great predictive value for stroke, and even greater if it is combined with comorbidities. Gillum et al. proved there may be a U-shaped connection between iron status and the risk of stroke [24]. However, the data on iron status and its influence on stroke prevalence is limited and conflicting, there is a need to conduct further research on the prognostic significance and treatment ID in patients with cerebrovascular events [12]. Current trends indicate thepossible use of hematologic parameters such as ID as biomarkers in HF [25].

Table 1 presents selected studies regarding HF and ID and their correlation with cerebrovascular events.

Significance and solutions — IRONMAN study

The only efficacious and recommended treatment for reversing ID is intravenous (IV) ferric carboxymaltose. However, the approved treatment of ID in the setting of left ventricle ejection fraction < 50%, there is currently no approved treatment for ID in the setting of HFpEF [4]. To our knowledge, IRONMAN was the first large clinical trial that investigated

Table 2. A comparison of selected clinical trials regarding intravenous iron administration in HF patients

	FAIR-HF [36]	CONFIRM-HF [37]	EFFECT-HF [38]	AFFIRM-HF [34]	IRONMAN [33]
Type of study	Prospective, randomized, multicenter	Prospective, randomized, multicenter	Prospective, randomized, open-label, SoC-controlled	Prospective, randomized, multicenter	Prospective, randomized, open-label, SoC-controlled
N	FCM: 305 Placebo: 154	FCM: 152 Placebo: 152	FCM: 88 SoC: 86	FCM: 559 Placebo: 551	FDI: 569 SoC: 568
Study population	Chronic HF NYHA class II (LVEF ≤ 40%) or III (LVEF ≤ 45%) with ID	Chronic HF NYHA class II/III (LVEF ≤ 45%) BNP > 100 pg/mL and/or NT-proBNP > 400 pg/mL with ID	Chronic HF NYHA class II/III (LVEF ≤ 45%) BNP > 100 pg/mL and/or NT-proBNP > 400 pg/mL with ID Peak VO_2 10–20 mL/kg/min	Acute HF Hospitalized for acute HF, treated with at least 40 mg furosemide (or equivalent) LVEF < 50% with ID	Chronic HF NYHA II–IV and recent HF hospitalization or elevated NPs (LVEF ≤ 45%) Ferritin < 100 µg/L or TSAT < 20%
Primary endpoint result	Improvement in self-reported PGA (50% for FCM vs. 28% placebo; OR 2.51; 95% CI: 1.75–3.61; p < 0.001) and NYHA class I/II at 24 week (47% vs. 30%; OR 2.40; 95% CI: 1.55–3.71; p < 0.001)	Change in 6WMT distance from baseline to week 24 for FCM vs. placebo — both LS means ± SE (18 ± 8 meters vs. 16 ± 8 meters; difference FCM vs. placebo: 33 ± 11 meters; p = 0.002)	Change from baseline in peak VO_2 at week 24 for FCM vs. control (SoC) — LS mean ± SE (−0.16 ± 0.387 vs. −1.19 ± 0.389 mL/min/kg; p = 0.020) Sensitivity analysis in which missing data were not imputed for FCM vs. control: (−0.16 ± 0.37 vs. −0.63 ± 0.38 mL/min/kg; p = 0.23)	Composite of total HF hospitalizations and CV deaths up to 52 weeks after randomization for FCM vs. placebo (293 primary events [57.2 per 100 patient-years] vs. 372 [72.5 per 100 patient-years] RR 0.79; 95% CI: 0.62–1.01; p = 0.059) (Pre-COVID-19 sensitivity analysis: 274 primary events [55.2 per 100 patient-years] vs. 363 [73.5 per 100 patient-years] RR 0.75; 95% CI: 0.59–0.96; p = 0.024)	Composite of CV deaths and hospitalizations for HF for FDI vs. SoC: (336 primary events [22.4 per 100 patient-years] vs. 411 [27.5 per 100 patient-years] RR 0.82; 95% CI: 0.66–1.02; p = 0.070)
Secondary endpoint result	Improvement (p < 0.001) with FCM vs. placebo in: • Self-reported PGA at weeks 4 and 12 • 6 MWT distance at weeks 4, 12, and 24 • QoL (EQ-5D visual assessment) at weeks 4, 12, and 24 • Overall KCCQ score at weeks 4, 12, and 24	Improvements with FCM vs. placebo in: • PGA at week 12 (p = 0.035) week 24 (p = 0.047), weeks 36 and 52 (both p < 0.001) • NYHA class at week 24 (p = 0.004) and weeks 36 and 52 (both p < 0.001) • 6 MWT difference in changes at week 36 (42 meters with 95% CI of 21–62; p < 0.001) and week 52 (36 meters with 95% CI of 16–57; p < 0.001) • Fatigue score at week 12 (p = 0.009), week 24 (p = 0.002), week 36 (p < 0.001), and week 52 (p = 0.002)	• Improvements with FCM vs. control in: • NYHA class at weeks 6, 12 and 24 (with imputation; all p < 0.05) • PGA at weeks 12 and 24 (with imputation; p < 0.05)	Total CV hospitalizations and CV deaths with FCM vs. placebo: • 370 vs. 451 (RR 0.80; 95% CI: 0.64–1.00; p = 0.050) CV deaths • 77 (14%) vs. 78 (14%) (HR 0.96; 95% CI: 0.70–1.32; p = 0.81) lower number HF hospitalizations • 217 vs. 294 (RR 0.74; 95% CI: 0.58–0.94; p = 0.013) treatment for time to first hospitalization or CV death — 181 (32%) vs. 209 (38%) (HR 0.80; 95% CI: 0.66–0.98; p = 0.030)	Composite of CV deaths or hospital admission for HF, stroke or MI with FDI vs. placebo: 209 vs. 246 (RR 0.83; 95% CI: 0.69–1.00; p = 0.045)

6 MWT — 6-min walking test; AFFIRM-AHF — Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency; BNP — brain natriuretic peptide; CONFIRM-HF — Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure; CI — confidence interval; CV — cardiovascular; EFFECT-HF — Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure; EQ-5D — EuroQol-5 Dimension; FAIR-HF — Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure; FCM — ferric carboxymaltose; FDI — ferric derisomaltose; HF — heart failure; HR — hazard ratio; ID — iron deficiency; IRONMAN — Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK; KCCQ — Kansas City Cardiomyopathy Questionnaire; LS — least squares; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; PGA — patient global assessment; OR — odds ratio; QoL — quality of life; RR — rate ratio; SE — standard error; SoC — standard of care; TSAT — transferrin saturation

the long-term effect of IV ferric derisomaltose (FDI) administration on cardiovascular (CV) outcomes, including recurrent hospitalizations for HF [33]. 1137 patients were randomized, 569 received IV FDI treatment and 568 usual care. The primary endpoint, which included a composite of CV deaths and hospitalizations for HF occurred for FDI treatment vs. standard of care: (336 primary events [22.4 per 100 patient-years] vs. 411 [27.5 per 100 patient-years] RR [rate ratio] 0.82; 95% CI [confidence interval]: 0.66–1.02; p = 0.070) [33], what was on the borderline of statistical significance, such as in AFFIRM trial [34]. IRONMAN study proved that IV administration of iron reduced the combined secondary endpoint (CV death, hospital admissions for stroke, HF, and myocardial infarction) (HR = 0.82; 95% CI: 0.69–1.00; p = 0.045) [33]. The recommended COVID-19 analysis showed consistent results (HR = 0.78; 95% CI: 0.62–0.98; p = 0.030 respectively) [33]. To our knowledge, previous studies of ID in HF did not include stroke hospitalization as endpoint, which needs to be strongly emphasized [33]. Subsequently, important differences between IRONMAN and another clinical trial regarding ID, for instance, AFFIRM-AHF, are worth noticing [34]. Firstly, the follow-up was longer in IRONMAN (median follow-up 2.7 years [IQR 1.8–3.6]) than in AFFIRM-AHF, in which IV iron treatment was finalized after 24 weeks [33, 34]. Hence, IRONMAN study confirmed the long-term safety of IV FDI, since there were no excessive serious adverse events [33]. Subsequently, there was no collection of phosphate samples in IRONMAN, since the risk of hypophosphataemia is significantly lower in FDI [35]. A comparison of selected clinical trials is shown in Table 2.

Conclusions

HF with ID may predispose the patient to a higher risk of suffering from cerebrovascular events. Numerous studies emphasize that ID in clinical practice is often unrecognized and definitely underdiagnosed even though it is in the ESC treatment guidelines for HF. Better screening for ID should be implemented to reverse this health issue. HF with ID should be recognized and promptly treated by the clinician and the risk of stroke should be assessed as ID is a positive predictive value for stroke. Finally, upcoming randomized clinical trials should focus on assessing whether IV iron administration is an effective treatment for ID in HF patients with LVEF ≥ 45%

Conflict of interest

None declared.

Streszczenie

Niewydolność serca (HF) jest główną przyczyną hospitalizacji wśród pacjentów w wieku 65 lat i starszych. Jedną z najczęstszych chorób współistniejących w HF jest niedobór żelaza (ID), występujący u około 50% wszystkich pacjentów z HF. Wykazano, że ID w HF zmniejsza wydolność wysiłkową, zwiększa ryzyko incydentów naczyniowo-mózgowych, chorobowość i śmiertelność pacjentów. Udowodniono, że związek między niewydolnością serca z obniżoną frakcją wyrzutową (HFrEF) a ID prowadzi do zwiększonego ryzyka incydentów sercowo-naczyniowych, a niektóre badania wskazują na podobny związek między niewydolnością serca z zachowaną frakcją wyrzutową (HFpEF) a ID. ID może prowadzić do nadkrzepliwości, co w HF może wiązać się ze zwiększonym ryzykiem udaru mózgu/przemijającego ataku niedokrwiennego.

Chociaż obecne wytyczne dotyczące leczenia HF uznają ID za istotny problem, jest ono nadal rzadko rozpoznawane i niedostatecznie leczone.

Słowa kluczowe: niedobór żelaza, niewydolność serca, udar mózgu, TIA, incydenty mózgowo-naczyniowe

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REVIEW ARTICLE

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Coffee and lipid profile: from theory to everyday practice

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Abstract

Lipid disorders have been the most common cause of atherosclerotic cardiovascular diseases in Poland for years. The latest data indicate that about 20 million people in Poland have hypercholesterolaemia. Nutritional habits have a very significant impact on the lipid profile. Therefore, considering the fact that coffee is an important component of the diet of Poles (on average, 1–2 cups of coffee are consumed in our country per inhabitant per day, and 66% of Poles declare regular consumption), its impact on the lipid profile cannot be overlooked. Coffee contains over 1000 chemical compounds, of which kahweol and cafestol are the most important in the context of lipidology. These are compounds that can have a hyperlipidaemic effect. On the other hand, compounds such as caffeine, chlorogenic acid, trigonelline, and melanoidins are characterized by antioxidant activity, which can limit lipid peroxidation. The effect of consuming coffee prepared in different ways has been analysed in numerous clinical studies. This article summarizes the current knowledge on the effects of coffee on the lipid profile and risk of atherosclerosis.

Key words: coffee, lipid disorders, atherosclerotic cardiovascular diseases

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Introduction

For years, lipid disorders have been ranked as the most common atherosclerotic cardiovascular disease (ASCVD) risk factor worldwide [1].

The most common lipid disorder in Poland is hypercholesterolemia, involving elevated levels of LDL-C (low-density lipoprotein cholesterol) fraction above the recommended values for a given cardiovascular risk group [2]. The WOBASZ II study (Multi-centre National Population Health Examination Survey), which included 5947 subjects aged 20–99, revealed that hypercholesterolemia was present in 67.1% of them (64.3% of women and 70.3% of men, respectively) [3]. These results indicate that the number of patients with hypercholesterolemia in Poland may be as high as 20 million.

Dietary habits have a very important effect on lipid profile [4]. Therefore, given that coffee is an important component of the Polish diet (on average, 1–2 cups of coffee per capita/day are consumed in our country and 66% of Poles declare regular consumption of coffee), its effect on lipid profile cannot be ignored.

Coffee and lipid profile

A systematic review and meta-analysis of randomised clinical trials by Schoeneck and Iggman concluded the effects of different dietary components on LDL-C levels. In the case of coffee, its effect on serum LDL-C levels was found to be dependent on whether filter or non-filter coffee was consumed. Consumption of filter coffee *versus* non-consumption of this beverage was not significantly associated with

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changes in serum LDL-C levels (MD = 0.03 mmol/L; 95% CI: –0.05 to 0.11). There was no significant difference between coffee and tea consumption in relation to LDL-C (MD = 0.14 mmol/L; 95% CI: –0.01 to 0.28). The comparison of filter coffee consumption and non-filter coffee consumption revealed that the latter increased serum LDL-C levels (MD = –0.39 mmol/L; 95% CI: –0.49 to –0.30). There was no significant effect on LDL-C of black coffee *versus* decaffeinated coffee (MD = –0.02 mmol/L; 95% CI: –0.08 to 0.04), nor on consumption of more roasted *versus* less roasted coffee (MD = 0.07 mmol/L; 95% CI: –0.08 to 0.23). Based on the results of this meta-analysis, the effect of coffee consumption on LDL-C depends on whether the brew is filter or non-filter [5].

A study by Miranda et al. [6], involving 4736 Brazilians, assessed the effect of the intensity of coffee consumption (≤ 1, 1–3 and >3 cups/day; cup = 50 mL espresso) on lipid profile. After including other risk factors, it was found that consumption of up to 3 cups of coffee a day did not alter the lipid profile (total cholesterol [β = 2.67; 95% CI: –0.10 to 5.41], triglycerides [β = 5.61; 95% CI: –0.71 to 11.93], LDL-C [β = 2.13; 95% CI: –0.13 to 4.40], HDL-C [β = 0.11; 95% CI: –0.89 to 1.11] and triglyceride-rich lipoproteins [β = 5.26; 95% CI: –0.46 to 10.97]). Consumption of >3 cups of coffee a day was associated with some lipoprotein-increasing effects (total cholesterol [β = 4.13; 95% CI: 0.81 to 7.45], triglycerides [β = 9.53; 95% CI: 1.65–17.42], LDL-C [β = 2.39; 95% CI: –0.37 to 5.14], HDL-C [β = 0.44; 95% CI: –0.75 to 1.64] and triglyceride-rich lipoproteins [β = 8.42; 95% CI: 1.24–15.60]). The results of this study indicate that the consumption of 1–3 cups of coffee a day does not affect the lipid profile [6].

A randomised clinical trial by Gonçalinho et al. [7], involving 53 healthy subjects analysed the effect of consuming 450–600 mL/day of filter Arabica or a filter blend of Arabica and Robusta on sirtuin-1, homocysteine and lipid levels. It should be borne in mind that Arabica is considered the oldest and the most high-quality type of coffee, originating in Ethiopia. It is cultivated in mountainous areas, at approximately 20–25 degrees Celsius, contains less caffeine than Robusta, while it may contain more fats and sugars than Robusta (fats in Arabica beans are approximately 6–9% while for Robusta they are approximately 3–7%, and sugars are 15–17% of Arabica beans compared to 10–11.5% for Robusta). Robusta, or Congolese coffee, originates from Central Africa but is also grown in other areas of the world (mainly in the intertropical zone). After 8 weeks of intervention, it was revealed that consumption of Arabica or a blend of Arabica and Robusta significantly increased sirtuin-1 levels (0.51 to 0.58 ng/mL; p = 0.004, and from 0.40 to 0.49 ng/mL; p = 0.003) but had no effect on homocysteine levels. In terms of the lipid profile, it was found that consumption of a blend of Arabica and Robusta was associated with increases in total cholesterol (from 4.70 to 5.17 mmol/L; p < 0.001), LDL-C (from 2.98 to 3.32 mmol/L; p < 0.001) and HDL-C (from 1.26 to 1.36 mmol/L; p < 0.001). In this study, coffee consumption did not affect triglyceride levels. The observed differences in terms of the effects of pure Arabica and its blend with Robusta are probably due to the different polyphenol content (more caffeine, less polyphenols in Robusta). The results of this study indicate that, with a view to the lipid profile, filter Arabica coffee should be preferred [7]. A study by Gebeyehu et al. [8], involving 70 healthy subjects, assessed the effect of consuming 100% filter Ethiopian Arabica on lipid profile. Consumption of filter Arabica was found to be associated with a reduction in triglyceride levels (p < 0.01), while having a non-significant effect on total cholesterol and LDL-C levels [8]. The results of a study by Svatun et al. [9], involving 21 083 subjects from the Tromsø Study in Northern Norway, cannot be overlooked. This study analysed the effect of coffee consumption on serum total cholesterol levels. It was found that consumption of 1–2 cups of espresso or filter coffee a day did not have a statistically significant effect on serum total cholesterol levels (in contrast to consumption of 3–5 cups of these brews a day). Consumption of 1–2 cups of boiled coffee/ /day revealed how significant the effect on an increase in serum total cholesterol levels was. Instant coffee at 1–2 cups/ /day significantly increased serum total cholesterol levels in men; this effect was not observed in women [9]. The results of this study indicate that there should be a preference to consume espresso or filter coffee at 1–2 cups/day, bearing in mind the lipid profile.

Zhou and Hyppönen's study of 36 2571 subjects from the UK Biobank database assessed the effect of regular coffee consumption on lipid profile. There was a dose-dependent slight increase in LDL-C (1–2 cups of coffee/day: β = 0.06 mmol/L; 95% CI: 0.05–0.07; > 6 cups of coffee/ /day: β = 0.13 mmol/L; 95% CI: 0.11–0.15) and this effect did not differ significantly by the type of coffee consumed: ground, decaffeinated or instant. HDL-C also revealed increased levels (1–2 cups of coffee/day: β = 0.01 mmol/L; 95% CI: 0.01–0.01; > 6 cups of coffee/day: β = 0.01 mmol/L; 95% CI: 0.01–0.02), however, this effect only applied to ground and instant coffee. Coffee consumption was also dose-dependently associated with increased total cholesterol levels (1–2 cups of coffee/day: β = 0.08 mmol/L; 95% CI: 0.07–0.09; > 6 cups of coffee/day: β = 0.15 mmol/L; 95% CI: 0.13–0.18), regardless of the type of brew consumed. In terms of triglycerides, the information is more optimistic since consumption of coffee did not affect or could even gently reduce their levels (1–2 cups of coffee/day: β = 0.01 mmol/L; 95% CI: 0.00–0.02; > 6 cups of coffee/day: β = –0.07 mmol/l; 95% CI: –0.09 to –0.05), and this effect was common across all analysed types of coffee. The effect of coffee consumption on apolipoprotein B (apoB) and apolipoprotein A1 (apoA1) levels was also analysed. There was a dose-dependent increase in apoB levels

(1–2 cups of coffee/day: β = 0.01 g/L; 95% CI: 0.01–0.01; > 6 cups of coffee/day: β = 0.02 g/l; 95% CI: 0.02–0.03), which was independent of coffee type. In terms of apoA1, coffee consumption may or may not have increased its levels (1–2 cups of coffee/day: β = 0.01 g/L; 95% CI: 0.00––0.01; > 6 cups of coffee/day: β = 0.00 g/L; 95% CI: –0.01 to 0.01), with the most beneficial effect observed when ground coffee was consumed, followed by instant coffee. Another study found a positive association between coffee consumption and LDL-C/total cholesterol/ /apoB. The results of this prospective study indicate that coffee consumption may be associated with increased LDL-C, total cholesterol and apoB levels. **Nevertheless, it should be emphasised that in terms of Polish conditions, where 1–3 cups of coffee/day are consumed on average, an increase in LDL-C of approximately 2 mg/dL and total cholesterol of 3 mg/dL can be expected, which is not clinically significant.** Furthermore, as the authors of the study point out, an important limiting factor is that the respondents reported coffee consumption in a questionnaire. It is also impossible to assess exactly what the kahweol and cafestol content of coffees consumed by the subjects was. The importance of this issue is indicated, for example, by the fact that consumption of instant coffee increased LDL-C and total cholesterol levels to a lesser extent compared to ground coffee, while this is the coffee that contains less kahweol and cafestol [10].

A meta-analysis of 12 randomised clinical trials by Du et al. [11], involving 1182 subjects, concluded the effects of coffee consumption on the risk of dyslipidemia. The results of this meta-analysis are shown in Table 1.

The results of this meta-analysis indicate that consumption of higher amounts of coffee may be associated with increased levels of specific lipid fractions. A dose-effect analysis revealed that consumption of 1–3 cups of coffee/ /day (preferably filter coffee) had no effect on LDL-C, HDL-C and triglyceride levels, whereas it had a borderline effect on total cholesterol levels [11]. The results obtained in this meta-analysis are in line with those obtained several years ago in a meta-analysis of 12 randomised clinical trials by Cai et al. [12]. It was found that consumption of filter coffee had a slight effect on total cholesterol levels (difference: 3.6 mg/dL; 95% CI: 0.6–6.6), while it had no significant effect on LDL-C and triglycerides. Moreover, a dose-dependent effect was also found. Consumption of up to 6 cups of coffee/day had little effect on total cholesterol levels (difference: 4.2 mg/dL; 95% CI: 1.3–7.1) and no effect on LDL-C and triglycerides [12]. Moreover, these results are fully in line with the results of the meta-analysis review of the effects of coffee on human health by Poole et al. It was found that consumption of non-filter coffee significantly increased total cholesterol, LDL-C and triglyceride levels, while consumption of filter brew increased total cholesterol levels only slightly. Decaffeinated coffee consumption was not associated with changes in lipid profile [13]. The results of this meta-analysis indicate that the consumption of 1–3 cups of coffee/day, preferably filter, remains safe from the point of view of the risk of lipid disorders.

A systematic review by Penson et al. [14], involving 640 subjects, analysed the effect of coffee consumption on lipoprotein (a) levels. It was found that consumption of filter coffee might be associated with a reduction in lipoprotein (a) levels, while non-filter coffee had the opposite effect. The authors indicate that the effect of coffee consumption on lipoprotein (a) depends on how coffee is prepared [14].

In terms of lipid profile, the less investigated green coffee should be mentioned. A meta-analysis of 17 randomised clinical trials by Ding et al. [15], revealed that decaffeinated coffee consumption was associated with a reduction in total cholesterol levels (weighted mean difference [WMD] = –4.51 mg/dL; 95% CI: –6.90 to –2.13), increased HDL-C levels (WMD = 2.64 mg/dL; 95% CI: 2.21 to 3.07), decreased LDL-C levels (WMD = –4.38 mg/dL; 95% CI: –6.45 to –2.32), and a non-significant effect on triglyceride levels (WMD = –4. 34 mg/dL; 95% CI: –9.00 to 0.32) [15]. The results of this meta-analysis indicate that green coffee consumption has some hypolipemic effects.

In summary, the results of recent studies and meta-analyses indicate that the consumption of 1–3 cups of coffee/ /day, preferably filter coffee, has no effect on lipid profile.

From coffee through lipid profile to atherosclerosis

The strong interest in the effect of coffee consumption on lipid disorders is also associated with previous observations showing that consumption of this beverage was associated with a higher risk of coronary artery disease (CAD). A very interesting paper by Shirai et al. [16] reviewed studies evaluating the effect of coffee consumption on CAD risk, published from 1990 to 2018. The analysis covered more than one million subjects from 147 countries. Interestingly, it was found that the assessment of the association between coffee consumption and the risk of CAD and death in CAD over the period 1990–2018 changed from unfavourable to favourable [16]. There are several explanations for this. A multi-centre study by Tverdal et al. [17], involving more than 500 000 subjects who were observed for 20 years, found that cardiovascular disease (CVD) mortality was higher in those who consumed non-filter coffee than those who consumed filter coffee. Furthermore, a similar relationship was found in terms of CAD risk [17]. The explanation for these differences lies in the way the coffee is prepared, as filtering the brew leads to a reduction in kahweol and cafestol, i.e., diterpenoids with hyperlipidemic effects [18]. There was a significant difference in terms of the effect of

Table 1. Effect of coffee consumption on lipid profile — results of a meta-analysis by Du et al. 2020 [11]

Lipid fraction [mmol/L]	Study group/subgroup	Number of RCT	Effect (WMD [95% CI]); mmol/L
Total cholesterol	Overall effect	12	0.21 (0.04–0.39)
	Filter coffee	3	0.10 (0.17–0.37)
	Boiled coffee	3	0.30 (0.06–0.53)
	Instant coffee	2	0.08 (0.06–0.21)
	1–3 cups/day	3	0.11 (0.03–0.23)
	3–5 cups/day	5	0.14 (0.03–0.31)
	≥ 6 cups/day	4	0.52 (0.40–0.54)
	≤ 6 weeks	5	0.24 (0.06–0.41)
	> 6 weeks	7	0.20 (0.04–0.36)
LDL-C	Overall effect	10	0.14 (0.05–0.24)
	Filter coffee	2	0.12 (0.24–0.47)
	Boiled coffee	3	0.14 (0.08–0.46)
	1–3 cups/day	2	0.10 (–0.17 to 0.36)
	3–5 cups/day	5	0.12 (0.06–0.30)
	≥ 6 cups/day	4	0.43 (0.19–0.67)
	≤ 6 weeks	3	0.13 (0.00–0.25)
	> 6 weeks	7	0.18 (0.03–0.33)
HDL-C	Overall effect	10	–0.01 (–0.06 to –0.04)
	Filter coffee	2	–0.02 (–0.12 to 0.09)
	Boiled coffee	2	–0.05 (–0.15 to 0.05)
	1–3 cups/day	2	–0.01 (–0.12 to 0.11)
	3–5 cups/day	5	–0.02 (–0.06 to 0.02)
	≥ 6 cups/day	3	0.00 (–0.07 to 0.07)
	≤ 6 weeks	4	–0.01 (–0.04 to 0.02)
	> 6 weeks	6	–0.04 (–0.10 to 0.03)
Triglycerides	Overall effect	7	0.12 (0.03–0.20)
	Boiled coffee	2	0.25 (0.08–0.41)
	Decaffeinated coffee	2	0.00 (–0.09 to 0.09)
	1–3 cups/day	2	0.04 (–0.26 to 0.50)
	3–5 cups/day	3	0.12 (0.01–0.24)
	≥ 6 cups/day	2	0.25 (0.16–0.34)
	≤ 6 weeks	3	0.08 (0.02–0.18)
	> 6 weeks	4	0.15 (0.02–0.33)

CI — confidence interval; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; RCT — randomized controlled trial; WMD — weighted mean difference

filter and non-filter coffee on lipid profile in the previously discussed meta-analysis by Du et al. (Table 1) [11], as well as the meta-analysis by Cai et al. [12]. The evidence in the 1990s of the effect of coffee filtering in reducing adverse changes in lipid profile led to the spread of this method of preparing this brew. Currently, filtering coffee using a paper filter is common in many parts of the world, especially in high-income countries [16]. In recent years, some coffee drinkers may have switched from non-filter (Turkish) coffee to filter coffee [16].

In terms of atherosclerosis, it is useful to examine the effect of coffee consumption on the risk of peripheral artery disease (PAD), which is a very good model for research into this process. A study by Hoek et al. [19] assessed the relationship between different dietary components and the risk of PAD. Participants of the Million-Veteran-Program (MVP)

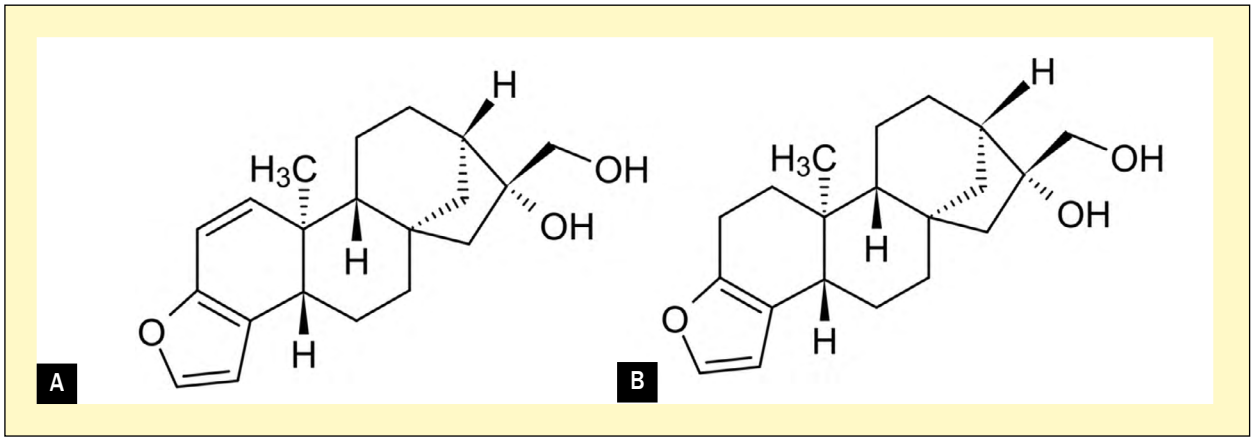

Figure 1. Chemical structure of diterpenoids: **A.** kahweol and **B.** cafestol

genome-wide association studies (cases: 31 307, controls: 211 753) and the GoLEAD-SUMMIT genome-wide association studies (cases: 12 086, controls: 449 548) were included in the study. There was no significant cause-and--effect relationship between coffee consumption and the risk of PAD (MVP, OR = 1.19; 95% CI: 0.92–1.54 and GoLEAD-SUMMIT, OR = 1.13; 95% CI: 0.75–1.69) [19].

In conclusion, the consumption of filter coffee does not affect, and may even be beneficial in preventing the process of atherosclerosis.

Chemical explanation of the difference in terms of the effect of coffee consumption on lipid profile

The way coffee is prepared significantly influences the effects on changes in lipid profile. In the course of filtering coffee, excess diterpenoids — kahweol and cafestol — are removed (Figure 1) [18, 20].

Compared to traditionally brewed Turkish coffee, i.e. non-filter coffee, the kahweol and cafestol content in filter coffee is not significant. It should also be borne in mind that the content of kahweol and cafestol depends on the type of coffee [20].

Kahweol and cafestol have hyperlipidemic effects (especially cafestol in humans). In hepatocytes, these compounds reduce the number of receptors for LDL-C (down--regulation), while in plasma they increase cholesteryl ester transfer protein and phospholipid transfer protein levels [18]. Furthermore, a mixture of kahweol and cafestol can reduce LCAT (lecithin: cholesterol acyltransferase) activity [17]. Kahweol and cafestol, through activation of the nuclear receptors FXR and PXR, can reduce the synthesis of sterol 27-hydroxylase and oxysterol 7-αhydroxylase, thereby reducing the conversion of cholesterol into bile acids [18]. It should be noted that with long-term coffee consumption, the hyperlipidemic effect of these diterpenoids is reduced [18]. Interestingly, in addition to the adverse hyperlipidemic effects of these diterpenoids, they show several beneficial effects, such as anti-inflammatory effects, anti-cancer effects, anti-diabetic effects, and anti-osteoporotic effects [18]. Hence the widespread recommendation to prefer filter coffee, which seems justified in those with uncontrolled, severe hypercholesterolemia but is controversial in other populations. It cannot be ruled out that many of the pleiotropic benefits that are observed with regular coffee consumption may result precisely from the presence of kahweol and cafestol in coffee.

Consumption of caffeinated coffee was found to increase lipid levels compared to decaffeinated brew [13]. Caffeine — through antagonism to certain adenosine receptor subtypes, reduction of phosphodiesterase activity in adipocytes and increased secretion of catecholamines — enhances lipolysis, resulting in the release of free fatty acids into the circulation [21]. This can have an adverse effect with a sedentary lifestyle and poor eating habits. The released free fatty acids are then not re-deposited in adipose tissue, however, they can serve to produce *de novo* triglycerides and subsequently very low-density lipoprotein and LDL-C [22]. In conclusion, the effect of caffeine on lipid profile depends not so much on its consumption but on eating habits and lifestyle of a given person.

Interestingly, *in vitro* and *in vivo* studies by Ontawong et al. [23] revealed that coffee pulp — an aqueous extract of coffee bean waste from the first stage of coffee production — acted similarly to ezetimibe, i.e., it reduced the activity of Niemann-Pick C1-Like 1 (NPC1L1) protein [23]. Furthermore, an *in vivo* study revealed that coffee polyphenols inhibited diet-induced fat accumulation by reducing the expression (down-regulation) of sterol regulatory element-binding transcription factor 1c (SREBP-1c) protein [24]. Caffeine, chlorogenic acid, trigonelline, melanoidins,

and kahweol and cafestol, as a result of their antioxidant properties, can also reduce lipid peroxidation and thus the formation of highly proatherogenic oxidised LDL fractions [25].

The resultant effect of coffee on lipid profile depends on the content of kahweol, cafestol, as well as other biologically active compounds such as chlorogenic acid (high content in green coffee, the consumption of which had a beneficial effect on lipid profile) or trigonelline, which have beneficial effects on lipid metabolism [26].

According to consumer research conducted by the SW Research Agencja Badań Rynku i Opinii on behalf of the Nespresso Poland brand, more than half of Poles consume non-filter coffee (39% ground coffee; 14% coffee from an espresso machine, 11% coffee from a moka pot), i.e. coffee with a higher diterpenoid content. Therefore, it seems useful to raise the issue of the effect of coffee on lipid profile in Polish society.

Coffee and lipids through the prism of guidelines/recommendations of scientific societies

The European Society of Cardiology CVD prevention guidelines (2021) indicate that consumption of non-filter coffee may increase LDL-C and the risk of ASCVD [27].

The Interdisciplinary Expert Position Statement supported by the Cardiovascular Pharmacotherapy Section of the Polish Cardiac Society on the treatment of dyslipidemia in Poland (Sopot Declaration IV) indicated that the consumption of decaffeinated and filter coffee does not affect the lipid profile, while the consumption of non-filter coffee may have a moderate to high hyperlipidemic effect [28].

Conclusions

Lipid disorders are a significant global problem. The main risk factors for their occurrence are poor eating habits and a sedentary lifestyle. Coffee consumption plays an important role in the diet of Poles. Results from large studies and meta-analyses in recent years indicate that consumption of 1–3 cups of filter coffee is safe in terms of the risk of lipid disorders. It should be stressed, however, that this is black coffee (espresso) without added sugar or milk. It should also be noted that dietary habits have been changing in recent years, with a trend towards drinking a higher average number of cups of coffee a day, even 3–5/day, which may be associated with a slight increase in cholesterol levels but still without clinical significance, especially for patients at low and moderate cardiovascular risk.

When considering the effect of coffee on lipid profile, several principles are useful to follow:

The effect of chronic coffee consumption, in the average number of cups/day typical of Poland, does not appear to be clinically relevant.

Although nearly 20 million Poles suffer from lipid disorders, proper treatment of these should in no way interfere with a coffee-drinking habit of 1–3 cups a day.

For a small group of individuals with uncontrolled high lipid values, a preference for filter, kahweol- and cafestol-free, optimally pure Arabica coffee could be recommended.

However, the widespread application of this principle is questionable due to the potential benefits of the pleiotropic effects of kahweol and cafestol contained in coffee on other physiological activities in addition to the effect on lipid profile.

Conflict of interest

None declared.

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Kawa a lipidogram — od teorii do uwag praktycznych

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Streszczenie

Zaburzenia lipidowe od lat są najczęstszą przyczyną chorób układu krążenia pochodzenia miażdżycowego w Polsce. Najnowsze dane wskazują, że około 20 milionów osób w Polsce ma hipercholesterolemię. Bardzo istotnie na profil lipidowy wpływają nawyki żywieniowe. Dlatego, biorąc pod uwagę fakt, że ważnym składnikiem diety Polaków jest kawa (średnio w naszym kraju spożywa się 1–2 filiżanki kawy/mieszkańca/dobę, a 66% Polaków deklaruje regularne jej spożywanie), nie można pominąć jej wpływu na profil lipidowy. Kawa zawiera ponad 1000 związków chemicznych, z których w kontekście lipidologii najważniejsze są kahweol i kafestol — związki które mogą działać hiperlipemizująco. Z kolei kofeina, kwas chlorogenowy, trigonelina oraz melanoidyny charakteryzują się działaniem antyoksydacyjnym przez co mogą ograniczać peroksydację lipidów. Wpływ spożywania kawy przyrządzonej w różny sposób był analizowany w licznych badaniach klinicznych. W tym artykule podsumowano aktualną wiedzę w zakresie wpływu kawy na profil lipidowy i ryzyko miażdżycy.

Słowa kluczowe: kawa, zaburzenia lipidowe, choroby układu krążenia pochodzenia miażdżycowego

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Wprowadzenie

Zaburzenia lipidowe od lat znajdują się na czołowym miejscu wśród najczęściej występujących na świecie czynników ryzyka chorób układu krążenia pochodzenia miażdżycowego (ASCVD, *atherosclerotic cardiovascular disease*) [1].

Najczęściej występującym zaburzeniem lipidowym w Polsce jest hipercholesterolemia przebiegająca z podwyższonym stężeniem cholesterolu frakcji lipoprotein o niskiej gęstości (LDL-C, *low-density lipoprotein cholesterol*) przekraczającym wartości zalecane w danej grupie ryzyka sercowo-naczyniowego [2]. W badaniu WOBASZ II (Wielośrodkowe Ogólnopolskie Badanie Stanu Zdrowia Ludności), które obejmowało 5947 osób w wieku 20–99 lat wykazano, że hipercholesterolemia występowała u 67,1% z nich (odpowiednio u 64,3% kobiet i 70,3% mężczyzn) [3]. Wyniki te wskazują, że liczba chorych z hipercholesterolemią w Polsce może sięgać nawet 20 milionów.

Bardzo istotny wpływ na profil lipidowy mają nawyki żywieniowe [4]. Dlatego, biorąc pod uwagę fakt, że ważnym składnikiem diety Polaków jest kawa (średnio w naszym kraju spożywa się 1–2 filiżanki kawy/mieszkańca/dobę, a 66% Polaków deklaruje regularne jej spożywanie), nie można pominąć jej wpływu na profil lipidowy.

Kawa a profil lipidowy

W przeglądzie systematycznym i metaanalizie badań klinicznych z randomizacją przeprowadzonej przez Schoeneck i Iggman [5] dokonano podsumowania wpływu różnych

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składników diety na stężenie LDL-C. W przypadku kawy wykazano, że jej oddziaływanie na stężenie LDL-C w surowicy było zależne od tego, czy spożywano kawę filtrowaną czy niefiltrowaną. Spożywanie kawy filtrowanej *versus* niespożywanie tego napoju nie było istotnie związane z zmianami w stężeniu LDL-C w surowicy [różnica średnich (MD, *mean difference*) = 0,03 mmol/l; 95–procentowy przedział ufności (CI, *confidence interval*): –0,05 do 0,11). Nie wykazano istotnej różnicy pomiędzy spożywaniem kawy a herbaty w odniesieniu do LDL-C (MD = 0,14 mmol/l; 95% CI: –0,01 do 0,28). Porównując spożywanie kawy filtrowanej ze spożywaniem kawy niefiltrowanej wykazano, że ta druga zwiększała stężenie LDL-C w surowicy (MD = –0,39 mmol/l; 95% CI: –0,49 do –0,30). Nie wykazano istotnego wpływu na LDL-C czarnej kawy *versus* kawy bezkofeinowej (MD = –0,02 mmol/l; 95% CI: –0,08 do 0,04) ani spożywania kawy bardziej palonej *versus* mniej palonej (MD = 0,07 mmol/l; 95% CI: –0,08 do 0,23). Na podstawie wyników tej metaanalizy należy stwierdzić, że wpływ spożywania kawy na LDL-C zależy od tego, czy napar jest filtrowany.

W badaniu Miranda i wsp. [6], obejmującym 4736 Brazylijczyków oceniano wpływ intensywności spożywania kawy (≤ 1, 1–3 oraz > 3 filiżanki/dobę; filiżanka = 50 ml espresso) na profil lipidowy. Badano stężenia cholesterolu całkowitego (TC, *total cholesterol*), triglicerydów (TG, *triglicerydes*), LDL-C i cholesterolu frakcji lipoprotein o wysokiej gęstości (HDL-C, *high-density lipoprotein cholesterol*). Po uwzględnieniu innych czynników ryzyka wykazano, że spożywanie do 3 filiżanek kawy/dobę nie wpływało na zmianę profilu lipidowego [TC (β = 2,67; 95% CI: −0,10 do 5,41), TG (β = 5,61; 95% CI: −0,71 do 11,93), LDL-C (β = 2,13; 95% CI: −0,13 do 4,40), HDL-C (β = 0,11; 95% CI: −0,89 do 1,11) oraz lipoproteiny bogate w TG (β = 5,26; 95% CI: −0,46 do 10,97)]. Spożywanie > 3 filiżanek kawy/dobę zwiększało stężenie lipoprotein [TC (β = 4,13; 95% CI: 0,81–7,45), TG (β = 9,53; 95% CI: 1,65–17,42), LDL-C (β = 2,39; 95% CI: −0,37 do 5,14), HDL-C (β = 0,44; 95% CI: −0,75 do 1,64) oraz lipoproteiny bogate w TG (β = 8,42; 95% CI: 1,24–15,60)]. Wyniki tego badania wskazują, że spożywanie 1–3 filiżanek kawy/dobę nie wpływa na profil lipidowy.

W badaniu klinicznym z randomizacją autorstwa Gonçalinho i wsp. [7], obejmującym 53 osoby zdrowe analizowano wpływ spożywania 450–600 ml/dobę filtrowanej arabiki lub filtrowanej mieszanki arabiki i robusty na stężenie sirtuiny-1, homocysteiny i lipidów. Warto przypomnieć, że arabikę uznaje się za najszlachetniejszy i najstarszy rodzaj kawy, pochodzący z Etiopii. Uprawiana na terenach górzystych, w temperaturze około 20–25 st. C, zawiera mniej kofeiny niż robusta, natomiast może więcej tłuszczów i cukrów (tłuszcze w ziarnie arabiki stanowią około 6–9%, podczas gdy dla robusty jest to około 3–7%, natomiast cukry to 15–17% ziarna arabiki, przy 10–11,5% dla robusty). Robusta, czyli inaczej kawa kongijska, wywodzi się ze środkowej Afryki, ale jest też uprawiana w innych rejonach świata (głównie w strefie międzyzwrotnikowej). Po 8 tygodniach interwencji wykazano, że spożywanie arabiki lub mieszanki arabiki i robusty istotnie zwiększało stężenie sirtuiny-1 (0,51 do 0,58 ng/ml, p = 0,004, oraz z 0,40 do 0,49 ng/ml, p = 0,003), natomiast nie wpływało na stężenie homocysteiny. W kontekście profilu lipidowego stwierdzono, że spożywanie mieszanki arabiki i robusty było związane ze zwiększeniem stężenia TC (z 4,70 do 5,17 mmol/l, p < 0,001), LDL-C (z 2,98 do 3,32 mmol/l, p < 0,001) oraz HDL-C (z 1,26 do 1,36 mmol/l, p < 0,001). W tym badaniu spożywanie kawy nie wpływało na stężenie TG. Obserwowane różnice we wpływie czystej arabiki i jej mieszanki z robustą wynikają zapewne z zróżnicowanej zawartości polifenoli (w robuście więcej kofeiny, mniej polifenoli). Wyniki tego badania wskazują, że mając na względzie profil lipidowy, należy preferować filtrowaną kawę gatunku arabika [7]. W badaniu Gebeyehu i wsp. [8], obejmującym 70 zdrowych osób, oceniano wpływ spożywania w 100% filtrowanej etiopskiej arabiki na profil lipidowy. Wykazano, że zmniejszało ono stężenia TG (p < 0,01), natomiast nieistotnie wpływało na stężenie TC i LDL-C. Nie można nie wspomnieć o wynikach badania Svatun i wsp. [9], obejmującego 21 083 osób z Tromsø Study in Northern Norway. W badaniu tym analizowano wpływ spożywania kawy na stężenie TC w surowicy. Wykazano, że spożywanie dziennie 1–2 filiżanek espresso lub kawy filtrowanej nie wpływało istotnie statystycznie na stężenie TC w surowicy (w przeciwieństwie do spożywania 3–5 filiżanek tych naparów/dobę). W przypadku spożywania 1–2 filiżanek kawy gotowanej/dobę wykazano, jak istotny jest wpływ na zwiększenie stężenia TC w surowicy. Kawa rozpuszczalna w ilości 1–2 filiżanek/dobę istotnie zwiększała stężenie TC w surowicy u mężczyzn, a efektu tego nie obserwowano u kobiet. Wyniki tego badania wskazują, że powinno się preferować spożywanie espresso lub kawy filtrowanej w ilości 1–2 filiżanek/dobę, mając na uwadze profil lipidowy.

W badaniu Zhou i Hyppönen [10], obejmującym 362 571 osób z bazy UK Biobank oceniano wpływ regularnego spożywania kawy na profil lipidowy. Wykazano zależne od dawki niewielkie zwiększenie LDL-C (1–2 filiżanki kawy/dobę: β = 0,06 mmol/l; 95% CI: 0,05–0,07; > 6 filiżanek kawy/dobę: β = 0,13 mmol/l; 95% CI: 0,11–0,15) i efekt ten nie różnił się istotnie ze względu na typ spożywanej kawy: mielona, bezkofeinowa czy rozpuszczalna. W przypadku HDL-C także wykazano zwiększenie stężenia (1–2 filiżanki kawy/dobę: β = 0,01 mmol/l; 95% CI: 0,01–0,01; > 6 filiżanek kawy/dobę: β = 0,01 mmol/l; 95% CI: 0,01–0,02), przy czym efekt ten dotyczył jedynie kaw mielonej i rozpuszczalnej. Spożywanie kawy było także w sposób zależny od dawki związane ze zwiększeniem stężenia TC (1–2 filiżanki kawy/dobę: β = 0,08 mmol/l; 95% CI: 0,07–0,09; > 6 filiżanek kawy/dobę: β = 0,15 mmol/l; 95% CI: 0,13–0,18), bez względu na typ spożywanego naparu. W odniesieniu do TG informacje są bardziej optymistyczne, bowiem spożywanie

kawy nie wpływało, a nawet mogło delikatnie zmniejszać ich stężenie (1–2 filiżanki kawy/dobę: β = 0,01 mmol/l; 95% CI: 0,00–0,02; > 6 filiżanek kawy/dobę: β = –0,07 mmol/l; 95% CI: –0,09 do –0,05), a efekt ten był wspólny dla różnych typów kawy. Analizowano także wpływ spożywania kawy na stężenie apolipoproteiny B (apoB) oraz apolipoproteiny A1 (apoA1). Wykazano zależne od dawki zwiększenie stężenia apoB (1–2 filiżanki kawy/dobę: β = 0,01 g/l; 95% CI: 0,01–0,01; > 6 filiżanek kawy/dobę: β = 0,02 g/l; 95% CI: 0,02–0,03), które było niezależne od typu kawy. W odniesieniu do apoA1 spożywanie kawy mogło zwiększać bądź nie wpływało na jej stężenie (1–2 filiżanki kawy/dobę: β = 0,01g/l; 95% CI: 0,00–0,01; > 6 filiżanek kawy/dobę: β = 0,00 g/l; 95% CI: –0,01 do 0,01), przy czym najkorzystniejszy efekt obserwowano w przypadku spożywania kawy mielonej, a następnie rozpuszczalnej. W innej analizie stwierdzono dodatni związek pomiędzy spożywaniem kawy a LDL-C, cholesterolem całkowitym i apoB. Wyniki tego prospektywnego badania wskazują, że spożywanie kawy może być związane ze zwiększeniem stężenia LDL-C, TC oraz apoB. Należy jednak podkreślić, że **w przeliczeniu na polskie warunki, gdzie spożywa się średnio 1–3 filiżanki kawy/dobę można oczekiwać zwiększenia stężenia LDL-C o około 2 mg/dl, a cholesterolu całkowitego o 3 mg/dl, co z klinicznego punktu widzenia nie ma istotnego znaczenia.** Co więcej, jak wskazują autorzy badania, istotnym czynnikiem ograniczającym jest to, że badani raportowali spożycie kawy w kwestionariuszu. Nie można także dokładnie ocenić, jaka była zawartość kahweolu i kafestolu w spożywanych przez badanych kawach. Na istotną rolę tego zagadnienia wskazuje na przykład to, że spożywanie kawy rozpuszczalnej w mniejszym stopniu zwiększało stężenie LDL-C i TC w porównaniu do kawy mielonej, a to właśnie ta kawa zawiera mniej kahweolu i kafestolu.

W metaanalizie 12 badań klinicznych z randomizacją, przeprowadzonej przez Du i wsp. [11], obejmującej 1182 osoby dokonano podsumowania wpływu spożywania kawy na ryzyko wystąpienia dyslipidemii. Wyniki tej metaanalizy przedstawiono w tabeli 1.

Wyniki tej metaanalizy wskazują, że spożywanie większych ilości kawy może być związane ze zwiększeniem stężenia poszczególnych frakcji lipidów. Analiza zależności dawka–efekt wykazała, że spożywanie 1–3 filiżanek kawy/dzień (najlepiej filtrowanej) nie wpływało na stężenie LDL-C, HDL-C oraz TG, natomiast granicznie wpływało na stężenie cholesterolu całkowitego [11]. Uzyskane w tej metaanalizie wyniki są zgodne z tymi uzyskanymi kilka lat temu w metaanalizie 12 badań klinicznych z randomizacją, przeprowadzonej przez Cai i wsp. [12]. Stwierdzono w niej, że spożywanie kawy filtrowanej w niewielkim stopniu wpływało na stężenie TC (różnica: 3,6 mg/dl; 95% CI: 0,6–6,6), natomiast nie wpływało znamiennie na LDL-C i TG. Co więcej, wykazano także efekt zależny od dawki. Spożywanie do 6 filiżanek kawy/dobę w niewielkim stopniu wpływało na stężenie TC (różnica: 4,2 mg/dl; 95% CI: 1,3–7,1) i nie wpływało na LDL-C i TG [12]. Co więcej, w pełni korespondują z nimi wyniki przeglądu metaanaliz wpływu kawy na zdrowie człowieka, przeprowadzonego przez Poole i wsp. [13]. Stwierdzono w nim, że spożywanie kawy niefiltrowanej istotnie zwiększało stężenie TC, LDL-C i TG, natomiast spożywanie naparu filtrowanego zwiększało jedynie w niewielkim stopniu stężenie TC. Spożywanie kawy bezkofeinowej nie było związane ze zmianami profilu lipidowego [13]. Wyniki tej metaanalizy wskazują, że spożywanie 1–3 filiżanek kawy/dobę, najlepiej filtrowanej, z punktu widzenia ryzyka zaburzeń lipidowych, pozostaje bezpieczne.

W przeglądzie systematycznym autorstwa Penson i wsp. [14], obejmującym 640 osób analizowano wpływ spożywania kawy na stężenie lipoproteiny (a). Wykazano, że spożywanie filtrowanej kawy może być związane ze zmniejszeniem stężenia lipoproteiny (a), natomiast kawy niefiltrowanej z efektem przeciwnym. Autorzy wskazują, że wpływ spożywania kawy na Lp(a) zależy od sposobu jej przygotowania.

W kontekście profilu lipidowego warto wspomnieć o mniej przebadanej zielonej kawie. W metaanalizie 17 badań klinicznych z randomizacją, przeprowadzonej przez Ding i wsp. [15], wykazano, że spożywanie kawy bezkofeinowej było związane ze zmniejszeniem stężenia TC [WMD (*weighted mean difference*) = –4,51 mg/dl; 95% CI: –6,90 do –2,13], zwiększeniem stężenia HDL-C (WMD = 2,64 mg/dl; 95% CI: 2,21–3,07), zmniejszeniem stężenia LDL-C (WMD = –4,38 mg/dl; 95% CI: –6,45 do –2,32) oraz nieistotnym wpływem na stężenie TG (WMD = –4,34 mg/dl; 95% CI: –9,00 do 0,32) [15]. Wyniki tej metaanalizy wskazują, że spożywanie zielonej kawy charakteryzuje się pewnym działaniem hipolipemizującym.

Podsumowując, wyniki najnowszych badań i metaanaliz wskazują, że spożywanie 1–3 filiżanek kawy/dobę, najlepiej filtrowanej, pozostaje bez wpływu na profil lipidowy.

Od kawy przez profil lipidowy do miażdżycy

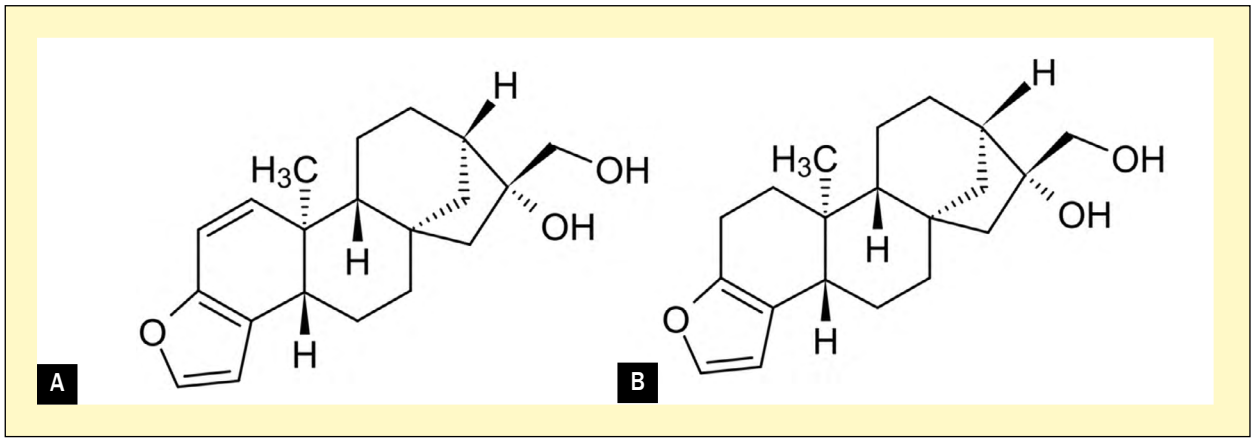
Duże zainteresowanie wpływem spożywania kawy na zaburzenia lipidowe jest związane także z wcześniejszymi obserwacjami wskazującymi, że spożywanie tego napoju było związane z większym ryzykiem choroby naczyń wieńcowych (CAD, *coronary artery disease*). W bardzo interesującej pracy autorstwa Shiari i wsp. [16] dokonano przeglądu badań oceniających wpływ spożywania kawy na ryzyko CAD, które publikowano w latach 1990–2018. Analiza objęła ponad milion osób z 147 krajów. Co interesujące, stwierdzono, że ocena związku pomiędzy spożywaniem kawy a ryzykiem wystąpienia CAD i zgonu w jej przebiegu na przestrzeni 1990–2018 uległa zmianie z niekorzystnej na korzystną. Istnieje kilka wytłumaczeń takiego stanu rzeczy. W wieloośrodkowym badaniu, przeprowadzonym przez Tverdal i wsp. [17], obejmującym ponad 500 tysięcy

Tabela 1. Wpływ spożywania kawy na profil lipidowy — wyniki metaanalizy przeprowadzonej przez Du i wsp. 2020 [11]

Frakcja lipidów [mmol/l]	Grupa badana/ podgrupa	Liczba RCT	Efekt (WMD [95% CI]) [mmol/l]
Cholesterol całkowity	Efekt ogólny	12	0,21 (0,04–0,39)
	Kawa filtrowana	3	0,10 (0,17–0,37)
	Kawa gotowana	3	0,30 (0,06–0,53)
	Kawa rozpuszczalna	2	0,08 (0,06–0,21)
	1–3 filiżanki/dobę	3	0,11 (0,03–0,23)
	3–5 filiżanek/dobę	5	0,14 (0,03–0,31)
	≥ 6 filiżanek/dobę	4	0,52 (0,40–0,54)
	≤ 6 tygodni	5	0,24 (0,06–0,41)
	> 6 tygodni	7	0,20 (0,04–0,36)
LDL-C	Efekt ogólny	10	0,14 (0,05–0,24)
	Kawa filtrowana	2	0,12 (0,24–0,47)
	Kawa gotowana	3	0,14 (0,08–0,46)
	1–3 filiżanki/dobę	2	0,10 (–0,17 do 0,36)
	3–5 filiżanek/dobę	5	0,12 (0,06–0,30)
	≥ 6 filiżanek/dobę	4	0,43 (0,19–0,67)
	≤ 6 tygodni	3	0,13 (0,00–0,25)
	> 6 tygodni	7	0,18 (0,03–0,33)
HDL-C	Efekt ogólny	10	–0,01 (–0,06 do –0,04)
	Kawa filtrowana	2	–0,02 (–0,12 do 0.09)
	Kawa gotowana	2	–0,05 (–0,15 do 0,05)
	1–3 filiżanki/dobę	2	–0,01 (–0,12 do 0,11)
	3–5 filiżanek/dobę	5	–0,02 (–0,06 do 0,02)
	≥ 6 filiżanek/dobę	3	0,00 (–0,07 do 0,07)
	≤ 6 tygodni	4	–0,01 (–0,04 do 0,02)
	> 6 tygodni	6	–0,04 (–0,10 do 0,03)
Trójglicerydy	Efekt ogólny	7	0,12 (0,03–0,20)
	Kawa gotowana	2	0,25 (0,08–0,41)
	Kawa bezkofeinowa	2	0,00 (–0,09 do 0,09)
	1–3 filiżanki/dobę	2	0,04 (–0,26 do 0,50)
	3–5 filiżanek/dobę	3	0,12 (0,01–0,24)
	≥ 6 filiżanek/dobę	2	0,25 (0,16–0,34)
	≤ 6 tygodni	3	0,08 (0,02–0,18)
	> 6 tygodni	4	0,15 (0,02–0,33)

RCTs (*randomized controlled trials*) — randomizowane badania kliniczne; WMD (*weighted mean difference*) — ważona średnia różnica; LDL-C (*low-density lipoprotein cholesterol*) — cholesterol lipoprotein frakcji niskiej gęstości; HDL-C (*high-density lipoprotein cholesterol*) — cholesterol lipoprotein frakcji wysokiej gęstości

osób, które obserwowano przez 20 lat, wykazano, że śmiertelność z powodu chorób układu krążenia (CVD, *cardiovascular disease*) była wyższa u tych, którzy spożywali kawę niefiltrowaną niż tych, którzy spożywali kawę filtrowaną. Co więcej, podobną zależność stwierdzono w kontekście ryzyka wystąpienia CAD. Wyjaśnieniem tych różnic jest sposób przygotowania kawy, bowiem filtrowanie naparu prowadzi do ograniczenia ilości kahweolu i kafestolu, czyli diterpenoidów o działaniu hiperlipemizującym [18]. Istotną różnicę we wpływie kawy filtrowanej i niefiltrowanej na profil lipidowy wykazano w uprzednio omówionej metaanalizie autorstwa Du i wsp. (tab. 1) [11], jak i metaanalizie Cai i wsp. [12].



Rycina 1. Struktura chemiczna diterpenoidów — (**A**) kahweolu i (**B**) kafestolu

Wykazanie w latach 90. XX wieku wpływu filtrowania kawy na ograniczenie niekorzystnych zmian w profilu lipidowym spowodowało rozpowszechnienie tej metody przygotowywania tego naparu. Obecnie filtrowanie kawy przy pomocy papierowego filtra jest powszechne w wielu częściach świata, zwłaszcza w krajach o wysokich dochodach [16]. Część osób spożywających kawę mogła w ostatnich latach przestawić się z kawy niefiltrowanej (parzonej po „turecku") na tę filtrowaną [16].

W kontekście miażdżycy warto przyjrzeć się wpływowi spożywania kawy na ryzyko wystąpienia choroby naczyń obwodowych (PAD, *peripheral artery disease*), która jest bardzo dobrym modelem dla badan nad tym procesem. W badaniu autorstwa Hoek i wsp. [19], oceniano związek pomiędzy różnymi składnikami diety a ryzykiem wystąpienia PAD. Badaniem objęto uczestników *Million–Veteran-Program (MVP) genome-wide association studies* (przypadki: 31 307, kontrola: 211 753) oraz *GoLEAD-SUMMIT genome-wide association studies* (przypadki: 12 086, kontrola: 449 548). Nie wykazano istotnego związku przyczynowo-skutkowego pomiędzy spożywaniem kawy a ryzykiem wystąpienia PAD [MVP, iloraz szans (OR, *odds ratio*) = 1,19; 95% CI: 0,92–1,54 oraz GoLEAD-SUMMIT, OR = 1,13; 95% CI: 0,75–1,69].

Podsumowując, spożywanie filtrowanej kawy nie wpływa, a nawet może być korzystne w zapobieganiu procesowi miażdżycy.

Chemiczne wytłumaczenie różnicy we wpływie spożywania kawy na profil lipidowy

Sposób przygotowania kawy w istotny sposób wpływa na efekty dotyczące zmian profilu lipidowego. W przebiegu filtrowania kawy dochodzi do usunięcia nadmiaru diterpenoidów — kahweolu i kafestolu (ryc. 1) [18, 20].

W porównaniu do kawy parzonej tradycyjnie „po turecku" czyli niefiltrowanej, w tej filtrowanej zawartość kahweolu i kafestolu jest marginalna. Należy także pamiętać, że zawartość kahweolu i kafestolu zależą od rodzaju kawy [20].

Kahweol i kafestol charakteryzują się działaniem hiperlipemizującym (u ludzi zwłaszcza kafestol). W hepatocytach związki te zmniejszają liczbę receptorów dla LDL-C (*down-regulation*), natomiast w osoczu zwiększają stężenie białka przenoszącego estry cholesterolu (CETP, *cholesteryl ester transfer protein*) oraz białka przenoszącego fosfolipidy (PLTP, *phospholipid transfer protein*) [18]. Co więcej, mieszanina kahweolu i kafestolu może zmniejszać aktywność acylotransferazy lecytynowo-cholesterolowej (LCAT, *lecithin:cholesterol acyltransferase*) [17]. Kahweol i kafestol poprzez aktywację receptorów jądrowych FXR i PXR mogą zmniejszać syntezę 27-hydroksylazy sterolowej oraz 7α hydroksylazy oksysterolowej, a co za tym idzie, redukować przetwarzanie cholesterolu w kwasy żółciowe [18]. Należy podkreślić, że przy długotrwałym spożywaniu kawy hiperlipemizujący efekt tych diterpenoidów ulega ograniczeniu [18]. Co interesujące, poza niekorzystnym działaniem hiperlipemizujących tych diterpenoidów, wykazują one wiele korzystnych działań, takich jak: efekt przeciwzapalny, efekt przeciwnowotworowy, efekt przeciwcukrzycowy oraz efekt przeciwosteoporotyczny [18]. Dlatego powszechne zalecanie wybierania kawy filtrowanej wydaje się uzasadnione u osób z niekontrolowaną, ciężką hipercholesterolemią, jest natomiast kontrowersyjne w innych populacjach. Nie można wykluczyć, że wiele z plejotropowych korzyści obserwowanych przy regularnym spożywaniu kawy może wynikać właśnie z obecności w niej kahweolu i kafestolu.

Stwierdzono, że spożywanie kawy zawierającej kofeinę zwiększa, w przeciwieństwie do naparu bezkofeinowego, stężenie lipidów [13]. Kofeina poprzez antagonizm

w stosunku do niektórych podtypów receptorów adenozyny, zmniejszanie aktywności fosfodiesterazy w adipocytach oraz zwiększenie wydzielania amin katecholowych nasila lipolizę, w wyniku której dochodzi do uwolnienia wolnych kwasów tłuszczowych (FFAs, *free fatty acids*) do krążenia [21]. Może to mieć niekorzystny efekt w przypadku siedzącego trybu życia, niewłaściwych nawyków żywieniowych. Wówczas uwolnione FFAs nie ulegają ponownemu zdeponowaniu w tkance tłuszczowej, tylko mogą służyć do wytwarzania *de novo* TG, a następnie lipoprotein o bardzo niskiej gęstości (VLDL, *very low density lipoprotein*) i LDL-C [22]. Podsumowując, efekt kofeiny na profil lipidowy zależy nie tyle od jej spożywania, ile od nawyków żywieniowych i stylu życia danej osoby.

Co interesujące, w badaniu *in vitro* i *in vivo* autorstwa Ontawong i wsp. [23] wykazano, że pulpa kawowa — wodny ekstrakt odpadków po ziarnach kawy z pierwszego etapu produkcji kawy działała podobne jak ezetimib, czyli zmniejszała aktywność białka *Niemann-Pick C1–Like 1* (NPC1L1). Co więcej, w badaniu *in vivo* wykazano, że polifenole kawy hamują akumulację tkanki tłuszczowej wywołaną dietą poprzez zmniejszanie ekspresji (*down-regulation*) białka wiążącego element regulacyjny steroli 1c (SREBP-1c, *sterol regulatory element-binding transcription factor 1c*) [24]. Kofeina, kwas chlorogenowy, trigonelina, melanoidyny oraz kahweol i kafestol dzięki swoim właściwościom antyoksydacyjnym mogą również ograniczać peroksydację lipidów i tym samym tworzenie silnie proaterogennych oksydowanych frakcji LDL [25].

Wypadkowy efekt wpływu kawy na profil lipidowy zależy od zawartości kahweolu, kafestolu, a także innych związków aktywnych biologicznie, takich jak kwas chlorogenowy (duża zawartość w zielonej kawie, której spożycie korzystnie wpływało na profil lipidowy) czy trigonelina, które charakteryzują się korzystnym wpływem na gospodarkę lipidową [26].

Jak wynika z badań konsumenckich przeprowadzonych przez SW Research Agencja Badań Rynku i Opinii na zlecenie marki Nespresso Polska, ponad połowa Polaków spożywa kawę niefiltrowaną (39% sypana; 14% z ekspresu ciśnieniowego, 11% z kawiarki), czyli tę o większej zawartości diterpenoidów. Wydaj się zatem, że warto podnosić kwestię wpływu kawy na profil lipidowy w polskim społeczeństwie.

Kawa a lipidy przez pryzmat wytycznych/rekomendacji towarzystw naukowych

W wytycznych Europejskiego Towarzystwa Kardiologicznego (ESC, *European Society of Cardiology*) dotyczących prewencji CVD (2021) wskazano, że spożywanie niefiltrowanej kawy może zwiększać LDL-C i ryzyko wystąpienia CVD o podłożu miażdżycowym (ASCVD, *atherosclerotic cardiovascular disease*) [27].

W Interdyscyplinarnym Stanowisku Ekspertów wspartym przez Sekcję Farmakoterapii Sercowo-naczyniowej Polskiego Towarzystwa Kardiologicznego dotyczącego leczenia dyslipidemii w Polsce (IV Deklaracja Sopocka) wskazano, że spożywanie kawy bezkofeinowej i filtrowanej nie wpływa na profil lipidowy, natomiast spożywanie kawy niefiltrowanej może działać hiperlipemizująco w stopniu umiarkowanym do dużego [28].

Podsumowanie

Zaburzenia lipidowe stanowią istotny problem w wymiarze globalnym. Podstawowym czynnikiem ryzyka ich wystąpienia są niewłaściwe nawyki żywieniowe i siedzący tryb życia. W diecie Polaków istotną rolę zajmuje spożywanie kawy. Wyniki dużych badań i metaanaliz z ostatnich lat wskazują, że spożywanie 1–3 filiżanek filtrowanej kawy jest bezpieczne z punktu widzenia ryzyka wystąpienia zaburzeń lipidowych. Warto jednak podkreślić, że mówimy o kawie czarnej (espresso) bez dodatku cukru ani mleka. Warto też zaznaczyć, że nawyki żywieniowe ostatnich lat zmieniają się, z trendem picia większej średniej liczby kaw dziennie, nawet 3–5/dobę, co może się wiązać z niewielkim wzrostem stężenia cholesterolu, ale nadal bez znaczenia klinicznego, szczególnie dla pacjentów obarczonych niskim i umiarkowanym ryzykiem sercowo-naczyniowym.

Rozważając wpływ kawy na profil lipidowy warto kierować się zatem kilkoma zasadami:

- wpływ długotrwałego spożywania kawy, średniej liczby filiżanek/dobę charakterystycznej dla Polski, nie wydaje się istotny klinicznie;
- mimo że prawie 20 milionów Polaków cierpi na zaburzenia lipidowe, ich leczenie prawidłowe nie powinno w żaden sposób interferować z przyzwyczajeniem picia kawy w liczbie 1–3 filiżanek dziennie;
- dla wąskiej grupy osób z niekontrolowanymi, wysokimi wartościami lipidów, można by zalecić preferowanie kawy filtrowanej, pozbawionej kahweolu i kafestolu, optymalnie czystego gatunku arabika;
- powszechnie stosowanie tej zasady jest jednak wątpliwe z uwagi na potencjalne korzyści z plejotropowego działania kahweolu i kafestolu zawartego w kawie na inne działania fizjologiczne poza wpływem na profil lipidowy.

Konflikt interesów

Nie zgłoszono.

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Adult with uncorrected Tetralogy of Fallot, anomalous coronary artery origin, left ventricular non-compaction, atrial septal defect and recurrent right ventricular outflow tract stenosis

Dorosła z Tetralogią Fallota, anomalią odejścia tętnicy wieńcowej, niescaleniem lewej komory, ubytkiem w przegrodzie międzyprzedsionkowej i nawracającym zwężeniem w drodze odpływu prawej komory

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Abstract

Advances in therapeutical possibilities for patients with complex congenital heart defects are unquestionable. Nonetheless, it is still probable to encounter unique challenges.

The study presents a case of a symptomatic 25-year-old female patient with uncorrected Tetralogy of Fallot who has never been qualified for surgery due to an unusual constellation of cardiac congenital comorbidities: anomalous coronary artery origin and non-compaction of the left ventricle.

Key words: Tetralogy of Fallot, anomalous coronary artery origin, non-compaction, uncorrected

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Introduction

Tetralogy of Fallot (ToF) is the most common complex cyanotic congenital heart defect observed in humans [1]. It contains ventricular septal defect (VSD), pulmonary stenosis, overriding aorta and right ventricular (RV) hypertrophy. Typically, it is diagnosed prenatally or soon after birth due to the quick presentation of desaturation and cyanosis. Proper diagnosis is usually followed by anatomical correction — the open-heart cardiac surgery as the natural history is linked with a bad prognosis. Untreated ToF results in progressive hypertrophy of the RV, increasing desaturation due to right-to-left shunt through the VSD and development of congestive heart failure (HF) [2].

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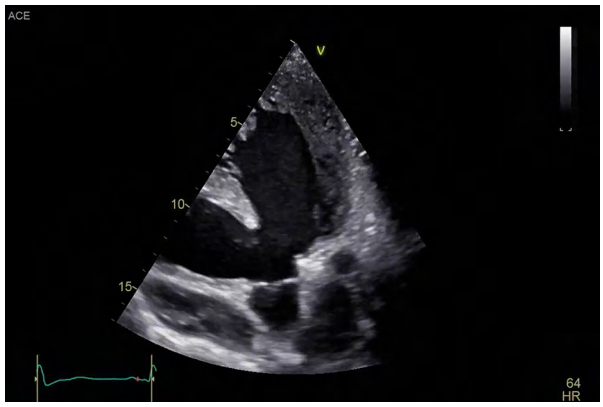

Figure 1. Modified apical view — visible features of Tetralogy of Fallot: large ventricular septal defect with the overriding aorta and visible features of left ventricle non-compaction

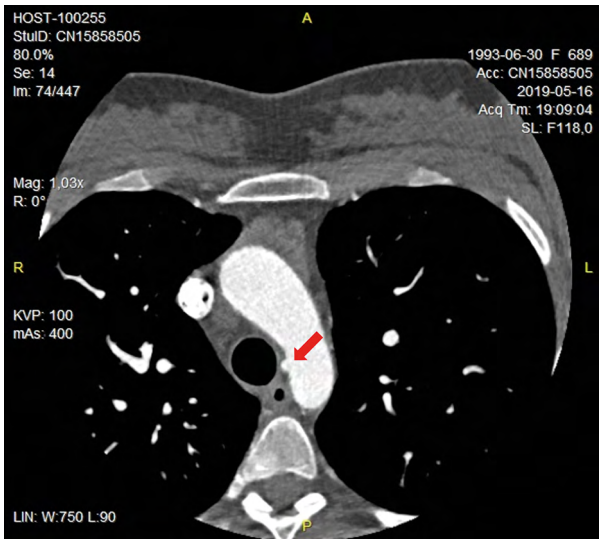

Figure 2. Computed tomography angiography scan — the visible anomalous origin of a single coronary artery in the aortic arch (red arrow)

Case report

The 25-year-old female patient with uncorrected ToF with a history of serial pulmonary balloon valvuloplasties providing temporary reduction of the RV overload was admitted to the study department due to exacerbation of the right-sided HF — up to New York Heart Association (NYHA) III class, central cyanosis and irregular heartbeat. According to previous data anomalous single coronary artery origin and non-compaction of the left ventricle (LV) were the main contraindications for repair surgery in extracorporeal circulation in early life. At the time of admission, the patient was cyanotic, with maximum oxygen saturation ($SatO_2$) of 86% at rest while breathing room air, with blood pressure of 110/60 mm Hg and heart rate of 60 bpm. A loud systolic murmur was heard over the pulmonary valve and Erb's point.

During the 6-minute walk test (6MWT) the patient reached a distance of 500.5 m but with ongoing dyspnoea and severe desaturation ($SatO_2$ 74%). Lab tests revealed an increase of plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level — 2320 pg/mL. In Holter-ECG monitoring ventricular multifocal arrhythmia with several episodes of non-sustained ventricular tachycardia were observed. Echocardiographic examination revealed enlarged and hypertrophic LV with prominent features of non-compaction with preserved systolic function with LV ejection fraction (EF) of 65% and reduced global longitudinal strain (GLS: –15.7%), normal parameters reflecting RV function: tricuspid annular plane systolic excursion 28 mm, peak systolic tricuspid annular velocity (RV S') 11 cm/s, hypertrophic perpendicular RV with narrowed outflow tract, significant complex pathology of pulmonary valve (PV) after 3 balloon valvuloplasties (last one in 2015) — recurrent high grade stenosis with mild pulmonary regurgitation (PV max velocity: 5.38 m/s, peak gradient: 116 mm Hg, mean gradient 57 mm Hg, PHT [pressure half-time] 200 ms), mild tricuspid regurgitation, non-collapsible inferior vena cava (estimated RV systolic pressure 40 mm Hg), overriding aorta without significant pressure gradients, large ventricular septal defect (26 mm) with bidirectional flow, small atrial septal defect, small additional vessel of unknown origin between aortic arch and pulmonary trunk (Figure 1).

Further therapeutic decisions were postponed after the completion of the scheduled multimodality approach. The hybrid-computed tomography angiography and magnetic resonance imaging (angio-CT/MRI) scans of the heart, great vessels and coronary arteries were obtained. MRI revealed disproportion of pulmonary and aortic inflow volume (168 and 57 mL respectively), severe subvalvular pulmonary stenosis with increased velocity (480 cm/s), hypoplastic RV with reduced function (EF 41%, SV 28 mL) and enlarged left chamber and atrium with preserved EF (EF 64%, SV 207 mL). Angio-CT scan revealed VSD with the size of 37 × 34 mm, tri-commissural bicuspid pulmonary valve, dilated pulmonary trunk (38 × 33 mm), proximally stenotic left pulmonary artery (diameters: 14 × 10 mm) with post-stenotic dilation (diameters: 36 × 32 mm), dilated right pulmonary artery (36 × 30 mm), optimal dimensions of ascending aorta, small patent ductus arteriosus with a pinpoint lumen. What is more, a single coronary vessel (diam. 3.0–3.5 mm) with the origin on the right side of the aortic arch was found (Figure 2).In its proximal section, it was laying between the curvature of the aortic arch and the superior wall of the left pulmonary artery (at this level 70% area reduction was observed due to compression by great vessels). In the distal part, it was coming between the pulmonary trunk and ascending aorta

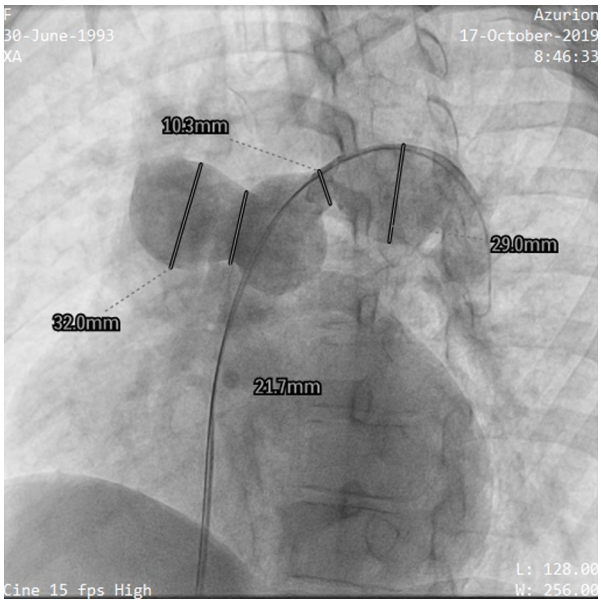

Figure 3. Cardiac angiography — visible pulmonary artery bifurcation with visible left branch artery stenosis

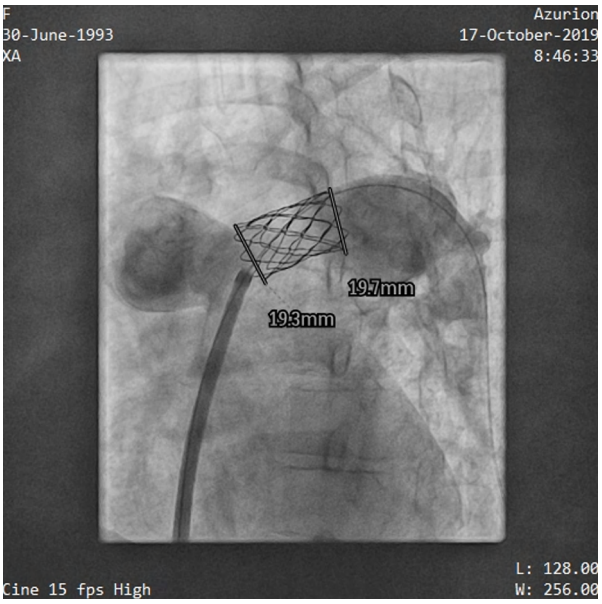

Figure 4. Cardiac angiography — visible stent in left pulmonary branch artery after successful pulmonary balloon angioplasty

without compression reaching the anterior interventricular groove. In its later part, it was expanding into a wide vascular sinus (10 × 5 mm) connected with the lumen of the RV and heading towards the apex, splitting in the end into 3 vessels supplying the RV myocardium and the apical segments of the LV. The heart catheterization procedure was scheduled and performed with general anaesthesia. The examination revealed left pulmonary branch artery stenosis and supravalvular stenosis of the pulmonary valve. After additional heart team assessment, the left pulmonary branch artery angioplasty procedure was performed with simultaneous CP 34 mm stent implantation with a good final result (Figure 3 and 4). During the periprocedural period, the patient reported a short episode of chest pain, but no troponin elevation, nor electrocardiographic changes were observed.

The echocardiography was performed just after the procedure revealed an immediate reduction of pressure gradients in the RV outflow tract (PV max velocity: 4.14 m/s, peak gradient 68 mm Hg, mean gradient 43 mm Hg). The plasma level of NT-proBNP dropped to 1102 pg/mL. At discharge, the patient's symptoms were of II NYHA class. However, the second Holter-ECG performed a few days after the catheterization revealed an increased number of premature ventricular beats (from 1198/day up to 9198/ /day). It could be due to the left pulmonary artery stent and anomalous coronary artery proximity, but no further ischemic symptoms were observed. Nonetheless, another heart catheterization was scheduled in 6 months to prepare the patient for a plausible heart transplant as future exacerbation of HF was inevitable. However, after a few months of follow-up, the patient was still in II NYHA class, feeling much better than before the described procedure.

Discussion

Patients with uncorrected complex congenital heart defects who reach adulthood are out of any guidelines as they are not common due to unfavourable natural history [3, 4]. What is more, most of the survivors do not belong to any homogenous group. Each case is a genuine challenge for physicians and the healthcare system as usually a late correction is not a viable option. When such a patient is encountered, it is necessary to perform a full examination to determine the patient's condition. If any instability is observed, all accessible diagnostic modalities must be taken into consideration as any deterioration may be reversible if the direct cause is detected and treated properly. For the presented patient, the culprit was pulmonary branch artery stenosis affecting the haemodynamics between the ventricles, which was depicted as significant only after a combination of myocardial CT/MRI scan and cardiac angiography.

Pulmonary branch artery stenosis is a common finding in patients with congenital heart defects [5]. It may be diagnosed as a congenital comorbidity but also as an acquired disease complicating the initial therapeutic approach. It is a life-threatening condition leading to cardiopulmonary ventilation/perfusion mismatch and increased overload of the pulmonary circulation and RV predisposing to congestive HF [6]. Narrowing of the pulmonary branch artery may also alter existing shunts — in the case of VSD, the flow is prone

to be bidirectional or right-to-left, especially during exercise. Proper management requires optimal visualisation of the stenotic vessel and surrounding structures to choose adequate and safe interventional therapy. The method of choice is balloon angioplasty of the stenotic pulmonary branch artery with simultaneous implantation of stent selected in advance [7]. The outcome is usually good as ventilation/perfusion mismatch is reduced although restenoses may be observed during long-term follow-up thus such patients should be considered candidates for life-long specialistic grown-up congenital heart care [8].

On the other hand, patients unfit for full correction of the defect may also develop severe HF without any curable causes. Optimal management is based on life-long care and regular check-ups providing continuous observation of the severity of the symptoms. Patients in the II NYHA class and those without any significant ventricular tachyarrhythmias may persist in such an approach. However, any unexplained deterioration or new dangerous arrhythmias may be the landmark for considering intracardiac devices and heart transplantation qualification [9]. Cardiac transplantation in patients with congenital heart defects is associated with higher risk than in the general population, but eligible candidates may benefit from longer life with preserved quality [10]. It is a great challenge to determine the perfect moment for such intervention, especially without typical criteria of ventricular insufficiency and with altered morphology of the native heart.

Conclusion

Patients with complex uncorrected congenital defects who develop progressive symptoms of HF require a full multi-modality approach as repairable structural lesions such as pulmonary arteries stenoses may be the culprits. Even patients with such anatomical cardiac odds as presented may be responders for specific interventions. Lifelong care in specialistic grown-up congenital heart centres should be provided to every patient with uncorrected defects. Proper monitoring at follow-up and cooperation with the patients being aware of their condition are key factors in terms of upcoming diagnostic and therapeutic decisions.

Conflict of interest

None declared.

Streszczenie

Postępy w możliwościach terapeutycznych dla pacjentów ze złożonymi wrodzonymi wadami serca są nie do zakwestionowania. Jednakże wciąż istnieje prawdopodobieństwo napotkania wyjątkowych wyzwań. W niniejszej pracy zaprezentowano przypadek objawowej 25-letniej pacjentki z nieskorygowaną Tetralogią Fallota, która nigdy nie była zakwalifikowana do operacji z powodu unikatowej konstelacji wrodzonych schorzeń serca: anomalii odejścia tętnicy wieńcowej i kardiomiopatii z niescalenia lewej komory.

Słowa kluczowe: Tetralogia Fallota, anomalia odejścia tętnicy wieńcowej, niescalenie, nieskorygowana

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Complications of pacemaker replacement: a case report of female patient with the upper extremity deep vein thrombosis

Powikłania wymiany stymulatora serca — opis przypadku pacjentki z zakrzepicą żył głębokich kończyny górnej

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Abstract

Deep venous thrombosis of the upper extremity (UEDVT) after pacemaker implantation (PM) is often an underestimated problem, but should be considered as a potential complication, because the number of implanting PM is increasing every year. This case report presents a history of a 57-years old woman with a pacemaker implanted in 1996 due to the 3rd-degree atrioventricular block. The patient was admitted to the hospital for the replacement of the stimulating system. The procedure was complicated by hemorrhage from the pocket of the device and in the postoperative period — the left upper extremity deep vein thrombosis.

Key words: deep venous thrombosis of the upper extremity, pacemaker implantation, leads extraction, complications, compression-ultrasonography

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Introduction

Upper extremity deep vein thrombosis (UEDVT) is defined as thrombosis of either subclavian, axillary and/or brachial vein [1]. The etiology can be subdivided into primary, in which the cause would be either idiopathic or due to anatomical variation such as in the thoracic-outlet syndrome; and secondary, i.e., due to central venous catheters and cardiac pacemaker implantation [2]. The thrombus is most frequently located in the left subclavian vein in its proximal portion, due to the route used for transvenous lead placement [3]. The presence of multiple leads poses a higher risk of venous thrombosis than a singular lead [4]. In the last few decades, the incidence of UEDVT has steadily increased, just in 2018, it accounted for 2–3% of cases with DVT [5] while in 2021 for 6% [6].

Case report

A 57-years old woman with a pacemaker (PM) implanted in 1996 due to 3rd-degree atrioventricular block, was admitted to the hospital for replacement of the stimulating system. About the patient's medical history, she had myocarditis in childhood and nowadays is suffering from paroxysmal

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supraventricular tachycardia which is treated with sotalol. On admission, the patient was hemodynamic stable and had no major complaints. In electrocardiogram there was effective atrial and ventricular stimulation with a ventricular response rate of 75/min. Laboratory tests revealed an increased serum concentration of N-terminal pro-brain natriuretic peptide (226 pg/mL), while other parameters were within their respective reference ranges. A transthoracic echocardiography demonstrated a normal left ventricle size with a good global contraction and ejection fraction of around 60%, a normal left ventricle diastolic function, and small mitral and tricuspid regurgitation.

The replacement of PM was complicated by the hemorrhage from the PM-pocket. Due to the use of a large-diameter mechanical electrode release system, significant local bleeding was observed both during electrode release and after the removal of the system. The patient lost 1000 mL of blood and the presence of fluid in the pericardium was observed (without the impending cardiac tamponade). The patient received intensive fluid therapy, 1 unit of erythrocyte concentrate, and noradrenaline *via* continuous *i.v.* infusion. In the following days, the patient remained stable and the control echocardiographies revealed no expansion of fluid in the pericardium. Prior to the procedure, she was neither taking anticoagulation nor antiplatelet medication.

On the second day after the procedure, the woman started to complain about pain, cyanosis and edema of her upper left limb. On closer examination, there was no palpable pulse detected on the left upper limb, but the warmth was preserved. The performed doppler ultrasonography revealed thrombosis of the left internal jugular, subclavian and axillary vein, as well occlusion of the left radial artery and a residual thrombus in the proximal part of the right internal jugular vein.

Anticoagulation treatment was initiated with rivaroxaban yielding clinical improvement. Taking the occlusion of the left radial artery into consideration, compression therapy of the left arm was not recommended, instead, the patient's left upper limb was solely kept elevated. According to the vascular-surgical consultation that case posed no indication for invasive treatment of thrombosis and suggested continuation of the conservative management.

Discussion

The pathogenesis of venous obstruction is related to the presence of a foreign body, i.e., the pacemaker leads in the blood vessel which injures endothelium causing disturbance in laminar blood flow and therefore activates factors involved in the Virchow's triad and subsequent thrombosis and/or fibrosis [3]. The risk factors of UEDVT consist of age over 40 years old, prior episodes of venous thromboembolism, cancer, family history of venous thromboembolism, New York Heart Association III or IV heart failure, arrhythmia, venous anomalies, tobacco smoking and use of oral contraception or hormone replacement therapy [7]. The most frequent cause is the catheterization of the central vein for constant drug administration, parenteral nutrition or inserting leads for PM [8].

The UEDVT develops from several days to years after implantation of the device [8]. In the described case, several factors probably contributed to the development of thrombosis in a relatively short time after pacemaker implantation (after 2 days). Our patient is 57 years old, had no previous anticoagulation treatment, and has a negative family history of hemostatic disorders.

The clinical presentation of the UEDVT typically includes pain, heaviness, edema, cyanosis, and perhaps visible collateral veins of the upper limb or it can be asymptomatic.

Compression-/colorduplexsonography (CUS) is the key method of confirming vein thrombosis and the measurement of plasma D-dimer levels is performed to exclude it. For hospitalized patients it is necessary to perform CUS due to the low specificity and predictive value of positive D-dimer test results [7].

Regarding the treatment, one can either follow the conservative path and initiate anticoagulation with low molecular weight heparin (unfractionated heparin in chronic kidney disease) for 5 days and then maintenance therapy with either vitamin K antagonist or dabigatran as well as directly without bridging rivaroxaban or apixaban for at least 3 months and according to indication perhaps longer. In cases of intense symptoms and time since onset is shorter than 10 days, invasive methods are indicated such as catheter-directed thrombolysis or percutaneous/surgical thrombectomy [9].

According to the literature, 6% of UEDVT cases are complicated by pulmonary embolism, 5% will develop post-thrombotic syndrome, and 9% report recurrency (18% of cases are coexistent with tumors) [9].

Conclusions

Taking into consideration the progressively increasing number of pacemaker implantations and PM-related incidence of UEDVT, it is of high importance to remember this potential complication with its signs and symptoms in the postoperative period. Especially because of its simplicity to diagnose and therefore immediate initiation of treatment, the awareness of the patient of possible symptoms is very crucial and may accelerate the process.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Zakrzepica żył głębokich kończyny górnej po implantacji stymulatora serca jest często bagatelizowanym problemem, chociaż powinna być brana pod uwagę jako potencjalne powikłanie zabiegu w związku z rosnącą liczbą implantowanych stymulatorów serca każdego roku. W niniejszym tekście opisano przypadek 57-letniej pacjentki po wszczepieniu stymulatora serca z powodu bloku przedsionkowo-komorowego 3. stopnia w 1996 roku, która została przyjęta do szpitala w celu wymiany urządzenia. Zabieg był powikłany krwawieniem z loży stymulatora oraz masywną zakrzepicą żył głębokich kończyny górnej lewej w okresie pozabiegowym.

Słowa kluczowe: głęboka zakrzepica kończyny górnej, implantacja stymulatora, usunięcie elektrod, komplikacje, uciskowa ultrasonografia

Folia Cardiologica 2023; 18, 1: 42–44

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CASE REPORT

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The sky is the limit to the number of stents

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Abstract

We present the case of a 65-year-old man with type 2 diabetes mellitus, arterial hypertension, hypercholesterolemia, salicylate allergy and diagnosed with ischemic heart disease since 2000. The patient, despite intensive pharmacotherapy according to European Society of Cardiology guidelines and the insertion of as many as 11 stents into the coronary arteries, had persistent recurrent acute coronary syndromes, including 4 myocardial infarctions (twice ST-elevation myocardial infarction, twice non-ST-elevation myocardial infarction) between 2000 and 2021. Eventually, the patient underwent left coronary artery bypass surgery. Some potential options for the pharmacological treatment of recurrent acute coronary syndromes are presented in the discussion.

Key words: acute coronary syndrome, percutaneous coronary intervention, salicylate allergy, pharmacotherapy

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Introduction

According to the Institute for Health Metrics and Evaluation (2019), coronary artery disease (CAD) has been the leading cause of death in Poland for many years [1]. These data indicate that the prevalence rate of CAD in 2019 was 4.8% (1.5 million patients) for the Polish population [2]. The death rate of patients with acute coronary syndrome (ACS) has been on a downward trend in recent years. According to a report published in 2020 by the National Health Fund, the death rate was decreasing in ACS patients from 2014 to 2018 (Figure 1) [3].

The occurrence of recurrent incidents of ACS in individual patients despite intensive pharmacotherapy in accordance with current European Society for Cardiology guidelines and interventional therapy involving implantation of antimitotic drug-eluting stents is a cause for concern. In 2010, a case of a patient who had as many as 67 stents inserted into his coronary arteries [4], which is a record number in the history of cardiology, was described. This article presents the case of a patient who required the implantation of as many as 11 stents over the 21-year course of CAD.

Case study

A 65-year-old male patient with type 2 diabetes, hypertension, hypercholesterolaemia, salicylate allergy and with a diagnosis of CAD since 2000 was admitted to Outpatient Cardiac Rehabilitation Center (OCRC) for rehabilitation treatment following arterial bypass grafting of the left anterior descending branch of the left coronary artery after previous multiple percutaneous coronary interventions. From 2000 to 2021, he had 4 myocardial infarctions (STEMI [ST-elevation myocardial infarction] — twice; NSTEMI [non-ST-elevation myocardial infarction] — twice), treated with percutaneous coronary interventions. The areas of coronary artery stenoses requiring both primary angioplasty and elective angioplasty are shown in Figure 2.

Echocardiography prior to the rehabilitation programme revealed segmental dysfunction of the left ventricle

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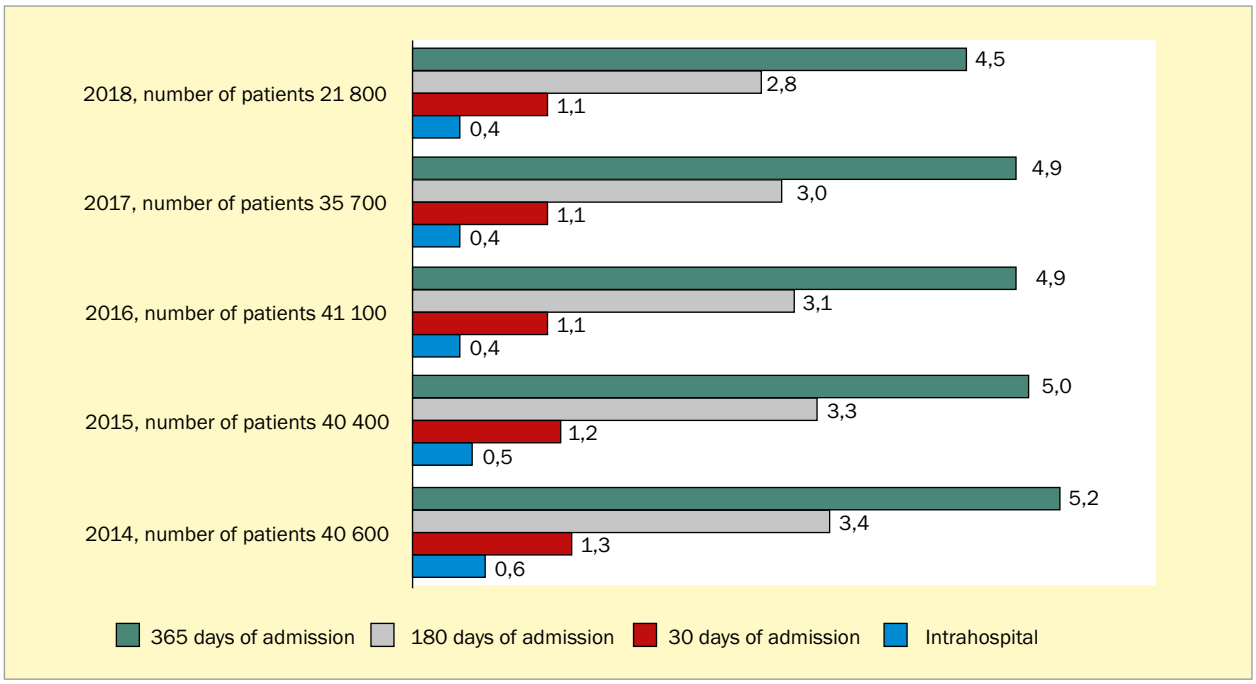

Figure 1. Mortality due to acute coronary syndromes for patients with no previous hospitalization caused by acute coronary syndrome in the years 2014–2018. Data provided by National Heath Fund in 2020

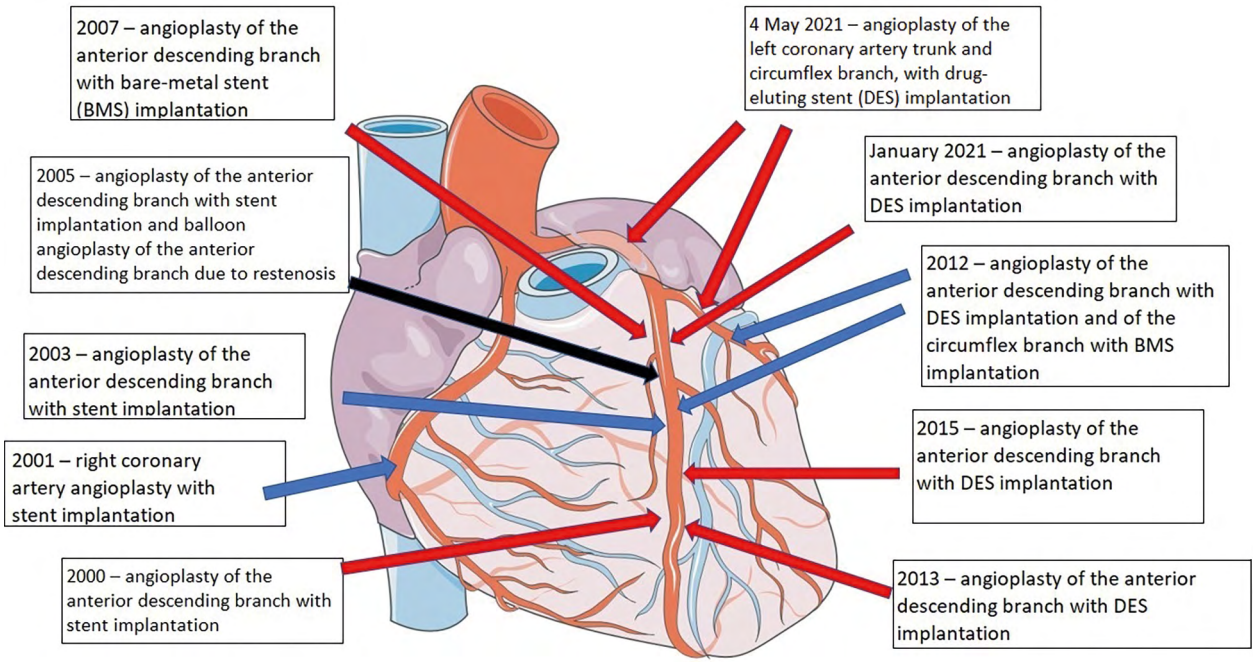

Figure 2. Location of critical narrowing in coronary arteries together with the date of the procedure. Red arrows show primary percutaneous coronary intervention (PCI), blue arrows — show elective PCI, and black arrows — PCI for in-stent restenosis

contractility with a significantly reduced ejection fraction of up to 20%. Pharmacotherapy included the following drugs (daily doses given): clopidogrel 75 mg, bisoprolol 5 mg, torasemide 5 mg, ramipril 5 mg, eplerenone 25 mg, atorvastatin 80 mg. There was also a proposal to include flozin and replace ramipril with sacubitril/valsartan; however, the

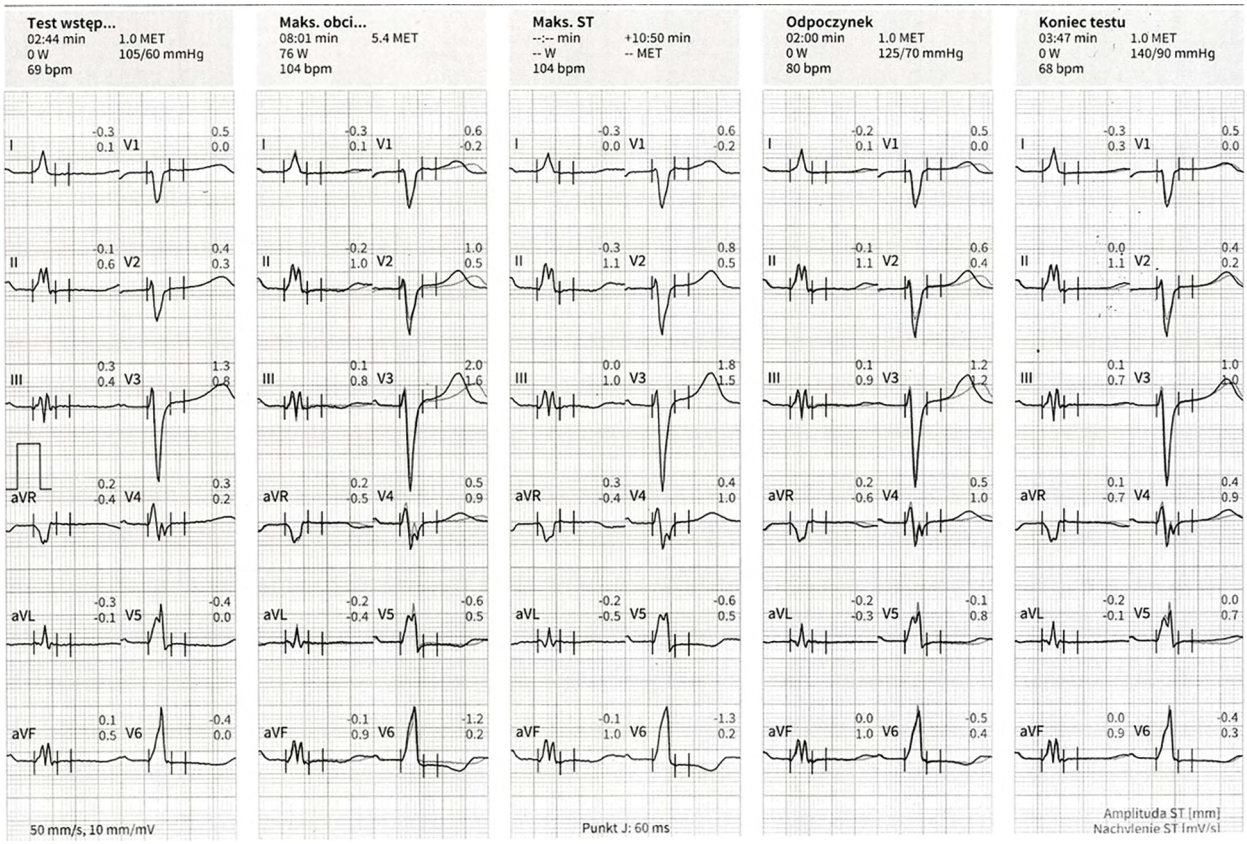

Figure 3. Electrocardiogram changes induced by physical effort were observed during stress test performed after the rehabilitation programme — the 1.3 mm isolated ST-segment depression was observed at the peak of the exercise

patient did not accept this option. The patient was made aware of the possibility of primary prevention of sudden cardiac death; however, at the time of discharge from the centre, he did not opt for the option of preventing the consequences of dangerous ventricular arrhythmias by implanting a cardioverter-defibrillator. Due to the period of SARS-CoV-2 epidemic risk, the rehabilitation programme was in the form of telerehabilitation — the patient received 18 sessions of 20–30 minutes, consisting of walking training with remote monitoring of electrocardiogram signals, body weight and blood pressure. The initial and final cardiac diagnostic tests were performed according to the Naughton protocol — their durations were 07'03" and 08'01", respectively, and the exercise load in both cases was 4.5 metabolic equivalent, which was 51% of the load by sex and age. ST-segment changes at peak exercise are shown in Figure 3.

Discussion

The leading problem of the patient in question was recurrent incidents of ACS. Inflammation plays a major role in their atherosclerotic pathogenesis. In terms of the drugs used, statins have anti-inflammatory potential — as shown in Figure 4, the patient did not achieve treatment goals with this group of drugs during the initial treatment period. Recent studies have shown that anti-inflammatory drugs such as colchicine or canakinumab (not previously used in the treatment of CAD) are highly effective in the prevention of recurrent ACS. The description of the COLCOT clinical trial, published in 2020, reveals that recent (up to 30 days) post-myocardial infarction patients who took colchicine at a dose of 0.5 mg per day had a significantly reduced rate of myocardial ischemia incidents [6]. A trial with the acronym CANTOS used canakinumab in post-myocardial infarction patients, as well as a monoclonal antibody that specifically binds interleukin 1 beta (IL-1β), and a cytokine that promotes the progression of atherosclerosis [7]. Patients who received standard treatment and canakinumab at a subcantenous dose of 150 mg per quarter had a lower incidence rate — by 15% — of ACS or stroke compared to those who received standard treatment and placebo. The patient in question participated at OCRC in a trial evaluating polymorphisms of the IL-1β gene and its natural receptor antagonist. The analysis of the patient's DNA revealed that he had a rare combination of variants at *loci* –31 and –511

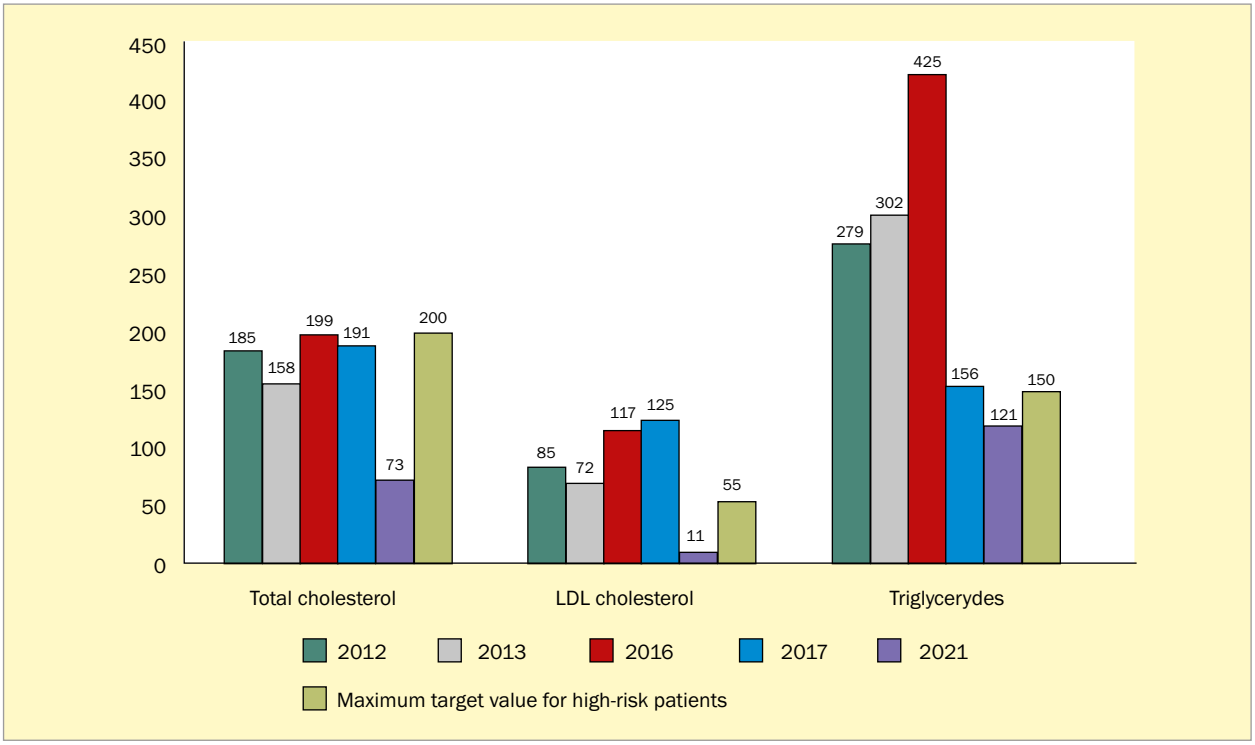

Figure 4. The comparison of lipidogram results in 2012, 2013, 2016, 2017 and 2021. The target value for low-density lipoprotein cholesterol according to ESC/EAS Guidelines for management in dyslipidemias published in 2019 is shown in green [5]

in the IL-1 gene and a tandem repeat polymorphism variant in the natural IL-1 antagonist gene — (–31TT, –511CC, IL-RN 12). However, these characteristics were not associated with an increased incidence rate of coronary incidents in the group studied at OCRC [8]. The latest pharmacotherapy that improves prognosis in high-risk patients also includes the combination of low-dose rivaroxaban (2 times 2.5 mg/ /day) and low-dose acetylsalicylic acid (ASA) (100 mg/day) used in the COMPASS trial. When comparing dual therapy (rivaroxaban + ASA) with ASA monotherapy, the risk of stroke or myocardial infarction was significantly reduced in this study group [9]. Due to salicylate allergy, the use of a treatment regimen as in COMPASS would not have been possible in this patient, and there is no sufficiently reliable experience of therapy combining clopidogrel and rivaroxaban to date.

Conclusions

In the patient in question, the use of conventional pharmacotherapy and interventions in the prevention of ACS was not fully effective. The possibility of future use of anti-inflammatory drugs or dual therapy with rivaroxaban to prevent further cardiovascular events opens up the possibility of more effective treatment for patients with similarly severe CAD.

Conflict of interest

None declared.

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Do ilu stentów sztuka?

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DOI: 10.5603/FC.a2022.0064. Należy cytować wersję pierwotną

Streszczenie

Przedstawiono przypadek 65-letniego mężczyzny chorego na cukrzycę typu 2, z nadciśnieniem tętniczym, hipercholesterolemią, uczuleniem na salicylany i ze zdiagnozowaną od 2000 roku chorobą niedokrwienną serca. U pacjenta pomimo zastosowania intensywnej farmakoterapii zgodnej z wytycznymi Europejskiego Towarzystwa Kardiologicznego i implantacji do tętnic wieńcowych 11 stentów, w latach 2000–2021 występowały nawracające ostre zespoły wieńcowe, w tym czterokrotne zawały serca (dwukrotnie STEMI, dwukrotnie NSTEMI). Ostatecznie u pacjenta wszczepiono pomost tętniczy do lewej tętnicy wieńcowej. W dyskusji przedstawiono potencjalne opcje farmakoterapii nawracających zaostrzeń choroby wieńcowej.

Słowa kluczowe: ostry zespół wieńcowy, przezskórna interwencja wieńcowa, uczulenie na salicylany, farmakoterapia

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Wstęp

Choroba niedokrwienna serca (CAD, *coronary artery disease*) jest od wielu lat, według *The Institute for Health Metrics and Evaluation* z 2019 roku główną przyczyną zgonów w Polsce [1]. Dane te wskazują, że współczynnik chorobowości na przewlekłą chorobę niedokrwienną serca w 2019 roku wynosił dla populacji polskiej 4,8% (1,5 mln osób) [2]. Śmiertelność pacjentów z ostrym zespołem wieńcowym (OZW) ma w ostatnich latach tendencję spadkową. Zgodnie z raportem opublikowanym w 2020 roku przez Narodowy Fundusz Zdrowia malała ona u pacjentów z OZW w latach 2014–2018 (ryc. 1) [3].

Niepokojącym zjawiskiem jest występowanie u poszczególnych chorych nawracających incydentów OZW, pomimo stosowania intensywnej farmakoterapii zgodnej z obowiązującymi wytycznymi ESC oraz terapii interwencyjnej polegającej na implantacji stentów uwalniających leki antymitotyczne. W 2010 roku opisano przypadek pacjenta, któremu wprowadzono do tętnic wieńcowych aż 67 stentów [4], co jest rekordową liczbą w historii kardiologii. W niniejszym artykule zaprezentowano przypadek chorego, który w ciągu 21 lat przebiegu swojej choroby wieńcowej wymagał implantacji aż 11 stentów.

Opis przypadku

Pacjent, lat 65, chory na cukrzycę typu 2, z nadciśnieniem tętniczym, hipercholesterolemią, uczuleniem na salicylany i ze zdiagnozowaną od 2000 CAD został przyjęty do Ośrodka Dziennego Rehabilitacji Kardiologicznej w celu leczenia usprawniającego po wszczepieniu tętniczego pomostu gałęzi przedniej zstępującej lewej tętnicy wieńcowej po wcześniejszych wielokrotnych interwencjach przezskórnych na tętnicach wieńcowych. W latach 2000–2021 przebył 4 zawały serca [dwukrotnie STEMI (*ST-segment elevation myocardial infarction*), dwukrotnie NSTEMI (*non-ST-segment elevation myocardial infarction*)], leczone interwencją przezskórną. Lokalizację zwężeń tętnic wieńcowych wymagających zarówno pierwotnej angioplastyki, jak i angioplastyki w trybie planowym przedstawiono na rycinie 2.

W badaniu echokardiograficznym poprzedzającym program usprawniania stwierdzono odcinkowe zaburzenia kurczliwości lewej komory z krytycznie obniżoną do 20%

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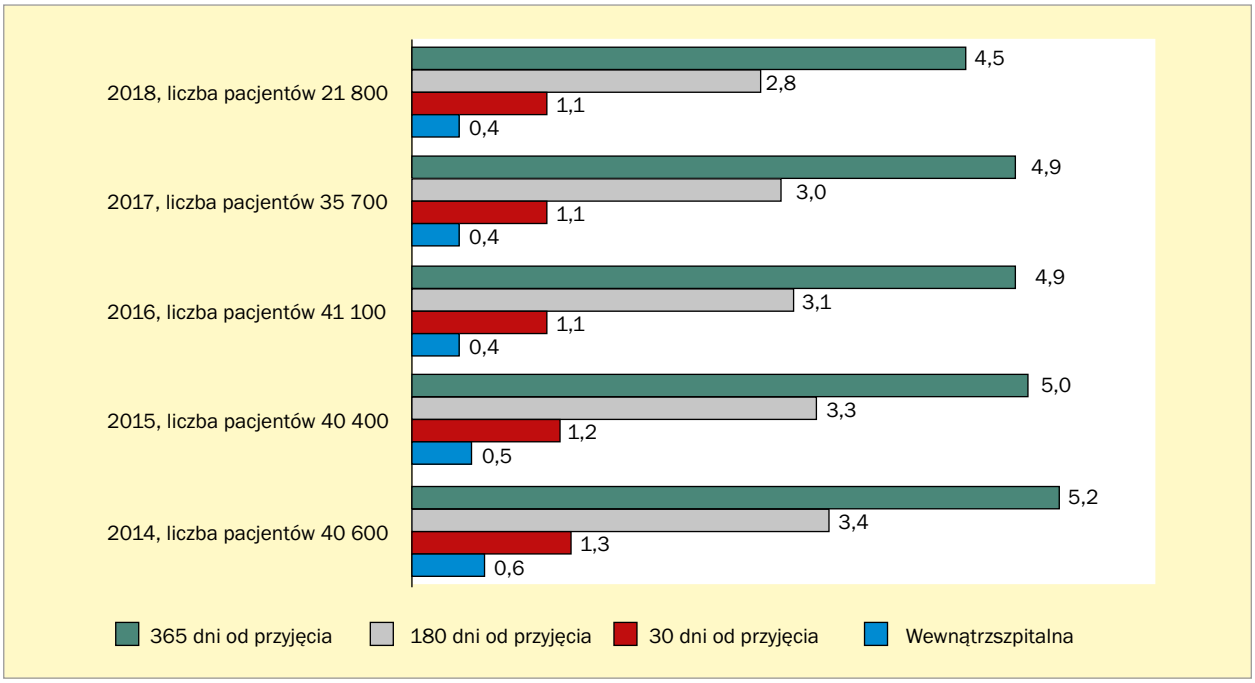
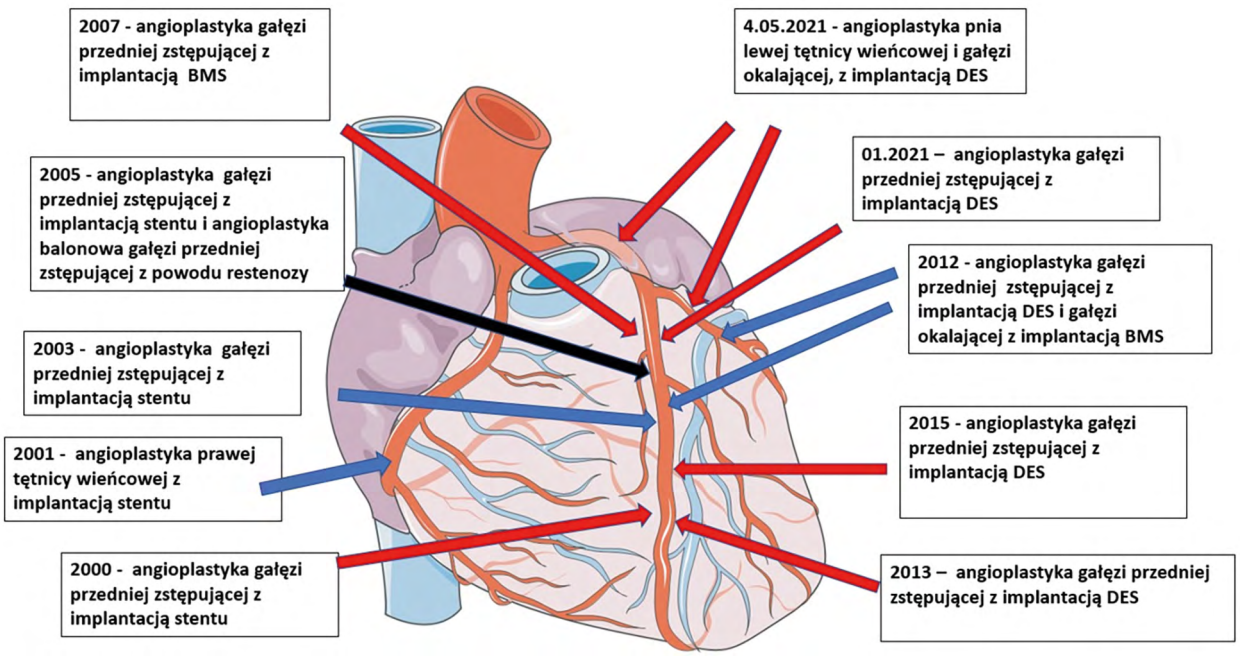
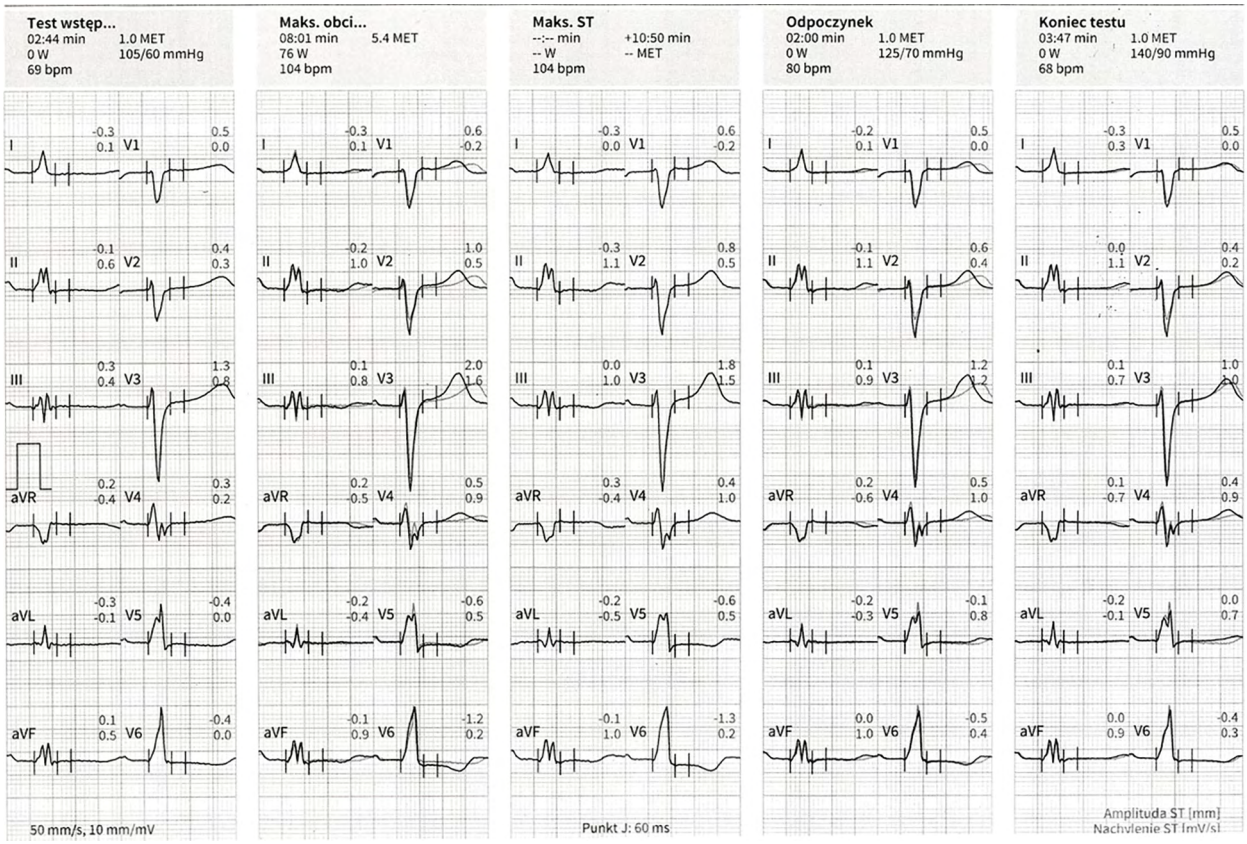


Rycina 1. Śmiertelność pacjentów z niestabilną dławicą piersiową, dla których nie odnotowano hospitalizacji z powodu ostrego zespołu wieńcowego w poprzednich trzech latach (2014–2018). Dane z raportu NFZ z 2020 roku



Rycina 2. Lokalizacja krytycznych zwężeń tętnic wieńcowych z datą zabiegu. Kolorem czerwonym zaznaczono pierwotne angioplastyki, kolorem niebieskim — angioplastyki wykonane elektywnie, a kolorem czarnym wyróżniono angioplastyki wieńcowe wykonane z powodu restenozy w stencie

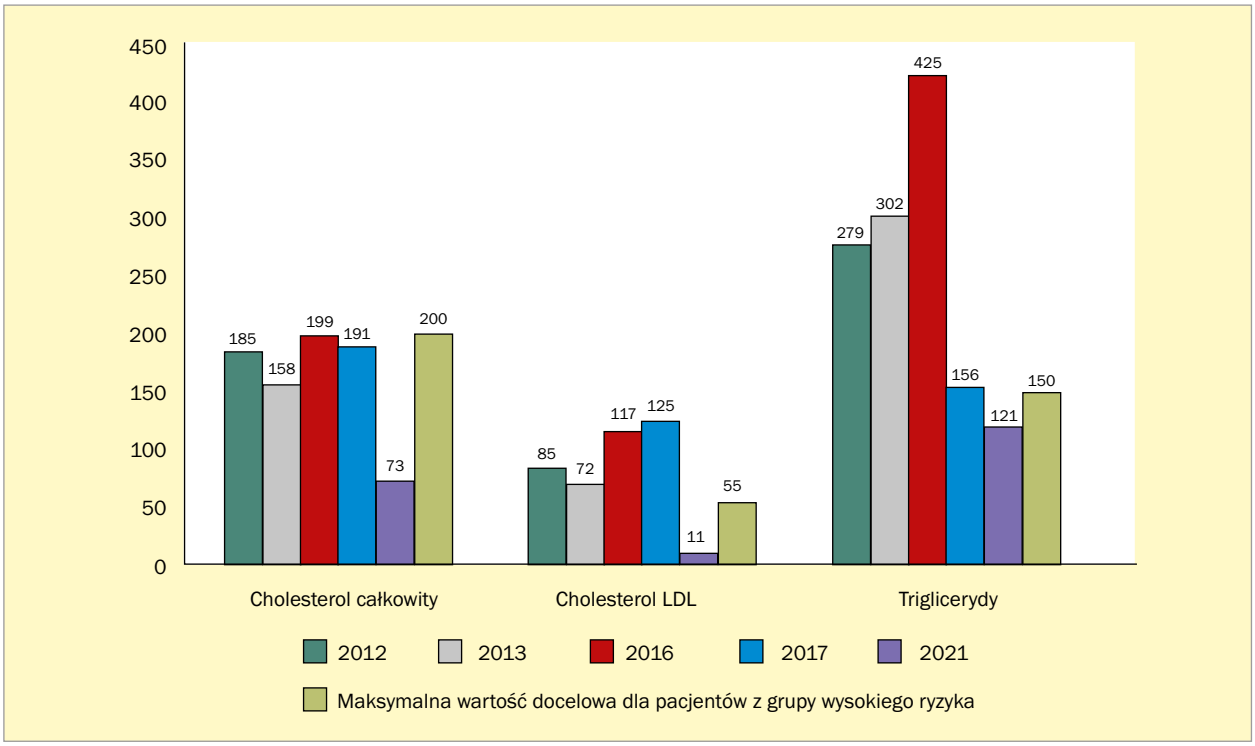


Rycina 3. Zmiany w elektrokardiogramie podczas próby wysiłkowej wykonanej po odbyciu programu rehabilitacji kardiologicznej przez opisywanego pacjenta — na szczycie wysiłku wyindukowano izolowane obniżenie odcinka ST o 1,3 mm w odprowadzeniu V6

frakcją wyrzutową. W leczeniu farmakologicznym stosowano następujące leki w dobowych dawkach: klopidogrel 75 mg, bisoprolol 5 mg, torasemid 5 mg, ramipryl 5 mg, eplerenon 25 mg, atorwastatyna 80 mg, zaproponowano także włączenie flozyny i zamianę ramiprylu na sakubitryl/ /walsartan, ale pacjent nie zaakceptował tej opcji. Poinformowano go o możliwości prewencji pierwotnej nagłego zgonu sercowego, lecz w momencie opuszczania ośrodka nie zdecydował się on na opcję zapobiegania skutkom groźnych arytmii komorowych poprzez wszczepienie kardiowertera-defibrylatora. Program usprawniania odbywał się, z uwagi na okres zagrożenia epidemicznego zakażeniem SARS-CoV-2, w formie telerehabilitacji — pacjent odbył 18 sesji trwających 20–30 minut, polegających na treningach marszowych ze zdalnym monitorowaniem EKG, masy ciała i ciśnienia tętniczego. Początkową i końcową próbę wysiłkową wykonano według protokołu Naughtona — ich czas trwania wynosił odpowiednio 07'03" i 08'01", a obciążenie wysiłkiem w obu przypadkach — 4,5 MET, co stanowiło 51% obciążenia należnego dla płci i wieku. Zmiany odcinka ST na szczycie wysiłku przedstawiono na rycinie 3.

Dyskusja

Wiodącym problemem opisanego chorego były nawracające incydenty OZW. W ich patogenezie na tle miażdżycowym dużą rolę odgrywa stan zapalny. Spośród zastosowanych leków potencjał przeciwzapalny mają statyny. Jak wynika z ryciny 4, pacjent w początkowym okresie leczenia nie uzyskiwał celów leczenia tą grupą leków. Wyniki badań ostatnich lat wskazują na dużą skuteczność leków przeciwzapalnych jak kolchicyna czy kanakinumab (niestosowanych wcześniej w leczeniu choroby wieńcowej) w prewencji nawrotów OZW. Z opublikowanego w 2020 roku opisu badania klinicznego *Colchicine Cardiovascular Outcomes Trial* (COLCOT) wynika, że u chorych po świeżo przebytym zawale serca (do 30 dni), którzy przyjmowali kolchicynę w dawce 0,5 mg na dobę znamiennie zmniejszył się odsetek incydentów niedokrwiennych miokardium [6]. W próbie o akronimie CANTOS u pacjentów po zawale serca zastosowano kanakinumab, przeciwciało monoklonalne wiążące swoiście interleukinę 1 beta (IL-1β) cytokinę promującą progresję miażdżycy [7]. U chorych, którym



Rycina 4. Porównanie wyników lipidogramu pacjenta w latach: 2012, 2013, 2016, 2017 oraz 2021. Wartość docelowa w leczeniu hipercholesterolemii (zaznaczona kolorem zielonym) zgodna z wytycznymi ESC/EAS dotyczącymi postępowania w dyslipidemiach z 2019 roku [5]

podawano standardowe leczenie i kanakinumab w dawce 150 mg podskórnie raz na kwartał częstość występowania OZW czy udaru była o 15% mniejsza niż u tych, u których zastosowano standardowe leczenie i placebo. Opisywany pacjent uczestniczył w naszym ośrodku w badaniu oceniającym polimorfizmy genu *IL-1β* i naturalnego antagonisty jej receptora. Z analizy jego DNA wynikało, iż pacjent posiadał rzadką (występującą u 4% badanej grupy) kombinację wariantów w *loci* –31 i –511 genu *IL-1β* oraz wariantu polimorfizmu wielokrotnych powtórzeń w genie naturalnego antagonisty IL-1 (–31TT, –511CC, IL-RN 12), jednak cechy te nie wiązały się w badanej w ośrodku autorów niniejszej pracy grupie ze zwiększona częstością ponownych incydentów wieńcowych [8]. Do najnowszej farmakoterapii poprawiającej rokowanie u pacjentów z grupy wysokiego ryzyka należy także zastosowane w badaniu COMPASS połączenie małych dawek rywaroksabanu (2 razy 2,5 mg dziennie) i kwasu acetylosalicylowego (100 mg/dobę). W porównaniu podwójnej terapii (rywaroksaban + kwas acetylosalicylowy) z monoterapią kwasem acetylosalicylowym ryzyko wystąpienia udaru mózgu czy zawału serca zostało w tej grupie badanych znamiennie zmniejszone [9]. Z uwagi na uczulenie na salicylany zastosowanie schematu leczenia jak w programie COMPASS nie byłoby możliwe u tego chorego. Nie ma dotychczas wystarczająco wiarygodnych doświadczeń w terapii łączącej klopidogrel z rywaroksabanem.

Wnioski

U opisanego pacjenta zastosowanie tradycyjnej farmakoterapii i zabiegów w prewencji OZW nie było w pełni skuteczne. Możliwość włączenia w przyszłości leków przeciwzapalnych czy terapii podwójnej z użyciem rywaroksabanu w celu zapobiegania kolejnym zdarzeniom sercowo-naczyniowym otwiera możliwość większej skuteczności leczenia chorych o podobnie ciężkim przebiegu choroby wieńcowej.

Konflikt interesów

Nie zgłoszono.

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A rare case of a double atrial septum in a 4-year-old boy with a large an ostium secundum atrial septal defect

Rzadki przypadek podwójnej przegrody międzyprzedsionkowej u 4-letniego chłopca z dużym ubytkiem przegrody międzyprzedsionkowej typu *ostium secundum*

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Abstract

The work presents a case of a 4-year-old boy diagnosed with a large atrial septal defect type ostium secundum (ASD2) and additional abnormal structures in the direction of the left atrium in the echocardiogram. The patient was qualified for interventional defect closure, however, in the transoesophageal echocardiography, in addition to a very large ASD2 (approx. 2 cm), a double interatrial septum was diagnosed. The extra wall layer was parallel to the atrial septum and did not obstruct blood flow from the pulmonary veins or through the mitral valve. No signs of clotting material were observed in the space between the two layers. The closure was withdrawn during cardiac catheterization and the boy was qualified for scheduled surgery. Currently, the boy is asymptomatic and leads a normal lifestyle.

Key words: double atrial septum, interatrial space, congenital heart disease

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Introduction

Double atrial septum (DAS) is a very rare congenital defect of the interatrial septum, where there is a free space in the atria between the native septum and the accessory septum located in the left or the right atrium (RA) [1]. As an etiology, Roberson [2] suggests that if the accessory membrane is in the left atrium (LA), it may be an abnormality of the atrial primum septum, while when the layer is on the right side, then it is formed by accessory structures.

According to van Praagh and Corsini [3] the accessory septal structure distinguishes this space from the RA, it is presumed it might be a persistent left ventricular valve attached to the sinus venosus in the fetal period.

Taking into consideration the fact that the double septum may be secondary to an intramural hematoma, that may delaminate the interatrial septum. The extra layer of DAS must be distinguished from the cor triatriatum, where the supplemental membrane runs parallel to the mitral annulus (cor triatriatum sinistrum) or parallel to the tricuspid

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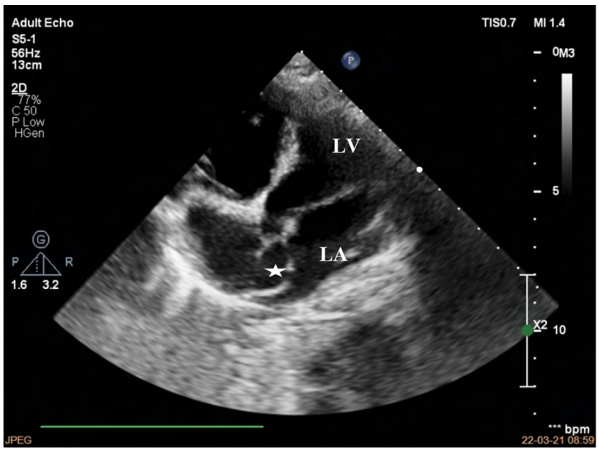

Figure 1. Echocardiography, 4-chamber view. In the LA additional septum. Free space and no thrombus between 2 layers (asterisk); LA — left atrium; LV — left ventricle

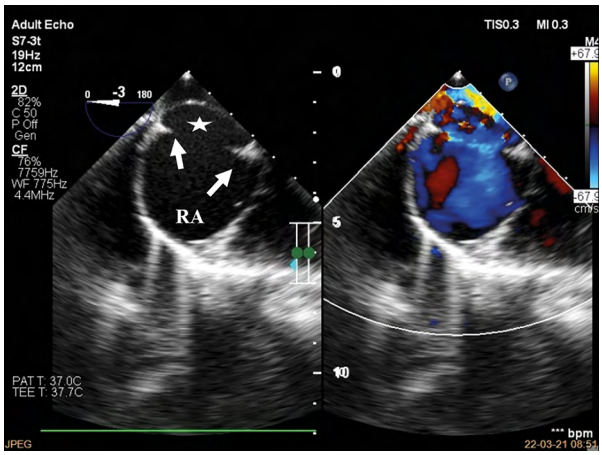

Figure 2. Transoesophageal echocardiography. Large intra-atrial defect (2 cm) of the ostium secundum type (arrows). Enlarged right atrium (RA). In the left atrium additional septum and free space. No thrombus between 2 layers (asterisk). In the color Doppler, undisturbed blood flow between the atria

annulus (cor triatriatum dextrum). What is vital, in DAS the mitral valve connects freely with the pulmonary veins, unlike the triatrial heart [4].

In children DAS is usually asymptomatic and, similarly to adults, it is diagnosed incidentally [5]. However, clots, that may later become an embolic material, can form in the space between the 2 layers, causing a transient ischemic attack or full-spectrum ischemic stroke [6, 7]. Single cases of DAS have been described in the world literature [8]. Among children, one of the youngest patients described in the literature was a case of a 6-year-old boy, whose only symptom was a murmur over the heart. Further diagnostics of the murmur revealed DSA, which was not taken into consideration in the initial differential diagnostics [9].

Case report

A 4-year-old boy was referred to the pediatrician due to recurrent infections and the next he was referred for a cardiological consult. Transthoracic echocardiography revealed a large defect in the atrial septal defect type ostium secundum of 2 cm in diameter and within the lumen of the LA, the presence of a second septum was established (Figure 1). In addition, the RA and the right ventricle were enlarged, as well as the pulmonary artery was dilated. Color Doppler examination revealed a profuse left-right shunt through the atrial septum. The electrocardiogram showed a right axis deviation and features of a partial right bundle branch block. The child was qualified for transoesophageal echocardiography (TEE), which was performed in a hemodynamic laboratory with intention of simultaneous interventional closure.

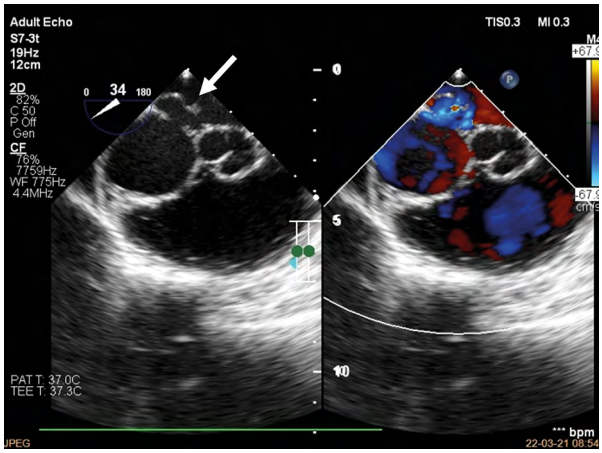

Figure 3. Transoesophageal echocardiography. In the left atrium normal and additional septum and free space between them (arrow)

TEE examination confirmed the presence of two partitions in the atrium, with a space in between the layers, excluding the existence of a thrombus (Figure 2 and 3). The decision on interventional closure of atrial septal defect has been changed and the boy was qualified for cardiac surgery.

Discussion

The interatrial defect is one of the most common congenital heart defects [10], while the detection of an additional septum inside the RA or LA is extremely rare. There are

single case reports in the world literature [8, 9]. The present patient was only 4 years old and, to the authors' knowledge, is probably one of the youngest to be diagnosed with this defect. If the accessory layer is located on the side of the LA, then the space between the septum may be a source of thrombus and cerebral embolism or other complications [6, 7]. Therefore, especially in the case of an increased risk of embolism (e.g., congenital thrombophilia), the patient should be qualified for surgical removal of the accessory septum and defect closure. Transthoracic echocardiography, supplemented with TEE, is usually a modality sufficient enough to assess the defect, although it sometimes requires an extension to computed tomography or magnetic resonance imaging.

The differential diagnostics of DAS should include the three-atrial heart (most often left-sided), in which the additional septum is located in the LA and is parallel to the mitral annulus

Conclusions

During echocardiography, the assessment of the atrial septum must be conducted with precision. Any unusual image of the atrial septum should prompt TEE and other imaging methods. The double atrial septum creates a high risk of thrombus formation and stroke.

Conflict of interest

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Streszczenie

Praca dotyczy przypadku 4-letniego chłopca, u którego w badaniu echokardiograficznym zdiagnozowano duży ubytek przegrody międzyprzedsionkowej typu *ostium secundum* (ASD2) oraz dodatkowe nieprawidłowe struktury od strony lewego przedsionka. Pacjent został zakwalifikowany do interwencyjnego zamknięcia ubytku, jednak w echokardiografii przezprzełykowej oprócz bardzo dużego ASD2 (ok. 2 cm) rozpoznano podwójną przegrodę międzyprzedsionkową. Warstwa dodatkowej ściany była równoległa do przegrody międzyprzedsionkowej i nie utrudniała przepływu krwi z żył płucnych ani przez zastawkę mitralną. W przestrzeni pomiędzy dwiema warstwami nie stwierdzono skrzeplin. Zrezygnowano z zamknięcia ASD2 podczas cewnikowania serca i pacjenta zakwalifikowano do planowego leczenia operacyjnego. Obecnie chłopiec nie wykazuje objawów i prowadzi normalny tryb życia.

Słowa kluczowe: podwójna przegroda przedsionkowa, przestrzeń międzyprzedsionkowa, wrodzona wada serca

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