FOLIA CARDIOLOGICA

PISMO SEKCJI POLSKIEGO TOWARZYSTWA KARDIOLOGICZNEGO: CHORÓB SERCA U KOBIET, ECHOKARDIOGRAFII, ELEKTROKARDIOLOGII NIEINWAZYJNEJ I TELEMEDYCYNY, KARDIOLOGII DZIECIĘCEJ, KARDIOLOGII EKSPERYMENTALNEJ, INTERWENCJI SERCOWO-NACZYNIOWYCH, NIEWYDOLNOŚCI SERCA, REHABILITACJI KARDIOLOGICZNEJ I FIZJOLOGII WYSIŁKU, INTENSYWNEJ TERAPII KARDIOLOGICZNEJ I RESUSCYTACJI, RYTMU SERCA, WAD ZASTAWKOWYCH SERCA, FARMAKOTERAPII SERCOWO-NACZYNIOWEJ

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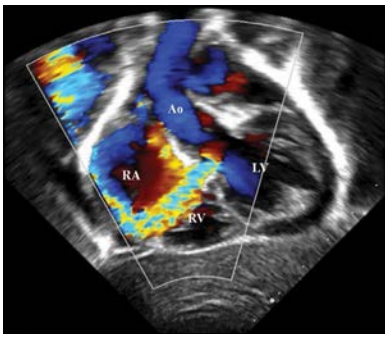

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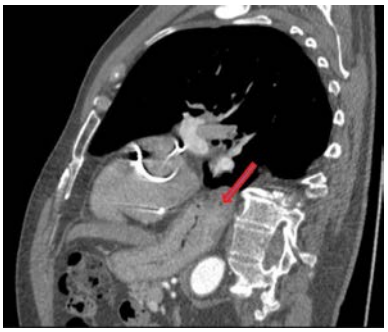

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FOLIA CARDIOLOGICA

23 kwietnia 2022 roku

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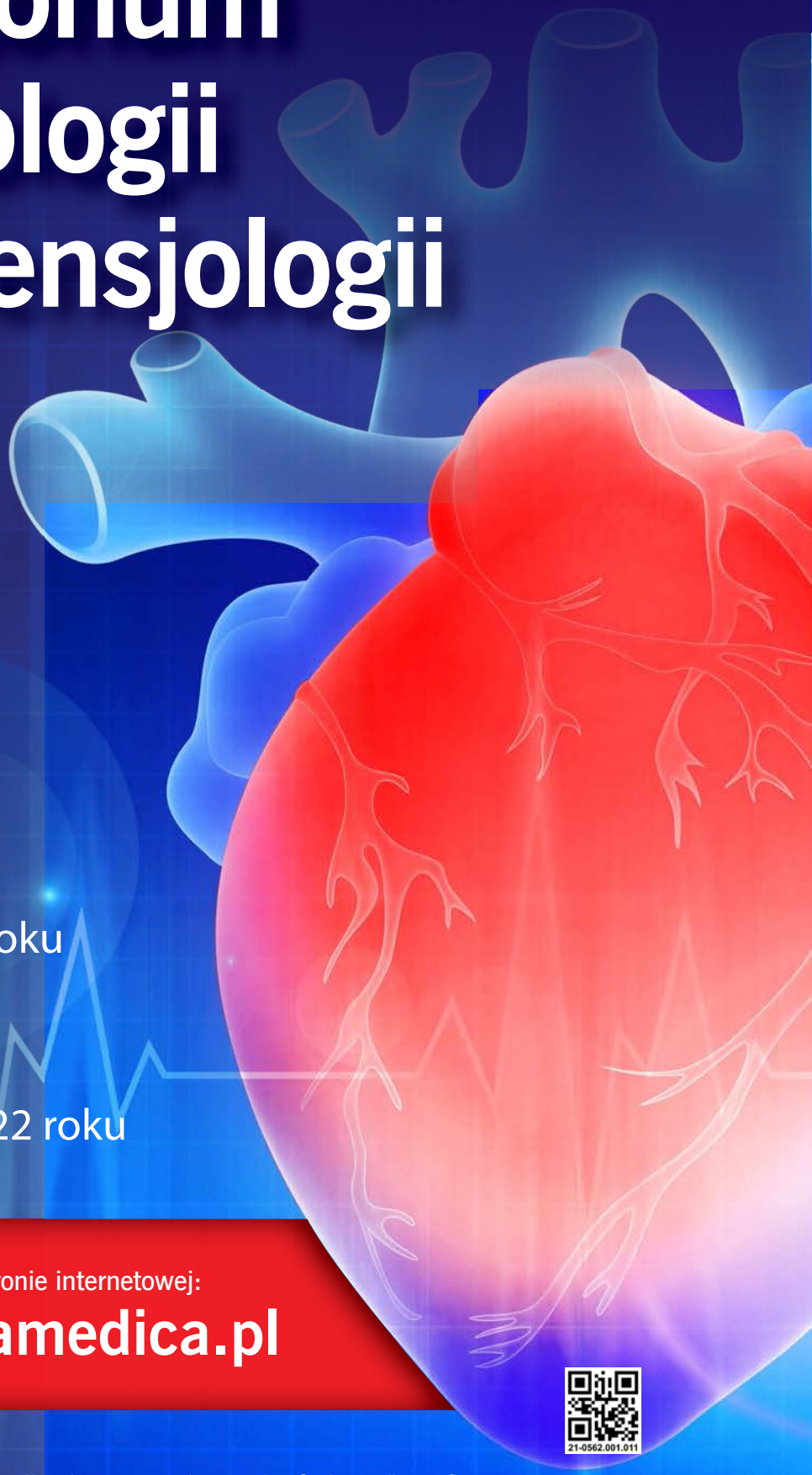

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Od Redaktora

Szanowni Czytelnicy,

oddajemy w Państwa ręce ostatni 6. numer *Folia Cardiologica*, kończąc tym samym kolejny rok wydawniczy naszego czasopisma. Zachęcając tradycyjnie do lektury, przedstawiam dwa artykuły oryginalne afiliowane przez polskie ośrodki. Pierwszy z nich, zatytułowany „Does the CHA_2DS_2-VASc score determine anticoagulant treatment in atrial fibrillation patients? Data from the POLish Atrial Fibrillation (POL-AF) Registry", autorstwa Anny Szpotowicz i wsp. stanowi analizę leczenia przeciwkrzepliwego chorych z migotaniem przedsionków na podstawie polskiego rejestru POL-AF obejmującego niemal 4 tysiące pacjentów z rozpoznaniem tej arytmii, prowadzonego w 10 ośrodkach kardiologicznych naszego kraju. Wysokie ryzyko powikłań zakrzepowo-zatorowych zidentyfikowano we wspomnianej populacji u 91% pacjentów, a niskie u 2% chorych. Doustne leczenie przeciwzakrzepowe stosowano u 81% chorych; szansę na zastosowanie antykoagulacji zmniejszały niedokrwistość i choroba nowotworowa. Wśród pacjentów z grupy niskiego ryzyka powikłań, powodem przejściowego zastosowania antykoagulacji była kardiowersja elektryczna. W kolejnej pracy oryginalnej, pt. „Transcatheter closure of congenital and acquired Gerbode defects with Nit-Occlud Lê VSD (PFM)-Coil. Immediate and mid-term results" Piotra Weryńskiego i wsp. z Kliniki Kardiologii Dziecięcej Polsko-Amerykańskiego Instytutu Pediatrii w Krakowie, przedstawiono doświadczenia Autorów (w afiliacji podano również ośrodek gdański) w przezskórnym zamykaniu rzadkiego typu ubytków międzykomorowych typu Gerbode z zastosowaniem zestawów Nit-Occlud Lê VSD-Coils jako alternatywy dla klasycznej korekcji kardiochirurgicznej. Artykuł jest opatrzony ciekawym komentarzem eksperckim prof. Ireneusza Haponiuka i wsp.

Poza pracami oryginalnymi numer zawiera dwie prace poglądowe; pierwsza autorstwa Ewy Kruszyńskiej i wsp. z Oddziału Kardiologii Dolnośląskiego Szpitala Specjalistyczny im. T Marciniaka we Wrocławiu, pt. „Arterial stiffness in metabolic syndrome: sex-specific differences, clinical consequences, how to prevent?", dotyczy zespołu metabolicznego w kontekście zmian naczyniowych, druga, zatytułowana „Sodium-glucose co-transporter 2 inhibitors therapy not only for diabetologists" Marii Sawościan i Małgorzaty Lelonek z Zakładu Kardiologii Nieinwazyjnej Katedra Chorób Wewnętrznych i Kardiologii Uniwersytetu Medycznego w Łodzi jest poświęcona znaczeniu trzech kluczowych w leczeniu niewydolności serca przedstawicieli inhibitorów kotransportera sodowo-glukozowego 2: dapagliflozyny, empagliflozyny i sotagliflozyny. Zawartość numeru uzupełniają cztery niezmiernie interesujące prace kazuistyczne oraz zajmujący artykuł w dziale „Elektroterapia".

Zachęcając do lektury, składam Państwu życzenia zdrowia i dobrych dni w 2022 roku.

Redaktor Naczelna

B. Wożakowska-Kapłon

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

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Does the CHA_2DS_2-VASc score determine anticoagulant treatment in atrial fibrillation patients? Data from the POLish Atrial Fibrillation (POL-AF) Registry

Czy wynik w CHA_2DS_2-VASc determinuje leczenie przeciwzakrzepowe u pacjentów z migotaniem przedsionków? Dane z POLish Atrial Fibrillation (POL-AF) Registry

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Abstract

Introduction. Oral anticoagulants (OAC) should be used in patients with atrial fibrillation (AF) depending on the thromboembolic risk assessed using the CHA_2DS_2-VASc score. The aim of the study is to verification if the CHA_2DS_2-VASc score influences using OACs in patients with AF and also to analyse predictors of OAC use in AF patients at non-high (intermediate and low) thromboembolic risk.

Material and methods. The presented study has been based on the data from the POL-AF Registry which is a prospective, multicentre study including patients with diagnosed AF consecutively hospitalized in 10 cardiology centres from January to December 2019.

Results. The study comprised 3,956 patients. A high risk of thromboembolic complications was observed in 91.4%, intermediate in 6.3% and low in 2.3% of them. OACs were administered to 81.1% of patients, including 91.5% at high, 90.3% at intermediate and 86.2% at low thromboembolic risk. CHA_2DS_2-VASc score was not a predictor of using OACs in all patients with AF [odds ratio (OR) 1.02, confidence interval (CI): 0.96–1.08, p = 0.747]. In the group of patients with non-high thromboembolic risk, the factor predisposing to OAC prescription was hospitalization due to electrical cardioversion [OR 6.55, CI: 1.52–28.21, p = 0,012], contrary to anaemia (OR 0.27, CI: 0.12–0.64, p = 0,003) and cancer (OR 0.14, CI: 0.03–0.57, p = 0.006), which decreased the chance of using OACs in this group.

Conclusions. The CHA_2DS_2-VASc score was not a predictor of OAC use in the whole study cohort. In the significant proportion of non-high thromboembolic risk patients with AF, OACs were administered, mainly because of temporary indications.

Key words: oral anticoagulant, atrial fibrillation, thromboembolic risk

Folia Cardiologica 2021; 16, 6: 359–368

Introduction

Thromboembolic events are among the major complications of atrial fibrillation (AF) [1, 2]. In patients with AF, thromboembolic risk depends on sex, age and co-morbidities. To assess it, it is recommended to use the CHA_2DS_2-VASc score. In all the European guidelines, oral anticoagulants (OACs) are recommended for patients at high thromboembolic risk. On the contrary, guidelines recommend against OAC use in patients at low thromboembolic risk, as the bleeding risk is considered to outweigh potential benefits of thromboembolic risk reduction [3–5]. Patients with low thromboembolic risk should not receive antithrombotic treatment except for periablation and pericardioversion period in patients with AF lasting longer than 48 hours [5]. OACs should be considered in patients at intermediate thromboembolic risk. Despite these clearly defined stroke prevention rules, it is possible to observe a large proportion of low thromboembolic risk patients prescribed OACs [6–8].

The study aimed to check if CHA_2DS_2-VASc score was a predictor of OAC use in patients with AF and also to assess predictors of OAC prescription in non-high thromboembolic risk patients with AF.

Material and methods

Study population

The POL-AF Registry (NCT04419012) was a prospective, observational study enrolling AF patients hospitalized in 10 cardiology departments in Poland (eight of them were academic and two regional). Details on the study design have been reported elsewhere [9–11]. In brief, consecutive hospitalized patients were included in the study on the condition that they were at least 18 years of age and had AF history reported by electrocardiography or in their case record. Diagnosis of AF was made by attending physicians by the European Society of Cardiology (ESC) guidelines [5]. Patients who died during hospitalization and those with valvular AF (valve prosthesis, mitral stenosis — at least moderate) were excluded from the study. Also, patients hospitalized to have AF substrate ablation were not included because not all the centres perform catheter ablation. Moreover, patients undergoing ablation due to AF have a clinical profile different from most patients with AF (they are younger and do not have concomitant diseases).

Patients were recruited to the study between January and December 2019. Those hospitalized a few times

during the study period obtained the same number in the database.

In the presented study, based on the results of the POL-AF Registry, all patients with AF included in this registry were evaluated.

Covariates

Investigators collected data regarding demographics, medical history, type of AF, laboratory test results and anticoagulant pharmacotherapy. Bleeding risk was assessed according to HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding, labile international normalized ratio (INR), elderly (> 65 years), drug/alcohol consumption] score [12].

The assessment of patients' kidney function was done with the use of the estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Anaemia was defined as haemoglobin concentration < 12 g/dL.

The study obtained the approval of the Ethics Committee of the Świętokrzyska Medical Chamber in Kielce (104/2018) which also waived the obligation of acquiring informed consent from the patients.

Stroke risk assessment

The thromboembolic risk was defined according to the CHA_2DS_2-VASc score. The CHA_2DS_2-VASc score was calculated by giving 1 point each for congestive heart failure or left ventricular systolic dysfunction, hypertension, diabetes mellitus, vascular disease (prior myocardial infarction, vascular revascularization or aortic plaque), age 65–74 years, and female gender, and 2 points for previous thromboembolic events and age ≥ 75 years [13].

Patients with CHA_2DS_2-VASc score 0 for males and 1 for females were categorized as low, with CHA_2DS_2-VASc score 1 for males and 2 for females as an intermediate and with CHA_2DS_2-VASc score ≥ 2 for males and ≥ 3 for females as high stroke risk.

Stroke prevention in the study group

The study provides an evaluation of antithrombotic therapy suggested during the patients' discharge from the hospital. The following groups of patients according to stroke prevention were defined: OAC group and no-OAC group. OAC group included patients treated with vitamin K antagonist (VKA) and non-vitamin K oral anticoagulants (NOACs) alone or with antiplatelet drug/drugs. In Poland apixaban, dabigatran and rivaroxaban are available for stroke prevention in patients with AF. Edoxaban has been registered in Europe, however, it is not available in Poland. No-OAC group included patients treated with antiplatelet drugs (acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor), heparin and patients without any stroke prevention.

Statistical analyses

Statistical analysis was conducted with the use of STATISTICA 13.3 statistical package. Descriptive statistics were presented as numbers with percentages or mean values with standard deviation. Univariate logistic regression and multivariate logistic regression were conducted to assess the odds ratio along with a 95% confidence interval. The value which was considered to be statistically significant was $p < 0.05$.

Results

Characteristic of the study group

The study cohort contained a total of 3,956 patients (42.6% female, mean age 72.1 years) with AF. The most common co-morbidity was hypertension, which occurred in 83.7% of patients. Heart failure appeared as a concomitant diagnosis in 65.3% of patients. Most common among non-cardiac diseases was impaired renal function — 45.4%. Paroxysmal AF was observed in 48.3% of patients whereas 28.3% suffered from permanent AF.

In the study group, 2.3% of patients were at low risk of stroke, 6.3% of patients were at intermediate risk of stroke, and most patients (91.4%) were at high risk of stroke. The high bleeding risk score was noted in 30.6 % of patients. Baseline characteristics of patients according to stroke risk were presented in Table 1.

Stroke prevention according to stroke risk

Among the total study population in most of the patients (91.3%), OAC therapy was used. Also, antiplatelet therapy was prescribed for 3.6% of patients, heparin for 2.6% of patients and 2.6% of patients who did not receive any stroke prevention.

Of those on OACs, most of the patients (82.3%) were treated with NOACs. In the group treated with NOACs, 32.1% of patients received apixaban, 27.5% dabigatran and 40.4% rivaroxaban. In the study group, 36% of patients were treated with a reduced NOAC dose.

Table 2 showed stroke prevention strategy according to the stroke risk. OACs were prescribed for 91.5% of patients with high, 90.3% of patients with intermediate and 86.2% of patients with low risk of stroke ($p = 0.170$). The proportion of patients not receiving anticoagulant or antiplatelet therapies was higher in patients at low (9.6%) and intermediate (6%) thromboembolic risk than in patients at high (2.1%) thromboembolic risk ($p < 0.001$).

Assessment of predictors of oral anticoagulant use in all patients

Among the total study group, factors predisposing to OAC prescription were assessed. Table 3. showed the results of univariate logistic regression analysis. The factor associated with OAC prescription was hospitalization due to

Table 1. Baseline characteristics of the study group

Clinical characteristic	All n = 3956	High stroke risk group n = 3614	Intermediate stroke risk group n = 248	Low stroke risk group n = 94
Age	72.1 (11.4)	73.6 (10.3)	58.2 (9.3)	50.5 (10.5)
Mean (SD), years				
< 65	895 (22.6)	598 (16.5)	203 (81.9)	94 (100)
65–74	1330 (33.6)	1285 (35.6)	45 (18.1)	0 (0.0)
≥ 75	1731 (43.8)	1731 (47.9)	0 (0.0)	0 (0.0)
Female	1686 (42.6)	1572 (43.5)	89 (35.9)	25 (26.6)
Type of atrial fibrillation				
Paroxysmal	1909 (48.3)	1723 (47.7)	129 (52.0)	57 (60.6)
Persistent	928 (23.5)	803 (22.2)	90 (36.3)	35 (37.2)
Permanent	1119 (28.3)	1088 (30.1)	29 (11.7)	2 (2.2)
Medical history				
Hypertension	3312 (83.7)	3174 (87.4)	138 (55.6)	0 (0.0)
Heart failure	2584 (65.3)	2529 (70.0)	55 (22.2)	0 (0.0)
Vascular disease	2214 (56.0)	2207 (61.1)	7 (2.8)	0 (0.0)
Coronary artery disease	1984 (50.2)	1979 (54.8)	5 (2.0)	0 (0.0)
Previous myocardial infraction	882 (22.3)	881 (24.4)	1 (0.4)	0 (0.0)
Peripheral artery disease	566 (14.3)	564 (15.6)	2 (0.8)	0 (0.0)
Previous stroke/TIA/peripheral embolism	648 (16.4)	648 (17.9)	0 (0.0)	0 (0.0)
Diabetes mellitus	1344 (34.0)	1341 (37.1)	3 (1.2)	0 (0.0)
Any previous bleeding	124 (3.1)	118 (3.3)	5 (2.0)	1 (1.1)
Intracranial bleeding	29 (0.7)	29 (0.8)	0 (0.0)	0 (0.0)
Gastrointestinal bleeding	151 (3.8)	149 (4.1)	2 (0.8)	0 (0.0)
Malignancy	195 (4.9)	186 (5.1)	5 (2.0)	4 (4.3)
Anaemia	911 (23.0)	872 (24.1)	29 (11.7)	10 (10.6)
eGFR < 60 mL/min/1.73 m^2	1798 (45.4)	1731 (47.9)	53 (21.4)	14 (14.9)
Bleeding risk				
HAS-BLED score Mean (SD)	2.1 (0.9)	2.2 (0.8)	0.9 (0.5)	0.1 (0.4)
≥ 3	1210 (30.6)	1208 (33.4)	2 (0.8)	0 (0.0)
Reason for hospitalization				
Electrical cardioversion	893 (22.6)	796 (22.0)	67 (27.0)	30 (31.9)
Planned coronarography/PCI	382 (9.7)	372 (10.3)	8 (3.2)	2 (2.1)
CIED implantation/reimplantation	360 (9.1)	346 (9.6)	13 (5.2)	1 (1.1)
Acute coronary syndrome	242 (6.1)	240 (6.6)	2 (0.8)	0 (0.0)
Heart failure	811 (20.5)	788 (21.8)	22 (8.9)	1 (1.1)
Ablation other than AF	210 (5.3)	189 (5.2)	13 (5.2)	8 (8.5)
AF without any procedures	251 (6.3)	191 (5.3)	42 (16.9)	18 (19.1)

SD — standard deviation; TIA — transient ischemic attack; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention; CIED — cardiac implantable electronic device; AF — atrial fibrillation

Table 2. Stroke prevention according to stroke risk

Stroke prevention	All n = 3956	High stroke risk n = 3614	Intermediate stroke risk n = 248	Low stroke risk n = 94	p
OAC	3611 (91.3)	3306 (91.5)	224 (90.3)	81 (86.2)	0.170
APT	142 (3.6)	135 (3.7)	5 (2.0)	2 (2.1)	0.276
Heparin	103 (2.6)	96 (2.7)	5 (2.0)	2 (2.1)	0.794
No	101 (2.6)	77 (2.1)	15 (6.0)	9 (9.6)	**< 0.001**

APT — antiplatelet drugs; OAC — oral anticoagulant

Table 3. Factors increasing the chances of using oral anticoagulants (OACs) in all patients — univariate logistic regression analysis

Clinical characteristic	OAC group n = 3611	No-OAC group n = 345	OR	95% CI	p
Age Mean (SD), years	72.0 (11.2)	73.1 (12.95)	1.00	0.99–1.01	0.084
Female	1548 (42.9)	138 (40.0)	1.13	0.90–1.41	0.304
Type of atrial fibrillation					
Permanent	1005 (27.8)	114 (33.0)	0.78	0.62–0.99	**0.040**
Medical history					
Hypertension	3045 (84.3)	267 (77.4)	1.58	1.21–2.06	**< 0.001**
Heart failure	2361 (65.4)	223 (64.6)	1.04	0.83–1.31	0.781
Vascular disease	2010 (55.7)	204 (59.1)	0.87	0.70–1.09	0.216
Coronary artery disease	1799 (49.8)	185 (53.6)	0.86	0.69–1.08	0.178
Previous myocardial infraction	783 (21.7)	99 (28.7)	0.69	0.54–0.89	0.003
Peripheral artery disease	502 (13.9)	64 (18.6)	0.71	0.54–0.95	0.019
Previous stroke/TIA/peripheral embolism	599 (16.6)	49 (14.2)	1.21	0.88–1.65	0.254
Diabetes mellitus	1220 (33.8)	124 (35.9)	0.91	0.73–1.15	0.420
Any previous bleeding	98 (2.7)	26 (7.5)	0.35	0.22–0.54	**< 0.001**
Previous intracranial bleeding	18 (0.5)	11 (3.2)	0.16	0.08–0.33	**< 0.001**
Gastrointestinal Bleeding	109 (3.0)	42 (12.2)	0.23	0.16–0.33	**< 0.001**
Malignancy	153 (4.2)	42 (12.2)	0.32	0.23–0.46	**< 0.001**
Anaemia	779 (21.6)	132 (38.3)	0.45	0.36–0.57	**< 0.001**
eGFR < 60 ml/min/1.73 m^2	1617 (44.8)	181 (52.5)	0.75	0.6–0.93	0.010
CHA_2DS_2-VASc score Mean (SD)	4.4 (1.8)	4.3 (1.9)	1.02	0.96–1.08	0.747
HAS-BLED score Mean (SD)	2.1 (0.9)	2.2 (1.0)	0.93	0.82–1.04	0.175
Reason for hospitalization					
Electrical cardioversion	879 (24.3)	14 (4.1)	7.61	4.44–13.06	**< 0.001**
Planned coronarography/PCI	348 (9.6)	34 (9.9)	0.98	0.68–1.42	0.896
CIED implantation/reimplantation	342 (9.5)	18 (5.2)	1.91	1.17–3.10	0.010
Acute coronary syndrome	197 (5.5)	45 (13.0)	0.39	0.28–0.55	**< 0.001**
Heart failure	736 (20.4)	75 (217)	0.93	0.71–1.21	0.551
Ablation other than AF	191 (5.3)	19 (5.5)	0.96	0.59–1.56	0.864
AF without any procedures	234 (6.5)	17 (4.9)	0.75	0.46–1.24	0.260

OR — odds ratio; CI — confidence interval; SD — standard deviation; TIA — transient ischemic attack; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention; CIED — cardiac implantable electronic device; AF — atrial fibrillation

electrical cardioversion [odds ratio (OR) 7.61, confidence interval (CI) 4.44–13.06, p < 0.001]. On contrary, the CHA_2DS_2-VASc score was not a predictor of OAC use in all patients.

Assessment of predictors of oral anticoagulant use in non-high (intermediate and low) stroke risk patients

The supplementary table at the end of the article (Table S1) shows a comparison of OAC treated and no-OAC treated patients in the group of non-high (low and intermediate) thromboembolic risk. In the group of non-high thromboembolic risk, in univariate logistic regression analysis, it was indicated that hospitalization due to electrical cardioversion was a predictor of OAC prescription whereas anaemia and cancer significantly decreased chances to use OACs (Table 4). The above factors were included in multivariate logistic regression analysis. It was observed that hospitalization to have electrical cardioversion was a predictor of OAC use (OR 6.55, CI 1.52–28.21, p = 0.012). Anaemia (OR 0.27, CI 0.12–0.64,

Table 4. Factors increasing the chances of using oral anticoagulants (OACs) in the group of patients with non-high (low and intermediate) stroke risk — univariate logistic regression analysis

Clinical characteristic	OAC group n = 305	No-OAC group n = 37	OR	95% CI	p
Age	56.3 (9.7)	53.9 (13.5)	1.03	1.00–1.06	0.173
Mean (SD), years					
Female	103 (33.8)	11 (29.7)	1.21	0.58–2.54	0.623
Permanent AF vs. other	3 (8.1)	28 (9.2)	1.15	0.33–3.97	0.830
Medical history					
Hypertension	127 (41.6)	11 (29.7)	1.69	0.81–3.54	0.167
Heart failure	50 (16.4)	5 (13.5)	1.26	0.47–3.38	0.654
Vascular disease	5 (1.6)	2 (5.4)	0.30	0.06–1.56	0.150
Coronary artery disease	3 (1.0)	2 (5.4)	0.18	0.03–1.08	0.060
Previous myocardial infarction	1 (0.3)	0 (0)	–	–	–
Peripheral artery disease	2 (0.7)	0 (0)	–	–	–
Diabetes mellitus	2 (0.7)	1 (2.7)	0.24	0.03–2.69	0.246
Any previous bleeding	5 (1.6)	1 (2.7)	0.61	0.07–5.28	0.646
Previous intracranial bleeding	0 (0)	0 (0)	–	–	–
Gastrointestinal Bleeding	2 (0.7)	0 (0)	–	–	–
Malignancy	4 (1.3)	5 (13.5)	0.09	0.03–0.34	**< 0.001**
Anaemia	28 (9.2)	11 (29.7)	0.24	0.11–0.53	**< 0.001**
eGFR < 60 mL/min/1.73 m^2	62 (20.3)	5 (13.5)	1.68	0.63–4.5	0.303
CHA_2DS_2VASc score Mean (SD)	1.1 (0.7)	1.0 (0.7)	1.32	0.80–2.19	0.286
HAS-BLED score Mean (SD)	0.7 (0.60)	0.6 (0.60)	1.31	0.73–2.35	0.382
Reason for hospitalization					
Electrical cardioversion	95 (31.1)	2 (5.4)	7.92	1.87–33.6	**0.006**
Planned coronarography/PCI	10 (3.3)	0 (0)	–	–	–
CIED implantation/reimplantation	13 (4.3)	1 (2.7)	1.61	0.21–12.62	0.655
Acute coronary syndrome	2 (5.4)	0 (0)	–	–	–
Heart failure	22 (7.2)	1 (2.7)	2.80	0.37–21.4	0.322
Ablation other than AF	19 (6.2)	2 (5.4)	0.87	0.20–3.86	0.844
AF without any procedures	54 (17.7)	6 (16.2)	1.12	0.45–2.8	0.823

OR — odds ratio; CI — confidence interval; SD — standard deviation; AF — atrial fibrillation; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention; CIED — cardiac implantable electronic device

Table 5. Factors increasing the chances of using oral anticoagulants in the group of patients with non-high (low and intermediate) stroke risk — multivariate logistic regression analysis

Clinical characteristic	OR	95% CI	p
Electrical cardioversion as a reason for hospitalization	6.55	1.52–28.21	**0.012**
Malignancy	0.14	0.03–0.57	**0.006**
Anaemia	0.27	0.12–0.64	**0.003**

OR — odds ratio; CI — confidence interval

p = 0.003) and cancer (OR 0.14, CI 0.03–0.57, p = 0.006) were factors predisposing to no-OAC use in the group of non-high thromboembolic risk patients (Table 5).

Discussion

The present study provides an important view of actual antithrombotic therapy in patients with AF based on the multicentre, national registry. The main results of this study are presented in this paper. Firstly, the CHA_2DS_2-VASc score was not a predictor of OAC use in the AF population and in patients with intermediate and low risk of stroke the percentage of OAC treated patients was high. Secondly, factors predisposing to OAC prescription in non-high stroke risk patients were identified.

In the presented study OACs were used respectively in 91.5%, 90.3%, 86.2% of patients at high, intermediate and low risk of thromboembolic complications. A large proportion of non-high thromboembolic risk patients who received OACs is very surprising. According to the current guidelines of ESC, anticoagulant prophylaxis should be used in patients at high thromboembolic risk, considered in patients at intermediate risk of thromboembolic complications and should not be used persistently in low thromboembolic risk patients [5].

In the analysis of GARFIELD-AF, it was found that almost half of the patients with the CHA_2DS_2-VASc score equal to 0 (men) or 1 (women) received OACs [14]. In the Balkan Registry, in the group of 2,712 patients included between 2014 and 2015, 56.5%, truly low-risk patients were recommended OACs [8]. In the PINNACLE Registry, 31.3% of patients without risk factors in CHA_2DS_2-VASc score received OACs [15]. The GRASP-AF Registry showed that from 2009 to 2018, the percentage of patients with low thromboembolic risk receiving OACs was 36.2–46.4% [16]. In PREFER in AF, more than half of AF patients at low and intermediate thromboembolic risk received OACs: 70.1% of the patients with CHA_2DS_2-VASc score 1 and 62.5% of patients without any CHA_2DS_2-VASc stroke risk factor [17].

To explain a similar proportion of OAC treated patients with AF and low, intermediate and high risk of stroke, some limitations of CHA_2DS_2-VASc score in thromboembolic risk assessment should be considered. Despite being specifically constructed and validated for this purpose, the CHA_2DS_2-VASc score allows to notice only a part of this risk. Therefore, the study cohort with a low risk of stroke was potentially enriched with emerging risk factors increasing the stroke risk but not included in CHA_2DS_2-VASc score, e.g., AF type, cancer, chronic kidney disease. This can be the explanation why so many patients with low thromboembolic risk according to their CHA_2DS_2-VASc score did receive OACs. It seems to be the main reason for such a state of things, insufficient adherence to the guidelines should not lie at the bottom of OAC application in this group of patients.

In some of the patients with AF and low/intermediate stroke risk, there are temporary indications to apply such OACs as electrical cardioversion or ablation. In the present study, app. half of the patients with low risk of stroke had a temporary indication, such as hospitalization due to electrical cardioversion, hospitalization due to AF without any procedures (but probably with the planned cardioversion or ablation) to OAC prescription. Hospitalization due to electrical cardioversion was the strongest factor predisposing to use OACs in non-high-risk patients. Application of OACs shortly after cardioversion due to AF is obligatory in all patients regardless of thromboembolic risk [5]. Therefore, in the present study, most non-high thromboembolic risk patients treated with OACs receive them in compliance with the guidelines. Interestingly, in the presented study, AF type or impaired kidney function were not shown to be the predictors of OAC use in patients at low thromboembolic risk. It has been reported that the aforementioned factors increase the risk of thromboembolic complications in patients with AF or predispose them to thrombus formation in the left atrial appendage [8–20]. Study results connected with anticoagulant overtreatment of patients with AF prove that it is common and most likely stems from using OACs due to temporary indications to anticoagulant therapy and from the presence of thromboembolic risk factors not included in the CHA_2DS_2-VASc score.

Limitation of the study

The presented study demonstrates clinical practice concerning the anticoagulant treatment in the Polish population of hospitalized patients with AF. The main limitation of the study, proceeding from its construction, is the lack of long-term observation which prevents evaluation of OAC use and no-OAC use influence on patients' prognosis. Another limitation is a small number of patients in the groups of low and intermediate thromboembolic risk, who were evaluated in this study. It results from the fact that POL-AF Registry comprised only hospitalized patients who are usually at high thromboembolic risk.

Table S1. Comparison of patients with non-high (low and intermediate) stroke risk treated and not treated with oral anticoagulant

Clinical characteristic	Intermediate stroke risk group n = 248			Low stroke risk group n = 94		
	OAC group n = 224	No-OAC group n = 24	p	OAC group n = 81	No-OAC group n = 13	p
Age Mean (SD), years	58.2 (9.0)	57.6 (11.8)	0.762	51.1 (9.8)	47.0 (14.3)	0.201
Female	80 (35.7)	9 (37.5)	0.863	23 (28.3)	2 (15.4)	0.335
Permanent AF	2 (2.5)	0 (0)	0.897	0 (0)	2 (2.5)	0.998
Medical history						
Hypertension	127 (56.7)	11 (45.8)	0.312	0 (0)	0 (0)	–
Heart failure	50 (22.3)	5 (20.8)	0.868	0 (0)	0 (0)	–
Vascular disease	5 (2.2)	2 (8.3)	0.111	0 (0)	0 (0)	–
Coronary artery disease	3 (1.3)	2 (8.3)	0.044	0 (0)	0 (0)	–
Previous myocardial infraction	1 (0.4)	0 (0)	0.998	0 (0)	0 (0)	–
Peripheral artery disease	2 (0.9)	0 (0)	0.998	0 (0)	0 (0)	–
Diabetes mellitus	2 (0.9)	1 (4.2)	0.206	0 (0)	0 (0)	–
Any previous bleeding	4 (1.8)	1 (4.2)	0.445	0 (0)	1 (1.2)	–
Gastrointestinal bleeding	2 (0.9)	0 (0)	0.998	0 (0)	0 (0)	–
Malignancy	1 (0.4)	4 (16.7)	< 0.001	3 (3.7)	1 (7.7)	0.518
Anaemia	20 (8.9)	9 (37.5)	< 0.001	8 (8.9)	2 (15.4)	0.495
eGFR < 60 mL/min/1.73 m^2	65 (29.0)	3 (12.5)	0.232	12 (14.8)	2 (15.4)	0.910
CHA_2DS_2VASc score Mean (SD)	1.4 (0.48)	1.4 (0.5)	0.863	0.3 (0.5)	0.15 (0.4)	0.335
HAS-BLED score Mean (SD)	0.9 (0.5)	0,8 (0.5)	0.350	0.1 (0.3)	0.2 (0.6)	0.231
Reason for hospitalization						
Electrical cardioversion	65 (29.0)	2 (8.9)	0.046	30 (37.0)	0 (0)	0.997
Planned coronarography/PCI	8 (3.6)	0 (0)	0.998	2 (2.5)	0 (0)	0.998
CIED implantation/reimplantation	12 (5.4)	1 (4.2)	0.805	1 (1.2)	0 (0)	0.998
Acute coronary syndrome	0 (0)	2 (8.3)	0.998	0 (0)	0 (0)	–
Heart failure	21 (9.4)	1 (4.2)	0.408	1 (1.2)	0 (0)	0.998
Ablation other than AF	12 (5.4)	1 (4.2)	0.805	7 (8.6)	1 (7.7)	0.910
AF without any procedures	40 (17.9)	2 (8.3)	0.251	14 (17.3)	4 (30.8)	0.260

OAC – oral anticoagulant; SD – standard deviation; AF – atrial fibrillation; eGFR – estimated glomerular filtration rate; PCI – percutaneous coronary intervention; CIED – cardiac implantable electronic device

Conclusions

The CHA_2DS_2-VASc score was not a predictor of OAC use in hospitalized AF patients. In the group of low thromboembolic risk patients with AF, temporary indications to use OACs have a big influence on a high percentage of OAC prescriptions.

Conflict of interests

Szpotowicz A, Uziębło-Życzkowska B, Maciorowska M, Wójcik M, Błaszczyk R, Budnik M, Gawałko M, Tokarek T, Rajtar-Salwa R, Bil J, Wojewódzki M, Bakuła-Ostalska E, Szyszowska A, Wełnicki M, Mamcarz M, Krzciuk M.: none. Gorczyca-Głowacka I: speaker for Boehringer-Ingelheim and

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Streszczenie

Wstęp. Doustne leki przeciwzakrzepowe (OAC) powinny być stosowane u pacjentów z migotaniem przedsionków (AF) zależnie od ryzyka zakrzepowo-zatorowego ocenianego za pomocą skali CHA_2DS_2-VASc. Celem badania była weryfikacja, czy wynik uzyskany w CHA_2DS_2-VASc wpływa na stosowanie OAC u pacjentów z AF, a także analiza predyktorów stosowania OAC u pacjentów cechujących się z niewysokim (pośrednim i niskim) ryzykiem zakrzepowo-zatorowym.

Materiał i metody. Prezentowane badanie oparto na danych z Rejestru POL-AF, który jest prospektywnym, wieloośrodkowym badaniem obejmującym pacjentów ze zdiagnozowanym AF hospitalizowanych kolejno w 10 ośrodkach kardiologicznych od stycznia do grudnia 2019 roku.

Wyniki. Badaniem objęto 3956 pacjentów. Wysokie ryzyko powikłań zakrzepowo-zatorowych zaobserwowano u 91,4%, pośrednie u 6,3%, a niskie u 2,3%. Doustne leki przeciwzakrzepowe podano 81,1% pacjentów, w tym 91,5% obciążonych wysokim, 90,3% cechujących się pośrednim i 86,2% z niskim ryzykiem zakrzepowo-zatorowym. Wynik uzyskany w CHA_2DS_2-VASc nie był predyktorem stosowania OAC u wszystkich pacjentów z AF (iloraz szans [OR] 1,02; przedział ufności [CI]: 0,96–1,08; p = 0,747]. W grupie pacjentów z niskim ryzykiem zakrzepowo-zatorowym czynnikiem predysponującym do przepisania OAC była hospitalizacja z powodu kardiowersji elektrycznej (OR 6,55; CI: 1,52–28,21; p = 0,012), w przeciwieństwie do niedokrwistości (OR 0,27; CI: 0,12–0,64; p = 0,003) oraz raka (OR 0,14; CI: 0,03–0,57; p = 0,006), co zmniejszało szansę na zastosowanie OAC w tej grupie.

Wnioski. Wynik uzyskany w CHA_2DS_2-VASc nie był predyktorem stosowania OAC w całej badanej kohorcie. U znacznej części pacjentów z AF nieobciążonych wysokim ryzykiem zakrzepowo-zatorowym zastosowano OAC, głównie ze wskazań przejściowych.

Słowa kluczowe: doustny antykoagulant, migotanie przedsionków, ryzyko zakrzepowo-zatorowe

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Transcatheter closure of congenital and acquired Gerbode defects with Nit-Occlud Lê VSD (PFM)-Coil. Immediate and mid-term results

Wyniki przezskórnego zamknięcia ubytku typu Gerbode z zastosowaniem Nit-Occlud Lê VSD (PFM)-Coil

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Abstract

Introduction. Left ventricle-to-right atrial (LV-RA) communications termed Gerbode defects are a special and very rare type of ventricular septal defect. Transcatheter closure using Nit-Occlud Lê VSD-Coils is a new and not well-known alternative to cardiac surgery in selected cases. This study aimed to describe results and experience with interventional closure of Gerbode defects using Nit-Occlud Lê VSD-Coil.

Material and methods. The procedures were performed between October 2014 and October 2018. Patients were selected based on detailed transthoracic echocardiography (TTE). The diameter of the defects based on the TTE study was verified and comparable to values found in the angiocardiography. Despite the fluoroscopy guidance the intraprocedural transoesophageal echocardiography was carried out in every case. Finally, the effectiveness of the procedure and the occurrence of complications during the observation were assessed in each case.

Results. The study involved eight children, including an infant with native Gerbode defect and seven older children with acquired post-operative LV-RA shunts. Age ranged from 8 months to 17.8 years, bodyweight from 7.4 kg to 56 kg, bodyweight from 7.4 kg to 56 kg, 5/8 females. The diameter mean of the defects in the angiocardiography was 3.86 ± 0.82 mm and it was comparable to values from TTE. All procedures were successful. The coils ranged from 8 × 6 mm to 12 × 6 mm. Early complications after the procedure: one case of transient haemolysis which required blood transfusion and steroids, one case of temporary arrhythmia. The follow-up period ranged 2–36 months, with only one case of a permanent small residual shunt was observed.

Conclusions. The interventional treatment of very rare Gerbode defects seems to be a safe alternative to surgery in selected cases. This study is one of the largest suchlike published.

Key words: Gerbode defect, congenital heart disease, interventional cardiology, ventricular septal defect, Nit-Occlud Lê VSD-Coil

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Introduction

Left ventricle-to-right atrial (LV-RA) shunts represent an unusual type of ventricular septal defect (VSD) often called "Gerbode defect" since the report by Gerbode et al. in 1958 [1]. They may be congenital or acquired [2–5]. The direct and indirect type was suggested by Riemenschneider and Moss, depending on defect location above or below the insertion of the septal leaflet of the tricuspid valve [6]. Sakakibara and Konno [7] introduced differentiation of these defects into three types, in which type I and II corresponded to Riemenschneider classification and the third was a combination of both types. Direct congenital LV-RA communication (the so-called true Gerbode defect) is very rare. Kelle et al. reported 6 patients with this type of defect among over 400 subjects with various types of VSD, operated on at Children's Memorial Hospital Chicago IL between 1990 and 2008 [8]. Congenital indirect type is more common, in which perimembranous ventricular septal defect (pmVSD) coexists with various anomalies of the septal leaflet of the tricuspid valve (malformation, perforation, widened commissure, clefts) [9]. Nowadays the most common are acquired LV-RA defects due to various reasons for example (e.g.): the complication of surgical treatment of pmVSD, atrioventricular septal defects, implantation of the mitral or aortic valve, as a consequence of infective endocarditis, myocardial infarction or even chest trauma [2–5]. Regardless of their type and origin, the LV-RA defects were previously the domain of cardio-surgical treatment. Progress in interventional cardiology has recently made it possible to employ transcatheter methods in selected cases. So far, the most widespread type of used devices has been the Amplatzer Duct Occluder (ADO) II occluders [10, 11].

The objective of this study was to present the authors' experience with still not a well-described method of transcatheter closure of Gerbode defects using Nit-Occlud Lê VSD-Coil (PFM: Produkte für die Medizin AG, Cologne, Germany).

Material and methods

The study material consisted of children with LV-RA shunts selected by detailed transthoracic echocardiography (TTE) (showing enlarged RA, presence of high-velocity shunt and direction of jet flow in the colour Doppler between LV and RA, Qp/Qs ratio ≥ 1.5:1), verified with the transoesophageal echocardiography (TEE) in four cases of the oldest children. The detailed assessment included the location and dimension of the defect and its structural relationship with nearby valvular structures. The parents were informed about the benefits and risks of transcatheter closure of the defect and that the final decision will be taken during cardiac catheterization. All of them gave informed consent to the procedure and participation in the study. The study protocol complies with local applicable ethical requirements.

The procedures were performed between October 2014 and October 2018. Right and left heart catheterizations were performed to estimate the diameter of the defect, pulmonary artery pressure and Qp/Qs ratio. The device description and technique used to close the Gerbode defects in the study patients has been similar to the EUROVECO-Registry by Haas et al. [12]. All procedures were performed under general anaesthesia with antibiotics as prophylactic. Every patient received a heparin bolus appropriate for body weight. Despite the fluoroscopy guidance an intraprocedural TEE was carried out in every case. In the beginning, the right femoral venous (RFV) and right femoral arterial (RFA) accesses were obtained. Furthermore, left ventriculography was performed to confirm the size and the localization of the defect in each case. The size of the used coils was selected after final evaluation and ranged from 8 × 6 mm to 12 × 6 mm. The LV-RA defect was crossed with Berenstain 4F catheter in a retrograde fashion from RFA access through the aorta, LV to RA. The guidewire was snared at the superior or inferior vena cava and withdrawn through the femoral venous sheath (femoral arteriovenous loop was made). By RFV access the long delivery sheath was advanced into the ascending aorta and the Nit-Occlud Lê VSD (PFM)-Coil was passed through it. The first loops of the device were released in the aorta and then retracted into LV and the defect area. After confirming the correct position of the device and closure effect in control angiography, the device was slowly pulled back into the defect and final loops were deployed in RA. Another control angiography was performed and providing that the effect was satisfactory the device was released. Finally, the TTE and TEE control examinations were performed. The follow-up consists of regular ambulatory visits with detailed physical examination and TTE. The results are presented as mean ± standard deviation (SD).

Results

The total number of patients enrolled in the present study was eight children (5 females, 3 males). The group consisted of one infant with native and seven children with acquired post-operative LV-RA shunts: one after correction of atrial septal defect type 1 (ASD I) and presented with mitral regurgitation due to significant anterior mitral valve cleft and in six children after a closure of pmVSD [coexisting in five infants with other congenital heart defects: coarctation of the aorta (CoAo) — in two, interrupted aortic arch (IAA) type B — in another two and double outlet right ventricle (DORV) — in one patient]. The age of patients who underwent a surgical correction of a congenital heart defect was highly heterogeneous due to a personalized approach to the treatment of various heart malalignments and ranged

Table 1. Selected data including echocardiography of patients with left ventricle-to-right atrial (LV-RA) defects before the transcatheter treatment

Pts	Gender F/M	Age at the procedure (years)	Weight [kg]	Diagnosis	Selected echocardiographic data				
					Shunt Ø at the LV side [mm]	TVR*	RA enlargement	RV enlargement	Qp/Qs
1. GM	F	0.7	7.4	Native, direct LV--RA shunt	5	II/III°	Moderate	Moderate	2.2:1
2. PK	F	14.7	50	Direct LV-RA-shunt (post-operative: ASD I, with a cleft in the AMVL)	6	≤ I°	Moderate	Moderate	1.7:1
3. RM	M	17.8	56	Indirect LV-RA shunt (post-operative: pmVSD, subAS, CoAo with Ao arch hypoplasia)	4	III°	Severe	Moderate	1.5:1
4. CK	F	7.5	24	Indirect LV-RA shunt (post-operative: IAA type B, bicuspid Ao-valve, pmVSD), Di George S	2.5	≤ II°	Mild	Mild	1.2:1
5. KA	F	14.5	52	Indirect LV-RA shunt (post--operative: DORV, pmVSD)	4.5	≤ II°	Moderate	Moderate	1.7:1
6. KA	M	9	3	Indirect LV-RA shunt (post-operative: pmVSD, CoAo with Ao arch hypoplasia)	3.5	≤ II°	Mild	None	1.7:1
7. MM	M	7	28	Indirect LV-RA shunt (post-operative: IAA type B, pmVSD)	4	< II°	Moderate	Moderate	2:1
8. PZ	F	12.5	40	Indirect LV-RA shunt (post-operative: pmVSD, PDA)	4.5	< II°	Moderate	None	1.6:1
Total	5F 3M	10.46 ± 5.5	35.55 ± 20.3	1 — native true Gerbde defect 7 — acquired, post--cardiac surgery	4.25 ± 1	6 — ≤ II° 1 — II/III° 1 — III°	2 — mild 5 — moderate 1 — severe	5 — moderate 1 — mild 1 — none	1.7 ± 0.3

*≤ II° — mild, II/III° — moderate, III° significant type I — above the tricuspid valve, type II — below tricuspid valve; pts — patients; F — female; M — male; LV — left ventricle; TVR — tricuspid valve regurgitation; RA — right atrium; RV — right ventricle; ASD I — atrial septal defect type 1; AMVL — anterior mitral valve leaflet; pmVSD — perimembranous ventricular septal defect; subAS — membranous subaortic stenosis; CoAo — coarctation of the aorta; Ao — aorta; IAA — interrupted aortic arch; DORV — double outlet right ventricle; PDA — patent ductus arteriosus

from 3 weeks to 13.5 years (2.4 ± 4.95 years). Selected data of patients qualified for the procedure are presented in Table 1. The LV-RA shunt was properly diagnosed in the first postoperative TTE study in five children. In three patients, the initial assessment was incorrect: in one — residual VSD with the tricuspid regurgitation and in the rest (after ASD I and mitral valve repair) only the tricuspid regurgitation were suggested. All patients included in this study were not initially qualified for re-operation. Instead, the children were recommended to continue ambulatory visits and undergo

Table 2. The results of interventional transcatheter closure of left ventricle-to-right atrial shunt with Nit-Occlud Lê VSD (PFM)-Coil

Pts	Shunt Ø (on angiography at LV side) in mm	Device size [mm × mm]	Procedure time [min]	Fluoro-scopy-time [min]	Residual shunt directly after the procedure	Significant complication	Time of hospitalization (days)	Follow-up (months)/ /residual shunt (±)
1. GM	4.5	8 × 6	40	14	Mild	Haemolysis	12	19 (–)
2. PK	3.8	10 × 6	65	19	Trivial*	No	3	36 (+)
3. RM	4.2	12 × 6	65	18	Trivial*	No	4	2 (–)
4. CK	3.5	8 × 6	50	15	No	No	3	25 (–)
5. KA	4.5	10 × 6	60	14	Trivial*	No	3	26 (–)
6. KA	4.2	10 × 6	55	16	No	No	4	13 (–)
7. MM	4.2	10 × 6	40	7	Trivial*	No	3	24 (–)
8. PZ	2.0	8 × 6	45	16	Trivial*	No	5	17 (–)
Total	3.86 ± 0.82		52.5 ± 10.4	14.9 ± 3.6	1 – mild** 5 – trivial* 2 – none	1/8 (12.5%)	4.6 ± 3.1 (3–12)	20.3 ± 10.1

*Trivial: < 1 mm in diameter; **mild: 1–2 mm in diameter; pts – patients; LV – left ventricle

periodic TTE control. In follow-up, the decision was changed and closure of shunt was suggested. In five children, including an infant with true Gerbode defect, enalapril and/or spironolactone were administered due to presentation of congestive heart failure symptoms (e.g., *tachypnoe*, excessive perspiration, early fatigability *etc.*). The age of patients at the time of procedure ranged from 8 months to 17.8 years (10.46 ± 5.5 years), body weight was from 7.4 kg to 56 kg (35.55 ± 20.3 kg). The angiocardiographic study revealed the defect located above the tricuspid valve in three patients (type I) and below in five patients (type II). The diameter of defects based on the TTE was verified and comparable to values found in the angiocardiographic study (4.2 ± 1 mm vs. 3.86 ± 0.82 mm), Qp/Qs ratio was 1.7 ± 0.3. The implantation of a coil was successful in all patients. The procedure time extended from 40 to 65 min (52.5 ± 10.4 min). A procedure of Gerbode defect closure is shown in Figures 1–2. Immediately after the procedure, a residual shunt was observed in six patients: one mild (case of congenital LV-RA shunt) and nonsignificant in five others. In two children the defect was completely closed. The follow-up period was 2–36 months (20.3 ± 10 months). Control TTE studies revealed no residual shunt in seven patients. In one, with the longest follow-up, the residual shunt was still present (≤ 2 mm in diameter, below the implant). In two patients, significant tricuspid regurgitation co-existing with LV-RA defect decreased to benign: in an infant immediately, in the teenager – 2 months after the procedure. The results of transcatheter treatment are shown in Table 2.

In an infant with true Gerbode defect, soon after the procedure haemolysis was observed with a decreased level of haemoglobin – 9.1 g/dL, haematocrit – 27.7% and proteinuria (++). After a blood transfusion and an administration of steroids and propranolol, haematological parameters normalized and proteinuria regressed within 10 days. In another child with pre-existing benign ventricular ectopy, the arrhythmia temporarily worsened immediately after the procedure, but afterwards, it spontaneously relieved in a few following days.

Discussion

LV-RA shunts are an unusual form of VSD. The term "Gerbode defect" was assigned to the anomaly after Gerbode's et al. publication of successful surgical repair in five patients. In their material only one patient had direct and the others – tetralogy of Fallot (TOF) indirect types of LV-RA defects [1]. The very first description of this anomaly was given by Thurnam in 1838 [13], followed by Buhl in 1857 [14]. The first successful surgical closure of LV-RA shunt was performed by Kirby et al. in 1956 [15]. Until recently, the LV-RA defects, regardless of their nature and location have been the domain of cardiac surgical treatment. Progress in interventional transcatheter methods has recently made it possible to close those defects using different types of occluders. The first who performed successful transcatheter treatment of acquired RA-LV shunt (post pmVSD repair) by the Amplatzer ventricular septal occluder was Trehan et al. in 2006 [16]. Moreover, Dangol

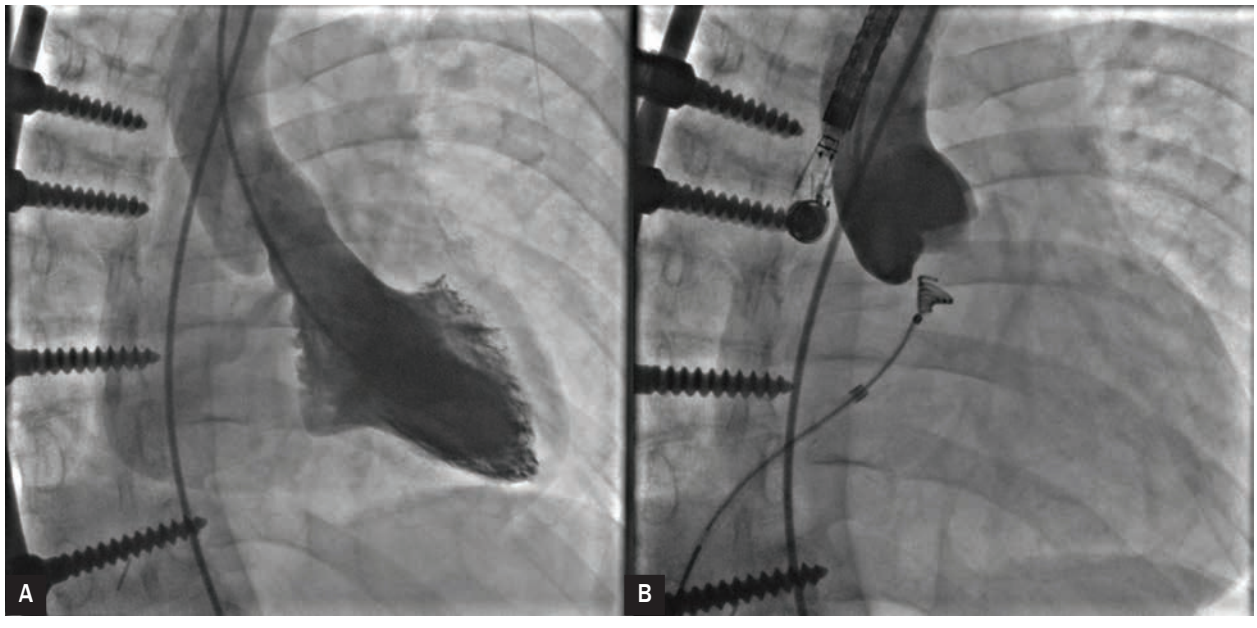

Figure 1. Angiocardiographic image of acquired left ventricle-to-right atrial shunt (type I) before and after closing by Nit-Occlud Lê VSD-Coil: **A.** Left ventriculography (LAO projection) in patient 2 showing the shunt flow to the right atrium; **B.** The same projection illustrating the occluder closing the defect (Nit-Occlud Lê VSD-Coil) at the place of the shunt; VSD — ventricular septal defect

et al. in 2012 described closure of acquired LV-RA shunt in an infant post-TOF repair with the use of ADO occluder [17]. In the group of devices used in the treatment of various types of VSD a specific type of nickel-titanium spiral coil (Nit-Occlud Lê VSD-Coil) became available in August 2010 [12]. This system was applied for the first time by Lê et al. [18] in the population of adult patients. The significant data regarding this device in closing various types of VSD except for Gerbode type defects was presented by Haas et al. [12]. The advantages of that device are its plasticity and that it is fully retrievable. In the case of any complications or incorrect configuration, the device can be removed and implanted again or another size of the device can be used [9, 12]. Moreover, it has low-risk trauma to the conduction system [12].

Clinical symptoms of LV-RA defect are similar to those found in other VSD and depend on the size of the shunt. The key to diagnosis is accurate TTE, especially using parasternal long-axis and apical five-chamber views. However, the LV-RA shunt in TTE may sometimes be misdiagnosed as tricuspid regurgitation. In doubtful and demanding diagnostic cases TEE is necessary and decisive.

In the present material, Gerbode defects closure was successful in all enrolled patients. After the procedure, one case of intravascular haemolysis was observed. This complication has already been described after the use of Nit-Occlud Coils in transcatheter treatment of various types of VSD [12]. Odemis et al. [19] reported a similar frequency (3/20) of this complication among patients who underwent transcatheter closure of pmVSD with Nit-Occlud Lê VSD-Coil. Saygı et al. [20] reported management of intractable haemolysis after the closure of pmVSD with this system in two children. Re-intervention with the use of another coil in one patient was not successful and the child required cardiac surgery with removal of implants. In another case, the residual shunt was successfully closed with the ADO II occluder [20]. Severe haemolysis may require a blood transfusion as in one patient. Propranolol and steroids are also helpful in the treatment of it. In this patient, haemolysis resolved after three days of such combined therapy. Low doses of steroids were administered as prophylaxis for the subsequent several days. However, in very serious cases or if a condition deteriorates despite the treatment, surgical removal of the occluder may be necessary [19, 20]. Haemolysis may also occur when other types of occluders are used in the transcatheter treatment of PDA, ASD or VSD [21, 22]. However, it was suggested that the Nit-Occlud Lê VSD-Coils may have a higher risk of this complication [12, 19, 20].

In mid-term follow-up (17 months after the procedure) non-significant residual shunt was shown in TTE in only one patient. Noteworthily, no conduction disturbances immediately after the procedure and in the follow-up were observed in the study patients. The risk of this complication is probably low due to the flexibility and plasticity of the occluder.

The procedure of LV-RA shunt closure with occluder is demanding and requires a lot of experience. In infants

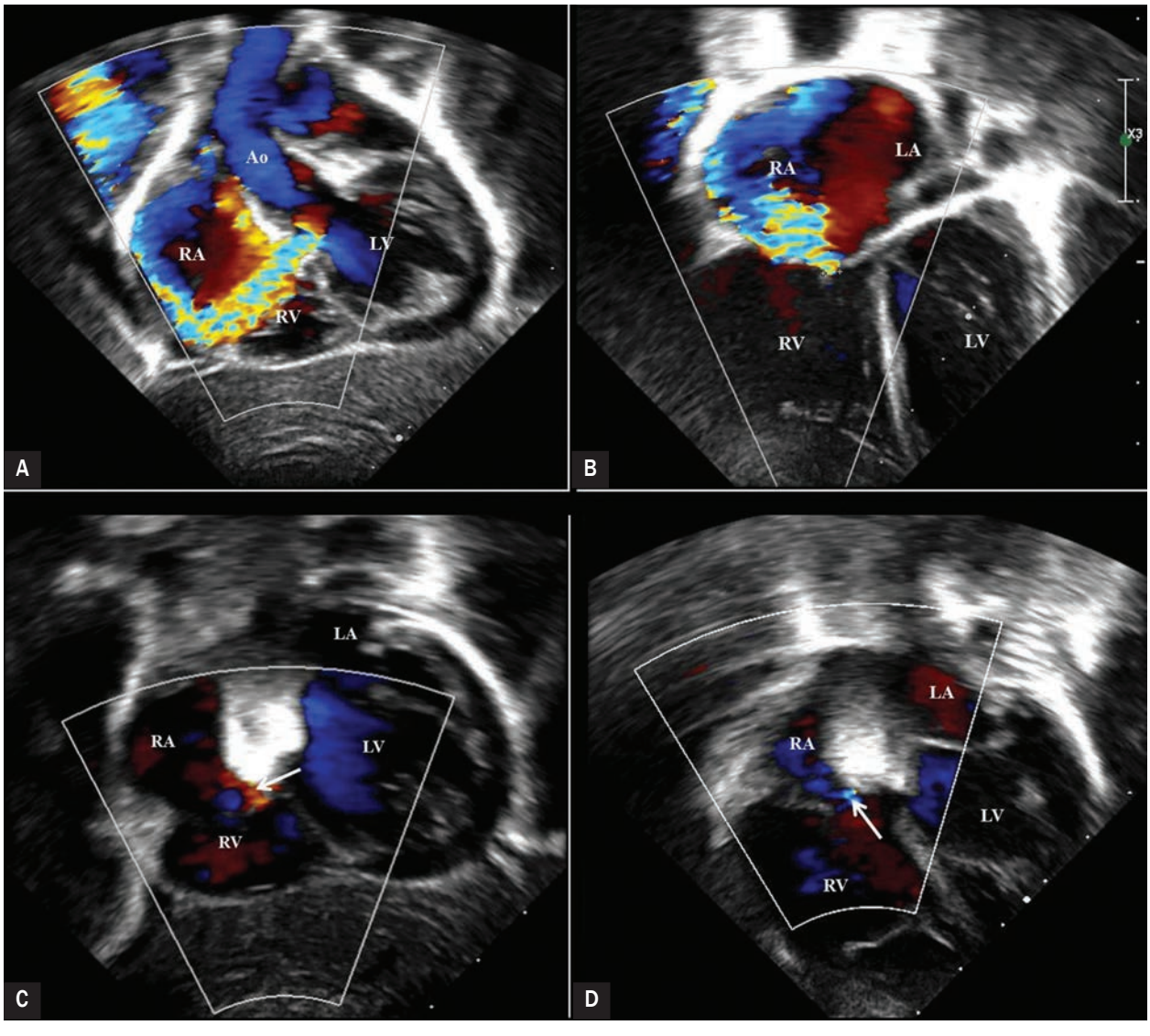

Figure 2A, B. Transthoracic echocardiography image of native, true Gerbode shunt coexisting with significant tricuspid regurgitation in an infant before; **C, D.** After closure with Nit-Occlud Lê VSD device. **A.** A subxiphoid view of the congenital, direct left ventricle-to-right atrial shunt in an 8-month-old infant before the procedure; **B.** Four-chamber view of the same patient showing regurgitation of the tricuspid valve, due to prolapsing of the septal leaflet. No shunts below the septal leaflet of the tricuspid valve were seen; **C.** A subxiphoid transthoracic echocardiography projection demonstrating mild, residual shunt (white arrow) after the closure of true Gerbode defect with Lê VSD-Coil (a bright hourglass-like shadow); **D.** A four-chamber view showing trivial retrograde flow across the tricuspid valve after the procedure in this patient; VSD — ventricular septal defect

a diameter of the ascending aorta evaluation is crucial for the proper formation of the device left loops and their safe movement through the aortic valve. Due to the specific anatomy of the Gerbode type defects (longer and more torturous than muscular or membranous VSD), ADOs and especially Nit-Occlud Lê VSD-Coils seem more suitable to close such defects than other VSD occluders. An additional benefit was decreasing coexisting tricuspid regurgitation in two of the patients. Two mechanisms might explain that phenomenon. In the infant, the length of the Nit Occlud device was sufficient to counteract and stabilize the prolapsing septal leaflet of the tricuspid valve. In the other patient, it was a residual pmVSD jet elimination that improved TV function. Such observations were also presented by Kerst et al. [9].

To the best of the authors' knowledge, this study enrolled one of the biggest groups of patients with different Gerbode defects who underwent closure with Nit-Occlud Lê VSD-Coils. It is also the first suchlike description in the Polish population.

Conclusions

LV-RA shunts closure with use Nit-Occlud Lê VSD-Coils seems to be effective and safe. It requires, however, a lot of experience in transcatheter treatment, especially in the group of the youngest patients. It is a great advantage and alternative for surgery, especially for high-risk patients. More studies in a larger group of patients and longer observation are needed for the more accurate evaluation of this method.

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Conflict of interest

The authors declared no conflict of interest concerning the authorship and/or publication of this article.

Streszczenie

Wstęp. Ubytki typu Gerbode są szczególnym i rzadkim typem ubytków międzykomorowych (VSD) i umożliwiają przeciek między lewą komorą a prawym przedsionkiem (LV-RA). Często mogą być błędnie interpretowane jako VSD z niedomykalnością zastawki trójdzielnej i znacznym nadciśnieniem płucnym. Do niedawna jedynym wyjściem było leczenie chirurgiczne. Jednakże obecnie ich przezskórne leczenie z zastosowaniem zestawów Nit-Occlud Lê VSD-Coils jest nową, ciekawą alternatywą do klasycznego chirurgicznego postępowania. Celem badania była ocena skuteczności i bezpieczeństwa interwencyjnego leczenia ubytków typu Gerbode z zastosowaniem Nit-Occlud Lê VSD-Coils.

Materiał i metody. W przeprowadzonych zabiegach autorzy wykorzystali swoje dotychczasowe doświadczenie w przezskórnym zamykaniu okołobłoniastych VSD. Zabiegi przeprowadzono od października 2014 do października 2018 roku. Dotyczyły pacjentów z ubytkami LV-RA wyselekcjonowanymi na podstawie przezklatkowego badania echokardiograficznego (TTE). Wymiar każdego ubytku ponownie weryfikowano podczas angiografii. W każdym przypadku wykonano również śródoperacyjne przezprzełykowe badanie echokardiograficzne. U wszystkich pacjentów oceniono skuteczność zabiegu i wystąpienie powikłań w czasie obserwacji.

Wyniki. Ostatecznie badana grupa składała się z 8 pacjentów pediatrycznych, w tym 1 niemowlęcia z natywnym i 7 starszych dzieci z nabytym, resztkowym ubytkiem typu Gerbode. Wiek badanych wahał się od 8 miesięcy do 17,8 roku, masa ciała od 7,4 kg do 56 kg, 5 spośród 8 było płci żeńskiej. Średni wymiar ubytku w angiografii wynosił 3,86 ± 0,82 mm i był porównywalny z wartością uzyskaną w TTE. Zabieg był skuteczny u wszystkich pacjentów. Wielkość coili wahała się od 8 × 6 mm do 12 × 6 mm. Po zabiegu odnotowano jeden przypadek hemolizy i jeden przypadek przejściowej arytmii. Okres obserwacji wynosił od 2 do 36 miesięcy. W kontrolnym TTE wykazano tylko mały, rezydualny przeciek u tylko jednego pacjenta.

Wnioski. W wybranych przypadkach interwencyjne leczenie ubytków typu Gerbode stanowi bezpieczną alternatywę dla korekcji chirurgicznej. Niniejsze opracowanie jest jednym z największych dotychczas opublikowanych na temat tej bardzo rzadkiej wady.

Słowa kluczowe: ubytek typu Gerbode, wrodzona wada serca, kardiologia interwencyjna, wada przegrody międzykomorowej, Nit-Occlud Lê VSD-Coil

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Commentary on the original article "Transcatheter closure of congenital and acquired Gerbode defects with Nit-Occlud Lê VSD (PFM) Coil. Immediate and mid-term results" by Piotr Weryński et al.

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In the publication "Transcatheter closure of congenital and acquired Gerbode defects with Nit-Occlud Lê VSD (PFM) Coil. Immediate and mid-term results", the Authors analyze the results of percutaneous closure of left ventricular-to-right atrial defects (LV-RA) using Nit-Occlud Lê VSD-Coil. The study group included 8 patients; one of them was diagnosed with a congenital defect while the rest had LV-RA leak as a complication of previous cardiac surgery [1].

The congenital LV-RA leak defect described by Gerbode et al. [2] in 1958 is rare [< 1% of congenital heart defects (CHDs)]. Acquired leaks, which are also customarily named after the author of the first scientific paper, are more commonly described [2]. Due to the very low prevalence of LV-RA leak, the literature is dominated by descriptions of the treatment of individual cases of this defect. The largest series of patients treated percutaneously with Amplatzer Duct Occluder II kits (12 patients) was described by Vijayalakshimi et al. [3]. In view of casuistic observations and as a result of the lack of treatment guidelines, different criteria for diagnosis and eligibility are used, as well as treatment approaches — conservative, operative or interventional [4–6]. LV-RV leak kits have not been developed for interventional therapy either; therefore, vascular occluders and conventional implants designed for standard closure of atrial septal defect II (ASD II), ventricular septal defect (VSD) and patent ductus arteriosus (PDA) are used — with satisfactory results [4].

Nit-Occlud Lê VSD-Coil is an implant that has been known and successfully used in the interventional therapy of ventricular defects of various morphologies for more than 10 years. Weryński et al. [1] also point to the potential of this method in the treatment of LV-RA leaks. Notwithstanding the limitations associated with a comparative analysis of treatment results of small groups of patients in other reports, it should be emphasised that the effectiveness of the Nit-Occlud Lê VSD-Coil method for the treatment of LV-RA leaks (100%) is very good according to the present study, with a low rate of early complications (transient haemolysis was only described once) [1]. It should also be noted that, as a result of interventional therapy, the majority of patients who underwent cardiac surgery in the past (8 out of 9 patients in the presented group) avoided additional risks and adverse sequelae associated with the need for extensive reoperation due to Gerbode defect.

We would like to congratulate the Authors on the original paper, with an emphasis on a uniquely large group of patients treated with a single method, with clinical evaluation of the results over the 3-year medium-term follow-up. We confidently recommend this publication to the Editorial Committee of *Folia Cardiologica*.

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Komentarz do pracy oryginalnej „Wyniki przezskórnego zamknięcia ubytku typu Gerbode z zastosowaniem Nit-Occlud Lê VSD (PFM) Coil" autorstwa Piotra Weryńskiego i wsp.

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Materiał jest tłumaczeniem komentarza: Haponiuk I, et al. Commentary on the original article "Transcatheter closure of congenital and acquired Gerbode defects with Nit-Occlud Le VSD (PFM) Coil. Immediate and mid-term results" by Piotr Weryński et al. Folia Cardiol. 2021; 16(6): 377–378 DOI: 10.5603/FC.2021.0055. Należy cytować wersję pierwotną

W pracy „Wyniki przezskórnego zamknięcia ubytku typu Gerbode z zastosowaniem Nit Occlud Lê VSD (PFM) Coil" autorzy analizują wyniki przezskórnego zamknięcia ubytku typu lewa komora–prawy przedsionek (LV-RA) z zastosowaniem Nit-Occlud Lê VSD-Coil. W badanej grupie jest 8 pacjentów; u jednego z nich rozpoznano wrodzony ubytek, u pozostałych natomiast przeciek typu LV-RA był powikłaniem wykonanej wcześniej operacji kardiochirurgicznej [1]. Wrodzony ubytek z przeciekiem LV-RA, opisany przez Gerbode i wsp. w 1958 roku [2], występuje rzadko (< 1% wrodzonych wad serca), częściej są opisywane przecieki nabyte, także nazywane zwyczajowo od nazwiska autora pierwszego opracowania naukowego. Ze względu na rzadkie występowanie przecieku typu LV-RA w literaturze dominują opisy leczenia pojedynczych przypadków tej wady. Największą grupę kolejnych pacjentów leczonych przezskórnie z użyciem zestawów Amplatzer Duct Occluder II (12 chorych) opisali Vijayalakshimi i wsp. [3]. Ze względu na obserwacje kazuistyczne, i w następstwie braku wytycznych dotyczących terapii, stosuje się różne kryteria w zakresie diagnostyki i kwalifikacji oraz sposoby leczenia — zarówno zachowawcze, operacyjne, jak i interwencyjne [4–6]. Nie opracowano również przeznaczonych do stosowania w przypadku przecieków typu LA-RV zestawów do leczenia interwencyjnego, dlatego stosuje się klasyczne implanty zaprojektowane do standardowego zamykania ubytków typu otworu wtórnego (ASD II, *atrial septal defect II*), ubytków w przegrodzie międzykomorowej (VSD, *ventricular septal defect*) czy przetrwałego przewodu tętniczego (PDA, *patent ductus arteriosus*) oraz okludery naczyniowe — z dobrymi wynikami [4].

Nit-Occlud Lê VSD-Coil jest implantem znanym i stosowanym z powodzeniem od ponad 10 lat w interwencyjnym leczeniu ubytków międzykomorowych o różnej morfologii. Weryński i wsp. [1] wskazują także na potencjał tej metody w leczeniu przecieków typu LV-RA. Niezależnie od ograniczeń związanych z analizą porównawczą wyników leczenia małych grup pacjentów w innych doniesieniach należy podkreślić, że przedstawiona w pracy skuteczność metody zastosowania Nit-Occlud Lê VSD-Coil w leczeniu przecieków LV-RA (100%) jest bardzo dobra, z obserwowanym małym odsetkiem wczesnych powikłań (opisana jednokrotnie przejściowa hemoliza) [1]. Na uwagę zasługuje również fakt, że większość pacjentów poddanych uprzednio operacji kardiochirurgicznej (8/9 w prezentowanej grupie), dzięki zastosowanemu leczeniu interwencyjnemu, uniknęła dodatkowego ryzyka i niekorzystnych następstw związanych z koniecznością rozległej reoperacji z powodu przecieku typu Gerbode.

Pragniemy pogratulować Autorom oryginalnej pracy, z podkreśleniem unikatowo dużej grupy pacjentów leczonych jedną metodą, z kliniczną oceną wyników w średnio odległym okresie 3 lat, którą z przekonaniem rekomendujemy Komitetowi Redakcyjnemu *Folia Cardiologica*.

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REVIEW ARTICLE/PRACA POGLĄDOWA

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Arterial stiffness in metabolic syndrome: sex-specific differences, clinical consequences, how to prevent?

Sztywność tętnic w zespole metabolicznym — różnice płci, konsekwencje kliniczne, jak zapobiegać?

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Abstract

Non-invasively assessed arterial stiffness has been recently growing interest as a novel marker of cardiovascular (CV) risk. The effects of risk factors on the progression of arterial changes and the development of CV diseases seem to be different in women and men. Arterial stiffness was shown to be primarily determined by age and mean arterial pressure (MAP). Hyperglycaemia and resistance to insulin were identified as contributors to increased arterial stiffness. Metabolic syndrome (MS) accelerates age-related arterial stiffening, leading to the so-called early vascular ageing. Arterial stiffness was also shown to increase with the number of MS components. The effects of MS and its components on arterial stiffness are stronger in women than in men. The sex-specific differences in age-related changes within the cardiovascular system might explain why heart failure with preserved ejection fraction occurs more often in older women than in men. Published evidence suggests that arterial stiffness may be associated with left ventricular diastolic dysfunction in MS patients. Hence, a question arises whether a therapy aimed at optimal control of glycaemia and reduction of arterial stiffness could slow down the development of diastolic heart failure? Lifestyle modifications and pharmacological interventions(de-stiffening) may exert a beneficial effect on arterial stiffness independently from the reduction of blood pressure.

Key words: arterial stiffness, metabolic syndrome

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Introduction

Arterial stiffness is determined by cellular processes, the function of the endothelium and vascular smooth muscle cells and the extracellular matrix's integrity. Stiffening of the arteries was shown to be associated with the risk of cardiovascular diseases (CVD) and all-cause mortality, regardless of the presence of conventional risk factors. Moreover, published evidence suggests that the effects of the risk factors on the progression of vascular changes and development of CVD may be different in women and men [1–4].

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Metabolic syndrome (MS), a cluster of disorders including obesity, resistance to insulin/hyperinsulinemia, dyslipidaemia and arterial hypertension, plays a significant role in the development of CVD through the promotion of inflammation, thrombosis and atherosclerosis. These unfavourable effects of MS lead to vascular damage, and as a result, to a worse prognosis. In MS endothelial dysfunction, the inflammatory response of cytokines, sympathetic overdrive and the renin-angiotensin system's activation contribute to an increase in vascular tone, promote hyperplasia and hypertrophy of smooth muscle cells, enhance the synthesis of collagen and eventually lead to increased arterial stiffness. However, the role of MS as a contributor to arterial stiffness is a matter of debate. The question of whether metabolic syndrome itself as an interplay of several risk factors exerts an additional effect on the progression of arterial stiffening, or the latter is rather associated with the co-existence of various conventional CVD risk factors being components of MS, still raises some controversies [1]. The increase in arterial stiffness is postulated to be an intermediate stage in the development of cardiovascular complications, and recent evidence points to non-invasively assessed arterial stiffness as a novel marker for cardiovascular risk [1–3].

Measurement of a regional parameter, carotid-femoral pulse wave velocity (cfPWV) through applanation tonometry constitutes the gold standard in the assessment of arterial stiffness. The measurement is most often taken with the Complior or Sphygmocor system. Other frequently determined regional parameters of arterial stiffness include cardio-ankle vascular index (CAVI), which is independent of blood pressure (BP) and brachial-ankle PWV (baPWV). Local arterial stiffness can be determined with the Esaote method or through echo-tracking [1, 4–7]. The latter technique allows for simultaneous assessment of arterial stiffness and intima–media thickness (IMT) and hence, provides information about both functional and structural changes within the arteries [1, 4].

Arterial stiffness: sex-specific differences

It is still unclear whether the effects of risk factors on pulse wave velocity (PWV) and augmentation index (AI), a measure of wave reflection, are modulated by sex. Due to the cardioprotective effect of oestrogens, premenopausal women are less likely to suffer from CVD and they develop this condition one decade later than men. Oestrogen deficiency associated with menopause harms cardiovascular function and metabolism, promoting unfavourable changes in adipose tissue distribution, vasculitis, increased sympathetic drive and resistance to insulin. Younger women typically present with lower arterial stiffness than men, but their stiffness indices increase dramatically during the perimenopausal period. The question of whether hormone replacement therapy could reduce arterial stiffness in women is yet to be answered. The sex-specific differences in age-related changes within the cardiovascular system, including changes in arterial stiffness, might explain why older women present with isolated systolic hypertension and heart failure with preserved ejection fraction (HFpEF) more often than men [3, 8–10].

Effects of metabolic syndrome and its components on arterial stiffness

Arterial stiffness was shown to depend primarily on age and mean arterial pressure (MAP). Age is a key determinant of arterial stiffness. Other factors that were demonstrated to contribute to increased arterial stiffness include hyperglycaemia, and/or insulin resistance. According to literature, an increase in arterial stiffness is mediated by advanced glycation end-products (AGEs), tobacco smoking and leptin. The role of the autonomic nervous system and increased heart rate has been postulated as well [1, 2, 4].

Some evidence suggests that premature arterial stiffening can be observed already in persons with increased fasting glucose (IFG) and resistance to insulin associated with prediabetes. In Hoorn study, conducted in a Dutch population (n = 2,500), elevated fasting glucose level was associated with increased arterial stiffness after adjustment for age and blood pressure [11].

A large body of evidence suggests that type 2 diabetes mellitus may be associated with increased arterial stiffness [12, 13]. Increased arterial stiffness, expressed as cfPWV, was shown to be a predictor of mortality in a population of patients with type 2 diabetes [12]. Cardiovascular mortality risk in women with diabetes is 3.3-fold higher than in the general population, compared with "only" 1.8-fold increase in diabetic men. This sex-related difference is postulated to be associated with more rapid arterial stiffening in diabetic women. Enhanced arterial stiffening in diabetes may be a consequence of the increased activity of AGEs and endothelial dysfunction [12, 14, 15]. The question of whether the effect of diabetes on arterial stiffness in women is stronger than in men is yet to be answered and requires further research.

Impaired metabolism of glucose plays a key role in the increase in arterial stiffness in MS. In Bogalusa Heart Study, a growing prevalence of MS components in the young population (24–44 years) was associated with an increase in arterial stiffness. This implies, that MS may accelerate the stiffening processes associated with age, leading to the so-called early vascular ageing (EVA) [16]. In hypertensive perimenopausal women components of MS are stronger predictors of subclinical organ damage than MS itself [17].

The effects of MS and its components on vascular stiffness in various populations are summarized in Table 1. The results of many previous studies suggest that MS has

Table 1. The effects of metabolic syndrome (MS) and its components on arterial stiffness in various populations

No.	Reference	Study population and method	Results
1	Li S et al. Atherosclerosis 2005 [16]	baPWV in 806 asymptomatic healthy young adults (22–44 years, white and black), participants of Bogalusa Heart Study	Arterial stiffness increased with the number of MS components; MS was shown to modulate arterial stiffness in young adults
2	Lin HF et al. Atherosclerosis 2010 [18]	Effects of MS, age and sex on IMT and arterial stiffness determined by means of echotracking in Chinese population from Taiwan (1,245 patients, 22% with MS)	MS contributed to an increase in IMT and arterial stiffness, as shown by higher values of Ep, β and PWVβ; the relationships were more evident in younger women
3	Kim HL et al. J Cardiol. 2015 [19]	Sex-specific differences in the effects of MS components on arterial stiffness determined based on baPWV in Korean population (537 patients, 22.7% with MS)	The association between MS components and arterial stiffness determined based on baPWV was stronger in women aged < 55 years than in men; while the effects of SBP, DBP and TG on baPWV were similar regardless of sex, the significant effect of waist circumference on baPWV was observed solely among women and the effect of fasting glucose only in men
4	Protogerou AD. Atherosclerosis 2007 [20]	Effects of MS on arterial stiffness determined based on PWV and AI in European patients with arterial hypertension (41% with MS)	The effects of MS on PWV and AI were modulated by sex; MS proved to be an independent determinant of arterial stiffness and wave reflection solely in hypertensive women
5	Weng Cet et al. Int J Med Sci. 2012 [21]	Age- and sex-specific differences in the effects of MS on arterial stiffness determined based on baPWV in Chinese population (12,900 patients, 19.4% with MS)	The effects of MS on arterial stiffness differed depending on age and sex; blood pressure turned out to be the strongest predictor of arterial stiffness determined based on baPWV; TG correlated with increased baPWV in middle-aged women and younger men
6	Scuteri A et al. Atherosclerosis 2014 [22]	Effects of MS and its components on arterial stiffness determined based on cfPWV in European and American population (MARE Consortium Metabolic Syndrome and Arteries Research; 20,570 patients, 24.2% with MS)	MS accelerated age-related arterial stiffening in both women and men
7	Gomez-Sanchez L et al. Cardiovasc Diabetol. 2016 [23]	Sex-specific differences in the effects of MS and its components on arterial stiffness determined based on CAVI and baPWV in the European population (MARK study; 2,351 patients, 51.9% with MS)	Among patients with MS, CAVI and baPWV values were higher in men than in women; the effects of MS components on arterial stiffness were sex-specific, with stronger impact observed among men
8	Della-Morte D. Int J Stroke 2010 [24]	Effects of MS on arterial stiffness in 1,133 patients participating in Northern Manhattan Study (older multiethnic population with a mean age of 65 ± 9 years, 49% with MS)	Higher BP and waist circumference had a significant effect on arterial stiffness; MS contributed to higher arterial stiffness, which explains why patients with this condition are at increased risk of stroke
9	Topouchian J et al. J Hypertens. 2018 [25]	Effects of age and MS on arterial stiffness determined with two methods, based on CAVI and cfPWV, in the European population (Triple A — Stiffness Study; 2,224 patients, including 1,664 with MS)	The effects of age and MS differed depending on whether arterial stiffness was determined based on CAVI or cfPWV; age exerted a stronger effect on CAVI while MS had a greater impact on cfPWV; TG and HDL cholesterol levels correlated with cfPWV but not with CAVI; waist circumference correlated positively with cfPWV and inversely with a CAVI
10	Kruszyńska E et al. Diabetes Metab Syndr Obes. 2020 [26]	Sex-specific differences in the effect of MS on arterial stiffness determined by means of echotracking in the European population (419 patients, including 51% with MS)	The effect of MS on arterial stiffness was stronger among women; MS exerted a significant effect on the pulsatile component of blood pressure (PP) in women and steady component (MAP) among men; a paradoxical relationship was found between waist circumference and arterial compliance (AC) in women

baPWV — brachial-ankle pulse wave velocity; IMT — intima-media thickness; Ep — pressure-strain elastic modulus; β — β-stiffness index; PWVβ — one-point pulse wave velocity; TG — triglyceride; PWV — pulse wave velocity; AI — augmentation index; cfPWV — carotid-femoral pulse wave velocity; CAVI — cardio-ankle vascular index; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG — triglycerides; HDL — high-density lipoproteins

a substantial contribution to enhanced arterial stiffening in middle-aged and older populations, especially women, especially Asians [18–21]. As already mentioned, the reasons behind the sex-specific differences in arterial stiffening are still not fully understood. It is postulated that MS contributes to preterm loss of oestrogens' protective effect on the cardiovascular system. However, the effect of MS on arterial stiffening in the European and American population (MARE Consortium) was similar regardless of sex, the number of MS components present in a given patient had a more profound effect in men than in women [22]. Individual components of MS also had a greater contribution to arterial stiffening in males than in female patients in another European population, participants of the MARK trial. These discrepancies might at least in part result from differences in the characteristics of studied populations and methods used to assess arterial stiffness [16, 18, 19–26]. (Table 1).

The relationship between arterial stiffness and hypertension is bidirectional and is referred to as a "vicious circle" in literature, as the two processes accelerate one another. However, the question of which of them, arterial stiffening or hypertension, is a primary component of the circle is still a matter of debate. Elevated blood pressure promotes arterial wall thickening and fibrosis, the two processes involved in the pathogenesis of arterial stiffening [27]. On the other hand, higher arterial stiffness contributes to an increase in blood pressure and pulse pressure (PP), microcirculatory disorders and impaired vasodilation, which leads to the progression of arterial hypertension [27]. In the MARK trial [23] elevated blood pressure, either systolic blood pressure (SBP) or diastolic blood pressure (DBP), turned out to be the strongest determinant of increased arterial stiffness in European patients with MS. Similar results were also obtained in American and Korean populations [19, 24].

Recently, blood pressure is being described with two components, the so-called "steady component" expressed as MAP and the "pulsatile component" expressed as PP. MAP was shown to be a predictor of CVD events, heart and kidney failure, whereas PP is known primarily as a predictor of atherosclerotic changes [28].

Only a few published studies verified whether the link between PP and arterial stiffness depends on patient sex. In this context, particularly interesting is the observation that in a population exposed to risk factors, the pulsatile component of blood pressure PP was associated with the indices of local stiffness determined through echo-tracking in women, but not in men [29]. An association between the echo-tracking determined parameters of local stiffness and PP was also found in women with MS. Meanwhile, in men with this condition, the measures of local stiffness correlated with MAP [26].

Published evidence points to a likely link between blood lipids and arterial stiffness in healthy subjects. Blood triglycerides were identified as an independent predictor of both regional cfPWV and local echo-tracking arterial stiffness in a group of 210 healthy Brazilians [30]. However, the results of some prospective studies imply, that the association between the lipid profile of the blood and arterial stiffness may be different in women and men. In a Swiss observational study SAPALDIA, including 2,545 persons without symptomatic CVD, but with risk factors, higher arterial stiffness was associated with elevated blood triglycerides in women, elevated low-density lipoprotein (LDL) cholesterol in men and increased body mass index (BMI) regardless of sex [31].

Available data on the relationship between obesity and increased arterial stiffness are inconclusive. In pathophysiological terms, the link between the two conditions can be explained by insulin resistance and the overactivation of the renin-angiotensin-aldosterone system in obese persons. Abdominal obesity was shown to be associated with increased arterial stiffness and a higher risk of CVD in young women, counterbalancing the protective effect of hormones. In a study of young Polish women, obesity was associated with increased arterial stiffness indices [32]. Interestingly, in the TRIPLE study, waist circumference correlated positively with cfPWV, but an inverse correlation was found between this parameter and another measure of arterial stiffness, CAVI. The latter relationship was particularly evident in older women [25]. Such a paradoxical association between waist circumference and arterial compliance was also observed in the present study involving the group of middle-aged women [26]. Further research is needed to address the discrepancies mentioned above.

Arterial stiffness and left ventricular diastolic dysfunction

A cardiac complication of MS can be diastolic heart failure. A growing body of evidence suggests that an increase in arterial stiffness may play a vital role in the pathophysiology of heart failure with preserved ejection fraction (HFpEF). To understand the pathophysiology of HFpEF, a concept of ventricular-arterial coupling (VAC) was developed, according to which an increase in arterial stiffness is associated with the increase in the stiffness of the left ventricle. HFpEF is twice as common in women as in men. Women are predisposed to HFpEF because of higher aortic stiffness, lesser arterial compliance and increased pulsatile load [33]. However, little is known about the relationship between the heart and arteries at the early stages of heart failure. An increase in arterial stiffness results in a premature return of wave reflection, which is associated with a raise of central systolic pressure and afterload, eventually leading to

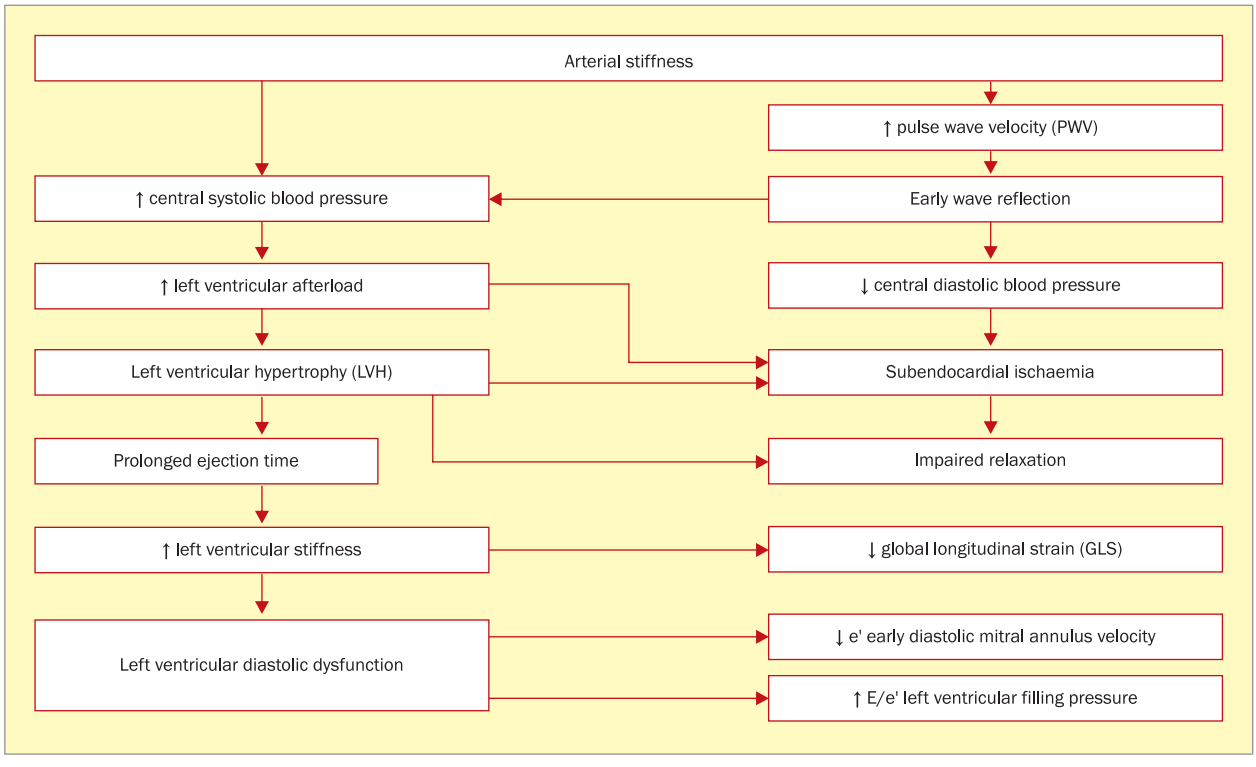

Figure 1. Relationship between arterial stiffness and left ventricular diastolic dysfunction

left ventricular hypertrophy (LVH), prolongation of ejection time and impairment of ventricular relaxation. A concomitant decrease in diastolic pressure contributes to the reduction of coronary perfusion, left ventricular ischemia and relaxation impairment, with a subsequent increase in the stiffness of the left ventricle and its diastolic dysfunction [8, 33] (Figure 1). Recently, tissue Doppler imaging (TDI) has been applied to assess left ventricular diastolic dysfunction. A decrease in global longitudinal strain (LGS) on TDI reflects an increase in left ventricular stiffness. In turn, a decrease in early diastolic mitral annulus velocity (e') is a marker of impaired left ventricular relaxation, and an increase in E/e' ratio (the ratio of early diastolic mitral inflow to early diastolic mitral annulus velocity) reflects an increase in left ventricular filling pressure (Figure 1).

The results of some published studies suggest that the link between arterial stiffness and left ventricular diastolic dysfunction might occur in different populations. In a group of older women without structural heart disease (n = 819), arterial stiffness expressed as baPWV was shown to be associated with some TDI indices. Namely, an inverse correlation was found between baPWV and e' wave as a measure of left ventricular relaxation, along with a positive correlation between baPWV and E/e', a marker of left ventricular filling pressure [34]. In another study, including 127 asymptomatic persons with risk factors for heart failure (stage A), a significant association was observed between increased vascular stiffness determined through echo-tracking and left ventricular diastolic dysfunction [35]. A significant relationship between the local stiffness index (PWV beta) determined with echo-tracking and left ventricular diastolic dysfunction was also demonstrated in a study of patients with untreated arterial hypertension [36].

In a group of 1,119 patients with MS and left ventricular diastolic dysfunction, a significant determinant of the latter turned out to be cfPWV determined through applanation tonometry [37]. In another study of 131 patients with MS, arterial compliance (AC) was an independent predictor of left ventricular diastolic dysfunction in men, but not in women [38]. Finally, in patients with diabetes mellitus, glycated haemoglobin level was shown to correlate with left ventricular mass and aortic stiffness [39]. Considering all the above, a question arises, if a therapy aimed at optimal control of glycemia and reduction of arterial stiffness could slow down the progression of diastolic heart failure?

Pharmacological and non-pharmacological strategies to improve arterial stiffness

Many previous studies demonstrated that lifestyle modifications and pharmacological interventions might exert a beneficial effect on arterial stiffness independently from the reduction of blood pressure. A concept of de-stiffening, i.e., reduction of arterial stiffness and/or wave

reflection, has been proposed as a way to prevent arterial hypertension and cardiovascular diseases. This concept has been derived from the observation that the renin–angiotensin–aldosterone system's (RAAS) blockade exerts an antiproliferative effect on vascular smooth muscle cells. The inhibition of the RAAS was shown to contribute to a decrease in PWV and wave reflection. Research showed that aside from anti-atherosclerotic, anti-inflammatory and anti-proliferative action, angiotensin-converting enzyme inhibitors (ACEI) and sartans can also target the mechanisms involved in arterial stiffening. Reduction of MAP was identified as a primary mechanism contributing to a decrease in arterial stiffness. However, the reduction of central SBP and central PP should be considered important de-stiffening mechanisms independent of MAP changes. Modulators of the renin-angiotensin system, Ca blockers and insulin were shown to reduce both wave reflection and central SBP [3, 28]. Moreover, some drugs, such as ACEI, angiotensin receptor II inhibitors, aldosterone antagonists and calcium antagonists are known to increase arterial compliance. Also, cardio-selective beta-blocker nebivolol and statins were shown to exert a beneficial effect on arterial function. Main non-pharmacological strategies that were proven to decrease arterial stiffness include regular physical activity and the reduction of dietary salt intake [3].

Conclusions

To summarize, published evidence suggests that the effects of metabolic syndrome and its components on arterial stiffness are stronger in women than in men. An increase in arterial stiffness plays a crucial role in the development of diastolic heart dysfunction. Lifestyle modifications and pharmacological interventions (de-stiffening) may exert a beneficial effect on arterial stiffness independently of blood pressure reduction.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Ostatnio zwiększa się zainteresowanie nieinwazyjną oceną sztywności tętnic jako nowym markerem ryzyka sercowo-naczyniowego (CV). Zwraca się uwagę na odrębny wpływ czynników ryzyka na postęp zmian naczyniowych i rozwój chorób CV u kobiet i mężczyzn. Udowodniono, że sztywność tętnic w głównej mierze zależy od wieku i średniego ciśnienia tętniczego. Wykazano wpływ hiperglikemii i oporności na insulinę na wzrost sztywności naczyń. Dowiedziono, że zespół metaboliczny (MS) akceleruje procesy sztywności związane z wiekiem, tak zwany wczesny wiek naczyniowy. Zanotowano wyższe wartości sztywności ze wzrostem komponent zespołu metabolicznego. Wpływ MS i jego komponent na sztywność tętnic jest silniej zaznaczony u kobiet niż u mężczyzn. Odmienny przebieg zmian w układzie CV z wiekiem i płcią, w tym także dotyczących sztywnienia tętnic, może odpowiadać za częstsze występowanie niewydolności serca z zachowaną frakcją wyrzutową u starszych kobiet niż u mężczyzn. W literaturze pojawiają się prace, których autorzy wskazują na zależność między sztywnością tętnic a dysfunkcją rozkurczową lewej komory w MS. Czy zatem terapia zmierzająca do optymalnej kontroli glikemii i ograniczenia sztywności naczyń może opóźnić rozwój rozkurczowej niewydolności serca? Zmiana stylu życia i interwencje farmakologiczne mogą korzystnie wpływać na sztywność tętnic (*de-stiffening*) niezależnie od obniżenia ciśnienia tętniczego.

Słowa kluczowe: sztywność tętnic, zespół metaboliczny

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Sodium-glucose co-transporter 2 inhibitors therapy: not only for diabetologists

Terapia inhibitorami kontransportera sodowo-glukozowego 2 — nie tylko dla diabetologów

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Abstract

Recently, sodium-glucose co-transporter 2 inhibitors have made a major breakthrough in the treatment of type 2 diabetes mellitus and heart failure (HF). Dapagliflozin and empagliflozin are advised to decrease risk of HF hospitalization as well as cardiovascular (CV) death in heart failure with reduced ejection fraction. Moreover, dapagliflozin has also been shown to be an effective drug in the chronic kidney disease patients' population, reducing the number of renal events and CV mortality.

And sotagliflozin, which is also an inhibitor of sodium-glucose co-transporter 1, occurred to be a beneficial therapy in patients with diabetes, hospitalised due to HF exacerbation. Subsequently, it also seems to be a drug that could be used in heart failure with preserved ejection fraction, however, more studies are needed to support this conclusion.

Key words: SGLT2 inhibitors, heart failure, chronic kidney disease

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Introduction

In recent years, large clinical trials have been conducted to prove the effectiveness of sodium-glucose co-transporter 2 inhibitors (SGLT2i), not only in patients with type 2 diabetes mellitus (T2DM) but also among the chronic heart failure with reduced ejection fraction (HFrEF) population. HF often coexists with T2DM [1]. This fact significantly aggravates patients' prognosis as well as increases the risk of major adverse cardiovascular effects (MACE) and hospitalization for HF [1, 2]. Therefore, glycaemic levels should be monitored periodically to minimize the risk of cardiovascular (CV) events [3]. For this reason, the effects of empagliflozin in patients with T2DM and high CV risk were first investigated [4]. The next step was the obvious question of whether SGLT2i would therefore affect HFrEF patients with or without coexisting T2DM.

This paper aims to summarize the results of the Dapagliflozin And prevention of Adverse outcomes in Heart Failure trial (DAPA-HF), EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction trial (EMPEROR-Reduced), Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial as well as to indicate the conclusions that can be drawn from them.

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Heart failure with a reduced ejection fraction

The results of both studies are similar, although there are subtle differences [5]. To start with, the EMPEROR-Reduced patients' population was significantly smaller (n = 3,730) compared to the DAPA-HF trial (n = 4,744). EMPEROR--Reduced, as well as DAPA-HF researchers, divided the group of patients depending on left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level related to the heart rhythm (sinus rhythm vs atrial fibrillation). Subsequently, EMPEROR-Reduced respondents were divided into four clinical groups based on the abovementioned parameters. Consequently, EMPEROR-Reduced patients occurred to have a higher level of NT-proBNP compared to the DAPA-HF population [5–7]. Moreover, the estimated glomerular filtration rate (eGFR) level for inclusion criterion was also lower in EMPEROR--Reduced (20 mL/min/1.73 m^2) than in DAPA-HF (30 mL/ /min/1.73 m^2) [5].

Regarding the characteristics of the studied populations, it is worth noting that T2DM likewise non-diabetic patients accounted for ~ 50% in each of the studies [8].

When it comes to treatment, it should be noted that the recommended angiotensin receptor-neprilysin inhibitor (ARNi) treatment was almost twice as high in EMPEROR--Reduced than in DAPA-HF as well as a more effective treatment in the field of an implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT) [5, 8].

In the EMPEROR-Reduced trial, primary compound result of death from CV reasons or HF hospitalization for HF happened in 361 among 1,863 patients in the treatment group and in 462 among 1,867 patients in the control group. The rate of primary end-point events was 15.8 per 100 patient-years in the empagliflozin group and 21.0 per 100 patient-years in the placebo group [hazard ratio (HR), 0.75; 95% confidence interval (CI): 0.65–0.86, p < 0.001].

The secondary outcomes were consistent with the results of the primary outcome analysis (total number of hospitalizations for HF) — 388 events in the empagliflozin group and 553 in the placebo group (HR 0.70, 95% CI: 0.58–0.85, p < 0.001). During the double-blind treatment period the eGFR decreased lesser in the empagliflozin group than in the placebo group (–0.55 mL/ /min/1.73 m^2 per year vs. –2.28 mL/min/1.73 m^2 per year), for a between-group difference of 1.73 mL/min/1.73 m^2 per year (95% CI: 1.10–2.37, p < 0.001) [9].

In the DAPA-HF trial, the primary composite outcome of HF exacerbation or death because of CV causes occurred in 386 of 2,373 patients in the dapagliflozin group compared to 502 of 2,371 patients (21.2%) in the placebo group. The rate of primary end-point events was 11.6 per 100 patient-years in the dapagliflozin group and 15.6 per 100 patient-years in the placebo group (HR 0.74; 95% CI: 0.65–0.85, p < 0.001).

When it comes to secondary composite outcomes, the incidence of worsening of HF or death due to CV causes was lower in the dapagliflozin group — 382 events — than in the placebo group — 495 events (HR 0.75, 95% CI: 0.65–-0.85, p < 0.001) [6].

Despite slight differences, the EMPEROR-Reduced and DAPA-HF studies share common conclusions. The Heart Failure Association of the European Society of Cardiology has updated its statement on SGLT2i in the treatment of HF and concluded that the effectiveness of canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin in preventing hospitalization due to HF in patients with T2DM and those who are at high CV risk was proven [10]. A comparison of the abovementioned studies, as well as SOLOIST-WHF, is provided in Table 1.

What do we know so far about sotagliflozin?

While the effects of SGLTi on HFrEF are already known, the question of how these drugs might work on heart failure with preserved ejection fraction (HFpEF) has appeared.

Table 1. Summary of clinical trials of sodium-glucose co-transporter-1 and -2 inhibitors

Parameter	EMPEROR-Reduced	DAPA-HF	SOLOIST-WHF
Number of patients	3730	4744	1222
Median LVEF [%]	27	31	35
Median NT-proBNP [pg/mL]	~1900	1437	1799.7
Median eGFR [mL/min/1.73 m^2]	62	66	49.7
Diabetes [%]	50	42	100
ARNi treatment [%]	19	11	16.8
Primary endpoint [HR (95% CI)]	0.75 (0.65–0.86)	0.74 (0.65–0.85)	0.67 (0.52–0.85)
Secondary endpoint [HR (95% CI)]	0.70 (0.58–0.85)	0.75 (0.65–0.85)	0.64 (0.49–0.83)

LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro B-type natriuretic peptide; eGFR — estimated glomerular filtration rate; ARNi — angiotensin receptor-nephrilysin inhibitor; HR — hazard ratio; CI — confidence interval

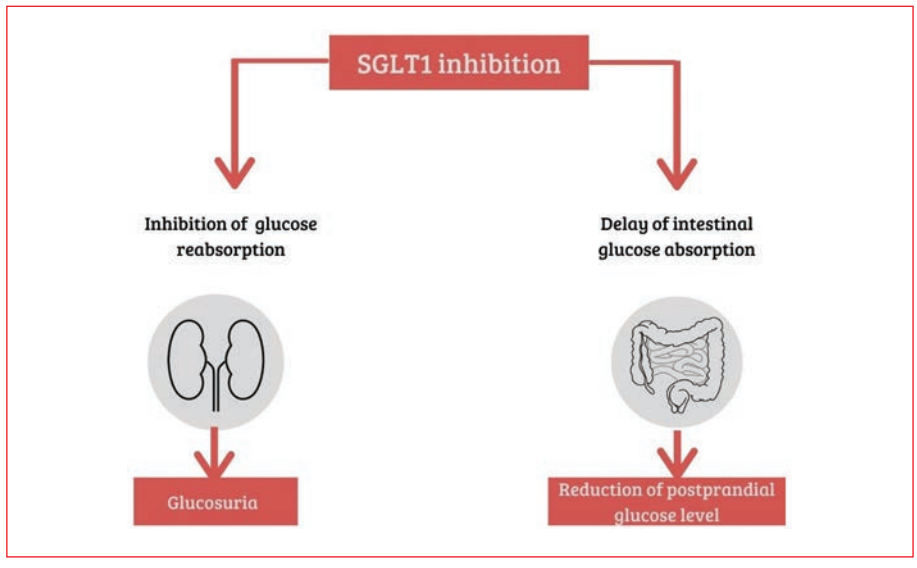

Figure 1. Mechanism of sodium-glucose co-transporter 1 (SGLT1) inhibition

Moreover, the effectiveness of SGLTi after an incident of HF exacerbation remains unknown [11]. The effect of SOLOIST-WHF trial was a consequence of the abovementioned considerations.

Sotagliflozin is not only an SGLT2i, but it also ensures gastrointestinal SGLT1 inhibition, which causes the delay of intestinal glucose absorption that leads to reduction of postprandial glucose level [11].

Patients enrolled in the study were required to have been hospitalized due to worsening of HF with an left ventricular ejection fraction (LVEF) < 50% and ≥ 50% and had been administered intravenous diuretic therapy on hospitalization. Another including criterion required a previous diagnosis of T2DM. The population also needed to have elevated NT-proBNP at the time of randomization. The median glycated haemoglobin level was 7.1%. The patients received adequate therapy for HF, and 85.4% of them were being treated with a glucose-lowering medication. The first intake of sotagliflozin or placebo was administered prior to discharge in 48.8% and a median of 2 days following the discharge in 51.2% [11].

Several 600 primary end-point events happened among 1,222 patients — 245 in the sotagliflozin group and 355 in the placebo group. The rate of primary end-point events was 51.0 per 100 patient-years in the sotagliflozin group and 76.3 per 100 patient-years in the placebo group (HR 0.67; 95% CI: 0.52–0.85, p < 0.001).

The results of the first secondary endpoint analysis (the total number of hospitalizations and urgent visits for HF) were corresponding with the results of the primary end-point analysis — 194 patients in the sotagliflozin group and 297 in the placebo group. The rate of the first secondary endpoint events was 40.4 per 100 patient-years in the sotagliflozin group and 63.9 per 100 patient-years in the placebo group (HR 0.64, 95% CI 0.49–0.83, p < 0.001).

When it comes to the change in the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) score, the difference between those groups was 4.1 points (95% CI: 1.3–7.0) in favour of the sotagliflozin group, and the between-group difference in the change in the eGFR during follow-up was –0.16 mL per minute per 1.73 m^2 (95% CI, −1.30 to 0.98) in favour of the placebo group [11]. Bhatt et al. [11] suggested that SGLT2i with contemporary inhibition of SGLT1 could be beneficial in HFpEF. However, it is too early to draw firm conclusions and more research is needed on a larger patients' HFpEF population than in the SOLOIST-WHF study (n = 256). The mechanism of SGLT1 inhibition is shown in Figure 1.

SGLT2i — not only diabetes and heart failure

Chronic kidney disease (CKD) is another condition where the coexistence of diabetes is very common. Furthermore, this group of patients is at a high risk of adverse renal or CV incidents [12]. Therefore, the DAPA-CKD trial was conducted to assess the influence of dapagliflozin on renal parameters and CV deaths in CKD patients with or without diabetes. The number of 4,304 patients with eGFR of 25 to 75 mL/ /min/1.73 m^2 and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5,000 were randomized to be treated with dapagliflozin (10 mg daily) or with placebo.

The primary outcome event (death from renal or CV causes, a decline of at least 50% in the eGFR or end-stage kidney disease) occurred in 197 of 2,152 participants (9.2%) in the dapagliflozin group and 312 of 2,152 participants (14.5%) in the placebo group (HR 0.61, 95% CI:

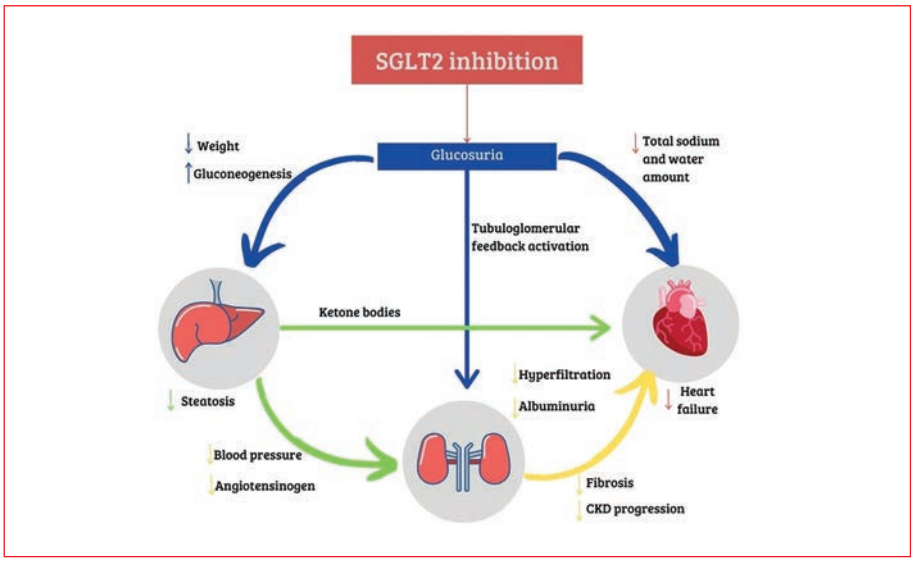

Figure 2. Pleiotropic effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors; CKD — chronic kidney disease

0.51–0.72, p < 0.001). The HR for the composite of a persistent decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI: 0.45–0.68, p < 0.001) [12]. In DAPA-CKD the results of dapagliflozin therapy were similar in participants with T2DM and those without T2DM. The known nephroprotective profile of dapagliflozin was confirmed [12]. Similarly, the nephroprotective effect of dapagliflozin was indicated in the EMPEROR-Reduced study by reducing clinically significant renal events by 50% [13]. The pleiotropic effect of SGLT2i is shown in Figure 2.

Conclusions

Dapagliflozin as well as empagliflozin treatment is recommended to reduce both the risk of HF hospitalization and CV death in symptomatic patients with HFrEF and last but not least — regardless of the presence of the T2DM [12]. Dapagliflozin is also the first nephrologic drug that improves the prognosis for renal and CV endpoints in the CKD patients' population.

Sotagliflozin therapy caused a reduced number of deaths from CV reasons and hospitalizations due to HF acute decompensation in patients with diabetes hospitalized due to worsening HF.

SGLT2i are drugs with multidirectional beneficial effects on the heart, kidneys and diabetes, therefore they are drugs in hands of diabetologists and cardiologists but also for nephrologists.

Conflict of interest

Sawościan M: none; Lelonek M: AstraZeneca, Boehringer Ingelheim — lectures and expert honoraria.

Streszczenie

Ostatnio inhibitory kotransportera sodowo-glukozowego 2 spowodowały, że dokonał się znaczący przełom w leczeniu cukrzycy typu 2 i niewydolności serca (HF). Zaleca się stosowanie dapagliflozyny i empagliflozyny w celu obniżenia ryzyka hospitalizacji z powodu HF i zgonu z przyczyn sercowo-naczyniowych (CV) w niewydolności serca ze zmniejszoną frakcją wyrzutową. Ponadto wykazano, że dapagliflozyna jest skutecznym lekiem w populacji pacjentów z przewlekłą chorobą nerek, zmniejszając liczbę incydentów nerkowych i śmiertelność z przyczyn CV.

Natomiast sotagliflozyna, która jest także inhibitorem kotransportera sodowo-glukozowego 1, okazała się korzystną terapią u chorych na cukrzycę hospitalizowanych z powodu zaostrzenia HF. Co więcej, wydaje się, że jest to lek, który można by stosować w niewydolności serca z zachowaną frakcją wyrzutową, jednak potrzebna jest większa liczba badań, aby potwierdzić ten wniosek.

Słowa kluczowe: inhibitory SGLT-2, niewydolność serca, przewlekła choroba nerek

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CASE REPORT

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An 84-year-old man with dyspnoea, tumour in the left atrium suspected and diaphragmatic hiatal hernia diagnosed

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Abstract

This article discusses the case of an 84-year-old patient who presented to the Clinic of Cardiology due to worsening dyspnoea. The patient's echocardiogram revealed a tumour in the left atrium, suggestive of myxoma.

Key words: cardiac tumour, myxoma

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Introduction

Tumour-like lesions in the heart can be neoplastic and non-neoplastic [1]. Cardiac tumours are structures located within the cardiac chambers, individual layers of the heart or the entire cross-section of the heart wall. Primary cardiac tumours are less common than metastatic tumours [2]. In the case of primary tumours, more than 75% of them are benign [2, 3]. The most common primary benign tumour is myxoma that can be usually found in the left atrium [4]. Almost all malignancies (excluding central nervous system tumours) can metastasise to the heart. The most common source of metastases to the heart is lung cancer (approx. 30–40% of cases). Others include breast cancer, oesophageal cancer, melanoma, leukaemia or lymphoma [5]. Additional structures that can be observed in the heart, in addition to proliferative lesions, may include thrombi, bacterial vegetations, inflammatory tumours, abscesses, *etc.* [1]. Differential diagnosis, based mainly on imaging tests, is thus necessary because the management is different in each of these cases [2]. The prognosis can vary greatly, depending on the established diagnosis. Complete cure is possible in cases of thrombus, bacterial vegetations or benign primary cardiac tumours. Malignant primary tumours and metastases have a very poor prognosis; usually, the survival time is less than one year after diagnosis.

Case report

An 84-year-old patient was admitted to the department of cardiology for dyspnoea that had been worsening for several weeks. The symptoms occurred primarily at night, causing sleeping difficulty. In addition, the patient suffered from occasional coughing. Otherwise, the patient did not complain about any other symptoms of respiratory tract infection. The patient was previously treated for chronic heart failure and preserved left ventricular ejection fraction. He was diagnosed with moderate aortic stenosis. Due to sinus node disease, he had a dual-chamber pacemaker implanted the previous year. Moreover, the replacement of the ventricular lead was performed due to its dysfunction approximately 3 months before the discussed hospitalisation.

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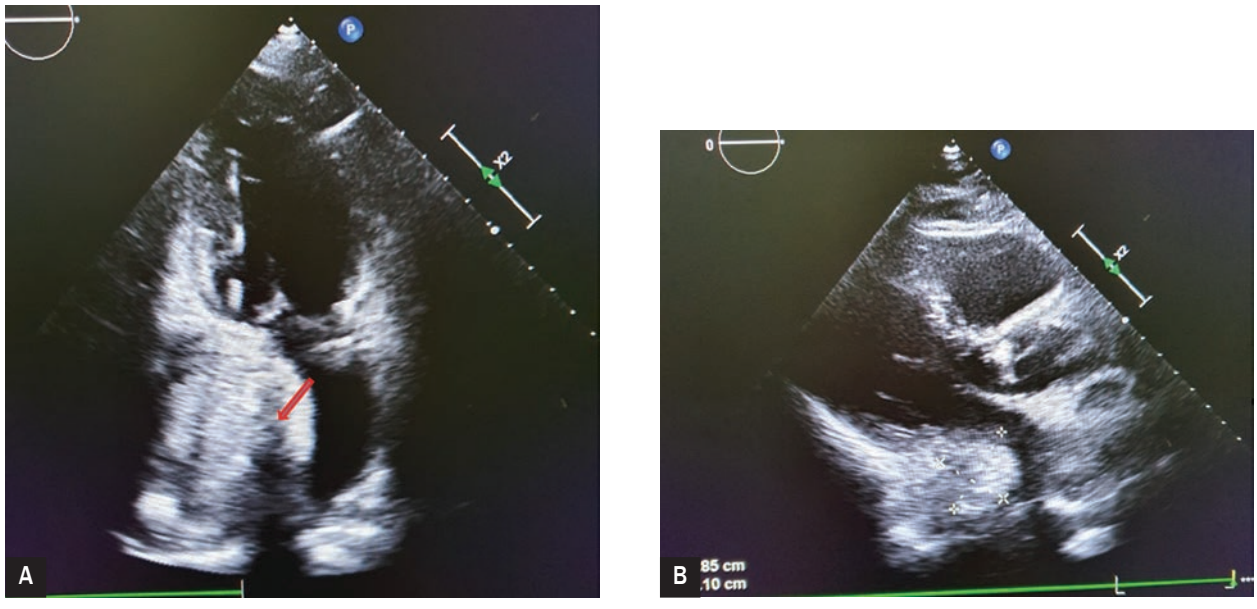

Figure 1. Transthoracic echocardiography: **A.** Dual-chamber view — a structure compressing the left atrium marked with an arrow; **B.** Parasternal long-axis view — a structure protruding into the left atrial chamber marked

On admission, the patient was in overall good condition. He reported mild dyspnoea, he was not febrile. The physical examination revealed a quiet systolic murmur during auscultation of the aortic valve, normal vesicular murmur over the lung fields. There was no evidence of peripheral oedema. The electrocardiographic (ECG) recording revealed DDD pacing at 65 bpm.

The laboratory tests revealed mild anaemia [haemoglobin (Hb) 10.8 g/dL], iron deficiency (Fe 53 µg/dL) and ferritin deficiency (15 ng/mL), slightly elevated C-reactive protein (CRP) levels (15.14 mg/dL) and elevated D-dimer levels (1,376 µg/L), as well as normal B-type natriuretic peptide (BNP) values (24 pg/mL) and a negative polymerase chain reaction (PCR) test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The chest X-ray revealed abnormalities such as fine fibrosis in the left lung apex, a 4 mm nodule of high density at the base of the right lung and calcifications in the aortic arch — these lesions were also observed on X-ray on the previous year; no progression. On the second day of hospitalisation, transthoracic echocardiography (TTE) was performed, which revealed enlargement of the left atrium (57 mm) and the presence of a tumour-like lesion in the left atrial chamber. As suggested by the echocardiographer, this lesion may be a structure originating from the left atrial wall or is a tumour protruding into the atrial chamber and originating from extracardiac structures (Figure 1). The patient was referred for further diagnostic testing of the suspected tumour and computed tomography (CT) scan was recommended. A chest CT scan revealed the presence of an oesophageal hiatal hernia measuring 35 × 55 mm, without any pathological structure in the left atrial chamber (Figure 2).

The patient was surgically consulted; conservative management was recommended. A proton-pump inhibitor was initiated, an appropriate diet was advised, and a referral to the Gastrology Outpatient Clinic was made. The patient was discharged home in stable condition.

Discussion

The tumour-like lesions occurring in the heart are largely benign [3]. The most common diagnosis is left atrial myxoma, which was suspected in the patient in question. Other primary benign lesions include papillary fibroelastoma, lipoma and rhabdomyoma [3]. Primary malignant lesions include various types of sarcomas, lymphomas or pericardial mesothelioma.

Symptoms of cardiac tumours depend primarily on their size and location, but less on their histological structure [6]. Depending on the location of the tumour, there may be consequences in the form of pulmonary embolism, peripheral embolism (usually stroke), cardiac arrhythmias [4, 7], cardiac tamponade or symptoms of heart failure. In an observational study conducted on 36 patients hospitalised for myxoma, as many as 8 patients (22%) presented with neurological symptoms. Stroke was the most common diagnosis (75%), followed by transient ischemic attack (TIA)

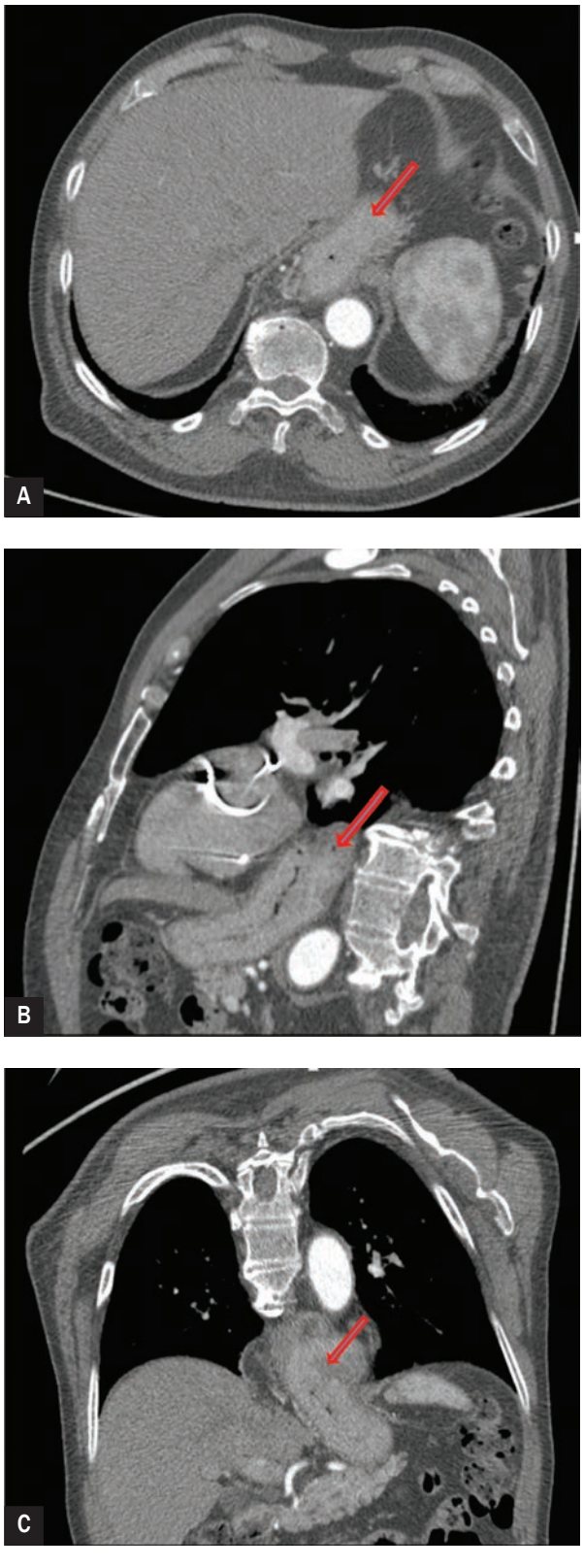

Figure 2. Chest computed tomography — diaphragmatic hiatal hernia marked with an arrow: **A.** Transverse section (cross-section); **B.** Sagittal section; **C.** Coronal section

[8]. Orthopnoea predominated in the patient in question [4]. He also suffered from occasional coughing. The aforementioned symptoms suggested heart failure.

The diagnosis of cardiac tumours is usually based on echocardiographic findings and CT or magnetic resonance imaging (MRI) scans [2]. Echocardiography can determine the location, extent, morphology and possible hemodynamic abnormalities. CT and MRI provide a complete assessment of tumour location and progression. They also better visualise the pericardium and large vessels. The MRI assesses myocardial infiltration, enables differentiation of the neoplasm from the thrombus, and sometimes makes it possible to indicate a histological type of the tumour [9]. It is advisable to seek a diagnosis as soon as possible and implement appropriate treatment to avoid the progression of symptoms and complications. Even benign lesions such as myxoma may cause severe symptoms due to their location and their relationship to the mitral valve. They may also cause severe complications (including death) such as peripheral embolism. Surgical treatment is the treatment of choice in patients with cardiac tumours, provided that the tumour is not a manifestation of advanced cancer. Out of the nineteen patients hospitalised in the Department of Cardiac Surgery in the period 2008–2014 and operated on for the cardiac tumour, three patients died in the early postoperative period, while sixteen patients were discharged home and survived the 2.5-year follow-up period. The long-term prognosis in patients operated on for the cardiac tumour is favourable [9].

In the patient in question, his symptoms were indicative of heart failure. The performed echocardiography raised the suspicion of the cardiac tumour, however, such diagnosis needed to be verified by an additional imaging test. A cardiac cause of the complaints was ruled out on a CT scan.

Summary

In the patient in question, GI disease was manifested by cardiac symptoms, and the echocardiographic picture suggested a cardiac tumour. Expanded diagnostic testing led to a formal diagnosis and management.

Conflict of interest

The authors declare no conflict of interest.

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Mężczyzna w wieku 84 lat z dusznością, podejrzeniem guza w lewym przedsionku i rozpoznaną przepukliną rozworu przełykowego przepony

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Artykuł jest tłumaczeniem pracy: Major A et al. An 84-year-old man with dyspnoea, tumour in the left atrium suspected and diaphragmatic hiatal hernia diagnosed. 2021; 16(6): 394–397. DOI: 10.5603/FC.a2021.0051. Należy cytować wersję pierwotną

Streszczenie

Omówiono przypadek 84-letniego chorego, który zgłosił się do kliniki kardiologii z powodu nasilającej się duszności. U pacjenta w badaniu echokardiograficznym opisano zmianę guzowatą w lewym przedsionku sugerującą śluzaka.

Słowa kluczowe: guz serca, śluzak

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Wstęp

Zmiany o morfologii guza występujące w sercu mogą mieć charakter nowotworowy i nienowotworowy [1]. Nowotwory serca to struktury zlokalizowane w obrębie jam serca, poszczególnych warstw lub całego przekroju jego ściany. Pierwotne guzy serca występują rzadziej niż guzy przerzutowe [2]. Wśród nowotworów pierwotnych ponad 75% ma charakter niezłośliwy [2, 3]. Najczęstszym pierwotnym guzem łagodnym jest śluzak lokalizujący się głównie w lewym przedsionku [4]. Prawie wszystkie nowotwory złośliwe (poza guzami ośrodkowego układu nerwowego [OUN]) mogą powodować przerzuty do serca. Najczęstszym źródłem takich przerzutów jest rak płuca (30–40%), do innych należą rak piersi, przełyku, czerniak, białaczka czy chłoniak [5]. Dodatkowymi strukturami obserwowanymi w sercu, oprócz zmian rozrostowych, mogą być skrzepliny, wegetacje bakteryjne, guzy zapalne, ropnie itp. [1]. Konieczna jest zatem diagnostyka różnicowa, oparta głównie na badaniach obrazowych, ponieważ postępowanie jest inne w każdym z tych przypadków [2]. W zależności od ustalonego rozpoznania rokowanie może być bardzo różne. W przypadku skrzepliny, wegetacji bakteryjnych czy łagodnych pierwotnych guzów serca możliwe jest całkowite wyleczenie. Złośliwe nowotwory pierwotne i przerzuty nowotworowe rokują bardzo źle; zwykle czas przeżycia nie przekracza roku od rozpoznania.

Opis przypadku

Do kliniki kardiologii został przyjęty 84-letni pacjent z powodu nasilającej się od kilku tygodni duszności. Objawy występowały przede wszystkim w nocy, utrudniając choremu sen. Dodatkowo okresowo występował kaszel, poza tym chory nie podawał innych objawów infekcji dróg oddechowych. Pacjent dotychczas był leczony z powodu przewlekłej niewydolności serca z zachowaną frakcją wyrzutową lewej komory, miał rozpoznane zwężenie zastawki aortalnej umiarkowanego stopnia oraz rok temu implantowany kardiostymulator dwujamowy z powodu choroby węzła

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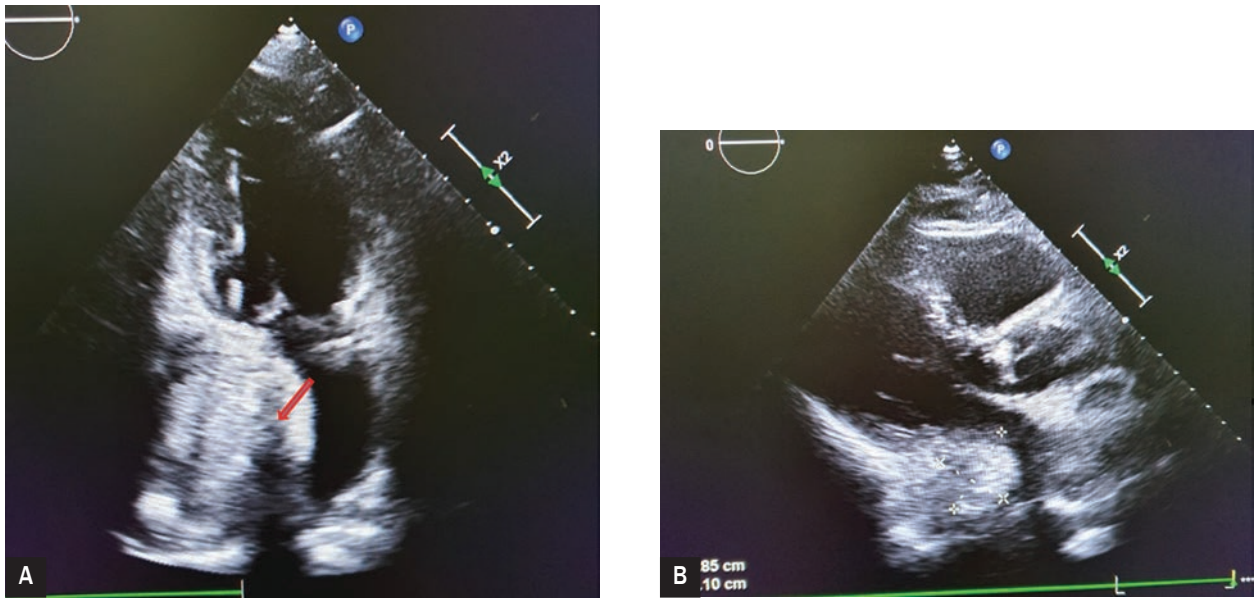


Rycina 1. Badanie echokardiograficzne przezklatkowe: **A.** Projekcja dwujamowa — strzałką zaznaczono strukturę uciskającą na lewy przedsionek; **B.** Projekcja przymostkowa w osi długiej — strzałką zaznaczona struktura wpuklająca się w jamę lewego przedsionka

zatokowego. Ponadto około 3 miesiące przed opisywaną hospitalizacją odbył się zabieg wymiany elektrody komorowej z powodu jej dysfunkcji.

Przy przyjęciu pacjent był w dość dobrym stanie ogólnym; zgłaszał niewielką duszność, nie gorączkował. W badaniu przedmiotowym stwierdzono cichy szmer skurczowy w polu osłuchiwania zastawki aortalnej i prawidłowy szmer pęcherzykowy nad polami płucnymi, nie obserwowano natomiast obrzęków obwodowych. W elektrokardiogramie (EKG) zapis stymulacji DDD 65/min.

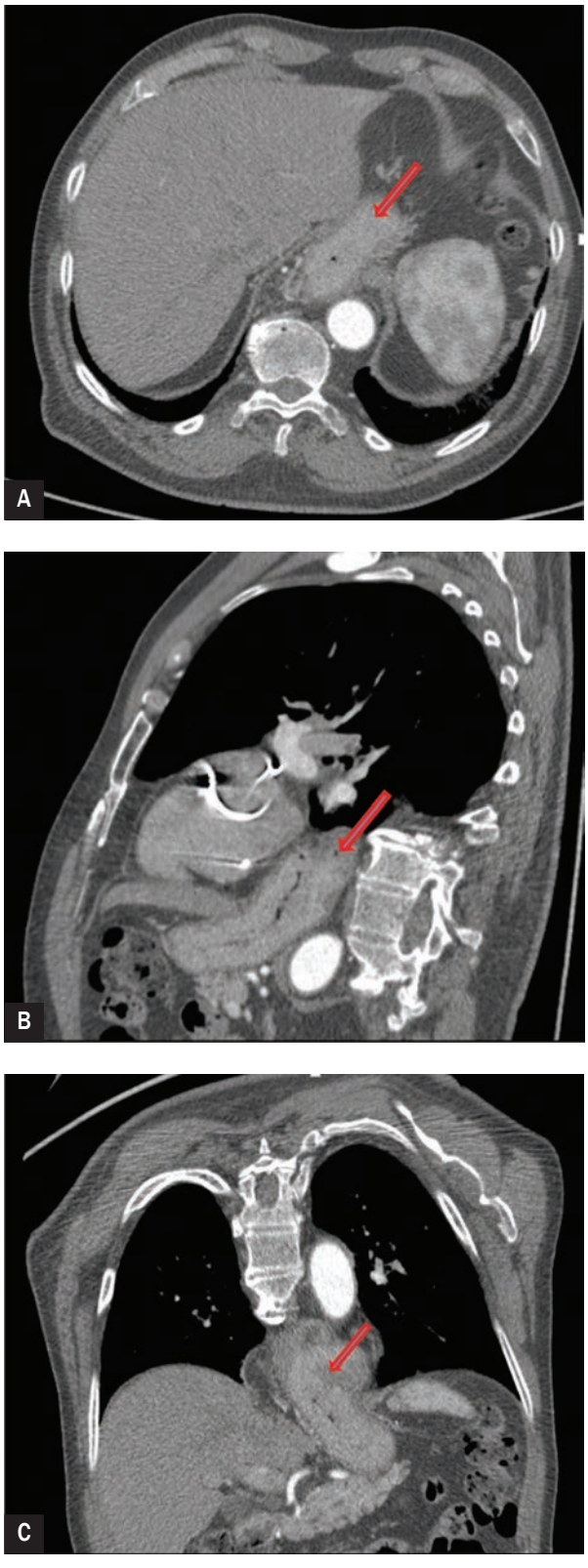
W badaniach laboratoryjnych stwierdzono łagodną niedokrwistość (stężenie hemoglobiny [Hb] 10,8 g/dl), niedobór żelaza (Fe 53 µg/dl) i ferrytyny (15 ng/ml), nieco podwyższone stężenia białka C-reaktywnego (CRP, *C-reactive protein*) (15,14 mg/dl) i D-dimerów (1376 µg/l) przy prawidłowej wartości peptydu natriuretycznego tupu B (BNP, *B-type natriuretic peptide*) (24 pg/ml) oraz negatywnym wyniku badania metodą reakcji polimerazy łańcuchowej (PCR, *polymerasie chain reaction*) w kierunku zakażenia koronawirusem zespołu ostrej niewydolności oddechowej 2 (SARS-CoV-2, *severe acute respiratory syndrome coronavirus 2*). W badaniu radiologicznym (RTG) klatki piersiowej spośród odchyleń opisano drobne zwłóknienia w szczycie lewego płuca, dobrze wysycony 4-milimetrowy guzek u podstawy prawego płuca i zwapnienia w łuku aorty (zmiany opisywane w badaniu RTG rok wcześniej nie uległy progresji). W drugiej dobie hospitalizacji wykonano przezklatkowe badanie echokardiograficzne (TTE, *transthoracic echocardiography*), w którym uwidoczniono powiększenie lewego przedsionka (57 mm) oraz obecność zmiany o charakterze guza w jamie lewego przedsionka. Według sugestii echokardiografisty zmiana ta mogła być strukturą wychodzącą ze ściany lewego przedsionka lub guzem wpuklającym się w jamę przedsionka, a wywodzącym się ze struktur pozasercowych (ryc. 1). Chorego zakwalifikowano do dalszej diagnostyki podejrzanej zmiany guzowatej i zalecono wykonanie tomografii komputerowej (CT, *computed tomography*). W badaniu CT klatki piersiowej opisano obecność przepukliny rozworu przełykowego o wymiarach 35 × 55 mm, nie stwierdzono natomiast patologicznej struktury w jamie lewego przedsionka (ryc. 2).

Chorego konsultowano chirurgicznie; zalecono leczenie zachowawcze. Włączono inhibitor pompy protonowej i poinformowano chorego o odpowiedniej diecie oraz skierowano do poradni gastrologicznej. Pacjenta wypisano do domu w stanie stabilnym.

Omówienie

Zmiany o charakterze guza występujące w sercu w znaczącej większości przypadków mają charakter łagodny [3]. Najczęściej rozpoznaje się śluzak lewego przedsionka, którego obecność podejrzewano u omawianego pacjenta. Do innych pierwotnych zmian o łagodnym charakterze można zaliczyć między innymi włókniak brodawkowaty, tłuszczak, mięśniak prążkowanokomórkowy [3]. Pierwotne zmiany złośliwe to różne rodzaje mięsaków, chłoniaków czy międzybłoniak osierdzia.

Objawy guzów serca zależą przede wszystkim od ich wielkości i lokalizacji, natomiast w mniejszym stopniu od



Rycina 2. Tomografia komputerowa klatki piersiowej — strzałką zaznaczono przepuklinę rozworu przełykowego przepony; **A.** Przekrój poprzeczny; **B.** Przekrój strzałkowy; **C.** Przekrój czołowy

budowy histologicznej [6]. Zależnie od umiejscowienia guza można obserwować konsekwencje w postaci zatorowości płucnej, zatorowości obwodowej (najczęściej udar mózgu), zaburzeń rytmu serca [4, 7], tamponady serca czy objawów niewydolności serca. W badaniu obserwacyjnym przeprowadzonym w grupie 36 pacjentów hospitalizowanych z powodu śluzaka u aż 8 osób (22%) występowały objawy neurologiczne. Najczęściej (w 75%) rozpoznawano udar mózgu, drugi w kolejności był przemijający epizod niedokrwienny (TIA, *transient ischemic attack*) [8]. U opisywanego chorego dominowała duszność typu *orhopnoe* [4], sporadycznie pojawiał się kaszel. Objawy te sugerowały niewydolność serca.

Podstawą rozpoznania zmian guzowatych w sercu jest zwykle wynik badania echokardiograficznego oraz CT lub rezonansu magnetycznego (MRI, *magnetic resonance imaging*) [2]. Badanie echokardiograficzne pozwala określić lokalizację, zasięg, morfologię, a także ewentualne zaburzenia hemodynamiczne. Z kolei badania CT i MRI umożliwiają pełną ocenę umiejscowienia i zaawansowania nowotworu oraz lepsze uwidacznienie osierdzia i dużych naczyń. Rezonans magnetyczny służy ocenie naciekania mięśnia sercowego i pozwala odróżnić nowotwór od skrzepliny, a niekiedy wskazać typ histologiczny guza [9]. Wskazane jest jak najszybsze dążenie do ustalenia rozpoznania i wdrożenie odpowiedniego leczenia w celu uniknięcia progresji objawów oraz powikłań. Nawet łagodne zmiany, takie jak śluzak, mogą powodować nasilone objawy, wynikające z lokalizacji zmiany, jej stosunku do zastawki mitralnej, a także być przyczyną ciężkich powikłań (w tym zgonu), na przykład w przebiegu zatorowości obwodowej. Leczenie operacyjne u chorych z guzami serca jest leczeniem z wyboru, pod warunkiem że guz ten nie jest manifestacją zaawansowanej choroby nowotworowej. Spośród 19 chorych hospitalizowanych w klinice kardiochirurgii w latach 2008–2014 i operowanych z powodu guza serca 3 osoby zmarły we wczesnym okresie pooperacyjnym, natomiast 16 pacjentów wypisanych do domu przeżyło okres 2,5-letniej obserwacji. Rokowanie długoterminowe u chorych operowanych z powodu guza serca jest pomyślne [9].

U opisywanego chorego zgłaszane przez niego objawy wskazywały na niewydolność serca. Wykonanie badania echokardiograficznego pozwoliło na wysunięcie podejrzenia guza serca, jednak rozpoznanie to wymagało weryfikacji w dodatkowym badaniu obrazowym. Na podstawie CT wykluczono kardiologiczną przyczynę dolegliwości.

Podsumowanie

U opisywanego pacjenta choroba przewodu pokarmowego manifestowała się objawami kardiologicznymi, a obraz echokardiograficzny nasuwał podejrzenie guza serca.

Poszerzenie diagnostyki doprowadziło do ustalenia ostatecznego rozpoznania i postępowania.

Konflikt interesów

Autorzy deklarują brak konfliktu interesów.

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Two problems during one pacemaker implantation procedure: axillary vein spasm and subclavian vein compression, or 'every cloud has a silver lining'

Dwa problemy jednej procedury CIED — spazm AV i supresja SV, a może „nie ma tego złego, co by na dobre nie wyszło"

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Abstract

Cardiac implantable electronic device (CIED) implantation procedures have become an indispensable part of treating the clinical manifestations of arrhythmias and/or heart conduction disorders.

The first stage of CIED implantation involves the insertion of cardiac leads into the venous system via a cephalic vein cut down and/or axillary vein/subclavian vein (SV) puncture using special kits designated for this purpose. Similar techniques are used for central venous catheter (CVC) placement. Nonetheless, the course and effectiveness of this stage of the procedure may be affected by mediastinal vein anomalies, atypical venous morphometry and/or topography, reflex venospasm, and — in the case of the SV — the very fact of its coursing through the costoclavicular space.

The rare coexistence of several unfavourable factors and the degree of such anomalies may sometimes prevent the originally planned approach, which happened in the case presented here.

Key words: venography, venospasm, venipuncture, venous compression, subclavian vein, axillary vein, CIED, CVC, TOS

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Introduction

The special tools used in obtaining access to the cardiovascular system during such procedures as cardiac implantable electronic device (CIED) implantation or central venous catheter (CVC) placement help introduce the cardiac leads/catheters without the necessity of venesection [1].

Nonetheless, despite the existence of alternative options, even this initial stage of the procedure may be hindered by difficulties in obtaining venous access. The risk of such difficulties increases in anomalies of the systemic veins of the mediastinum, considerably atypical venous morphometry and/or topography, venospasm, *etc.* [2–5].

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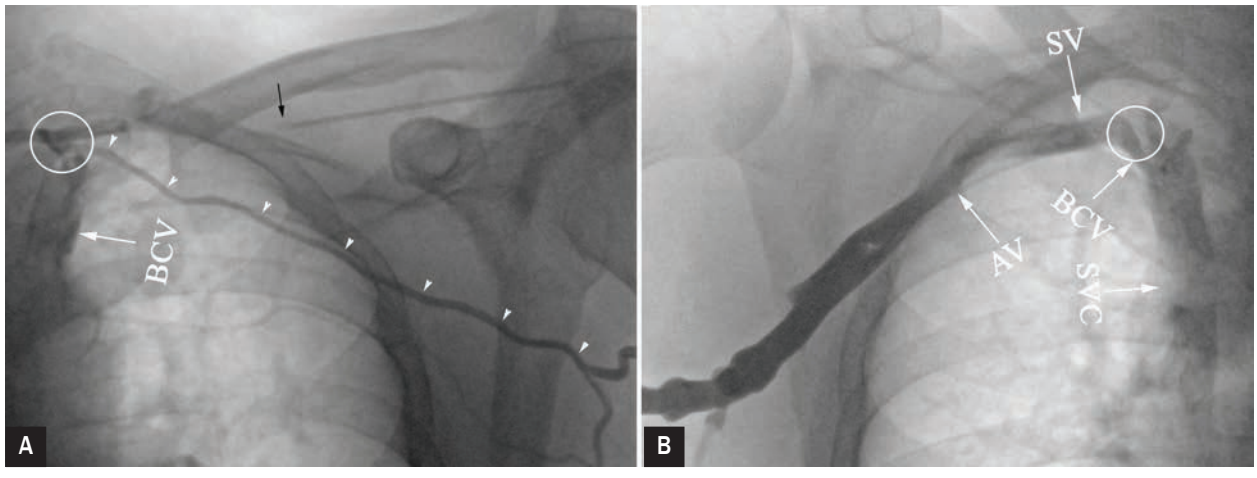

Figure 1. Contrast-enhanced radiographic images showing the morphometry and topography of the veins of both clavipectoral triangles (the left one in panel **A** and the right one in panel **B**) in the presented 59-year-old man, and their relationship to the bone structures of the chest. Both venography assessments were performed in posteroanterior (PA) views with the contrast agent administered through a cubital fossa vein. The differentiating characteristics of the drainage sites for the superficial vein (panel **A**) and the subclavian vein (SV) (panel **B**) have been marked with circles; namely, the circle in panel **A** marks the drainage site into a larger vein, which is not the left brachiocephalic vein (BCV), whereas the circle in panel **B** marks the drainage point of the right SV into the right BCV: **A.** The left side of the chest. An ineffective attempt at subclavian/axillary vein puncture under venographic guidance; the superficial vein (white arrowheads); the needle from the cardiac lead placement kit (black arrow); **B.** The right side of the chest. Contrast flow through the patent, lead-carrying veins: the axillary vein (AV) → subclavian vein (SV) → brachiocephalic vein (BCV) → superior vena cava (SVC)

In the case of using the SV, a possible compression of this vessel in the costoclavicular space may also produce a problem [6, 7].

In the case presented below, the failed attempt to establish venous access was due to several different phenomena of various aetiologies.

Case report

A 59-year-old male farmer, with no significant medical history, was admitted to the hospital to receive a CIED due to his Morgagni–Adams–Stokes attacks resulting from a paroxysmal complete atrioventricular conduction block.

The initially planned approach to cardiac lead insertion was via the veins of the left clavipectoral triangle. However, a failure to locate the CV in the deltopectoral groove led to the use of the AV/SV puncture approach instead, also under venographic guidance. The contrast agent, which was administered into a cubital fossa vein, visualized only a single narrow superficial vein coursing in the left clavipectoral triangle towards the angle formed by the clavicle and the first rib (Figure 1A). The position of the vessel in a posteroanterior (PA) view alone, may have been misinterpreted as that of the AV, albeit an underdeveloped, anomalous, or spastic one.

Considering this unexpected situation, the patient's pacemaker implantation procedure was ultimately rescheduled for the following day, with the pacemaker ultimately implanted on the right side of the chest. The cardiac leads were introduced via CV cut down, and the procedure itself was preceded by venography to assess the layout and accessibility of relevant veins (Figure 1B).

The phenomenon of superficial veins of the left clavipectoral triangle newly filled with the contrast agent (Figure 2A) in addition to just the single vein visualized during the first venography (Figure 1A), within the area for attempted access to the AV, indicates their previous reflex spasm in response to a traumatic stimulus.

Ultrasonography also showed a position-dependent SV compression by adjacent bone structures, which was due to their shifting location in space during movements in the left sternoclavicular joint (Figure 3).

Discussion

Classic CIED implantation procedures make use of the veins situated in the clavipectoral triangle (i.e. CV, AV, or SV) for cardiac lead insertion [1, 2, 4].

Forgoing the initially planned CV cut down due to a failure to locate the vessel in its typical anatomical position in the left deltopectoral groove was the key reason for changing the technique and using the left AV or SV puncture instead. Interestingly, the alternative technique also failed to produce the desired effect, and venography visualized only a single superficial vein on the thoracic wall within the left clavipectoral triangle (Figure 1A). Due to its

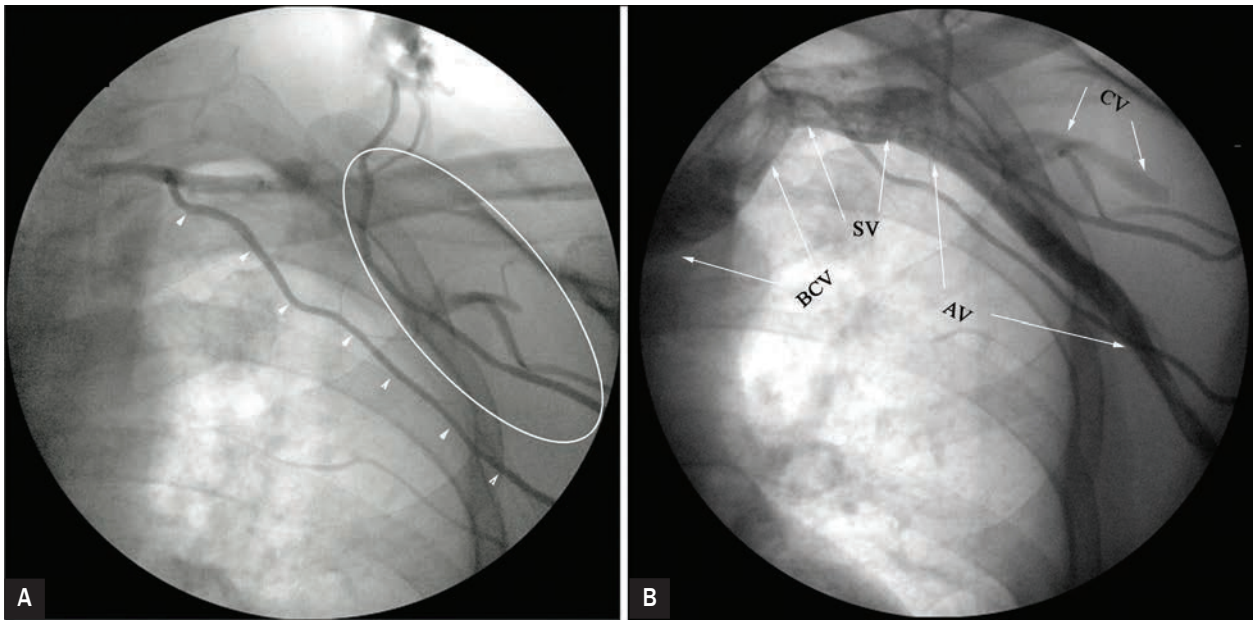

Figure 2. The venographic re-evaluation of the veins of the left infraclavicular region performed on the next day. The different numbers of contrast-enhanced vessels depend on the position of the upper limb (panels **A** and **B**); **A.** With the upper limb in the position typically adopted during the procedure (i.e., lying horizontally, adducted, along the torso), the flow of contrast is visible only in the superficial veins of the clavipectoral triangle; these include the vessel originally visualized (in Figure 1A, white arrowheads) and new, previously non-visualized veins (oval). The axillary vein (AV) and subclavian vein (SV) remain invisible, with no contrast enhancement of their lumen; **B.** A change in the upper limb position and the respective angle at the sternoclavicular joint reverses SV compression by adjacent bone structures (the clavicle and first rib) allowed the contrast to fill the AV and SV, as well as retrogradely fill the CV

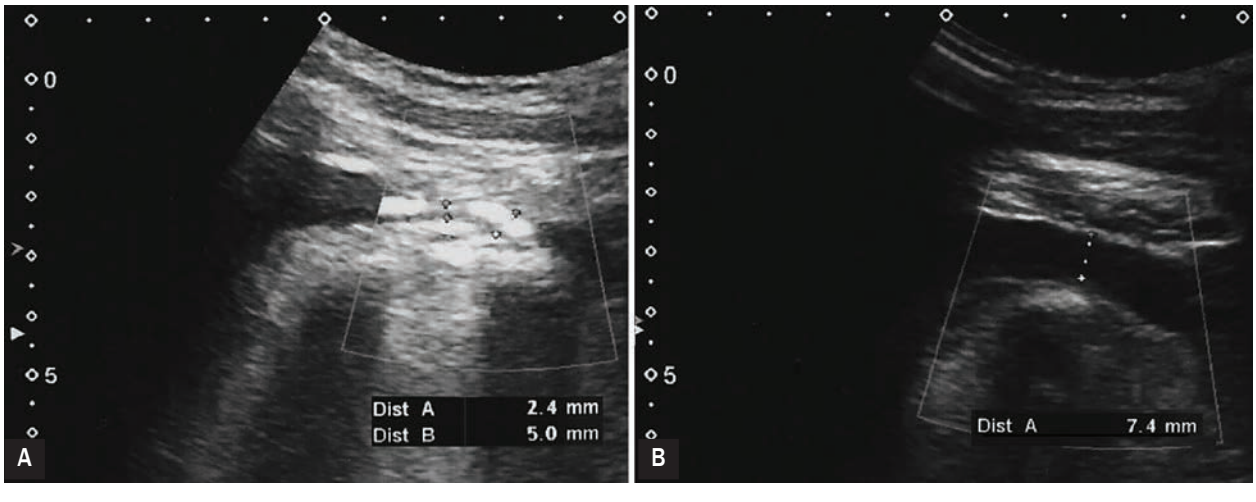

Figure 3. Ultrasound images: **A.** The patient in a horizontal position with the left upper limb lying along the torso — subclavian vein (SV) compression in its middle segment to a minimum diameter of 2–5–3 mm, depending on the respiratory phase; **B.** During the Valsalva manoeuvre (inspiration), the SV diameter increases to 7 mm

course, as visualized via PA fluoroscopy, the vein could be initially mistaken for an atypical AV. However, this conclusion was contradicted by the fact that the vein in question drained to a vessel that was not the left brachiocephalic vein (BCV) (Figure 1A and 2B).

The presence of the left AV and SV was confirmed on venography conducted the following day, which visualized the actual topography and morphometry of those vessels (Figure 2B). A comparison of the number and characteristics of the left clavipectoral triangle vessels visualized

during the two venographic assessments (Figure 2A and 1A) suggests an episode of venospasm triggered by venous puncture and affecting not only the AV and SV but also veins of the chest wall (Figure 1A). It is possible that a similar reflex venospasm was the reason why the CV could not be found, with the manoeuvres involved in searching for the vessel being the traumatic trigger for the spasm in that instance (Figure 1A and 2B).

The shape of the costoclavicular space is also subject to individual variations. This is one of the causes of venous thoracic outlet syndrome (TOS), with the severity of the resulting symptoms reflecting the extent of compression of the following structures: the brachial plexus, the subclavian artery and/or vein. The isolated vascular form of TOS associated with SV compression is found in 3–5% of TOS patients. This form of TOS often leads to localized venous thrombosis referred to as Paget–Schroetter syndrome [6, 7].

Another reason behind the absence of visualized vessels in the case presented here may have been a temporary compression of the SV by the clavicle. This may have been exacerbated by the patient's position during the procedure since a subsequent ultrasound examination revealed a position-dependent nature of this compression (Figure 3A). This position-dependent occlusion of the SV lumen prevented the contrast agent to fill and visualize the AV (Figure 2A).

It is likely that the decision to forgo the procedure on the left side reduced the risk of potential complications due to SV compression, such as thrombosis secondary to endothelial injury by the cardiac leads positioned within the narrowed venous lumen and/or mechanical damage to the cardiac leads by the bone and muscle structures compressing the vein, ultimately leading to CIED dysfunction [8–10].

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Procedury implantacji wszczepialnych urządzeń do elektroterapii serca (CIED) stały się obecnie niezbędnym elementem terapii klinicznych następstw zaburzeń rytmu i/lub przewodzenia układu bodźcowórczo-przewodzącego serca.

Pierwszym etapem implantacji CIED jest wprowadzenie elektrod do układu żylno-sercowego — z wenesekcji żyły odpromieniowej i/lub nakłucia żyły pachowej/podobojczykowej (SV) przeznaczonymi do tego celu zestawami. Analogiczne techniki stosuje się do wprowadzenia kateterów podczas procedur CVC (*central venous catheter*). Niemniej na przebieg i efektywność tego etapu zabiegu mogą wpłynąć takie czynniki, jak obecność wad systemowych naczyń żylnych śródpiersia, morfometria i/lub topografia naczyń inna niż typowo obserwowana, żylne odruchy spastyczne, a w przypadku SV — sam fakt jej lokalizacji w przestrzeni obojczykowo-żebrowej.

Zbieżność czasowa wystąpienia kilku niesprzyjających czynników i ich zaawansowanie może niekiedy wpłynąć na odstąpienie od realizacji procedury w miejscu pierwotnie zaplanowanym, podobnie jak w prezentowanym przypadku.

Słowa kluczowe: wenografia, spazm żylny, nakłucie żyły, ucisk żyły, żyła podobojczykowa, żyła pachowa, CIED, CVC, TOS

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Recurrent infective endocarditis in a patient with severe Crohn's disease

Nawracające infekcyjne zapalenie wsierdzia u pacjenta z ciężką postacią choroby Leśniowskiego-Crohna

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Abstract

A 27-year-old patient after mitral valve replacement because of infective endocarditis (IE) in 2013, treated with biological medicaments for Crohn's disease was admitted to the hospital because of fever and neurological symptoms. Electrocardiogram at the admission revealed signs of myocardial ischemia. In computed tomography scanning signs of septic embolism were found. In managed transoesophageal echocardiography (TEE) vegetation near mechanical prosthesis annulus was identified. Urgent coronary artery angiography revealed 100% stenosis in the circumflex artery. Because of the unsatisfactory result of the immediately managed percutaneous coronary intervention, pharmacological treatment of coronary artery disease was managed on the regular basis. Due to the definite diagnosis of IE empiric antibiotic therapy was initiated. After receiving microbiological blood test results the targeted antibiotic therapy was implemented. Anticoagulant treatment with acenocoumarol was being managed during the whole hospitalisation. The gradual improvement in general condition and regression of vegetation in TEE were observed.

Key words: infective endocarditis, Crohn's disease

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Introduction

After years of rapid development in cardiology, infective endocarditis (IE) remains a serious issue, both in diagnosis and treatment. The conditions that increase the risk of IE are the incidence of the mechanical valve prosthesis, IE in medical history and cyanotic congenital heart disease. The clinical manifestation varies in patients, including fever (90% of patients), murmurs in heart auscultation (85% of patients) and symptoms of embolism in several organs (brain, lung, spleen). In 30% of patients, embolism is the first clinical symptom of the disease which can lead to stroke or pulmonary embolism [1]. Atypical clinical manifestations of IE often occur in elderly patients and those with an impaired immunological system (autoimmunology disease, immunosuppressant administration, congenital immunodeficiency). Following the 2015 European Society of Cardiology (ESC) guidelines the diagnosis should consist of association between clinical symptoms, imaging procedures and previous medical history. Implementation

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of modified Duke criteria is recommended for further classification [2].

Case report

A 27-year-old patient was referred to the 1st Department of Cardiology, Medical University of Gdansk (MUG) because of fever (40 Celsius degree) with a preliminary diagnosis of IE. The medical history of the patient includes IE (2013) treated with mitral valve replacement (Sorin Biomedica Bicarbon Fitline), Crohn's disease (from 2017), and appendectomy (2012). The medicaments were prescribed on the regular basis: the anticoagulant therapy was conducted by acenocoumarol [international normalized ratio (INR) at admission 2.45), the treatment of Crohn's disease included prednisone (20 mg/day in one dose) and mesalazine (3 g/day in three doses). Three days before the fever incidence the patient was discharged from the Department of Gastroenterology of MUG where he was hospitalised for the scheduled continuation of biological treatment due to severe Crohn's disease (infliximab, third course). According to medical documentation, the patient was discharged in good condition after diagnostic procedures (gastroscopy and colonoscopy).

On admission day to the hospital, the patient was haemodynamically stable, measured non-invasive blood pressure was 120/70 mm Hg. The general condition was evaluated as average, the patient was fully responsive, assessed in Glasgow Coma Scale with 15 points. No murmurs instead of mechanical valve prosthesis click were found in heart auscultation. Following abnormalities were observed in the physical examination: numerous petechiae on the patient's hands and legs, left-side hemiparesis, left facial nerve paresis and left-side hemianopia. No stenocardia was reported. The results of conducted laboratory tests are shown in Table 1. Electrocardiogram (ECG) revealed sinus rhythm 110 beats/minute, cardiac axis — normal, no rhythm disturbances and persistent ST-segment elevation in II, III and aVF, which suggested ischemia of the inferior wall of the heart. Due to neurological symptoms, computed tomography (CT) of the central nervous system was managed. Hypodense structures in the precentral and postcentral gyrus of the right cerebral hemisphere and the right cerebellar hemisphere were discovered which aetiology was suggested by the consulting radiologist as septic embolism. The result of CT is presented in Figure 1A. In conducted transoesophageal echocardiography (TEE) left ventricle ejection fraction was evaluated as 40%. Moreover, vegetation of 10 mm length and 5 mm thickness near the annulus of mechanical valve prosthesis was identified. The collected images are shown in Figure 2A. The vegetation did not affect the movability of valvular discs nor generate paravalvular leaks. At this stage, the patient fulfilled modified Duke criteria for definite diagnosis of IE: one major (echocardiographic findings of vegetations) and three minor (predisposing valvular abnormality, pyrexia ≥ 38°C and embolism). Because of visual disturbances intensification magnetic resonance imaging (MRI) was managed. The result is presented in Figure 1B. Pathological structures in the frontal, parietal and occipital lobes of the left cerebral hemisphere were identified. In addition, in the parietal lobe of the right hemisphere structure with limited diffusion was observed. Consulting radiologist suggested numerous hematomas

Table 1. Results of laboratory tests

Parameter	Admission day	Discharge day	Reference range
Haemoglobin [g/dL]	11.8	11.2	13.0–17.0
MCV [fL]	84.9	90.3	80–96
PLT [× 10^9/L]	118	270	150–410
CRP [mg/L]	296.91	22.99	0.0–5.0
PCT [ng/mL]	68.9	0.03	0.0–0.5
hsTnI [ng/mL]	12.52	0.08	< 0.0342
CK-MB [ng/mL]	3.9	–	0.0–6.6
BNP [pg/mL]	682	29	0–73
Creatinine [mg/dL]	2.68	1.21	0.73–1.18
INR	2.45	–	0.9–1.3
Na^+ [mmol/L]	139	142	136–145
K^+ [mmol/L]	4.3	5.0	3.5–5.1

MCV — mean corpuscular volume; PLT — platelets; CRP — C-reactive protein; PCT — procalcitonin; hsTnI — high sensitive troponin I; CK-MB — creatine kinase myocardial bound; BNP — B-type natriuretic peptide B; INR — international normalized ratio

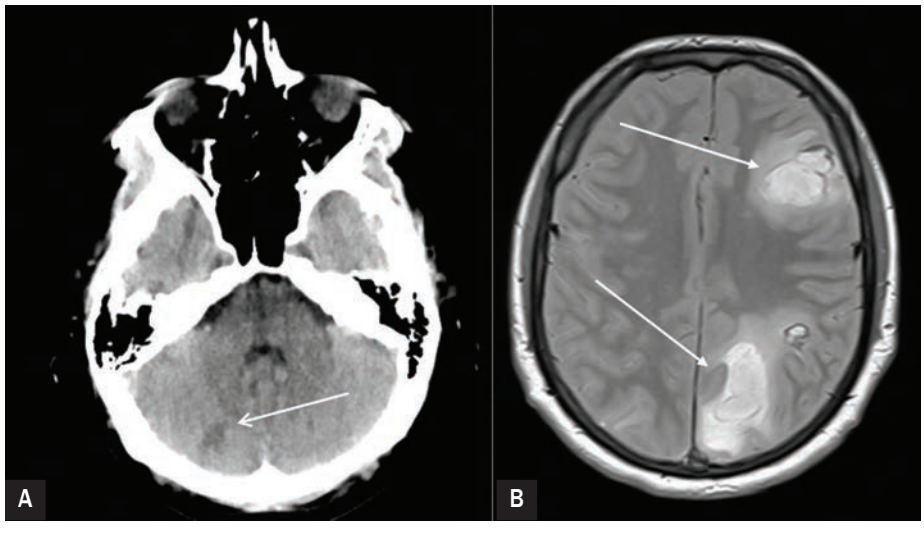

Figure 1. Results of imaging diagnostic procedures: **A.** Computed tomography (CT) — hypotensive structure in the right cerebellar hemisphere; **B.** Magnetic resonance imaging (MRI) in T2 fluid-attenuated inversion recovery (FLAIR) sequence — hyper intensive areas in the frontal and occipital lobe of the left hemisphere)

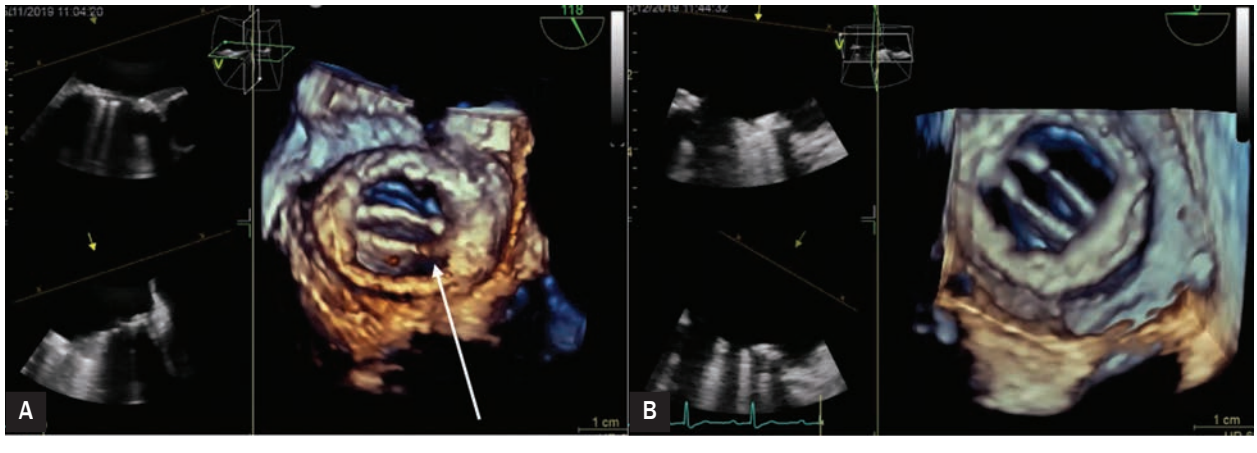

Figure 2. Results of transoesophageal echocardiography: **A.** At admission, vegetation visualised in 3D imaging; **B.** Two weeks later, no vegetation visualised in 3D imaging

in the left cerebral hemisphere and the abscess in the right cerebral hemisphere.

As a result of persistent ST-segment elevation, urgent coronary artery angiography was conducted. Because of 100% stenosis of the circumflex artery (Cx), the attempt of recanalization was managed although the result of the intervention was not satisfactory. The outcome of the intervention is shown in Figure 3. Due to the definite diagnosis of IE empiric antibiotic therapy with vancomycin [30 mg/kg intravenous (i.v.)/day in two doses] and gentamicin (200 mg i.v./day in one dose) was started. In consequence of cardiac surgeon consultation, the patient was disqualified from any surgical procedures. Results of microbiological tests revealed methicillin-sensitive *Staphylococcus aureus* in one of the samples. Therefore, the antibiotic treatment was modified: vancomycin was changed to cloxacillin (12 g i.v./day in four doses), moreover, ampicillin (200 mg/kg/day in four doses) was added. Both antibiotic treatment, as well as anticoagulant therapy with acenocoumarol, were being continued for two weeks of hospitalisation. In TEE managed after a few days of hospitalisation regression in vegetation dimension were detected, the maximal measurement was 3 mm. Two weeks after admission no vegetation was detected in 3D imaging (Figure 2B). Gradual improvement in the general condition (including regression of neurological symptoms) of the patient was observed. The patient was discharged with the following recommendations: life-long anticoagulant therapy [acenocoumarol

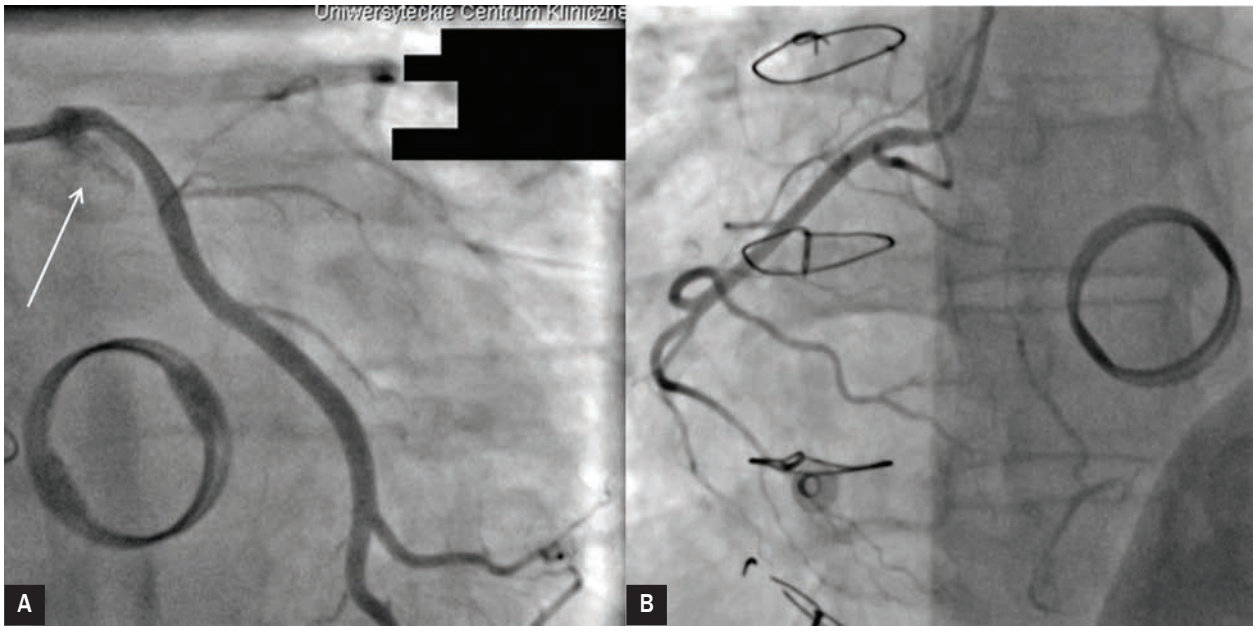

Figure 3. Coronary artery angiography: **A.** No pathological structures in left anterior descending, embolism in the proximal segment of the circumflex artery; **B.** No pathological structures in the right coronary artery

4 mg/day in one dose per os (p.o.) with timely INR tests], antibiotic therapy (amoxicillin with clavulanic acid 3 g/day in three doses p.o. until the next hospitalisation), regular treatment of Crohn's disease (mesalazine 3 g/day in three doses p.o.) and rehabilitation therapy (the term of hospitalisation was arranged two weeks after the discharge).

Discussion

Recent studies emphasize the higher incidence of IE in the group of patients with inflammatory bowel disease (IBD). Alzubi et al. [3] study based on the register from 26 United States centres revealed that 30-days risk of IE prevalence after IBD diagnosis was 0.17% in the group with Crohn's disease compared to 0.07% in the control group. Shah-Khan et al. [4] results emphasized that the prevalence of IE in the aforementioned group is still rising (from 14.5 cases per 10,000 in 2003 to 21.7 in 2014). In the reported case, the patient suffered from recurrent IE what in general supports the conclusions of the aforementioned studies. However, Bonovas et al. results suggested an increased risk of any infection after biological treatment of IBD but decreased risk of serious infections [5]. In the present case, the onset of IE with numerous complications was the result of biological and immunosuppressant treatment which stays in opposition to the outcomes of that study.

Conclusions

This patient persists at high risk of IE in the future. The crucial issue, in this case, is the coincidence of severe Crohn's disease which requires biological treatment and the prevalence of mechanical valve prosthesis which demand life-long anticoagulant therapy. Both avoidances of immunosuppressive therapy escalation and elimination of additional risk factors of IE are indispensable.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Pacjenta w wieku 27 lat, po wymianie zastawki mitralnej z powodu infekcyjnego zapalenia wsierdzia (IE) w wywiadzie, leczonego terapią biologiczną z powodu ciężkiej postaci choroby Leśniowskiego-Crohna, przyjęto do szpitala z powodu gorączki do 40°C oraz objawów neurologicznych. Badanie elektrokardiograficzne przy przyjęciu ujawniło objawy niedokrwienia mięśnia sercowego. W wykonanej tomografii komputerowej ośrodkowego układu nerwowego stwierdzono zatory septyczne. W przeprowadzonym badaniu echokardiografii przezprzełykowej (TEE) ujawniono wegetację blisko pierścienia mechanicznej protezy zastawkowej. Angiografia tętnic wieńcowych wykonana w trybie pilnym wykazała 100-procentowe zwężenie gałęzi okalającej. Próba rekanalizacji była nieskuteczna; leczenie farmakologiczne choroby wieńcowej prowadzono zgodnie z wytycznymi. W związku z ostatecznym rozpoznaniem IE włączono antybiotykoterapię empiryczną. Terapię przeciwkrzepliwą acenokumarolem prowadzono przez całą hospitalizację. Po uzyskaniu wyników badań mikrobiologicznych krwi włączono celowaną antybiotykoterapię. Po kilku dniach hospitalizacji zaobserwowano poprawę stanu ogólnego chorego oraz regresję wegetacji w TEE.

Słowa kluczowe: infekcyjne zapalenie wsierdzia, choroba Leśniowskiego-Crohna

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The change of the coronary sinus activation sequence during radiofrequency ablation of cavotricuspid isthmus

Zmiana sekwencji aktywacji w zatoce wieńcowej podczas ablacji cieśni trójdzielno-żylnej z użyciem prądu o częstotliwości radiowej

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Abstract

Typical atrial flutter (AFL) is one of the most common heart rhythm disorders appearing in clinical practice. According to the current guidelines, the recommended treatment method is percutaneous ablation. This procedure aims to obtain a permanent bidirectional conduction block in the cavotricuspid isthmus (CTI).

This report presents a patient with ongoing typical AFL referred to the radiofrequency (RF) ablation. During the RF applications on CTI, the change of coronary sinus activation sequence and prolongation of tachycardia cycle length was observed. Its occurrence is a rare phenomenon and may suggest a change in the course of the macro-re-entry arrhythmia loop.

Key words: typical atrial flutter, radiofrequency energy, catheter ablation

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Introduction

Typical atrial flutter (AFL) is one of the most common heart rhythm disorders appearing in clinical practice. The prevalence of this arrhythmia increases with age, ranging from 5/100,000 in patients under 50 years old to more than 500/100,000 in patients over 80 years old [1]. Diagnostic criteria for atrial flutter include saw-toothed F waves in the inferior leads of standard 12-leads electrocardiogram (II, III, aVF) and the lack of isoelectric line in limb leads. The frequency of atrial activation is usually above 250 beats per minute (bpm) with typically regular and slower ventricle frequency [2]. The initial efficacy of ablation in cavotricuspid isthmus (CTI) dependent AFL comes up to 95% making this procedure the most effective therapy for maintaining sinus rhythm [3, 4]. Ablation is recommended in symptomatic, recurrent episodes of CTI dependent AFL and should be considered after the first symptomatic episode [5].

Case report

A 74-year-old man with ongoing, symptomatic, typical AFL (Figure 1) was referred to the centre. On admission to the hospital, the patient underwent clinical examination and laboratory checks. After exclusion of thrombi in heart cavities in transoesophageal echocardiography (TEE) patient has been qualified for the radiofrequency (RF) ablation procedure. After the femoral veins puncture under

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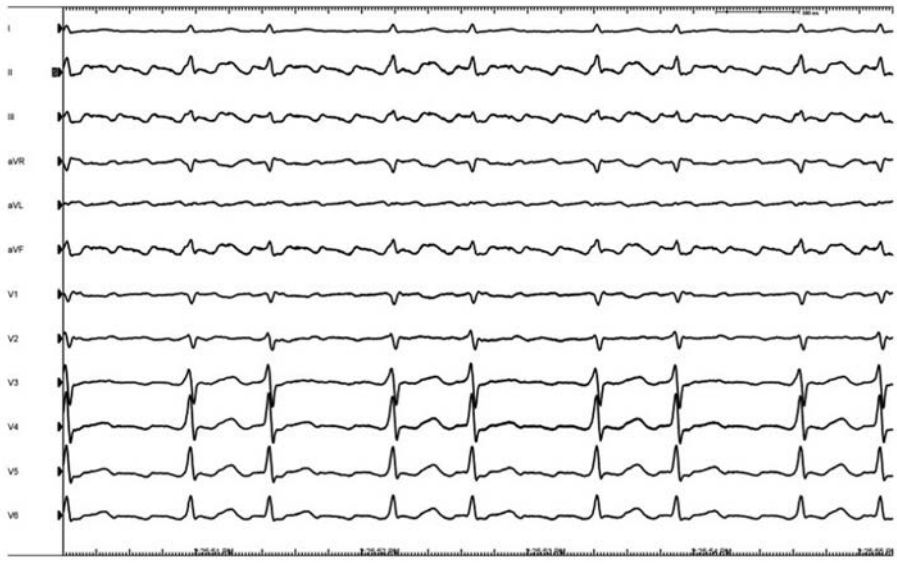

Figure 1A, B. 12-leads electrocardiogram of clinical arrhythmia obtained at 25 mm/sec paper speed

fluoroscopy guidance, decapolar steerable and quadripolar non-steerable catheters were placed in the coronary sinus and the right ventricular apex, respectively. The conducted electrophysiological manoeuvres confirmed a counterclockwise typical AFL with a tachycardia cycle length (TCL) of 210 ms. RF applications using non-irrigated 8 mm-tip ablation catheter were performed from the tricuspid valve side towards inferior vena cava (IVC) (with a power limit of 60 W and a target temperature of 60 °C, with a 60-seconds time limit for each ablation point). During the ablation, the change of the activation sequence on a 10-pole diagnostic electrode in CS with prolongation of the TCL was observed (Figure 2A). No change of a P wave morphology was detected. Repeated pacing manoeuvres confirmed the CTI-dependence of the ongoing arrhythmia. Subsequent RF applications terminated AFL and allowed to return the sinus rhythm (SR) with a P wave duration of 180 ms and with a PQ interval duration of 240 ms (Figure 2B). Differential atrial pacing manoeuvres have demonstrated a bidirectional conduction block in the CTI including the 20-minute latency. The procedure has been completed with a total procedure time of 40 minutes, fluoroscopy exposure of 153 mGy and sinus rhythm 70 bpm. No complications have been registered during hospitalization after the procedure.

Discussion

The re-entrant circuit in typical atrial flutter runs around the tricuspid annulus and embrace the cavotricuspid isthmus, which is crucial in its pathomechanism. A bidirectional conduction block created during ablation poses highly effective protection against recurrent arrhythmias with relatively low complication risk. In most cases, the direction of the arrhythmia loop is counterclockwise [6], which was also presented in the study patient. In these cases, the activation of the left atrium occurs via connections in the inferior segments of the atrial septum [6] associated with the coronary sinus (Figure 2A). This pathway is being inhibited by RF applications in CTI ranging from the tricuspid valve annulus towards the IVC and the by-stander (left atrium) is then activated through the remaining interatrial connections located in the anterosuperior and posterior part of the atrial septum [6, 7]. These changes in the inter-atrial conduction reveal a change in coronary sinus activation observed on the 10-pole electrode (Figure 2B).

Another interesting and rather surprising occurrence observed during the procedure was, apart from the change in the sequence of coronary sinus activation, a prolongation of TCL. In such a situation, it is recommended to repeat manoeuvres to confirm a CTI-dependent AFL. Not only entrainment mapping can be useful but also placing a hallo catheter into the right atrium or using the three-dimensional electroanatomic mapping system for atrial activation analysis. Among the possible hypotheses explaining the above phenomenon may be an impairment of conduction in the atrial septal area, which is involved in the re-entrant circuit. This may be confirmed by the prolonged P-wave duration (180 ms) of sinus rhythm, which occurrence increases the probability of arrhythmia presence [8]. Another explanation of this phenomenon could be the diversity of the CTI structure. In the proximal segment of IVC, it is composed mainly of fibrous and fatty tissue with minimal muscular fibres content [9], which may contribute to the lower velocity of the arrhythmia wave.

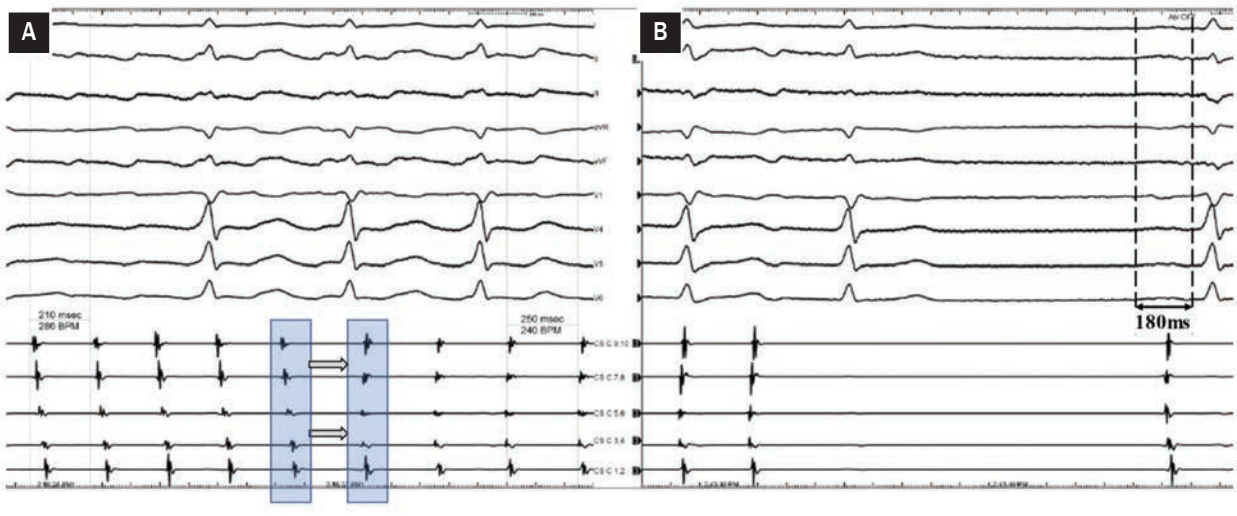

Figure 2. Change in the activation sequence observed on a 10-pole diagnostic electrode placed in the coronary sinus with prolongation of the tachycardia cycle length (TCL) (**A**) and subsequent termination of the arrhythmia and sinus rhythm (SR) recurrence with P wave duration of 180 ms observed during radiofrequency (RF) application on the CTI (**B**). 100 mm/sec sweep speed

Summary

Ablation of the CTI in patients with documented typical AFL is a highly effective and relatively simple procedure characterized by a low risk of periprocedural complications. The described phenomenon observed during RF application on CTI is quite rare. In this case, it has resulted from the interruption of interatrial conduction through the coronary sinus, which is a methodical consequence of this procedure. However, it must be considered that the prolongation of the arrhythmia cycle with activation sequence change in the coronary sinus may suggest a change in the macro-re-entry loop of the arrhythmia. Consequently, performing additional pacing manoeuvres should be considered to confirm the mechanism of the current arrhythmia. The abandonment of the controlled pacing may lead to unnecessary RF applications and increase the risk of complications with no efficacy increase.

Conflict of interest

All authors have no conflicts of interest to report.

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Streszczenie

Typowe trzepotanie przedsionków (AFL) to jedno z najczęstszych zaburzeń rytmu serca spotykane w praktyce klinicznej. Zgodnie z aktualnymi wytycznymi zalecaną metodą leczenia jest ablacja przezskórna. Celem zabiegu jest uzyskanie dwukierunkowego bloku przewodzenia w cieśni trójdzielno-żylnej (CTI).

W niniejszym doniesieniu przedstawiono przypadek pacjenta z typowym AFL poddanego ablacji prądem o częstotliwości radiowej (RF). Podczas aplikacji RF w obrębie CTI obserwowano zmianę sekwencji aktywacji rejestrowanej na elektrodzie umieszczonej w zatoce wieńcowej z wydłużeniem cyklu arytmii. Wystąpienie tego zjawiska jest rzadkie i może sugerować zmianę przebiegu pętli makroreentry arytmii.

Słowa kluczowe: typowe trzepotanie przedsionków, ablacja przezskórna, prąd o częstotliwości radiowej

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Cardiac pacing in vasovagal syncope in the light of the latest recommendations

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Abstract

Reflex syncope is among the most commonly encountered in the clinical practice. Most of these events are mild and do not require major therapeutic interventions. The major problem is recurrent syncope with injuries and a short prodromal symptom phase, usually related to a significant cardiodepressive response. One treatment method is implantation of a cardiac pacemaker. The aim of this article is to present the current knowledge on this subject.

Key words: vasovagal syncope, cardiac pacing

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Introduction

Syncope is a transient loss of consciousness due to hypoperfusion of the central nervous system. Syncope is typically characterized by an abrupt onset, short duration, and spontaneous and complete return of consciousness. Syncope may be categorized into reflex, orthostatic and cardiogenic [1]. The category of reflex syncope includes the most commonly occurring vasovagal syncope (VVS). Depending on the dominant response of the cardiovascular system, VVS may be further subcategorized into the cardiodepressive (with bradycardia < 40 beats per minute or asystole > 3 s), vasodepressive (with hypotension without significant slowing of the sinus rhythm), and mixed type [2].

In a large majority of cases, VVS is mild and does not require any intervention except for non-pharmacological management (informing and educating about the triggers, recognition of prodromal symptoms, and maneuvers to avoid loss of consciousness) [1]. Novel methods are also used to improve autonomic nervous system regulation, including tilt training and heart rate variability (HRV) training by biofeedback, which may aid non-pharmacological management [3, 4]. A major problem is "severe syncope" — frequent and recurring episodes, particularly with a short prodromal phase. These events are associated with a risk of injury, and significantly impair the quality of life of the patients, interfering with their school, professional and social activities. Currently, no universal therapy is available that would be effective in all forms of reflex syncope. The 2018 European Society of Cardiology (ESC) guidelines recommend isometric exercise (class I), orthostatic training (class IIb), drug therapy (with midodrine and fludrocortisone — class IIb), and cardiac pacing (class IIa/IIb) [1]. Cardiac pacing may be expected to be effective in patients with a predominant cardiodepressive component of VVS by preventing severe bradycardia or asystole. The present article summarizes the results of the studies on cardiac pacing in patients with reflex syncope.

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Role of cardiac pacing in vasovagal syncope

When selecting patients with reflex syncope for cardiac pacing, one should take into account the complex nature of the vasovagal reflex; the result of tilt testing does not always reflect actual syncopal events occurring in the patient's life [5]. This is particularly true with the most commonly used testing approach using nitroglycerin, often provoking prolonged asystole which may not necessarily occur during actual syncopal events in a given patient. In addition, syncopal events with vasodepressive and cardiodepressive components of varying severity may occur in the same patient, depending on specific circumstances and the patient's age [6, 7]. It was also shown that changes in heart rate and blood pressure do not occur simultaneously. Loss of consciousness may result from hypotension even before asystole occurs [8]. In such circumstances, syncope may continue to occur despite pacemaker implantation.

On the other hand, early initiation of pacing with the provision of appropriately rapid heart rate may help maintain normal cardiac output and prolong the prodromal phase, which gives the patient time to assume a safer body position to prevent syncope and related injuries [9, 10]. Another argument for pacing in VVS, particularly among patients above 60 years of age, is frequent concomitant presence of automaticity and conduction disorders within the sinoatrial node [11, 12].

Studies to prove the efficacy of implanted cardiac pacemakers in the management of VVS have been undertaken for many years. Initially, similarly to the management of paroxysmal third degree atrioventricular block, VVI pacing [13] followed by DDD pacing [14] was used. However, this therapy had no effect on the rate of syncopal events, while leading to a worsening of the quality of life in some patients (periods of inappropriate pacing, lack of atrioventricular synchrony, episodes of pacemaker-mediated tachycardia). The next step was the introduction of DDI pacing followed by hysteresis (initially negative, and then the search/scan hysteresis) [2, 15–17].

Based on the results of these studies, the rate drop response (RDR) algorithm was developed whereby sudden drop in the heart rate during VVS triggered a sequential atrioventricular pacing with a rate much higher compared to the basic pacing rate [18, 19]. The initial data were very promising. In the North American Vasovagal Pacemaker Study (VPS) I study, patients with at least 3 syncopal episodes and a positive tilt test result were randomized to dual-chamber pacing with the RDR algorithm or no pacing. In the pacing group, a reduction in the syncope rate by 85% was observed (confidence interval [CI] 59.7–94.7%, p = 0.00002) but the placebo effect of pacemaker implantation itself could not be excluded [10]. The latter issue was evaluated in the VPS II study. In this multi-center, randomized, double-blind trial, 100 patients with VVS had a dual chamber pacemaker implanted. The patients were then randomized to "active" pacing (DDD pacing with the RDR algorithm) or to the "inactive" stimulation (ODO stimulation, i.e. completely deactivated stimulation). Among 52 patients randomized to the ODO group, recurrent syncope at 6 months was noted in 22 (42%), compared to 16 (33%) of 48 patients in the DDD group. DDD pacing was found to be associated with a 30% reduction in the risk of syncope (95% CI from –33% to 63%; one-sided p = 0.14) but the effect was not statistically significant [9]. Similar results were obtained in the Vasovagal Syncope and Pacing Trial (SYNPACE) [20].

Another randomized, placebo-controlled, double-blind trial was the Third International Study on Syncope of Uncertain Etiology (ISSUE 3). It included patients at least 40 years of age (mean age 63 years) with at least 3 syncopal events over 2 years, in whom syncope was associated with asystole lasting at least 3 seconds, or asymptomatic asystole lasting more than 6 seconds was documented by an implantable loop recorder (ILR). The patients were randomized to DDD pacing with the RDR algorithm or rhythm monitoring only. The rate of recurrent syncope at 2 years was 57% (95% CI 40–74) in the no pacing group compared to 25% (95% CI 13–45) in the active treatment group (reduction by 57%, p = 0.039) [21].

Of note, with the RDR algorithm, pacing is initiated only in response to a drop in the heart rate, when the vasovagal reaction is already well underway (in VVS, bradycardia is usually preceded by hypotension and a fall in cardiac output). This may be one reason why pacing does not always prevent syncope.

Another evaluated approach to pacing in patients with VVS was the closed loop stimulation (CLS) algorithm. In this method, measurement of intracardiac impedance serves as an indirect indicator of right ventricular contractility. Based on the measured value, pacing is initiated and its rate adjusted so as to prevent the vasovagal reaction at its early stage (before development of bradycardia or asystole). In the Inotropy Controlled Pacing in Vasovagal Syncope (INVASY) study, patients with recurrent syncope of the cardiodepressive type were randomized to DDD-CLS or DDI pacing. A recurrent syncopal event occurred in 7 of 9 patients in the DDI group, compared to none of 41 patients in the DDD-CLS group [22]. Similar results were obtained in the Closed Loop Stimulation for Neuromediated Syncope (SPAIN) study. It was a randomized, double blind, crossover trial that included patients at least 40 years of age with a history of frequent syncope (≥ 5 episodes, or ≥ 2 episodes during the last 12 months) and a cardiodepressive reaction confirmed during the tilt test. An at least 50% reduction in the number of syncopal events was found in 72% (95% CI 47–90%)

of patients in the DDD-CLS group compared to 28% (95% CI 9.7–53.5%) of patients in the DDI group (p = 0.017) [23]. In a metaanalysis that compared conventional pacing with CLS-based pacing in patients with recurrent VVS (6 studies, 224 patients), a clear superiority of CLS-based pacing was shown [24]. Similar results were obtained when CLS-based pacing was compared with RDR--based pacing (a meta-analysis of 5 studies, n = 228) [25].

Conclusions

The proven efficacy of pacing does not mean it is always necessary. According to the 2018 ESC guidelines on the management of syncope [1], this therapy should be limited to a highly selected group of patients with severe reflex syncope. These are mostly older patients with recurrent loss of consciousness, short prodromal phase, and a high risk of injuries. The guidelines also noted that pacing should not be used (a class III recommendation) if the cardiodepressive mechanism of syncope was not shown. A class IIa recommendation was given for patients above 40 years of age with spontaneous symptomatic pause lasting more than 3 seconds or an asymptomatic one lasting more than 6 seconds. Pacing may also be considered in patients above 40 years of age with frequent abrupt syncopal event and asystole documented during the tilt test (a class IIb recommendation).

However, both these indications have a class I A recommendation in the most recent 2021 ESC guidelines on cardiac pacing [26]. This change is related to new studies on patients with asystole during the tilt test that were published since the publication of the previous guidelines. It was found that patients with at least 2 syncopal events per year and a pause lasting more than 3 seconds documented during the tilt test responded well to DDD pacing during reflex syncopal episodes. Thus, the tilt test was found to be useful not only for the diagnosis but also when selecting patients for this therapy. Patients with spontaneous asystole due to the vasovagal reflex (functional or adenosine-sensitive) were also given a class I recommendation for pacemaker implantation. Asystole during syncope induced during the tilt-test was also considered a class I recommendation, while a class IIb recommendation was retained for adenosine-induced asystole. Of note, despite these changes in the level of recommendation, available data are insufficient to recommend pacemaker implantation in individuals below 40 years of age, and thus no such recommendation was given in the guideline document. In younger patients with predominantly cardiodepressive VVS, a possibility of lead- and pacemaker-related late long--term complications should be always taken in account. In these patients, cardioneuroablation (CNA) may be an alternative treatment approach. Initial reports on CNA in VVS showed a relevant reduction in frequency or even complete elimination of syncopal events. However, this method requires further studies [27].

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Stała stymulacja serca w omdleniach wazowagalnych w świetle najnowszych zaleceń

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Streszczenie

Omdlenia odruchowe należą do najczęściej występujących w praktyce klinicznej. W większości przypadków ich przebieg jest łagodny i nie wymagają istotnych interwencji terapeutycznych. Problem stanowią omdlenia nawracające, z urazami i krótką fazą objawów prodromalnych, związane zwykle z istotną komponentą kardiodepresyjną. Jedna z metod ich leczenia to implantacja układu stymulującego serce. Celem artykułu jest przedstawienie dotychczasowej wiedzy na ten temat.

Słowa kluczowe: omdlenia wazowagalne, stała stymulacja serca

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Wstęp

Omdlenie (*syncope*) to przejściowa utrata przytomności spowodowana hipoperfuzją ośrodkowego układu nerwowego. Dla omdleń typowe są szybki początek, krótki czas trwania oraz samoistny i całkowity powrót przytomności. Omdlenia dzieli się na odruchowe, ortostatyczne oraz kardiogenne [1]. W grupie omdleń odruchowych znajdują się między innymi, najczęściej spotykane, omdlenia wazowagalne (VVS, *vasovagal syncope*). W zależności od dominującej odpowiedzi układu krążenia na bodziec wyróżnia się następujące postaci VVS: kardiodepresyjną (z bradykardią < 40/min lub asystolią > 3 s), wazodepresyjną (z hipotonią, bez istotnego zwolnienia rytmu zatokowego) oraz mieszaną [2].

W przeważającej większości przypadków VVS przebiegają łagodnie i poza postępowaniem niefarmakologicznym (informacja i edukacja dotycząca znajomości bodźców wywołujących, rozpoznawania objawów prodromalnych) oraz manewrów pozwalających uniknąć omdlenia) nie wymagają istotnych interwencji [1]. Stosuje się również nowe metody wpływające na odpowiednią regulację autonomicznego układu nerwowego — *tilt* trening czy trening zmienności rytmu serca (HRV, *heart rate variability*) metodą biofeedbacku — które mają dodatkowo pomóc w stosowaniu zaleceń niefarmakologicznych [3, 4]. Problem stanowią „ciężkie omdlenia" — częste i nawracające, zwłaszcza z krótką fazą wstępną. Wiążą się one z ryzykiem urazów, a także w znacznym stopniu upośledzają jakość życia chorych, wpływając na ich aktywność szkolną, zawodową i społeczną. Obecnie nie ma żadnego uniwersalnego leczenia, które byłoby skuteczne w każdej postaci omdlenia odruchowego. W zaleceniach Europejskiego Towarzystwa Kardiologicznego (ESC, *European Society od Cardiology*) z 2018 roku proponowane są ćwiczenia izometryczne (I klasa zaleceń), trening ortostatyczny (klasa zaleceń IIb), farmakoterapia (midodryna, fludrokortyzon — klasa zaleceń IIb) oraz stała

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stymulacja serca (klasa zaleceń IIa/IIb) [1]. Wydaje się, że stała stymulacja serca powinna być skuteczna u chorych z dominującą komponentą kardiodepresyjną VVS, zapobiegając wystąpieniu głębokiej bradykardii lub asystolii. W artykule przedstawiono wyniki dotychczasowych badań nad zastosowaniem elektrostymulacji u chorych z omdleniami odruchowymi.

Miejsce stymulacji serca w omdleniach wazowagalnych

Z jednej strony, kwalifikując chorych z omdleniami odruchowymi do leczenia za pomocą elektrostymulacji, trzeba wziąć pod uwagę złożony charakter odruchu wazowagalnego; nie zawsze wynik uzyskany w teście pochyleniowym odpowiada omdleniom występującym w życiu chorego [5]. Dotyczy to szczególnie najpowszechniej wykonywanych testów z zastosowaniem nitrogliceryny, w których często obserwuje się przedłużającą się asystolię, która nie musi występować podczas incydentów w życiu chorego. Co więcej, u tego samego pacjenta, w różnych okolicznościach i w przypadku różnego wieku, mogą występować omdlenia z różnie nasilonymi komponentami wazo- i kardiodepresyjną [6, 7]. Wykazano również, że zmiany częstości rytmu serca oraz ciśnienia tętniczego nie występują jednoczasowo. Do utraty przytomności może dojść przed wystąpieniem asystolii, wskutek wcześniejszej hipotonii [8]. W takiej sytuacji, mimo wszczepienia stymulatora u chorego, nadal będą występować omdlenia.

Z drugiej strony wczesne włączenie stymulacji z odpowiednio szybką częstością rytmu może pomóc w utrzymaniu prawidłowego rzutu serca i wydłużyć fazę objawów prodromalnych, dając choremu czas na przyjęcie bezpieczniejszej pozycji, aby zapobiec omdleniu i związanym z nim urazom [9, 10]. Dodatkowym argumentem przemawiającym za zastosowaniem stymulacji w VVS, zwłaszcza w grupie chorych powyżej 60. roku życia, jest częste współwystępowanie zaburzeń automatyzmu i przewodzenia w obrębie węzła zatokowo-przedsionkowego [11, 12].

Od wielu lat toczą się badania służące wykazaniu skuteczności leczenia omdleń wazowagalnych za pomocą implantowanych stymulatorów serca. Początkowo, podobnie jak w napadowym bloku przedsionkowo-komorowym III stopnia, stosowano stymulację typu VVI [13], a następnie DDD [14]. Terapia ta nie wpływała jednak na częstość występowania omdleń, a jednocześnie u części chorych powodowała pogorszenie jakości życia (okresy nieuzasadnionej stymulacji, brak synchronii przedsionkowo-komorowej, epizody częstoskurczu stymulatorowego). Kolejnym etapem było wprowadzenie stymulacji typu DDI, a następnie histerezy (początkowo ujemnej, następnie *search/scan*) [2, 15–17].

Na podstawie wyników tych badań opracowano następnie algorytm RDR (*rate drop response*), w którym nagły spadek częstości rytmu serca podczas VVS uruchamiał przez pewien czas sekwencyjną stymulację przedsionkowo-komorową z częstością znacznie szybszą niż podstawowa częstość stymulacji [18, 19]. Wstępne dane były bardzo obiecujące. W badaniu VPS I (*North American Vasovagal Pacemaker Study I*) pacjentów z co najmniej 3 epizodami omdleń i dodatnim wynikiem testu pochyleniowego objęto randomizacją do stymulacji dwujamowej z RDR lub braku stymulacji. W grupie stymulowanej uzyskano spadek częstości występowania omdleń o 85% (przedział ufności [CI, *confidence interval*]: 59,7–94,7%; p = 0,00002), nie można było jednak wykluczyć efektu placebo samej implantacji stymulatora [10]. Próbowano to ocenić w badaniu VPS II. W tym wieloośrodkowym, randomizowanym badaniu przeprowadzonym metodą podwójnie ślepej próby 100 pacjentom z VVS wszczepiono stymulator dwujamowy. Pacjenci byli następnie losowo przydzielani do „aktywnej" stymulacji (stymulacja DDD z RDR) lub stymulacji nieaktywnej (stymulacja ODO, czyli całkowicie wyłączona stymulacja). Spośród 52 pacjentów przydzielonych losowo do grupy ODO u 22 (42%) występowały nawracające omdlenia w ciągu 6 miesięcy w porównaniu z 16 (33%) u 48 pacjentów w grupie DDD. Stwierdzono 30-procentowe względne obniżenie ryzyka w czasie do omdlenia w przypadku stosowania stymulacji DDD (95-proc CI: od –33% do 63%; jednostronne p = 0,14), ale nie było ono istotne statystycznie [9]. Podobne wyniki uzyskano w badaniu SYNPACE (*The Vasovagal Syncope and Pacing Trial*) [20].

Kolejnym randomizowanym, kontrolowanym placebo badaniem metodą podwójnie ślepej próby było ISSUE 3 (*Third International Study on Syncope of Uncertain Etiology*). Obejmowało ono pacjentów w wieku co najmniej 40 lat (średni wiek wynosił 63 lata), z nie mniej niż 3 epizodami omdleń w ciągu 2 lat, którzy doznawali omdleń z asystolią trwającą co najmniej 3 sekundy lub bezobjawową asystolią przekraczającą 6 sekund udokumentowaną we wszczepialnym rejestratorze zdarzeń (ILR, *implantable loop recorder*). Pacjenci zostali losowo przypisani do stymulacji DDD z RDR lub tylko do monitorowania rytmu. Odsetek nawrotów omdleń po 2 latach wyniósł 57% (95% CI: 40–74) w grupie z wyłączoną stymulacją i 25% (95% CI: 13–45) w grupie leczonej aktywnie (57-proc. redukcja; p = 0,039) [21].

Należy zwrócić uwagę, że stymulacja typu RDR włącza się dopiero w odpowiedzi na zwolnienie rytmu serca, a więc w momencie, gdy reakcja wazowagalna jest już mocno rozwinięta (w VVS bradykardię zwykle poprzedzają spadek rzutu serca i hipotonia). Może to być jedną z przyczyn tego, że nie zawsze zapobiega ona omdleniom.

Kolejnym badanym sposobem stymulacji u chorych z VVS był algorytm CLS (*closed loop stimulation*). W ramach tej metody wykorzystuje się pomiar impedancji wewnątrzsercowej jako pośredni wskaźnik kurczliwości prawej komory. Na podstawie zmierzonej wartości uruchamia się i dopasowuje częstość stymulacji tak, aby zapobiec reakcji wazowagalnej na jej wczesnym etapie (przed wystąpieniem

bradykardii lub asystolii). W badaniu INVASY (*Inotropy Controlled Pacing in Vasovagal Syncope*) randomizacji poddano pacjentów z nawracającymi omdleniami typu kardiodepresyjnego do stymulacji DDD-CLS lub DDI. Spośród 9 pacjentów w grupie DDI u 7 doszło do nawrotu omdlenia, natomiast w grupie 41 chorych z DDD-CLS — u żadnego chorego [22]. Podobne wyniki uzyskano w badaniu SPAIN (*Closed Loop Stimulation for Neuromediated Syncope*). Było to randomizowane, przeprowadzone metodą podwójnie ślepej próby badanie krzyżowe, do którego włączono pacjentów w wieku co najmniej 40 lat z częstymi omdleniami w wywiadzie (≥ 5 epizodów lub ≥ 2 epizody w ostatnich 12 mies.) oraz kardiodepresyjnym wynikiem testu pochyleniowego. Wykazano, że 72% (95% CI: 47–90%) pacjentów w grupie DDD-CLS cechowała co najmniej 50-procentowa redukcja liczby epizodów omdleń w porównaniu z 28% (95% CI: 9,7–53,5%) w grupie DDI (p = 0,017) [23]. W metaanalizie, w której porównywano stymulację konwencjonalną ze stymulacją z CLS u pacjentów z nawracającym VVS (6 badań, 224 pacjentów), wykazano wyraźną wyższość stymulacji opartej na CLS [24]. Podobne wyniku uzyskano, porównując CLS ze stymulacją RDR (metaanaliza 5 badań, n = 228) [25].

Wnioski

To, że stymulacja jest skuteczna, nie oznacza, że zawsze jest ona konieczna. Według wytycznych ESC z 2018 roku dotyczących postępowania w omdleniach [1] powinno się ją ograniczyć do wysoce wyselekcjonowanej grupy chorych z ciężkimi omdleniami odruchowymi. Są to przede wszystkim starsi pacjenci z nawracającymi utratami przytomności, z krótką fazą objawów prodromalnych i obciążeni dużym ryzykiem urazów. Podkreślono też, że nie powinno się stosować stymulatorów (III klasa zaleceń) o tyle, o ile nie wykazano kardiodepresyjnego mechanizmu omdlenia. Zalecenie klasy IIa dotyczy pacjentów w wieku powyżej 40 lat ze spontaniczną objawową pauzą przekraczającą 3 sekundy lub bezobjawową trwającą ponad 6 sekund. Stymulację można też rozważyć u pacjentów powyżej 40. roku życia z częstymi, nagłymi omdleniami i asystolią podczas testu pochyleniowego (zalecenie klasy IIb).

Z kolei w najnowszych zaleceniach dotyczących stymulacji serca z 2021 roku oba te wskazania znalazły się w klasie IA [26]. Aktualnie zmienione zalecenia wynikają z tego, że od opracowania poprzednich ukazały się nowe badania dotyczące pacjentów z asystolią w teście pochyleniowym. Okazało się, że chorzy z co najmniej 2 omdleniami/rok i pauzą trwającą ponad 3 sekundy w teście pochyleniowym dobrze odpowiedzieli na stymulację serca w trybie DDD podczas incydentów omdleń odruchowych. Sam test okazał się pomocny nie tylko w diagnostyce, ale także w kwalifikacji do terapii. Ustalono więc, że chorych ze spontaniczną asystolią na tle odruchu wazowagalnego (czynnościową lub adenozynowrażliwą) obejmuje I klasa zaleceń pod względem konieczności implantacji stymulatora serca. Także asystolia w przebiegu omdlenia wyzwolonego testem pochyleniowym znalazła się w I klasie zaleceń. Natomiast wywołana podaniem adenozyny pozostała w klasie IIB. Należy podkreślić, że mimo zmiany poziomu zaleceń brakuje wystarczających danych, by rekomendować implantację rozrusznika u osób poniżej 40. roku życia, więc w dokumencie nie są one zalecane. U młodszych chorych z VVS o dominującym typie kardiodepresyjnym trzeba zawsze wziąć pod uwagę możliwość wystąpienia powikłań odległych związanych z układem elektrod i samym rozrusznikiem. Dla tych chorych alternatywnym sposobem leczenia może być kardioneuroablacja (CNA, *cardioneuroablation*). W pierwszych doniesieniach dotyczących zastosowania CNA w VVS wykazano znaczne zmniejszenie częstotliwości lub nawet całkowitą eliminację omdleń. Metoda ta wymaga jednak dalszych badań [27].

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