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

nr **2**/tom **14**/**2019**

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## PRACE ORYGINALNE

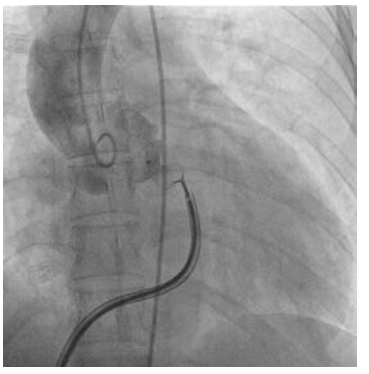


## PRACA POGLĄDOWA



## PRACE KAZUISTYCZNE







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# 2019

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FOLIA CARDIOLOGICA



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# VIII Zaawansowany kurs hipertensjologii dla specjalistów

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# Od Redaktora

**Szanowni Państwo,**
**Drodzy Czytelnicy,**

przedstawiamy drugi numer czasopisma *Folia Cardiologica* zawierającego cztery prace oryginalne, serię opisów przypadków i pracę poglądową. Prace oryginalne pochodzą tym razem z trzech znakomitych ośrodków warszawskich, natomiast Autor artykułu umieszczonego w dziale „Młoda kardiologia" reprezentuje ośrodek katowicki. Doktor n. med. Marcin Wełnicki i wsp. z III Kliniki Chorób Wewnętrznych i Kardiologii Warszawskiego Uniwersytetu Medycznego (WUM) przedstawiają temat zarówno interesujący, jak i aktualny — częstość występowania hiperurykemii u osób z grupy wysokiego ryzyka sercowo-naczyniowego. Jak wiadomo, ocena stężenia kwasu moczowego stała się obowiązującym zaleceniem nadciśnieniowych towarzystw naukowych europejskiego i polskiego. Pojawiły się międzynarodowe dokumenty wskazujące na korzyści terapii obniżającej stężenie kwasu moczowego w tej populacji poniżej 5 mg/dl. Zachęcam wobec tego do lektury artykułu zatytułowanego „Prevalence of hyperuricemia in very high cardiovascular risk patients — a single centre retrospective cohort study" i gratuluję Autorom przeprowadzenia badania. Kolejna praca, pod tytułem „Long-term observation in patients with implantable cardioverter-defibrillator with and without resynchronisation therapy", dr n. med. Agnieszki Kołodzińskiej i wsp. z I Katedry i Kliniki Kardiologii także z WUM jest efektem jednoośrodkowej obserwacji pacjentów z wszczepionym urządzeniem ICD/CRT-D. Z kolei lek. Mariusz Kozak i wsp. przygotowali artykuł pod tytułem „Characteristics of patients with acute peripheral arterial ischaemia — a single centre retrospective study" przedstawiający charakterystykę 208 pacjentów z objawami ostrego niedokrwienia tętnic, których przyjęto na Oddział Chirurgii Szpitala Bródnowskiego w Warszawie w ciągu 5 lat. Natomiast lek. Błażej Kusz i wsp. z I Katedry i Kliniki Kardiologii Śląskiego Uniwersytetu Medycznego w Katowicach swój artykuł zatytułowany „Ranolazine — a new drug for patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias?" poświęcili ocenie bezpieczeństwa i skuteczności ranolazyny u pacjentów z nawracającymi opornymi na leczenie komorowymi zaburzeniami rytmu. Oprócz interesującej serii prac kazuistycznych bogatą i ważną tematykę oferują również opracowania reprezentujące działy „Niewydolność serca", „Kardiochirurgia" i „Elektroterapia". Zapraszając do lektury drugiego numeru *Folia Cardiologica*, pragnę wspomnieć niezwykle udaną IV Konferencję pisma, dziękując tym samym Wykładowcom i Uczestnikom tego wydarzenia i zapraszając na kolejne spotkanie w przyszłym roku.

Redaktor Naczelna

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

VII KONFERENCJA CZASOPISMA

# ACTA ANGIOLOGICA

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**Gdańsk, 13–14 września 2019 roku**

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# Fotorelacja z IV Konferencji *Folia Cardiologica* Warszawa, 26–27 kwietnia 2019 roku


Warsztaty echokardiograficzne pod przewodnictwem prof. Piotra Hoffmana prowadzą dr n. med. Katarzyna Starzyk (u góry) i lek. Agnieszka Woronowicz-Chruściel (po lewej)

Warsztat hemodynamiczy prowadzi prof. Jacek Legutko

Lipidologia 2019 „*state of the art*" w wykładzie prof. Beaty Wożakowskiej-Kapłon

Debata hipertensjologiczna dwóch prezesów Polskiego Towarzystwa Nadciśnienia Tętniczego (PTNT): Prezes PTNT prof. Krzysztof J. Filipiak (po lewej), Past Prezes PTNT prof. Andrzej Tykarski (po prawej)

Co przyniosą najbliższe wytyczne *European Society of Cardiology* (ESC) próbują zgadnąć: prof. Artur Mamcarz (u góry), dr n. med. Iwona Gorczyca (u góry) i dr n. med. Marcin Wełnicki (po lewej)


Kardiologiczny kalejdoskop kliniczny przedstawiony przez lekarzy z I Kliniki Kardiologii i Elektroterapii Świętokrzyskiego Centrum Kardiologii: Olga Jelonek (u góry), Paweł Kośmider (u góry), Maciej Młodnicki (w środku, po lewej), Michał Bączek (w środku, po prawej), Paweł Wałek (u dołu po lewej) i Paweł Dybich (u dołu po prawej)


Doktor n. med. Dawid Bąkowski w wykładzie dotyczącym diagnostyki omdleń

W trakcie konferencji odbyły się wybory Zarządu Sekcji Farmakoterapii Sercowo-Naczyniowej na lata 2019–2021 (od lewej): dr n. med. Radosław Bartkowiak, dr n. med. Katarzyna Starzyk, ustępujący Prezes Sekcji dr n. med. Marcin Barylski, Prezes Elekt na lata 2021–2023 dr n. med. Iwona Gorczyca, dr n. med. Agnieszka Mickiewicz, Prezes obecnej kadencji (2019–2021) dr hab. med. Filip Szymański, lek. Anna Ryś, dr n. med. Daniel Śliż

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# Prevalence of hyperuricemia in very high cardiovascular risk patients — a single centre retrospective cohort study

## Występowanie hiperurykemii u pacjentów obciążonych bardzo wysokim ryzykiem sercowo-naczyniowym — jednoośrodkowe retrospektywne badanie kohortowe

Marcin Tomasz Wełnicki[1], Jakub Żółkiewicz[2], Daniel Śliż[1], Wiesława B. Duda-Król[1], Artur Mamcarz[1]

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[2]Student Society at the Third Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland

### Abstract

**Introduction.** Asymptomatic hyperuricemia is an established independent risk factor for cardiovascular (CV) disease. However, the awareness of this fact among physicians is still insufficient. Data are also lacking on the prevalence of asymptomatic hyperuricemia in a population of patients potentially requiring drug therapy.
The aim of the study was to assess the prevalence of asymptomatic hyperuricemia in the population of patients hospitalized in an internal medicine unit and the frequency of use of uricosuric drugs in this group of patients.

**Material and methods.** Single centre retrospective cohort study — evaluation of medical records of patients hospitalized in an internal medicine unit in the first half of 2018. The analysis included biochemical testing results, data on patients' medical conditions and drug therapy used. Based on the collected data, a group of patients with a very high CV risk was identified in whom serum uric acid level ≥ 5 mg/dL is considered abnormal. Typical statistical methods were used including descriptive statistics, appropriate parametric and non-parametric tests to evaluate significance of differences in the values of selected parameters between the study groups, and generalized regression models. Statistically significant differences were conventionally defined as $p < 0.05$.

**Results.** The analysis included data from 354 patients, of whom 194 (55%) met the criteria of a very high CV risk. These patients were older (75 vs. 62 years, $p < 0.001$) and had lower glomerular filtration rate values (85 vs. 118 mL/min/1.73 m$^2$, $p = 0.04$) and higher mean serum uric acid level (6.6 vs. 5.5 mg/dL, $p < 0.001$) compared to the control group (non-very high CV risk patients). No significant differences in lipid levels were found between the two groups. Serum uric acid level was measured in 55% of patients in the very high CV risk group. Abnormal renal function parameters were an independent predictor of serum uric acid level above 5 mg/dL in this group ($R^2 = 0.18$, $p < 0.001$). Serum uric acid level was above 5 mg/dL in 70% of very high CV risk patients in whom it was measured. Allopurinol was used in only 25% of these patients, and the mean serum uric acid level in those receiving uricosuric treatment was 8.1 mg/dL. The most commonly used allopurinol dose was 100 mg/day. The mean serum uric acid level in patients not receiving uricosuric treatment was 6.2 mg/dL.

**Conclusions.** Serum uric acid level measurement is too rarely considered in the biochemical profile of patients at a very high CV risk. Serum uric acid level may be an indication for the use of uricosuric drugs in most patients at a very high CV risk. In the light of the current expert consensus, allopurinol is underused and underdosed in the very high CV risk group.

Key words: allopurinol, uric acid

Folia Cardiologica 2019; 14, 2: 129–135

**Address for correspondence:** dr n. med. Marcin Tomasz Wełnicki, III Klinika Chorób Wewnętrznych i Kardiologii, II Wydział Lekarski, Warszawski Uniwersytet Medyczny, ul. Bursztynowa 2, 04–749 Warszawa, Międzyleski Szpital Specjalistyczny, Poland, e-mail: welnicki.marcin@gmail.com

## Introduction

Clinically, hyperuricemia has been traditionally associated with rheumatological and oncological disease. However, gout develops in only 30% of subjects with hyperuricemia, and an asymptomatic increase in serum acid level is an established but still underrated independent risk factor for cardiovascular disease [1–2]. In the general population, serum uric acid level in the range of 3–7 mg/dL (180–420 μmol/L) is considered normal, and for many years, the European League Against Rheumatism (EULAR) recommended to treat asymptomatic hyperuricemia only when serum uric acid level was > 12 mg/dL [3–6]. Currently, however, there is an expert consensus that asymptomatic hyperuricemia is associated with an increased risk of diabetes type 2, hypertension, chronic kidney disease, and cardiovascular mortality. Asymptomatic hyperuricemia becomes clinically important already at serum uric acid levels below 7 mg/dL [7–13]. Target serum uric acid level should be < 5 mg/dL in patients with at least two of the following conditions: hypertension, diabetes, dyslipidaemia, chronic kidney disease, recent myocardial infarction or stroke [13]. However, data are still lacking on the prevalence of asymptomatic hyperuricemia as defined above in patients at high cardiovascular risk, and on its effect on therapeutic decision making in the context of uricosuric drug use.

The aim of the study was to evaluate retrospectively the frequency of serum uric acid level measurements in patients admitted to an internal medicine unit. We also evaluated the relation between measured serum uric acid levels and therapeutic decisions in the context of treating hyperuricemia depending on the patient cardiovascular risk.

## Material and methods

We retrospectively evaluated admissions to the Internal Medicine Unit of the Międzylesie Specialist Hospital from January 1 to June 30, 2018. The analysis did not include hospitalizations that led to a patient's death. Very high cardiovascular risk was defined as the presence of generalized atherosclerosis (based on the data from medical history and/or hospital discharge diagnoses) or concomitant presence of at least two of the following conditions: hypertension, diabetes, chronic kidney disease [glomerular filtration rate (GFR) < 60 mL/min/1.73 $m^2$], ischaemic heart disease (previous myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention, stable ischemic heart disease), or previous stroke. The control group included patients who did not meet the above criteria of a very high cardiovascular risk. The two groups were compared in regard to renal function, lipid profile, serum uric acid level, age, comorbidities, and treatment with allopurinol. In case of repeated admissions, the one with serum uric acid level measurement was included in the analysis. If serum uric acid level was not measured during any of the repeated admissions, the one that provided the most of the analysed data was included in the analysis. Statistical analysis was performed using the STATISTICA 12 PL software. Significance of the differences in quantitative variables was assessed using the Student *t* test or the Mann-Whitney U test, depending on variable distribution. Significance of the differences in categorical variables was assessed using the chi-square test. Generalized linear regression models were used to evaluate variables that had an effect on the decision to measure serum uric acid level and to treat hyperuricemia in patients at a very high cardiovascular risk. For all tests, statistical significance was set at $p < 0.05$.

## Results

Among 428 admissions from January 1 to June 30, 2018, 50 led to the patient's death and were not included in the analysis. Of the remaining 378 admissions, 18 patients were hospitalized more than once (range 2–5). Ultimately, data from 354 admissions were included in the analysis, with 194 (55%) patients assigned to the very high cardiovascular risk group (Group A), and the remaining 160 (45%) patients not fulfilling the very high cardiovascular risk criteria as defined in the methods (Group B). The patients in Group A were older (75 vs. 62 years, $p < 0.001$), had higher mean serum uric acid level (6.6 vs. 5.5 mg/dL, $p < 0.001$; Figure 1), and lower GFR (85 vs. 118 mL/min/1.73 $m^2$, $p = 0.04$). We did not find significant differences in lipid levels between the two groups (Table 1). Serum uric acid level was measured in 55% patients in Group A and 45%

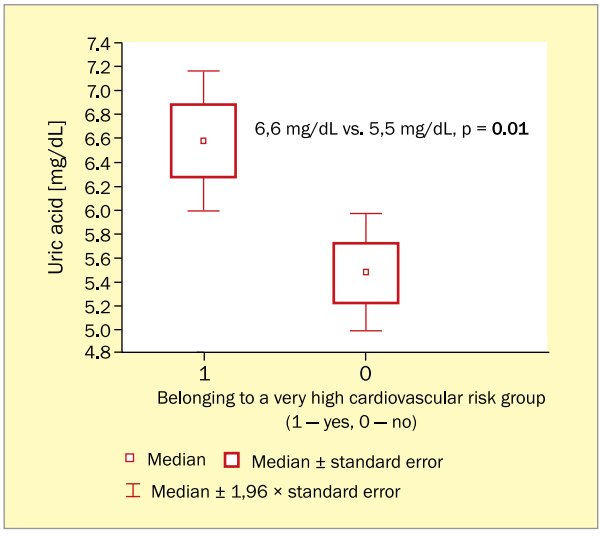


**Figure 1.** Box plot for serum uric acid level in the study population: very high cardiovascular risk group vs. control group

**Table 1.** Study population characteristics (age and biochemical testing results) in the very high cardiovascular (CV) risk group and the control group

| Variable (mean ± SD) | Very high CV risk group (N = 194) | Control group (N = 160) | p |
|---|---|---|---|
| Age [years] | 75.51 (± 11.9) | 62.06 (± 18.6) | **< 0.001** |
| GFR [mL/min/1.73 m$^2$] | 85.39 (± 43.8) | 118.00 (± 51.2) | **< 0.001** |
| Creatinine [mg/dL] | 1.24 (± 0.3) | 0.77 (± 0.3) | **< 0.001** |
| Urea [mg/dL] | 48.76 (± 28.8) | 32.53 (± 19.8) | **< 0.001** |
| Uric acid [mg/dL] | 6.57 (± 3.1) | 5.48 (± 2.14) | **0.01** |
| Total cholesterol [mg/dL] | 147.17 (± 47.6) | 154.08 (± 52.9) | 0.28 |
| HDL cholesterol [mg/dL] | 39.87 (± 13.5) | 42.32 (± 15.9) | 0.19 |
| LDL cholesterol [mg/dL] | 82.11 (± 35.7) | 84.86 (± 33.2) | 0.54 |
| TG [mg/dL] | 127.59 (± 73.3) | 136.32 (± 155.1) | 0.56 |

SD — standard deviation; GFR — glomerular filtration rate; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TG — triglycerides

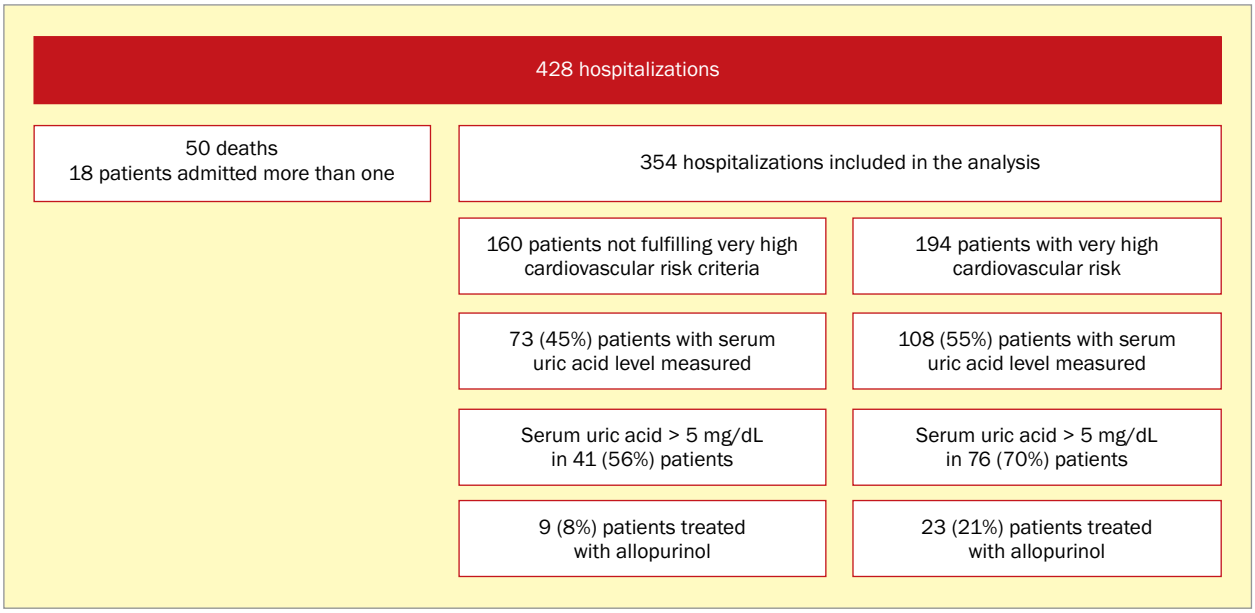


**Figure 2.** Patient flowchart showing serum uric acid measurements, prevalence of hyperuricemia, and allopurinol use in the study population

patients in Group B. In both groups, serum uric acid level showed a moderate but significant negative correlation with GFR (r = –0.4). In the very high cardiovascular risk group, a positive correlation was also seen with age (r = 0.25), urea level (r = 0.45) but not creatinine, and triglyceride level (r = 0.25). However, regression analysis showed that abnormal renal function was the only independent predictor of serum uric acid level > 5 mg/dl ($R^2$ = 0.18, p < 0.001).

In 70% of patients in Group A in whom serum uric acid level was measured, it was higher than 5 mg/dL. Allopurinol was given in only 25% of these patients (Figure 2). The mean serum uric acid level in these patients was 8.1 mg/dL compared to 6.2 mg/dL in those in whom allopurinol was not used.

Among concomitant conditions, the likelihood of serum uric acid level measurement was increased by the presence of diabetes, and concomitant chronic kidney disease affected whether allopurinol was given (Figures 3 and 4). The most commonly used allopurinol dose was 100 mg/day. No correlation was found between allopurinol dose and serum uric acid level. No difference in the mean drug dose was found between the evaluated subgroups.

## Discussion

Serum uric acid level is currently considered not only an independent risk factor for cardiovascular disease but also an independent risk factor for mortality [13]. Ndrepepa et

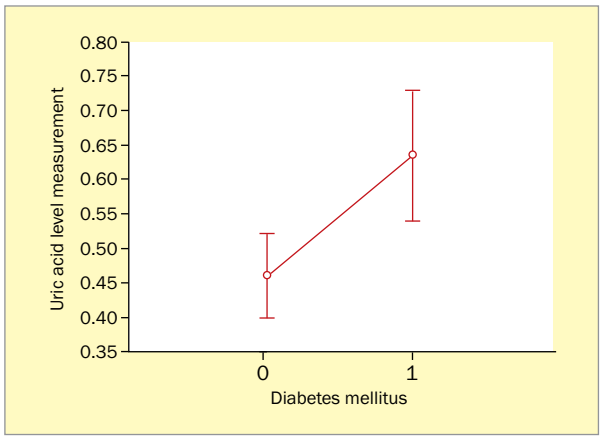


**Figure 3.** Main effects ANOVA. The effect of concomitant diabetes on the performance of serum uric acid level measurement. Vertical red lines indicate the 95% confidence interval. Current effect: F(1.352) = 9.1431, p = 0.003

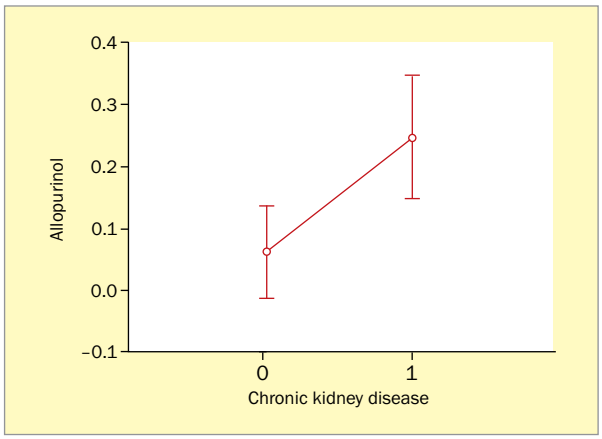


**Figure 4.** Main effects ANOVA. The effect of concomitant chronic kidney disease on allopurinol use. Vertical red lines indicate the 95% confidence interval. Current effect: (1.349) = 17.197, p < 0.001

al. [14] studied more than 5000 patients after an acute coronary syndrome and showed that after adjustment for conventional risk factors, each increase in serum uric acid level by 1 mg/dL was associated with an increase in the mortality risk by 12%. Korean authors reviewed medical data of more than 370,000 patients and found a U-shaped relationship between serum uric acid level and the risk of death. Serum uric acid level < 3.5 mg/dL in men and < 2.5 mg/dL in women was associated with a 58% and 80% higher mortality risk, respectively (hazard ratio [HR] 1.58, 95% confidence interval [CI] 1.18–2.1, and HR 1.8, 95% CI 1.1–2.93). For hyperuricemia, the cut-off values were > 9.5 mg/dL in men and > 8.5 mg/dL in women, associated with HR 2.39 (95% CI 1.57–3.66) and 3.77 (95% CI 1.17–12.17) for mortality risk in men and women, respectively [15]. In the PreCis study, each increase in serum uric acid level by 1 mg/dL was associated with an increase in mortality risk by 39% [16]. In the PAMELA study which evaluated cardiovascular disease risk factors in a random sample of the general population, the highest sensitivity and specificity was found for the cut-off serum uric acid level of 5.4 mg/dL for the cardiovascular mortality and 4.9 mg/dL for the overall mortality [17]. It can be thus concluded that the measurement of serum uric acid level should be included in the routine biochemical testing panel in hospitalized patients, particularly those at a very high cardiovascular risk. During our study period, however, this measurement was performed in our unit in only about half of patients at a very high cardiovascular risk. We have also shown that only the presence of diabetes independently increased the likelihood of the performance of this measurement. Paradoxically, this is justified by clinical studies but not guidelines. Liu et al. noted nephroprotective effects of allopurinol in patients with diabetes, along with a beneficial effect on insulin sensitivity and a reduction in high-sensitivity C-reactive protein (hsCRP) level and the intima-media thickness in the carotid arteries [18, 19]. However, current guidelines on the diagnosis and management of diabetes do not cover the issue of hyperuricemia at all [20]. Only the guidelines on the diagnosis and management of hypertension and rather obsolete 2013 guidelines on the management of stable coronary artery disease (new guidelines are to be published in 2019) mention the need to measure serum uric acid level and note the benefits of uricosuric drugs [21, 22]. In the guidelines on stable coronary artery disease, it has been highlighted that allopurinol has antianginal properties in subjects without gout, may reduce oxidative stress, and when used at 600 mg per day, it may prolong exercise time not only to chest pain, but also to ST segment depression [22].

In the recent years, a number of expert consensuses have been published that indicate the need for more frequent serum uric acid measurement and earlier initiation of uricosuric drugs [11, 13]. According to these documents, in patients with at least two metabolic and/or cardiovascular conditions, abnormal serum uric acid level should be defined as > 5 mg/dL in both genders [11, 13]. However, the prevalence of so defined asymptomatic hyperuricemia in the population of patients at a very high cardiovascular risk is not known. In our study, we have attempted to provide some early estimates the scope of this problem. For the purpose of our analyses, we defined the upper limit of normal values in patients at a very high cardiovascular risk as 5 mg/dl, consistent with the consensus by Borghi et al. [13]. Although a limitation of our study is its retrospective, single-centre nature, our findings indicate the need for more widespread educational efforts to promulgate the

knowledge on the importance of asymptomatic hyperuricemia and the measurement of serum uric acid level in the population of patients at cardiac and metabolic risk. Of note, we observed a tendency to use a single, lowest allopurinol dose. This is probably a result of long-held belief that uricosuric drug use is indicated only with much increased serum uric acid level and as chronic therapy in patients with a history of gout. It should also be noted that there is no consensus regarding the use of allopurinol doses exceeding 100–300 mg per day. In the expert statement of the Polish Cardiac Society Cardiovascular Pharmacotherapy Committee, the use of very high doses (600–900 mg per day) has been considered reasonable [11]. In contrast, Borghi et al. [13] stated in their consensus that the efficacy and safety of chronic use of allopurinol doses exceeding 300 mg per day requires further studies. In a study in over 7,000 patients, Wei et al. [23] showed that the cardiovascular event rate showed an inverse correlation with allopurinol dose, as it was 74.0 (95% CI 61.9–86.1) per 1,000 person-years in the 100 mg group compared to 69.7 (95% CI 49.6–99.8) per 1000 person-years in the 200 mg group and 47.6 (95% CI 38.4–56.9) per 1000 person-years in the ≥ 300 mg group. Use of allopurinol doses ≥ 300 mg/day vs. < 299 mg/day was associated with a lower risk of all-cause mortality (adjusted HR 0.65, 95% CI 0.42–0.99) [23]. Golmohammadi et al. indicated a potential nephroprotective effect of allopurinol [24]. In our study, abnormal renal function parameters were independently associated with the presence of hyperuricemia in the very high cardiovascular risk group. In the 2013 guidelines on the management of stable coronary artery disease, caution was advised when using uricosuric drugs in patients with reduced GFR. The above mentioned studies in diabetic patients and the findings of Golmohammadi et al. suggest, however, that allopurinol use should be considered in particular in these patients [18, 19, 22, 24]. At the same time Borghi et al. [25], in a study on the effects of allopurinol or probenecide in obese normotensive patients with serum uric acid level above 5 mg/dL, have questioned whether drug treatment of hyperuricemia has a protective effect on the endothelium.

Taking into account a large interest in the role of asymptomatic hyperuricemia as a contributor to the total cardiovascular risk in cardiac patients, the lack of data on the prevalence of asymptomatic hyperuricemia in this patient population in Poland, and ongoing uncertainties regarding chronic use of uricosuric drugs, a multicentre study seems warranted.

## Conclusions

1. Serum uric acid level measurement is too rarely considered in the biochemical profile of patients at a very high cardiovascular risk. 2. Serum uric acid level may be an indication for the use of uricosuric drugs in most patients at a very high cardiovascular risk. 3. In the light of the current expert consensus, allopurinol is underused and underdosed in the very high cardiovascular risk group.

## Conflict(s) of interest

Marcin Tomasz Wełnicki: Egis (lectures, training, opinions); Jakub Żółkiewicz: no conflicts of interest, Daniel Śliż: Egis (lectures, training, opinions); Wiesława B. Duda-Król: no conflicts of interest; Artur Mamcarz: no conflicts of interest.


## Streszczenie

**Wstęp.** Bezobjawowa hiperurykemia jest potwierdzonym i uznanym przez ekspertów niezależnym czynnikiem ryzyka sercowo-naczyniowego (CV). Świadomość tego faktu wśród lekarzy wciąż jednak pozostaje niewystarczająca. Brakuje również danych dotyczących rozpowszechnienia bezobjawowej hiperurykemii w populacji pacjentów potencjalnie wymagających farmakoterapii.

Celem badania była ocena częstości występowania bezobjawowej hiperurykemii w populacji pacjentów hospitalizowanych na oddziale internistycznym oraz częstości stosowania leków urykozurycznych w tej grupie chorych.

**Materiał i metody.** Jednoośrodkowe badanie kohortowe — retrospektywna ocena dokumentacji pacjentów hospitalizowanych na oddziale internistycznym w pierwszym półroczu 2018 roku. W analizie uwzględniono wyniki badań biochemicznych, dane dotyczące chorobowości pacjentów oraz stosowanej farmakoterapii. Na podstawie zebranych danych wyodrębniono grupę pacjentów obciążonych bardzo wysokim ryzykiem CV, w odniesieniu do których za nieprawidłowe uznaje się stężenie kwasu moczowego większe lub równe 5 mg/dl. Zastosowano typowe metody statystyczne: statystyki opisowe, odpowiednie testy parametryczne i nieparametryczne w celu oceny istotności różnic wartości wybranych parametrów między badanymi grupami chorych oraz ogólne modele regresji. Przyjęto standardową wartość p poniżej 0,05 dla różnic istotnych statystycznie.

**Wyniki.** W analizie uwzględniono dane 354 pacjentów, spośród których 194 (55%) spełniło kryterium przynależności do grupy bardzo wysokiego ryzyka CV. Pozostali chorzy stanowili grupę kontrolną. Chorzy z grupy bardzo wysokiego ryzyka CV byli starsi (75 *v.* 62 lata; p < 0,001), wyróżniali się niższą wartością współczynnika filtracji kłębuszkowej (85 *v.* 118 ml/min/1,73 $m^2$; p = 0,04) oraz wyższym średnim stężeniem kwasu moczowego (6,6 *v.* 5,5 mg/dl; p < 0,001). Nie wykazano natomiast istotnych różnic w stężeniach poszczególnych frakcji lipidogramu. Stężenie kwasu moczowego oznaczono u 55% pacjentów z grupy bardzo wysokiego ryzyka CV. Niezależnym predyktorem stężenia kwasu moczowego powyżej 5 mg/dl w tej grupie były nieprawidłowe parametry nerkowe ($R^2$ = 0,18; p < 0,001). W przypadku 70% pacjentów z grupy bardzo wysokiego ryzyka CV, u których oznaczono stężenie kwasu moczowego, przekraczało ono 5 mg/dl. Allopurinol zastosowano jedynie u 25% tych chorych, przy czym średnie stężenie kwasu moczowego u pacjentów, u których włączono leczenie urykozuryczne, wynosiło 8,1 mg/dl. Najczęściej stosowaną dawką allopurinolu było 100 mg/dobę. Średnie stężenie kwasu moczowego u pacjentów, u których leczenia nie wdrożono, wynosiło 6,2 mg/dl.

**Wnioski.** Oznaczenie stężenia kwasu moczowego jest zbyt rzadko uwzględniane w profilu badań biochemicznych pacjentów obciążonych bardzo wysokim ryzykiem CV. U większości pacjentów z grupy wysokiego ryzyka mogą istnieć wskazania do stosowania leków urykozurycznych. W świetle aktualnych konsensusów ekspertów allopurinol w grupie pacjentów obciążonych bardzo wysokim ryzykiem CV stosuje się zbyt rzadko i w zbyt małej dawce.

Słowa kluczowe: allopurinol, kwas moczowy

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# Long-term observation in patients with implantable cardioverter-defibrillator with and without resynchronisation therapy

## Obserwacja długoterminowa u pacjentów z wszczepialnym kardiowerterem-defibrylatorem i poddanych terapii resynchronizującej oraz bez niej

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### Abstract

**Introduction.** An implantable cardioverter-defibrillator (ICD) with or without resynchronisation therapy (CRT-D) is an effective treatment in heart failure patients (pts.).

**Materials and methods.** We retrospectively analysed 60 patients (50/60; 83.33% male) with implanted ICD or CRT-D followed-up in the Cardiology Department between May 1995 and February 2019 who had undergone at least one device exchange.

**Results.** Women rarely received ICD, and especially ICD with CRT-D, compared to men [9/26 females in ICD and 1/24 in CRT-D group (p = 0.035) OR 8.31 95% CI (0.98–70.56)] and presented higher left ventricular ejection fraction (LVEF) (38.11 ± 12.74% vs. 29.65 ± 12.63, p = 0.027). CRT-D in our patients was implanted mainly as primary prevention [22/25 vs. 18/35 (p = 0.0726) OR 6.93 95% CI (1.75–27.43)] and in patients with a lower LVEF compared to the ICD-only patients [24.75 ± 8.98 vs. 35.52 ± 13.55% (p = 0.001)]. Technical analysis of endocardial lead parameters at implantation and at the final follow-up revealed a decrease in impedance in cases of atrial, defibrillator and left-ventricular leads. In the ICD-only group, atrial impedance was 280.03 ± 335.3 vs. 218.29 ± 229.48 ohm (p = 0.0018), and defibrillator lead impedance was 768.66 ± 210.62 vs. 507.03 ± 131.67 ohm (p < 0.001) (at implantation vs. final follow-up respectively). In the ICD plus CRT-D group, mean atrial lead impedance was 511.05 ± 271.30 vs. 388.55 ± 231.75 ohm (p = 0.007), impedance of the defibrillator lead was 698.95 ± 165.45 vs. 547.13 ± 385.24 ohm (p = 0.002), and impedance of the left-ventricular lead was 1,036.28 ± 337.34 vs. 794.87 ± 274.99 ohm (p < 0.001).

**Conclusion.** Women receive CRT-D therapy less often than men. CRT-D is implanted in pts. with lower LVEF and mainly as primary prevention. All endocardial leads impedance decreased with the passing of time.

Key words: resynchronisation therapy, CRT, implantable cardiac defibrillator, ICD, heart failure, impedance lead

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## Introduction

Heart failure (HF) is a disease caused by cardiac dysfunction that is associated with high mortality. Among adults in developed countries, the prevalence of HF is about 1–2%. It is higher in older patients (pts.), reaching almost 10% among people aged above 70 years [1]. HF can be divided according to left ventricular ejection fraction (LVEF) into reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) [2]. It is important to note that different underlying aetiologies, demographics, and co-morbidities and varying responses to therapies are related to the degree of reduction of LVEF. Patients with HFpEF are older, more often female, and are less likely to have coronary artery disease compared to HFrEF pts [3, 4]. The treatment of HF has changed over the last 30 years, with nowadays implantable electronic devices and resynchronisation therapy more often being used [5–7]. Based on the current guideline criteria for a cardiovascular implantable electronic device (CIED), only 5–10% of pts with HF are indicated for CRT therapy and approximately 70% of them are responders. Wider QRS, left bundle branch block, non-ischaemic cardiomyopathy, and female gender are factors associated with a better response to CRT [8].

Despite the improvements in HF treatment, the disease is still associated with a poor prognosis. 20% of patients admitted to hospital due to HF die within the first year, and approximately 50% die within five years of diagnosis. Saxon et al. analysed the survival status in patients implanted with ICD and CRT devices from a single manufacturer across the United States. One- and five-year survival rates in 185,778 patients after ICD implantation were 92% and 68% respectively, and were 88% and 54% for CRT-D device recipients [9].

Endocardial lead problems may appear in the course of CIED therapy. Electrical integrity concerning electrical impedance is calculated by measuring the voltage (V) and the current (I) and by applying Ohm's law (R = V/I). The circuit comprises the connection between the generator's header and the lead, the conductors to the tip and ring electrodes, and the electrode-myocardial interface. The most common causes of lead failure are insulation break and conductor fractures. The aim of our study was to analyse the long-term follow-up in patients with ICD and CRT-D therapy.

## Material and methods

60 patients (male 50/60; 83.33%) with implanted ICD or CRT-D who had been followed-up in the Cardiology Department between May 1995 and February 2019 who had undergone one or more device exchange due to the end of battery life were retrospectively analysed. ICD and CRT-D had been implanted according to the prevailing guidelines [5, 8]. ICD had been implanted in 35/60; 58.33% pts. (male 26/35; 74.29%) and ICD plus CRT-D in 25/60; 41.66% pts. (male 24/25; 96%). In the medical histories, coronary artery disease had been diagnosed in 41 (68.33%) pts., chronic heart failure in 56 (93.3%) pts., hypertension in 36 (60%) pts., atrial fibrillation in 36 (60%) pts., diabetes mellitus in 19 (31.67%) pts., chronic renal disease in 33 (55%) pts., and previous stroke in seven (11.67%) pts. The clinical characteristics of the patients are set out in Table 1.

### Statistical analysis

All data were expressed as mean numbers with standard deviation (± SD). The variables were analysed with chi-square, Yates chi-square, Fisher exact tests, Shapiro-Wilk, Mann-Whitney and *t*-Student tests. P-value < 0.05 was

**Table 1.** Clinical characteristics of patients with implantable cardioverter-defibrillator (ICD) and patients with cardiac resynchronisation therapy with defibrillation (CRT-D)

| Clinical characteristics | Patients with CRT-D therapy | Patients with ICD therapy | p value |
|---|---|---|---|
| Number of patients | 25 | 35 | p > 0.05 |
| Male | 24/25 | 26/35 | p > 0.05 |
| Age at first implantation | 60.36 ± 10.54 | 60.51 ± 14.07 | p > 0.05 |
| Age at final intervention (replacement/up-grade) | 66.08 ± 10.31 | 68.43 ± 13.87 | p > 0.05 |
| Chronic kidney failure | 18 (72%) | 15 (42.86%) | p > 0.05 |
| Heart failure | 25 (100%) | 31 (88.57%) | p > 0.05 |
| Hypertension | 15 (60%) | 21 (60%) | p > 0.05 |
| Coronary artery disease | 18 (72%) | 23 (65.71%) | p > 0.05 |
| Atrial fibrillation | 17 (68%) | 19 (54.29%) | p > 0.05 |
| Diabetes mellitus | 9 (36%) | 10 (28.57%) | p > 0.05 |
| History of stroke | 4 (16%) | 3 (8.57%) | p > 0.05 |

identified as statistically significant. Predictive values were calculated and 95% confidence intervals for odds ratios were presented.

## Results

The 60 patients who had undergone ICD/CRT-D implantation were at a similar age at the time of implantation. Most of them had coronary artery disease, hypertension, and/or atrial fibrillation (Table 2). The mean dwell time of CIED therapy was 86.55 ± 36.11 months. Male patients were predominant. There were 9/26 females in the ICD group and 1/24 females in the CRT-D group (p = 0.035) OR 8.31 95% CI (0.98–70.56). Women presented with higher left ventricular ejection fraction compared to men 38.11 ± ± 12.74% vs. 29.65 ± 12.63 (p = 0.027). Patients with CRT-D when compared to those with ICD presented lower LVEF 24.75 ± 8.98 vs. 35.52 ± 13.55% (p = 0.001). CRT-D was mainly implanted as primary prevention 22/25 vs. 18/35 (p = 0.0726) OR 6.93 95% CI (1.75–27.43). Endocardial lead impedance in cases of atrial, defibrillator and left-ventricular leads were lower at the final follow-up compared to the values at implantation in both the ICD group and the CRT-D group (Table 3). In the ICD group, atrial impedance was 280.03 ± 335.3 vs. 218.29 ± 229.48 ohm (p = = 0.0018), defibrillator lead impedance was 768.66 ± ± 210.62 vs. 507.03 ± 131.67 ohm (p < 0.001) (at implantation vs. final follow-up respectively). In the CRT-D group, the mean atrial lead impedance was 511.05 ± ± 271.30 vs. 388.55 ± 231.75 ohm (p = 0.007), impedance of the defibrillator lead was 698.95 ± 165.45 vs. 547.13 ± ± 385.24 ohm (p = 0.002), and impedance of the left-ventricular lead was 1,036.28 ± 337.34 vs. 794.87 ± 274.99 ohm (p < 0.001) at implantation vs. final follow-up respectively.

## Discussion

8,467 ICD and 4,164 CRT devices were implanted in Poland in 2016 [10]. Implantable electronic devices for heart failure prolong a patient's life and, in cases of CRT-D, improve the quality of life. In our study, we took into consideration the clinical presentation of patients and endocardial lead technical parameters at implantation and at the final follow-up. Our main observation was gender-related. Women rarely receive ICD, and especially CRT-D, compared to men, and women present with higher LVEF. CRT-D in our patients was implanted mainly as primary prevention and in pts. with lower LVEF compared to ICD. Technical analysis of endocardial lead parameters at implantation and at final follow-up revealed a decrease in impedance in cases of atrial, defibrillator and left-ventricular leads.

Large ICD therapy-related trials such as MADIT, MADIT II, SCD-HeFT, MUSTT, and DEFINITE AVID have involved between 8% and 29% of women, while CRT trials such as MADIT-CRT and MIRACLE have contained a higher number of female patients (around 30%) [11–17]. In the MADIT trial, women were noted to have more advanced HF, as well as a higher incidence of hypertension, diabetes and

**Table 2.** Lead-associated electrical parameters at implantation in patients with implantable cardioverter-defibrillator (ICD) and patients with cardiac resynchronisation therapy with defibrillation (CRT-D)

| Parameter | Patients with CRT-D therapy | Patients with ICD therapy | p value |
|---|---|---|---|
| Atrial lead pacing threshold | 0.73 ± 0.59 | 0.34 ± 0.39 | p < 0.05 |
| Defibrillation lead pacing threshold | 0.69 ± 0.2 | 0.66 ± 0.22 | p > 0.05 |
| Left ventricular lead pacing threshold | 1.75 ± 1.71 | None | None |
| Atrial lead impedance | 511.05 ± 271.30 | 280.03 ± 335.30 | p < 0.05 |
| Defibrillation ventricular lead impedance | 547.13 ± 385.24 | 768.66 ± 210.62 | p > 0.05 |
| Left ventricular lead impedance | 1,036.28 ± 337.34 | None | None |

**Table 3.** Lead-associated electrical parameters at final follow-up in patients with implantable cardioverter-defibrillator (ICD) and patients with cardiac resynchronisation therapy with defibrillation (CRT-D)

| Parameter | Patients with CRT-D therapy | Patients with ICD therapy | p value |
|---|---|---|---|
| Atrial lead pacing threshold | 0.67 ± 0.36 | 0.73 ± 0.27 | p > 0.05 |
| Defibrillation lead pacing threshold | 0.97 ± 0.51 | 0.85 ± 0.26 | p > 0.05 |
| Left ventricular lead pacing threshold | 1.71 ± 1.36 | None | None |
| Atrial lead impedance | 388.55 ± 231.75 | 218.29 ± 229.48 | p > 0.05 |
| Defibrillation ventricular lead impedance | 698.95 ± 165.45 | 507.03 ± 131.67 | p > 0.05 |
| Left ventricular lead impedance | 794.87 ± 274.99 | None | None |

left bundle branch block (LBBB) [18, 19]. MacFadden et al. analysed 5,213 HF patients who received primary and secondary prevention ICDs for up to one year [20]. Of the 921 women who received ICDs for primary prophylaxis, and the 367 who received ICDs for secondary prophylaxis, they found no difference in mortality between men and women. Myocardial scarring post-infarction is more often seen in men, and men with out-of- hospital sudden cardiac arrest are more likely to have VT/VF compared to women (41% vs. 30%). Women are more likely to have asystole (8.8% vs. 7%) or pulseless electrical activity (24% vs. 18%) than men [21]. Women were more likely to have HF, non-ischaemic cardiomyopathy, and advanced NYHA class, and were more likely to receive CRT-defibrillators (CRT-D) compared to men [22]. In the MADIT-CRT trial, women demonstrated a lower mortality rate than men. Enina et al. [23] observed that the best response to CRT therapy is associated with female gender. In our population, men were eight times more likely to receive CRT-D implantation than women. Moreover, female pts presented with a higher LVEF than male pts [23].

We observed long-term stable pacing thresholds of atrial, defibrillation and left ventricular leads, but lead impedance varied at implantation as opposed to at final follow-up. The impedance increased with time in both ICD and CRT-D pts. Low impedance can be associated with insulation breaks, where a lead wire is exposed to a low resistance body fluid or another lead wire that induces a potential loss of capture or rapid battery depletion. Electrical dysfunction is usually related to a conducting wire fracture in cases of low-voltage circuits, where it can lead to oversensing, inappropriate shocks, and loss of capture. High-voltage circuit failure can lead to short circuiting with a failure to defibrillate [24]. In the literature, we found the devices most prone to failure to be Fidelis and Riata leads, 28% versus 15% respectively [25, 26]. Data has indicated that an impedance threshold above 100 ohm or an abrupt 75% increase in chronic impedance has identified a Fidelis fracture [27].

In CRT-D pts, primary prevention predominates, while in ICD pts primary and secondary prevention were balanced. The implantation of both ICD and CRT-D as primary and secondary prevention is associated with a decrease in the mortality rate [28–30].

## Conflict(s) of interest

Marcin Grabowski — fees from: Cook, Medtronic, Abbott, Biotronik, Boston Scientific.


## Streszczenie

**Wprowadzenie.** Wszczepialny kardiowerter-defibrylator (ICD) z terapią resynchronizującą (CRT-D) oraz bez niej stanowi efektywny element leczenia u pacjentów z niewydolnością serca.

**Metody i wyniki.** Sześćdziesięciu pacjentów (50/60; 83,33% mężczyzn) pozostających pod opieką kliniki kardiologii w latach od maja 1995 roku do lutego 2019 roku z wszczepionym ICD/CRT-D, u których wykonano przynajmniej jedną wymianę urządzenia, poddano retrospektywnej analizie. Kobietom rzadziej wszczepieniu zarówno ICD, jak i CRT-D niż mężczyznom (9/26 kobiet w grupie z ICD oraz 1/24 w grupie z CRT-D [p = 0,035], iloraz szans [OR] 8.31 95-proc. przedział ufności [CI] 0,98–70,56). Panie charakteryzowały się wyższą frakcją wyrzutową lewej komory (LVEF) (38,11 ± 12,74% *v.* 29,65 ± 12,63 [p = 0,027]). U opisywanych chorych CRT-D wszczepiano głównie w ramach w prewencji pierwotnej (22/25 *v.* 18/35 [p = 0,0726], OR 6,93 95% CI 1,75–27,43) oraz u pacjentów z niższą LVEF niż u osób z ICD (24,75 ± ± 8,98 *v.* 35,52 ± 13,55%; p = 0,001). Analiza parametrów technicznych elektrod endokawitarnych wykazała obniżenie oporności, gdy porównano parametry z dnia wszczepienia i ostatniej wizyty kontrolnej. W grupie z wszczepionym ICD oporność elektrod przedsionkowych wynosiła 280,03 ± 335,3 w porównaniu z 218,29 ± 229,48 omów (p = 0,0018), a elektrod defibrylujących 768,66 ± 210,62 w porównaniu z 507,03 ± 131,67 omów (p < 0,001) (dzień implantacji *v.* ostatnia kontrola). W grupie poddanych CRT-D średnia oporność elektrod przedsionkowych wynosiła 511,05 ± 271,30 w porównaniu z 388,55 ± 231,75 omów (p = 0,007), elektrod defibrylujących 698,95 ± 165,45 w porównaniu z 547,13 ± 385,24 omów (p = 0,002), a elektrod lewokomorowych 1036,28 ± 337,34 w porównaniu z 794,87 ± 274,99 omów (p < 0,001), gdy porównano dzień implantacji z dniem ostatniej kontroli.

**Wnioski.** Kobiety podlegają terapii resynchronizującej znacznie rzadziej niż mężczyźni. Ponadto CRT-D poddano pacjentów z niższą LVEF, głównie w ramach prewencji pierwotnej. Oporność wszystkich elektrod ulegała obniżeniu z upływającym czasem.


Słowa kluczowe: terapia resynchronizująca, CRT, wszczepialny kardiowerter-defibrylator, ICD, niewydolność serca, oporność elektrod

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# Characteristics of patients with acute peripheral arterial ischaemia — a single centre retrospective study

## Charakterystyka pacjentów z ostrym niedokrwieniem tętniczym — badanie retrospektywne, jednoośrodkowe

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## Abstract

**Introduction.** Acute peripheral arterial occlusion is a serious medical condition that requires an immediate action. Delays in diagnosis or treatment could lead to death or serious disability. The appropriate and early clinical evaluation of acute ischaemia is crucial. The goal of therapy for both acute embolic and thrombotic occlusion is reperfusion of the ischaemic organ.

**Materials and methods.** The aim of this study was a retrospective analysis of the demographic and epidemiological data of patients admitted to Surgical Department of Mazovian Brodnowski Hospital in Warsaw from 2014 to 2018 due to displaying symptoms of acute peripheral arterial ischaemia. 208 patients were evaluated. Our analysis included anthropometric parameters, history of cardiovascular and other important chronic diseases, and addictions. The aetiology, localisation, and type of primary surgery were also assessed.

**Results.** The analysed group contained 112 men (53.8%, average age: 67.9 years) and 96 women (46.2%, average age: 76.4). We find a statistically significant correlation was found between epidemiological factors [*i.e.* age, hypertension, atrial fibrillation (AF), peripheral artery disease, myocardial infarction, and smoking] and gender. Embolic ischaemia occurred in 50.5% of cases. Thrombosis was diagnosed in the remaining 49.5%. Lower extremity ischaemia occurred most frequently (81.3%). Open embolectomy/thrombectomy was the primary surgery in 155 cases. We find significance of the aetiology in relation to the type of intervention and to the ischaemia localisation, but there was no significance in terms of mortality. The presence of ischaemic heart disease, atherosclerosis and tobacco smoking were relevant factors affecting the aetiology of acute ischaemia.

**Conclusion.** Acute arterial ischaemia can occur regardless of gender. Embolic and thrombotic aetiologies occur with a very similar frequencies. Upper extremity arterial thrombosis occurs very rarely. An embolism is more often responsible for acute intestinal ischaemia. In patients with atherosclerosis and a history of previous vascular surgery, the presence of a vascular graft/stent graft is associated with a higher risk of arterial thrombosis. Among patients with AF and who were receiving vitamin K antagonists, the average level of international normalized ratio was non-therapeutic.

Key words: atherosclerosis, acute ischaemia, embolus, thrombosis, peripheral artery disease, atrial fibrillation

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## Introduction

Acute peripheral arterial occlusion is a serious medical condition that requires an immediate reaction. A delay in diagnosis or treatment can lead to death or serious disability. The appropriate and early clinical evaluation of acute ischaemia is crucial to identify the aetiology of the ischaemic organ. Acute arterial ischaemia can be caused by various factors (Table 1) [1]. The clinical manifestation of acute arterial occlusion depends on the affected organ. A painless acute onset of a neurologic deficit suggests brain ischaemia. Pain, loss of sensation, and later loss of motor function with coexisting low body temperature, pale extremities and pulselessness may be symptoms of upper/lower limb acute ischaemia. Bowel ischaemia manifests as abdominal pain, nausea, vomiting, intestinal paralysis and sometimes diarrhoea [2].

Despite having the same effect as that of acute ischaemia, the clinical presentation of acute embolism versus thrombosis may be different (Table 2) [3]. Most arterial emboli originate from the heart. Atrial fibrillation (AF) is the most common cause of embolism. The most frequent manifestations of cardiac embolic events are strokes and peripheral ischaemic events. Clots formed in the left side of the heart are responsible for 55–87% of peripheral arteries emboli including visceral vessels [4].

The goal of therapy for both acute embolic and thrombotic occlusion is reperfusion of the ischaemic organ. Intravenous heparin administration is the first step in treatment. This prevents propagation of the thrombus both proximally and distally, while maintaining the patency of collateral vessels. Therefore, it will help to reduce the extent of the ischaemic injury. The restoration of arterial blood flow requires open surgery or endovascular intervention (thrombolysis or thrombectomy). The type of treatment depends on the degree of limb ischaemia, the occlusion localisation, the cause of the occlusion (embolic vs. thrombotic), and the general condition of the patient [5].

The aim of this study was a retrospective analysis of the demographic and epidemiological data of patients admitted to the Department of General and Vascular Surgery from January 2014 to November 2018 due to symptoms of acute peripheral arterial ischaemia.

**Table 1.** Acute arterial ischaemia

| Embolic | Thrombotic |
|---|---|
| Atherosclerotic heart disease (CAD, MI, arrhythmia) | Atherosclerosis |
| Valvular heart disease (rheumatic, degenerative, congenital, bacterial, prosthetic) | Low flow states (CHF, hypovolemia, hypotension) |
| Artery-to-artery (aneurysm, atherosclerotic disease) | Genetic states of hypercoagulation |
| Idiopathic | Vascular grafts (progression of disease, intimal hyperplasia) |
| Paradoxical embolus | Arterial plaque rupture |
| Trauma | Aortic/arterial dissection |
| Iatrogenic | External compression |
| Other (air, amniotic fluid, fat, tumour, drugs, chemicals) | Trauma |
| | Iatrogenic |

CAD — coronary artery disease; MI —myocardial infarction; CHF — congestive heart failure

**Table 2.** Differences in clinical presentation of acute arterial ischaemia (embolism vs. thrombosis)

| Clinical presentation | Embolism | Thrombosis |
|---|---|---|
| Cardiac dysrhythmia | Yes | No |
| Onset | Sudden | Sudden or slower |
| Severity of signs and symptoms | Severe | Less severe |
| History of claudication or rest pain | No | Yes |
| Risk factors for peripheral vascular disease* | No | Yes |
| Contralateral pulse exam (limb ischaemia) | Normal | Abnormal |
| Exam findings of chronic limb ischaemia** | No | Yes |

*Risk factors include cardiac disease, prior myocardial infarction, hyperlipidaemia, stroke, family history of peripheral vascular disease, smoking, and diabetes mellitus; **diminished hair growth, thin skin, thick nails, and arterial ulcerations

## Materials and methods

Between January 2014 and November 2018, 212 patients were admitted to our Department with a diagnosis of acute arterial ischaemia. An eventual total of 208 patients were evaluated. Four patients were excluded due to the lack of full data. Analysis included basic anthropometrical parameters, a history of cardiovascular and other important chronic diseases, and addictions. The aetiology (embolic or thrombotic), the localisation (lower limb, upper limb, viscera), and the type of primary surgery was also assessed. Laboratory tests at admission were included. Mortality during hospitalisation and within three to 12 months after discharge was also considered. Patients with acute myocardial infarction, arterial injury or ischaemic stroke were excluded from evaluation. Basic statistical analysis regarding variables was made (*t*-Student, $\chi^2$, p value)

## Results

The analysed group contained 112 men (53.8%) aged from 31 to 101 years (average 67.9) and 96 women (46.2%) aged from 41 to 95 (average 76.4). The incidence of ischaemic heart disease was similar in the male and female groups, but its complications were significantly more common in men. Myocardial infarction (MI) occurred in 8.3% of the women, but in 25% of the men, despite the fact that males are more often treated invasively [percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG)]. The appearance of peripheral artery disease (PAD) was more frequently observed in the group of men. Atrial fibrillation was diagnosed twice as often as in women. In the female group stroke, hypothyroidism, peptic ulceration and arthritis were more frequently reported (Table 3). A statistically significant correlation between epidemiological factors (age, hypertension, AF, PAD, MI, PCI, smoking) and gender was found.

Embolic ischaemia occurred in 105 (50.5%) patients. Thrombosis was diagnosed in 103 (49.5%) cases. Lower extremity ischaemia occurred most frequently (81.3%). There were 30 cases of upper extremity ischaemia (14.4%), nearly all as a result of emboli (29 patients). Acute mesenteric ischaemia (AMI) was observed in nine patients (4.3%); in six of these cases superior mesenteric artery/celiac trunk embolism and in the remaining three cases thrombosis due to visceral vessel atherosclerosis.

Open embolectomy/thrombectomy was the primary surgery in 155 cases (74.5%). 54 such procedures (25.7%) were performed due to thrombosis. Endovascular mechanical thrombectomy was performed in 25 cases (12.0%) on 22 patients. Direct catheter thrombolysis (DCT) was the first choice for 26 patients (12.5%). Primary amputation was performed in two patients with thrombosis (1.0%) (Figure 1). Among patients with PAD and a history of previous vascular surgeries, occlusion caused by graft thrombosis occurred in 26 cases (12.5%). Of these, 16 concerned previous femoro-popliteal, one case ilio-femoral, one case femoro-femoral, and eight cases aorto-bifemoral bypass. Only one (0.5%) patient with a history of PAD (ilio-femoral bypass) and atrial fibrillation was admitted with acute limb ischaemia caused by graft embolic occlusion. Thrombosis after previous endovascular treatment occurred in five patients (2.4%) — in three after peripheral stent grafts — one after aortic stent graft — and one after bare stent graft. Popliteal artery aneurysm was the cause of acute limb ischaemia in three cases (1.4%); of these, one case was a primary aneurysm thrombosis, and two cases were of secondary stent graft thrombosis. There was statistical significance of the aetiology in correlation with the type of primary intervention and the ischaemia localisation.

There was no significance in the in-hospital and post-hospitalisation mortality. Overall in-hospital mortality was 13% (27 patients) — 15 deaths in consequence of embolism, and 12 deaths in the course of thrombosis. Post hospitalisation mortality, within three to 12 months of follow up, was 39 (18.8%). Seven patients died due to a stroke, and seven due to myocardial infarction. Peripheral arterial disease and its complications were responsible for seven deaths (3.4%). Cancer was the cause of death of four patients (1.9%). In the other 14 cases (6.7%) of post-hospitalisation death, the cause was different or unknown. Overall mortality in the study group was 66 (31.7%). Table 4 shows the detailed characteristics concerning the aetiology and localisation of ischaemia.

The comparative cardiovascular factors regarding thrombotic or embolic cause of ischaemia are summarised in Table 5. The presence of ischaemic heart disease (IHD), PAD and tobacco smoking were relevant factors according the aetiology of acute ischaemia.

Thrombotic peripheral arterial ischaemia occurred in 100 of 123 patients with a history of PAD (81.3%). Among 85 patients without a history of PAD, arterial thrombosis was observed in three cases (3.5%; one case PAA thrombosis, two cases of idiopathic thrombosis).

Laboratory tests analysis was divided into groups of either thrombotic (T) or embolic (E) aetiology. Mean haemoglobin level was similar in both groups (12.6 g/dL vs. 12.3 g/dL). Mean platelet level in the thrombotic group was 271.8 × $10^3$/mL vs. 236.4 × $10^3$/mL in the embolic group. Average serum creatinine level was 2.3 mg/dL (T) vs. 1.2 mg/dL (E). International normalized ratio (INR) vas similar in both groups: 1.26 (T) vs. 1.31 (B).

15 patients with a history of AF were treated by vitamin K antagonists (VKA). In this group, INR was below the therapeutic level (mean 1.7). Anticoagulants taken before hospitalisation were divided into two groups in relation to the

**Table 3.** Comorbidities in correlation with gender

| Parameter | Female | Male | | p value |
|---|---|---|---|---|
| Number of pts. (years) | 96 (46.2%) | 112 (53.8%) | – | – |
| Age (average) | 41–95 (76.4, SD: 10.9) | 31–101 (67.9, SD: 11.1) | t(206) = 5.57 | **p < 0.005** |
| BMI (average) | 27.1 (SD: 5.37) | 25.7 (SD: 4.05) | t(89) = 1.28 | p > 0.05 |
| Coronary disease: | 41 (42.7%) | 44 (39.3%) | $\chi^2(1) = 0.3$ | p > 0.05 |
| • myocardial infarction | 8 (8.3%) | 28 (25.0%) | $\chi^2(1) = 10.2$ | **p < 0.01** |
| • percutaneous coronary intervention | 5 (5.2%) | 15 (13.4%) | $\chi^2(1) = 4.0$ | **p < 0.05** |
| • coronary artery bypass grafting | 1 (1.04%) | 6 (5.36%) | $\chi^2(1) = 2.9$ | p > 0.05 |
| Chronic obstructive pulmonary disease | 3 (3.1%) | 7 (6.3%) | $\chi^2(1) = 1.1$ | p > 0.05 |
| Peripheral artery disease (PAD) | 40 (41.7%) | 83 (74.1%) | $\chi^2(1) = 22.5$ | **p < 0.0005** |
| Carotid stenosis | 2 (2.1%) | 5 (4.5%) | $\chi^2(1) = 0.9$ | p > 0.05 |
| Hyperlipidaemia | 19 (19.8%) | 23 (20.5%) | $\chi^2(1) = 0.1$ | p > 0.05 |
| Hypertension | 70 (72.9%) | 78 (69.6%) | $\chi^2(1) = 4.2$ | **p < 0.05** |
| Diabetes | 30 (31.3%) | 22 (19.6%) | $\chi^2(1) = 3.7$ | p > 0.05 |
| Atrial fibrillation (AF): | 43 (44.8%) | 25 (22.3%) | $\chi^2(1) = 11.9$ | **p < 0.001** |
| • paroxysmal AF | 11 (25.6%) | 5 (20.0%) | $\chi^2(1) = 2.6$ | p > 0.05 |
| Ventricular arrhythmia | 1 (1.0%) | 3 (2.7%) | – | – |
| Neurological symptoms: | | | | |
| • transient ischaemic attack (TIA) | 0 (0.0%) | 3 (2.7 %) | – | – |
| • stroke: | | | | |
| – ischaemic | 19 (19.8%) | 13 (11.6%) | $\chi^2(1) = 2.7$ | p > 0.05 |
| – haemorrhagic | 5 (5.2%) | 3 (2.7%) | $\chi^2(1) = 0.9$ | p > 0.05 |
| Chronic kidney disease | 8 (8.3%) | 9 (8.0%) | $\chi^2(1) = 0.0$ | p > 0.05 |
| Deep vein thrombosis (DVT) | 0 (0.0%) | 2 (1.8%) | – | – |
| Pulmonary embolism (PE) | 2 (2.1%) | 0 (0.0%) | | – |
| Active cancer | 5 (5.2%) | 4 (3.6%) | – | – |
| Hypothyroidism | 1 (1.0%) | 1 (0.9%) | – | – |
| Hyperthyroidism | 4 (4.2%) | 2 (1.8%) | $\chi^2(1) = 1.1$ | p > 0.05 |
| Peptic ulcer | 8 (8.33%) | 2 (1.8%) | $\chi^2(1) = 2.9$ | p > 0.05 |
| GI tract bleeding | 1 (1.0%) | 2 (1.8%) | – | – |
| Arthritis | 6 (6.1%) | 3 (2.7%) | $\chi^2(1) = 0.1$ | p > 0.05 |
| Alcohol abuse | 2 (2.1%) | 11 (9.8%) | – | – |
| Smoking: | 25 (26.0%) | 45 (40.2%) | $\chi^2(1) = 11.2$ | **p < 0.001** |
| • pack-years (average) | 29.7 | 38.1 | – | – |

presence of AF or PAD (Table 6, Figure 2A, B). Coexistence of both diseases was found in 34 patients (16.4%). Statistical analysis showed a significant correlation between the occurrence of AF/PAD and anticoagulants/antiplatelet drugs administration before hospitalisation.

## Discussion

Acute arterial ischaemia caused by an embolism secondary to valvular heart disease was the most common cause. Thrombosis occurred on the base of severe, vulnerable

**Table 4.** Aetiology, localisation and detailed characteristics of ischaemia

| Parameter | Embolism | | Thrombosis |
|---|---|---|---|
| Total | 105 (50.5%) | | 103 (49.5%) |
| Lower extremity | | 169 (81.3%) | |
| | 70 (33.7%) | | 99 (47.6%) |
| Upper extremity | | 30 (14.4%) | |
| | 29 (13.9%) | | 1 (0.5%) |
| Acute mesenteric ischaemia | | 9 (4.3%) | |
| | 6 (2.9%) | | 3 (1.4%) |
| **Type of primary intervention** | | | |
| Open surgery | | 155 (74.5%) | |
| | 101 (48.6%) | | 54 (26.0%) |
| Endovascular thrombectomy | | 25 (12.0%) | |
| | 3 (1.4%) | | 22 (10.6%) |
| Direct catheter thrombolysis (DCT) | | 26 (12.5%) | |
| | 1 (0.5%) | | 25 (12.0%) |
| Primary amputation | 0 (0.00%) | | 2 (1.0%) |
| Vascular graft occlusion | 1 (0.5%) | | 26 (12.5%) |
| Stent occlusion | 0 (0.00%) | | 5 (2.4%) |
| Popliteal artery aneurysm (PAA) | – | | 3 (1.4%) |
| In-hospital mortality | | Overall: 27 (13.0%) | |
| | 15 (7.2%) | | 12 (5.8%) |
| Post-hospitalisation mortality | | Overall: 39 (18.8%) | |
| | 25 (12.0%) | | 14 (6.7%) |
| | $\chi^2$ | | p value |
| **Type of primary intervention** | **54.031** | | **0.000** |
| Previous vascular surgeries | – | | – |
| **Location** | **32.820** | | **0.000** |
| In-hospital mortality | 0.383 | | 0.536 |
| Post-hospitalisation mortality | 3.819 | | 0.051 |

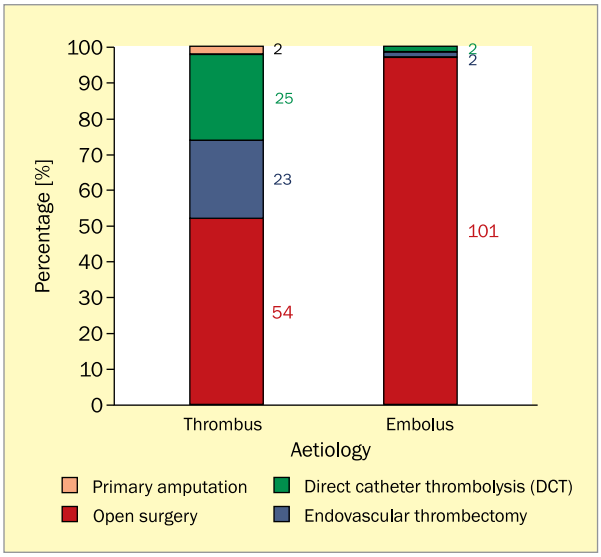


**Figure 1.** Type of primary intervention depending on the aetiology

atherosclerotic lesions [6]. Theories concerning the aetiology of acute ischaemia have changed over recent years. More recent studies have confirmed the increasing rate of a thrombotic cause of acute ischaemia [7].

In our presented study, the number of patients was comparable in both groups. In the material presented by Hemingway et al., acute limb ischaemia caused by arterial thrombosis was observed four times more often compared to an embolism [8], and a similar result was demonstrated by Genovese et al. [9]. After excluding thrombosis related to previous surgery, the primary cause of ALI was similar to our material. Serum creatinine level was higher in the thrombotic group and it has been proved that impaired renal function is a risk factor for PAD and thrombotic complications [10]. Some studies have shown that patients with acute limb ischaemia have a slightly higher rate of cerebrovascular disease (CVD) [11]. Our study showed no difference between the thrombotic and embolic groups in terms of CVD rate. The thrombosis group represents an

**Table 5.** Comparison of cardiovascular factors regarding the aetiology of acute ischaemia

| Parameter | Total | Embolism | Thrombosis | | p value |
|---|---|---|---|---|---|
| Average BMI | 26.3 | 26.6 | 26.1 | t(89) = 0.71 | p > 0.05 |
| PAD | 123 (59.1%) | 23 (21.9%) | 100 (97.1%) | **$\chi^2(1) = 124.2$** | **p < 0.0005** |
| Diabetes | 52 (25.0%) | 30 (28.6%) | 22 (21.4%) | $\chi^2(1) = 1.6$ | p > 0.05 |
| Smoking | 63 (30.3%) | 23 (21.9%) | 40 (38.8%) | **$\chi^2(1) = 10.0$** | **p < 0.01** |
| IHD | 85 (40.9%) | 51 (48.6%) | 34 (33.0%) | **$\chi^2(1) = 5.5$** | **p < 0.05** |
| MI | 36 (17.2%) | 15 (14.3%) | 21 (20.4%) | $\chi^2(1) = 2.2$ | p > 0.05 |
| CVD | 43 (20.7%) | 20 (19.1%) | 23 (22.3%) | $\chi^2(1) = 0.8$ | p > 0.05 |
| Carotid stenosis | 7 (3.4%) | 4 (3.8%) | 3 (2.9%) | $\chi^2(1) = 0.2$ | p > 0.05 |

BMI — body mass index; PAD — peripheral artery disease; IHD — ischaemic heart disease; MI — myocardial infarction; CVD — cerebrovascular disease (transient ischaemic attack/stroke)

**Table 6.** Anticoagulants and antiplatelet drugs administration before hospitalisation

| | Disease (no. of patients) | AF (68) | PAD (123) |
|---|---|---|---|
| Antithrombotic drug | VKA | 16 (23.5%) | 8 (6.5%) |
| | Anti-IIa | 4 (5.9%) | 3 (2.4%)) |
| | Anti-Xa | 6 (8.8%) | 6 (4.9%) |
| | LMWH | 3 (4.4%) | 2 (1.6%) |
| | ASA | 6 (8.8%) | 23 (18.7%) |
| | SAPT | 2 (2.9%) | 13 (10.6%) |
| | DAPT | 1 (1.5%) | 15 (12.2%) |
| | None | 37 (54.4%) | 53 (43.1%) |
| | $\chi^2$ | p value | |
| AF | 50.342 | 0.000 | |
| PAD | 19.275 | 0.004 | |

AF — atrial fibrillation; PAD — peripheral artery disease; VKA — vitamin K antagonists; Anti-IIa — direct thrombin inhibitor; Anti-Xa — factor Xa inhibitor; LMWH — low molecular weight heparin; ASA — acetylsalicylic acid only; SAPT — single antiplatelet therapy (clopidogrel or cilostazol); DAPT — dual antiplatelet therapy

extremely high percentage of PAD (97.1%). Active smoking was observed more often (38.8%) in the thrombotic group. Smoking is also an obvious risk factor for atherosclerosis and renal failure [12].

In the analysed group of patients treated due to arterial embolism while receiving VKA, the INR level was non-therapeutic (mean 1.7) [13]. In the groups of patients with AF and PAD history, there was a very high rate of patients without any antithrombotic treatment before hospitalisation (AF 54.4%. PAD 43.1%).

Acute upper limb ischaemia occurs less frequently than the lower limb variation. The most common cause of arm ischaemia is a cardiac embolism. Atherosclerosis, except of the subclavian arteries, is rare in upper limb arteries. Thoracic outlet syndrome and proximal subclavian artery aneurysm are other rare causes of embolisation. Arm ischaemia threatens the limb to a lesser extent, and the treatment decision is thus less urgent. The main reason

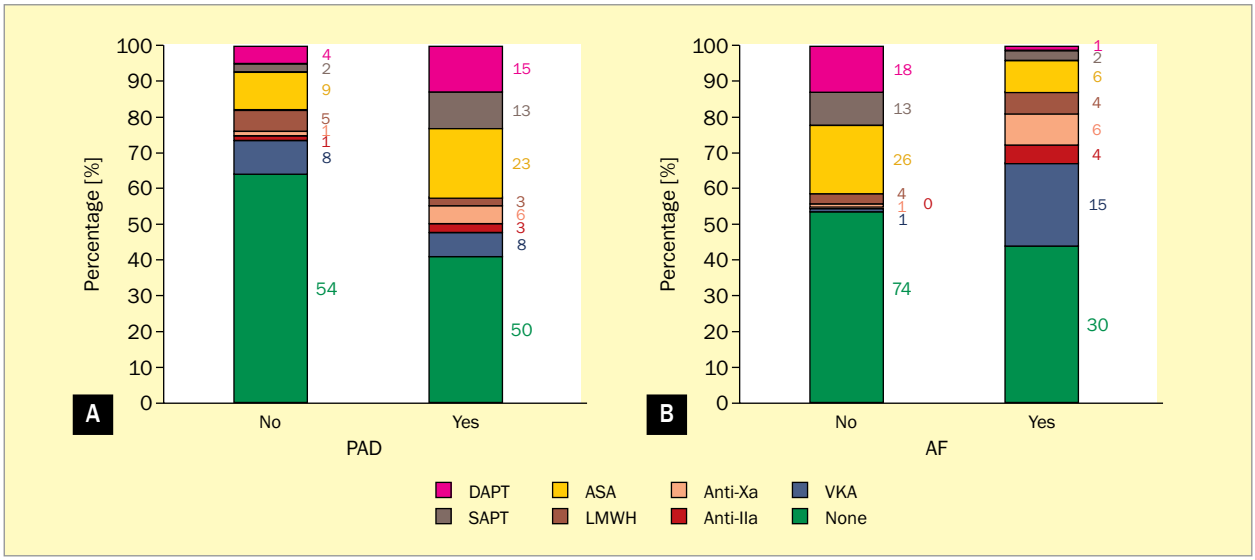


**Figure 2A, B.** Anticoagulants and antiplatelet drugs administration in correlation to presence of peripheral artery disease (PAD)/atrial fibrillation (AF); DAPT — dual antiplatelet therapy; SAPT — single antiplatelet therapy; ASA — acetylsalicylic acid; LMWH — low molecular weight heparin; Anti-Xa — factor Xa inhibitor; — direct thrombin inhibitor; VKA — vitamin K antagonists;

is to prevent late complications such as arm fatigue and chronic pain [14–16].

Acute mesenteric ischaemia (AMI) is uncommon. Women are affected three times more often than men [17]. Arterial embolism is the most common pathophysiology of AMI [18]. In contrast, data from our study shows that AMI occurred 3.5 times more often in the male group (seven males vs. two females) despite a significantly lower AF rate.

Popliteal artery aneurysm is relatively uncommon, with an estimated incidence rate of 0.1–2.8% and has been shown to be a rare cause of thromboembolism [19].

Our study presents the comprehensive characteristics of patients with acute arterial ischaemia. However, in order to draw clinical conclusions, a multi-centre analysis and a larger group of patients would be required.

## Conclusions

Acute arterial ischaemia occurs regardless of gender. In our material, ischaemia caused by embolus and thrombus occurred with similar frequencies. Upper extremity arterial thrombosis occurs very rarely. An embolism is more often responsible for acute intestinal ischaemia. In patients with a history of PAD and a history of previous vascular interventions, the presence of a vascular graft/stent graft is associated with a higher risk of arterial thrombosis. Among patients with AF and receiving VKA, the average of level of INR is non-therapeutic.

## Conflict(s) of interest

The authors report no conflict of interest.


### Streszczenie

**Wstęp.** Ostra niedrożność tętnicy obwodowej może prowadzić do niedokrwienia zaopatrywanego przez nią narządu wymagającego pilnej reakcji. Opóźnienie w rozpoznaniu i leczeniu może doprowadzić do śmierci lub inwalidztwa.

**Materiał i metody.** Celem pracy była retrospektywna analiza danych demograficznych i epidemiologicznych pacjentów z objawami ostrego niedokrwienia przyjętych do kliniki autorów w latach 2014–2018. Badana grupa obejmowała 112 mężczyzn (53,8%; średni wiek 67,9 roku) i 96 kobiet (46,2%; średni wiek 76,4 roku). Ocena uwzględniała dane antropometryczne, wywiad chorób układu sercowo-naczyniowego, innych chorób przewlekłych i uzależnień. Analizowano przyczynę i lokalizację niedokrwienia oraz rodzaj interwencji chirurgicznej.

**Wyniki.** Zauważono istotny związek między płcią a wiekiem, nadciśnieniem tętniczym, migotaniem przedsionków, miażdżycą obwodową, zawałem serca, paleniem tytoniu. Niedokrwienie na podłożu zatorowym wystąpiło w 50,5% przypadków, a zakrzepica tętnicza — w 49,5%. Niedokrwienie kończyny dolnej występowało najczęściej (81,3%). Otwarta embolektomia/trombektomia była pierwotną operacją w 155 przypadkach. Stwierdzono istotny związek między etiologią niedokrwienia a chorobą niedokrwienną serca, niedokrwieniem kończyn dolnych, paleniem tytoniu, rodzajem interwencji i lokalizacją zmian. Nie stwierdzono istotnej różnicy w śmiertelności.

**Wnioski.** Ostre niedokrwienie tętnicze może wystąpić niezależnie od płci. Ostre niedokrwienie kończyny górnej w następstwie zakrzepu tętniczego występuje bardzo rzadko. Zator jest częściej odpowiedzialny za ostre niedokrwienie jelit. Pacjentów z miażdżycą tętnic obwodowych i po przebytych operacjach naczyniowych cechuje zwiększone ryzyko zakrzepicy tętniczej. Wśród pacjentów z wywiadem migotania przedsionków przyjmujących antagonistów witaminy K wartość międzynarodowego współczynnika znormalizowanego jest często nieterapeutyczna.


Słowa kluczowe: miażdżyca, ostre niedokrwienie, zator, zakrzep, choroba tętnic obwodowych, migotanie przedsionków

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# Ranolazine — a new drug for patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias?

## Ranolazyna — nowy lek w nawracających opornych na leczenie arytmiach komorowych?

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Lekarz Błażej Kusz jest absolwentem Wydziału Lekarskiego Śląskiego Uniwersytetu Medycznego w Katowicach. Obecnie odbywa szkolenie specjalizacyjne w I Katedrze i Klinice Kardiologii pod kierownictwem prof. dr hab. n. med. Katarzyny Mizi-Stec. Jest uczestnikiem studiów doktoranckich Wydziału Lekarskiego Śląskiego Uniwersytetu Medycznego w Katowicach oraz kierownikiem projektu „Szybka screeningowa analiza fazy wydechowej i osocza u pacjentów z tętniczym nadciśnieniem płucnym", realizowanego w ramach konkursu 'Preludium' Narodowego Centrum Nauki. Zainteresowania pozamedyczne dr. Kusza obejmują muzykę, literaturę oraz grę w tenisa. W wolnych chwilach uwielbia podróżować.

## Abstract

**Introduction.** The pharmacological treatment of ventricular arrhythmias (VA) has significant limitations. Ranolazine is a relatively new drug with documented antianginal and anti-ischaemic mechanisms and where preclinical data provides evidence of additional antiarrhythmic properties.

The aim of this article was to evaluate the safety and efficacy of ranolazine in patients with recurrent antiarrhythmic therapy-refractory VA.

**Material and methods.** This prospective evaluation included 30 patients (pts) (male/female: 26/4; mean age: 65 ± 10 years; coronary artery disease/dilated cardiomyopathy: 20/10; New York Heart Association class I/II/III/IV: 2/14/12/2, left ventricular ejection fraction: 27 ± 10%; implantable cardioverter-defibrillator (ICD): 15 pts, implantable cardioverter-defibrillator with cardiac resynchronisation therapy (CRT-D): 14 pts with recurrent significant VA [ventricular fibrillation, sustained ventricular tachycardia (VT) and/or non-sustained VT, multiple ventricular premature complexes > 1,000/day, biventricular stimulation (BiV) < 95%] and where standard treatment options, *i.e.* pharmacotherapy, coronary revascularisation, and percutaneous ablation, had proved ineffective. The severity of the arrhythmia was assessed by 24-hour electrocardiographic (ECG) Holter monitoring and in ICD/CRT-D memory recording. The patients received, in addition to the standard pharmacotherapy (amiodarone: 18 pts, beta-blocker: 26 pts) ranolazine 375 mg twice daily for three months. Baseline data was compared to the data obtained after the three months of ranolazine treatment.

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**Results.** We observed a significant reduction of total ventricular extrasystoles determined by ECG Holter monitoring (median: 1,737 vs. 1,260, p = 0.04). Similarly, significant VA in ICD/CRT-D memory recording was diminished (67.7 vs. 35.5%, p = 0.03). The number of ICD interventions in terms of both antitachycardia pacing (9 pts vs. 2 pts, p = 0.01), and shock delivery (8 pts vs. 2 pts, p = 0.01), was lower after the three-month observation. The therapy was ineffective for nine (29%) patients — two were hospitalised during the three-month follow-up because of recurrent arrhythmia and in seven pts there was no noticeable reduction in the amount of VA. Adverse effects, in the form of gastrointestinal symptoms (diarrhoea: two, constipation: one), occurred in three (10%) patients.

**Conclusions.** Authors observed no significant QT prolongation in any patient. There were no differences between the baseline and the post-ranolazine patient clinical characteristics. Ranolazine seems to be a safe and effective second-line therapy in the reduction of VA and ICD interventions in patients with recurrent antiarrhythmic therapy-refractory events.

Key words: ranolazine, ventricular arrhythmias, therapy-refractory arrhythmias

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## Introduction

Ventricular arrhythmias remain a complex and challenging problem. Treatment comprises pharmacotherapy, which however has significant limitations, as well as invasive procedures such as coronary artery revascularisation and catheter ablation.

Therefore, there is a clear need to seek new anti-arrhythmic drugs that could be implemented into therapy.

A potential option could be ranolazine. This is a relatively new, well-tolerated drug with proven antianginal activity [1–3] and with a biochemical structure similar to that of lidocaine. As ranolazine is an inhibitor of ion channels, it can modify the excitability of atrial and ventricular myocardium cells. It inhibits both extracellular (depolarising) currents: sodium ($Na^+$) along with L-type calcium channels (Ical), as well as cellular (repolarising) potassium ($K^+$) currents. The clinical effects of ranolazine, which are based on the protection of the myocardium during ischaemia/reperfusion (an antianginal effect), an improvement in mechanical dysfunction, and an 'electrical' stabilisation of cells, are mainly associated with the inhibition of sodium channels.

The anti-arrhythmic activity of ranolazine has been recorded among patients with atrial fibrillation [4–6], but its role in the treatment of ventricular arrhythmias has not yet been fully investigated. It appears that the drug could primarily be used in the treatment of such arrhythmias in patients with coronary artery disease (CAD), but potentially also in other groups, *i.e.* dilated cardiomyopathy (DCM).

Thus, the aim of our study was to evaluate the safety and efficacy of ranolazine in patients with the highest risk of sudden cardiac death (SCD) — in patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias.

## Material and methods

This prospective evaluation included a group of 30 patients enrolled into the study between 2013 and 2018 (26 male/4 female, mean age: 65 ± 10 years; CAD/DCM: 20/10; New York Heart Association (NYHA) class: I/II/III/IV: 2/14/12/2, left ventricular ejection fraction (LVEF): 27 ± 10%; implantable cardioverter-defibrillator (ICD): 15 pts, cardiac resynchronisation therapy with defibrillator (CRT-D): 14 pts) (Table 1), all of whom had recurrent significant antiarrhythmic therapy-refractory ventricular arrhythmias.

The inclusion criteria were: ventricular fibrillation (VF), sustained (sVT) and/or non-sustained ventricular tachycardia (nsVT), and multiple ventricular premature complexes (VEs) obtained after exhausting the standard treatment options, *i.e.* pharmacotherapy, coronary revascularisation and percutaneous ablation.

The exclusion criteria were: acute coronary syndrome, severe heart failure decompensation, current infection of potential significance for the occurrence of ventricular arrhythmias, thyroid function abnormalities, hypokalemia, implanted device without Holter monitoring, liver failure, chronic kidney disease with GFR < 30 ml/min., neurological diseases/conditions such as a past history of clinically apparent ischaemic stroke, and active subarachnoid haemorrhage.

Of the 30 patients enrolled into the study, 20 suffered from coronary artery disease (LVEF: 28 ± 12%, ICD: 9; CRT-D: 10) and 10 from dilated cardiomyopathy (LVEF 25 ± 6%, ICD: 6; CRT-D: 4). In all patients, standard pharmacotherapy administered according to the current ESC guidelines as well as invasive procedures including coronary artery revascularisation and catheter ablation had proved ineffective. All patients had been re-hospitalised due to recurrent arrhythmia. They were on stable therapy.

**Table 1.** Clinical characteristics

| Parameter | All patients N = 30 | Patients with CAD N = 20 | Patients with DCM N = 10 |
|---|---|---|---|
| | | Mean value ± SD N (%) | |
| Age [years] | 65 ± 10 | 68 ± 7 | 60 ± 13 |
| Height [cm] | 173 ± 9 | 171 ± 10 | 176 ± 4 |
| Weight [kg] | 87 ± 15 | 83 ± 14 | 95 ± 16 |
| BMI [kg/m$^2$] | 29 ± 5 | 29 ± 5 | 31 ± 5 |
| LVEF [%] | 27 ± 10 | 28 ± 12 | 25 ± 7 |
| LV EDD [mm] | 70 ± 11 | 69 ± 10 | 72 ± 12 |
| LV ESD [mm] | 58 ± 11 | 56 ± 11 | 61 ± 11 |
| ICD | 15 (50%) | 9 (45%) | 6 (60%) |
| CRT-D | 14 (47%) | 10 (50% | 4 (40%) |
| DDDR | 1 (3%) | 1 (5%) | 0 |

All modifications/interventions were done during the previous hospitalisation.

These patients received ranolazine 375 mg twice daily for three months in addition to their standard pharmacotherapy. Eighteen patients were on chronic amiodarone therapy.

Clinical assessment, resting ECG, ECG Holter monitoring, ICD/CRT-D memory recording, transthoracic echocardiography as well as standard laboratory examinations were obtained at baseline and again after three months of ranolazine treatment. The severity of the arrhythmia was assessed by 24-hour ECG Holter monitoring (significant ventricular arrhythmia was defined as: nsVT/VT/VEs > 1,000/day) and in ICD/CRT-D memory recording (significant ventricular arrhythmia was defined as: nsVT/VT/VF, BiV < 95%).

Baseline data was compared to data obtained after the three-month ranolazine treatment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. All patients gave their written consent for participation in the study prior to enrollment.

## Statistical analysis

Statistical analysis was performed using Statistica 10.0 (StatSoft Poland) software. Continuous variables were presented as median, and categorical as absolute counts and percentages. The type of distribution was verified using a Shapiro-Wilk test. In cases of normally-distributed variables, Student's t test for unpaired samples was used, while Mann–Whitney U test was implemented in non-normally distributed parameters. Wilcoxon test was used for paired samples. A p-value of less than 0.05 was considered statistically significant.

## Clinical characteristics

Comparison of the baseline clinical data and the data obtained after the three-month ranolazine therapy did not reveal any significant changes in the patients' clinical status. We observed no significant improvement in effort tolerance expressed in the NYHA scale. In several cases we found an improvement in CCS scale (5 pts) as well as a reduction of the subjective sensation of palpitations (5 pts). The echocardiographic parameters remained similar after the treatment, including LVEF (28% ± 12 vs. 29% ± 12, p = NS). The level of potassium remained normal, at a stable level (avg. 4.4 mEg/L). Serum NT-proBNP level did not significantly change during the observation (median value 412 vs. 365 pg/mL).

## Efficacy of ranolazine treatment

Significant ventricular arrhythmia determined via Holter monitoring was reduced after ranolazine therapy (77.4 vs. 48.4%, p = 0.01). A significant reduction of total VEs was observed in the Holter monitoring (median: 1,737 vs. 1,260, p = 0.04) (Table 2).

**Table 2.** Efficacy of ranolazine treatment

| Parameter | Baseline | Post--ranolazine | p value |
|---|---|---|---|
| Total VEs in Holter ECG (median) | 1,737 | 1,260 | 0.04 |
| Ventricular arrhythmia in ICD/CRT-D memory recording [%] | 67.7 | 35.5 | 0.03 |
| ATP, N [%] | 9 (30) | 2 (7) | 0.01 |
| Shock delivery, N [%] | 8 (27) | 2 (7) | 0.01 |

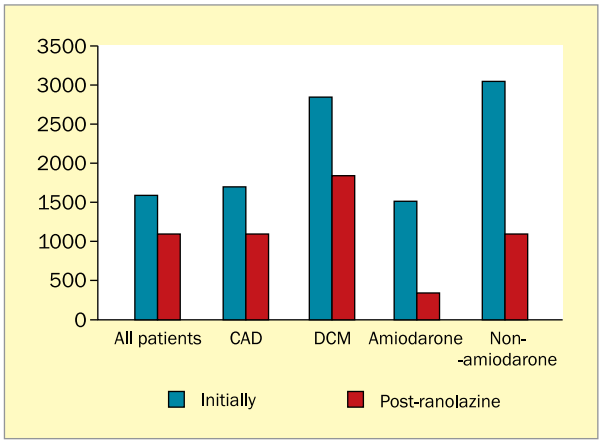


**Figure 1.** Median value of total ventricular extrasystoles in electrocardiographic Holter monitoring before and post-ranolazine treatment; CAD — coronary artery disease; DCM — dilated cardiomyopathy

Similarly, significant ventricular arrhythmia in ICD/ /CRT-D memory recording was diminished (67.7 vs. 35.5%, p = 0.03). The number of ICD interventions in terms of both antitachycardia pacing (9 pts vs. 2 pts, p = 0.01) and shock delivery (8 pts vs. 2 pts, p = 0.01) was lower after the three-month observation (Table 2).

The therapy was ineffective for nine (29%) of the pts — two were hospitalised during the three-month follow-up, and in seven pts there was no noticeable reduction in the amount of ventricular arrhythmia.

## Ranolazine treatment: CAD vs. DCM

The total value of VEs in Holter ECG in patients with CAD was insignificantly higher at baseline than in cases of DCM (median value 1,864 vs. 3,074).

After the ranolazine treatment, we observed a significant reduction in total VE values determined via Holter ECG in the CAD patients (median value 1,864 vs. 1,271, p < 0.05).

In the group of patients with DCM, a reduction in total VE values was observed in five cases (50%, median value 6,460 vs. 500), although the result was statistically non--significant for the whole subgroup (median value 3,074 vs. 2,000) (Figure 1).

## Ranolazine treatment: amiodarone vs. non-amiodarone

The total value of VEs determined via Holter ECG in patients treated with amiodarone was insignificantly lower than the value in subjects without amiodarone at baseline (1,529 vs. 4,100).

In the group of patients treated with amiodarone, we observed a significant reduction in total VEs in Holter ECG (median value 1,529 vs. 500, p < 0.05).

In the group of patients treated with ranolazine without amiodarone, we observed reduced total VEs in Holter ECG in five cases (42%, median value 5,000 vs. 1,281), but the efficacy of the drug was statistically insignificant for the whole subgroup (median value 4,100 vs. 1,281).

## Safety of ranolazine treatment

Adverse effects in the form of gastrointestinal symptoms (diarrhoea: two, constipation: one) occurred in three (10%) pts. We observed no significant QT prolongation in any patient, and no significant changes in the average heart rate (66 ± 8 vs. 63 ± 9 bpm, p = 0.31).

# Discussion

The crucial finding of our research is that ranolazine can be used effectively as a second-line therapy in ventricular arrhythmias.

The drug was effective with statistical significance in patients with CAD. Perhaps this was due to its better effect in people with this disease; however, due to the small number of patients in the study group, further research is needed to objectify this claim.

It should be noted that we analysed a very specific group of patients. Our study group consisted of patients with the highest risk of SCD — patients with recurrent antiarrhythmic therapy-refractory ventricular arrhythmias. Both standard pharmacotherapy and invasive procedures had proved ineffective. Ranolazine was administered over and above the current available therapy.

Additionally, all subjects presented symptoms of chronic heart failure with a reduced ejection fraction. Regardless of their stable haemodynamic status, the LVEF was below 30% in most of the patients. All these figures underline the clinical importance of our findings.

Whereas until now the efficacy of the drug has been proved in atrial fibrillation [4–6], studies are still ongoing regarding its possible use in ventricular arrhythmias. A recently completed RAID trial in which a comparable group of patients was enrolled into the study showed however that in high-risk ICD patients, treatment with ranolazine did not significantly reduce the incidence of the first VT or VF or death.

But, in prespecified secondary endpoint analyses similar to our study, ranolazine administration has been associated witha significant reduction in recurrent VT or VF requiring ICD therapy, without evidence for increased mortality [7]. Another study, conducted by Yeung E et al., showed a significant reduction in median premature ventricular complexes burden, as well as the elimination of VT in chosen patients and the prevention of recurrent defibrillator therapy, something which was also found in our study [8]. The efficacy of ranolazine in the treatment of ventricular arrhythmias has also been observed in patients with symptomatic non-obstructive hypertrophic cardiomyopathy. Olivotto et al. [9] examined a group

of 80 patients who were treated with ranolazine 1,000 mg bid for five months. However, their primary endpoint was to observe possible changes in peak $VO_2$ compared to baseline using a cardiopulmonary exercise test. The severity of the ventricular arrhythmia was also assessed, and a significant reduction was observed in the 24-hour burden of premature ventricular complexes compared to a placebo [9].

It is worth mentioning that several studies have demonstrated the additional efficacy of ranolazine treatment in combination with amiodarone or dronedarone. Although differences have been observed in atrial fibrillation, from our study it appears that a similar relationship exists in the case of severe ventricular arrhythmias [5, 10, 11].

Overall, in the vast majority of studies, ranolazine has proved to be safe and well tolerated.

We are aware of some limitations of our study, of which the most important remains the relatively small group of patients enrolled. This was because the study included patients with both advanced cardiac insufficiency and an exhausted option of standard therapy. It seems safe to assume that this is inherently a rare group. It should probably be contemplated using higher doses of the drug to investigate possible intensification of its action.

## Conclusion

Ranolazine seems to be an effective and safe second-line therapy in reducing the number of ventricular arrhythmia episodes and ICD interventions in patients with recurrent antiarrhythmic therapy-refractory events. Further research is however needed in order to provide more evidence.

## Funding

The study was supported by a grant from the Medical University of Silesia (grant No. KNW-1-078/N/6/K to K.M.S.).

## Conflict(s) of interest

All authors declare no conflict of interest.

## Streszczenie

**Wstęp.** Farmakologiczne leczenie komorowych zaburzeń rytmu (VA) jest ograniczone. Ranolazyna to stosunkowo nowy lek o udokumentowanym działaniu przeciwdławicowym i przeciwniedokrwiennym oraz z danymi przedklinicznymi wskazującymi na dodatkowe właściwości antyarytmiczne.

Celem pracy była ocena bezpieczeństwa i skuteczności ranolazyny u pacjentów z nawracającymi opornymi na leczenie VA.

**Materiał i metody.** Prospektywną oceną objęto 30 pacjentów (pts) (mężczyźni/kobiety: 26/4, średnia wieku: 65 ± 10 lat; choroba wieńcowa/kardiomiopatia rozstrzeniowa: 20/10, klasa I/II/III/IV według *New York Heart Association*: 2/14/12/2, frakcja wyrzutowa lewej komory: 27 ± 10%; kardiowerter-defibrylator [ICD]: 15 pts, terapia resynchronizująca serce z funkcją defibrylacji [CRT-D]: 14 pts) z nawracającymi istotnymi VA (migotanie komór, utrwalony częstoskurcz komorowy [VT] i/lub nieutrwalony VT, liczne pojedyncze ekstrasystolie komorowe > 1000/d., stymulacja biwentrikularna (BiV) < 95%) i z wyczerpaną standardową opcją leczenia, tj. farmakoterapią, rewaskularyzacją wieńcową i przezskórną ablacją. Nasilenie arytmii oceniano w 24-godzinnym monitorowaniu elektrokardiograficznym (EKG) metodą Holtera oraz w pamięci holterowskiej ICD/CRT-D. U pacjentów do standardowej farmakoterapii (amiodaron: 18 pts, beta-adrenolityk: 26 pts) dołączono ranolazynę w dawce 375 mg 2 razy/dobę przez 3 miesiące. Wyjściowe dane porównano z danymi uzyskanymi po 3-miesięcznym leczeniu.

**Wyniki.** Autorzy zaobserwowali istotną redukcję liczby ekstrasystolii komorowych w monitorowaniu EKG metodą Holtera (mediana: 1737 *v.* 1260; p = 0,04). Podobnie odnotowano istotne zmniejszenie częstości istotnej VA w zapisie pamięci ICD/CRT-D (67,7 *v.* 35,5%; p = 0,03). Liczba interwencji ICD zarówno pod względem stymulacji antyarytmicznej (9 pts *v.* 2 pts; p = 0,01), jak i wyładowań (8 pts *v.* 2 pts; p = 0,01) była niższa po 3-miesięcznej obserwacji. Terapia była nieskuteczna u 9 (29%) pacjentów — 2 hospitalizowano w trakcie 3-miesięcznej obserwacji z powodu nawrotu VA, a u 7 nie stwierdzono zauważalnego zmniejszenia występowania VA. Działania niepożądane pod postacią dolegliwości żołądkowo-jelitowych (biegunka: 2, zaparcie: 1) wystąpiło u 3 (10%) chorych. U żadnego z pacjentów nie obserwowano istotnego wydłużenia odstępu QT. Nie obserwowano istotnych różnic w charakterystyce klinicznej pacjentów wyjściowo i po podaniu ranolazyny.

**Wnioski.** Ranolazyna wydaje się bezpiecznym i skutecznym lekiem drugiego rzutu, który może być stosowany w redukcji VA i liczby interwencji ICD u pacjentów z nawracającymi opornymi na leczenie VA.

Słowa kluczowe: ranolazyna, arytmie komorowe, arytmie oporne na leczenie

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# Zalecenia dietetyczne dotyczące spożywania jodu — w poszukiwaniu konsensusu między kardiologami a endokrynologami

## Iodine dietary recommendations — in search of a consensus between cardiologists and endocrinologists

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### Streszczenie

Jod jest pierwiastkiem należącym do niezbędnych bioaktywnych składników diety, który ma udział w syntezie hormonów tarczycy, a te z kolei wpływają na prawidłowy rozwój i funkcjonowanie organizmu. W sytuacji gdy spożycie jodków jest mniejsze niż 50 μg/dobę, gruczoł tarczowy nie jest w stanie utrzymać syntezy hormonów tarczycy na prawidłowym poziomie. Wyniki badań z lat 1992/1993 Polskiej Komisji ds. Kontroli Zaburzeń z Niedoboru Jodu były bezpośrednim powodem powrotu do obowiązkowego jodowania soli kuchennej. Sól kuchenna jest powszechnie stosowanym nośnikiem jodu. Zgodnie z zaleceniami Światowej Organizacji zdrowia dzienne spożycie soli nie powinno przekraczać 5 g NaCl (2 g Na) na osobę. Kontrolowanie zawartości Na w diecie jest metodą prewencji chorób sercowo-naczyniowych. Prowadzone są równocześnie działania mające na celu zwiększenie spożycia innych naturalnych nośników jodu (mleko, woda mineralna). Alternatywnym źródłem jodu w diecie są między innymi: dorsz, mintaj, łosoś, jaja, otręby pszenne, brokuły, suche nasiona grochu i orzechy laskowe. Zasadna jest idea wdrożenia jodowania wody mineralnej i mleka, a także biofortyfikacji wybranych warzyw oraz podawania jodu trzodzie i bydłu w celu zapewnienia odpowiedniej jego podaży w związku z zaleceniami ograniczenia spożycia soli kuchennej.

Słowa kluczowe: jod, dieta, nadciśnienie tętnicze, jodowanie soli, amiodaron

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## Wstęp

Jod jest pierwiastkiem należącym do niezbędnych bioaktywnych składników diety, który ma udział w syntezie hormonów tarczycy, a te z kolei wpływają na prawidłowy rozwój i funkcjonowanie organizmu. Jest jednym z najsilniejszych antyoksydantów i wykazuje ochronne działanie w procesach zapalnych i nowotworowych [1].

Jod należy do składników odżywczych, które nie są magazynowane w organizmie człowieka i musi być dostarczany

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z dietą. Niedostateczna podaż tego pierwiastka prowadzi do wystąpienia jego niedoborów, nadmiar zaś może wywoływać nadczynności tarczycy [1, 2].

## Zalecenia dietetyczne dotyczące podaży jodu

Rekomendacje Światowej Organizacji Zdrowia (WHO, *World Health Organization*) co do optymalnego dziennego spożycia jodków są następujące: dla osób dorosłych — 150 μg/dobę, dla kobiet w ciąży i podczas laktacji — 250 μg/dobę, w pierwszym roku życia 50 μg/dobę, w wieku od 1–5 lat — 90 μg/dobę oraz w wieku 6–12 lat — 120 μg/dobę [3]. W sytuacji gdy spożycie jodków jest mniejsze niż 50 μg/dobę, gruczoł tarczowy nie jest w stanie utrzymać syntezy hormonów tarczycy na prawidłowym poziomie. W następstwie czynnościowo przerasta i zmienia swoją strukturę, co ostatecznie prowadzi do rozwoju niedoczynności tarczycy. Brak hamowania wydzielania hormonu tyreotropowego (TSH, *thyroid-stimulating hormone*) przez przysadkę mózgową dodatkowo potęguje przerost gruczołu (TSH jest także czynnikiem wzrostowym) [1].

Należy zatem dążyć do utrzymania prawidłowego spożycia jodu, ponieważ przede wszystkim jego niedobór (ale również — spotykane stosunkowo rzadko — nadmierne spożycie jodu) niekorzystnie wpływa na zdrowie populacji. Stosowanie profilaktyki jodowej powinno być stale monitorowane, aby oceniać jej efektywności, a także ustalać optymalne zaopatrzenie w jod [1, 4].

Polska Komisja ds. Kontroli Zaburzeń z Niedoboru Jodu (PCCIDD, *Polish Council for Control of Iodine Deficiency Disorders*) zdecydowała o przeprowadzeniu badań epidemiologicznych w latach 1992–1993, obejmujących dzieci i młodzież szkolną, noworodki i kobiety w ciąży. Wyniki tych badań były bezpośrednim powodem powrotu do powszechnego, obowiązkowego jodowania soli kuchennej (20–40 mgKJ/kg) od 1997 roku [1, 2, 4]. Komisja określiła także pozostałe wskazania do prowadzenia profilaktyki: dodatkowe jodowanie żywienia wstępnego i następnego dla noworodków (10 μg/100 ml mleka) oraz dodatkowej suplementacji kobiet w ciąży i kobiet karmiących w dodatkową dawkę jodu 150–200 μg/dobę [1].

Model ten okazał się bardzo efektywny. Występowanie wola u dzieci szkolnych zmniejszyło się o 30–80% w porównaniu z latami 1992–1993; a u najmłodszej grupy (6–8 lat) występowało ono tylko u 2,6% dzieci, czyli poniżej poziomu endemicznego [1]. Obserwowany wcześniej wzrost stężenia TSH u noworodków powyżej 20 μjm./ml zmniejszył się z 2,0% do 0,16%, częstość występowania wola u kobiet w ciąży zmalała z 80% do 19%, zmniejszyła się także częstość występowania zróżnicowanego raka tarczycy u kobiet [1].

W 2002 roku uznano polski model profilaktyki niedoborów jodu za efektywny i bezpieczny. Stwierdzono, że nie ma ryzyka populacyjnego niedoczynności tarczycy w przebiegu niedoboru jodu i nadwrażliwości w wyniku spożywania jodu [1, 3].

Należy jednak dodać, że nie udało się osiągnąć całkowitego sukcesu. U starszych dzieci (będących zwłaszcza w okresie dojrzewania) wole występuje nadal w 7–8% w zależności od regionu, a częstość wydalania jodu z moczem powyżej 100 μg/l nie osiągnęła pożądanej wartości 50%. Ciągle tylko 70% kobiet w ciąży otrzymuje zalecaną dawkę jodu i chociaż częstość występowania raka tarczycy u kobiet jest mniejsza, nadal jest 3–4-krotnie większa niż w okresach regularnego jodowania. Wreszcie jakość jodowania soli obejmuje 96% zalecanych norm [1, 5].

Narodowy Program Eliminacji Zaburzeń w Przebiegu Niedoboru Jodu został przerwany w latach 2003–2005, ponowne powrócono do niego w roku 2006 i jest kontynuowany [1].

## Dieta z ograniczeniem soli w profilaktyce chorób układu sercowo-naczyniowego a podaż jodu

Osobnym zagadnieniem jest prowadzenie profilaktyki jodowej i zalecane ograniczenie spożycia soli do 5 g/dobę. Sól kuchenna jest bowiem powszechnie stosowanym nośnikiem jodu.

Zalecenia opracowane przez Światową Organizację Zdrowia (WHO, *World Health Organization*) (Paryż 2006, Luksemburg 2007) wynikają z udokumentowanej roli soli w zwiększeniu ryzyka chorób układu sercowo-naczyniowego, w tym: nadciśnienia tętniczego, miażdżycy, udarów i zawałów serca oraz niektórych chorób nowotworowych. Zgodnie z zaleceniami WHO dzienne spożycie soli nie powinno przekraczać 5 g NaCl (2 g Na) na osobę [6]. Średnie dzienne spożycie soli w Polsce wynosi 13,5 g/osobę, w tym 8,8 g soli kuchennej, a w niektórych regionach kraju dochodzi do 15,0 g/osobę [4].

Według Standardów Postępowania Dietetycznego w Kardiologii — stanowiska Polskiego Towarzystwa Dietetyki z 2016 roku — wcześniejsze lata obfitowały w ponad milion zgonów powiązanych ze spożyciem NaCl w ilości przekraczających 5 g/dobę rekomendowanych przez WHO (1,65 mln zgonów w 2010 r.) [7].

Raport opracowany przez Światową Federację Serca (WHF, *World Heart Federation*), Europejskie Towarzystwo Nadciśnienia Tętniczego (ESH, *European Society of Hypertension*) oraz Europejskie Stowarzyszenie Zdrowia Publicznego (EUPHA, *European Public Health Association*) dotyczące wpływu spożycia sodu na występowanie chorób układu krążenia w krajach o niskim i średnim poziomie produktu krajowego brutto dowodzi, że zmniejszenie spożycia sodu o 1,76 g/dobę/osobę przyczynia się do obniżenia ciśnienia tętniczego o 3,39/1,54 mm Hg [7, 8]. Kontrolowanie zawartości Na w diecie jest więc metodą prewencji chorób

sercowo-naczyniowych ze szczególnym uwzględnieniem wystąpienia nadciśnienia tętniczego, natomiast w przypadku osób, które chorują na nadciśnienie tętnicze, znacząco wpływa na obniżenie podwyższonych wartości [9].

Zgodnie z wytycznymi Polskiego Towarzystwa Nadciśnienia Tętniczego (PTNT) z 2015 roku dieta bogata w NaCl może być przyczyną wystąpienia trudności w leczeniu nadciśnienia tętniczego, w związku z tym u chorych należy zwracać szczególną uwagę na ograniczenie soli kuchennej poniżej 5,0 g/dobę [8]. Uważa się, że efekt hipotensyjny redukcji zawartości Na w diecie u osób starszych, „sodowrażliwych", z rozpoznaną cukrzycą, zespołem metabolicznym oraz przewlekłą niewydolnością nerek jest zdecydowanie większy i może skutkować ograniczeniem liczby i dawek leków stosowanych przez tych pacjentów [8].

Kypridemos i wsp. [10] zastosowali model mikrosymulacyjny do oceny wpływu prowadzonych działań w zakresie ograniczenia spożycia NaCl w Wielkiej Brytanii na profilaktykę chorób sercowo-naczyniowych. Wprowadzenie polityki zmniejszenia spożycia NaCl w latach 2003–2015 spowodowało zapobieżenie lub opóźnienie wystąpienia chorób sercowo-naczyniowych u 52 000 osób, jednocześnie zapobiegło 10 000 zgonom z przyczyn sercowo-naczyniowych [10].

Wobec przedstawionych opinii ważne jest, aby znaleźć „złoty środek" między podażą jodu zabezpieczająca prawidłową funkcję tarczycy a ograniczeniem spożycia soli kuchennej zalecanym przez towarzystwa kardiologiczne. Należy przy tym pamiętać, że sól kuchenna jest głównym dostarczycielem jodu w codziennej diecie [10].

Opracowane przez grono ekspertów Instytutu Żywności i Żywienia „Stanowisko w sprawie podjęcia inicjatywy zmniejszenia spożycia soli w Polsce" określa kierunki działania obejmujące zmiany receptur przetworów spożywczych w przemyśle spożywczym i placówkach żywienia zbiorowego, wzmożenie nadzoru organów urzędowej kontroli żywności, kontynuacje odpowiednich działań legislacyjnych [7]. Dotyczą one również działań edukacyjnych skierowanych do różnych grup: konsumentów, producentów, pracowników ochrony zdrowia i instytucji zdrowia publicznego oraz innych grup mających wpływ na nasz styl życia. Ważne w kształtowaniu tych zaleceń jest także Stanowisko PTNT zmierzające do ograniczenia spożycia soli przez działania profilaktyczne i promocyjne [11]. Wymaga to jednak ścisłej współpracy z PCCIDD w zakresie niezbędnych modyfikacji systemu profilaktyki jodowej [8].

Autorom programu zarzucono, że w profilaktyce jodowej jako nośnik jodu zastosowali mało pożądaną substancję — chlorek sodu, przeciwwskazany w nadciśnieniu tętniczym i innych chorobach układu sercowo-naczyniowego. Tymczasem w Polsce spożycie chlorku sodu było i jest nadal nadmierne, jeszcze kilka lat temu norma spożycia wyznaczona przez WHO była przekroczona 3-krotnie [2].

Jak już wspomniano, obecnie spożycie soli w naszym kraju znacznie przekracza dzienną normę spożycia, konieczne jest zatem poszukiwanie innych alternatywnych źródeł jodu, które zabezpieczyłyby jego dzienne zapotrzebowanie. Endokrynolodzy zgadzają się z kardiologami, że nie należy nikogo zachęcać do spożywania soli. Jednak jednocześnie obawiają się, że dalszy spadek spożycia soli jodowanej niekorzystnie odbije się na profilaktyce jodowej i epidemiologii chorób tarczycy. Przeciętna zawartość jodu w 100 g soli kuchennej jodowanej wynosi 2293 μg [12]. Aby z soli dostarczyć wymagane 150 μg dziennego zapotrzebowania w jod, należy spożyć 6,5 g samej soli jodowanej, co przekracza zalecane 5,0 g według WHO [13]. Taka sytuacja wymusza więc zastosowanie innych rozwiązań, które godzić będą zalecenia kardiologów z założeniami profilaktyki jodowej promowanych przez endokrynologów. Może nim być na przykład dopuszczenie dodatkowo do jodowania produktów spożywczych zawierających jodan potasu ($KIO_3$) [2].

Prowadzone są działania mające na celu zwiększenie spożycia innych naturalnych nośników jodu (mleko, woda mineralna) [14]. Rozważa się także możliwości zwiększenia zawartości jodu w wybranych warzywach za pomocą ich biofortyfikacji [15]. Innym działaniem jest wprowadzenie jodu do łańcuchów pokarmowych przez podawanie go trzodzie i bydłu.

## Leki a podaż jodu

Omawiając podaż jodu, nie można nie wspomnieć o lekach i środkach kontrastowych zawierających jod. Farmakologiczne dawki jodu (mogące przekraczać wielokrotnie dobowe zapotrzebowanie) są zawarte w wielu substancjach stosowanych w diagnostyce i leczeniu. Zalicza się do nich na przykład radiologiczne środki cieniujące (zawierające 140–400 mg w 1 ml), środki odkażające (jodopowidon — 10 mg jodu w 1 ml), mocny płyn Lugola (127 mg jodu w 1 ml, czyli ok. 20 kropli) [16]. Również niektóre leki antyarytmiczne, skądinąd bardzo skuteczne — zwłaszcza amiodaron — mogą indukować zaburzenia funkcji tarczycy przez dużą zawartość jodu (1 tabl. amiodaronu w dawce 200 mg zawiera ok. 75 mg jodu). Dawkowanie leku ze wskazań kardiologicznych zakłada przyjmowanie nawet kilku tabletek dziennie, a to znacznie przekracza dobowe zapotrzebowanie organizmu na jod [1]. Ponadto lek kumuluje się w tkance tłuszczowej i mięśniowej, a ze względu na długi okres półtrwania (ok. 100 dni), uwalnianie jodu odbywa się także po odstawieniu preparatu [16].

Amiodaron ma wielokierunkowy wpływ na metabolizm hormonów tarczycy. Jego cząsteczka wykazuje podobieństwo do cząsteczki T4 i być może współzawodniczy z T4 o wiązanie z odpowiednim receptorem; lek hamuje monodejodynację obwodową T4 do T3 oraz indukuje procesy

**Tabela 1.** Zawartość jodu w wybranych produktach spożywczych (na podstawie [12])

| Nazwa produktu | Zawartość jodu [μg/100g produktu] |
|---|---|
| **Ryby** | |
| Dorsz świeży | 110 |
| Mintaj świeży | 103 |
| Łosoś świeży | 44 |
| Makrela wędzona | 40 |
| Śledź solony/śledź wędzony | 30 |
| Śledź świeży | 24,3 |
| Tuńczyk w oleju | 25 |
| Flądra świeża | 20 |
| Pstrąg tęczowy świeży | 13 |
| Szczupak świeży | 8 |
| **Mleko i jego przetwory** | |
| Ser rokpol tłusty | 40 |
| Ser edamski tłusty | 30 |
| Ser *brie* tłusty | 11,2 |
| Kefir 2% tłuszczu | 7,5 |
| Ser topiony edamski | 7,1 |
| Maślanka 0,5% tłuszczu | 5,9 |
| **Jaja** | |
| Jaja kurze, całe | 9,5 |
| Białko jaja kurzego | 6,8 |
| Żółtko jaja kurzego | 12 |
| **Produkty zbożowe** | |
| Otręby pszenne | 31 |
| Płatki owsiane | 5,9 |
| Płatki żytnie | 5,7 |
| **Warzywa** | |
| Brokuły | 15 |
| Groch (suche nasiona) | 13,9 |
| Szpinak | 12 |
| Rzodkiewka | 8 |
| Soja (nasiona suche) | 6,3 |
| Bób | 6 |
| **Orzechy** | |
| Laskowe | 17 |
| Arachidowe | 13 |
| Włoskie | 9 |
| **Inne** | |
| Sól biała, jodowana | 2293 |
| Jodowana woda mineralna ‘Ustronianka’ | 150 μg/l |

immunologiczne w tarczycy [16]. Może wywoływać zarówno niedoczynność tarczycy (rzadziej), jak i nadczynność tarczycy (częściej). O ile niedoczynność zdarza się zwykle już w trakcie przyjmowania amiodaronu, o tyle czas wystąpienia nadczynności bywa różny; może ona bowiem objawić się nawet po kilku miesiącach od zaprzestania przyjmowania leku [17]. Środki cieniujące i amiodaron mogą wywoływać tyreotoksykozę w przebiegu destrukcyjnego zapalenia tarczycy [18].

## Źródła jodu w diecie

Niewiele jest znanych, tak skutecznych interwencji w zakresie profilaktyki zdrowotnej jak program profilaktyki niedoboru jodu realizowany w Polsce od wielu lat [1, 13]. Jak opisano, korzyści zdrowotnych programu jest bardzo wiele i dotyczą one nie tylko prawidłowej funkcji dokrewnej gruczołu tarczowego, profilaktyki wrodzonej niedoczynności tarczycy, zmniejszenia śmiertelności okołoporodowej noworodków, ale także rozwoju nowotworu złośliwego [19].

Wobec współistnienia zaleceń będących odpowiedzią na coraz częstsze występowanie chorób układu krążenia, a dotyczących ograniczenia podaży soli, należy szukać alternatywnych źródeł jodu, które zapewniłyby prawidłową jego podaż i pokryły dzienne zapotrzebowanie. W tabeli 1 przedstawiono źródła jodu w diecie [12].

Zalecając więc pacjentom dietę z ograniczeniem soli kuchennej, można zaproponować alternatywne źródła jodu pod postacią innych produktów spożywczych, godząc w ten sposób na pierwszy rzut oka niedające się pogodzić zalecenia towarzystw naukowych.

## Wnioski

Ze względu na podkreślaną przez lekarzy endokrynologów konieczność podaży jodu w celu prewencji zaburzeń funkcjonowania gruczołu tarczowego, a także zalecenie lekarzy kardiologów ograniczenia spożycia jodowanej soli kuchennej w związku ze zwiększonym ryzykiem chorób układu sercowo-naczyniowego, w szczególności nadciśnienia tętniczego, należy podjąć alternatywne działania dostarczenia jodu do organizmu. W tej sytuacji zasadna jest idea wdrożenia jodowania wody mineralnej i mleka, a także biofortyfikacji wybranych warzyw oraz podawania jodu trzodzie i bydłu. Warto również pamiętać o produktach spożywczych, które są źródłem jodu, aby konsekwentnie umieszczać je w codziennym jadłospisie.

## Konflikt interesów

Autorzy deklarują brak konfliktu interesów.

## Abstract

Iodine is one of the essential bioactive components of a diet and which has an influence on the thyroid hormones synthesis, and these hormones affect the proper development and functioning of the organism. In the situation when the iodides consumption is less than 50 μg/day, it is unable to maintain the thyroid hormones synthesis at a normal level by the thyroid gland. The 1992/1993 Polish Council for Control of Iodine Deficiency Disorders study results were a direct reason for the compulsory resumption of table salt iodination. Table salt is a, commonly used, iodine carrier. According to the World Health Organization recommendations, the daily salt intake should not exceed 5 g NaCl (2 g Na) per person. Verification of Na content in the diet is a method for cardiovascular diseases prevention. Actions aimed at increasing of the other natural iodine carriers (milk, mineral water) intake are taken. Alternative sources of iodine in the diet are include: codfish, pollock, salmon, eggs, wheat bran, broccoli, dried pea seeds and hazelnuts. Iodination of mineral water and milk, as well as biofortification of the selected vegetables and feeding flock and cattle by food rich in iodine should be concerned according to salt restriction diet.

Key words: iodine, diet, hypertension, salt iodination, amiodarone

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REVIEW ARTICLE

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# Dietary recommendations for iodine intake — in search of a consensus between cardiologists and endocrinologists

## Zalecenia dietetyczne dotyczące spożywania jodu — w poszukiwaniu konsensusu między kardiologami a endokrynologami

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### Abstract

Iodine is one of the essential bioactive components of the diet which has an effect on the synthesis of the thyroid hormones, and the latter affect proper development and functioning of the organism. If iodide intake is below 50 μg/day, the thyroid gland cannot maintain adequate synthesis of thyroid hormones. The 1992/1993 Polish Council for Control of Iodine Deficiency Disorders study results were a direct reason for resumption of compulsory table salt iodination. Table salt is the commonly used iodine carrier. According to the World Health Organization recommendations, daily salt intake should not exceed 5 g of sodium chloride (2 g of sodium) per person. Reduction of dietary sodium intake may thus prevent cardiovascular disease. Actions are also being taken to increase the intake of other natural iodine carriers (milk, mineral water). Alternative iodine sources in the diet include codfish, Alaska pollock, salmon, eggs, wheat bran, broccoli, dried pea seeds, and hazelnuts. Iodination of mineral water and milk, as well as biofortification of the selected vegetables and feeding flock and cattle by food rich in iodine should be concerned according to salt restriction diet. It is also justified to introduce iodination of mineral water and milk, as well as biofortification of selected vegetables and feeding flock and cattle with food rich in iodine to provide adequate iodine intake in the setting of coexisting recommendations to reduce salt intake.

Key words: iodine, diet, arterial hypertension, salt iodination, amiodarone

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## Introduction

Iodine is one of the essential bioactive components of the diet which has an effect on the synthesis of the thyroid hormones, and the latter affect proper development and functioning of the organism. Iodine is one of the most potent antioxidants and has a protective effect in inflammatory and malignant processes [1].

Iodine is a dietary constituent that cannot be stored in the human body and thus must be consumed in a diet. Inadequate iodine intake leads to iodine deficiency, and excess intake may result in hyperthyroidism [1, 2].

## Dietary recommendations regarding iodine intake

The World Health Organization (WHO) recommends the following optimal daily iodide intake: 150 μg/day in adult subjects, 250 μg/day in pregnant and lactating women, 50 μg/day in children under 1 year of age, 90 μg/day in children at 1–5 years of age, and 120 μg/day in children at 6–12 years of age [3]. If iodide intake is below 50 μg/day, the thyroid gland cannot maintain adequate synthesis of thyroid hormones. This results in a functional hypertrophy and structural changes that ultimately lead to the development of hypothyroidism. Thyroid hypertrophy is potentiated by the lack of thyroid-stimulating hormone (TSH) inhibition by the pituitary gland, as TSH is also a growth hormone [1].

Thus, it is necessary to maintain adequate iodine intake, as its deficiency (and also relatively rarely occurring excess iodine intake) has a negative effect on the population health. Prophylactic iodine supplementation should be constantly monitored, so its effectiveness can be evaluated, and the optimal level of iodine supplementation determined [1, 4].

The Polish Council for Control of Iodine Deficiency Disorders (PCCIDD) decided to undertake an epidemiological study in 1992–1993 that included schoolchildren, neonates, and pregnant women. Results of these studies prompted resumption of universal, compulsory salt fortification with iodine (20–40 mgKJ/kg) since 1997 [1, 2, 4]. The council also determined other indications for prophylactic iodine supplementation: additional fortification of infant formulas with iodine (10 μg/100 mL of milk) and additional iodine supplementation of 150–200 μg/day in pregnant and lactating women [1].

This model proved very effective. The prevalence of goitre in schoolchildren decreased by 30–80% compared to 1992–1993, and in the youngest children (6–8 years of age), the prevalence was only 2.6%, *i.e.*, below the endemic level [1]. The prevalence of neonatal TSH levels above 20 μIU/mL decreased from 2.0% to 0.16%, the prevalence of goitre in pregnant women decreased from 80% to 19%, and a reduction in the prevalence of differentiated thyroid cancer in women was observed [1].

In 2002, the Polish model of prophylaxis of iodine deficiency was judged effective and safe. It was found that there was no population risk of both hypothyroidism due to iodine deficiency and hyperthyroidism due to increased iodine intake [1, 3].

It should be noted, however, that this success was not absolute. In older children (particularly those in the puberty period), goitre is still present in 7–8% depending on the region, and the rate of urinary iodine excretion above 100 μg/L did not achieve the desired level of 50%. No more than 70% of pregnant women receive the recommended iodine dose and although the prevalence of thyroid cancer in women has decreased, it is progress rate of thyroid carcinoma in women is slower its incidence is still 3–4 times higher than in 1990. Finally, the quality of salt fortification with iodine was estimated at 96% of the recommended norm [1, 5].

The National Program to Eliminate Iodine Deficiency-related Abnormalities (Narodowy Program Eliminacji Zaburzeń w Przebiegu Niedoboru Jodu) was interrupted in 2003–2005, reintroduced in 2006 and has been continued until present [1].

## Reduction of dietary salt intake for cardiovascular disease prevention and iodine intake

A separate issue is prophylactic iodine supplementation in the setting of the recommended reduction of salt intake to 5 g/day, as salt is the commonly used carrier for iodine.

The WHO recommendations (Paris 2006, Luxembourg 2007) are based on the established role of salt in increasing the risk of cardiovascular disease including arterial hypertension, atherosclerosis, stroke and myocardial infarction, as well as some malignancies. According to the WHO recommendation, daily salt intake should not exceed 5 g of sodium chloride (2 g of sodium) per person [6]. The mean daily salt intake in Poland is 13.5 g per person, including 8.8 g of table salt, reaching as much as 15.0 g per person in some regions of the country [4].

According to the Standards of Dietary Management in Cardiology (Standardy Postępowania Dietetycznego w Kardiologii), the 2016 Polish Society of Dietetics statement, more than 1 million of deaths annually in the past years might be attributed to sodium chloride intake exceeding 5 g/day, the level recommended by WHO (1.65 million of deaths in 2010) [7].

The World Heart Federation (WHF), European Society of Hypertension (ESH), and European Public Health Association (EUPHA) report on the effect of sodium intake on the incidence of cardiovascular disease in low-to-moderate income countries indicates that a reduction of sodium intake by 1.76 g/day per person results in blood pressure lowering by 3.39/1.54 mm Hg [7, 8]. Reduction of dietary sodium intake may thus prevent cardiovascular disease, in particular hypertension, and it may significantly lower elevated blood pressure in hypertensive subjects [9].

According to the 2015 Polish Society of Hypertension (PTNT, *Polskie Towarzystwo Nadciśnienia Tętniczego*) guidelines, a diet rich in sodium chloride may reduce the effectiveness of antihypertensive treatment and thus much attention should be paid to reducing salt intake below 5.0 g per day in patients with hypertension [8]. It is believed that the blood pressure lowering effect of a reduced dietary sodium intake is much higher in the elderly patients, salt-sensitive subjects, and those with diabetes, metabolic syndrome or chronic kidney disease, and thus it may lead to a reduction in the number of drugs and their doses in such patients [8]

Kypridemos et al. [10] used a microsimulation model to evaluate the effect of efforts to reduce sodium chloride intake in the United Kingdom on the prevention of cardiovascular disease. Introduction of a policy to reduce sodium chloride intake in 2003–2015 prevented or delayed cardiovascular disease in 52,000 persons, and prevented 10,000 cardiovascular deaths [10].

In view of the above opinions and data, it is important to find the right balance between adequate iodine intake to allow normal thyroid function and a reduction in salt intake recommended by cardiac societies. Of note, salt is the main source of iodine in the diet [10].

The National Institute of Food and Nutrition statement on efforts to reduce salt intake in Poland has defined the directions of these actions, including changes in recipes in food industry and catering facilities, increased supervision by food safety agencies, and continuation of appropriate legislation efforts [7]. These actions should also include educational efforts targeted at various groups: consumers, producers, health care and public health institution workers, and other groups influencing the lifestyle of the population. The PTNT guidelines are also important for these efforts, as they recommend salt intake reduction by appropriate prevention and promotion initiatives [11]. Of note, close cooperation with PCCID is required to introduce necessary modifications to the program of prophylactic iodine supplementation [8].

The authors of the program were criticised by using an undesirable substance as the iodine carrier for prophylaxis, as sodium chloride intake is not recommended in hypertension and other cardiovascular disease. In addition, sodium chloride intake in Poland has been and continues to be excessive; only several years ago, intake levels recommended by WHO were exceeded threefold [2].

As noted above, the current sodium chloride intake in our country much exceeds the recommended daily intake, and thus alternative sources of iodine are needed to provide its adequate daily intake. Endocrinologists agree with cardiologists that nobody should be encouraged to consume salt. They are concerned, however, that a further reduction in the intake of iodine-fortified salt will have an adverse effect on prophylactic iodine supplementation and the epidemiology of thyroid disease. The average iodine content in 100 g of iodine-fortified table salt is 2293 micrograms [12]. To provide the necessary daily iodine intake of 150 μg from salt, it is necessary to consume 6.5 g of iodine-fortified salt, which exceeds the 5.0 g level recommended by WHO [13]. This situation necessitates other solutions that will reconcile recommendations of the cardiologists and the principles of prophylactic iodine supplementation promoted by endocrinologists. One solution may be to additional use of potassium iodate ($KIO_3$) for food fortification with iodine [2].

Efforts are being made to increase intake of other natural iodine carries (milk, mineral water) [14]. A possibility to increase iodine content in selected vegetables by their biofortification has also been considered [15]. Another possible solution is introducing iodine into the food chain by feeding flock and cattle with iodine-containing foods.

## Drugs and iodine intake

When discussing iodine intake, iodine-containing medications and contrast agents also need to be mentioned. Pharmacological iodine doses (which may exceed daily requirement by many times) are present in many substances used for diagnostic or therapeutic purposes. These include radiological contrast agents (containing 140–400 mg of iodine in 1 mL), disinfectants (iodopovidone — 10 mg of iodine in 1 mL), high-potency Lugol's iodine (127 mg of iodine in 1 mL, *i.e.*, approximately 20 drops) [16]. Also some antiarrhythmic agents, otherwise very effective, particularly amiodarone, may induce thyroid dysfunction due to high iodine content (a single 200 mg amiodarone tablet contains about 75 mg of iodine). Cardiac amiodarone dosing may involve administration of even several tablets per day, thus largely exceeding daily iodine requirement [1]. In addition, the drug accumulates in the fat and muscles, and due to a long half-life (about 100 days), iodine is released also after amiodarone is discontinued [16].

Amiodarone has a multidirectional effect on thyroid hormone metabolism. Its moiety is similar to that of T4 and

**Table 1.** Iodine content in selected food products (based on [12])

| Product | Iodine content [μg/100 g of product] |
|---|---|
| **Fish** | |
| Codfish, fresh | 110 |
| Alaska pollock, fresh | 103 |
| Salmon, fresh | 44 |
| Mackerel, smoked | 40 |
| Herring, salted/smoked | 30 |
| Herring, fresh | 24.3 |
| Tuna in oil | 25 |
| Flounder, fresh | 20 |
| Rainbow trout, fresh | 13 |
| Northern pike, fresh | 8 |
| **Dairy products** | |
| 'Rokpol' cheese, full-fat | 40 |
| 'Edamski' cheese, full-fat | 30 |
| Brie cheese, full-fat | 11.2 |
| Kefir, 2% fat | 7.5 |
| 'Edamski' melted cheese | 7.1 |
| Buttermilk, 0.5% fat | 5.9 |
| **Eggs** | |
| Chicken eggs, whole | 9.5 |
| Chicken egg white | 6.8 |
| Chicken egg yolk | 12 |
| **Cereals** | |
| Wheat bran | 31 |
| Oatmeal | 5.9 |
| Rye flakes | 5.7 |
| **Vegetables** | |
| Broccoli | 15 |
| Dried pea seeds | 13.9 |
| Spinach | 12 |
| Radish | 8 |
| Dried soy seeds | 6.3 |
| Broad beans | 6 |
| **Nuts** | |
| Hazelnuts | 17 |
| Peanuts | 13 |
| Walnuts | 9 |
| **Other** | |
| White table salt, iodinated | 2293 |
| Iodinated mineral water 'Ustronianka' | 150 μg/L |

perhaps competes with T4 for receptor binding; the drug inhibits peripheral monodeiodination of T4 to T3 and induces immune processes in the thyroid [16]. It may induce both hypothyroidism (less frequently) and hyperthyroidism (more frequently). While hypothyroidism usually develops during treatment with amiodarone, hyperthyroidism may develop at various times, even several months after the drug is discontinued [17]. Radiological contrast agents and amiodarone may induce thyrotoxicosis caused by destructive thyroiditis [18].

## Dietary sources of iodine

There are only few other health prevention interventions that may be considered as effective as the program of iodine deficiency prevention that has been in operation in Poland for many years [1, 13]. As described above, the multiple health benefits of this program are not limited to normal endocrine function of the thyroid gland, prevention of congenital hypothyroidism, and reduction of neonatal mortality in the perinatal period but also include reduction in the development of malignancies [19].

Due to the coexisting recommendations to reduce salt intake in response to an increasing rates of cardiovascular disease, alternative iodine sources are needed to allow adequate daily intake. Table 1 shows dietary sources of iodine [12].

When recommending a reduction of dietary salt intake to the patients, we can also recommend alternative iodine sources from other food products, thus reconciling apparently incompatible recommendations of various societies

## Conclusions

Due to the need for adequate iodine intake to prevent thyroid dysfunction, as highlighted by endocrinologists, and a recommendation by cardiologists to reduce intake of iodinated table salt due to an increased cardiovascular disease risk, alternative approaches for providing adequate iodine intake are necessary. Thus, it is justified to introduce iodination of mineral water and milk, as well as biofortification of selected vegetables and feeding flock and cattle with food rich in iodine. We should also remember about food products that are sources of iodine, so as to include them regularly in our menus.

## Conflict(s) of interests

The authors declare no conflicts of interest.

## Streszczenie

Jod jest pierwiastkiem należącym do niezbędnych bioaktywnych składników diety, który ma udział w syntezie hormonów tarczycy, a te z kolei wpływają na prawidłowy rozwój i funkcjonowanie organizmu. W sytuacji gdy spożycie jodków jest mniejsze niż 50 μg/dobę, gruczoł tarczowy nie jest w stanie utrzymać syntezy hormonów tarczycy na prawidłowym poziomie. Wyniki badań z lat 1992–1993 Polskiej Komisji ds. Kontroli Zaburzeń z Niedoboru Jodu były bezpośrednim powodem powrotu do obowiązkowego jodowania soli kuchennej. Sól kuchenna jest powszechnie stosowanym nośnikiem jodu. Zgodnie z zaleceniami Światowej Organizacji zdrowia dzienne spożycie soli nie powinno przekraczać 5 g NaCl (2 g Na) na osobę. Kontrolowanie zawartości Na w diecie jest metodą prewencji chorób układu sercowo-naczyniowego. Równocześnie są prowadzone działania służące zwiększeniu spożycia innych naturalnych nośników jodu (mleko, woda mineralna). Alternatywne źródło jodu w diecie to między innymi dorsz, mintaj, łosoś, jaja, otręby pszenne, brokuły, suche nasiona grochu i orzechy laskowe. Zasadna jest idea wdrożenia jodowania wody mineralnej i mleka, a także biofortyfikacji wybranych warzyw oraz podawania jodu trzodzie i bydłu w celu zapewnienia jego odpowiedniej podaży w związku z zaleceniami ograniczenia spożycia soli kuchennej.


Słowa kluczowe: jod, dieta, nadciśnienie tętnicze, jodowanie soli, amiodaron

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# Myocardial infarction with simultaneous acute stroke in a patient with prior aortic graft replacement — what is the origin of the embolic incident?

## Zawał serca współistniejący z udarem mózgu po wszczepieniu protezy aorty wstępującej z powodu ostrego rozwarstwienia typu A — jakie jest źródło materiału zatorowego?

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**Abstract**

Myocardial infarction as a reflection of advanced coronary artery disease is often associated with atherosclerosis of other arteries, especially renal, peripheral and carotid, resulting in chronic renal disease, peripheral artery disease, or stroke. Nevertheless, atherosclerosis is not always the only cause of those diseases. In this article, was presented the case of a patient with myocardial infarction and concomitant stroke probably caused by percutaneous coronary intervention.

Key words: myocardial infarction, stroke, embolic incident

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## Case report

A 62 year-old male patient with a history of cigarette smoking, hypertension, acute ascending aortic dissection repaired with graft replacement of the ascending aorta and resuspension of incompetent aortic valve six months previously (computed tomography of coronary arteries executed then revealed no signs of coronary artery disease), with symptoms of typical resting chest pain radiating to left upper extremities was admitted to the Intensive Cardiac Therapy Clinic in the fourteenth hour of acute coronary syndrome – myocardial infarction with inferior ST segment elevation concomitant with newly registered left bundle branch block.

On admission, the patient was conscious [Glasgow Coma Scale (GCS) 10, E3V3M4] haemodynamically stable, with persistent chest pain, abnormal speech, left-side facial drop, and left-side hemiparesis. ECG showed a maximum 2 mm ST-segment elevation in leads II, III, aVF, and a 1.5 mm ST-segment depression in leads I, aVL, V2–V6. During the recording of the ECG, left bundle branch block occurred. The patient was transferred immediately to the cardiac catheterisation lab for urgent coronary angiography which revealed isolated critical stenosis of the right coronary artery with coexisting thrombus blocking the entire artery (Figure 1). At the beginning of the procedure, a thrombectomy was performed (Figure 2). A percutaneous intervention was conducted with successful sirolimus eluting stent

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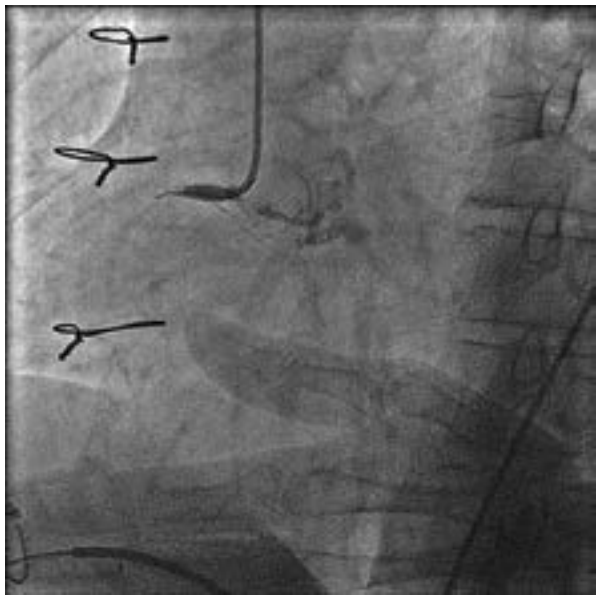

**Figure 1.** Critical stenosis of the right coronary artery with coexisting thrombus

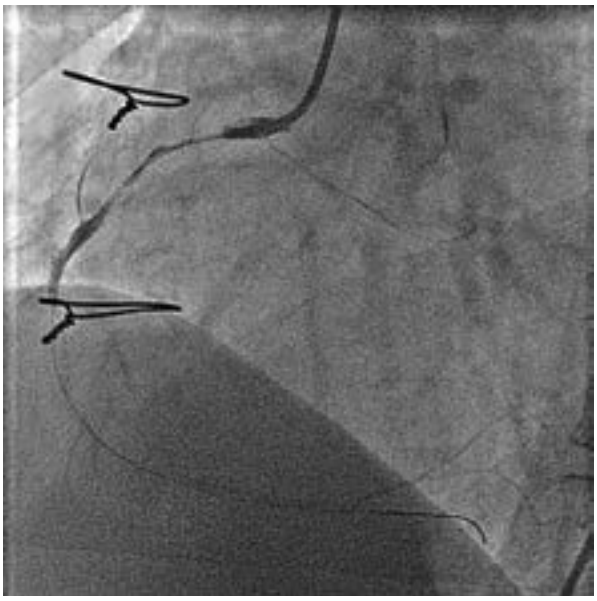

**Figure 2.** Right coronary artery thrombectomy

implantation to right coronary artery with intracoronary and subsequent intravenous eptifibatide ejection. Due to his neurological state, the patient was transferred to the radiology department in order to perform a computed tomography of the brain. This procedure revealed no signs of intracranial bleeding with slightly increased density of the left middle cerebral artery. The patient was consulted by a neurologist and disqualified from thrombolysis with recombinant tissue plasminogen activator due to previous heparin administration. Over the following period of observation the state of the patient gradually started to stabilise, and his overall neurological condition improved, with only the paresis of the left upper extremities (4/5 according to Lovett) remaining.

Echocardiography revealed concentric hypertrophy of the left ventricle with regional wall motion abnormalities in both the inferior wall and the basal inferolateral segment as well as the right ventricular free wall. Ejection fraction was assessed using the modified Simpsons method to be 49%. In addition, the examination showed severe tricuspid insufficiency with mild pulmonary hypertension [systolic pulmonary artery pressure (SPAP) 32 mm Hg].

In order to detect the cause of the stroke, a transoesophageal echocardiography was performed. This revealed a patent foramen ovale, with residual left-to-right shunt at rest with no change of the blood flow direction during the Valsalva manoeuvre. An aortic graft implanted six months previously due to acute ascending aorta dissection showed no signs of additional masses.

Taking all the results into consideration, the most likely cause of the stroke concomitant to acute myocardial infarction in this patient was distribution of the thrombus origins from the aortic graft to the right coronary artery and cerebral artery.

The patient was discharged home on the seventh day of hospitalisation in optimal health status, with a recommendation for regular ambulatory cardiological and neurological check-ups.

## Discussion

Atherosclerosis is a disease affecting all types of arteries and causing different types of conditions based on its localisation. The clinical presentation of this state in the area of the coronary arteries is coronary disease, which is the most common cause of myocardial infarction. Therefore, according to the third universal definition of myocardial infarction, not all types of acute coronary syndromes are caused by atherosclerotic disease [1].

Type 2 of acute coronary syndrome is secondary to ischaemic imbalance in comparison with type 1 which is a spontaneous myocardial infarction. Type 2 includes such causes as, for example, coronary artery spasm, anaemia and coronary embolism. The remaining types pertain to myocardial infarction resulting in death before cardiac biomarkers were obtained (type 3), infarction secondary to percutaneous intervention (type 4a), stent thrombosis (type 4b) and artery bypass grafting (type 5).

There are multiple potential origins of thrombus in the cardiovascular system, most of them related to ageing of the organism which include gradual dysfunction of vessels, arrhythmias, and diseases with prothrombotic profile of the

blood. In young patients, we often search for anatomical structures which predispose to an ischaemic episode secondary to a thombotic one.

Nevertheless, an increasing number of patients acquire different types of prosthetic devices such as stents and grafts implanted into vessels due to numerous health conditions [2]. Those foreign bodies are more likely to induce a thrombotic reaction to thrombotic events such as myocardial infarction or ischaemic stroke [3].

There are many difficulties associated with such a coexistence of diseases [4]. In view of the clinical status of the patient, there is no easy way of deciding which type of procedure or treatment should be employed first [5].

There are reports concerning such cases in which there is one question reccurring — what type of treatment should be introduced? By this we mean which disease takes priority and as a result which treatment course should precede, remembering that choosing treatment of one thrombosed vascular bed delays the management of the other territory [6, 7].

Due to multiple variables, this decision is always multi-faceted and is based on the current situation, focusing on the clinical presentation, aggravation of symptoms, and accessible diagnostic methods [8].

In our case, taking into consideration the ECG image and recurring chest pain, we decided to refer the patient for primary percutaneous coronary intervention. After finding a thrombus in the right coronary artery, the patient was administered eptifibatide. There are numerous studies covering a novel course of treatment for patients with stroke administered another platelet glycoprotein IIb/IIIa inhibitor intravenously [9, 10].

## Conclusion

There are no guidelines for the management of a patient with concomitant acute coronary syndrome and stroke, so the treatment decision must always be individualised. A constant evaluation of patient state and ongoing changes remains crucial for the eventual outcome.


### Streszczenie

Zawał serca jako odzwierciedlenie zaawansowanej miażdżycy tętnic wieńcowych często współistnieje z miażdżycą innych tętnic, zwłaszcza nerkowych, obwodowych i szyjnych, które objawia się odpowiednio przewlekłą chorobą nerek, chorobą tętnic obwodowych oraz udarem mózgu. Niemniej nie zawsze miażdżyca jest przyczyną powyższych stanów chorobowych. W niniejszej pracy zaprezentowano przypadek pacjenta z ostrym zespołem wieńcowym — zawałem serca i współistniejących udarem mózgu najprawdopodobniej wtórnie do interwencji w obrębie tętnic wieńcowych.



Słowa kluczowe: ostry zespół wieńcowy, udar mózgu, incydent zakrzepowo-zatorowy

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# Percutaneous trans-mitral commissurotomy in juvenile mitral stenosis with aneurysmal left atrium — a technically challenging situation

## Przezskórna komisurotomia mitralna u nastolatka ze stenozą mitralną i tętniakiem lewego przedsionka — zabieg trudny technicznie

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### Abstract

Percutaneous trans-mitral commissurotomy (PTMC) using an Accura balloon is an effective procedure for the management of patients with rheumatic mitral stenosis. It is not infrequent to encounter an aneurysmal left atrium (LA), especially in the developing world where patients often present very late. This is a technically challenging procedure as the septum often bulges into the right atrial side, making the puncture often difficult. Furthermore, it bulges anteriorly and inferiorly so it becomes even more challenging. Because of the vertical lie of the septum, the needle often dissects the septum rather than puncturing it.

Here, we describe the case of a 17 year-old boy with severe mitral stenosis with a giant, aneurysmal left atrium (LA — 13.5 × 16 cm) where an inter-atrial septal puncture was achieved by probing the fossa ovalis to enter the left atrium instead of a conventional transseptal puncture. PTMC was successfully done, increasing the mitral valve area from 0.8 $cm^2$ to 1.9 $cm^2$.

Key words: aneurysmal left atrium, probing fossa ovalis, Brockenbrough needle, percutaneous trans-mitral commissurotomy, trans-septal puncture

Folia Cardiologica 2019; 14, 2: 169–173

## Introduction

Percutaneous trans-mitral commissurotomy (PTMC), introduced in 1984 by Inoue et al [1], opened a new window for the treatment of patients with symptomatic mitral stenosis (MS) with suitable valve anatomy. In the presence of a left atrial clot, left atrial appendage clot, or calcified valve, the complication rate may rise [2]. Another challenging substrate is an aneurysmal left atrium (LA) where the inter-atrial septum becomes fatter with a more horizontal orientation. The fossa ovalis lies lower down. As LA pressure is high, the atrial septum usually bulges into the right atrium. For these reasons, the needle tends to make a tangential track in the atrial septum. These factors pose a formidable challenge during a trans-septal puncture. The conventional technique requires some modifications when faced with these atypical situations.

## Case report

A 17 year-old boy presented with exertional dyspnoea — New York Heart Association (NYHA) class II for the past three

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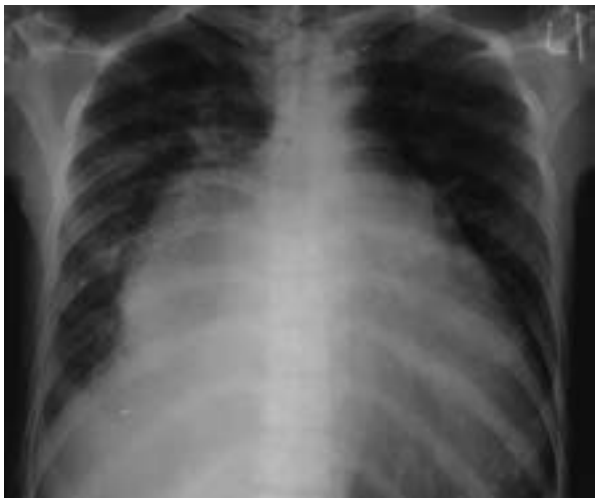

**Figure 1.** Chest X-ray postero-anterior view showing aneurysmal left atrium

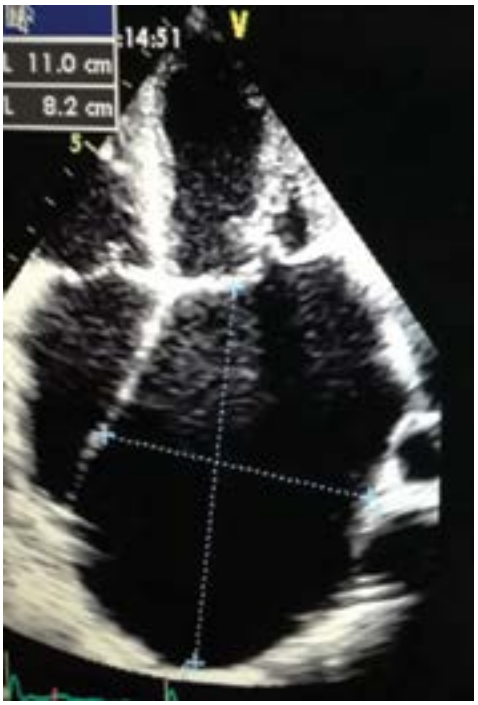


**Figure 2.** 2D trans-thoracic echocardiogram in apical four-chamber view showing aneurysmal left atrium (11 × 9 cm)

years, progressing to class III for the past eight months. His chest X-ray showed an aneurysmal left atrium (Figure 1). Transthoracic echocardiogram revealed severe mitral stenosis with a mitral valve area of 0.8 $cm^2$ by planimetry, and Wilkin's score – 8/16 ($M_2$, C2, T2, S2). Mean gradient across the mitral valve was 35 mmHg by pressure half time (PHT). His left atrium was aneurysmally dilated, with the size being 11 × 9 cm on echocardiogram (Figure 2). His height was 163 cm. Transoesophageal echocardiography was performed to look for a left atrial clot, degree of mitral regurgitation (MR), and the suitability of PTM. Pre-procedural consent was obtained. Femoral artery and vein were accessed with a 6 F and a 8 F sheath respectively. A Mullins sheath over a 0.035" guidewire was parked in the left brachiocephalic vein. The wire was removed and a Brockenbrough needle was inserted into the sheath. LA entry was facilitated using the **probing fossa ovalis** technique after making a gradual descent. A small puff of dye was injected to confirm the left atrial entry. Subsequently, the Mullins sheath was advanced over the needle and contrast was injected through the sheath following removal of the needle, which opacified the left atrium, confirming its aneurysmal dilatation (Figure 3A). Inter-atrial septum was

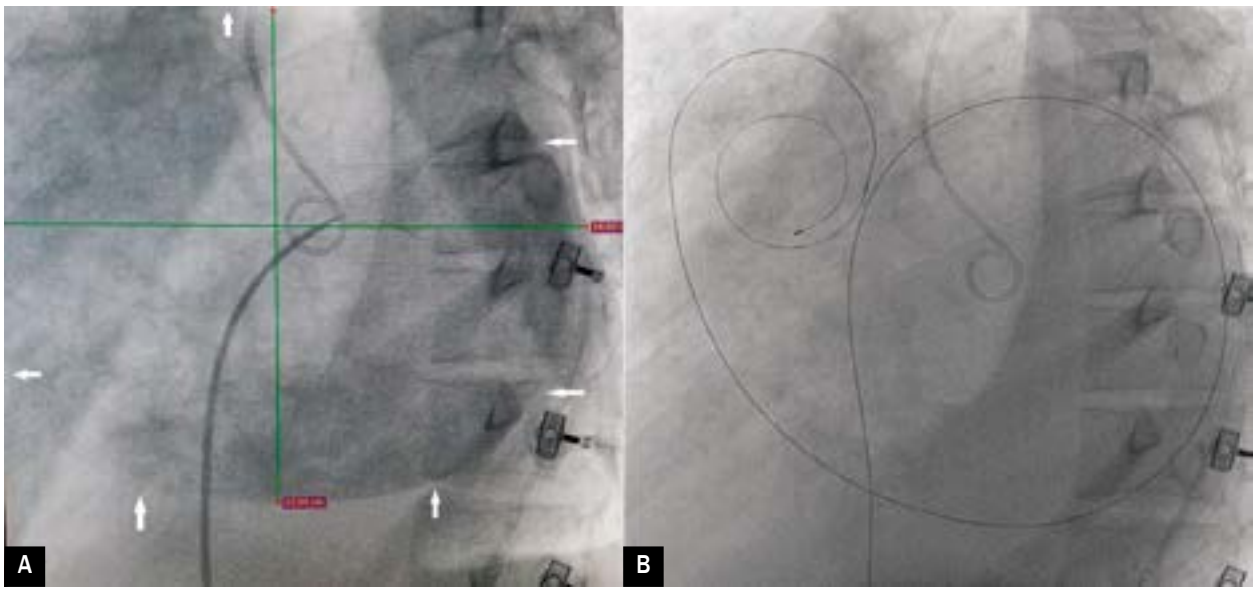


**Figure 3A.** Contrast being injected through the sheath opacifying the left atrium (LA); **B.** Looped LA wire was parked in LA

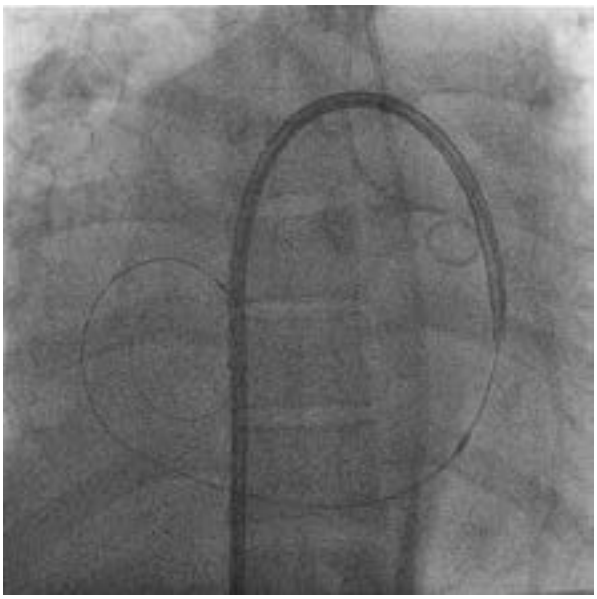

**Figure 4.** Because of giant left atrium (LA), Accura balloon was pushed over wire very deep inside LA

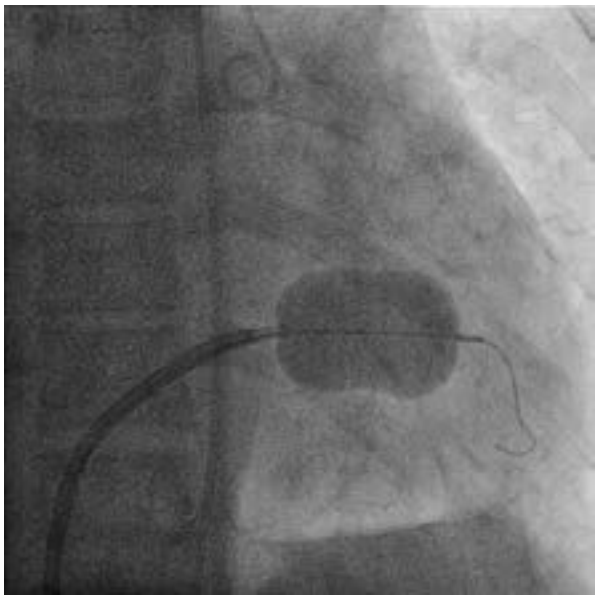

**Figure 5.** The balloon was inflated in its distal part and pulled back to anchor it at the mitral valve and inflated further to achieve its full dilatation

dilated in a left atrial oblique (LAO) 30° view. Looped LA wire was parked in left atrium (Figure 3B). An Accura balloon (Vascular Concepts, Essex, UK) was sized to 26.5 mm based on Hung's formula. Preprocedure LA pressure was 49/28 mm Hg (mean = 39 mm Hg). Following septal dilatation, the Accura balloon was placed in the LA. Because of the giant LA, the Accura balloon was pushed over the wire very deep inside the LA (Figure 4). LA wire was removed, and J-shaped metallic stylet was introduced. A gentle anticlockwise twist was applied to the metallic stylet, and the Accura balloon was gradually pulled until a bobbing movement at its tip was noted. Once the bobbing movement of the Accura balloon was established, it was pushed into the left ventricle through the mitral valve. Once in the left ventricle, the J-shaped metallic stylet was exchanged for a 0.035" wire. The balloon was inflated in its distal part and pulled back to anchor it at the mitral valve and inflated further to achieve its full dilatation (Figure 5). The procedure was performed successfully, thereby bringing the LA mean pressure to 6 mm Hg, and achieving a mitral valve area of 1.9 $cm^2$.

## Discussion

In a developing country like India, where patients with rheumatic mitral stenosis often present very late, it is not uncommon to find an aneurysmal left atrium. In such situations, the anatomy of the interatrial septum is often distorted. Wood et al have proposed a radiological classification of LA enlargement wherein grade-3 denotes where the left atrium bulges conspicuously on both sides of the heart, extending beyond the shadow of the right atrium on that side. This gross enlargement is described as aneurysmal [3].

Due to the high left atrial pressure in mitral stenosis, an atrial septum will usually bulge into the right atrium, where the atrial septum becomes flatter with a more horizontal orientation, which distorts the anatomy of the region of the fossa ovalis as it lies lower down [4]. These factors combined make septal puncture challenging because the needle tends to dissect the septum rather than puncturing it because it tends to track tangentially. Also, if it punctures the muscular part of the septum, sometimes septal catch is encountered, which makes negotiating the balloon across the mitral valve difficult. Moreover, there are potential risks during transseptal puncture in the form of needle tip perforation < 3%, tamponade < 1%, and death < 0.5% [5].

Instead of a conventional transseptal puncture, the **fossa ovalis probing** technique, as described by Krishnamoorthy et al [6], may be tried, as in our case. Under fluoroscopic guidance, the needle and the sheath as an assembly make a gradual descent into the right atrium. When the Mullins sheath snaps into the fossa ovalis, it is firmly pressed against the atrial septum, keeping the needle tip just inside the sheath (by about 2–3 mm). This gives support to the sheath without risk of injury to the left atrial wall. Proper positioning of the sheath tip prior to probing should be ensured on fluoroscope, and a test injection with contrast material made to identify any tenting of the atrial septum at the site of the fossa. Left atrial entry should

be sought by repeated attempts to probe the fossa using gentle and controlled pressure applied to the sheath tip. Once entry to the left atrium is suspected, with a feeling of giving way, only 2–3 mm of the tip of the sheath should be allowed to enter the chamber. Further advancement of the sheath should be done only after confirming its entry into the left atrium.

These precautions avoid damage to the left atrial wall at a site other than the fossa, and consequent damage to aorta or pericardium. This avoids the production of an iatrogenic atrial septal defect, although the incidence of this is itself much less frequent with a conventional transseptal puncture. One should avoid the risk of a tear outside the fossa ovalis by keeping the needle tip well inside the sheath throughout the procedure. Surgeons should ensure proper positioning of the sheath tip, the application of gentle and controlled pressure allowing only 2–3 mm of the tip of the sheath to enter the left atrium after probing, and final advancement of the sheath only after the confirmation of left atrial entry by a puff injection. One should avoid probing the fossa with force. This will be successful as high left atrial pressure leads to stretching and thinning. This has the additional advantage in certain situations such as a distorted atrial septum, a significant right or left atrial enlargement, for those on anticoagulants, and for pregnant women, because it reduces fluoroscopy time and complications.

If this fails, a transseptal puncture will be the default choice. This requires slight modification in the form of increasing the curvature of the Brockenbrough needle so that it can face more posteriorly to enable the puncture, especially when the LA is aneurysmal. In difficult cases, transthoracic, transoesophageal, or intracardiac ultrasound navigated transseptal puncture may be employed [6].

Usually, the balloon is negotiated in a right anterior oblique view because it profiles the left ventricular long axis. In a situation of aneurysmal LA, a lateral view (90°) may be better sometimes. Other improvisations may include a non-ideal puncture site such as more cephalad or leftward (closer to mitral valve), very low punctures, changing the shape of the stylet, and different techniques of balloon entry such as the over the wire technique [7, 8], and floating a Swan-Ganz catheter into the left ventricle [9].

Our method was a modification of an existing technique that turned a complex situation into a simple one.

## Conflict(s) of interest

The authors declare no conflict of interest.


### Streszczenie

Przezskórna komisurotomia mitralna (PTMC) przy użyciu balonu *Accurato* to skuteczny zabieg stosowany w leczeniu chorych ze stenozą mitralną (MS) spowodowaną chorobą reumatyczną. Nierzadko spotyka się u tych chorych tętniak lewego przedsionka (LA), zwłaszcza w krajach rozwijających się, gdzie pacjenci często bardzo późno zgłaszają się do lekarza. Zabieg ten jest trudny technicznie, ponieważ przegroda często wpukla się do prawego przedsionka, utrudniając wykonanie nakłucia. Co więcej, przegroda wybrzusza się w kierunku przednio-dolnym, co dodatkowo zwiększa trudność zabiegu. Ze względu na pionowe położenie przegrody igła często rozdziela przegrodę, zamiast ją przebić.

W niniejszej pracy opisano przypadek 17-letniego chłopca z ciężką MS i olbrzymim tętniakiem LA (LA — 13.5 × 16 cm). Aby dostać się do LA, sondowano otwór owalny zamiast konwencjonalnego nakłucia przegrody. Przeprowadzono z powodzeniem zabieg PTMC, zwiększając powierzchnię zastawki mitralnej z 0,8 $cm^2$ do 1,9 $cm^2$.



Słowa kluczowe: tętniak lewego przedsionka, sondowanie otworu owalnego, igła Brockenbrougha, przezskórna komisurotomia mitralna, nakłucie przegrody międzyprzedsionkowej

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# Trans-femoral percutaneous coronary intervention in an anomalous right coronary artery using a 5 F TIG diagnostic catheter

## Przezskórna interwencja wieńcowa z dostępu przez tętnicę udową w obrębie nieprawidłowej prawej tętnicy wieńcowej przeprowadzona za pomocą cewnika diagnostycznego 5 F TIG

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### Abstract

Anomalous coronary arteries, especially when they are right with a high take-off, are challenging substrates for percutaneous coronary intervention (PCI). Here, we report the case of a 63 year-old female who had a critical lesion in proximal anomalous right coronary artery having an abnormal take-off, where the ostium failed to get cannulated using multiple guiding catheters. Successful PCI was done using a 5 F TIG diagnostic catheter (Optitorque, Terumo, Japan) through the transfemoral route. The unique shape of the TIG diagnostic catheter allowed coaxial engagement of anomalous right coronary artery, with adequate lesion assessment and stent delivery.

Key words: anomalous right coronary artery, TIG catheter, transfemoral percutaneous coronary intervention, high take-off

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## Introduction

Coronary artery anomalies are found in 0.6–1.5% of coronary angiograms, and are usually incidental findings [1]. Anomalous origin of coronary arteries is reported to be 0.6–1.2% in patients among the various angiographic series [2]. Percutaneous coronary intervention (PCI) of congenitally anomalous coronary arteries poses unique challenges, and needs special consideration regarding their site of origin, orifice configuration, take-off angle, site and type of lesion, and the route the artery traverses [3]. Guiding catheter selection is the most important step for any PCI, but even more so for an anomalous coronary because the coaxial alignment and stent delivery on the wire are the keys to success.

## Case report

A 63 year-old female presented with exertional angina of three years' duration which had worsened in the last three weeks. Smoking, diabetes, and dyslipidemia were her risk factors. Her treadmill test was strongly positive for reversible ischaemia. Her physical examinations and biochemistry were all unremarkable. Electrocardiogram

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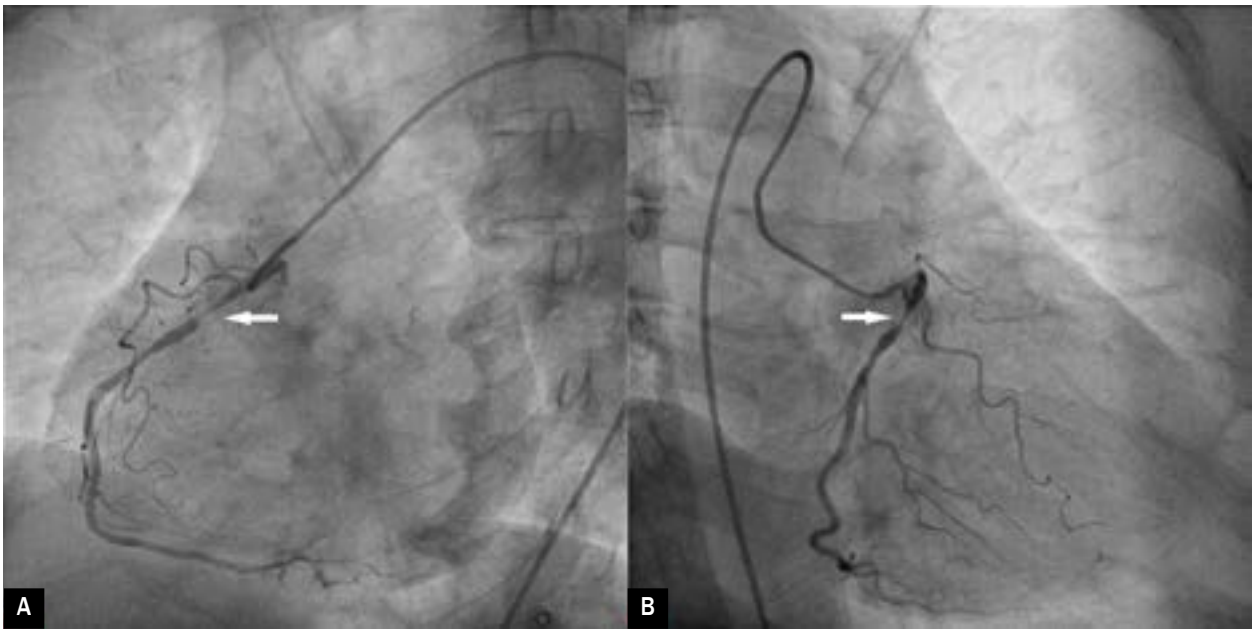


**Figure 1A, B.** Right coronary artery having an anomalous origin with a high take-off (white arrow showing the lesion in proximal part)

revealed nonspecific ST-T changes in precordial leads. Echocardiography revealed mild concentric hypertrophy, mild mitral leak, and normal ejection fraction. Trans-femoral catheterisation was planned after proper consent. The left main artery was cannulated in the usual fashion using a Judkins left diagnostic catheter which revealed normal left main, left anterior descending artery, and left circumflex artery. Right coronary artery (RCA) could not be selectively hooked with a Judkins right diagnostic catheter, but non-selective injection showed its anomalous origin with a high take-off. RCA had tubular lesion with critical stenosis in its proximal segment. Percutaneous coronary RCA was planned and 7,000 U of heparin was given further. Cannulation was attempted with a Judkins right guiding catheter, but it failed. It subsequently failed to be hooked with other catheters including an Amplatz right and left (AR, AL), multipurpose (MP), hickey stick (HS), Voda catheter, and Judkins left (JL). Finally, a 5F TIG diagnostic catheter (Optitorque; Terumo, Japan) was chosen for the job. RCA was hooked although it was not co-axial (Figure 1). As alignment was not co-axial, RCA was wired using the floating wire technique with a runthrough wire (Asahi, Japan) and parked distally. As it was difficult to manoeuvre the catheter over the wire because of anomalous origin and high take-off, another runthrough wire was parked as a buddy wire into the RCA (Figure 2A). With this improved support, the catheter was engaged selectively and the buddy wire was withdrawn (Figure 2B). The lesion was pre-dilated with a 2 × 10 mm, and a 2.5 × 10 mm Minitrak balloon (Abbott, USA) inflated to 12 atm (Figure 3A). It was stented by deploying a 2.75 × 28 mm Xience Prime stent (everolimus-eluting stent, Abbott, USA) up to 13 atm pressure and further post dilated by a 2.75 × 10 mm Minitrak non-compliant balloon up to 20 atm pressure achieving TIMI 3 flow (Figures 3B, 4). She was discharged on the third day with acetylsalicylic acid 150 mg/day, prasugrel 10 mg/day, atorvastatin 80 mg/day, metoprolol 100 mg/day and ramipril 2.5 mg/day. The patient has been doing fine since then, with regular follow-ups at our institute.

## Discussion

Anomalous RCA with high anterior take-off, although rare, is a technically challenging and time-consuming substrate. Selection of a guide catheter should be based on configuration of the ostium, dimensions of the aortic root, location of the origin, and the type of lesion. The origin of RCA based on the angulation can be divided into four types: type I — 90° angle from aorta; type II — below 90° angle from aorta; type III — above 90° angle from aorta; and type IV — anomalous or ectopic origin wherein it is subdivided into three types based on the height of origin: normal take-off *i.e.* 1–1.5 cm from aortic valve; high take-off *i.e.* > 1.5 cm from aortic valve; and low take-off *i.e.* < 1 cm from aortic valve [4]. Coaxial engagement and adequate back-up support from a guide catheter are the keys to successful PCI. Anomalous right coronary artery can be cannulated using Amplatz, El Gamal, Voda, and multipurpose catheters, oversized left Judkins catheters, thrombus aspiration catheters, and rarely GuideLiner catheters [5].

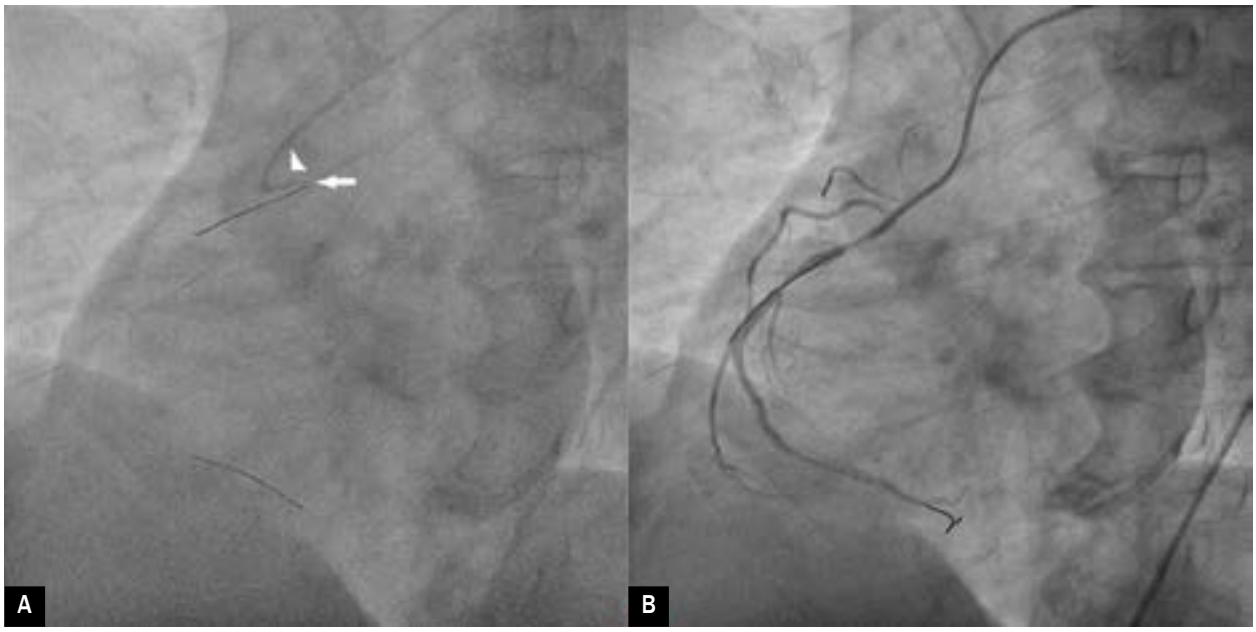


**Figure 2.** Right coronary artery (RCA) was wired using floating wire technique as alignment was not co-axial (arrowhead — tip of catheter, arrow — ostium of RCA; **A**); another runthrough wire was parked as a buddy wire into the RCA to facilitate the coaxial alignment (**B**)

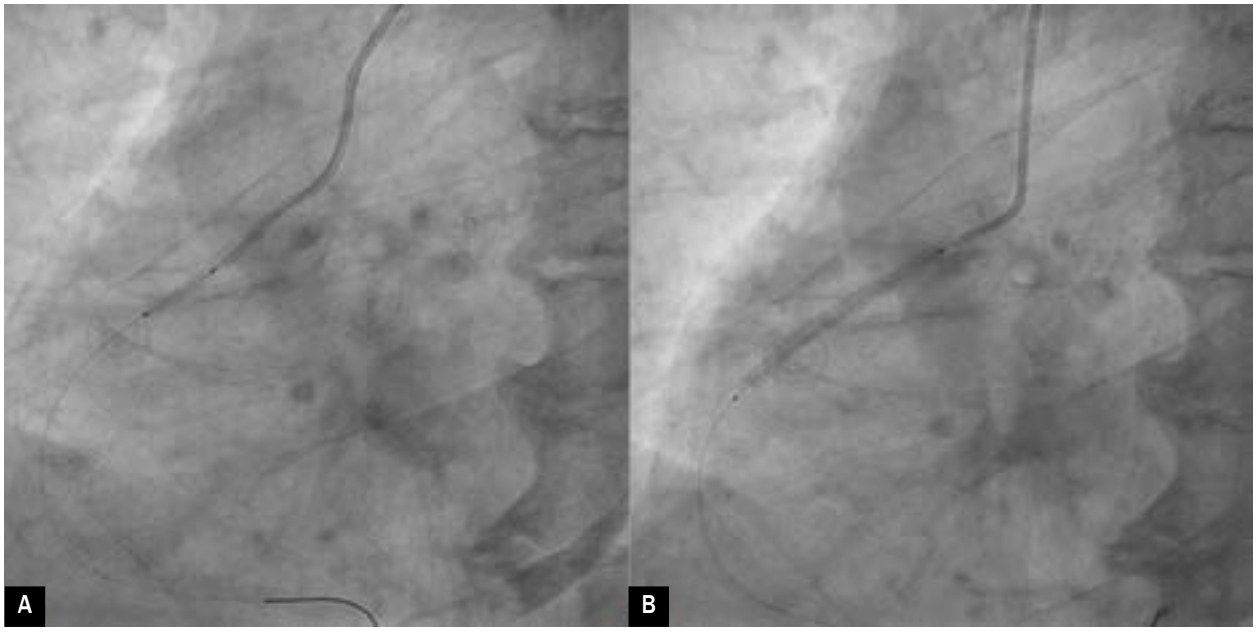


**Figure 3.** The lesion was pre-dilated using Minitrak balloon (**A**); it was stented by deploying 2.75×28 mm Xience Prime stent up to 13 atm pressure (**B**)

A 5 F TIG catheter is a diagnostic catheter which is used for transradial interventions. It has a unique shape with three loops. The first loop compensates for unfavourable angle between innominate artery and ascending aorta. The flat portion between the second and third loops rests against the opposite side of aortic wall and provides back up support. The catheter has a long tip and it points upwards. In a case of anomalous RCA with high anterior take-off, short tipped right catheters don't reach the ostium, while left catheters don't provide adequate back-up as they tend to maintain their original configuration to the right side of ascending aorta. However, a TIG catheter,

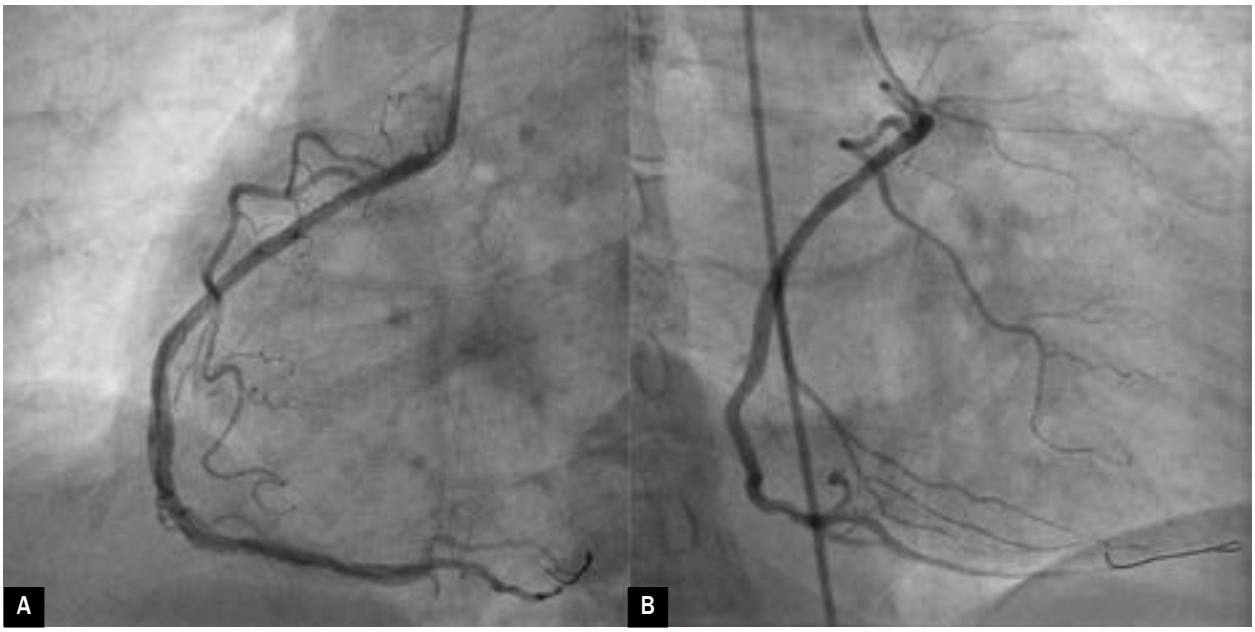


**Figure 4.** Right coronary artery showing TIMI III flow after post dilatation with non-compliant balloon (**A** — left anterior oblique view; **B** — right anterior oblique view)

due to its versatile design, rests against the posterior wall of ascending aorta and the long tip easily reaches the ostium. Another advantage of this catheter is that it can take different shapes by means of push, pull, torque, and rotation. Furthermore, there is less chance of dissection because its tip is very soft. As it is a 5 French catheter, it can be seated deep in the RCA, and can cause damping of pressure.

Since the use of a 5 F diagnostic catheter for PCI was first reported by Salinger et al [6], it has become increasingly popular due to the trend toward using a slender catheter for a transradial approach. It has also been seen that guiding catheters sometimes may not be able to selectively engage the coronary ostium even though its diagnostic counterpart may be able to cannulate the coronary ostium successfully because of the differences in shape between the two catheters in the form of a shorter tip and a lack of tip tapering for the guiding catheter. This can result in multiple guide selection attempts [7].

The disadvantages are the unsatisfactory vessel opacification because of small calibre, the need for deep engagement which may be associated with coronary dissections, and the poor support for complex interventions. Nonetheless, a type-A lesion can easily be treated by a 5 F diagnostic catheters. As the contrast volume injected through a 5 F catheter is comparably less, it has the potential to reduce the nephrotoxicity, especially in patients with renal dysfunction. We had adequate vessel opacification at all times, enabling us to accurately position and implant the stent without increasing the total radiation time or dye consumption. Sufficient support was achieved without the need for deep catheter intubation, with easy positioning of the stent across the stenotic lesion.

In conclusion, PCI via a 5 F TIG diagnostic catheter is technically safe and feasible, and allows for significant resource savings. This may be an attractive technical alternative in selected cases when all other catheters have failed.

## Conflict(s) of interest

The authors declare no conflict of interest.

## Streszczenie

Anomalie dotyczące tętnic wieńcowych, zwłaszcza wysokie odejście prawej tętnicy wieńcowej (RCA), wiążą się z trudnościami w trakcie przezskórnej interwencji wieńcowej (PCI). W niniejszym artykule przedstawiono przypadek 63-letniej kobiety, u której stwierdzono krytyczne zwężenie w bliższym odcinku RCA o nieprawidłowym odejściu. U chorej próby kaniulacji ujścia tętnicy kończyły się niepowodzeniem mimo użycia wielu cewników prowadzących. Zabieg PCI udało się skutecznie wykonać za pomocą cewnika diagnostycznego 5 F TIG (Optitorque, Terumo, Japonia) z dostępu przezudowego. Unikatowy kształt cewnika diagnostycznego TIG umożliwił jego współosiowe wprowadzenie do nieprawidłowej RCA i dokonanie odpowiedniej oceny zwężenia oraz umieszczenie stentu.



Słowa kluczowe: nieprawidłowa prawa tętnica wieńcowa, cewnik TIG, przezskórna interwencja wieńcowa z dostępu przezudowego, wysokie odejście

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# Transcatheter closure of a large ruptured sinus of Valsalva aneurysm to right ventricle — technical challenges

## Przezcewnikowe zamknięcie pęknięcia dużego tętniaka zatoki Valsalvy do prawej komory — trudności techniczne

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### Abstract

Sinus of Valsalva aneurysm, usually a congenital anomaly, almost always ruptures into the right sided cardiac chambers, causing a left-to-right shunt with profound haemodynamic consequences. With the availability of the current generation of devices and hardware, transcatheter closure has gradually replaced the surgical route. To date, most closures have been performed using an Amplatzer duct occluder (ADO). Here, we report the case of a 21 year-old male where a very large (18 mm) rupture of a sinus of Valsalva aneurysm from non-coronary cusp to right ventricle was closed by a percutaneous approach using a 20/18 mm Cocoon duct occluder (CDO; Vascular Innovations, Nonthaburi, Thailand).

Key words: sinus of Valsalva aneurysm, right ventricle, Amplatzer duct occluder, Cocoon duct occluder, transcatheter closure

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## Introduction

A ruptured sinus of Valsalva aneurysm (RSOVA) is a rare cardiac abnormality, accounting for < 1% of all congenital heart defects. It forms due to a congenital weakness at the junction of the aortic media and annulus fibrosus [1]. Aneurysms arise from the right coronary sinus (RCS) in 70% of cases of RSOVA, from noncoronary sinus (NCS) in 29%, and rarely, 1%, from the left coronary sinus [2]. Its presentation varies from asymptomatic findings to the sudden onset of chest pain due to acute heart failure associated with a severe left-to-right shunt if communicating with the right-sided heart chambers, with rapid deterioration causing death, with a mean survival period for untreated RSOVA patients of 1–3.9 years [3]. Early surgical intervention is the treatment of choice. Although surgery is the gold standard, percutaneous transcatheter closure (TCC) has now become equally efficacious, and brings with it fewer complications.

## Case report

A 21 year-old manual labourer with no other significant comorbidities presented with a history of palpitations and breathlessness on exertion of six weeks' duration. On admission, his functional status was New York Heart Association (NYHA) class III. On examination, he was found to have continuous murmurs in the right second and third intercostal spaces, with peripheral signs of aortic run-off. Electrocardiogram showed left ventricular hypertrophy with right ventricular enlargement, and chest X-ray showed mild cardiomegaly with right ventricular enlargement. Transthoracic echocardiography showed aneurysmally dilated right sinus of Valsalva which was communicating into right ventricle (RV) with continuous flow revealing a classical **windsock deformity**. Colour Doppler examination revealed a ruptured aneurysm of the right coronary sinus of Valsalva causing a large left-to-right

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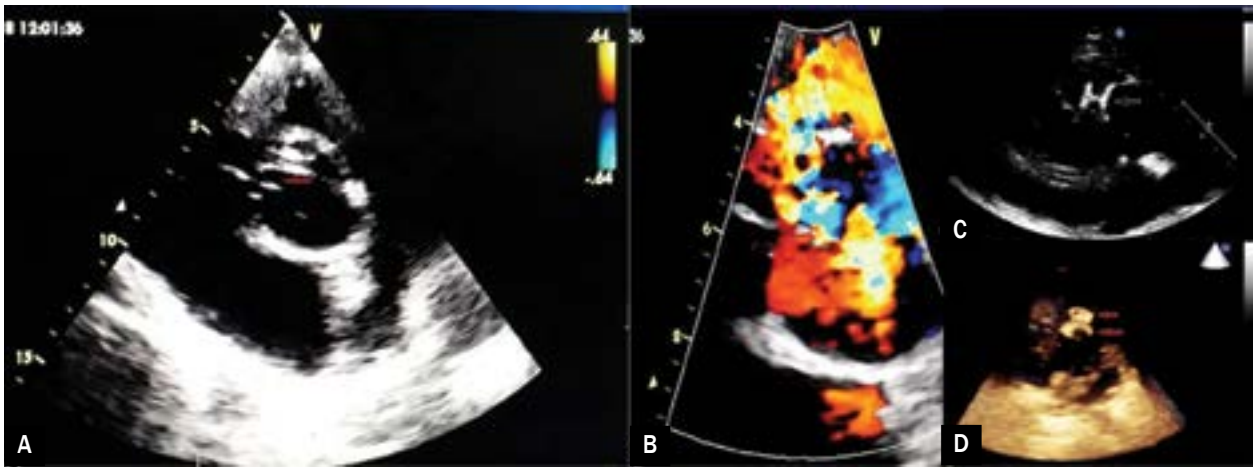


**Figure 1A–D.** Transthoracic echocardiography showing right sinus of Valsalva communicating into right ventricle (red arrow; **A**); colour Doppler showing the ruptured sinus of Valsalva aneurysm (RSOVA) in right ventricle (**B**); well apposed device with both the discs (2D echo — white arrow; **C**) (3D; **D**)

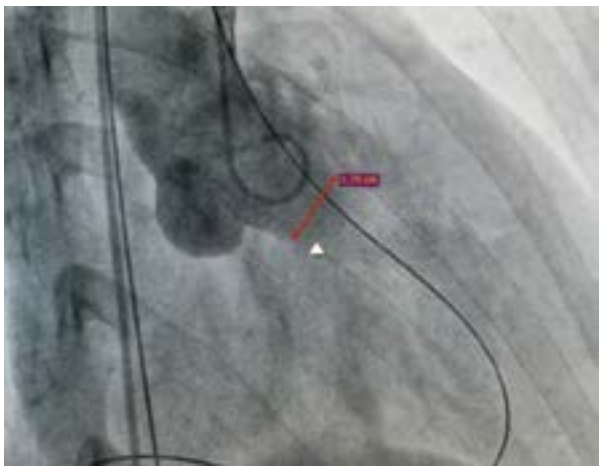

**Figure 2.** Aortic root angiogram showing aneurysmal sac (arrowhead) of right coronary sinus rupturing into right ventricle. The largest diameter of defect was 17 mm

shunt into the right ventricle (Figure 1). There were no associated defects such as ventricular septum defect or aortic regurgitation. Subsequently, it was confirmed on aortic root angiogram. This also revealed a mean pulmonary artery pressure of 58 mmHg and the Qp/Qs was 2.2. The communication was profiled in different views, and the largest diameter was 16–17 mm as measured by quantitative coronary analysis (Figure 2). Percutaneous device closure was planned with informed consent. The right femoral vein and artery and left femoral artery were all accessed with 6 F sheaths. Intravenous heparin (100 IU/kg) and ceftriaxone-1 gm were injected. The defect was crossed from the aortic side using a straight tip, 0.035 inch, 190 cm terumo wire (Terumo, Japan) over a 6 F Multipurpose diagnostic catheter (MP-1) (Figure 3A). Once the wire had reached into the right ventricle (RV), the catheter was further advanced into the RV. With the

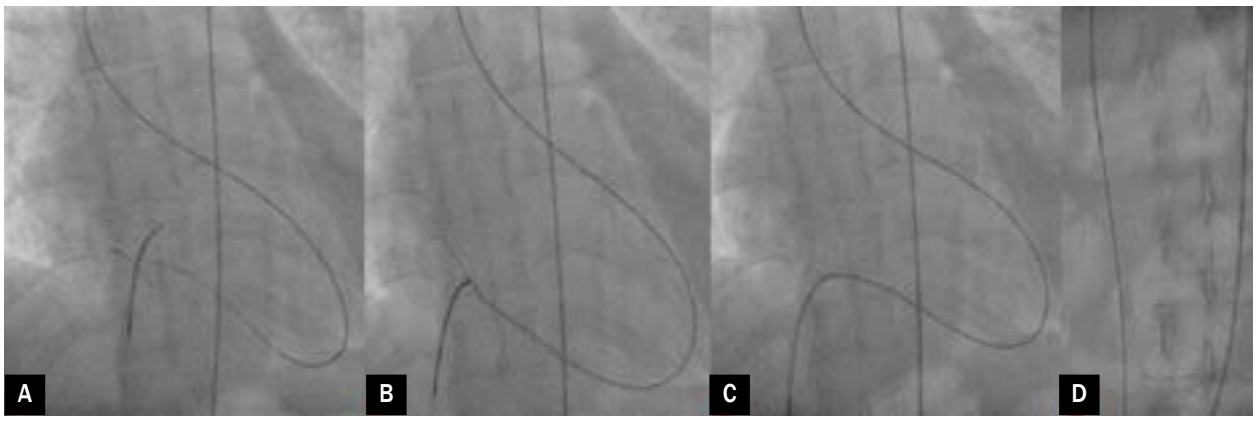


**Figure 3A–D.** The defect was crossed from the aortic side using straight tip terumo wire (**A**); the wire was exchanged for along terumo wire, which was pushed into right atrium where it was snared using a 2 cm EnSnare (**B–D**)

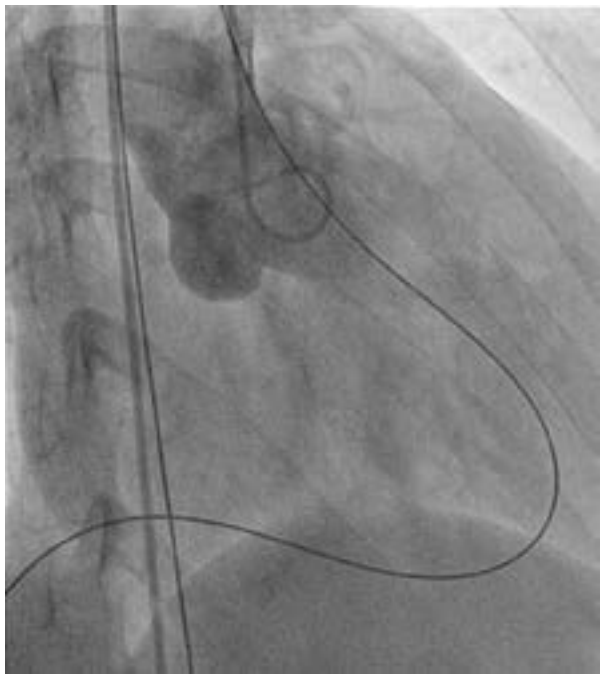

**Figure 4.** Arteriovenous wire loop was established

catheter kept within the RV, the wire was exchanged for a long (330 cm, 0.035 inch) terumo wire, which was pushed into the right atrium (Figure 3B). It was snared using a 2 cm EnSnare (Merit Inc, USA), and brought out of the right femoral vein, thereby establishing a stable arteriovenous wire loop (Figures 3C, D, 4). As the largest diameter of defect was 17 mm, we chose a duct occluder device (Cocoon duct occluder, CDO; Vascular Innovations, Thailand) of 20/18 mm, meaning that its aortic segment was 2 mm larger than the diameter of the defect. As the device was compatible with a 12 F sheath, a 6 F venous sheath was pulled out and a 12 F long delivery sheath was introduced over the terumo exchange length wire from the venous side into ascending aorta across the defect. As the defect was opening into RV, and sheath being 12 F, we encountered great difficulty while negotiating it beyond the RV into ascending aorta as it tended to prolapse back to RV. The long sheath was pulled out and another 6 F MP catheter was pushed from venous side into descending aorta over the terumo wire. The terumo wire was exchanged for a 0.035 inch superstiff Amplatz wire (St Jude Med, Germany). This was pushed down to descending thoracic aorta where it was snared and brought out of the femoral artery, thereby creating another arterio-venous loop, but this time over the superstiff Amplatz wire. The long sheath was pushed over the Amplatz wire, but again the same difficulty was encountered as it tended to prolapse back to RV. Both the ends of Amplatz wire were grasped with artery forceps to keep the wire taut, and the delivery sheath was pushed with a gentle clockwise twist to facilitate its smooth delivery. With the help of this manoeuvre, it was successfully pushed beyond the ascending aorta to proximal descending thoracic

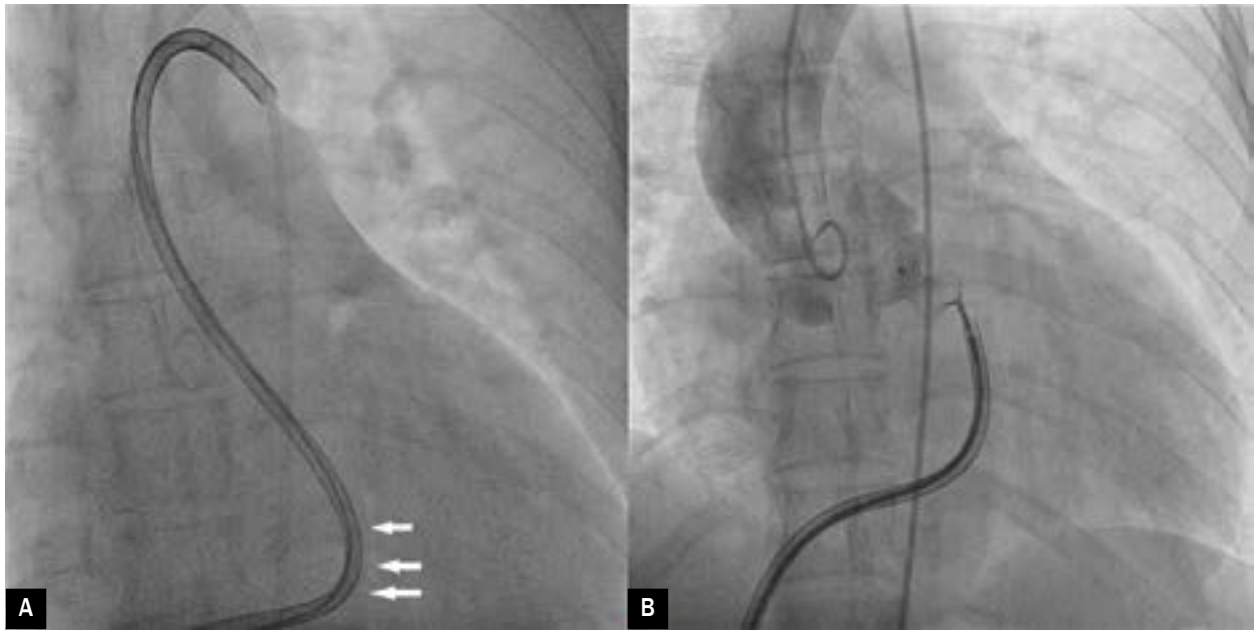


**Figure 5A, B.** 12 F long delivery sheath was pushed beyond the ascending aorta into descending thoracic aorta (white arrow shows the bend across right ventricular outflow tract (RVOT), **A**); aortic end of Cocoon duct occluder (CDO) was positioned to perfectly align with the aortic end of the ruptured sinus (**B**)

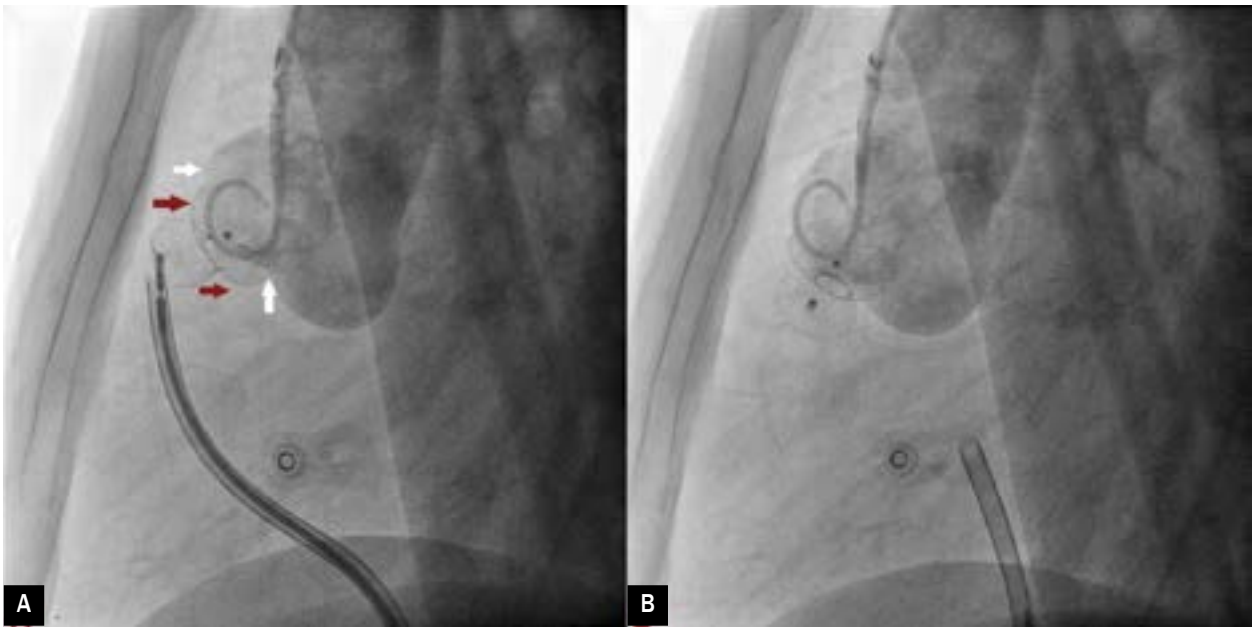


**Figure 6A, B.** Position of the device and complete sealing of the defect was confirmed in straight lateral position as no contrast was flowing across the device (**A**); device position after its deployment (**B**)

aorta (Figure 5A). CDO, attached to the delivery cable, was then inserted into the delivery sheath and pushed to open its aortic disc in the ascending aorta. The whole assembly was pulled back and positioned carefully until the aortic disc perfectly aligned with the aortic end of the ruptured sinus. This was ensured after injecting contrast through the pigtail catheter which was positioned into aortic sinus from the left femoral route. The position was ensured via two views: right anterior oblique with cranial angulation (RAO cranial), and straight lateral projection (Figures 5B, 6A). After confirming the precise placement, the rest of the CDO was deployed on the right side across the defect by gently pulling the delivery sheath. During this manoeuvre, a gentle traction was exerted on the delivery cable, but taking special care to ensure that the aortic disc was seated on the aortic side, with no slippage into the aneurysm. After a 10 minute delay, aortic root angiogram was again performed to ensure proper device positioning and rule out any para-device leak. The CDO was then released from the delivery cable by turning the pin-vice anticlockwise (Figure 6B). Device position was confirmed and any embolisation was ruled out on fluoroscopy (Figure 7). Echocardiogram on the following day showed no residual flow across the device (Figure 1C, D). The patient was discharged in a stable condition the next day on aspirin 75 mg once daily for the next six months.

## Discussion

Sinus of Valsalva aneurysm almost always ruptures into the right side of the heart causing a left-to-right shunt with profound haemodynamic effects, especially when the rupture is sudden. Most SVAs arise from right coronary sinus ruptures in right ventricle and those arising from non-coronary sinus ruptures into RA [4]. Since the first report of a device closure of a RSOVA in 1994, there have been various case reports of RSOVA closure using a patent ductus arteriosus (PDA) occluder, a ventricular septal defect (VSD) occluder, an atrial septal defect (ASD) occluder, and a Rashkind umbrella, for example. Therefore, the transcatheter approach has become the gold standard for RSOVA if it is amenable to device closure.

The technique is similar to device closure of a perimembranous VSD, although the defect is located just above the aortic valve instead of below. Sizing of the defect can be done by angiographic measurement, and/ /or periprocedural echocardiography with colour Doppler interrogation which helps in device selection (2–4 mm larger than the aortic end). However, echocardiogram also gives additional information about its neighbouring structures, namely the aortic valve, tricuspid valve, and right ventricular outflow tract, and it does the periprocedural monitoring of acute aortic, and tricuspid regurgitation, and residual shunting. Some authors have also employed the

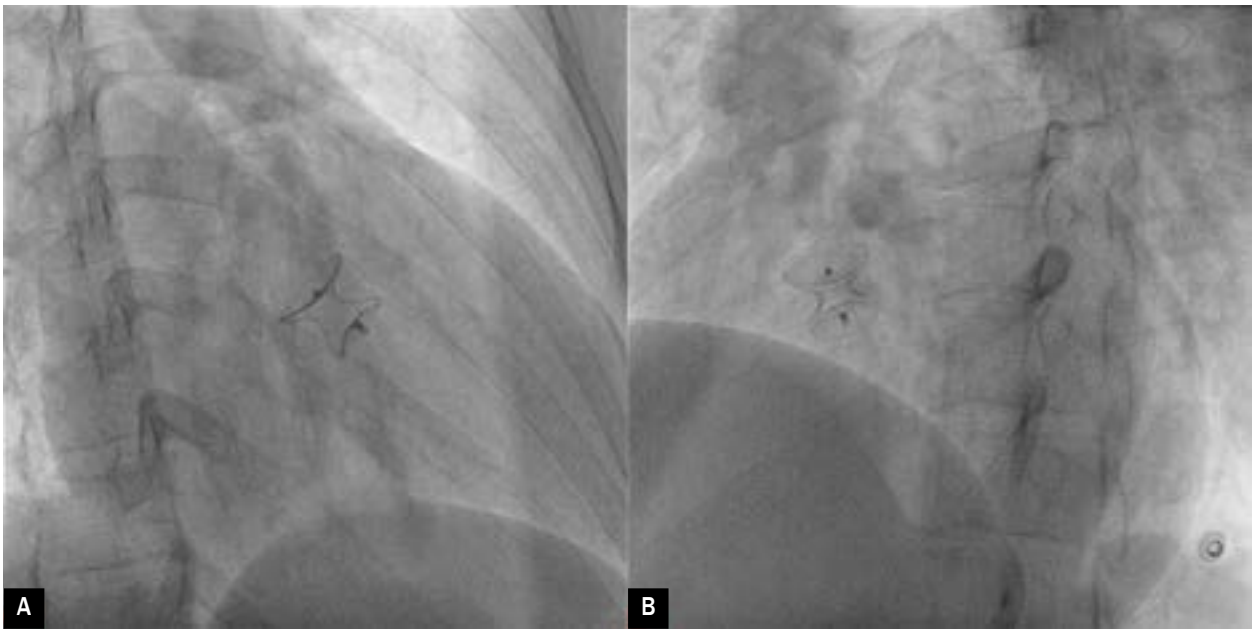


**Figure 7A, B.** Fluoroscopy showing stable device position (right anterior oblique view, **A**; straight lateral view, **B**)

technique of balloon sizing of the defect to choose the appropriate device [5]. In our case, the ruptured RSOVA was closed at the aortic end similarly to a 'surgeon's repair' since closure at the rupture site (exit point) would leave behind an aneurysmal sac which could rupture at another site in the long term as it remains exposed to arterial pressure [6]. Although the surgical incidence of post-procedural aortic regurgitation (AR) is 6%, most surgical incidences are based on aortography and not on the sensitive colour Doppler modality [7], it was not seen in our case. If it is moderate or more, one should not perform the device deployment as it speaks of mal--coaptation of disc with the aortic sinus. If the degree of procedure-related AR is only trivial (less than Grade I), it may not be a concern as progression of such AR, if at all, is likely to be very gradual and stable over the next 10–20 years. But it should be serially and closely monitored by transoesophageal echocardiography, and needs a longer follow-up than usual.

In our case, the sinus was rupturing into right ventricle where the antegrade delivery of the sheath (from right atrium to aorta via right ventricle) is sometimes difficult. In such a case, one should use an Amplatz superstiff wire to make a veno-arterial loop. If this does not work, one should tightly grip both ends of the wire with artery forceps and gradually push the delivery sheath over the wire with a clockwise twist. Once it crosses the right ventricle into aorta, it should be pushed as distally as possible, at least into the proximal descending aorta, as in our case.

The Cocoon duct occluder (CDO) is a platinum-coated, self-expandable, mushroom-shaped device made from a nitinol wire mesh. Its mushroom-shaped retention skirt ensures accurate positioning at the aortic sinus of the aneurysm. Multiple poly-propylene patches sewn securely to the side of the device helps in the introduction of thrombosis, thus closes the defect. Nano platinum coating prevents nickel leeching into the bloodstream and the corrosion of the nitinol wire frame in long term implants. Platinum provides better radio-opacity, which enables easy positioning of the device in the defect.

TCC of a ruptured sinus of Valsalva can be safely and effectively carried out using CDO, and is a good alternative to surgery.

## Conflict(s) of interest

The authors declare no conflict of interest.

## Streszczenie

Tętniak zatoki Valsalvy, zwykle spowodowany wrodzonym defektem, prawie zawsze pęka, tworząc przetokę do prawostronnych komór serca i powodując przeciek lewo-prawy z poważnymi konsekwencjami hemodynamicznymi. Dzięki dostępności najnowszej generacji urządzeń i sprzętu przezcewnikowe zamknięcie przecieku stopniowo zastąpiło drogę chirurgiczną. Do tej pory większość zamknięć wykonywano za pomocą urządzenia zamykającego (zapinki) typu Amplatzer (ADO, *Amplatzer duct occluder*). W niniejszej pracy opisano przypadek 21-letniego mężczyzny, u którego metodą przezskórną zamknięto pęknięcie bardzo dużego (18 mm) tętniaka niewieńcowej zatoki Valsalvy do prawej komory za pomocą urządzenia *Cocoon duct occluder* 20/18 mm (CDO; Vascular Innovations, Nonthaburi, Tajlandia).


Słowa kluczowe: tętniak zatoki Valsalvy, prawa komora, *Amplatzer duct occluder*, *Cocoon duct occluder*, zamknięcie przezcewnikowe

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# Atrial fibrillation with rapid ventricular rate during thyroid storm

## Migotanie przedsionków z szybką czynnością komór w czasie przełomu tarczycowego

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### Abstract

We present the case of an unconscious 81 year-old woman admitted to the Emergency Department with fever and significant tachycardia up to 210 bpm. The patient was referred by the general physician to the neurology department with suspected stroke. Atrial fibrillation (AF) with rapid ventricular rate was found. The causes of significant tachycardia, in this case, were complex and associated with dehydration, fever, infection and thyroid storm. It could be assumed that the deterioration of the patient's general condition and a decreased fluid intake had caused hypertonic dehydration which could have led to further acceleration of the heart rhythm and loss of consciousness.

Thyroid function tests are indicated in all cases of paroxysmal AF. In the presented case, the suspicion of thyroid storm was based on the results of analysis and it was confirmed later by the results of free traction of thyroid hormones' levels. The very fast ventricular rate was related to metabolic disorders and the influence of thyroid hormones on the electrophysiological properties of the atrioventricular junction. In order to stabilise the condition of the patient, passive oxygen therapy, an antipyretic drug, the correction of water and electrolyte disturbances, and digoxin were administered. This treatment improved the patient's general condition and state of consciousness, resulting in slowing heart rate and respiratory rate.

Key words: atrial fibrillation, dehydration, thyroid storm

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## Case report

An 81 year-old female patient was transported to the emergency department (ED) from a nursing home after losing consciousness. She was referred to the neurology department with a stroke diagnosis made by a doctor at the nursing home. The medical transport team provided information that the patient suffered from hypertension and dementia. Loss of consciousness was not sudden but gradual. On the day of admission, she had completely stopped eating and drinking and became unresponsive. The patient's documentation contained an electrocardiogram that had been recorded a few months earlier which showed sinus rhythm. The patient was treated chronically with amlodipine, nicergoline, and acetylsalicylic acid.

The patient was immediately admitted to the red area. On the Glasgow Coma Scale (GCS) she scored 3 points. The patient's airway was patent, but respiration was rapid

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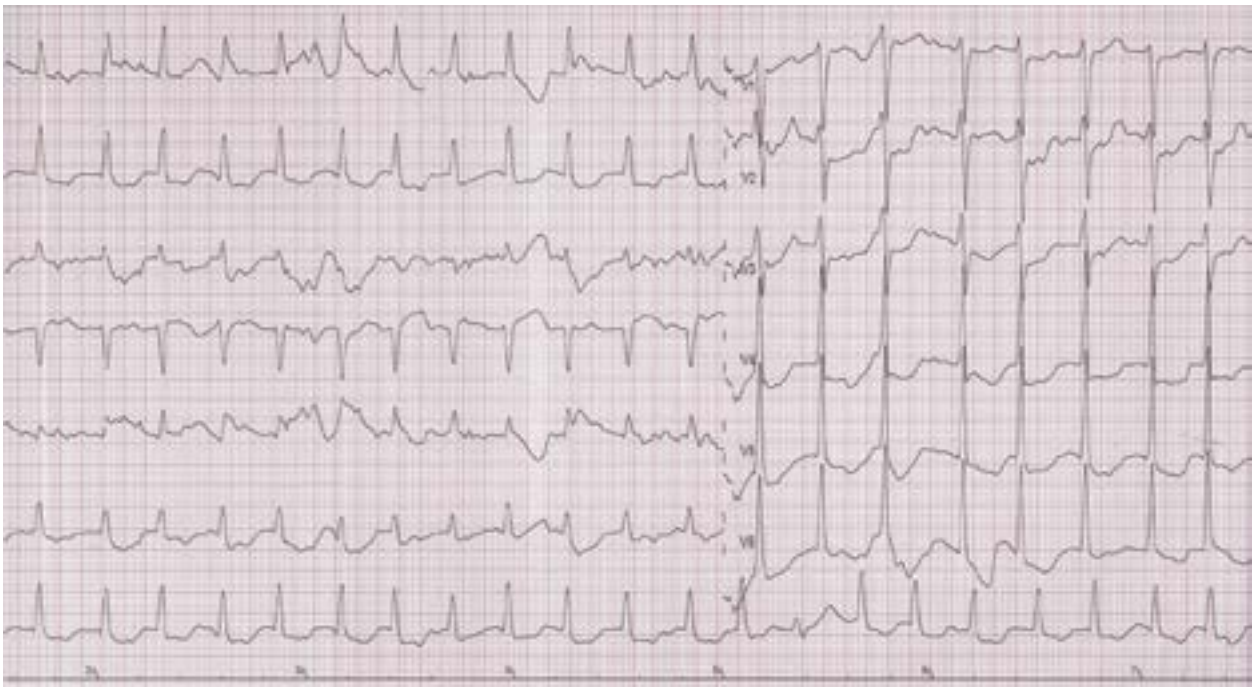

**Figure 1.** An electrocardiogram at admission. Atrial fibrillation with mean ventricular rate of 210/min (paper speed 50 mm/s)

(30 breaths per min) and laboured. Pulse oxymetry revealed oxygen saturation at 85% and a pulse rate of 220/min. The patient was immediately given oxygen via a nasal cannula with a flow of 3 L/min. Blood pressure was 150/90 mm Hg and temperature was 38°C. Venous blood gas analyses showed $pO_2$ 45.6 and $pCO_2$ 45.6 FOHb 73.6%. Other critical biochemical parameters were: normal glucose level, high level of sodium, and low level of potassium. The electrocardiogram (ECG) revealed atrial fibrillation (AF) with ventricular rate up to 210 bpm (Figure 1). Diagnostics for infection (including the urinary and respiratory tracts), acute cerebral ischaemia and hyperthyroidism were initiated. At the same time, the patient was hydrated with a hypotonic solution of 5% dextrose in water with potassium chloride and insulin. Furthermore, 0.25 mg of digoxin and 1 g of paracetamol were administered. Her consciousness level, body temperature, breathing frequency, and heart rate gradually improved. After three hours, the patient started to spontaneously open her eyes and look towards an approaching person. Blood pressure was within the same range as at admission, however pulse oximetry had increased to 95%, and heart rate was 104 bpm.

The results of laboratory tests are presented in Table 1. C-reactive protein (CPR), D-dimer and troponin T levels were slightly elevated. The troponin level was increased but stable and three hours later was on the same level as at admission. Intracerebral haemorrhage and skull bone injury were not found in the computed tomography scan of the head. There were no signs of infection in the chest X-ray or urinalysis.

**Table 1.** Laboratory results

| Parameter | Value | Norm |
|---|---|---|
| Sodium [mmol/L] | 164 | 135–145 |
| Potassium [mmol/L] | 3.4 | 3.5–5.1 |
| Haemoglobin [g/dL] | 14.6 | 11.0–16.0 |
| RBC [T/L] | 4.92 | 3.50–5.0 |
| Troponin T [pg/mL] | 88 | < 13.0 |
| D-dimer [ng/mL] | 1,993 | < 500.0 |
| CRP [mg/L] | 21.66 | < 6.0 |
| TSH [μU/mL] | 0.012 | 0.27–4.2 |
| fT4 [pmol/L] | 50.3 | 12–22 |
| fT3 [pmol/L] | 6.08 | 6.7–13.13 |
| Serum lactate [mmol/L] | 5.37 | < 1.2 |

RBC — red blood cells; CRP — C-reactive protein; TSH — thyroid-stimulating hormone (thyrotropin); fT4 — free thyroxine; fT3 — free triiodothyronine

Levels of free thyroid hormone fractions were checked. Because the free thyroxine (fT4) level was significantly increased, the diagnosis of thyroid storm was made. The patient was transferred to the department of internal diseases.

## Discussion

Admissions to the ED of an unconscious patient account for 0.4–1% of all admissions. Unconscious patients are

at a high risk of death. A prompt and accurate diagnosis is crucial for their survival. The main reasons for non-traumatic loss of consciousness are seizures, glucose level disturbances, and intoxication. About 30% of such patients have no obvious cause and 1% of patients have unsuspected traumatic brain injury.

In the presented case, discovering the cause of the extremely rapid ventricular rate of the first diagnosed atrial fibrillation was crucial. The ventricular rate during AF depends on the activity of the autonomic system and the properties of the atrioventricular node. Rapid ventricular rate (RVR) during AF has been defined as an average ventricular rate > 110/min in many studies [1]. The mean ventricular rate in patients with the first AF in the study by Naffaa et al. [2] was 128 ± 30. AF with RVR may occur during many disorders and disease processes that may co-exist, including sepsis, hypoxia, acute heart failure, dehydration, fever, pre-excitation syndrome, and thyroid storm. Especially in the last two of these cases, very high ventricular rates exceeding 200 bpm have been described [3].

The first step in selecting a treatment strategy for AF is to assess the influence of AF on the patient's haemodynamic status, duration of AF, anticoagulant therapy, current complications and coexisting conditions. In the presented case, the parameters that could indicate haemodynamic instability were unconsciousness, rapid breathing, and increased lactate level. However, normal blood pressure, the absence of signs of fluid retention in physical examination and chest X-ray, and no pulse deficit assessed by pulse oximetry all argued against the assumption that the cause of unconsciousness was haemodynamic instability. The duration of AF was certainly shorter than a few months, but could not be exactly determined. Therefore cardiac electrocardioversion was not performed at the patient's admission to ED.

The clinical picture suggested that the cause of the patient's state could be sepsis, although the slightly elevated CRP concentration and normal chest X-ray and urinalysis argued against this. Even before obtaining the results of additional tests and determining the full diagnosis, it was necessary to correct metabolic disorders, including hypertonic dehydration, with an infusion of nonelectrolyte fluids. High sodium concentrations indicate hypertonic dehydration, which may be a consequence of hyperventilation or reduced water intake. Both of these causes could co-exist within the patient. The patient did not have a thyroid-related medical history. However, abnormal results of hormonal tests together with the whole clinical picture comprising increased body temperature, impaired consciousness, and AF with RVR, helped towards a diagnosis of thyroid shock. In Burch-Wartofsky score, the patient scored 75 points consisting of thyrotoxicosis [elevated free triiodothyronine (fT3) and/or fT4 level] with coma (30 points), tachycardia of 220/min (25 points), AF (10 points) and fever 38°C (10 points). A total of points ≥ 45 is required for a diagnosis of thyroid storm [3, 4]. Therefore, attention should be paid to the existence of contraindications to the administration of amiodarone, which could be considered due to the absence of a depressive effect on the myocardial contractility [5].

It cannot be ruled out that if a medical emergency team was called to the patient, the decision to administer amiodarone intravenously could have been made. Recommendations regarding the management of patients with thyroid crisis and AF with rapid ventricular rate include administration of a beta-blocker: esmolol infusion or metoprolol in an intravenous bolus, but cases of effective control of the ventricular rate using digoxin [5–7] have also been reported in the literature.

AF with RVR may also occur if there is an additional conduction pathway (as in Wolff-Parkinson-White syndrome), but in those circumstances a large variation in the morphology of QRS complexes would be expected, which was not observed in the presented case [3]. One explanation for the presence of AF with RVR could be an excess of thyroid hormones that have a positive chronotropic effect [8, 9]. They affect atrial cells by shortening their repolarisation period, which can lead to AF arrhythmia.

Another property of triiodothyronine is its effect on the atrioventricular node, where it shortens the conduction period and the relative refraction time, which explains the rapid rhythm of the ventricles in the described case.

The case we have presented allows us to emphasise the occurrence of two findings: lack of pulse deficit, which indicated hyperkinetic circulation, and a significant slowdown of the heart rate after administration of fluids and digoxin, which has a weak effect in the case of an activated sympathetic nervous system. The RVR in this case seems to have been mainly driven by dehydration and fever. However, thyroid hormones acting on the electrophysiological properties of the cardiac conduction system could enhance this response [8, 9]. Moreover, the fever could be at least partially caused by thyrotoxicosis. Weakness caused by fever and thyrotoxicosis could enhance dehydration due to reduced water intake.

## Conclusions

1. Thyroid storm can occur at any age, including among elderly people. It can lead to coma as a result of metabolic disturbances, fever, and dehydration. 2. AF with a rapid ventricular rate, as well as coma of unknown cause, are indications for the assessment of thyroid function simultaneously with other diagnostic tests and ongoing treatment.

## Conflict(s) of interest

The authors declare no conflict of interest.

## Streszczenie

W pracy przedstawiono przypadek nieprzytomnej 81-letniej kobiety przywiezionej na szpitalny oddział ratunkowy z gorączką i znaczną tachykardią do 210/min skierowanej przez lekarza rodzinnego na neurologię z podejrzeniem udaru mózgu. W zapisie elektrokardiograficznym stwierdzono migotanie przedsionków (AF) z szybką czynnością komór. Przyczyny wystąpienia znacznej tachykardii w tym przypadku były złożone i związane z odwodnieniem, gorączką, infekcją oraz przełomem tarczycowym. Pogorszenie stanu pacjentki i zmniejszone przyjmowanie płynów prowadziło do odwodnienia hipertonicznego, co mogło prowadzić do dalszego przyspieszenia rytmu serca i utraty przytomności.

Badanie czynności tarczycy jest wskazane u wszystkich pacjentów z napadowym AF. W prezentowanym przypadku pozwoliło ono podejrzewać przełom tarczycowy, potwierdzony następnie w badaniu stężeń wolnych frakcji hormonów tarczycy. Bardzo szybka częstość komór w tym wypadku wiązała się z zaburzeniami metabolicznymi oraz wpływem hormonów tarczycy na właściwości elektrofizjologiczne łącza przedsionkowo-komorowego. W celu wstępnej stabilizacji stanu pacjentki zastosowano nawadnianie, tlenoterapię bierną, podano lek przeciwgorączkowy, uzupełniano niedobór elektrolitów i podano digoksynę, co pozwoliło na poprawę stanu ogólnego pacjentki i jej stanu świadomości, zwolnienie czynności serca i częstotliwości oddychania.


Słowa kluczowe: migotanie przedsionków, odwodnienie, przełom tarczycowy

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# Pułapka diagnostyczna — dławica piersiowa i intermitujący blok lewej odnogi pęczka Hisa u 68-letniej kobiety z zatorowością płucną Opis przypadku z obserwacją po roku

## A diagnostic pitfall: angina pectoris and intermittent left bundle branch block in a 68 year-old woman with pulmonary embolism — one year follow-up. A case report

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**Streszczenie**

W pracy zaprezentowano przypadek pacjentki w wieku 68 lat, która była konsultowana w poradni kardiologicznej z powodu dolegliwości dławicowych w III klasie według *Canadian Cardiovascular Society*. W badaniu elektrokardiograficznym (EKG) obserwowano intermitujący blok lewej odnogi pęczka Hisa. W badaniu echokardiograficznym uwidoczniono cechy sugerujące zatorowość płucną. Rozpoznanie potwierdzono w angiografii tomografii komputerowej. Przypadek ilustruje, jak duże znaczenie ma badanie echokardiograficzne w diagnostyce różnicowej dolegliwości dławicowych oraz wskazuje, że zapis EKG może niekiedy utrudnić postawienie właściwej diagnozy.

Słowa kluczowe: dławica piersiowa, intermitujący blok lewej odnogi pęczka Hisa, zatorowość płucna

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## Wstęp

Zatorowość płucna (PE, *pulmonary embolism*) nie ma swoistej manifestacji klinicznej, dlatego początkowo może pozostawać nierozpoznana [1–3]. Ból w klatce piersiowej stanowi częsty objaw PE. Zazwyczaj jest spowodowany podrażnieniem opłucnej z powodu zatorów obwodowych prowadzących do zawału płuca [4]. W centralnej PE ból w klatce piersiowej może mieć charakter typowo stenokardialny i odzwierciedlać niedokrwienie prawej komory, co wymaga różnicowania z ostrym zespołem wieńcowym [5]. Z kolei bóle w klatce piersiowej i współistniejący z nimi przemijający blok lewej odnogi pęczka Hisa (LBBB, *left bundle branch block*) sugerują deficyt ukrwienia układu przewodzącego, co także przemawia za wieńcowym tłem dolegliwości. Znaczenie kliniczne przemijającego LBBB — zarówno indukowanego wysiłkiem, jak i występującego spontanicznie — nie zostało jednoznacznie ustalone. Ten rodzaj bloku obserwowano zarówno u pacjentów z chorobą organiczną serca, jak i u pacjentów bez zmian organicznych w sercu [6, 7]. Ze względu na to, że pojawienie się LBBB w czasie próby wysiłkowej sugeruje duże prawdopodobieństwo zmian w tętnicach wieńcowych, tacy pacjenci często są kierowani na koronarografię.

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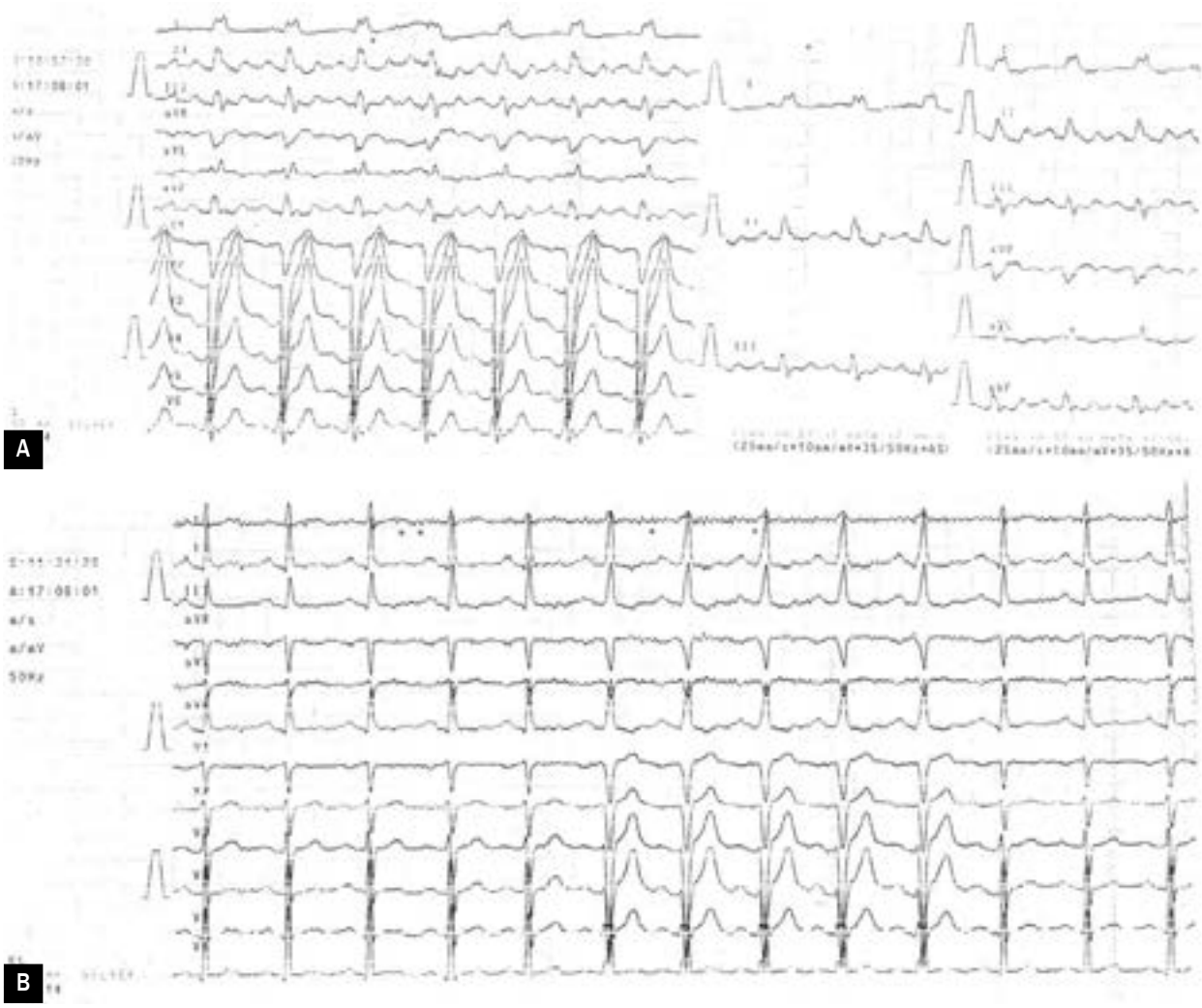
W niniejszym artykule zaprezentowano przypadek pacjentki, która była hospitalizowana z powodu dolegliwości stenokardialnych w III klasie według *Canadian Cardiovascular Society* (CCS). W teście wysiłkowym wystąpił u niej przemijający LBBB i wstępnie zakwalifikowano ją do koronarografii. Na podstawie wykonanego 2 dni po opuszczeniu szpitala badania echokardiograficznego wysunięto podejrzenie PE; rozpoznanie to potwierdzono w angiografii tomografii komputerowej (CT, *computed tomography*). Pozwoliło to wdrożyć właściwe leczenie i uzyskać ustąpienie dolegliwości. Po roku od epizodu pacjentka nie zgłasza dolegliwości dławicowych, wykazuje dobrą tolerancję wysiłku. Po odstawieniu propafenonu w zapisie elektrokardiograficznym nie obserwuje się zaburzeń przewodzenia śródkomorowego.

## Opis przypadku

Pacjentka w wieku 68 lat, niepaląca, leczona od kilku lat z powodu nadciśnienia tętniczego, choroby wieńcowej i napadowego migotania przedsionków (AF, *atrial fibrillation*), stosująca w ostatnim czasie następujące leki: bisoprolol w dawce 5 mg raz/dobę, ramipril w dawce 5 mg raz/dobę, simwastatynę w dawce 20 mg raz/dobę, kwas acetylosalicylowy w dawce 75 mg raz/dobę i propafenon w dawce 150 mg 2 razy/dobę, zgłosiła się po raz pierwszy do poradni kardiologicznej z powodu występujących od kilkunastu dni dolegliwości dławicowych w III klasie według CCS. Dwa dni wcześniej opuściła oddział wewnętrzny, gdzie była z tego powodu hospitalizowana. Z analizy karty informacyjnej wynikało, że przy przyjęciu pacjentka miała prawidłowe ciśnienie tętnicze, w elektrokardiogramie (EKG) spoczynkowym nie opisano nieprawidłowości, a wyniki badań laboratoryjnych pozostawały bez odchyleń (hemoglobina [Hb] 13,2 g/dl, liczba płytek krwi [PLT, *platelets*] 179 tys./mm$^3$, leukocyty 6400/mm$^3$, kreatynina 1,0 mg/dl, potas 4,3 mEq/l, cholesterol całkowity 150 mg/dl, glukoza 100 mg/dl, aminotransferaza alaninowa [AlAT, *alanine aminotranferase*] 13 j./l, hormony tarczyny [TSH, *thyroid-stimulating hormone*] 1,47 μjm./ml, frakcja sercowa kinazy kreatynowej [CK-MB, *creatine kinase myocardial bound*] 17,6 j./l, troponina T 9,1...8 pg/ml). W trakcie hospitalizacji nie oznaczono D-dimerów. W wykonanym badaniu radiologicznym klatki piersiowej nie wykazano odchyleń od normy. Przeprowadzono również test wysiłkowy, który przerwano po 3 minutach z powodu wystąpienia dolegliwości dławicowych oraz pojawienia się w EKG przemijającego LBBB. W czasie pobytu w szpitalu nie przeprowadzono badania echokardiograficznego. Pacjentkę zakwalifikowano do planowej koronarografii. Podczas oczekiwania na zabieg zgłosiła się do miejscowej poradni z powodu nawracających dolegliwości dławicowych pojawiających się przy małym wysiłku fizycznym. W badaniu przedmiotowym nie stwierdzono nieprawidłowości. W badaniu EKG wykonanym w spoczynku 2-krotnie — w pierwszym zapisie miarowy rytm zatokowy 90/min, LBBB (ryc. 1A), w drugim zapisie w początkowym fragmencie brak cech bloku lewej odnogi, następnie pojawił się niezupełny LBBB, który w końcowym fragmencie ustąpił (ryc. 1B). W badaniu echokardiograficznym stwierdzono prawidłowe wymiary lewych jam serca, mierne powiększenie prawego przedsionka i prawej komory, prawidłową frakcję wyrzutową lewej komory (ok. 65%), okresowo paradoksalny ruch przegrody międzykomorowej, fuzję fal E i A napływu mitralnego, skrócenie czasu akceleracji wyrzutu płucnego (AcT, *acceleration time*) wyrzutu płucnego (82 ms), umiarkowaną niedomykalność trójdzielną oraz podwyższone ciśnienie skurczowe w prawej komorze (42,6 mm Hg oraz ośrodkowe ciśnienie żylne), sugerujące umiarkowane prawdopodobieństwo nadciśnienia płucnego. Mimo mylącego zapisu EKG wysunięto podejrzenie PE i chorą skierowano do szpitala. Pacjentka zgłosiła się do kontroli po roku od epizodu. Z analizy karty informacyjnej z ponownej hospitalizacji wynikało, że w dniu skierowania pacjentki do szpitala oznaczono stężenie D-dimerów(18 tys. pg/ml) oraz wykonano angio-CT klatki piersiowej, w której wykazano obecność materiału zatorowego w tętnicach płucnych poniżej miejsca podziału pnia płucnego. U pacjentki rozpoznano PE niewysokiego ryzyka, wdrożono terapię riwaroksabanem w początkowej dawce 15 mg 2 razy/dobę przez 3 tygodnie, a następnie 20 mg raz/dobę. Zalecono również kontynuację leczenia propafenonem w profilaktyce napadowego AF. Pacjentka podczas wizyty kontrolnej po roku nie zgłaszała dolegliwości dławicowych, wykazywała dobrą tolerancję wysiłku, nie pamiętała, kiedy wystąpił u niej ostatni odczuwalny napad arytmii. W wykonanym zapisie EKG stwierdzono miarowy rytm zatokowy 65/min, LBBB (ryc. 2). W badaniu echokardiograficznym obserwowano prawidłowe wymiary jam serca, prawidłową funkcję skurczową lewej i prawej komory, prawidłowe ciśnienie skurczowe w prawej komorze (28 mm Hg), prawidłowy AcT wyrzutu płucnego (122 ms). Wysnuto podejrzenie, że zaburzenia przewodzenia śródkomorowego mogą się wiązać ze stosowaniem propafenonu. Ze względu na sporadyczne występowanie arytmii zadecydowano o odstawieniu leku i dalszym leczeniu pacjentki tylko bisoprololem w dawce 5 mg raz/dobę. Po odstawieniu propafenonu 2-krotnie przeprowadzono kontrolę EKG. W placówce podstawowej opieki zdrowotnej po 2 tygodniach wykonano badanie EKG, w którym nie stwierdzono cech bloku. Kolejne badanie przeprowadzono miesiąc po odstawieniu propafenonu w miejscowej poradni; w tym zapisie również nie stwierdzono LBBB (ryc. 3). Pacjentka od czasu zaprzestania stosowania propafenonu nie odczuwała zaburzeń rytmu.

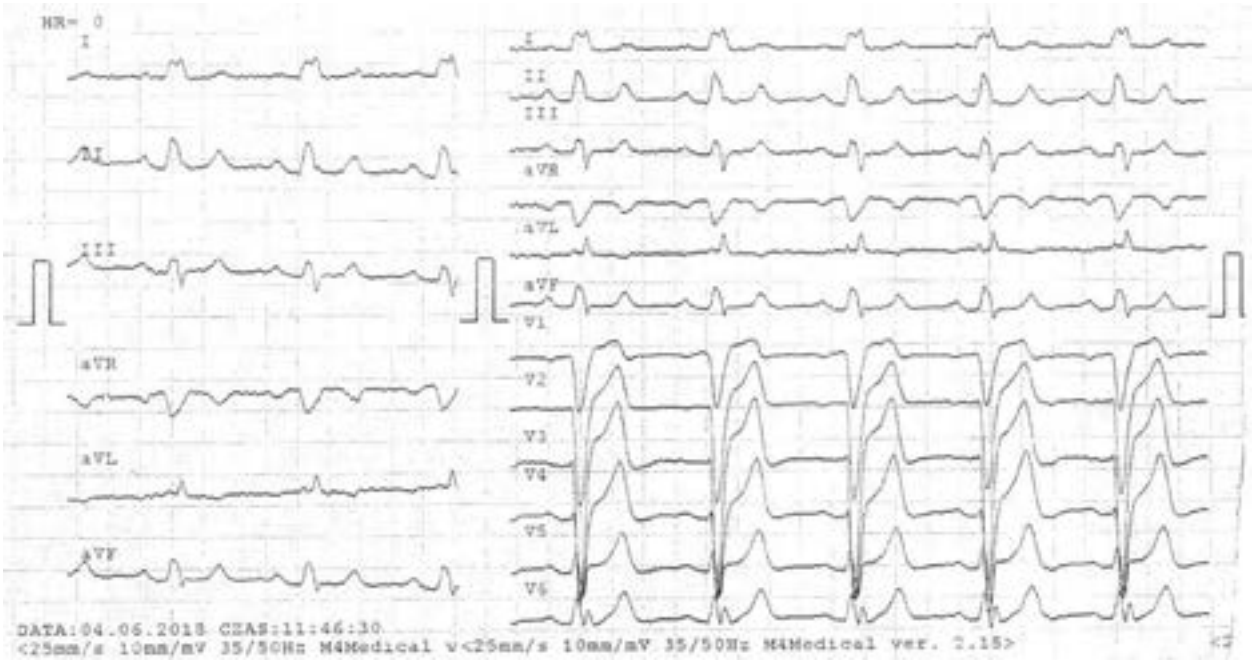
## Dyskusja

Rozpoznanie PE jest wyzwaniem dla lekarza. Zarówno obraz kliniczny, jak i zapis EKG mogą pomóc w postawieniu

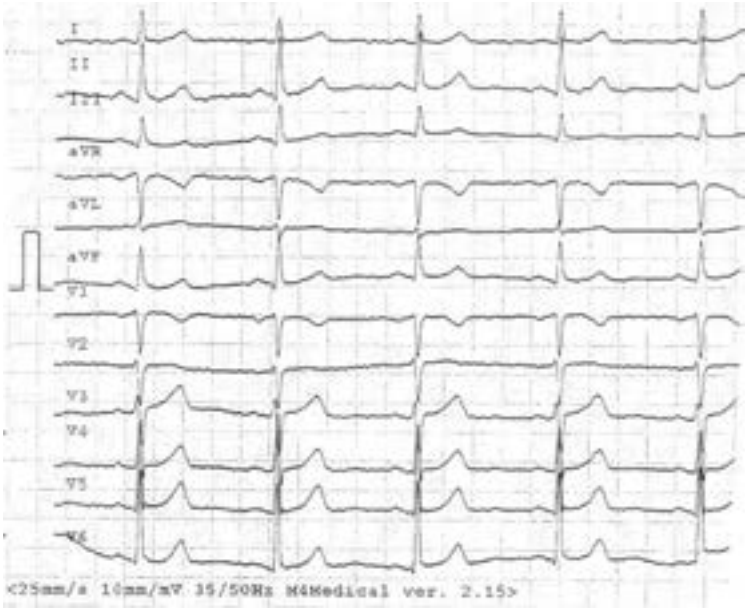



**Rycina 1.** Zapis elektrokardiograficzny podczas pierwszej wizyty: **A.** Miarowy rytm zatokowy 90/min, blok lewej odnogi pęczka Hisa (LBBB, *left bundle branch block*); **B.** Miarowy rytm zatokowy 90/min, intermitujący niezupełny LBBB

właściwej diagnozy, ale mogą też wprowadzić w błąd i utrudnić ustalenie rozpoznania. Typowe dolegliwości dławicowe rzadko występują w PE; znacznie częściej są to bóle opłucnowe, a więc w omawianym przypadku wywiad bardziej sugerował tło wieńcowe. Jeśli chodzi o zapis EKG, to w piśmiennictwie opisywano zmiany w przebiegu PE wskazujące na przeciążenie prawej komory, takie jak odwrócenie załamka T w odprowadzeniach V1–V4, zespół QR w odprowadzeniu V1, zespół $S_1Q_{III}T_3$ oraz niezupełny lub zupełny blok prawej odnogi pęczka Hisa. Te zmiany są opisywane w cięższych przypadkach, natomiast w łagodniejszych jedyną nieprawidłowością może być tachykardia zatokowa [8]. Nie znaleziono w piśmiennictwie opisu PE, której towarzyszyłby LBBB. Wydaje się, że najbardziej prawdopodobną przyczyną zaburzeń przewodzenia śródkomorowego u opisanej pacjentki było stosowanie propafenonu. Potwierdzenie tej hipotezy sugerują zapisy EKG wykonane 2-krotnie po odstawieniu tego leku, w których nie stwierdza się zaburzeń przewodzenia śródkomorowego. W opisanym przypadku kluczem do rozpoznania okazało się badanie echokardiograficzne. Obraz echokardiograficzny przemawiał za PE, ale nie był jednoznaczny. Diagnozę potwierdzono w angio-CT. Na podkreślenie zasługuje fakt, że u chorej w wywiadzie stwierdzono epizody napadowego AF, a u pacjentów z takim wywiadem opisywano przypadkowo wykryte skrzepliny w tętnicach płucnych w wielorzędowej CT [9, 10]. W tym konkretnym przypadku nie wiadomo, czy miał znaczenie fakt, że chora nie otrzymywała przed rozpoznaniem PE leku przeciwkrzepliwego, do którego miała wskazania (3 pkt. w skali $CHA_2DS_2$-VASc). Obecnie pacjentka ma podwójne wskazania do długotrwałej antykoagulacji. Z jednej strony jest to wywiad AF i wysokie ryzyko powikłań zakrzepowo-zatorowych (I klasa zaleceń wg Europejskiego Towarzystwa Kardiologicznego [ESC, *European Society of*




**Rycina 2.** Zapis elektrokardiograficzny podczas drugiej wizyty — utrzymujący się blok lewej odnogi pęczka Hisa




**Rycina 3.** Zapis elektrokardiograficzny podczas trzeciej wizyty, miesiąc po odstawieniu propafenonu — bez zaburzeń przewodzenia śródkomorowego

*Cardiology*]), z drugiej — idiopatyczna PE przy aktualnie niskim ryzyku krwawienia (IIa klasa zaleceń wg ESC).

## Podsumowanie

Przedstawiony przypadek sugeruje, że w diagnostyce dolegliwości dławicowych powinno się zawsze wykonywać badanie echokardiograficzne, ponieważ może ono być kluczowe dla rozpoznania. Ponadto świadczy o tym, że zapisEKG bywa niekiedy pułapką diagnostyczną.

## Konflikt interesów

Autorka nie zgłasza konfliktu interesów.

## Abstract

In the present communication, a case of a 68 year-old woman consulted at a cardiology service due to angina pectoris is reported. The electrocardiogram (ECG) showed intermittent left bundle branch block. Transthoracic echocardiography revealed signs of pulmonary embolism. The diagnosis was confirmed by computed tomography angiography. The presented case highlights the role of echocardiography in the differential diagnosis of anginal pain and shows that making a correct diagnosis based on ECG may sometimes be challenging.

Key words: angina pectoris, intermittent left bundle branch block, pulmonary embolism

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# A diagnostic pitfall: angina pectoris and intermittent left bundle branch block in a 68-year-old woman with pulmonary embolism — one year follow-up. A case report

## Pułapka diagnostyczna — dławica piersiowa i intermitujący blok lewej odnogi pęczka Hisa u 68-letniej kobiety z zatorowością płucną Opis przypadku z obserwacją po roku

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### Abstract

In the present communication, a case of a 68 year-old woman consulted at a cardiology service due to angina pectoris is reported. The electrocardiogram (ECG) showed intermittent left bundle branch block. Transthoracic echocardiography revealed signs of pulmonary embolism. The diagnosis was confirmed by computed tomography angiography. The presented case highlights the role of echocardiography in the differential diagnosis of anginal pain and shows that making a correct diagnosis based on ECG may sometimes be challenging.

Key words: angina pectoris, intermittent left bundle branch block, pulmonary embolism

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## Introduction

Pulmonary embolism (PE) does not have any specific clinical presentation and thus may initially remain unrecognized [1–3]. Chest pain is a common symptom of PE. It is usually caused by pleural irritation due to peripheral embolism leading to lung infarction [4]. In centrally located PE, chest pain may have typical anginal characteristics, reflecting right ventricular ischaemia, which requires differentiation from an acute coronary syndrome [5]. Chest pain associated with intermittent left bundle branch block (LBBB) suggests ischaemia involving the cardiac conduction system, which also suggests coronary ischaemia. The clinical significance of intermittent LBBB, both exercise-induced or occurring spontaneously, has not been clearly established. This type of block has been noted both in patients with structural heart disease and in those without structural heart disease [6, 7]. Due to the fact that development of left bundle branch block during an exercise test strongly suggests coronary artery disease, such patients are often referred for coronary angiography.

In the present article, a case is presented of a female patient who was admitted due to Canadian Cardiovascular Society (CCS) class III angina, had intermittent left bundle branch block during an exercise test and was referred for coronary angiography. Based on echocardiography performed two days after the discharge, pulmonary embolism was suspected and then confirmed by pulmonary computed

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tomography angiography. This allowed institution of appropriate treatment with resolution of symptoms. At one year after the acute event, the patient does not report angina and exercise tolerance is good. Following withdrawal of propafenone, no intraventricular conduction disturbances are seen on the electrocardiogram (ECG).

## Case report

A 68 year-old patient, non-smoker, treated for several years for hypertension, coronary artery disease, and paroxysmal atrial fibrillation, presented for the first time to a cardiac outpatient service due to CCS class III angina occurring for several days. Her medications were bisoprolol 5 mg omne in die (OD), ramipril 5 mg OD, simvastatin 20 mg OD, acetylsalicylic acid 75 mg OD, and propafenone 150 mg bis in die (BID). Two days earlier, the patient was discharged from an internal medicine unit, where she had been admitted to due to the above symptoms. The discharge summary indicated that the patient had normal blood pressure on admission, resting ECG was normal, and laboratory tests were unremarkable (haemoglobin 13.2 g/dL, platelet count 179,000/mm$^3$, white blood count (WBC) 6,400/mm$^3$, creatinine 1.0 mg/dL, potassium 4.3 mEq/L, total cholesterol 150 mg/dL, glucose 100 mg/dL, alanine aminotranferase (AlAT) 13 U/l, thyroid-stimulating hormone (TSH) 1.47 μIU/mL, creatine kinase myocardial bound (CK-MB) 17.6 U/m, troponin T 9.1 and 8 pg/mL). D-dimer level was not measured. Chest X-ray was normal. An exercise test was performed, terminated at 3 minutes due to angina and development of an intermittent left bundle branch block on the ECG. Echocardiography was not performed during the hospital stay. The patient was referred for coronary angiography. While waiting for a scheduled coronary angiography, she presented to the outpatient cardiology service due to recurrent angina at low levels of exercise. The physical examination was unremarkable. Resting ECG was performed twice and initially showed normal sinus rhythm at 90 bpm and LBBB (Figure 1A). In the second ECG tracing, bundle branch block is initially absent, then incomplete left bundle

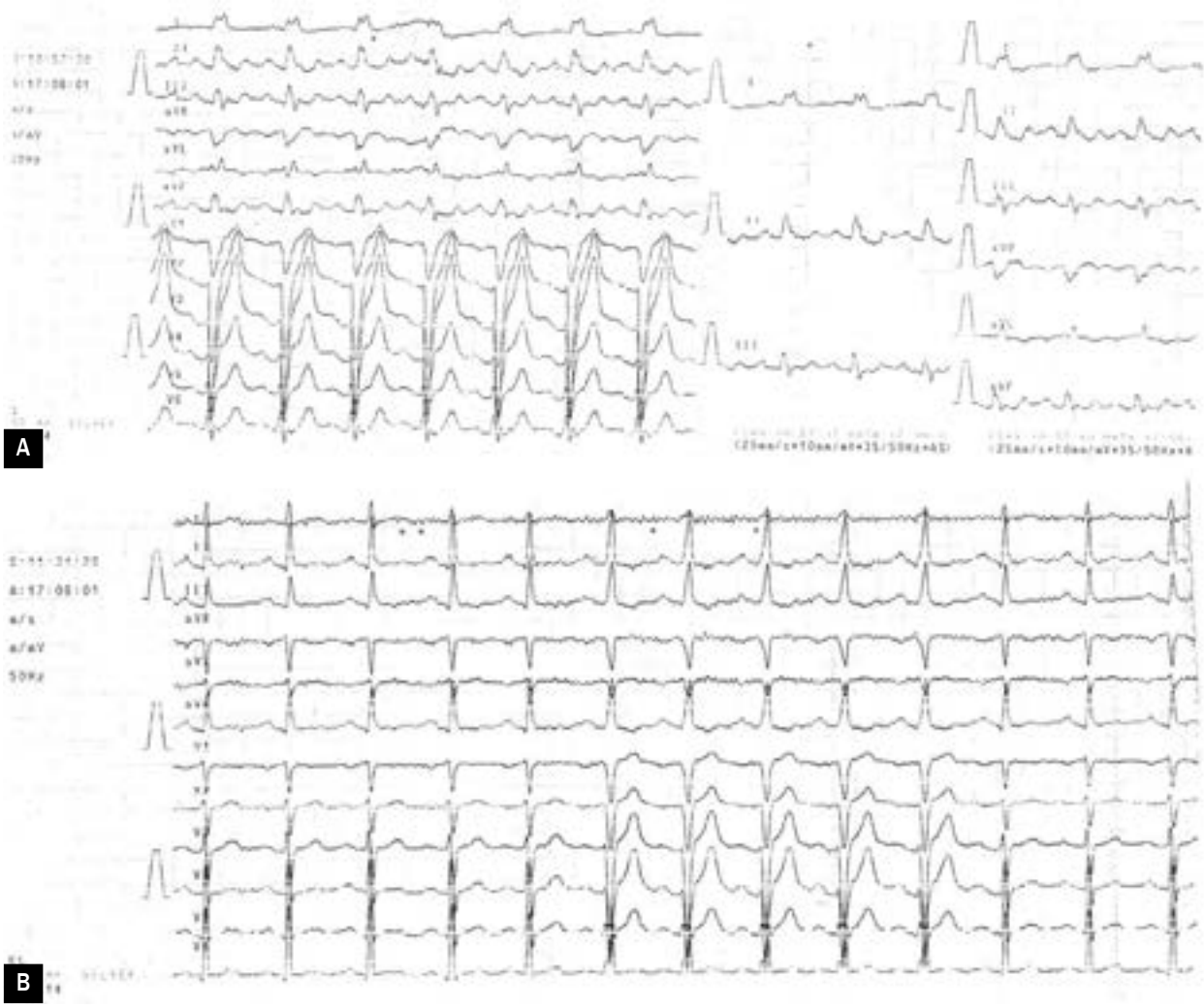


**Figure 1.** Electrocardiogram during the initial visit: **A.** Normal sinus rhythm at 90 bpm, left bundle branch block (LBBB); **B.** Normal sinus rhythm at 90 bpm, intermittent incomplete LBBB

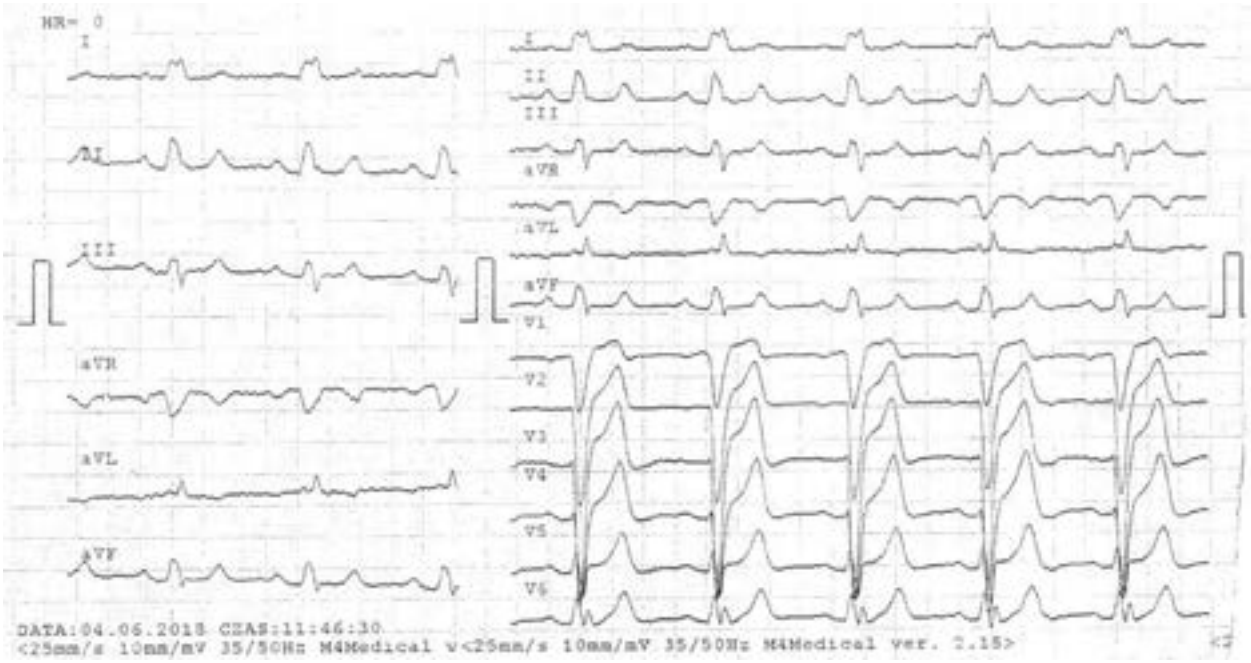


**Figure 2.** Electrocardiogram during the second visit — persisting left bundle branch block

branch block can be seen which subsequently resolves (Figure 1B). Echocardiography showed normal left heart chamber dimensions, modest enlargement of the right atrium and the right ventricle, normal left ventricular ejection fraction (about 65%), intermittent paradoxical movement of the interventricular septum, fused E and A waves of the mitral inflow, shortened pulmonary ejection acceleration time (AcT) (82 ms), moderate tricuspid regurgitation, and increased right ventricular systolic pressure (42.6 mm Hg plus central venous pressure), suggesting a moderate likelihood of pulmonary hypertension. Despite a misleading ECG pattern, a suspicion of pulmonary embolism was made and the patient was referred to a hospital. Currently, the patient presented again for a follow-up visit one year later. The discharge summary from the second hospitalization indicates that on the day the patient was referred to a hospital, D-dimer level was measured (18,000 pg/mL) and pulmonary computed tomography angiography (angio-CT) was performed, showing pulmonary emboli in the pulmonary arteries, distal to the main pulmonary artery bifurcation. Low-risk PE was diagnosed and treatment with rivaroxaban was instituted, initially at 15 mg BID for 3 weeks, followed by 20 mg OD. Continuation of propafenone treatment for prevention of atrial fibrillation was also recommended. During follow-up visit at one year, the patient does not report angina, her exercise tolerance is good, and she does not recall any recent discernible arrhythmia episode. ECG shows sinus rhythm at 65 bpm and left bundle branch block (Figure 2). Echocardiography showed cardiac chambers of normal size, normal systolic function of the left and right ventricle, normal right ventricular systolic pressure (28 mm Hg), and normal pulmonary ejection AcT (122 ms). A suspicion of intraventricular conduction disturbances related to propafenone use was made. Due to sporadic occurrence of arrhythmia, the drug was withdrawn, while bisoprolol 5 mg OD was continued. Following discontinuation of propafenone, follow-up ECG was recorded twice. Both the initial ECG recorded at the primary care 2 weeks after propafenone was stopped and another ECG recorded at the cardiology service one month after drug discontinuation showed no LBBB (Figure 3). The patient did not feel any arrhythmia since discontinuation of propafenone.

## Discussion

The diagnosis of PE is challenging for a physician. Both the clinical presentation and the ECG pattern may help in making the correct diagnosis but may also be misleading. Typical angina is rare in pulmonary embolism and pleuritic chest pain is a much more common finding, and thus history in this case was suggestive of coronary artery disease. Regarding the ECG pattern, findings reported in pulmonary embolism may indicate right ventricular overload, including negative T waves in V1 through V4, QR in V1, S1Q3T3 configuration, and incomplete or complete right bundle branch block. These changes were reported in more severe cases, while sinus tachycardia maybe the only ECG abnormality in milder cases [8]. No literature reports of pulmonary embolism accompanied by left bundle branch block were identified. It seems

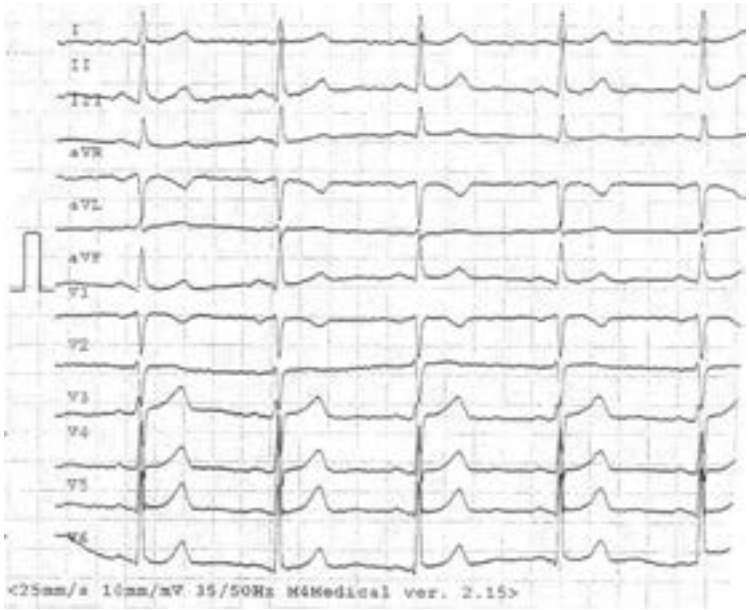


**Figure 3.** Electrocardiogram during the third visit, one month after discontinuation of propafenone. No intraventricular conduction disturbances

that the most likely cause of intraventricular conduction disturbances seen in the reported patient was the use of propafenone. This hypothesis is supported by ECG recorded twice after drug discontinuation and showing no intraventricular conduction disturbances. In the reported case, echocardiography was the key to the diagnosis. The echocardiographic pattern was suggestive of but not diagnostic for PE. The diagnosis was confirmed by angio-CT. Of note, the patient had a history of paroxysmal atrial fibrillation, and accidental findings of pulmonary artery thrombi by multidetector computed tomography were reported in such patients [9, 10]. It is not known whether in this particular case, it was of importance that the patient did not receive anticoagulation before the diagnosis of pulmonary embolism, although such treatment was indicated with the $CHA_2DS_2$-VASc score of 3. Currently, the patient has dual indications for long-term anticoagulation, including both a history of atrial fibrillation with a high risk of thromboembolic complication [a class I indication by the European Society of Cardiology (ESC) guidelines] and unprovoked pulmonary embolism with a low bleeding risk (a class IIa indication by the ESC guidelines).

## Summary and conclusions

The presented case suggests that the diagnostic workup of angina should always include echocardiography which may be the key to the diagnosis, while the ECG pattern may be a diagnostic pitfall.

## Conflict(s) of interest

The author declares no conflicts of interests.


### Streszczenie

W pracy zaprezentowano przypadek pacjentki w wieku 68 lat, która była konsultowana w poradni kardiologicznej z powodu dolegliwości dławicowych w III klasie według Canadian Cardiovascular Society. W badaniu elektrokardiograficznym (EKG) obserwowano intermitujący blok lewej odnogi pęczka Hisa. W badaniu echokardiograficznym uwidoczniono cechy sugerujące zatorowość płucną. Rozpoznanie potwierdzono w angiografii tomografii komputerowej. Przypadek ilustruje, jak duże znaczenie ma badanie echokardiograficzne w diagnostyce różnicowej dolegliwości dławicowych oraz wskazuje, że zapis EKG może niekiedy utrudnić postawienie właściwej diagnozy.



Słowa kluczowe: dławica piersiowa, intermitujący blok lewej odnogi pęczka Hisa, zatorowość płucna

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# Przerwa w terapii empagliflozyną u pacjenta z niewydolnością serca z obniżoną frakcją wyrzutową i hospitalizacja z powodu zaostrzenia niewydolności serca

## A break in pharmacotherapy with empagliflozin in a patient with heart failure with reduced ejection fraction and hospitalization caused by exacerbation of heart failure

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**Streszczenie**

Mężczyznę w wieku 56 lat z ciężką dysfunkcją lewej komory przyjęto na oddział z powodu zaostrzenia objawów przewlekłej niewydolności serca z obniżoną frakcją wyrzutową lewej komory. W trakcie hospitalizacji stosowano standardowe leczenie niewydolności serca, ale także modyfikowano terapię chorób współistniejących, w tym cukrzycy. Na podstawie opisu przypadku klinicznego w artykule przedstawiono aktualny stan wiedzy na temat korzystnego wpływu empagliflozyny na układ sercowo-naczyniowy.

Słowa kluczowe: niewydolność krążenia z obniżona frakcją wyrzutowa lewej komory, empagliflozyna

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## Wstęp

Według wytycznych Europejskiego Towarzystwa Kardiologicznego (ESC, *European Society of Cardiology*) z 2016 roku [1] niewydolność serca (HF, *heart failure*) to zespół typowych objawów podmiotowych (tj. duszność, obrzęki kończyn dolnych, obniżenie tolerancji wysiłku), którym mogą towarzyszyć odchylenia w badaniu przedmiotowym (takie jak poszerzenie żył szyjnych, trzeszczenia nad płucami, obrzęki obwodowe), spowodowane zaburzeniami w budowie i/lub czynności serca powodujące zmniejszony rzut serca i/lub zwiększone ciśnienia wewnątrzsercowe w spoczynku lub w trakcie wysiłku. Do oceny nasilenia ciężkości objawów stosuje się klasyfikację według *New York Heart Association* (NYHA), która — choć słabo koreluje z większością parametrów opisujących funkcję lewej komory — pozostaje istotnym parametrem w ocenie chorego z HF [1]. Wiadomo, że nasilenie objawów w klasyfikacji według NYHA wiąże się ze zwiększonym ryzykiem hospitalizacji, a także zgonu [2, 3].

Ponadto choroby współistniejące mogą nasilać objawy HF, zwiększając tym samym ryzyko hospitalizacji oraz zgonu w przebiegu zaostrzenia HF. Według wytycznych ESC obecność cukrzycy wiąże się z gorszym stanem czynnościowym i gorszym rokowaniem. W badaniu *Framingham* [4] udowodniono, że ryzyko wystąpienia HF u chorego na cukrzycę jest prawie 2,4-krotnie wyższe u mężczyzn oraz 5-krotnie wyższe u kobiet niż u osób niechorujących na cukrzycę. Wykazano także, że wzrost stężenia hemoglobiny glikowanej ($HbA_{1c}$, *glycated haemoglobin*) o 1% powoduje wzrost ryzyka HF o 8% niezależnie od wieku, obecności choroby wieńcowej, wartości ciśnienia tętniczego czy stopnia otyłości [5].

Co więcej, relacja między HF a cukrzycą jest niczym miecz obosieczny, ponieważ pacjentów chorujących na cukrzycę cechuje większe prawdopodobieństwo rozwoju

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HF w związku z procesami toczącymi się w obrębie układu sercowo-naczyniowego. Hiperinsulinemia, hiperglikemia, kwasica oraz insulinooporność to czynniki, które poprzez modyfikację szlaków komórkowych w kardiomiocycie prowadzą do remodelingu serca. Obecnie można wyróżnić dwa dominujące procesy toczące się w sercu chorego na cukrzycę. Pierwszy prowadzi do dysfunkcji lewej komory (LV, *left ventricle*) i wynika głównie z intoksykacji kardiomiocytów poprzez substraty nieprawidłowych procesów metabolicznych w komórce (w tym składowanie wolnych kwasów tłuszczowych, a w konsekwencji stłuszczenie komórek serca; zmiany w mechanizmach regulacji równowagi elektrolitowej wewnątrz- i zewnątrzkomórkowej, a co za tym idzie — właściwości elektrofizjologicznej miokardiocytu). Nie bez znaczenia pozostają także modyfikacje w zakresie szlaków przemian metabolicznych, stres oksydacyjny, dysfunkcja mitochondriów czy uszkodzenie śródbłonka naczyń, co prowadzi do obumarcia komórek mięśnia sercowego. Drugi wynika z przewlekłej reakcji zapalnej i zwiększonej w konsekwencji syntezy kolagenu i nasilonego włóknienia [6].

Wśród chorych na cukrzycę częściej rejestrowano dysfunkcje skurczową i rozkurczową oraz arytmię. Polineuropatia cukrzycowa i przewaga aktywności układu współczulnego nad aktywnością układu przywspółczulnego wraz ze zmianami w budowie histopatologicznej serca (proces włóknienia) oraz obniżeniem frakcji wyrzutowej LV predysponują u tych chorych do rozwoju arytmii, w tym zagrażającej życiu arytmii komorowej.

## Opis przypadku

Mężczyzna w wieku 56 lat został przyjęty do szpitala z powodu pogorszenia tolerancji wysiłku do III klasy według NYHA, duszności oraz narastania obrzęków kończyn dolnych do wysokości kolan z ciśnieniem tętniczym 135/85 mm Hg (chory ciepły, mokry wg klasyfikacji Forrestera).

W wywiadzie stwierdzono:

- ciężką dysfunkcję skurczową LV;
- stan po implantacji kardiowertera-defibrylatora z funkcją resynchronizacji (CRT-D, *cardiac resynchronization therapy with defibrillator*);
- umiarkowaną stenozę aortalną;
- przewlekłą chorobę wieńcową — stan po zawale serca z uniesieniem odcinka ST ściany dolnej i prawej komory leczony dwukrotną nieskuteczną próbą rewaskularyzacji prawej tętnicy wieńcowej powikłaną przemijającym blokiem przedsionkowo-komorowym III stopnia; stan po zawale serca bez uniesienia odcinka ST leczonym angioplastyką gałęzi okalającej z implantacją dwóch stentów uwalniających lek (DES, *drug-eluting stent*);
- nadciśnienie tętnicze (maks. ciśnienie tętnicze 170/90 mm Hg);
- cukrzycę typu 2 w trakcie terapii metforminą;
- hiperlipidemię mieszaną w trakcie terapii statyną;
- otyłość (wskaźnik masy ciała [BMI, *body mass index*] 40,56 kg/m$^2$, wzrost 172 cm, masa ciała 120 kg), zespół metaboliczny;
- napadowe migotanie przedsionków.

W badaniach laboratoryjnych spośród istotnych odchyleń od normy stwierdzono obniżone parametry nerkowe oraz podwyższone stężenia glukozy i triglicerydów oraz N-końcowego propeptydu natriuretycznego typu B (NT-proBNP, *N-terminal pro-B-type natriuretic peptide*), aczkolwiek — ze względu na otyłość — wynik był niewspółmiernie niski do objawów występujących u chorego (tab. 1 — pobyt 1.).

W elektrokardiogramie (EKG) przy przyjęciu rejestrowano miarowy zatokowy rytm serca (HR, *heart rate*) około 90/min ze skuteczną stymulacją resynchronizującą o typie AS-BiVP (*atrial synchronous biventricular pacing*). Wyczuwanie i stymulacja były prawidłowe.

W trakcie hospitalizacji wykonano badanie echokardiograficzne serca, potwierdzając ciężką dysfunkcję skurczową lewej komory (LVEF [*left ventricular ejection fraction*] 24%, wymiar końcoworozkurczowy lewej komory [LVEDd, *left ventricular end-diastolic diameter*] 65 mm, stosunek objętości końcoworozkurczowej do objętości końcowoskurczowej lewej komory [EDV/ ESV, *end-diastolic volume/end-systolic volume*] 250/190 ml) z odcinkowymi zaburzeniami kurczliwości ścian dolnej i tylnej oraz z umiarkowanym zwężeniem zastawki tętnicy głównej i upośledzoną funkcją skurczową powiększonej prawej komory (amplituda ruchu pierścienia zastawki trójdzielnej [TAPSE, *tricuspid annular plane systolic excursion*] 16 mm, S' 9 cm/s, wymiar proksymalny prawej komory [RVD *prox, right ventricular diameter proximal*] 35 mm).

W trakcie hospitalizacji chorego poddano intensywnemu moczopędnemu leczeniu dożylnemu oraz utrzymano standardowe leczenie HF (inhibitorami konwertazy angiotensyny [ACE, *angiotensin-converting enzyme*], beta-adrenolitykami, antagonistami receptora mineralokortykoidowego [MRA, *mineralocorticoid receptor antagonists*]). Po uzyskaniu poprawy stanu ogólnego oraz zmniejszeniu objawów HF przeprowadzono 6-minutowy test marszu (6-MWT, *6-minute walk test*), w którym chory osiągnął 290 m.

W wykonanej kontrolnej koronarografii uwidoczniono dobry efekt implantacji stentów do gałęzi okalającej oraz amputację prawej tętnicy wieńcowej z wytworzonym krążeniem obocznym. Chorego zakwalifikowano do dalszego leczenia zachowawczego.

W MAGGIC (*Meta-Analysis Global Group in Chronic Heart Failure*) *score* rokowanie oceniono na poważne (26 pkt., śmiertelność roczna 17,5%, śmiertelność 3-letnia 39,7%.) W okresie przedwypisowym zmodyfikowano terapię cukrzycy, dołączając do metforminy empagliflozynę.

Chorego wypisano z zaleceniem dalszego leczenia ambulatoryjnego na następującym leczeniu: dabigatran 2 razy 110 mg, atorwastatyna 20 mg, bisoprolol 7,5 mg, amiodaron 200 mg, ramipril 5 mg, lerkanidipina 10 mg,

**Tabela 1.** Wyniki podstawowych badań laboratoryjnych podczas kolejnych hospitalizacji

| Parametr | Wynik | | | Norma |
|---|---|---|---|---|
| | Pobyt 1. | Pobyt 2. | Pobyt 3. | |
| WBC [× $10^3/\mu l$] | 7,30 | 10,57 | 6,84 | 4,00–11,00 |
| RBC [× $10^6/\mu l$] | 5,32 | 4,38 | 4,84 | 4,20–6,10 |
| Hb [g/dl] | 15,9 | 14,2 | 15,1 | 14,0–18,0 |
| TC [mmol/l] | 3,83 | Brak danych | 5,07 | 3,00–5,00 |
| LDL [mmol/l] | 1,25 | Brak danych | 2,59 | < 1,8 |
| HDL [mmol/l] | 0,95 | Brak danych | 1,24 | > 1,00 |
| TG [mmol/l] | 3,58 | Brak danych | 2,73 | < 1,70 |
| Glukoza | 8,55 | 8,28 | 7,97 | 4,1–5,5 |
| Kreatynina [μmol/l] | 148 | 150 | 131,7 | 59–104,0 |
| eGFR [ml/min/1,73 $m^2$] | 46,5 | 54,44 | 67 | > 60 |
| Na [mmol/l] | 136 | 141 | 140,1 | 136–146 |
| K [mmol/l] | 4,38 | 4,3 | 4,26 | 3,5–5,1 |
| AspAT [j./l] | 34 | Brak danych | 36,7 | 0,0–35 |
| AlAT [j./l] | 35 | 30 | 28,8 | 0,0–45 |
| CRP [mg/l] | 2,9 | 8,48 | 2,8 | 0,0–6,0 |
| TSH [μjm./l] | 0,672 | Brak danych | 0,588 | 0,27–4,20 |
| NT-proBNP [pg/ml] | 488 | Brak danych | 324,7 | < 125 |
| TnT [ng/ml] | Brak danych | Brak danych | 39 | < 14 |

WBC (*white blood count*) — liczba krwinek białych; RBC (*red blood count*) — liczba krwinek czerwonych; Hb (*haemoglobin*) — hemoglobina; TC (*total cholesterol*) — cholesterol całkowity; LDL (*low-density lipoproteins*) — lipoproteiny o niskiej gęstości; HDL (*high-density lipoproteins*) — lipoproteiny o wysokiej gęstości; TG (*triglycerides*) — triglicerydy; eGFR (*estimated glomerular filtration rate*) — szacowany współczynnik filtracji kłębuszkowej; Na — wapń; K — potas; AspAT (*aspartate aminotransferase*) — aminotransferaza asparaginianowa; AlAT (*alanine aminotransferase*) — aminotransferaza alaninowa; CRP (*C-reactive protein*) — białko C-reaktywne; TSH (*thyroid-stimulating hormone*) — hormon tarczycy; NT-proBNP (NT-proBNP, *N-terminal pro-B-type natriuretic peptide*) — N-końcowy propeptyd natriuretyczny typu B; TnT (*troponin T*) — troponina T

eplerenon 50 mg, pantoprazol 20 mg, empagliflozyna 10 mg, torasemid 10 mg, metformina 3 razy 850 mg.

W trakcie kontrolnej wizyty w poradni kardiologicznej po około 2 miesiącach od hospitalizacji obserwowano stabilny stan kliniczny i zadowalającą tolerancja wysiłku II klasy według NYHA; stężenie NT-proBNP wyniosło 153 pg/dl. W kontroli CRT rejestrowano istotne zmniejszenie impedancji korespondujące z poprawą kliniczną. Jednak po 4 miesiącach chory był hospitalizowany z powodu kolejnego zaostrzenia HF, ze stężeniem NT-proBNP 1586 pg/ml, i podczas tej hospitalizacji został włączony do programu terapii lekiem sakubitril/walsartan w dawce 97/103 mg. Przez ponad rok pozostawał stabilny klinicznie, nie wymagając hospitalizacji z powodu nasilenia HF.

Kolejna hospitalizacja wiązała się z infekcją dróg oddechowych, w przebiegu której doszło do zaostrzenia HF. Chorego hospitalizowano na rejonowym oddziale chorób wewnętrznych z powodu duszności o typie *ortopnoë*, kaszlu z odkrztuszaniem żółto-szarej wydzieliny w przebiegu infekcji dróg oddechowych i narastania obrzęków kończyn dolnych. W badaniu ogólnym moczu przy przyjęciu wykryto obecność glukozy, a glikemia z krwi żylnej wynosiła 149 mg/dl (tab. 1 — pobyt 2.), było to zatem efektem leczenia empagliflozyną. Po zastosowaniu antybiotykoterapii oraz dożylnego leczenia moczopędnego chorego wypisano do domu z poprawą kliniczną. Nie kontynuowano terapii empagliflozyną.

Po kontrolnej wizycie (ok. 3 miesiące od ostatniej hospitalizacji) w poradni kardiologicznej, ze względu na znaczne zwiększenie masy ciała (ok. 10 kg), nasilenie obrzęków kończyn dolnych do kolan oraz nasilenie HF do III/IV klasy według NYHA chorego skierowano do szpitala z rozpoznaniem zaostrzenia HF (wyniki badań laboratoryjnych w tab. 1 — pobyt 3.). Zastosowano pełne leczenie niewydolności krążenia, w tym dożylne leki moczopędne i wlew z lewosimendanu, uzyskując znaczną poprawę stanu ogólnego, zmniejszenie masy ciała i ograniczenie obrzęków oraz duszności. W okresie okołowypisowym, zważywszy na HR powyżej 75/min w spoczynku, do beta-adrenolityku dołączono iwabradynę. Wynik $HbA_{1c}$ miał wartość 9,10%, co świadczyło o niezadawalających glikemiach w ostatnich 3 miesiącach rzędu 11,8 mmol/l (tj. 212 mg/dl).

U opisywanego pacjenta dotychczasowe postępowanie niefarmakologiczne okazało się, niestety, nieskuteczne. Należy podkreślić, że z jednej strony otyłość olbrzymia (BMI 40,56 $g/m^2$) łączy się z hiperinsulinemią, co prowadzi do aktywacji układu renina–angiotensyna–aldosteron (RAA) i, wtórnie, nasilenia HF. Z drugiej strony stosowanie

u tego typu chorego insuliny, która powoduje retencję sodu i przy jednoczesnym zmniejszaniu glikozurii może nasilać retencję płynów, nie byłoby optymalnym rozwiązaniem. Dlatego po osiągnięciu stabilności klinicznej w okresie okołowypisowym powrócono do leczenia empagliflozyną. W 6-MWT chory osiągnął dystans marszu 330 m. Poddano go edukacji dotyczącej HF i cukrzycy.

Chorego wypisano do domu z zaleceniami niefarmakologicznymi oraz z następującymi zaleceniami dotyczącymi farmakoterapii: dabigatran 2 razy 110 mg, sakubitril/walsartan 2 razy 97/103 mg, iwabradyna 2 razy 5 mg, atorwastatyna 80 mg, bisoprolol 10 mg, amiodaron 200 mg, lerkanidipina 10, eplerenon 25 mg, pantoprazol 20 mg, empagliflozyna 10 mg, furosemid 40 mg, torasemid 20 mg, metformina 3 razy 1000 mg. W trakcie kolejnej wizyty kontrolnej po miesiącu stosowania przez chorego powyższego leczenia obserwowano stabilny obraz kliniczny, ciśnienie tętnicze 125/70 mm Hg i glikemię do 150 mg/dl na czczo oraz zmniejszenie masy ciała o 5 kg. W ocenie echokardiograficznej zarejestrowano nieznaczną poprawę LVEF (28%) i zmniejszenie wymiarów LVEDd (61 mm). W ergospirometrii chory przy obciążeniu 100 W osiągnął objętość tlenu zużywanego przez organizm ($VO_2$) 12,74 ml/kg mc./min, współczynnik wymiany oddechowej (RER, *respiratory exchange ratio*) 1,16, $VO_2$ na tak zwanym progu wentylacyjnym (AT, *anaerobic threshold*) 10,42 ml/kg mc./min. Utrzymano dotychczasową terapię.

## Dyskusja

Przedstawiono przypadek pacjenta z niewydolnością serca i obniżoną frakcją wyrzutową lewej komory (HFrEF, *heart failure with reduced ejection fraction*) leczonego zgodnie z aktualnymi wytycznymi najnowocześniejszą terapią, w tym antagonistą receptora AT1 dla angiotensyny II i inhibitora neprilizyny (ARNI, *angiotensin receptor-nephrilysin inhibitor*) oraz empagliflozyną. Według wytycznych empagliflozyna ma zalecenia klasy IIa przy poziomie wiarygodności danych B i jest rekomendowana w celu zapobiegania HF lub opóźniania jej wystąpienia i przedłużania życia.

Inhibitory kotransportera sodu i glukozy typu 2 (SGLT2, *sodium-glucose co-transporter 2*) to jedne z najnowocześniejszych leków stosowanych w cukrzycy. Główny efekt ich działania wiąże się z wpływem na kanaliki nerkowe i zwiększeniem wydalania glukozy z moczem (glukozurią) poprzez zahamowanie jej zwrotnego transportu. Dzięki regulacji siły działania w zależności od stężenia glukozy we krwi ryzyko hipoglikemii w trakcie terapii pozostaje stosunkowo niskie, co umożliwia ich łączenie z praktycznie każdą grupą leków przeciwcukrzycowych. Spodziewane obniżenie wartości $HbA_{1c}$ w trakcie stosowania wyżej wspomnianej grupy leków wynosi 0,4–0,9 [7]. Ze względu na mechanizm transportu zwrotnego u tych chorych glukozurii towarzyszy natriureza. Wobec powyższego leki te charakteryzują się działaniem moczopędnym, które prowadzi do zmniejszenia objętości krwi krążącej, zmniejszenia masy ciała (m.in. wynikającej u chorych z HF z przewodnienia), obniżenia ciśnienia tętniczego i wzrostu hematokrytu [8]. Ponadto wyżej wymieniona grupa leków pozytywnie wpływa na inne parametry, takie jak otyłość brzuszna czy zmniejszenie stężenia kwasu moczowego czy mikroalbuminurii [9].

W coraz większej liczbie artykułów pojawiają się dowody korzystnego wpływu stosowania empagliflozyny na zmniejszenie ryzyka zdarzeń sercowo-naczyniowych ([MACE, *major adverse cardiac event*] określonych jako zgon z przyczyn sercowo-naczyniowych lub udar mózgu czy zawał serca niezakończony zgonem), jak również zmniejszenie liczby hospitalizacji z powodu zaostrzenia niewydolności krążenia — to efekt nieosiągany przy użyciu leków z innych grup stosowanych w farmakoterapii cukrzycy.

W trakcie badania EMPA-REG OUTCOME [10] wykazano 35-procentową redukcję ryzyka hospitalizacji z powodu zaostrzenia HF w grupie stosującej empagliflozynę. Ze względu na fakt, że badanie EMPA-REG OUTCOME nie było przeznaczone dla populacji z HF, zaprojektowano kolejne badania z udziałem tej populacji chorych, by ustalić miejsce empagliflozyny w terapii pacjentów z HF.

W badaniu CVD-REAL 2 [11] obejmującym ponad 300 tys. chorych na cukrzycę typu 2 z 6 krajów potwierdzono, że stosowanie leków z wyżej wymienionej grupy obniża ryzyko hospitalizacji z powodu zaostrzenia HF oraz śmiertelność. Według autorów badania możliwy jest efekt klasy, gdyż stosowanie innych inhibitorów SGLT2, a nie tylko empagliflozyny (stanowiącej < 10% leków z tej grupy w powyższym badaniu) potwierdziło zmniejszenie liczby hospitalizacji z powodu HF oraz redukcję częstości innych niepożądanych zdarzeń sercowo-naczyniowych (tj. udaru mózgu, zawału serca) obserwowaną w badaniu EMPA-REG OUTCOME. W tabeli 2 przedstawiono najważniejsze, przeprowadzone dotychczas badania z zastosowaniem inhibitorów SGLT2 [10, 12, 13].

Mechanizmy wpływające na tak zaskakujące wyniki obniżenia ryzyka zdarzeń sercowo-naczyniowych przez inhibitory SGLT2 nie są do końca poznane. Wydaje się jednak oczywiste, że nie wynikają one jedynie z wpływu na SGLT2 i kontroli glikemii, między innymi ze względu na niską ekspresję genów dla SGLT2 na powierzchni kardiomiocytów, a także wczesny efekt działania wyżej wymienionych leków na istotne punkty końcowe oraz brak korelacji między glikemią czy wartością $HbA_{1c}$ w trakcie wizyt kontrolnych a redukcją liczby hospitalizacji z powodu HF.

Wśród istotnych czynników wymienia się wpływ tych substancji na hemostazę jonową w komórkach miokardium chorych na cukrzycę. Prawidłowe stężenie jonów wapnia ($Ca^{2+}$), a także szybkie zmiany ich wewnątrzkomórkowego stężenia odgrywają kluczową rolę w transmisji sygnału komórkowego, a więc odpowiadają za prawidłową regulację HR czy skurczu miokardiocytów. Na dynamikę zmian

**Tabela 2.** Wybrane badania kliniczne dotyczące wpływu inhibitorów kotransporterów sodu i glukozy typu 2 (SGLT2, *sodium-glucose co-transporter 2*) na ryzyko sercowo-naczyniowe (na podstawie [10–13])

| Parametr | Nazwa badania | | | | | |
|---|---|---|---|---|---|---|
| | EMPA-REG OUTCOME [10, 12] | CVD-REAL 2 [11, 12] | CVD-REAL [12] | EASEL [12] | CANVAS/ /CANVAS-R [12] | DECLARE--TIMI 58 [13] |
| Rodzaje stosowanych inhibitorów SGLT2 | Empagliflozyna | Dapagliflozyna(75%), empagliflozyna (9%), ipragliflozyna (8%), kanagliflozyna (4%), tofogliflozyna (3%), luseogliflozyna (1%) | Kanagliflozyna (53%), dapagliflozyna (42%), empagliflozyna (5%) | Kanagliflozyna (58%), empagliflozyna (26%), dapagliflozyna (16%) | Kanagliflozyna | Dapagliflozyna |
| Liczba uczestników badania (n) | > 7000 | > 400 000 | > 300 000 | > 25 000 | > 10 000 | > 17 000 |
| Zawał serca | 0,87 (0,70–1,09) | 0,81 (0,74–0,88) | Brak danych | 0,81 (0,64–1,03) | 0,89 (0,73–1,09) | 0,89 (0,77–1,01) |
| Udar mózgu | 1,18 (0,89–1,56) | 0,68 (0,55–0,84) | Brak danych | 0,85 (0,66–1,10) | 0,87 (0,69–1,09) | 1,01 (0,84–1,21) |
| Śmiertelność | 0,68 (0,57–0,82) | 0,51 (0,37–0,70) | 0,49 (0,41–0,57) | 0,57 (0,49–0,66) | 0,87 (0,74–1,01) | 0,93 (0,82–1,04) |
| Hospitalizacja z powodu niewydolności serca | 0,65 (0,50–0,85) | 0,64 (0,50–0,82) | 0,61 (0,51–0,73) | 0,57 (0,45–0,73) | 0,67 (0,52–0,87) | 0,73 (0,61–0,88) |

stężenia jonów wapnia wpływa stężenie jonów sodu regulowane między innymi przez pompę sodowo-potasową, pompę $Na^+/H^+$ (NHE, *$Na^+$-$H^+$ exchange*). Hemostaza — zarówno sodowa, jak i wapniowa — jest zachwiana w komórkach serca chorych na cukrzycę. W wyniku hipoksji, nasilenia wewnątrzkomórkowych procesów anaerobowych dochodzi do wytworzenia kwasu mlekowego, a w efekcie zmniejszenia pH wewnątrzkomórkowego i wyrównawczego uruchomienia pompy $Na^+/H^+$, co skutkuje przeładowaniem cytoplazmy jonami sodowymi [14].

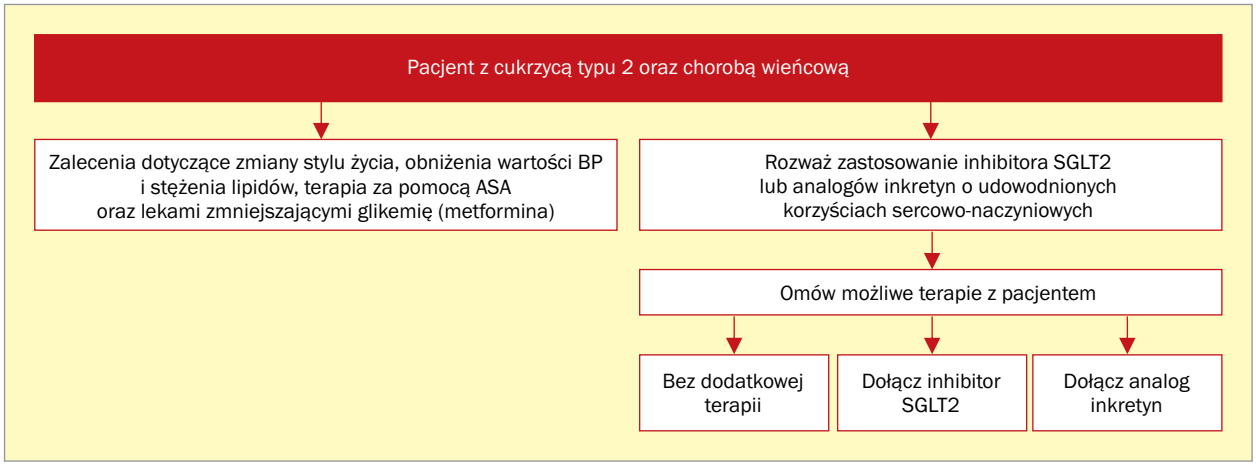
Inhibitory SGLT2, poprzez zmniejszenie wewnątrzkomórkowego stężenia $Na^+$, przesunięcie jonów wapnia do mitochondriów, a w konsekwencji poprawienie siły skurczu miocytów, prowadzą do poprawy funkcji skurczowej serca i zmniejszenia aktywacji układu współczulnego, co wydaje się szczególnie istotne w odniesieniu do serca chorego z obniżoną frakcją wyrzutową lewej komory, na przykład w przebiegu choroby wieńcowej, jak u opisanego pacjenta.

Według innej teorii stosowanie inhibitorów SGLT2 zmniejsza stres oksydacyjny (który odgrywa istotną rolę w utrzymaniu przewlekłej reakcji zapalnej w tkance mięśnia sercowego chorego na cukrzycę, a w konsekwencji prowadzi między innymi do apoptozy i włóknienia, przyczyniając się do niekorzystnego remodelingu serca), zmniejsza produkcję wolnych rodników i modyfikuje przemianę kwasów tłuszczowych w komórce, preferując jako substrat reakcji kwas betahydroksymasłowy, który jest najbardziej energetycznie korzystnym związkiem [14].

Warto także wspomnieć o bezpiecznym profilu empagliflozyny. Stosowana w monoterapii wiąże się z niskim ryzykiem hipoglikemii. Ze względu na główny efekt hipoglikemizujący, związany głównie z diurezą osmotyczną, wymaga względnie prawidłowej funkcji nerek, natomiast jednym z najczęstszych powikłań w związku z glukozurią są zakażenia układu moczowo-płciowego. Jednakże powikłane zakażenia dróg moczowych (np. odmiedniczkowe zapalenie nerek lub posocznica moczopochodna) występowały z podobną częstością u pacjentów otrzymujących empagliflozynę i placebo. W przedstawianym przypadku w trakcie terapii nie obserwowano infekcji dróg moczowych, rejestrowano natomiast zmniejszenie masy ciała i poprawę profilu glikemii, a sam lek był dobrze tolerowany przez chorego. Warto jeszcze wspomnieć o innym powikłaniu związanym prawdopodobnie z modyfikacją szlaku oksydacji tłuszczów, tj. kwasicą ketonową przy względnie prawidłowych glikemiach. Jednak w przeprowadzonych badaniach randomizowanych udowodniono, że ryzyko takiego powikłania jest bardzo niskie, zwłaszcza u chorych niewymagających insulinoterapii [12].

Mechanizmy prowadzące do nasilenia HF wynikają głównie z trzech przyczyn — zwiększenia obciążenia wstępnego (*preload*), obciążenia następczego (*afterload*) oraz zdolności „skurczowej" miokardiocytów. Według obecnego stanu wiedzy inhibitory SGLT2 działają wielokierunkowo. Poprzez diurezę osmotyczną i zmniejszenie ilości krwi krążącej zmniejszają *preload*. W wyniku obniżenia ciśnienia tętniczego oraz oporu naczyniowego zmniejszają *afterload*. Ponadto, wpływając na hemostazę jonów sodowych i wapniowych w komórkach, wpływają na siłę i „jakość" skurczu miokardiocytów.

W 2018 roku w Ameryce [12] ukazał się konsensus, w którym wysoko pozycjonowano inhibitory SGLT2 w algorytmie leczenia chorych z cukrzycą typu 2 i chorobą wieńcową. Już na poziomie edukacji dotyczącej zmiany stylu życia oraz włączenia metforminy zaleca się




**Rycina 1.** Algorytm leczenia pacjenta z cukrzycą typu 2 oraz chorobą wieńcową (na podstawie [12]); BP (*blood pressure*) — ciśnienie tętnicze; ASA (*acetylsalicylic acid*) — kwas acetylosalicylowy; SGLT2 (*sodium-glucose co-transporter 2*) — kotransporter sodu i glukozy typu 2

rozważenie dołączenia między innymi inhibitora SGLT2 (*patrz* ryc. 1).

## Wnioski

Empagliflozyna jest nowym narzędziem terapeutycznym dla pacjentów z HFrEF i współistniejącą cukrzycą. Przedstawiony przypadek kliniczny pacjenta obciążonego licznymi chorobami towarzyszącymi wskazuje na duży udział empagliflozyny w terapii HFrEF, o czym świadczy wystąpienie zaostrzenia niewydolności serca z koniecznością hospitalizacji po odstawieniu leku u pacjenta leczonego optymalną standardową terapią dla HFrEF z użyciem ARNI. Opisany przypadek pokazuje jak istotne może być wczesne wdrażanie nowoczesnej farmakoterapii i stosowanie zaleceń towarzystw eksperckich w codziennej praktyce klinicznej.

## Konflikt interesów

Udział w badaniu klinicznym z zastosowaniem empagliflozyny.


### Abstract

A 56 year-old man with severe dysfunction was admitted to the Department due to exacerbation of chronic heart failure with reduced left ventricular ejection fraction. During hospitalization the standard treatment of heart failure was used, but also there was a modification of pharmacotherapy in diabetes. Based on the clinical case description, the article shows the current state of knowledge on the beneficial effects of empagliflozin on the cardiovascular system.



Key words: heart failure with reduced ejection fraction, empagliflozin

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# A break in pharmacotherapy with empagliflozin in a patient with heart failure with reduced ejection fraction and hospitalization caused by exacerbation of heart failure

## Przerwa w terapii empagliflozyną u pacjenta z niewydolnością serca z obniżoną frakcją wyrzutową i hospitalizacja z powodu zaostrzenia niewydolności serca

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### Abstract

A 56 year-old man with severe left ventricular dysfunction was admitted due to exacerbation of chronic heart failure with reduced left ventricular ejection fraction. During hospitalisation, standard heart failure treatment was used, but with a modification of pharmacotherapy to address concurrent conditions including diabetes. Here we discuss this case and the current state of knowledge regarding the beneficial effects of empagliflozin.

Key words: heart failure with reduced ejection fraction, empagliflozin

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## Introduction

Guidelines from the European Society of Cardiology (ESC) [1] state that heart failure (HF) is a set of typical secondary symptoms including shortness of breath, swelling of the lower limbs, and reduced tolerance to strain. These symptoms can be accompanied by neck vasodilation, lung crackles, and peripheral oedema caused by disturbances in cardiac structure and/or function, causing reduced cardiac output and/or increased intracardiac pressure at rest and during strain. Symptom intensity is based on the New York Heart Association's classification, an important measure for assessing patients with heart failure, even though it correlates only weakly with most of the parameters relevant to left ventricular function [1]. It is recognised that any exacerbation of symptoms in the NYHA classification is linked to higher risks of hospitalisation and death [2, 3].

Moreover, concurrent conditions can exacerbate symptoms of HF, thus increasing the risk of hospitalisation and death due to worsening HF. According to ESC guidelines, the additional presence of diabetes is linked to reduced physical function and a worse prognosis. Studies by Framingham [4] showed that the risk of HF in a diabetic patient is almost 2.4 times higher in men, and 5 times higher in women, compared to non-diabetic individuals. It was also shown that a 1% increase in glycated haemoglobin causes an 8% increase in the risk of heart failure, irrespective of age, presence of coronary heart disease, blood pressure, or obesity [5].

In addition, the relationship between heart failure and diabetes is a double-edged sword, because diabetic patients are at greater risk of developing heart failure due to processes taking place in the cardiovascular system. Hyperinsulinaemia, hyperglycaemia, acidosis and insulin

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resistance are factors causing heart remodelling by modifying cellular pathways in cardiomyocytes. Two dominant processes in the diabetic heart have been identified. The first is left ventricular (LV) dysfunction caused mostly by the intoxication of cardiomyocytes by the substrates of incorrect metabolic processes taking place in the cell, including storage of free fatty acids, leading to lipidosis of heart cells, altered intra- and extracellular metabolite balance, and cardiomyocyte electrophysiological properties. In this respect, one should also consider modifications to metabolic pathways, mitochondrial dysfunction and oxidative stress, and damage to the vascular endothelium, which can all lead to heart muscle necrosis. The second process is that of chronic inflammation, which is associated with increased collagen synthesis and fibrosis [6].

Diabetic patients commonly have systolic and diastolic dysfunction and arrhythmia. Diabetic polyneuropathy and the involvement of the sympathetic nervous system, along with fibrotic changes in the heart and reduced ejection function, predispose these patients to the development of arrhythmias, including life-threatening ventricular arrhythmias.

## Case description

A 56 year-old male was admitted with class III heart failure according to the NYHA, i.e. shortness of breath, oedema of the lower limbs up to the knees, and blood pressure of 135/85 mm Hg. The patient was warm and damp as per Forrester's classification.

Patient history:

- severe systolic dysfunction of the LV;
- implantation of a cardiac resynchronisation therapy defibrillator (CRT-D);
- moderate aortic stenosis;
- chronic coronary heart disease – cardiac infarction with ST-segment elevation in the wall of the lower and right ventricles treated with two unsuccessful attempts at revascularisation of the right coronary artery, complicated by transient third degree atrioventricular block; following the infarction, ST-segment was no longer elevated, and was treated with angioplasty of the circumflex branch of the coronary artery with implantation of two drug-eluting stent (DES) stents;
- arterial hypertension (blood pressure max. 170/90 mm Hg);
- type 2 diabetes currently treated with metformin therapy;
- mixed hyperlipidemia currently treated with statins;
- obesity [body mass index (BMI) 40.56 kg/m$^2$, height: 172 cm, body weight: 120 kg], metabolic syndrome;
- paroxysmal atrial fibrillation.

Laboratory studies found significant deviations from the norm in the following parameters: reduced kidney parameters, increased levels of glucose, triglycerides and N-terminal pro-B-type natriuretic peptide (NT-proBNP), though, due to the patient's obesity, these parameters are consistent with the other symptoms presented by the patient (Table 1 — stay 1).

On admission to the hospital, an electrocardiogram (ECG) found a regular sinus rhythm of 90/min with type atrial synchronous biventricular pacing (AS-BiVP) stimulation, and correct stimulation and sensing was found.

During hospitalisation, another ECG confirmed severe systolic dysfunction of the left ventricle [left ventricular ejection fraction (LVEF) 24%, left ventricular end-diastolic diameter (LVEDd) 65 mm, end-diastolic volume/exhalation volume [EDV/EV] 250/190 mL) with segmental dysfunction of contractility of the lower and back walls and moderate aortic stenosis and impaired contractile function of the enlarged right ventricle [tricuspid annular plane systolic excursion (TAPSE) 16 mm, S' 9 cm/s, right ventricular diameter proximal (RVD prox) 35 mm].

During hospitalisation, the patient received intensive intravenous diuretics and standard therapy for HF was maintained [angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRA)]. The patient's general condition and heart failure symptoms improved. A 6-minute walk test (6-MWT) was conducted, in which the patient achieved 290 m.

A control coronary angiography showed a good response to the stent implanted in the circumflex branch and the amputated right coronary artery, creating collateral circulation. The patient qualified for further conservative treatment.

The patient's MAGIC (Meta-Analysis Global Group in Chronic Heart Failure) prognostic score was found to be serious — 26 points, with 1-year mortality of 17.5% and 3-year mortality of 39.7%. Prior to being discharged, the patient's diabetes treatment was modified with the addition of empagliflozin to metformin.

The patient was discharged to outpatient care on the following medications: dabigatran 2 × 110 mg, atorvastatin 20 mg, bisoprolol 7.5 mg, amiodarone 200 mg, ramipril 5 mg, lercanidipine 10 mg, eplerenone 50 mg, pantoprazole 20 mg, empagliflozin 10 mg, torasemide 10 mg, and metformin 3 × 850 mg.

Two months after hospitalisation, during a follow-up visit at a cardiology clinic, a stable clinical state was observed with a satisfactory (NYHA class II) strain tolerance, and with NT-proBNP of 153 pg/dL. The CRT found a significant reduction in obstruction, corresponding with improved clinical outcomes.

After four months, the patient was once again hospitalised due to an exacerbation of HF, with NT-proBNP of 1,586 pg/mL, and during this stay he was included in a sacubitril/valsartan treatment programme at a dosage

**Table 1.** Results of basic laboratory studies during consecutive hospitalisations

| Parameter | Result | | | Normal |
|---|---|---|---|---|
| | Stay 1 | Stay 2 | Stay 3 | |
| WBC [× $10^3/\mu L$] | 7.30 | 10.57 | 6.84 | 4.00–11.00 |
| RBC [× $10^6/\mu L$] | 5.32 | 4.38 | 4.84 | 4.20–6.10 |
| Hb [g/dL] | 15.9 | 14.2 | 15.1 | 14.0–18.0 |
| TC [mmol/L] | 3.83 | Not determined | 5.07 | 3.00–5.00 |
| LDL [mmol/L] | 1.25 | Not determined | 2.59 | < 1.80 |
| HDL [mmol/L] | 0.95 | Not determined | 1.24 | > 1.00 |
| TG [mmol/L] | 3.58 | Not determined | 2.73 | < 1.70 |
| Glucose [mg/dL] | 8.55 | 8.28 | 7.97 | 4.1–5.5 |
| Creatine [μmol/L] | 148 | 150 | 131.7 | 59–104.0 |
| eGFR [mL/min/1.73 $m^2$] | 46.5 | 54.44 | 67 | > 60 |
| Na [mmol/L] | 136 | 141 | 140.1 | 136–146 |
| K [mmol/L] | 4.38 | 4.30 | 4.26 | 3.5–5.1 |
| AspAT [U/L] | 34 | Not determined | 36.7 | 0–35 |
| AlAT [U/L] | 35 | 30 | 28.8 | 0–45 |
| CRP [mg/L] | 2.9 | 8.48 | 2.8 | 0–6.0 |
| TSH [μIU/L] | 0.672 | Not determined | 0.588 | 0.27–4.20 |
| NT-proBNP [pg/mL] | 488 | Not determined | 324.7 | < 125 |
| TnT [ng/mL] | Not determined | Not determined | 39 | < 14 |

WBC — white blood count; RBC — red blood count; Hb — haemoglobin; TC — total cholesterol; LDL — low-density lipoproteins; HDL — high-density lipoproteins; TG — triglycerides; eGFR — estimated glomerular filtration rate; Na — calcium; K — potasium; AspAT — aspartate aminotransferase; AlAT — alanine aminotransferase; CRP — C-reactive protein; TSH — thyroid-stimulating hormone; NT-proBNP — N-terminal pro-B-type natriuretic peptide; TnT — troponin T

of 97/103 mg. For more than a year he was clinically stable and did not require further hospitalisation due to HF exacerbations.

The next hospitalisation was due to an airway infection, during which his HF worsened. The patient was hospitalised in the regional department for internal medicine due to orthopnea, coughing up yellow-grey fluid over the course of the airway infection, and increasing lower limb oedema. While being admitted, a urine test detected glycosuria, with venous blood glucose levels of 149 mg/dL (Table 1 — stay 2), which was considered to be the result of empagliflozin treatment. Following antibiotic treatment and intravenous diuretics, the patient was discharged with clinical improvements. Empagliflozin treatment was discontinued.

After a visit to a cardiology clinic three months after the previous hospitalisation, due to a notable increase in body weight (around 10 kg), exacerbation of lower limb oedema up to the knees, and worsening of HF up to NYHA Class III/IV, the patient was referred to the hospital with acute heart failure. Results of laboratory studies are shown in Table 1 — stay 3. Full treatment for cardiac failure was given, including intravenous diuretics and levosimendan infusion, resulting in significant clinical improvement, reduced body weight and decreased oedema and breathlessness. Following discharge, due to a resting heart rate (HR) above 75/min, additional treatment with the beta-blocker ivabradine was prescribed. Glycated haemoglobin was 9.10%, suggestive of unsatisfactory levels of glycaemia in the last three months in the range of 11.8 mmol/L (212 mg/dL).

For this patient, previous non-pharmacological treatments were unfortunately unsuccessful. It should be emphasised that morbid obesity (BMI 40.56 $kg/m^2$) is linked to hyperinsulinemia, leading to the activation of the renin–angiotensin–aldosterone (RAA) system and renewed HF exacerbations. On the other hand, treating this type of patient with insulin, which causes sodium retention with simultaneous decrease of glycosuria, can increase fluid retention and would therefore not be an optimal solution. After the patient became clinically stable during the peri-discharge period, empagliflozin treatment was resumed. In a 6-MWT, the patient achieved a distance of 330 m. The patient was given full information regarding HF and diabetes.

The patient was discharged home with non-pharmacological treatment suggestions and with the following recommendations of pharmacotherapy: dabigatran 2 × × 110 mg, sacubitril/valsartan 2 × 97/103 mg, ivabradine 2 × 5 mg, atorvastatin 80 mg, bisoprolol 10 mg, amiodarone 200 mg, lercanidipine 10 mg, eplerenone 25 mg,

**Table 2.** Selected clinical studies on the effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on cardiovascular risk

| Parameter | Name of study | | | | | |
|---|---|---|---|---|---|---|
| | EMPA-REG OUTCOME [10, 12] | CVD-REAL 2 [11, 12] | CVD-REAL [12] | EASEL [12] | CANVAS/ /CANVAS-R [12] | DECLARE-TIMI 58 [13] |
| Type of SGLT2 inhibitor used | Empagliflozin | Dapagliflozin (75%), empagliflozin (9%), ipragliflozin (8%), canagliflozin (4%), tofogliflozin (3%), luseogliflozin (1%) | Canagliflozin (53%), dapagliflozin (42%), empagliflozin (5%) | Canagliflozin (58%), empagliflozin (26%), dapagliflozin (16%) | Canagliflozin | Dapagliflozin |
| Number of participants | N > 7,000 | N > 400,000 | N > 300,000 | N > 25,000 | N > 10,000 | N > 17,000 |
| Heart attack | 0.87 (0.70–1.09) | 0.81 (0.74–0.88) | No data | 0.81 (0.64–1.03) | 0.89 (0.73–1.09) | 0.89 (0.77–1.01) |
| Stroke | 1.18 (0.89–1.56) | 0.68 (0.55–0.84) | No data | 0.85 (0.66–1.10) | 0.87 (0.69–1.09) | 1.01 (0.84–1.21) |
| Mortality | 0.68 (0.57–0.82) | 0.51 (0.37–0.70) | 0.49 (0.41–0.57) | 0.57 (0.49–0.66) | 0.87 (0.74–1.01) | 0.93 (0.82–1.04) |
| Hospitalisation due to heart failure | 0.65 (0.50–0.85) | 0.64 (0.50–0.82) | 0.61 (0.51–0.73) | 0.57 (0.45–0.73) | 0.67 (0.52–0.87) | 0.73 (0.61–0.88) |

pantoprazole 20 mg, empagliflozin 10 mg, furosemide 40 mg, torasemide 20 mg, and metformin 3 × 1,000 mg. On the above treatment, subsequent control check-ups presented a stable clinical picture, with arterial blood pressure of 125/70 mm Hg, fasting glycaemia up to 150 mg/dL, and a reduction in body mass of 5 kg. In an ECG there was a slight improvement in left ventricular systolic function (LVEF 28%) and a reduction in LVEDd to 61 mm. In ergospirometry with a load of 100 W, the patient achieved a $VO_2$ of 12.74 mL/kg/min, respiratory exchange ratio (RER) 1.16, $VO_2$ anaerobic threshold (AT) 10.42 mL/kg/min. The current therapy was maintained.

## Discussion

We present the case of a patient with heart failure and reduced ejection fraction of the left ventricle (HFrER) treated according to current recommendations with the newest therapy for HFrEF, including $AT_1$ receptor antagonists for angiotensin II and neprilysin inhibitor (ARNI, angiotensin receptor-neprilysin inhibitor) and empagliflozin. Following guidelines, empagliflozin has class IIa recommendations with a data reliability level of B, and is recommended for the prevention or delay of HF and increased lifespan.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are among the newest drug classes for the treatment of diabetes. Their mode of action is thought to be linked to the renal tubule excretion of glucose into the urine (glycosuria) by reducing reverse glucose transport. Owing to the regulation of their strength in response to blood glucose concentration, the risk of hypoglycaemia with these drugs is relatively low, which allows for their combination with practically all groups of antidiabetic drugs. The expected reduction in levels of glycated haemoglobin over the course of using the aforementioned group of drugs is 0.4–0.9 [7]. Due to the mechanism of reverse transport, glycosuria is accompanied in these patients by natriuresis. Because of this, the above medications are characterised by diuretic effects, which lead to reduced circulating blood volume, decreased body mass (reduced over-hydration), reduced arterial blood pressure, and increased haematocrit [8]. Moreover, the above group of drugs causes improvements in abdominal obesity, uric acid levels, and microalbuminuria [9].

A growing number of publications have shown a positive effect of empagliflozin on major adverse cardiac events (MACE — defined as death from cardiovascular causes, non-lethal strokes or cardiac infarctions) and decreased hospitalisations due to HF exacerbations – a result not seen with other commonly used diabetes drug groups.

The EMPA-REG OUTCOME study [10] found a 35% decrease in the risk of hospitalisation due to exacerbated heart failure in the group treated with empagliflozin. Due to the fact that the EMPA-REG OUTCOME study was not dedicated to an HF population, a further study was designed in this patient group to establish the place of empagliflozin in the treatment of HF patients.

The CVD-REAL 2 study [11], comprising over 300,000 patients with type 2 diabetes from six countries, confirmed that the use of drugs from the above group reduces the risk of hospitalisation due to exacerbation of heart failure as well as mortality. According to the authors of the study, a class effect may be possible, as using other SGLT2 inhibitors and not only empagliflozin (making up less than 10%

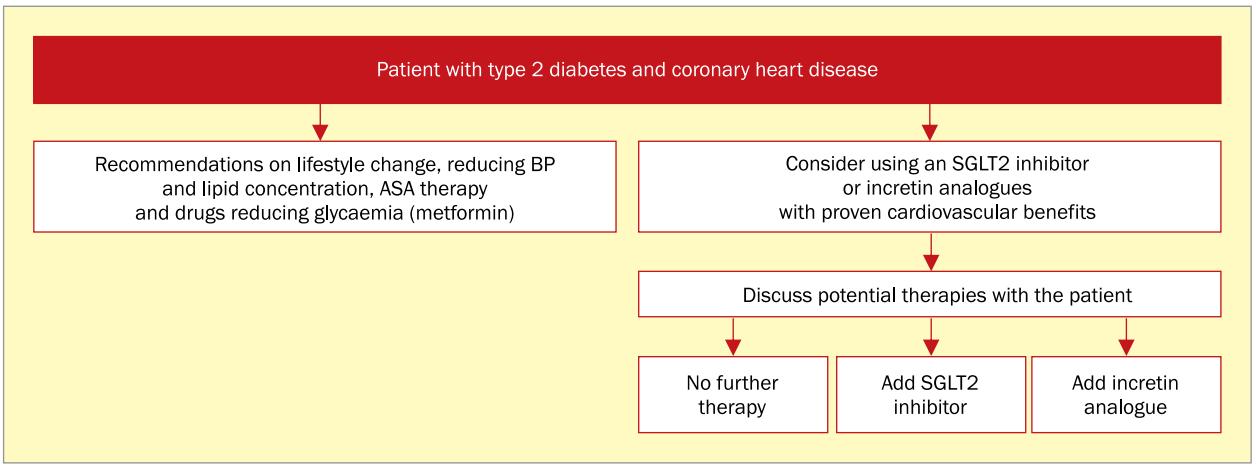


**Figure 1.** Treatment algorithm for a patient with type 2 diabetes and coronary heart disease (based on [12]); BP — blood pressure; ASA — acetylsalicylic acid; SGLT2 — sodium glucose co-transporter 2

of the drugs from this group in the above study), confirmed the reduction in the number of hospitalisations due to heart failure and a reduction in other adverse cardiac events such as stroke and cardiac infarction observed in the EMPA-REG OUTCOME study. Table 2 shows the most important studies on SGLT2 inhibitors conducted so far [10, 12, 13].

The mechanisms behind such a surprising reduction in major adverse cardiac events by SGLT2 inhibitors are not fully understood. However, it appears obvious that they are not caused only by the effects on SGLT2 or due to controlling levels of glycaemia, owing to (amongst other factors) a low expression of SGLT2 genes on the surface of cardiomyocytes, early action of the above drugs on important endpoints, and the absence of a correlation between levels of glycaemia and glycated haemoglobin during control visits, and a reduction in hospitalisations due to heart failure. Among the significant factors, the effect of these substances on haemostasis in diabetic myocardiocytes is often cited. An appropriate $Ca^{2+}$ concentration and rapid changes in its intracellular concentration play a key role in transmitting cellular signals, and is therefore responsible for the appropriate regulation of cardiac rhythm and myocardiocyte contraction. The dynamics of calcium levels are affected by sodium levels, which are regulated by sodium-potassium pumps or $Na^+/H^+$ pumps (NHE). Sodium and calcium haemostasis in diabetic patients is dysregulated. Hypoxia, or the increase in intracellular anaerobic processes, triggers lactic acid production and a consequent decrease of intracellular pH and $Na^+/H^+$ pump activation, resulting in excessive intracellular sodium [14].

Through a combination of reduced intracellular $Na^+$ levels and improved mitochondrial calcium transport, and consequently improved myocyte contraction strength, SGLT2 inhibitors lead to improved contractile function in the heart and reduce parasympathetic nervous system activation. This is important in respect of coronary disease-afflicted hearts with left ventricle ejection fraction impairment, such as in the patient in our case.

According to another theory, the use of SGLT2 inhibitors reduces oxidative stress, which plays an important role in maintaining a chronic inflammatory response, apoptosis and fibrosis in diabetic patients' heart muscle, leading to unfavourable heart remodelling and fatty acid metabolism modification, with a preference for beta-hydroxybutyric acid as a substrate, which is the most energetically favourable compound [14].

It is also worth mentioning the safety profile of empagliflozin. When used as a monotherapy, it carries a low risk of hypoglycaemia. Due to the main hypoglycaemia-inducing effect being associated mainly with osmotic diuresis, use of this drug requires relatively normal kidney function. However, one of the most common complications of glycosuria is urogenital infection, with complications of urinary tract infections such as pyelonephritis or urosepsis occurring with similar frequency in patients taking either empagliflozin or a placebo. In this case, no urinary tract infections were observed over the course of treatment, while body mass reduction and improved glycaemic profile were observed, and the medication itself was well tolerated by the patient. It is also worth mentioning a different complication that is probably related to lipid oxidation pathway alterations, such as ketoacidosis with relatively normal glycaemic levels. However, randomised studies have shown that such complications are rare in patients not requiring insulin therapy [12].

Mechanisms leading to heart failure exacerbations mostly have three causes: increased preload, increased afterload, and decreased myocardiocyte contractile ability. According to the current state of knowledge, SGLT2 inhibitors have multi-targeted effects. They decrease afterload

through osmotic diuresis and reduce circulating blood volume. They also influence sodium and calcium ion haemostasis in cells, thus impacting the force and 'quality' of myocardiocyte contractions.

In 2018, a consensus appeared in the US [12] that positioned SGLT2 inhibitors high in the algorithm for treating patients with type 2 diabetes and coronary heart disease. SGLT2 inhibitors were recommended to be considered in addition to lifestyle change education and metformin treatment (Figure 1).

## Conclusions

Empagliflozin is a new therapeutic tool for patients with HFrEF with concurrent diabetes. The presented clinical case of a patient suffering from multiple concurrent conditions implies an important role for empagliflozin in HFrEF therapy, which is demonstrated by the exacerbation of heart failure necessitating hospitalisation in a patient being treated with an optimal standard HFrEF therapy with ARNI when administration of empagliflozin was stopped. Our case demonstrates the importance of the early adoption of novel pharmacotherapies, and highlights the need for expert recommendations in everyday clinical practice.

## Conflict(s) of interest

The authors are participating in a clinical trial using empagliflozin.


### Streszczenie

Mężczyznę w wieku 56 lat z ciężką dysfunkcją lewej komory przyjęto na oddział z powodu zaostrzenia objawów przewlekłej niewydolności serca z obniżoną frakcją wyrzutową lewej komory. W trakcje hospitalizacji stosowano standardowe leczenie niewydolności serca, ale także modyfikowano terapię chorób współistniejących, w tym cukrzycy. Na podstawie opisu przypadku klinicznego w artykule przedstawiono aktualny stan wiedzy na temat korzystnego wpływu empagliflozyny na układ sercowo-naczyniowy.



Słowa kluczowe: niewydolność krążenia z obniżona frakcją wyrzutowa lewej komory, empagliflozyna

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# Infective endocarditis in children — lasting problem and growing incidence

## Infekcyjne zapalenie wsierdzia u dzieci — wzrastający problem

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### Abstract

Infective endocarditis (IE) is becoming a more common illness in children, especially in patients with congenital heart disease. There remains no consensus as to the optimal diagnosis, treatment and prophylaxis. One of the most challenging problems in this group of patients is surgery, because of the often extremely small dimensions and the lack of proper valve prosthesis. In light of this growing problem, there is a need for better knowledge regarding IE if this insidious disease is to to be promptly identified and and effectively treated.

Key words: infective endocarditis, paediatric cardiac surgery, valve replacement, children

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## Introduction

Over the last few decades, the epidemiology of infective endocarditis (IE) in the paediatric population has changed. In the 1970s roughly 30–50% of cases of IE in children were related to rheumatic heart disease [1], whereas nowadays congenital heart disease (CHD) is the most common reason for IE. Moreover, the increased frequency of IE is strongly connected with the increased survival rate among patients with CHD. The incidence of IE has been estimated to be approximately 0.05–0.12 cases per 1,000 paediatric admissions by different centres [2–5], while the figure reported from the USA is 0.43 cases per 100,000 children [3]. The increasing prevalence of IE in the paediatric population is associated with general immune deficiency, invasive devices, and innovative surgical procedures designed for complex cyanotic CHD, especially those associated with artificial material implantation, as well as the complexity of comprehensive treatment in intensive care units. Nevertheless, 8–10% of cases of IE in children are not associated with CHD or any evident risk factor [6]. In such cases, IE usually affects the aortic or mitral valves and comes from *Staphylococcus aureus* bacteraemia [7].

Although the incidence of IE in children is lower than in adults, it is more difficult to treat. The lack of clear guidelines for the treatment of endocarditis in children makes it an even more complicated and problematic challenge.

## Cardiac surgery and transcatheter procedures

Cardiac surgery and postoperative intensive care is an important independent risk factor for the development of IE. In particular, residual defects and surgical shunts contribute to damage of the endocardium and infiltration by bacteria. Those most susceptible to IE are cyanotic children after

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they have undergone corrective, palliative or physiological palliation surgery for CHD [8].

Although always possible, the risk of endocarditis in the first month after cardiac surgery is low. The risk usually rises as time goes by. IE can be a late complication of cardiac surgery for CHD, but unfortunately such a late occurrence is connected with rapid development and poor antibiotic response [9, 10].

Patients after transcatheter device implantation are also at risk of endocarditis, especially before the endothelialisation of the implants. The residual defects could be an additional risk factor for IE [11–13].

## Pathogenesis

The interaction of two factors is necessary for IE to develop — endothelium damage and bacteraemia [14]. Turbulent flow (*i.e.* valvular disease, stenosis or regurgitation, residual shunt, recurrent stenosis) causes mechanical stress, which destroys the endothelium, followed by the deposition of platelets and fibrin, and finally the creation of nonbacterial thrombotic endocarditis (NBTE). NBTE is a perfect nidus for bacterial or fungal colonisation. Bacteraemia or fungemia can appear in the blood from any infection site, and even as a result of everyday activities such as brushing teeth or chewing food. The pathogens after nidus colonisation and multiplication cause a further adhesion of platelets and fibrin. In chronic cardiac patients, the endothelium surface is frequently damaged by catheters or pacing wires; endocarditis can also develop due to direct infection from implantable devices.

## Diagnosis

Infective endocarditis is a difficult diagnostic problem, mostly because of its non-specific clinical symptoms. Clinical findings differ between neonates, children and adolescents. Infants with IE usually present feeding difficulties, tachycardia, respiratory disorders, hypotension, and a variety of neurological signs such as seizures, hemiparesis or apnoea. During physical examination, a new or changing heart murmur can be heard. However, in older children and adolescents, IE is associated with prolonged low-grade fever, fatigue, weight loss, weakness, arthralgias, myalgias and diaphoresis. In some cases, the symptoms of IE can develop rapidly with a high fever and progressive heart failure. These patients usually require urgent intervention, and the most likely aetiological factors are usually *Streptococcus pneumoniae* or *Staphylococcus aureus* [8, 10].

Due to its nonspecific clinical findings, endocarditis should be taken into consideration in every case of prolonged, nonresponding to antibiotics infection with fever, especially in children with congenital heart disease, and also in long term follow-up after corrective surgery. Extracardiac findings such as petechiae, haemorrhages, Janeway lesions, Roth's spots or Osler nodes, are uncommon in children. The emboli of vessels in the abdominal viscera, in the heart, or in the brain, although rare, can be life threatening.

In clinical practice, a diagnosis of IE depends on proving a relationship between the signs of infection and echocardiographic changes on the endocardium. Both the European Society of Cardiology (ESC) and the American Heart Association (AHA) recommend using the Duke criteria for diagnosing IE in adults [15].

Modifications of the Duke criteria for children have been used in several studies, but because of the small number of patients, there remain doubts about their universal applicability [16, 17]. The Duke criteria are based on clinical, microbiological and echocardiographic findings (Table 1). The original Duke criteria have only 80% sensitivity in epidemiologic studies and less than 65% (63.2%) in clinical practice [18]. To improve the accuracy of diagnosis in adults, it is recommended to consider new imaging techniques such as multi-slice computer tomography (MSCT) and single-photon emission computed tomography/computed tomography (SPECT/CT) [19, 20]. These techniques have thus far no applications or certification in the paediatric population.

The gold standard of IE diagnosis is microbiological and histological examination of surgically excised tissue specimens such as valves, a damaged endocardium, or vegetations.

## Imaging

The most important imaging techniques in IE are transthoracic (TTE) and transoesophageal (TEE) echocardiography. Echocardiographic examination should be performed in every patient with a suspicion of IE [14]. It has an important role in diagnosis, evaluation of treatment, and monitoring of recurrence. In children, TTE is usually sufficient to visualise changes in the endocardium and dysfunction of the valves. TEE could be helpful in the evaluation of paravalvular leakage, left ventricle outflow tract complication, root abscesses, or endocarditis over a prosthetic valve (Figure 1). Those patients with chest deformations after surgery, trauma or congenital lesions, can also be better assessed with TEE.

## Microbiology

Identifying the pathogen responsible for IE is very important, so it is crucial to take blood samples for microbiological examination as quickly as possible in every patient suspected of IE, especially where there is fever of an unexplained origin (FUO), a new heart murmur, a congenital diaphragmatic hernia (CDH), or a previous history of endocarditis. The process involves taking three blood cultures

**Table 1.** Modified Duke criteria for diagnosis of infective endocarditis in children (based on [15])

| Major criteria |
|---|
| 1. Positive blood culture for IE:<br>a) typical microorganism consistent with IE from ≥ 2 blood cultures:<br>• *Viridans streptococci, Streptococcus bovis, or HACEK group; or*<br>• community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus; or<br>b) microorganisms consistent with IE from persistently positive blood cultures, defined as:<br>• ≥ 2 positive cultures of blood samples drawn > 12 h apart; or<br>• all of three or a majority of ≥ 4 blood cultures, irrespective of the timing<br>c) 1 positive blood culture for *Coxiella burnetii* or antiphase-I immunoglobulin G antibody titre > 1:800 |
| 2. Evidence of endocardial involvement:<br>a) echocardiogram positive for IE (TEE recommended in prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE; TTE as the first test in other patients) for IE, defined as:<br>• oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or<br>• abscess; or<br>• new partial dehiscence of prosthetic valve |
| b) new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient) |
| **Minor criteria** |
| 1. Predisposition: predisposing heart condition or IV drug use |
| 2. Fever: temperature ≥ 38.0°C |
| 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions |
| 4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor |
| 5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE |

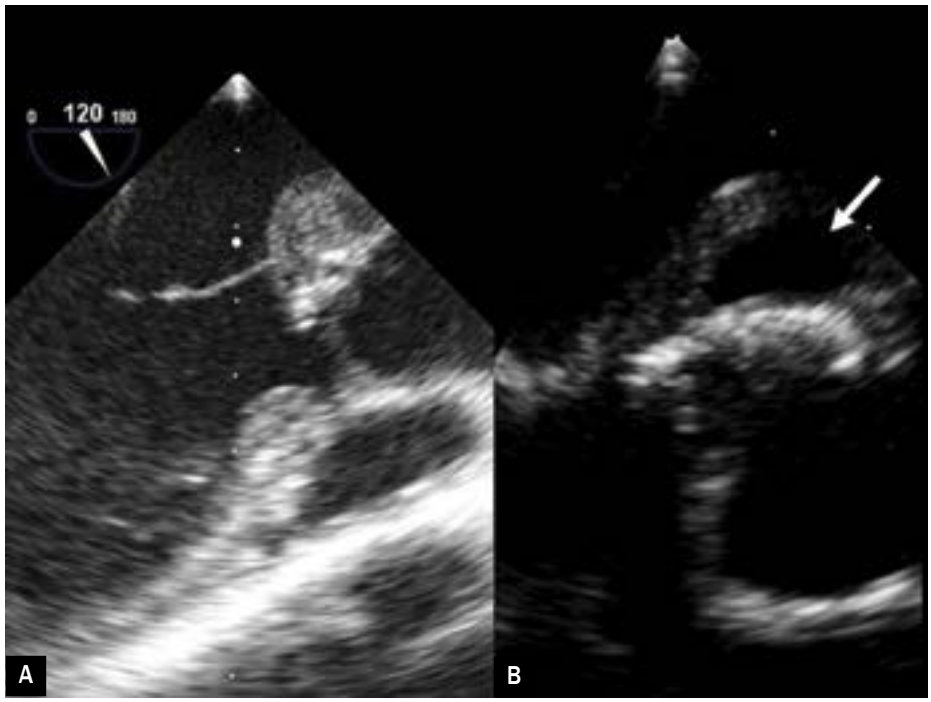


**Figure 1.** Transoesophageal echocardiography (TEE) in a 9 year-old boy with infective endocarditis caused by *Cardiobacterium hominis*. Periannular abscess (arrow) and vegetations attached to leaflets of aortic valve

by separate venous punctures on the first day of fever; if there is no growth after two days of incubation, another 2–3 blood samples should be taken.

Because of the relatively lower volume of circulating blood in children, the blood samples have to be smaller. In infants and younger children they should be limited to 1–3 mL, and 5–7 mL in older children. Bacteraemia is usually constant in IE, so there is no need to wait for pyrexia. Isolated growth in one sample should be taken into consideration with great care, due to the high possibility of contamination [15].

Most cases of IE are caused by the 'big three' pathogens — viridans group streptococci (VGS, like *Streptococcus sanquis*, *Streptococcus mitis* group, *Streptococcus mutans*), staphylococci (*Staphylococcus aureus,* coagulase-negative staphylococci), β-haemolytic streptococci and *Enterococcus* species (less common in children). Less common aetiological pathogens are microorganisms from the HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species) group.

If fastidious organisms or unusual pathogens are suspected, the microbiological laboratory should be forewarned so that it can use longer incubation and more specific tests. From the age of 12 months onwards, the most common endocarditis pathogen in children with CHD is VGS. However, after cardiac surgery *S. aureus* and coagulase-negative staphylococci are more common [1, 6].

## Culture-negative endocarditis

Up to 36% of patients with diagnosed endocarditis have negative blood cultures [21]. The reason behind a culture-negative endocarditis (CNE)-diagnosis is antibiotic therapy introduction before the collection of blood samples, or the need to make maximum efforts to search for organisms, which require more demanding conditions. Because of the nonspecific, slowly developing signs, the majority of patients are treated with antibiotics by a paediatrician or a general practitioner prior to IE being suspected.

Fastidious microorganisms, some bacteria and fungi, require more specific media and longer incubation times. Except for extended incubation, in some cases it is worth performing serological tests or using molecular techniques such as polymerase chain reaction (PCR) to detect RNA/DNA of the microorganisms [22].

The tests over surgically excised tissue can help to determine the aetiological factor behind IE, but they should be interpreted cautiously, because 13–55% of results are false-positive. Surgical materials remain positive for months after antibiotic therapy has begun, but unfortunately can detect microorganisms from previous episodes of endocarditis up to 12 years before surgery [22, 23].

## Treatment

The treatment of IE consists of two complementary parts — antibiotic therapy and surgery. The immediate implementation of appropriate antibiotic therapy is extremely important for a successful outcome. Antibiotic therapy depends on having a diagnosed or suspected aetiological factor. There are different antibiotic strategies and durations of therapy, which usually lasts a minimum of 6–8 weeks. There are also therapeutic strategies for CNE, which should be re-evaluated as soon as a more precise diagnosis is made, *i.e.* after histological tests. Preoperative antibiotics therapy should be taken into account for the total duration of therapy, unless there is a need to change antibiotics based on blood cultures. Although there has been an improvement in IE treatment, the mortality rate is still 5–10% [15], and is higher in patients with previous heart disease.

## Surgical treatment

The two major goals of surgical treatment of IE are to excise the infected tissues, and to restore the correct cardiac function.

The vegetations can cause valvular dysfunction, periannular progression of infection, sinus of Valsalva rupture, myocardial dysfunction, obstruction of conduits and shunts, pericardial effusion, coronary embolisation or dysfunction of artificial valves. Surgery is usually urgently required, especially in life-threatening conditions [24]. The most important indications for surgery are the progression of heart failure, uncontrolled infection, and emboli prevention.

Cardiac surgery for IE in children is an enormous challenge which grows more demanding the smaller the patient is. The first surgical challenge relates to the size of the patient. Even a fairly small vegetation on the valve or a periannular abscess can lead to resection of large cardiac structures or whole cusps of infected valve. The second basic problem of paediatric IE is the lack of proper valve prosthesis and materials to reconstruct cardiac morphology. There is no 'paediatric' size of artificial valve, either mechanical or biological. In addition, it should be remembered that no prosthetic valve has growth potential and a small prosthesis will have to be changed as the child grows. However, there have been promising initial reports on the use of a biological valve placed on a stent (Melody® valve; Figure 2) that could be percutaneously widened with balloons in the future [25].

It is vital to clear all current and suspected extracardiac sites of infection before cardiac surgery.

## Prevention

Both the AHA and the ESC limit the use of antibiotic prophylaxis to patients with the highest risk for IE and patients

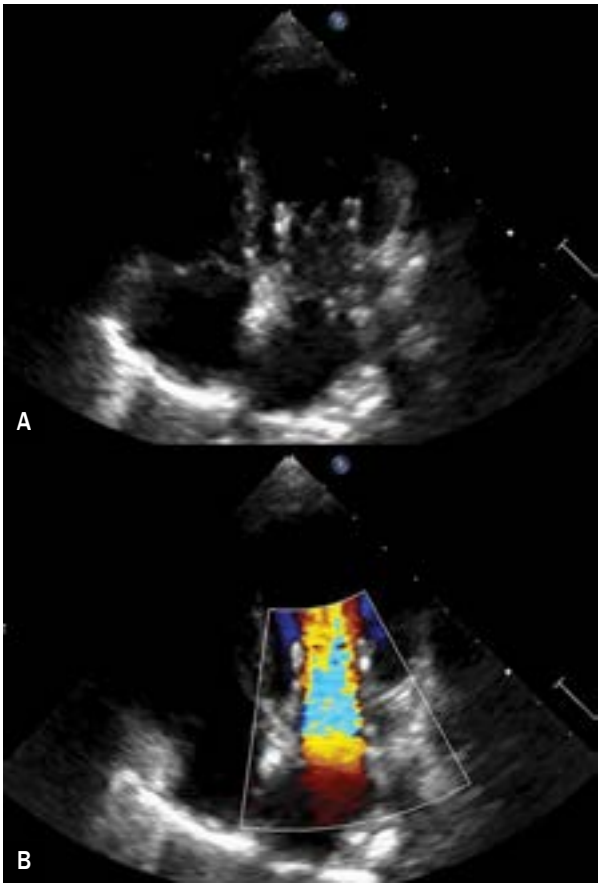


**Figure 2A, B.** Melody valve® in mitral position in a 3 year-old girl — 12 months after implantation because of acute mitral insufficiency in the course of infective endocarditis. There is possibility to percutaneous widen the diameter of the valve calibrated foramen in interatrial septum

with the highest risk for mortality or morbidity from IE. This is a consequence of the data that shows that up to 20% of IE could be associated with invasive procedures. Transient bacteraemia appears during everyday activities such as brushing teeth or chewing food. The oral flora in children and adults differs, and changes with age. Nonetheless, dental hygiene and careful treatment of any oral infection should be undertaken [26].

The other issue is for a patient with CHD, particularly cyanotic heart disease. The presence of implanted foreign prosthetic materials such as patches, shunts or conduits, increases the risk of endocarditis, even many years after cardiac surgery. The AHA recommends antibiotic prophylaxis before high-risk dental procedures for all patients with unrepaired cyanotic CHD, as well as those individuals who underwent the repair of a CHD with prosthetic materials, or with diagnosed residual defects, and after percutaneous device implantation (for a period of six months). Particular attention should be paid to oral hygiene in children with cyanosis, who have specific periodontal concerns [27].

## Conclusions

1. The growing number of children and adolescents with corrected CHD is the cause of the growing risk of IE. Therefore this particular group of patients should be treated by highly specialised teams familiar with congenital heart surgery. 2. There is a need for better knowledge about IE in children among general practitioners and paediatricians, as well as dentists, to provide a proper prophylaxis and shorten the time to diagnosis, introduce effective treatment, and improve outcomes. 3. The growing number of children suffering from IE should encourage progress in the field of prosthetic implantable materials that could minimise the risk of IE, while considering the potential to expand following children's growth.

## Conflict(s) of interest

The author declares no conflicts of interests.


### Streszczenie

Zachorowalność na infekcyjne zapalenie wsierdzia (IE) wzrasta w populacji dziecięcej, zwłaszcza u pacjentów z wrodzoną wadą serca. Właściwe postępowanie, diagnostyka, leczenie oraz właściwa profilaktyka pozostają przedmiotem wielu dyskusji. Leczenie chirurgiczne IE u dzieci stanowi szczególne wyzwanie, głównie z powodu małych rozmiarów pacjenta, konieczności zachowania potencjału do wzrostu i braku odpowiednich protez zastawkowych. W obliczu narastającego problemu należy zwiększać świadomość i propagować wiedzę o IE, żeby wcześnie rozpoznawać i skutecznie leczyć tę podstępną chorobę na wcześniejszych etapach.



Słowa kluczowe: infekcyjne zapalenie wsierdzia, kardiochirurgia dziecięca, zastawki, dzieci

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# Ineffective cardioverter-defibrillator therapy due to an increase in defibrillation threshold

## Nieskuteczne terapie kardiowertera-defibrylatora spowodowane wzrostem progu defibrylacji

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### Abstract

We present the case report of a 28 year-old man with postmyocarditis cardiomyopathy and cardioverter-defibrillator (ICD) implantation in secondary prevention. He survived an episode of circulatory arrest due to ventricular fibrillation/ /polymorphic ventricular tachycardia. All high energy therapy delivered by ICD was unsuccessful. The reason for the failure of the therapy was an increase in the defibrillation threshold. The implantation of an additional subcutaneous lead lowered the defibrillation threshold.

Key words: high defibrillation threshold, unsuccessful ICD defibrillation, subcutaneous defibrillation lead

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## Introduction

The implantation of cardioverter-defibrillator (ICD) systems decreases the total mortality of sudden cardiac death survivors due to ventricular tachycardia/ventricular fibrillation (VT/VF). In the modern era, with a diversity of lead types, including double coil leads, biphasic shocks and high energy devices, the clinical problem of a high or increasing defibrillation threshold is marginal, but it still exists and can have fatal consequences [1, 2].

## Case report

A 28 year-old man with postmyocarditis cardiomyopathy and double circulatory arrest with secondary prevention ICD implantation at the age of 19 was admitted to our Department after cardiac arrest and successful reanimation. He presented with circulatory arrest due to ventricular fibrillation in the vicinity of our hospital. Sinus rhythm restoration was achieved by an external biphasic defibrillator shock of 200 J.

Admission basic blood test results presented no significant deviations, normal electrolytes, high-sensitivity troponin T(hsTnT) 26 ng/L (N < 14), pro-B-type natriuretic peptide (proBNP) 26 ng/L (N < 84). Electrocardiogram (ECG) revealed a sinus rhythm 53 bpm, normogram, no R-wave progression in V1–V4 leads, negative T-wave in I, V1–V6 leads, resembling the former ECGs. Left ventricular ejection fraction (LVEF) was 37–42%, septal and medial anterior segments hypokinesis and left ventricular end-diastolic diameter (LVEDD) — 58 mm with left ventricular end-systolic diameter (LVESD) — 42 mm was seen in echocardiography. ICD records revealed a ventricular fibrillation (VF) episode and six unsuccessful defibrillations with a maximal 36 J of energy (Figure 1). The total circulatory arrest time was almost 10 minutes.

Two more VF episodes with an unsuccessful first defibrillation at 30 J, restored by a second shock of 36 J had been recorded two-and-a-half and three-and-a-half years earlier (Figure 2).

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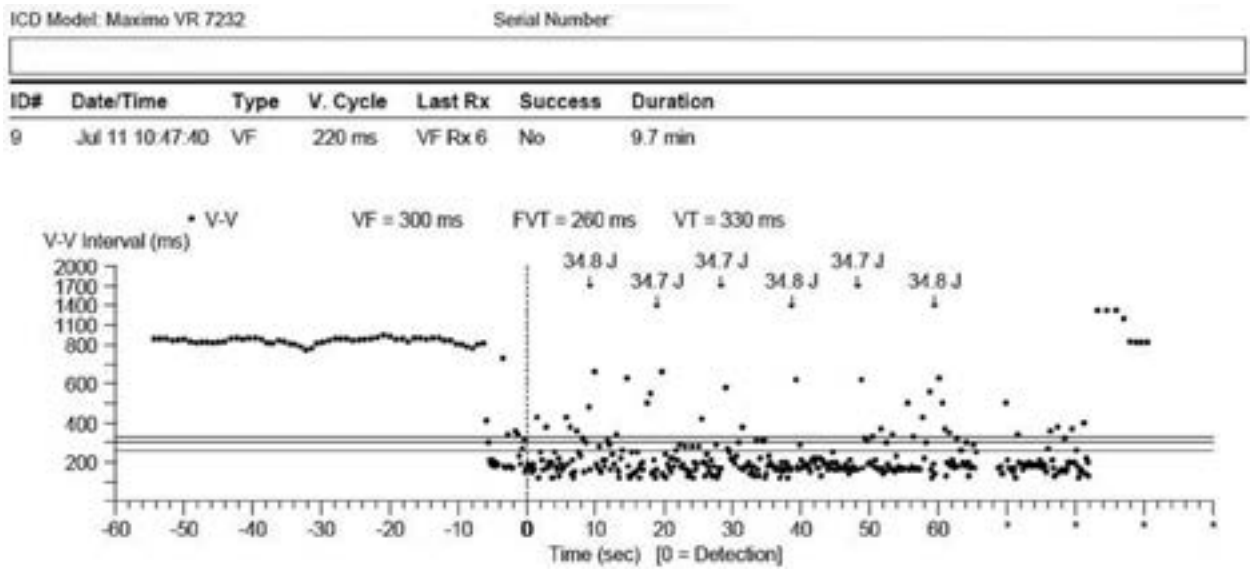


**Figure 1.** Six unsuccessful shocks with 36 J

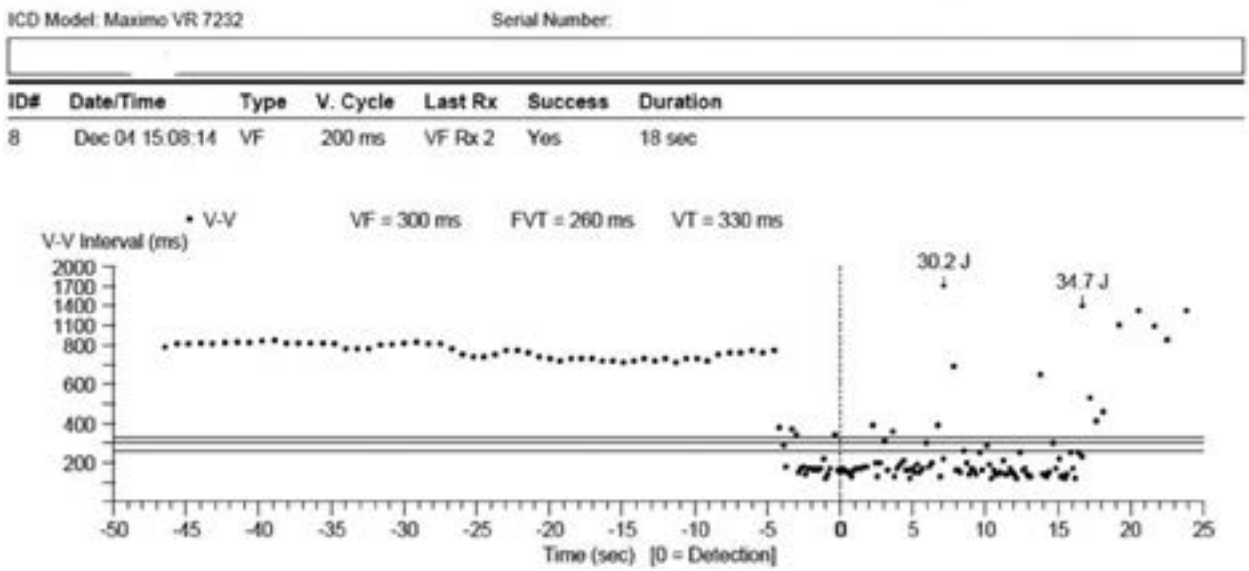


**Figure 2.** Unsuccessful first 30 J defibrillation; the second 36 J shock interrupts arrhythmia

No procedural reasons that could have been held responsible for the unsuccessful defibrillation, such as significant dyselectrolytemia, extreme circulatory insufficiency, *etc.* were found. An effective 20 J shock during the implantation procedure defibrillation test, and consecutive efficacious 30 J shocks during follow-up were recorded. Therefore, an increase of defibrillation threshold was diagnosed. The patient was qualified to subcutaneous lead implantation. The additional lead was connected to the SVC port (Figure 3).

The defibrillation test settled a positive 20 J shock. A further three-year observation revealed a further four episodes of ventricular arrhythmia classified to VF zone (cycle length of arrhythmia 170, 190, 195, 260 ms) effectively captured with 36 J. The patient is still alive.

## Discussion

Defibrillation efficacy is reported to be lower in everyday life compared to its efficacy during implantation. The risk of ineffective ICD shocks is higher in patients with hypertrophic cardiomyopathy and catecholaminergic cardiomyopathy, and when they are applied for polymorphic ventricular tachycardia or bidirectional ventricular tachycardia, but not

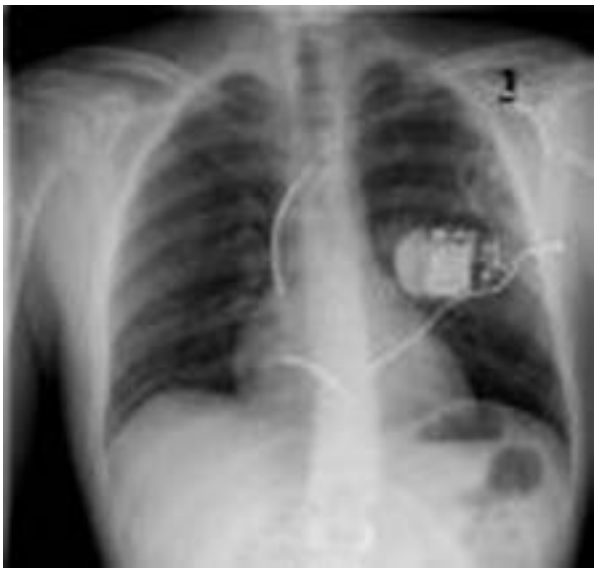

**Figure 3.** Chest X-ray with subcutaneous lead implanted

for ventricular fibrillation, in the same patient [3]. There are no studies devoted to defibrillation threshold changes due to disease progression and automatic system ageing during further follow-up. There have only been a few case reports describing patients who have survived when all high-energy therapies have proved unsuccessful. In some of them, the system was modified, however none of them have presented more of the patient's history or the efficiency of the adapted method [4–7].

In our opinion, ineffective shocks with 30 J of energy were the cause of the defibrillation threshold increase. The question remains, should we routinely modify the system in case of a single unsuccessful shock with submaximal energy (*i.e.* more than 10 J below the maximal available device energy) to avoid the grim scenario of unsuccessful therapies in the future? To the best of our knowledge, this is the first reported case of subcutaneous lead implantation for a survivor of six unsuccessful ICD high energy therapies due to a defibrillation threshold increase.


## Streszczenie

Przedstawiono przypadek kardiomiopatii pozapalnej i wszczepienia implantowalnego kardiowertera-defibrylatora (ICD) w ramach prewencji wtórnej u 28-letniego pacjenta, który przeżył epizod zatrzymania krążenia w przebiegu migotania komór/polimorficznego częstoskurczu komorowego. Wszystkie zastosowane terapie wysokoenergetyczne z ICD były nieskuteczne. Za przyczynę nieskuteczności terapii uznano zwiększenie progu defibrylacji. Próg defibrylacji obniżono, implantując elektrodę podskórną.



Słowa kluczowe: wysoki próg defibrylacji, nieskuteczna terapia ICD, elektroda podskórna

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# IV Warszawskie Dni Nadciśnienia Tętniczego 2019

## INTERDYSCYPLINARNIE — RÓŻNE PROBLEMY, RÓŻNE SPOJRZENIA

## Warszawa, 21 września 2019 roku

**Komitet Naukowy:**

prof. dr hab. n. med. Andrzej Januszewicz
dr hab. n. med. Aleksander Prejbisz, prof. nadzw.
dr hab. n. med. Marek Kabat, prof. nadzw.
dr hab. n. med. Piotr Dobrowolski

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**PRZEWODNICZĄCY KOMITETU NAUKOWEGO:**

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