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THE CZECH SOCIETY OF CARDIOLOGY

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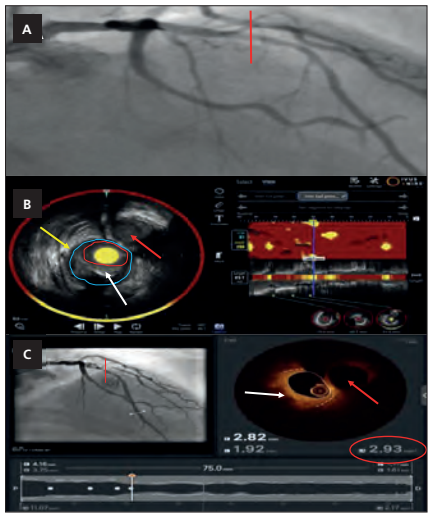
Cor et Vasa



Comparison of CAG, IVUS-NIRS and OCT images from the same part of the artery. *(M. Hudec M, Kaňovský J, Brázdil V, Poloczek M, Kask I, Hochmanová K, Smitalová R, Boček O, Jeřábek P, Štípal R, Littnerová S, Jarkovský J, Benešová K, Kala P. Near-infrared spectroscopy derived indexes as a potential predictor of plaque burden volume progression after unprotected left main coronary artery intervention. Původní sdělení, str. 6–15).*

Cor et Vasa

S PŘÍLOHOU Kardio

Časopis České kardiologické společnosti a České společnosti kardiovaskulární chirurgie *Cor et Vasa* vychází šestkrát ročně a pokrývá všechny aspekty kardiologie, angiologie, kardiovaskulární chirurgie, kardiovaskulárního zobrazování, pediatrické kardiologie, hypertenze, kardiovaskulární prevence a některé z aspektů intervenční radiologie.

Obsahuje úvodníky, původní sdělení, přehledové články i krátká sdělení z klinické a experimentální kardiologie. Počínaje rokem 2012 jsou v *Cor et Vasa* publikovány také souhrny (5 000 slov) z doporučených postupů Evropské kardiologické společnosti, připravené předními českými odborníky.

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It features editorial, original articles, review articles, as well as short communications from clinical and experimental cardiology. Beginning 2012, *Cor et Vasa* has also been publishing summaries (5 000 words) of the European Society of Cardiology guidelines, developed by leading Czech experts in the field.

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Vyhlášení soutěže o nejlepší publikaci v roce 2025

Vážené kolegyně, vážení kolegové,

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Za výbor ČKS a redakční radu Cor et Vasa,
prof. MUDr. Michael Aschermann, DrSc., FACC, FESC,
vedoucí redaktor Cor et Vasa

Seznam inzerentů

Původní sdělení | Original research article

Near-infrared spectroscopy derived indexes as a potential predictor of plaque burden volume progression after unprotected left main coronary artery intervention

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Objem plátu
Progrese plátu

SOUHRN

Úvod: Ischemická choroba srdeční (ICHS) je celosvětově hlavní příčinou úmrtí, což je jedním z důvodů významných technologických pokroků intervenční kardiologie v posledních dekádách. Kombinace intravaskulárního ultrazvuku (IVUS) a infračervenému spektru blízké spektroskopie (NIRS) nabízí detailní pohled na morfologii koronárních tepen a složení aterosklerotických plátů. Tyto pokročilé zobrazovací technologie umožňují přesnější hodnocení ICHS a zlepšují terapeutické strategie.
Cíl: NIRS dokáže detekovat a určitým způsobem kvantifikovat obsah lipidů v aterosklerotickém plátu pomocí indexů LCBI (Lipid-Core Burden Index) a maxLCBI4mm (Maximal Lipid Core Burden Index ve 4mm segmentu). V této studii jsme zkoumali vztah mezi těmito indexy a progresí aterosklerotického plátu v období 9–12 měsíců od perkutánní koronární intervence (PCI) s implantací lékového stentu v kmeni levé koronární tepny.
Metody: Jednalo se o prospektivní, monocentrickou studii zahrnující 27 pacientů s významnou stenózou kmene levé věnčité tepny, kteří podstoupili IVUS-NRS vedenou PCI. Sériově byly hodnoceny LCBI, maxLCBI-4mm a objem plátu (PV) před PCI, bezprostředně po PCI a v rámci kontrolního vyšetření za 9 až 12 měsíců u 18 pacientů.
Výsledky: Průměrný věk pacientů dosahoval 72,7 roku, přičemž převládali muži (88 %). Průměrný LCBI před PCI byl 128,9 ± 122,0, zatímco maxLCBI4mm byl 263,7 ± 172,0. Volumetricky pomocí IVUS měřený PV po PCI byl 418,7 ± 203,3 mm³, při kontrole se zvýšil na 454,5 ± 209,4 mm³ (p = 0,105). Analýza neodhalila významnou korelaci mezi rozdílem PV (po PCI a při kontrole) a výchozími hodnotami LCBI, resp. maxLCBI4mm (p = 0,626, resp. 0,786).
Závěr: Výsledky neprokázaly statisticky významnou korelaci mezi počátečními hodnotami LCBI, resp. maxLCBI4mm a progresí PV v kmeni levé věnčité tepny. Korelační grafy však naznačují trend ke snížení PV u pacientů s vysokými výchozími hodnotami LCBI a maxLCBI4mm jako možný efekt vysoce intenzivní statinové terapie.

Keywords:
Intravascular imaging
IVUS
LCBI
Left main
MaxLCBI4mm
NIRS
Plaque progression
Plaque volume

ABSTRACT

Background: Coronary artery disease (CAD) is the leading cause of death worldwide, which has driven significant advances in the field of interventional cardiology. The combination of intravascular ultrasound (IVUS) and near-infrared light spectroscopy (NIRS) offers a detailed view of coronary artery morphology and plaque composition. This advanced imaging capability facilitates a more accurate assessment of CAD and enhances therapeutic strategies.

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Objective: NIRS can detect and quantify lipid content in atherosclerotic plaque using the Lipid Core Burden Index (LCBI) and the Maximal Lipid Core Burden Index in a 4 mm segment (maxLCBI4mm). In this study, we examined the relationship between these indices and atherosclerotic plaque progression in the crucial area of the left main coronary artery (LM) during a follow-up period of 9 to 12 months after percutaneous coronary interventions (PCI).

Methods: A prospective, single-centre study was conducted involving 27 patients with significant left main stenosis who underwent IVUS-NIRS guided PCI. Serial assessments of the LCBI, maxLCBI4mm, and IVUS-derived plaque volume (PV) were performed at baseline, immediately post-PCI, and during follow-up at 9 to 12 months in 18 patients.

Results: The mean age of the study population was 72.7 years, with a predominance of male patients (88%). The average LCBI of the LM coronary artery before PCI was 128.9 ± 122.0, while maxLCBI4mm was 263.7 ± 172.0. The IVUS-measured PV post-PCI was 418.7 ± 203.3 mm³, increasing to 454.5 ± 209.4 mm³ at follow-up (p = 0.105). Analysis revealed no significant correlation between the difference in PV and baseline LCBI or maxLCBI4mm, with p-values of 0.626 and 0.786, respectively.

Conclusion: This study found no significant association between initial LCBI and maxLCBI4mm segment values and subsequent changes in PV in the left main coronary artery. However, correlation graphs indicate a trend toward decreased PV in patients with high initial LCBI and maxLCBI4mm.

Introduction

Coronary artery disease remains the leading cause of death worldwide, according to recent data from the World Health Organization.[1,2] This fact is one of the reasons why interventional cardiology research has made significant advances over the last few decades. The use of intravascular imaging (IVI) has already become standard in contemporary clinical practice.

IVI provides more information about the vessel than conventional coronary angiography (CAG). The two most widely used methods of IVI are intravascular ultrasound (IVUS) and optical coherence tomography (OCT).[3] Both methods can be used to plan, guide and optimise the final result of percutaneous coronary interventions (PCI), in addition to stratifying the patient's future risk based on coronary data analysis. IVUS relies on the analysis of backscattered ultrasound signals, while OCT analyses the backscattering of light waves. Each of these methods presents certain advantages and disadvantages based on their underlying principles. Generally, IVI characterizes the morphological features of the coronary arteries before and/or after coronary interventions.[4,5]

A detailed analysis of the characteristics of vessel wall tissue regarding the presence of lipids and calcifications has been challenging until recently. In 2013, the FDA approved a new method – near-infrared light spectroscopy (NIRS). This system is typically coupled with IVUS and provides real-time analysis of the composition of atherosclerotic plaques, identifying the likelihood of lipid presence – known as lipid core plaque (LCP).[6]

The use of IVI is already established in European and American guidelines for myocardial revascularization. Clinical scenario in which the use of IVI is recommended includes PCI of the left main (LM) bifurcation, where IVUS is typically employed.[7,8] The LM bifurcation represents a critical area within the coronary system. A long-term successful outcome in this region necessitates not only an impeccable intervention guided by IVUS, ideally performed at a high-volume catheterization centre,[9] but also a comprehensive understanding of all factors influencing the vessel's post-intervention condition. NIRS can detect and quantify lipids in atherosclerotic plaques within coronary arteries. The probability of their presence is coded in different colours. Thus, NIRS may also be valuable in predicting the progression of atherosclerosis following PCI of the LM.

Near-infrared spectroscopy

NIRS is a catheter-based intravascular imaging tool. The fundamental principle of this method involves spectroscopic analysis to determine the unknown chemical composition.[10] The spectrometer emits radiation of a known wavelength into the sample, with a range of 780–2500 nm, which is classified as near-infrared light radiation. This wavelength range is advantageous because it does not interact with haemoglobin or water, unlike optical coherence tomography (OCT), and therefore does not require the use of contrast agents for blood clearance.[11–13]

Within the sample, the radiation is partially scattered and absorbed, based on the presence and concentration of specific chemical bonds.[14] The altered radiation is then returned to the spectrometer, where it is analysed to produce a graph of absorbance for each wavelength. Each chemical substance interacts uniquely with the wavelength, producing a distinct graph of absorbance. This allows for the identification of chemical composition within the analysed segment of the coronary artery.[10,15]

The qualitative results are represented by chemogram and block chemogram, while the quantitative analysis is expressed through Lipid Core Burden Index (LCBI) and LCBI for the most affected 4 milimetres (maxLCBI4mm).[16] NIRS provides a two-dimensional graphical representation of the analysed coronary artery segment. The technique conducts a detailed analysis every 1 mm, assessing up to 1300 points per millimetre. Each point in the analysed section is assigned a colour indicating the probability of lipid presence, ranging from red (indicating a low probability of lipids) to yellow (indicating a high probability of lipids).[17,18] The quantitative expression of NIRS results is labelled as the Lipid Core Burden Index (LCBI). This index serves as a numerical representation of the chemogram, providing a dimensionless value. It quantifies the number

of points within the analysed segment that exhibit a lipid presence probability greater than 0.6, multiplied by 1000. MaxLCBI4mm is the highest automatically determined LCBI value within any 4 mm segment, indicating the area with the most significant lipid-core plaque presence.[19,20]

Methods

Design

This prospective, single-centre study was designed to investigate the relationship between near-infrared spectroscopy (NIRS)-derived indexes (Lipid Core Burden Index [LCBI] and maxLCBI4mm of the left main coronary artery [LM]) and the volumetrically assessed plaque volume (PV) of the LM. The aim was to predict atherosclerosis progression following percutaneous coronary intervention (PCI) with the latest generation drug-eluting stent (DES). The study followed the Declaration of Helsinki, was approved by the local Ethics Committee and all patients signed the informed consent.

Sub-analysis of the cohort includes assessment of atherosclerosis progression according to statin dose – group of high intensity dosage of statin (HDS) and moderate intensity dosage of statin (MDS). High intensity dosage of statin includes patients with dose of atorvastatin 40 mg and more or dose of rosuvastatin 20 mg and more.[21]

Patients with coronary artery disease (CAD) underwent baseline IVUS-NIRS-guided PCI of the LM bifurcation, followed by serial IVUS-NIRS examination of the LM at follow-up catheterization between 9 to 12 months after baseline procedure. During both procedures, NIRS--derived LCBI and maxLCBI4mm of the LM, as well as IVUS--derived volumetric analysis of the LM, were obtained at baseline, immediately post-PCI, and during the follow-up catheterization.

Additionally, a clinical follow-up was conducted at 1, 3, 6, and 12 months post-index procedure for all enrolled patients. We were aiming to clinical events such as death, rehospitalization due to cardiovascular reasons, acute myocardial infarction (AMI), repeated coronary angiography (CAG), and target or non-target lesion revascularization (TLR or NTLR).

NIRS analysis

The NIRS analysis was conducted using a 3.2-French dual-modality intracoronary catheter (DualPro™; Infraredx Inc.). NIRS analysis was specifically restricted to the segment of the left main coronary artery (LM), identified by the proximal edge (ostium in the aorta) and the distal part (the last frame before the LM divides into the left anterior descending artery [LAD] and the left circumflex artery [RCx]). The software automatically calculated the Lipid-Core Burden Index (LCBI) and the maxLCBI4mm for this segment, as previously described.

Data were collected at three key stages: baseline (prior to PCI), immediately post-PCI, and during follow-up catheterization. These data helped in assessing the progression of atherosclerosis and the effectiveness of the PCI.

Figures are included to illustrate the NIRS analysis: **Figure 1** presents a simplified scheme of NIRS analysis of the coronary artery, **Figure 2** demonstrates the application of NIRS in clinical practice, and **Figure 3** compares images from coronary angiography (CAG), intravascular ultrasound combined with NIRS (IVUS-NIRS), and optical coherence tomography (OCT).

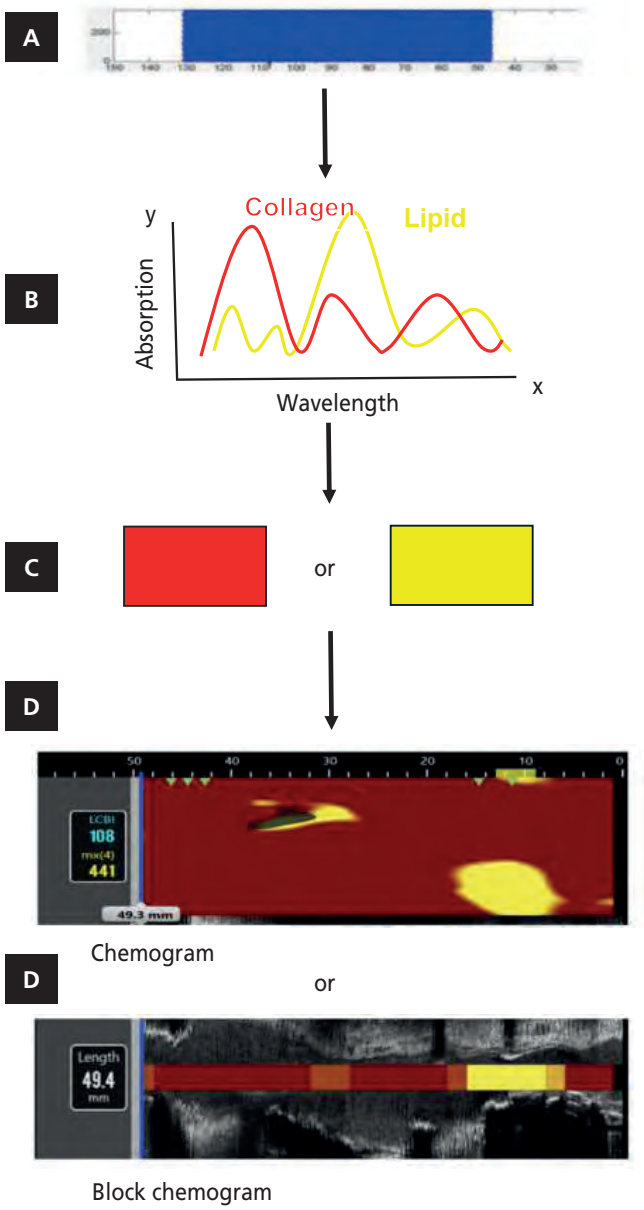

Fig. 1 – Simplified scheme of NIRS analysis of the coronary artery. (A) Section of the analysed coronary artery (x-axis shows the artery longitudinally, y-axis shows the transverse section). The section where the chemical analysis was carried out, point by point, is shown in blue. (B) Simplified graph of absorbance of different wavelengths for cholesterol and collagen (the shape of the curves does not correspond to the real curves of absorbance for the collagen and lipids). (C) According to the probability of the presence of lipids, each of the analysed points is assigned a value of 0–1, which corresponds to a colour scale from red to yellow. (D) Resulting chemogram with LCBI and maxLCBI4mm values and block chemogram with the length of the analysed section.

IVUS analysis

Intravascular ultrasound (IVUS) data were recorded simultaneously using the same dual-modality intracoronary

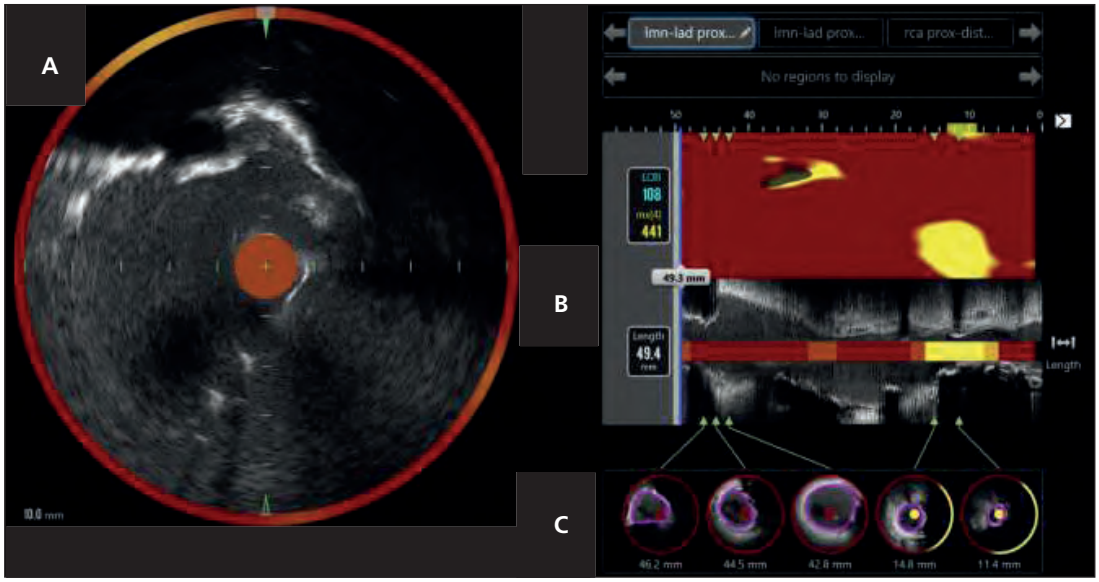

Fig. 2 – Combined imaging of the examined section from the latest version of IVUS-NIRS (Makoto Intravascular Imaging System™) in real practice. (A) Sagittal view in the distal part of the examined coronary artery segment. This is a co-registered IVUS and NIRS recording. Black and white IVUS image in the central part. Along its perimeter, a coloured bar expressing the chemogram in the adjacent section (according to the probability of cholesterol presence from red to yellow). In the very centre of the image, a coloured circle – expressing the block chemogram in this frame. (B) Chemogram and block chemogram of the entire examined part. By moving the cursor, you can select individual sections in the IVUS pull-back record. (C) Examples of 5 sections through the investigated vessel showing a high probability of the presence of cholesterol plaques in last images.

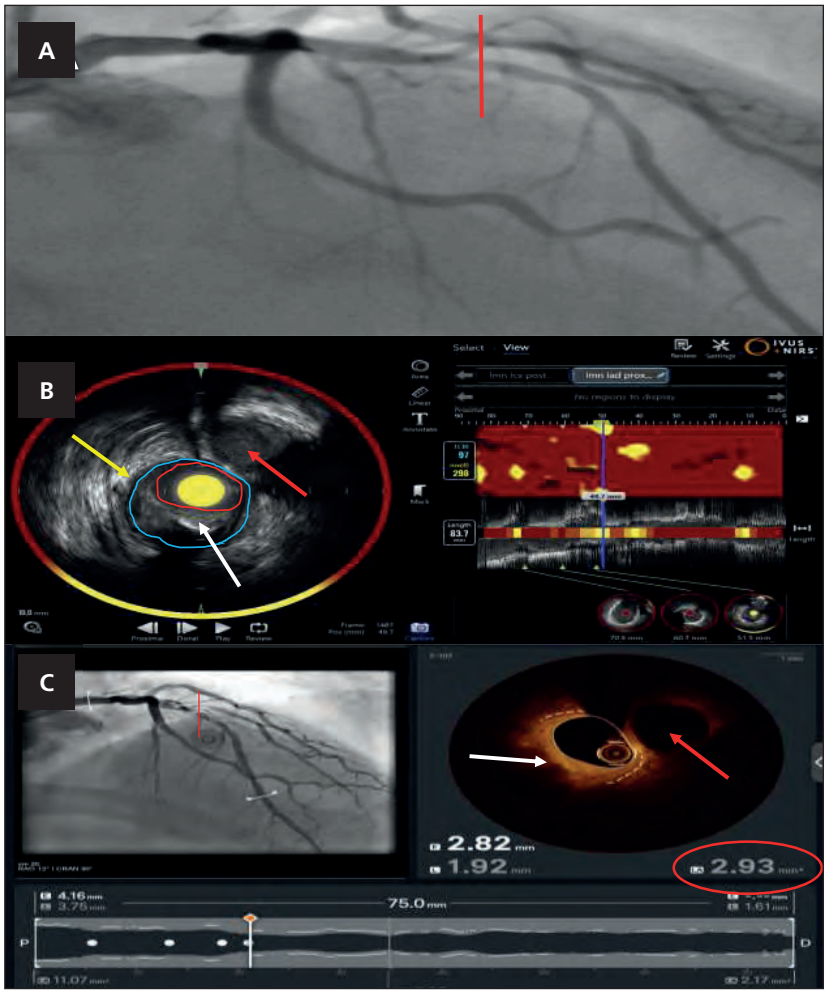

Fig. 3 – Comparison of CAG, IVUS-NIRS and OCT images from the same part of the artery. (A) CAG focused on the left coronary artery – middle part of the left anterior descending (LAD), just behind origin of the diagonal branch. The red line shows the segment further analysed by IVUS-NIRS and then OCT. (B) IVUS-NIRS analysis of the middle part of the LAD (mentioned above). In the left part of the figure, black and white sagittal IVUS section through the artery (yellow arrow – LAD, red arrow – side branch, blue circle – shows the external elastic membrane, red circle – shows the lumen of the artery, white arrow – fibrotic plaque with calcifications). Around perimeter, a coloured bar represents the chemogram of the adjacent section and in the middle a coloured circle represents the cumulative block chemogram in that section. On the right there is the chemogram and block chemogram of the entire analysed LAD with LCBI 97 and maxLCBI4mm 298. (C) OCT analysis of the identical segment. In the left part co-registered view with CAG. White brackets show the entire length of the analysed segment (75 mm totally), red line shows the currently analysed segment. In the right part of the figure OCT image. The white circle indicates the LAD area with a centrally placed OCT catheter, from which a dark shadowing bar emits. The red arrow points to the lateral diagonal branch, the white arrow to the fibrotic plaque with calcifications with maximum arterial involvement between 4 and 12 o'clock, the red circle highlights the lumen area of the segment.

Table 1 – Demographic characteristics of analysed sample	
Number of patients (enrolled/excluded)	27/9
Excluded patients	9 (33.3%)
Died	3 (33.3%)
Covid-19	2 (22.2%)
Incomplete data	4 (44.4%)
Male sex	15 (88%)
Age (years)	72.7 (± 5.5)
Acute myocardial infarction	7 (38.8%)
Chronic coronary disease	11 (61.1%)
Body mass index (kg/m^2)	27,9 (± 4.2)
Diabetes mellitus	8 (44%)
If yes: insulin-dependent	4 (50%)
Hypertension	17 (94.4%)
Chronic kidney disease (CKD)	3 (16.6%)
If yes: CKD G2	1 (33.3%)
If yes: CKD G3	2 (66.6%)
Dyslipidaemia	18 (100%)
If yes: atorvastatin 80 mg	2 (11.1%)
If yes: atorvastatin 40 mg	7 (38.9%)
If yes: atorvastatin 20 mg	5 (27.8%)
If yes: atorvastatin 10 mg	1 (5.6%)
If yes: rosuvastatin 40 mg	2 (11.1%)
If yes: rosuvastatin 20 mg	1 (5.6%)
High intensity dosage of statin*	12 (66.6%)
Moderate intensity dosage of statin*	6 (33.3%)
Current smoker	0 (0%)
History of CAD	8 (44%)
If yes: in target lesion	1 (12.5%)
2 and more stent technique of PCI	14 (77.8%)
P2Y$_{12}$ inhibitor	18 (100%)
Clopidogrel	15 (83.3%)
Ticagrelor	3 (16.6%)

* High intensity dosage of statin includes patients with dose of atorvastatin 40 mg and more or dose of rosuvastatin 20 mg and more.

catheter. The pullback speed was set at 0.5 mm per second. IVUS analysis was conducted in accordance with the criteria set forth by the American College of Cardiology consensus statement on IVUS.[22] Both baseline and follow-up IVUS images were evaluated by experienced analysts.

The external elastic membrane (EEM) and lumen were assessed at intervals of every 0.2 mm. The cross-sectional area defined by the EEM is referred to as the cross-sectional EEM area (EEM CSA), while the area defined by the lumen/stent is known as the cross-sectional minimal lumen/stent area (MLA/MSA CSA). The plaque burden area (PB) is calculated as the difference between the EEM CSA and the MLA/MSA CSA, expressed in square millimetres, alongside the entire length of LM in each timepoint of the analysis. Simpson's rule was applied to generate a volumetric model of the lumen and calculate the total plaque volume (PV) of the left main coronary artery in cubic millimetres.[23] The analysis was performed at three key stages: baseline (prior to PCI), immediately post-PCI, and during follow-up catheterization.

Statistical analysis

Basic characteristics of patients were divided into categorical variables and continuous variables. Continuous variables were described by mean and standard deviation, categorical variables were presented as frequencies and relative frequencies. The lumen area and plaque volume were evaluated as the sum of the volumes of the truncate cone between two measurements. Changes of lumen area or plaque burden volume were calculated as a difference between values before PCI and after PCI and after PCI and in the follow-up.

Statistical significances of plaque volume change in all dataset and in groups of statin dose were tested by Wilcoxon signed-rank test. The differences of plaque volume change between groups of statin dose were tested by Mann–Whitney U test. Relationship between PV change and LCBI index was tested by Spearman's correlation coefficient. Change of parameter analysis was performed using SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Results

Patient characteristics

Between May 2016 and July 2022, a total of 27 patients with significant left main stenosis were enrolled in the study after providing informed consent. All patients underwent baseline IVUS-NIRS-guided PCI. Prior to the final statistical analysis of the NIRS and IVUS data, nine patients were excluded for various reasons: three patients died before the scheduled IVUS-NIRS follow-up, two patients declined the follow-up IVUS-NIRS due to the COVID-19 pandemic, and for four patients, the data were deemed unevaluable due to technical issues or poor imaging quality. As a result, complete NIRS-IVUS data from both baseline and follow-up were available for 18 patients. The NIRS and IVUS data for these patients were analyzed and statistically evaluated. Clinical follow-ups, conducted as outpatient visits or by phone at 1, 3, 6, and 12 months after the index procedure, focused on major cardiovascular clinical events including death, rehospitalization due to cardiovascular reasons, acute myocardial infarction, and target or non-target lesion revascularization. The clinical follow-up was completed in all patients.

Population with complete data

The mean age of the patients was 72.7 ± 5.5 years, with 15 patients (83.3%) being male and a mean body mass index (BMI) of 27.9 ± 4.2. The indication for baseline PCI was acute myocardial infarction in 7 patients (39%), while the remainder underwent PCI due to chronic coronary disease. The mean left ventricular ejection fraction in the population was 53 ± 13%. Eight patients (40%) had dia-

Table 2 – Clinical characteristic of complete group	
Clinical follow-up control (at least 2 controls)	27 (100%)
Month 1	18 (66.7%)
Month 3	18 (66.7%)
Month 6	22 (81.5%)
Month 12	24 (88.9%)
Clinical events	15 (55.5%)
Death	3 (20%)
Cardiovascular reason	0
Acute myocardial infarction	1 (6.7%)
Rehospitalization	8 (53.3%)
Cardiovascular reason	2 (25%)
Target lesion revascularization	1 (6.7%)
Non-target lesion revascularization	2 (13.3%)

Table 3 – Basic IVUS-NIRS characteristics of patients	
	Mean ± SD
LM LCBI before PCI (mean)	128.9 ± 122.0
maxLCBI4mm before PCI (mean)	263.7 ± 172.0
LM LCBI post-PCI (mean)	48.1 ± 35.1
maxLCBI4mm post-PCI (mean)	129.6 ± 101.6
LM LCBI follow-up (mean)	57.6 ± 50.9
maxLCBI4mm follow-up (mean)	133.7 ± 136.7
Lumen volume before PCI (mean)	121.8 ± 68.4
Lumen volume post-PCI (mean)	184.3 ± 96.9
Lumen volume follow-up (mean)	195.9 ± 119.4
Lumen volume: difference between before PCI and post-PCI	62.5 ± 79.4; 61.6 (–29.0; 228.6)[1]*
PV baseline	368.1 ± 214.2
PV post-PCI	418.7 ± 203.3
PV follow-up	454.5 ± 209.4
PV difference between follow-up and post-PCI	35.7 ± 91.1; 20.3 (–70.0; 205.2)[1]
PV difference between follow-up and post-PCI according to statin dosage:	
High intensity dosage of statin	42.4 ± 102.5; 14.5 (–85.1; 209.3)[1]
Moderate intensity dosage of statin	22.5 ± 43.5; 30.5 (–45.8; 73.1)[1]
Average number of analysed cross sections per a patient	35.4 ± 15

[1] Parameter was described by mean with SD and median with 5th and 95th percentile.
* Statistically significant difference of change of lumen.

betes mellitus, and 3 patients (17%) had chronic kidney disease (CKD) at stage 2 or worse. A history of previously treated coronary artery disease (CAD) was present in 8 patients (44%), and no patients were active smokers at the time of enrolment.

A double stent technique was used in 8 patients (44%), and clopidogrel was utilized as the $P2Y_{12}$ inhibitor in the dual antiplatelet therapy strategy for 15 patients (83%). Patients were treated with the maximum tolerated statin dose: 12 patients (66.6%) received high intensity dosage of statin and 6 patients (33.3%) received moderate intensity dosage of statin. The baseline characteristics of the analyzed population are detailed in **Table 1**.

Clinical events in complete population

Clinical follow-up was conducted for all 27 patients, with at least two clinical assessments performed either via phone or outpatient visits. During the follow-up period, 3 patients (11%) died from non-cardiovascular causes, 1 patient (4%) experienced an acute myocardial infarction (AMI), and 2 patients (7.5%) were rehospitalized due to cardiovascular reasons. Target lesion revascularization (TLR) occurred in 1 patient (4%), while non-target lesion revascularization (NTLR) occurred in 2 patients (7.5%). Detailed clinical follow-up characteristics of the complete population are provided in **Table 2**. Statistical significance for differences in clinical events was not calculated, as this was not a primary endpoint of the study and the number of events was small.

IVUS and NIRS data

Mean length of the analysed segment – LM – was 11.9 ± 4.5 mm. The average LM LCBI before PCI was 128.9 ± 122.0, maxLCBI4mm 263.7 ± 172.0. Compared with baseline values, both indices showed a decrease after PCI and at follow-up. Mean values after PCI were LCBI 48.1 ± 35.1; maxLCBI4mm 129.6 ± 101.6 and at follow-up were LCBI 57.6 ± 50.9; maxLCBI4mm 133.7 ± 136.7. The mean plaque volume (PV) as measured by IVUS was 418.7 ± 203.3 mm³ post-PCI and 454.5 ± 209.4 mm³ at follow-up. The mean difference in PV between follow-up and post-PCI was 35.7 ± 91.1 mm³, with a median difference of 20.3 mm³ (range: –70.0 to 205.2), which was not statistically significant ($p = 0.105$).

The analysis also included the difference between mean lumen volume at baseline (121.8 ± 68.4 mm³) and post-PCI (184.3 ± 96.9 mm³), showing a mean difference of 62.5 ± 79.4 mm³. The median of this difference was highly statistically significant (range: 61.6 to –29.0, 228.6) with a p-value of 0.001. Detailed results are presented in **Table 3**. Spearman's correlation coefficient was used to analyse the relationship between PV change (post-PCI PV versus follow-up PV) and LCBI before PCI (–0.122; $p = 0.626$), maxLCBI4mm PCI (–0.069; $p = 0.786$) respectively. No statistically significant correlations were found. These analyses are detailed in **Figures 4** and **5**.

Effect of statin therapy

Patients were treated with the maximum tolerated statin dose – 15 patients (83%) with atorvastatin (in the dose of 38 ± 20 milligrams) and 3 patients (17%) with rosuvastatin (in the dose of 26 ± 21 milligrams). PV difference between follow-up and post-PCI according to dosage of statin was analysed. In HDS the mean difference in PV between follow-up and post-PCI was 42.4 ± 102.5 and in MDS the mean difference was 22.5 ± 43.5 mm³. There was not a statistically significant difference between HDS and MDS in PV difference. Detailed results are presented in **Table 3**.

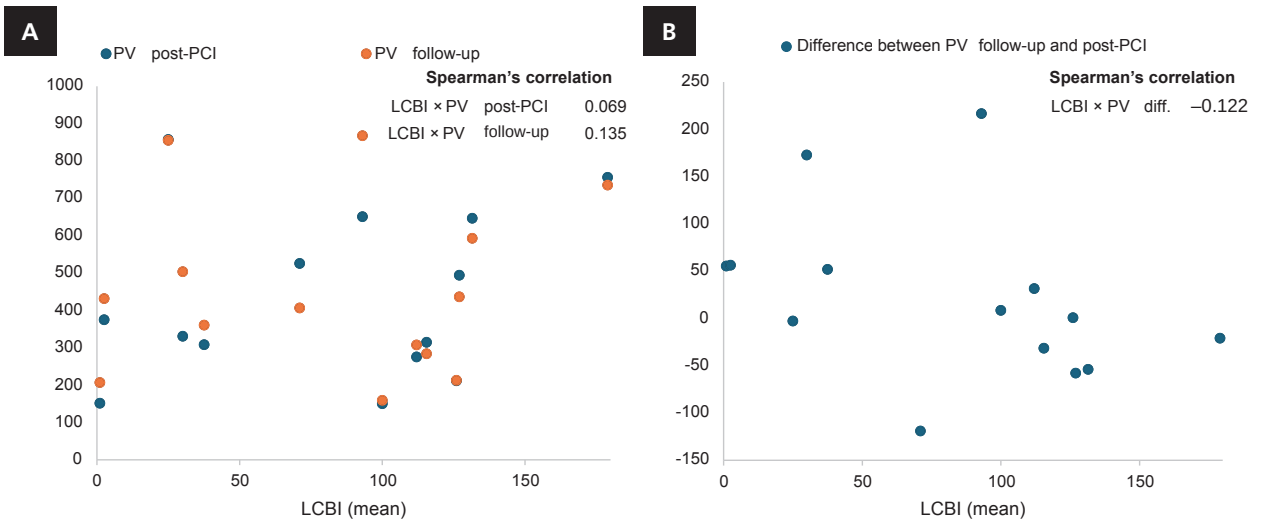

Fig. 4 – (A) Relationships between PV post-PCI and in follow-up and LCBI. (B) Relationship between difference of PV follow-up and post-PCI and LCBI.

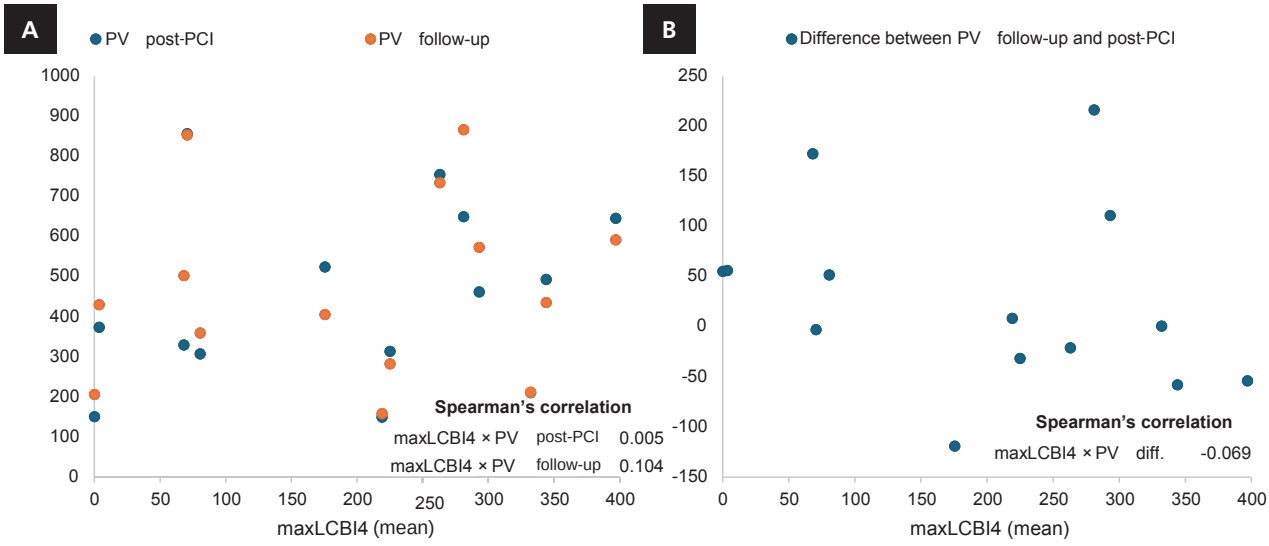

Fig. 5 – (A) Relationships between PV post-PCI and in follow-up and maxLCBI4mm. (B) Relationship between difference of PV follow-up and post-PCI and maxLCBI4mm.

Discussion

Although the patient cohort is relatively small, the presented data can be considered unique. To our knowledge, this is the first study to explore the relationship between baseline LCBI or maxLCBI4mm values and plaque volume (PV) progression. Previous studies have utilized NIRS data to assess PV, but not as a predictor of its progression after PCI.[24,25] Moreover, the coronary artery segment analysed is the left main of the left coronary artery, a critical area in the coronary system. According to current information, a similar analysis of the LM using NIRS data has not been published.

Our objective was to predict the relationship between NIRS-derived indexes (LCBI and maxLCBI4mm) and atherosclerotic plaque progression in the unique LM area over a 9- to 12-month follow-up period after percutaneous coronary interventions (PCI). Our data did not reveal a significant correlation between initial LCBI or maxLCBI4mm and PV progression during the follow-up. Despite a slight increase in PV observed during the control examination, the change was not statistically significant. This result suggests the potential excellent effect of high/moderate intensity lipid-lowering therapy.

We utilized NIRS as an intravascular tool to analyse atherosclerotic plaque. Although NIRS is predominantly used on an experimental basis in interventional cardiology, its routine clinical application remains limited. Nonetheless, NIRS has been shown to be an important tool across a wide range of recent studies.

One of the persistent complications in PCI is the occurrence of periprocedural acute myocardial in-

farction (PAMI), which affects 3–15% of all PCI procedures.[26] The likely mechanism involves distal embolization of lipid-rich material from the target lesion into the peripheral coronary vessels. NIRS has been employed to identify high-risk lesions that predispose patients to slow-flow or no-flow phenomena post-PCI. In the COLOR registry, lesions with an LCBI of 500 or greater were identified as being at risk for PAMI.[14] Similarly, the CANARY study identified lesions with an LCBI of 600 or greater as at risk for PAMI.[27] Identifying these high-risk lesions before PCI could assist in preventing complications, and it suggests that rigorous antithrombotic preparation of the patient prior to the procedure might be beneficial.

The ability to identify and quantify lipid materials using NIRS has been instrumental in evaluating the effects of antilipidemic therapies. In the YELLOW study, maximum doses of rosuvastatin were shown to decrease the maxLCBI4mm in non-intervened arteries, highlighting its effectiveness.[28,29] Recent findings from the PACMAN-AMI trial demonstrated incremental regression of coronary plaque, reduction of the lipid core, and plaque stabilization with the use of PCSK9 inhibitors in patients with acute coronary syndrome.[30] We are still awaiting the results of the FITTER study, which is evaluating the effect of evolocumab on the coronary lipid plaque component in non-culprit lesions.[31]

Finally, several studies have focused on the stratification of coronary lesions based on LCBI and maxLCBI4mm values. The most relevant studies include the LRP and PROSPECT II trials. Both of which assess lesion vulnerability in non-culprit arteries (NC) and the relationship between NIRS index values and the incidence of major cardiovascular events in these arteries (NC-MACE). In the LRP study, over 1500 patients with non-obstructive coronary artery disease (CAD) were evaluated. The study found a statistically significant association between maxLCBI4mm and NC-MACE within 24 months of assessment. Specifically, patients with a maxLCBI4mm of ≥400 had an 89% higher risk of NC-MACE (hazard ratio 1.89; *p*-value = 0.0021).[32] The PROSPECT II study explored the incidence of NC-MACE in patients following AMI over a 4-year period. Vulnerable lesions in this study were defined as those with maxLCBI4mm ≥325. Notably, most of these lesions were initially classified as non-significant angiographically.[33]

Our results corroborate previous studies demonstrating that LCBI and maxLCBI4mm decrease following coronary stent implantation. The observed reduction in LCBI can be attributed to several factors. First, microembolization of the lipid core may occur due to the disruption of the lipid cap during stent implantation, leading to the release of lipid material and subsequent micro-embolization to distal segments of the coronary vessels.[14,34] Additionally, stent implantation can result in the compression of the lipid core, causing a shift of lipid content towards the distal and proximal ends of the stent, as observed in the analyzed segment.[35,36] Finally, the structural design of the stent may reflect the NIRS catheter beam, partially obstructing analysis of the segment. Consequently, the LCBI value may be underestimated.[34]

Correlation graphs indicate a trend of decreased PV in patients with high initial LCBI and maxLCBI4mm. This decrease in PV may be attributed to plaque redistribution following PCI. These findings corroborate results from previous studies that have examined plaque redistribution after coronary stent implantation, verified through IVI.[35] Furthermore, the longitudinal redistribution of plaque is influenced by its composition. T. Roleder et al. demonstrated that in lesions characterized by a high lipid burden (HLB), defined as maxLCBI4mm >265, the decrease in PV is more pronounced compared to lesions with a lower lipid burden. HLB lesions are more susceptible to compression and are likelier to protrude through the stent struts.[36] Moreover, intensive lipid-lowering therapy may significantly contribute to the reduction of PV, particularly in lesions with a high lipid burden. Future studies should explore whether intensive lipid-lowering therapy is more effective in lesions presenting with elevated NIRS indices.

Limitations of the study

The study enrolled a relatively small group of patients, primarily due to the specific anatomical focus on the left main coronary artery. During the follow-up period, 33% of patients were excluded from the study either due to declined serial invasive examinations, due to the COVID-19 pandemic or due to insufficient image quality of the baseline examination recordings.

The identification of the external elastic membrane (EEM) and lumen could be enhanced with the use of artificial intelligence software, which is already implemented in some OCT and IVUS systems. However, current NIRS-IVUS systems lack this capability. As mentioned in the discussion, lipid detection using NIRS may be inaccurate when analysing plaque located behind stent strings. Therefore, we used before PCI indices for the final statistical analysis. Additionally, the authors identified a potential source of error stemming from the inability to co-register angiography with IVUS-NIRS data. This limitation complicated the manual analysis and accurate delineation of the proximal and distal edges of the left main coronary artery compared to co-registered systems.

Conclusion

Our trial did not demonstrate a significant correlation between initial LCBI or maxLCBI4mm and the development of plaque volume during the follow-up period in the left main coronary artery. However, correlation graphs indicate a trend toward decreased PV in patients with high initial LCBI and maxLCBI4mm, which aligns with findings from previously published studies. The potential favourable effect of high-intensity lipid-lowering therapy in high lipid burden (HLP) lesions warrants further investigation in subsequent studies.

Competing interest
The authors have no relevant financial or non-financial interests to disclose.

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Author contributions
All authors contributed to the study conception and design. Data collection (Martin Hudec, Jan Kaňovský, Vojtěch Brázdil, Martin Poloczek, Otakar Boček, Petr Jeřábek, Roman Štípal, Petr Kala), IVUS and NIRS data analysis (Martin Hudec, Ivona Kask, Kristýna Hochmanová, Radka Smitalová), statistical data analysis (Simona Littnerová, Jiří Jarkovský, Klára Benešová), review and editing (Jan Kaňovský) and supervision (Petr Kala). The first draft of the manuscript was written by (Martin Hudec), and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval
The study protocol was approved by the local ethics committee (Faculty Hospital Brno, EK610062015, 10th June 2015). The study was conducted in accordance with the Declaration of Helsinki.

Consent to participate
All patients provided written informed consent prior to enrolment.

Data availability statement
Dataset available in request from the authors.

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Původní sdělení | Original research article

18-Year Outcomes of Aortic Leaflet Extension Valvuloplasty Using Autologous Pericardium and Polytetrafluoroethylene: Single-Centre, Propensity-Matched Analysis

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Kľúčové slová:
Aortálna valvuloplastika pomocou extenzie cípov
Párovanie na základe propenzitných skórov
Polytetrafluóretylén
Trikuspidalizácia
Vrodená chyba aortálnej chlopne

SÚHRN

Úvod: Valvuloplastika aortálnej chlopne s extenziou cípov sa rutinne používa v liečbe chýb aortálnej chlopne u detí a dospievajúcich. Materiál použitý na valvuloplastiku môže ovplyvniť funkciu aortálnej chlopne a jej trvácnosť.
Ciele: Zhodnotiť dlhodobé výsledky valvuloplastiky aortálnej chlopne technikou extenzie cípov pomocou autológneho perikardu alebo polytetraflóretylénu (PTFE) a odhaliť rizikové faktory vedúce k reoperácii aortálnej chlopne na našom pracovisku.
Metódy: Retrospektívna analýza 89 pacientov, ktorí sa podrobili valvuloplastike aortálnej chlopne technikou extenzie cípov pomocou autológneho perikardu alebo PTFE na našom pracovisku v období 2005 – 2023.
Výsledky: 89 pacientov (75 % mužského pohlavia) sa podrobilo valvuloplastike aortálnej chlopne technikou extenzie cípov pomocou autológneho perikardu (n = 42) alebo PTFE (n = 47). Medián veku pacientov bol 14 rokov (IQR: 7 mesiacov – 26 rokov). Počas strednej dĺžky sledovania 13,3 roka (IQR: 1 mesiac – 18 rokov) sme zaznamenali 4 úmrtia a u 41 (46 %) pacientov bola potrebná reoperácia priemerne 7,8 ± 4,2 roka od primárnej operácie. V skupine s autológnym perikardom to nastalo u 24 (57 %) pacientov a v skupine s PTFE u 17 (36 %) pacientov. Celkové prežívanie pacientov v čase 18 rokov od operácie bolo 95 %. Reoperovanosť v celom súbore v 5 rokoch od operácie bola 12,4 %, v 10 rokoch 43 % a v 15 rokoch 64,6 %. Pri multivariabilnej Coxovej analýze boli identifikované nasledujúce rizikové faktory pre reoperáciu na aortálnej chlopni: aortálna insuficiencia ako primárna diagnóza, diameter aortálnej chlopne, infekčná endokarditída, dĺžka klemu na aorte a mimotelového obehu a predchádzajúca valvuloplastika v minulosti.
Záver: Dlhodobé výsledky aortálnej valvuloplastiky technikou extenzie cípov pomocou autológneho perikardu alebo PTFE u pacientov s vrodenou chybou aortálnej chlopne odrážajú vynikajúce prežívanie bez významného rozdielu z hľadiska výskytu reoperácií kvôli dysfunkcii aortálnej chlopne medzi obomi skupinami pacientov.

Keywords:
Aortic leaflet extension valvuloplasty
Congenital aortic valve disease
Polytetrafluoroethylene
Propensity score matching
Tricuspidalization

ABSTRACT

Background: Aortic valve repair with leaflet extension is routinely utilized in the management of aortic valve disease in children and adolescents. The material chosen may have an effect on the valve function and durability.
Aims: To evaluate long-term outcomes of aortic valve repair using autologous pericardium and polytetrafluoroethylene (PTFE) leaflet extensions and to investigate risk factors for aortic valve reoperation at single centre.
Methods: A retrospective single-centre review of 89 patients undergoing aortic valvuloplasty by leaflet extensions with either autologous pericardium or PTFE from 2005 to 2023.
Results: Eighty-nine patients (75% male) underwent aortic leaflet extension valvuloplasty, using either autologous pericardium (n = 42) or PTFE (n = 47). Median age was 14 years (IQR: 7 months–26 years). During median follow-up duration of 13.3 years (IQR: 1 month–18 years), there were 4 deaths and 41 (46%) patients required reoperation at a mean of 7.8 ± 4.2 years, 24 (57%) within autologous pericardium group, and 17 (36%) within PTFE group. Overall survival at 18 years was 95%. Overall reoperation-free survival at 5, 10 and

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15 years was 87.6%, 57%, and 35.4%, respectively. Multivariable Cox analysis identified primary diagnosis of aortic regurgitation, aortic annulus diameter, infective endocarditis, aortic cross-clamp and cardiopulmonary bypass time, and preoperative aortic surgical valvuloplasty as risk factors for aortic valve reoperation.
Conclusions: Long-term results of aortic leaflet extension valvuloplasty, utilizing either autologous pericardium or PTFE, in patients with congenital aortic valve disease suggest excellent survival with no significant difference in the reoperation rate for aortic valve dysfunction between the groups.

Introduction

Aortic valve plasty with leaflet extensions is a surgical technique used in both children and adolescents to manage aortic valve disease.[1] It has gained popularity among surgeons due to its efficiency in treating both aortic valve stenosis and regurgitation.[2] It also offers advantages of avoiding anticoagulation therapy, having a low risk of thrombosis, allows for potential growth of aortic annulus and has favorable hemodynamics.[3] Autologous pericardium, fresh or glutaraldehyde-treated was traditionally used for aortic leaflet extension valvuloplasty, although it has some disadvantages, including calcification and eventual attrition. In order to develop more durable materials for aortic valvuloplasty, alternative biological materials were introduced, such as decellularized bovine pericardium (CardioCel, Admedus, Queensland, Australia), CorMatrix (CorMatrix Cardiovascular, Inc, Atlanta, GA, USA) and equine pericardium (Matrix patch, Auto Tissue GmbH, Berlin, Germany).[2,4–6] Moreover, in 2008 we were the first to use 0.1-mm expanded polytetrafluroethylene (PTFE) membrane (W.L. Gore & Assoc., Flagstaff, AZ, USA) for aortic leaflet extension, and initial outcomes on 13 patients were published in 2012.[7] However, optimal material is yet unknown and needs to be explored further.

Only few studies reported the long-term results of aortic leaflet extension valvuloplasty in children and young adults.[1,3,8] Moreover, only one study in literature published mid-term results of using PTFE for aortic valvuloplasty,[9] and long-term outcomes are still to be investigated. Hence, we sought to assess long-term clinical outcomes of aortic valvuloplasty using autologous pericardium and PTFE with respect to patient survival, reoperation-free and aortic valve replacement (AVR) survival in pediatric patients, and adolescents with congenital aortic valve disease at our institution.

To our knowledge, this is the first retrospective comparison of autologous pericardium and PTFE patch material utilized for aortic leaflet extension valvuloplasty.

Aortic valvuloplasty by tricuspidalization with leaflet extension technique

Our surgical technique had been published previously,[7] and did not change throughout study period. In addition, surgical technique video is available online on a CTSnet website.[10] Autologous pericardium was treated with glutaraldehyde 0.625% solution for 8 minutes, and then rinsed in isotonic saline prior to use. Initially, we used autologous pericardium; however, since 2008, we have transitioned to utilizing a 0.1 mm PTFE membrane as a leaflet extension material. Briefly, all patients were operated through a full median sternotomy in mild hypothermia using cold blood Del Nido cardioplegia solution. The cardiopulmonary bypass was initiated via single or double caval and aortic cannulation.

The aortic valve was exposed through a transverse aortotomy. The raphe was divided to aortic wall, and a commissurotomy and shaving were performed in some cases if there was commissural fusion and thickening of the leaflets. After native leaflets were excised, the length of each leaflet was measured separately using a silk tie.

The height of leaflets was determined by mesuring the height of the native left coronary leaflet. Then rectangular patches of autologous pericardium or 0.1 mm PTFE (W.L. Gore & Assoc., Flagstaff, AZ, USA) were created and sewed to the free edges of leaflets with 6-0 polypropylene or polybutester (Vascufil) sutures. A central stitch was used to join the three patches to adjust and assess geometry and coaptation of the valve. The constructed leaflets were suspended at the level of newly created commissures using sutures' free ends and secured outside the aorta with pericardial pledgets. All procedures were done by the same surgeon at our centre.

Patients and methods

Patients

Study included patients who had undergone aortic valvuloplasty with leaflet extensions at Department of Pediatric Cardiac Surgery, Children's Heart Centre, Bratislava, Slovakia, between 31 August 2005 and 31 August 2023. Medical records of the patients were reviewed retrospectively.

The patients with congenital aortic valve disease, who were referred for aortic valvuloplasty by leaflet extension using autologous pericardium or PTFE were included. Patients without retrievable medical or operation records, and those undergoing aortic leaflet extension valvuloplasty using equine pericardium (Matrix patch, AutoTissue GmbH, Berlin, Germany) were excluded from the study.

Demographic data, primary diagnosis, gender, aortic valve morphology, previous procedures: surgical or balloon aortic valvuloplasty, aortic annulus and ascending aorta size, age at operation, extension height and material, pre- and post-operative echocardiographic findings, follow-up clinical data and reoperation data were collected. We also analyzed treatment outcomes, patient survival, and duration of freedom from reoperation.

All patients were evaluated by transthoracic echocardiography preoperatively, perioperatively by transesophageal echocardiography, and postoperatively at regular intervals (3–12 months). The aortic valve annulus and root dimensions were measured in parasternal long-axis views.

Patients were assigned to two groups (based on the extension material): autologous pericardium and PTFE. Propensity score-matching analysis method was done, and 38 patients (19 matched pairs) were chosen for comparison.

Study endpoints were survival, freedom from reoperation, and freedom from AVR. Freedom from reoperation was defined as the time period between aortic valvuloplasty and aortic valve reoperation. Freedom from AVR was defined as the time period between aortic valvuloplasty and aortic valve replacement with either mechanical or biological prosthesis. Patients in both groups received aspirin for 6 months postoperatively.

Decisions regarding the primary operation or reoperation were made individually in a multidisciplinary conference. Indication criteria for aortic valvuloplasty or reoperation were severe aortic stenosis (AS) with mean gradient ≥50 mmHg and/or severe aortic regurgitation (AR) with dilated left ventricle (Z-Score ≥3) and IE.

Statistical analysis

All continuous variables are expressed as mean and standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables are presented as numbers with percentages. Comparisons for categorical variables were calculated with chi-squared (χ^2) or Fisher's exact test. Shapiro–Wilk test was employed to determine the normality of distribution. Student's t-test was used to compare continuous variables in the unmatched cohort, unless the data were not distributed normally; in these instances, Mann–Whitney U-test was used. Comparisons within the matched cohort were constructed using a paired-sample t-test, or Wilcoxon signed rank test, where appropriate.

Kaplan–Meier survival analysis was used to evaluate freedom from reoperation and AVR, and to estimate a rate of survival. Comparisons between groups were tested by log-rank test. A univariable and multivariable Cox regression models were contructed to assess factors associated with reoperation. Variables with a *p*-value <0.1 in the univariable analysis were used for the multivariable stepwise Cox regression model.

Propensity score matching (PSM) method was used to match two groups on a set of 4 explanatory variables (age, weight, gender, and primary diagnosis). Propensity score was estimated using a logistic regression model with 1 : 1 nearest neighbor matching without replacement based on a caliper width of 0.2 times the standard deviation (SD) of the logit of propensity score.[11] Standardized difference in means between two groups pre- and post-matching was used to evaluate the matching quality.

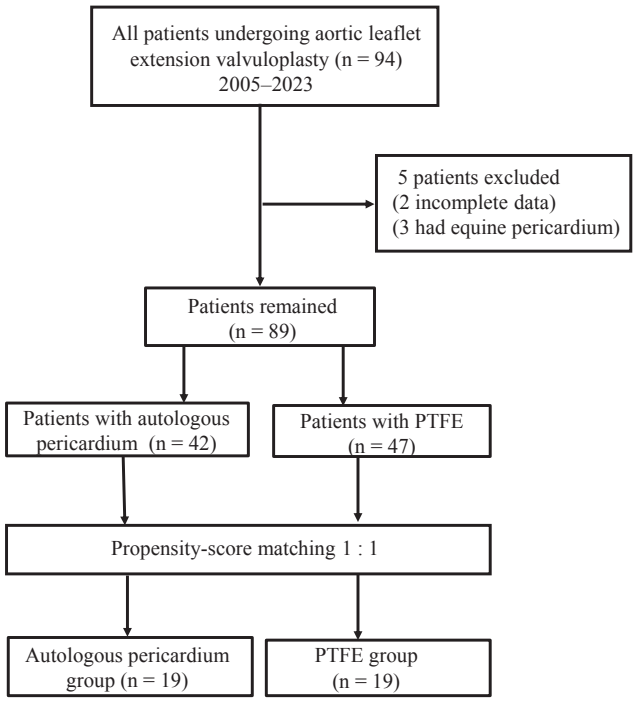

Fig. 1 – Flowchart of the study. PTFE – polytetrafluoroethylene.

For all tests, a $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using R statistical software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 89 patients were included. Of these, 42 (47%) underwent aortic valvuloplasty using autologous pericardium and 47 (53%) using PTFE. Median follow-up for the entire cohort was 13.3 years (IQR: 1 month–18 years). Median follow-up was 15.2 years (IQR: 1 month–18 years) for autologous pericardium group and 8 years (IQR: 2 weeks–14.8 years) for PTFE group ($p = 0.01$). The majority of the patients 71 (80%) had a bicuspid aortic valve (BAV). The study flow chart is shown in **Figure 1.**

Overall previous balloon valvuloplasty was performed in 34 (38%) patients. Additional previous procedures included surgical aortic valvuloplasty (n = 11), ventricular septal defect closure (n = 2), coarctation repair (n = 2), and correction of interrupted aortic arch with ventricular septal defect (n = 1). Baseline characteristics, operative, and postoperative data in each group are presented in **Tables 1** and **2**.

Survival

Survival rate at 1, 5, 10 and 18 years was 97.7% (95% CI 94–100%), 96.4% (95% CI 92–100%), 95% (95% CI 90–99.8%) and 95% (95% CI 90–99.8%), respectively (**Fig. 2**). Overall, 4 (4.5%) patients died during follow-up (including 30-day mortality), 1 (2%) patients in the autologous

Table 1 – Demographic characteristics of patients undergoing aortic leaflet extension valvuloplasty

	Before matching				After matching		
Variable	**Total (n = 89)**	**Autologous pericardium (n = 42)**	**PTFE (n = 47)**	**SMD**	**Autologous pericardium (n = 19)**	**PTFE (n = 19)**	**SMD**
Age (years)	13.5 (5.6)	13.9 (6.2)	13.1 (5.0)	0.14	12.2 (6.9)	12.6 (5.1)	0.06
BSA (m^2)	1.40 (0.46)	1.40 (0.48)	1.40 (0.45)	0.02	1.30 (0.55)	1.37 (0.44)	0.14
Weight (kg)	49 (22)	48 (22)	49 (22)	0.02	45 (25)	45 (20)	0.03
Follow-up (years)	11.4 (5.6)	15.4 (3.0)	7.9 (5.0)	1.8	14.3 (4.3)	8.2 (5.4)	1.2
Age group, n (%)				0.26			0.51
<5 years	9 (10%)	5 (12%)	4 (8.5%)		5 (26%)	2 (11%)	
5–10 years	10 (11%)	5 (12%)	5 (11%)		1 (5.3%)	3 (16%)	
10–15 years	29 (33%)	11 (26%)	18 (38%)		4 (21%)	5 (26%)	
>15 years	41 (46%)	21 (50%)	20 (43%)		9 (47%)	9 (47%)	
Gender, n (%)				0.06			0.001
Male	22 (25%)	11 (26%)	11 (23%)		4 (21%)	4 (21%)	
Female	67 (75%)	31 (74%)	36 (77%)		15 (79%)	15 (79%)	
Diagnosis, n (%)				1.1			<0.001
Aortic stenosis	43 (48%)	10 (24%)	33 (70%)		10 (53%)	10 (53%)	
Aortic regurgitation	10 (11%)	5 (12%)	5 (11%)		2 (11%)	2 (11%)	
Mixed aortic valve disease	36 (40%)	27 (64%)	9 (19%)		7 (37%)	7 (37%)	
History of balloon aortic valvuloplasty, n (%)	34 (38%)	17 (40%)	17 (36%)	0.08	7 (37%)	5 (26%)	0.22
History of surgical aortic valvuloplasty, n (%)	11 (12%)	5 (12%)	6 (13%)	0.02	1 (5.3%)	5 (26%)	0.6
Preoperative transaortic valve peak gradient (mmHg)	82 (24)	78 (13)	83 (27)	0.5	76 (12)	78 (29)	0.02
Preoperative aortic regurgitation grade, n (%)				0.75			0.4
None or trivial	14 (16%)	3 (7.1%)	11 (23%)		3 (16%)	4 (21%)	
Mild	14 (16%)	3 (7.1%)	11 (23%)		3 (16%)	5 (26%)	
Moderate	36 (40%)	22 (52%)	14 (30%)		7 (37%)	4 (21%)	
Severe	25 (28%)	14 (33%)	11 (23%)		6 (32%)	6 (32%)	
Aortic valve anatomy, n (%)				0.64			0.9
Unicuspid	5 (5.6%)	2 (4.8%)	3 (6.4%)		1 (5.3%)	2 (11%)	
Bicuspid	71 (80%)	29 (69%)	42 (89%)		12 (63%)	17 (89%)	
Tricuspid	13 (15%)	11 (26%)	2 (4.3%)		6 (32%)	0 (0%)	

Continuous and categorical variables are expressed as mean ± SD and n (%), respectively.
BSA – body surface area; PTFE – polytetrafluoroethylene; SD – standard deviation; SMD – standardized mean difference.

pericardium group and 3 (6.3%) patients in the PTFE group ($p = 0.28$).

There was one (1.2%) early death within post-operative period of 30 days. The patient was a 2-year-old male who could not have been weaned off cardiopulmonary bypass due to ventricular arrhythmia, and a left ventricular assist device was instituted. Later on, it was switched to extracorporeal membrane oxygenation. Eventually, he died of a *thromboembolic event* and cerebral edema 2 days postoperatively. There were three (3.4%) late deaths due to non-cardiac causes, and no deaths were related to the structural failure of aortic valve after valvuloplasty.

In a matched cohort, survival rate was 97.7% (95% CI 92–100%) at 1 year and 94.3% (95% CI 86.7–100%) at 5, 10, and 18 years. Overall 1 (2.6%) patient died during follow-up in autologous pericardium group, and no death occurred in PTFE group ($p = 0.93$). **Figures S1 A and B in the Supplementary material show overall survival and survival by groups after matching.**

Freedom from reoperation

During the study period, 41 patients (46%) underwent reoperation, with an incidence of 24 (57%) and 17 (36%) in autologous pericardium and PTFE group, respectively. Overall median time to reoperation was 8.4 years (IQR, 4 months to 14.7 years), and mean time was 7.8±4.2 years. Median interval to reoperation was 7.8 years (IQR: 4 months to 14.7 years) and 7.5 years (IQR: 2.4 to 13.6 years) for

Table 2 – Operative and postoperative data

	Before matching				After matching		
Variable	Total (n = 89)	Autologous pericardium (n = 42)	PTFE (n = 47)	SMD	Autologous pericardium (n = 19)	PTFE (n = 19)	SMD
Aortic annulus size (mm)	21.2 (5.0)	21.9 (5.1)	20.6 (4.9)	0.35	19.9 (5.7)	20.2 (4.9)	0.05
Ascending aorta size (mm)	29 (7)	30 (7)	28 (7)	0.22	27 (8)	27 (8)	0.019
Extension height (mm)	16 (3)	16 (2)	17 (3)	0.19	16 (3)	16 (2)	0.07
Cardiopulmonary bypass (min.)	144 (48)	165 (51)	125 (36)	0.89	166 (68)	125 (39)	0.73
Cross-clamp (min.)	105 (25)	114 (22)	96 (25)	0.76	113 (25)	92 (25)	0.83
Hospital LOS (days)	8 (5)	6 (3)	9 (6)	0.53	7 (2)	9 (5)	0.65
Reduction ascending aortoplasty, n (%)	12 (13.5%)	8 (19%)	4 (8.5%)	0.28	4 (21%)	2 (10.5%)	0.72
Postoperative aortic regurgitation grade, n (%)				0.35			0.38
None or trivial	60 (67.5%)	29 (69%)	31 (66%)		12 (63%)	11 (58%)	
Mild	29 (32.5%)	13 (31%)	16 (34%)		6 (32%)	8 (42%)	
Postoperative transaortic valve peak gradient (mmHg)	13 (11)	10 (10)	15 (12)	0.39	13 (12)	15 (13)	0.13

Continuous and categorical variables are expressed as mean±SD and n (%), respectively.
LOS – length of stay; PTFE – polytetrafluoroethylene; SD – standard deviation; SMD – standardized mean difference.

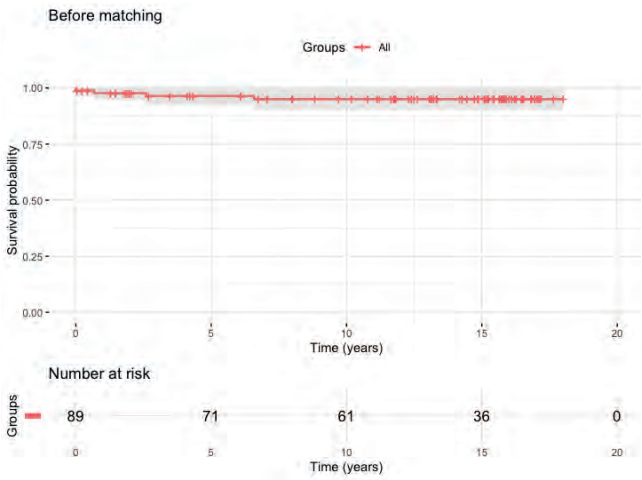

Fig. 2 – Kaplan–Meier curve showing overall survival.

autologous pericardium and PTFE group, respectively, (p = 0.25).

The indications for reoperation were severe AS (n = 18; 44%), severe AR (n = 16; 39%), and IE (n=7; 17%). Overall freedom from reoperation at 1, 5, 10 and 15 years was 98.8% (95% CI, 96.6–100%), 87.6% (95% CI 80–94.8%), 57% (95% CI 45.4–69%) and 35.4% (95% CI 22.7–48%), respectively (**Supplementary material, Fig. S2A**).

Among the 41 patients requiring reoperation, 33 underwent AVR, 5 had Bentall procedure, one had a re-aortic valvuloplasty with PTFE leaflet extensions, 1 had aortic root replacement with aortic homograft, and one underwent a Ross–Konno operation.

Freedom from reoperation at 1, 5 and 10 years was 97.6% (95% CI 92.8–100%), 88% (95% CI 77–97.8%) and 67.9% (95% CI 53.5–82%) in autologous pericardium group, and 100% (95% CI 100–100%), 86.2% (95% CI 75–97%) and 39.4% (95% CI 20–58%) in PTFE group, respectively. No statistically significant difference regarding the reoperation rate was observed between two groups (p = 0.14). Freedom from reoperation according to the type of patch material is shown in **Supplementary material, Fig. S2B**.

There were 18 (42.8%) reoperations in the matched cohort. Overall median time to reoperation was 8.2 years (IQR 4.5months to 14.7 years). Overall 15-years freedom from reoperation was 37.4% (95% CI 18.8–56%) (**Fig. 3A**). In autologous pericardium group, freedom from reoperation at 1, 5 and 10 years was 100% (95% CI 100–100%), 89% (95% CI 74–100%), and 54.2% (95% CI 30–77%), respectively. In PTFE group, the freedom from reoperation at 1, 5 and 10 years was 100% (95% CI 100–100%), 93% (95% CI 79–100%), and 34% (95% CI 7–60%), respectively. There was no statistically significant difference between the groups (p = 0.39). **Fig. 3B** shows freedom from reoperation in the matched cohort by groups.

Freedom from AVR

Overall, freedom from AVR at 1, 5, 10 and 15 years was 100% (95% CI 100–100%), 90% (95% CI 82–96%), 59% (95% CI 47–70%) and 37% (95% CI 24–50%), respectively (**Supplementary material, Figs S3A** and **S3B**).

In the matched cohort, the overall 15-year freedom from AVR was 41.7% (95% CI 22.2–61%) (**Fig. 4A)**. In autologous pericardium group, the freedom from AVR at 1, 5 and 10 years was 100% (95% CI 100–100%), 94% (95% CI 83–100%) and 57.4% (95% CI 33–81%), respectively. In PTFE group, freedom from AVR at 1, 5 and 10 years was 100% (95% CI 100–100%), 86% (95% CI 75–97.5%) and 39.4% (95% CI 20–58%), respectively (**Fig. 4B)**. No statistically significant difference between the groups was found (p = 0.18).

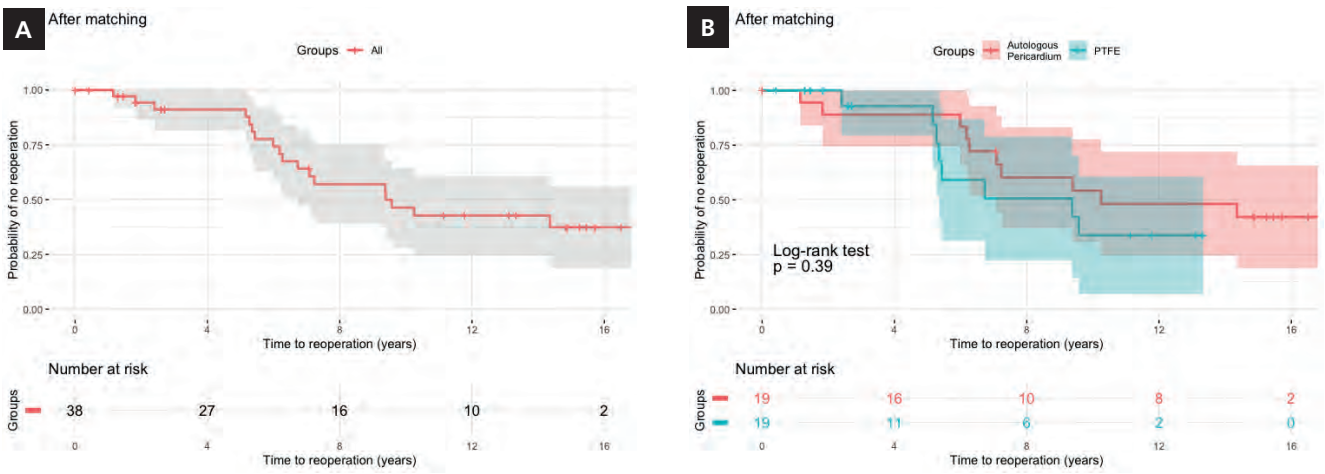

Fig. 3 – Kaplan–Meier curves showing freedom from reoperation in matched cohort, (A) all patients (B) by groups. PTFE – polytetrafluoroethylene.

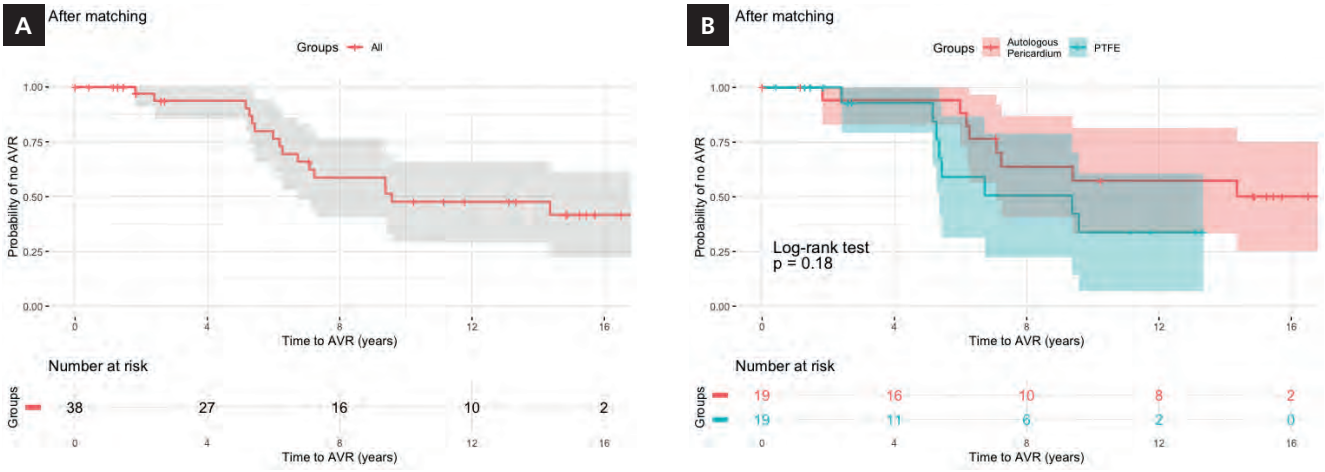

Fig. 4 – Kaplan–Meier curves showing freedom from AVR in matched cohort, (A) all patients, (B) by groups. PTFE – polytetrafluoroethylene.

Risk factors

The univariable and multivariable Cox regression analyses identified a primary diagnosis of AR (HR 2.5, 95% CI 1.2–5.2, p = 0.017), aortic annulus diameter (HR 1.1, 95% CI 1–1.2, p = 0.038), IE (HR 4.3, 95% CI 1.53–12.5, p = 0.006), aortic cross-clamp time (HR 0.96, 95% CI: 0.94–0.99, p = 0.014), cardiopulmonary bypass time (HR 1.02, 95% CI 1–1.2, p = 0.017) and previous surgical aortic valvuloplasty (HR 2.7, 95% CI 1.1–6.7, p = 0.027) as risk factors for aortic valve reoperation. The results of the Cox regression analysis of risk factors for reoperation are presented in **Table 3.**

Infective endocarditis

Overall 7 patients underwent reoperation due to IE: 5 of 42 (11.9%) in the autologous pericardium group, and 2 of 47 (4.2%) in the PTFE group. However, there was no statistically significant difference between the two groups (p = 0.24). During the follow-up, there was no recurrence of IE in these patients. Patients had reoperation after a mean of 29 days (20–42 days) of antibiotic therapy, with the exception of one patient who required urgent surgery due to large vegations on the valve. The most commonly used preoperative antibiotic was vancomycin (70%), followed by gentamicin (55%), ceftriaxone (50%), and piperacillin/tazobactam (35%).

Discussion

Aortic valvuloplasty by leaflet extension with tricuspidalization is a useful surgical procedure which effectively repairs aortic valve stenosis and regurgitation. In addition, it improves left ventricular dimensions in children and young adults.[1,3,4] Several patch materials have been used to extend and augment the aortic leaflets, including fresh or glutaraldehyde-treated autologous pericardium, bovine and equine pericardium. Furthermore, our group introduced and used the 0.1mm PTFE membrane, which showed a satisfactory result in the pulmonary position.[7,12,13]

PTFE has unique physical properties such as increased flexibility and exceptional tensile strength. Furthermore, it has high biocompatibility, and its microporous structure is believed to prevent cellular penetration and subsequent calcification, which is a typical cause of valve dysfunction.[7]

Overall survival rate in our cohort at 18 years was 95% (95% CI 90–99%). This is comparable to similar reports from Vergnat et al.[15] and Kwak et al.[16] Overall freedom from reoperation for the entire cohort at 5, 10 and 15 years was 87.6% (95% CI 80–94.8%), 57% (95% CI 45.4–69%) and 35.4% (95% CI 22.7–48%), respectively. Freedom from reoperation for the matched cohort at 5, 10 and 15 years was 91% (95% CI 81–100%), 46% (95% CI 28–64%), and 37.4% (95% CI 18.8–56%), respectively. This is in agreement with the data about similar patients published by Al Halees et al.[16] and Polimenakos et al.[1]

During the follow-up in the matched cohort, there were no significant differences between two groups regarding survival, reoperation-free, and AVR-free survival rates, with survival rate of 94.7% at 10 years in autologous pericardium versus 92.9% at 10 years in the PTFE group, (p = 0.93). Freedom from reoperation was 54% at 10 years in the autologous pericardium group versus 34% at 10 years in the PTFE group (p = 0.14). Furthermore, the freedom from AVR in autologous pericardium and PTFE group at 10 years was 57.4% and 39.4%, respectively (p = 0.18).

Multivariable Cox regression analysis identified the patients with a primary diagnosis of AR to be more at risk for reoperation. Other authors observed similar results and found that pre- amd postoperative AR was associated with the need for aortic valve reoperation.[1,17] This might be due to the difficulty of the left ventricular myocardium in adjusting volume overload compared to pressure overload.[18] In addition, the aortic annulus diameter, aortic cross-clamp, cardiopulmonary bypass time, and IE were associated with a higher risk for reoperation. Polimenakos et al.[1] and Vergnat et al.[15] published similar findings. The extension material type was not associated with either reoperation or AVR risk in our Cox regression analysis (**Table 3**).

Unlike Vergnat et al.[15] we found that prior surgical aortic valvuloplasty was a significant risk factor for reoperation (in multivariable Cox regression analysis). However, these patients included those with previously failed balloon aortic valvuloplasty. From our perspective, these patients had more dysplastic aortic valves, which could have affected the performance of the aortic valve following subsequent aortic leaflet extension valvuloplasty.

Our results differ from those published by Karliova et al.[9] who had used a PTFE patch material for aortic valvuloplasty and converting unicuspid into bicuspid aortic valves. In contrast, our aortic valvuloplasty technique restores tricuspid configuration while three neocomissures provide better support for the leaflet extensions. At the same time, we believe that tricuspidalization provides a larger central opening while minimizing blood turbulence.[1]

Aortic leaflet extension valvuloplasty also has the advantage of allowing aortic annular growth until a more permanent replacement alternative becomes available, such as the currently preferred Ross procedure with inclusion technique or prosthetic valve replacement.[5,19,20]

Infective endocarditis remains a concern for patients undergoing aortic valve surgery. The incidence varied across the literature, which could be related in part to the patch material utilized for leaflet reconstruction and the patient's dental hygiene habits. Overall the incidence of IE requiring reoperation in our study was 7.8% for all

Table 3 – Risk factors for reoperation and AVR by univariable and multivariable Cox regression analyses, all patients

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender	0.86 (0.42–1.76)	0.68		
Weight at surgery (kg)	0.99 (0.98–1.01)	0.57		
Age at surgery (years)	0.98 (0.93–1.04)	0.66	0.92 (0.85–1.01)	0.082
History of balloon aortic valvuloplasty	1.31 (0.69–2.48)	0.41		
Primary diagnosis				
AS	3.5 (1.48–8.6)	0.01	1.01 (0.51–1.97)	0.97
AR	3.2 (1.6–7.3)	0.037	2.5 (1.17–5.2)	0.017
Patch material	1.65 (0.83–3.2)	0.15		
AoV diameter (mm)	1.04 (0.97–1.12)	0.22	1.1 (1.01–1.21)	0.038
Infective endocarditis	2.21 (0.91–5.3)	0.078	4.3 (1.53–12.5)	0.006
History of surgical valvuloplasty	1.68 (0.74–3.8)	0.21	2.7 (1.12–6.7)	0.027
Extension height (mm)	1.04 (0.91–1.18)	0.54		
Extension height ≤ 12 mm	1.51 (0.46–4.96)	0.49		
Extension height ≤ 15 mm	0.92 (0.49–1.7)	0.79		
Reduction ascending aortoplasty	0.45 (0.12–0.6)	0.22		
Cross-clamp (min.)	0.99 (0.98–1.01)	0.60	0.96 (0.94-0.99)	0.014
Cardiopulmonary bypass (min.)	1 (0.99-1.01)	0.92	1.02 (1-1.04)	0.017

AR – aortic regurgitation; AS – aortic stenosis.

patients, with a lower incidence for PTFE (2/47) compared to autologous pericardium (5/42). Nevertheless, there was no statistically significant difference ($p = 0.24$). Moreover, Wiggins et al.[4] reported a 5% IE rate after aortic valve leaflet repair in children. Furthermore, Karliova et al.[9] showed that IE occurred in two (18%) of the eleven patients in their study.

Limitations

The limitations of our study include a single-centre character, retrospective analysis and the shorter median follow-up time for the PTFE group compared to the autologous pericardium group.

Conclusions

The long-term results of aortic leaflet extension valvuloplasty, utilizing either autologous pericardium or PTFE, in patients with congenital aortic valve disease suggest excellent survival with no significant difference in the rate of reoperation for aortic valve dysfunction between the groups.

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Conflict of interest
The authors have declared that no competing interests exist.

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Ethical statement
The Study was approved by Institutional Review Board of National Institute of Cardiovascular Diseases, Bratislava, Slovakia (Approval Number: 62/2023), and the need for informed consent was waived because of the retrospective nature of the study.

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Appendix A – Supplementary data
Supplementary data associated with this article can be found in the online version.

Původní sdělení | Original research article

The prognostic importance of the percentage of immature granulocyte in 28-day mortality in patients with acute coronary syndrome

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Nezralé granulocyty

SOUHRN

Kontext: Procento nezralých granulocytů (immature granulocytes, IG%) je časným markerem zánětu s prognostickou hodnotou u řady onemocnění.
Cíl: V této studii jsme se pokusili zjistit, zda má procento nezralých granulocytů prognostickou hodnotu z hlediska 28denní mortality pacientů s akutním koronárním syndromem (AKS).
Metoda: Jednalo se o retrospektivní studii provedenou v období mezi 1. lednem 2019 a 30. červnem 2019 na Klinice urgentní medicíny Lékařské fakulty Univerzity v tureckém Mersinu. Do studie byli zařazeni všichni pacienti ve věku nad 18 let, kteří byli dopraveni na kliniku urgentní medicíny s bolestí na hrudi a hospitalizováni s předběžnou diagnózou AKS. Pacienti byli rozděleni do dvou skupin, na ty, kteří přežili, a ty, kteří nepřežili. Byly zaznamenány hodnoty IG% a dalších laboratorních parametrů a následně byl analyzován vztah mezi hodnotami IG% a 28denní mortalitou. Kromě toho byla pro srovnání diagnostické přesnosti hodnot IG% a dalších proměnných provedena analýza ROC.
Výsledky: Do studie bylo zařazeno celkem 617 pacientů, z tohoto počtu bylo 423 (68,6 %) mužů. Průměrný věk pacientů dosahoval 63,9 ± 12,7 roku. Hodnota IG% byla vyšší u nepřeživších pacientů (1,2 ± 1,4) než u přeživších (0,5 ± 0,5) (p = 0,007). V predikci 28denní mortality, pokud byla mezní hodnota IG% > 0,6, byla zjištěna specificita ve výši 93,70 % a senzitivita 54,55 % (AUC = 0,717; p = 0,000). V predikci 28denní mortality na AKS představovalo IG% nezávislý rizikový faktor (poměr rizik [hazard ratio, HR] 632,962; 95% interval spolehlivosti 3,389–118 206,572; p = 0,016).
Závěr: U pacientů s AKS může hodnota IG% souviset s 28denní mortalitou.

Keywords:
28-day mortality
Acute coronary syndrome
Immature granulocytes

ABSTRACT

Background: The percentage of immature granulocytes (IG%) is an early marker of inflammation and has a prognostic significance in many diseases.
Objective: In this study, we tried to investigate whether the percentage of immature granulocytes has a prognostic value in 28-day mortality in patients with acute coronary syndrome (ACS).
Method: This study was carried out retrospectively between 1.1.2019 and 30.6.2019 at Mersin University Faculty of Medicine, Department of Emergency Medicine. Patients older than 18 years who applied to the emergency department with chest pain and were hospitalized with a preliminary diagnosis of ACS were included in the study. The patients were divided into two groups as survivors and non-survivors. IG% and other laboratory parameters were recorded. The relationship between IG% and 28-day mortality was analyzed. In addition, ROC analysis was performed to compare the diagnostic accuracy of IG% and other variables.
Results: A total of 617 patients, including 423 (68.6%) men, were included in the study. The mean age of the patients were 63.9 ± 12.7. IG% was higher in non-survivor patients (1.2 ± 1.4) than in surviving patients (0.5 ± 0.5) (p = 0.007). In predicting 28-day mortality, when the cut-off value for IG% was >0.6, the specificity was found to be 93.70% and the sensitivity to be 54.55% (AUC = 0.717, p = 0.000). In predicting 28-day mortality for ACS, IG% was an independent risk factor (hazard ratio [HR] 632.962, 95% confidence interval 3.389–118206.572, p = 0.016).
Conclusion: IG% may be associated with a 28-day mortality in patients with ACS.

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Introduction

Despite significant advances in the diagnosis and treatment of acute coronary syndrome, it remains the leading cause of death worldwide, and about half of these deaths are due to ischemic heart disease.[1] It is believed that high levels of inflammatory factors in the blood contribute to the development of cardiovascular events and that chronic inflammation plays a key role in the pathogenesis of atherosclerosis.[2] Presence of macrophages, T lymphocytes, dendritic cells and mast cells in atherosclerotic lesions; detection of HLA class II antigen expression; and the secretion of various cytokines points to the role of inflammatory mechanisms in the pathogenesis of atherosclerosis.[3]

Predicting the prognosis in acute coronary syndromes is a very important step in treatment and follow-up. Biomarkers such as cardiac troponins, CRP, and NT-BNP are frequently used in the prognosis of ACS patients. Despite this, clinicians are still searching for many new biomarkers that can be used to predict the prognosis of patients with ACS. Examples of these are biomarkers such as cortisol, neutrophil to lymphocyte ratio (NLR), D-dimer, adinopectin, and serum albumin, and HbA_{1c}.[4–9]

Immature granulocytes are cells secreted from the bone marrow and represent immature granulocytes. Normally, blood levels of these cells are low; however, they increase in the bone marrow during infection, inflammation or ischemic events. Since inflammatory processes in ACS may result in damage to cardiac tissue, the number of immature granulocytes is an important parameter when assessing the clinical status and prognosis of the patient.[10–13]

In this study, we will examine the effects of the percentage of immature granulocytes on 28-day mortality in ACS patients and provide potential prognostic information for the treatment process of patients. Aiming to contribute to both clinical practice and the existing literature, this study will be an important step towards understanding the role of inflammation in the management of cardiac diseases.

Materials and methods

Patients and study design

Patients who applied to the emergency department with chest pain complaints and were diagnosed with ACS using laboratory tests and imaging methods between 1.1.2019 and 31.6.2019 were included in this study. Our study was conducted by retrospectively scanning the data of patients from hospital electronic information operating systems. The patients included in the study were divided into two groups as those who were discharged and those who died within 28 days. Ethics committee approval (No: 2021/726 Date: 03/12/2021) was received.

Patients whose laboratory data could not be reached, patients with chest pain diagnosed as other than ACS, patients receiving chemotherapy, patients with immunosuppression, pregnant, patients with hematological disease and patients under 18 years of age were excluded from the study. 21 patients were excluded from the study and the study was completed with 617 patients (**Fig. 1**).

Age, gender, leucocyte, platelet, immature granulocyte percentage (IG%), NLR, glucose, C-reactive protein (CRP), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH, creatinine, CK, CK-MB, and troponin values of the patients were recorded. The patients were divided into two groups as those who survived and those who died in the first 28 days. All parameters were evaluated between groups. The primary endpoint of the study was 28-day mortality in ACS patients.

Laboratory examination

Blood samples for laboratory tests were collected within 2 h of admission. After blood samples were collected in the EDTA tube for the determination of leucocyte count, platelet count and IG%, measurements were performed on the automated blood cell analyzer (XN-1000, Sysmex Corp. Kobe, Japan). The normal reference values of the parameters in our study were as follows: leukocytes (4500–10000/mm^3), neutrophil percentage (42.2–75.2%), and immature granulocyte percentage (0–0.6), serum CRP (0–5 mg /dL).

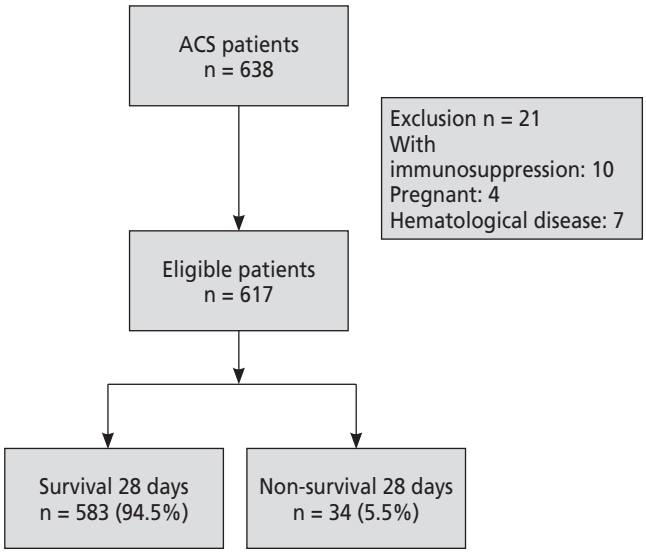

Fig. 1 – Flow chart of the study.

Table 1 – Demographic data of patients

Variables		n	Percentage
Gender	Male	423	68.6
	Female	194	31.4
IG%	Low	506	82.0
	High	111	18.0
Group	STEMI	98	15.9
	Non-STEMI	222	36.0
	USAP	297	48.1
Outcome	28-day mortality	34	5.5
	Survivor	583	91.4

Table 2 – Comparison of laboratory parameters between deceased and surviving patients

Variables	Deceased (n = 34)	Surviving (n = 583)	*p*
Age	73.0 ± 14.4	63.2 ± 12.3	**<0.001**
Leucocyte	12.92 ± 6.81	9.56 ± 3.45	**0.007**
Neutrophil	9.7 ± 6.8	6 ± 2.9	**0.003**
NLR	9.1 ± 9.8	3.1 ± 3.4	**0.001**
Lymphocytes	2.1 ± 1.7	2.6 ± 1.4	**0.034**
Platelets	238 ± 95.4	254.8 ± 79.2	0.237
IG%	1.2 ± 1.4	0.5 ± 0.5	**0.007**
Glucose	181.1 ± 80.9	167 ± 97	0.413
AST	83.1 ± 162	34.8 ± 53.5	0.097
ALT	42.5 ± 86	27 ± 38.2	0.309
LDH	628.5 ± 534.2	256.3 ± 108.1	0.149
CK	334.5 ± 1013.2	168.3 ± 236.1	0.385
CK-MB	49 ± 86	17.7 ± 47.6	**0.047**
Troponin	41.3 ± 68.9	4.6 ± 8.4	**0.008**
CRP	41.3 ± 68.9	11.2 ± 20.1	**0.018**

Statistical analysis

Statistical analyzes of this study were performed with SPSS Statistics for Windows program. Frequency distributions for categorical variables and normality controls for continuous measurements were tested with the Shapiro–Wilk test. Analysis of variance was used for group comparisons. Levene test was used for homogeneity of variances. One-way ANOVA was used for the differences between the group means in cases where the homogeneity of variances was provided, and the Welch test was used when the condition was not met. For pairwise comparisons, Bonferroni test was used when variances were homogeneous and Games Howell test was used when heterogeneous. Pearson correlation coefficient was used to control the relationship between continuous variables. Numbers and percentages were given as descriptive statistics. *P* <0.05 was taken as statistical significance. ROC analysis was performed for survival analysis and the area under the curve was calculated. *P* <0.05 value was used for statistical significance.

Results

A total of 617 ACS patients, including 423 (68.6%) men and 194 (31.4%) women, were included in the study. Ninety-eight (15.9%) of the patients were STEMI, 222 (36.0%) NSTEMI and 297 (48.1%) USAP patients._The mean age of the patients were 63.9 ± 12.7 (**Table 1, Fig. 1**).

When the laboratory parameters of the died and surviving patients were compared; IG% (1.2 ± 1.4, 0.5 ± 0.5, $p = 0.007$), leukocytes (12.92 ± 6.81, 9.56 ± 3.45, $p < 0.007$), CRP (41.3 ± 68.9, 11.2 ± 20.1, $p = 0.018$), neutrophil (9.7 ± 6.8) .6 ± 2.9, $p = 0.003$), NLR (9.1 ± 9.8, 3.1 ± 3.4, $p = 0.001$), troponin (41.3 ± 68.9, 4.6 ± 8.4 $p = 0.008$) and creatinine (1.52, 0.89, $p = 0.04$) values in the deceased group was found to be higher. Lymphocyte value was significantly lower among patients who died (2.1 ± 1.7, $p = 0.034$) (**Table 2**). In the ROC analysis performed to predict 28-day mortality, when the cut-off value for IG% was 0.6 and above; specificity was 93.70%, sensitivity 54.55%, PPV 15.93%, and 97.02% (AUC = 0.717, $p = 0.0001$) (**Fig. 2, Table 3**).

When Cox regression analysis (univariate Cox regression) was performed one by one with all parameters thought to affect death in the study, all variables except ALT value were found to be significant. After the variables thought to affect death in the study were determined as a result of univariate Cox regression analysis, multivariate Cox regression analysis was performed. As

Table 3 – Performance characteristic of laboratory parameters in predicting 28-day mortality

Variables	Cut-off	AUC (*p*)	Sensitivity	Selectivity	PPV	NPV
Leucocyte	>11.33	0.675 (**0.0008**)	55.88 (37.89–72.80)	77.53 (73.92–80.86)	12.67 (7.80–19.07)	**96.79** (94.76–98.19)
Neutrophil	>8.76	0.708 (**0.0001**)	50.00 (32.44–67.56)	**87.14** (84.14–89.75)	18.48 (11.15–27.93)	**96.76** (94.87–98.10)
NLR	>3.64	0.728 (**0.0001**)	67.65 (49.47–82.59)	76.84 (73.20–80.21)	14.56 (9.46–21.04)	**97.60** (95.75–98.80)
Lymphocytes	≤1.38	0.652 (**0.0005**)	50.00 (32.44–67.56)	**85.93** (82.84–88.765)	17.17 (10.34–26.07)	**96.72** (94.80–98.08)
IG%	>0.6	0.717 (**0.0001**)	54.55 (36.36–71.88)	**83.70** (80.45–86.61)	15.93 (9.73–24.00)	**97.02** (95.13–98.32)
CKMB	>6.2	0.681 (**0.0006**)	66.67 (48.17–82.02)	69.13 (65.20–72.86)	10.89 (6.95–16.03)	**97.34** (95.29–98.66)
Troponin	>0.484	0.693 (**0.0002**)	54.55 (36.36–71.88)	76.39 (72.70–79.80)	11.69 (7.08–17.84)	**96.70** (94.62–98.14)
CRP	>12.65	0.675 (**0.0009**)	51.52 (33.55–69.19)	78.73 (75.14–82.03)	12.32 (7.35–18.99)	**96.55** (94.46–98.02)

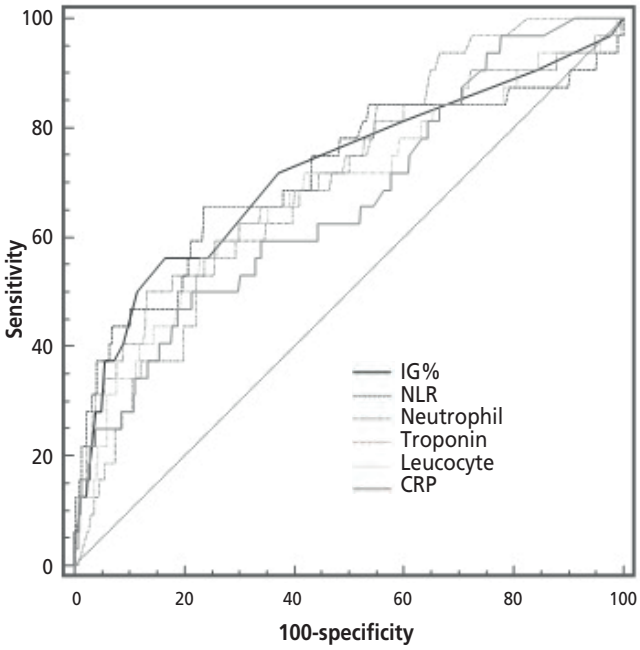

Fig. 2 – ROC curves for IG%, NLR, neutrophil, troponin, leucocytes, and CRP levels to predict 28-day mortality.

a result of the analysis, a statistically significant difference was found only in terms of IG% level (hazard ratio [HR] 632.962, 95% confidence interval 3.389–118206.572, p = 0.016). Accordingly, it can be said that the risk of death is 632.962 times higher as the IG% level increases (p = 0.016) (**Table 4**).

Discussion

Considering the important results of this study; The IG% was higher in patients who died (1.2 ± 1.4) than in patients who survived (0.5 ± 0.5) (p = 0.007). In predicting 28-day mortality, when the cut-off value for IG was >0.6%, the specificity was 93.70% and the sensitivity was 54.55% (AUC = 0.71, p = 0.000). In predicting 28-day mortality for ACS, IG was an independent risk factor of % (hazard ratio [HR] 632.962, 95% confidence interval 3.389–118206.572, p = 0.016).

In a study investigating sudden cardiac arrest and sudden cardiac death following unstable angina pectoris and myocardial infarction, the incidence rates were 45.8% for NSTEMI, 35.5% for STEMI, and 18.7% for USAP. In another study conducted in China, the incidence of USAP was found to be quite high.[14,15] In our study, STEMI occurred in 15.9% of cases, NSTEMI in 36%, and USAP in 48.1%. We believe that the high rate of USAP may be attributed to

Table 4 – Univariate and multivariate Cox regression analysis for 28-day mortality

Variables	Univariate analysis			Multivariate analysis		
	B	HR (95% CI)	p	B	HR (95% CI)	p
Age	0.058	1.060 (1.036–1.084)	**<0.001**	0.203	1.226 (1.03–1.457)	0.021
Leucocyte	0.114	1.121 (1.075–1.168)	**<0.001**	1.217	3.377 (0.033–343.458)	0.606
Neutrophil	0.135	1.144 (1.101–1.190)	**<0.001**	–1.253	0.86 (0.003–29.576)	0.597
NLR	0.098	1.103 (1.076–1.131)	**<0.001**	–0.054	0.948 (0.689–1.303)	0.740
IG%	1.615	5.028 (2.961–8.539)	**<0.001**	6.45	632.962 (3.389–118206.572)	**0.016**
Glucose	0.002	1.002 (1,000-1,004)	**0.023**	0.004	1.004 (0.984–1.025)	0.689
AST	0.003	1,003 (1.001–1.005)	**0.001**	–0.140	0.869 (0.673–1.121)	0.281
ALT	0.003	1.003 (0.999–1.007)	0.105	–0.185	0.831 (0.642–1.076)	0.160
LDH	0.002	1.002 (1.001–1.004)	**<0.001**	0.003	1.003 (0.996–1.010)	0.407
CK	0.001	1.001 (1.000–1.001)	**0.002**	–0.003	0.997 (0.970–1.025)	0.849
CKMB	0.005	1.005 (1.001–1.008)	**0.007**	0.013	1.013 (0.878–1.170)	0.857
CRP	0.014	1.014 (1.010–1.017)	**<0.001**	0.113	1.120 (0.969–1.294)	0.126

the absence of an hsTN kit in our hospital and the use of the classical troponin test.

Early evaluation and treatment in the emergency department is of great importance in patients with cardiovascular disease associated with high mortality, such as ACS.[16] Various biomarkers and clinical scoring, including troponin, CRP, NT-proBNP, and NLR, have been used as prognostic indicators in studies. The IG% is a simple hemogram parameter that is less well known among clinicians. Several recent studies have suggested that IG% can be used to predict both short-term and long-term mortality associated with many diseases.[17] Immature granulocytes are the common name of myelocytes, promyelocytes, and meta myelocytes, that is, granulocyte (neutrophil) precursors, which are not found in peripheral blood except in the neonatal period.[17,19] Studies show that immature granulocytes can be used as a marker of inflammation in the early period.[20] Recently, more studies have been carried out on this parameter, which is not used enough by clinicians. Its efficacy has been investigated for the prediction of sepsis in patients with severe burns, the prognosis of patients with acute pancreatitis, the prediction of in-hospital mortality in patients with upper gastrointestinal bleeding, the prognosis of patients with STEMI, the early prediction of mesenteric ischemia, and as an innovative biomarker for SARS-COV-2 infection.[11,12,21–24] As seen from these studies, it is seen that there is still a need for more research and evaluation by clinicians for the use of this biomarker in different clinical situations.

Krishnan et al. reported that IG count is an effective marker in estimating the severity of infection and in determining the need for early intervention in critically ill patients.[12] In another recent study, it was reported that the IG% was associated with mortality in upper gastrointestinal system diseases, and the IG5 helped predict mortality with a cut-off value of 0.95 with a sensitivity of 66.7% and a specificity of 75.7%.[25] Park et al. examined the diagnostic value of the IG count and its role in predicting the occurrence of complications in patients with acute appendicitis. In this study, it was shown that IG count is not as effective as other inflammatory markers in diagnosing and predicting the occurrence of complications.[26] Sinaga et al. reported that the IG count obtained at presentation to the emergency department serves as a marker that can effectively help predict 30-day mortality in patients with peritonitis, with a cut-off value of 1.05.[27] Huang et al. reported that IG count may be an indicator of possible pulmonary complications at the onset of acute pancreatitis.[28]

The relationship between ACS and inflammation has been known for many years. In addition, inflammation is closely associated with prognosis and possible complications in ACS patients.[29] Increasing the severity of inflammation increases the likelihood of atherosclerotic plaques causing MI.[30] In many previous studies, it has been reported that hemogram parameters (e.g. leucocyte, neutrophil counts, etc.) and the ratios of these parameters to each other have prognostic value in patients with CAD and STEMI.[31–34] Korkut et al. found the mean IG levels in patients with STEMI to be significantly higher in patients who died compared to those who survived (1.12 ± 0.22 vs 0.50 ± 0.28, p <0.001). They showed that IG predicted mortality with a sensitivity of 72.2% and a specificity of 77.8% at a cut-off value of 0.65 (area under the curve: 0.740, 95% CI 0.635–0.846, p <0.001). They emphasized that high IG values at the time of admission to the emergency department may be an indicator of mortality in patients with STEMI.[12] Kong et al. emphasized in their study that the increased DNI value, which reflects the proportion of immature granulocytes circulating in the blood, is an independent predictor of 30-day mortality and poor clinical outcomes in patients with acute STEMI after PPCI.[13]

As seen in the above studies, studies examining the relationship between ACS and IG% are limited. In our study, IG% was found to be higher in deceased patients than in surviving patients. In the ROC analysis performed to determine the 28-day mortality, when the cut-off value for IG% was 0.6 and above; specificity was 83.70% and sensitivity was 54.55%. When we examine in terms of IG (%) level, it can be said that while patients with a cut-off value of >0.6 die, individuals below this value live. Also, the area under the curve for this parameter is 0.717. In other words, the probability of distinguishing between the survivors and the deceased was found to be quite high and statistically significant. In predicting 28-day mortality for ACS, IG% was determined as an independent risk factor. The pathophysiology of the relationship between ACS and immature granulocytes is an issue that needs to be investigated. The possible mechanism is that in cases of sterile inflammation after ACS, the mechanism of increase of immature granulocytes is probably similar to that in sepsis. Rapid expansion of circulating neutrophils is a possible mechanism to compensate for the loss of active neutrophils due to the massive consumption and destruction of mature cells in severe inflammation.

This study has several limits. First, it is designed as a single-centered, retrospective study. Secondly, IG% serial measurements could not be made. Thirdly, the hs-troponin kit was not available in our hospital laboratory, so we could not include it in the study.

Conclusion

Overall, the percentage of immature granulocytes can serve as a prognostic marker in patients with acute coronary syndrome, particularly regarding short-term mortality risk. Further studies may continue to elucidate the mechanisms and refine the clinical applications of this measurement in risk assessment and management strategies in ACS patients.

Credit authorship contribution statement
HN and CC conceived and designed the study. HN and CC conducted the acquisition of the data. SE provided methodological and statistical expertise. CC and AY analyzed and interpreted the data. CA, AY provided support with the literature search. HN, CA, and ÖÖ provided content expertise about this topic. HN, CA, and ÖÖ drafted the manuscript and all authors contributed substantially to its revision with critical revision of the manuscript for important intellectual content.

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There are no conflicts of interest.

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Ethical statement
Ethics committee approval (No: 2021/726 Date: 03/12/2021) was received.

Informed consent
Informed consent was not obtained from the patients due to retrospective nature of the study.

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Původní sdělení | Original research article

Thyroid Doppler parameters association with coronary atherosclerosis burden

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SOUHRN

Kontext: Dosud se toho ví málo o možné spojitosti mezi cévním zásobením štítné žlázy a aterosklerotickou zátěží koronárních tepen u pacientů s podezřením na ischemickou chorobu srdeční.
Cíle: Posoudit možnou spojitost mezi dopplerovskými parametry horní štítné tepny a markery aterosklerózy koronárních tepen včetně závažnosti stenózy, kalcifikace koronárních tepen (CAC) a rozsahu plátu zjištěného koronarografickým vyšetřením pacientů s podezřením na ischemickou chorobu srdeční (ICHS) metodou multidetektorové výpočetní tomografie (MDCT).
Pacienti a metody: Do této průřezové studie bylo zařazeno 100 pacientů s bolestí na hrudi, u nichž byla pro vyloučení okluzivní ischemické choroby srdeční provedena koronarografie MDCT. Všichni zařazení pacienti byli z klinického hlediska eutyreoidní, bez klinických známek hypotyreózy nebo hypertyreózy. U zařazených pacientů byla pro stanovení cévních parametrů včetně indexu rezistence (RI), maximální rychlosti proudění krve v systole (PSV), rychlosti proudění krve na konci diastoly (EDV) a indexu pulsatility (pulsatility index, PI) sonograficky vyšetřena horní štítná tepna.
Výsledky: Byla nalezena statisticky významná spojitost mezi sníženými hodnotami PSV (16 cm/s vs. 15 cm/s; $p = 0{,}03$) a CAC ≥ 400, a to i po další adjustaci na rizikové faktory koronárních příhod (OR [CI] = 0,3 [0,1–0,8]; $p = 0{,}03$). Pacienti s významnou koronární stenózou (≥ 50%) vykazovali vyšší hodnoty RI (0,58 vs. 0,54; $p = 0{,}04$) než jedinci bez významné koronární stenózy (< 50%). Po adjustaci na jiné rizikové faktory koronárních příhod však již tato spojitost nepřetrvávala. Nebyla pozorována spojitost mezi parametry vyšetření štítné žlázy dopplerovským ultrazvukem včetně PSV, EDV, RI a PI na jedné straně, a přítomností koronárních plátů na straně druhé.
Závěr: Hodnoty PSV a RI v horní štítné tepně vykazovaly statisticky významnou spojitost se zátěží CAC a s významnou koronární stenózou. Tyto výsledky mohou naznačovat možné spojení mezi parametry rezistence cév štítné žlázy a zátěží aterosklerózou koronárních tepen.

Keywords:
Atherosclerosis
Coronary
CT angiography
Doppler ultrasonography
Thyroid

ABSTRACT

Background: Little is known about the potential association between thyroid vascular parameters and coronary atherosclerotic burden in patients with suspected coronary artery disease.
Objectives: To assess the potential association between superior thyroid artery Doppler parameters and coronary atherosclerotic markers, including stenosis severity, coronary artery calcification (CAC), and plaque assessed by multi-detector CT (MDCT) coronary angiography among patients with suspected coronary artery disease (CAD).
Patients and methods: This cross-sectional study included 100 patients with chest pain who underwent MDCT coronary angiography to exclude the presence of occlusive coronary artery disease. All of the enrolled patients were clinically euthyroid, with no clinical features of hypothyroidism or hyperthyroidism. The superior thyroid artery in enrolled patients was examined using ultrasound to assess vascular parameters, including resistive index (RI), peak systolic velocity (PSV), end-diastolic velocity (EDV), and pulsatility index (PI).
Results: There was a significant association between decreased PSV values (16 cm/s vs. 15 cm/s, $p = 0.03$) and CAC ≥400, even after further adjustment for coronary risk factors (OR (CI) = 0.3 (0.1–0.8. $p = 0.03$). Patients with significant coronary stenosis severity ≥50% had higher RI values (0.58 vs. 0.54, $p = 0.04$) than those with

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a non-significant coronary stenosis <50%. However, this association did not persist after adjustment for other coronary risk factors. No significant association was observed between thyroid Doppler parameters, including PSV, EDV, RI, and PI, and coronary plaque presence.
Conclusion: PSV and RI of the superior thyroid artery showed a significant association with CAC burden and significant coronary stenosis. These results may suggest a possible link between thyroid vascular resistance parameters and coronary atherosclerosis burden.

Introduction

The thyroid gland is a highly vascular tissue located in close proximity to carotid arteries. Superior thyroid artery, which is the chief artery supplying blood to the thyroid tissue arising from external carotid artery, is superficial and easily assessed by Doppler sonography in comparison to inferior thyroid artery. Assessing thyroid gland vascularity during carotid ultrasound examination is not time consuming and may have diagnostic implications.[1,2] Clinical and pathological studies have reported altered thyroid gland vascularity in clinically euthyroid individuals secondary to various diseases, including coronary artery disease (CAD).[3]

Vascular resistance parameters of thyroid arteries measured by pulsed-wave Doppler sonography, such as resistive index (RI), peak systolic velocity (PSV), end-diastolic velocity (EDV), and pulsatility index (PI) may reflect not only local vascular resistance or hemodynamic changes but also systemic arterial stuffiness or endothelial dysfunction.[4] Results from previous studies suggest that parameters of vascular resistance of renal or retinal arteries can estimate the severity of systemic atherosclerosis, particularly among persons with coronary risk factors.[4,5]

Thyroid hormones affect the heart and coronary vessels through different pathophysiological mechanisms, including endothelial dysfunction, increased intima-media thickness, and increased vascular resistance. Moreover, several clinical studies have reported an increased risk of all-cause mortality morbidity in patients with thyroid disorders, even after accounting for coronary risk factors such as dyslipidemia, diabetes, and hypertension.[6–8] Other studies have found a significant link between thyroid gland dysfunction and coronary calcification, even in patients with normal thyroid function.[9,10]

In contrast to primary thyroid disorders, peripheral thyroid hormone metabolism is impaired, as part of the non-thyroidal illness syndrome, in a variety of cardiovascular diseases such as myocardial infarction and heart failure. This abnormal alteration in thyroid hormone balance is proportional to the severity of the underlying heart disease and serves as a predictor of poor cardiovascular outcomes.[11]

In the literature, little is known about the possible link between thyroid vascular parameters and coronary atherosclerotic burden in patients with suspected CAD. The main aim of the present study was to assess the potential association between the superior thyroid artery Doppler parameters, including RI, PSV, EDV, and PI, and coronary atherosclerotic markers, including stenosis severity, coronary artery calcification (CAC), and plaque assessed by multi-detector CT (MDCT) coronary angiography among patients with suspected CAD.

Patients and methods

A cross-sectional study was conducted between January 2023 and October 2023. It included a sample of 100 patients with chest pain who underwent 64-MDCT coronary angiography at the Al-Sader teaching hospital in Al-Najaf city, Iraq, to exclude the presence of occlusive CAD. As described in detail in our previous study, each patient provided a thorough history at the time of the MDCT angiography examination regarding coronary risk factors such as sex, age, diabetes mellitus, hypertension, smoking, dyslipidemia, family history of premature CAD, and BMI.[12] All of the enrolled patients were clinically euthyroid, with no clinical features of hypothyroidism or hyperthyroidism. The exclusion criteria were as follows: (1) a history of hypothyroidism or hyperthyroidism or prior treatment with radioiodine; (2) use of medications that could interfere with thyroid function; (3) previous thyroid or neck surgery; and (4) thyroid nodules or altered parenchymal echo pattern identified during Doppler sonography examination.

MDCT examination

CT coronary angiography examination was conducted using a 64-slice scanner (Aquilon 64, v. 4.51 ER 010; Toshiba Medical Systems, Tochigi, Japan), with retrospective electrocardiography gating, and a non-contrast CT was acquired to measure the calcium score according to the Agatston method using a sequence scan with a slice thickness of 3 mm, as previously described in detail.[12] Coronary stenosis severity was graded as normal to non-significant stenosis (a mean lumen diameter reduction of <50%) and significant coronary stenosis as a mean lumen diameter reduction of ≥50% in a single vessel by comparing the lumen diameter of the narrowest segment with that of a more proximal or distal normal segment in two orthogonal projections. Coronary plaques were identified as thickening ≥1 mm in thickness within or adjacent to the coronary artery wall. Plaques were categorized into calcified plaques (plaques consisting of only calcium or containing both calcified and non-calcified components) and non-calcified plaques (plaques that were free of calcium). All CT angiography data analyses were assessed independently by two radiologists with over five years of expertise in coronary MDCT angiography interpretation. Verbal, informed consent was obtained from all enrolled participants. The study was approved by our medical college board.

Superior thyroid Doppler ultrasonography

The color Doppler ultrasound examination of the superior thyroid artery was performed by an experienced radiologist for all included patients before MDCT examination

using a ML probe (frequency 6–15 MHz) of the GE LOGIC E9 XD Clear ultrasound system (GE Healthcare, 2019, USA). The ultrasonography examination was conducted while the patient was in the supine position with a cushion under his shoulder and his neck extended. The superior thyroid artery was identified as the first branch of external carotid artery that arises anteriorly at the level of the hyoid bone and is traced up to the upper pole of the thyroid gland. The Doppler parameters of the left and right superior thyroid arteries measured were RI, PSV, EDV, and PI. RI was calculated according to the following formula: RI = PSV – EDV / PSV of the superior thyroid artery. The right and left superior thyroid artery-related Doppler parameter values were averaged to obtain a single mean for each parameter.

Statistical analysis

The statistical analysis of the data was conducted using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as numbers (%). The significance of the differences among groups was analyzed using a two-tailed Student t-test. A p-value <0.05 was considered statistically significant in all analyses. Binary logistic regression was used to assess the association between superior thyroid artery Doppler parameters and coronary risk factors, including age, sex, BMI, diabetes mellitus, hypertension, family history, and smoking with CAC ≥400 and significant coronary stenosis.

Results

A total of 100 patients (age = 59 ±5 years, male sex 46%) with suspected CAD and clinically euthyroid state who underwent 64 multi-slice MDCT coronary angiography to rule out the presence of occlusive coronary artery disease were enrolled in the present study. The prevalence of coronary risk factors was as follows: hypertension (55%), smoking (45%), obesity (42%), diabetes mellitus (39%), family history (30%), and dyslipidemia (30%). Eleven patients had CAC ≥400, whereas 15 patients had significant coronary artery stenosis (stenosis severity ≥50%). Coronary plaque was detected in 68 patients. Calcified plaque was detected in 66 patients, while only two patients had non-calcified plaque. The mean values of Doppler parameters of the superior thyroid artery were as follows: RI = 0.55 ± 0.09; PSV = 16 ± 0.78; EDV = 7 ± 0.89; PI = 0.89 ± 0.13. Clinical characteristics, as well as coronary atherosclerotic markers assessed by MDCT and Doppler parameters of the superior thyroid artery, are displayed in **Table 1**. There was a significant association between decreased PSV values (16 cm/s vs. 15 cm/s, $p = 0.03$) and CAC ≥400, even after further adjustment for coronary risk factors (OR (CI) = 0.3(0.1–0.8. $p = 0.03$). No significant association was found between other Doppler parameters and CAC ≥400, as in **Tables 2** and **3**. **Table 2** shows that patients with significant coronary stenosis severity ≥50% had higher RI values (0.58 vs. 0.54, $p = 0.04$) than those with non-significant coronary stenosis <50%. However, this association did not persist after adjustment for other coronary risk factors, as seen in **Table 3**. Other Doppler parameters, as shown in **Table 2**, showed no significant differences between coronary stenosis severity groups. No significant association was observed between thyroid Doppler parameters and coronary plaque presence, as seen in **Table 2**.

Discussion

In the literature, thyroid dysfunction is associated with accelerated coronary atherosclerosis and an increased risk of adverse cardiovascular events. This association can be explained by the effect of thyroid hormones on endothelial dysfunction, vascular resistance, and the higher prevalence of hypertension and lipid abnormalities in patients with thyroid dysfunction.7 Furthermore, evidence from clinical studies suggests that thyroid disorders when thyroid hormones are within the euthyroid range may be associated with significant coronary stenosis and carotid atherosclerosis, even in young people with low overall cardiovascular risk.[10]

Pulsed-wave Doppler parameters of thyroid arteries are quantitative and qualitative markers of arterial compliance and endothelial dysfunction, representing an early and reversible feature of atherosclerosis. PSV and RI indices of the superior thyroid artery measured by Doppler ultrasonography are affected by both vascular wall

Table 1 – Patients characteristics

Variables	Mean ± SD or n (%) or median (IQR)
Age (years)	59 ± 5
Male sex	46 (46)
Family history	30 (30)
BMI	27 ± 5
Obesity (BMI ≥30)	42 (42)
Diabetes mellitus	39 (39)
Hypertension	54 (55)
Smoking	45 (45)
Dyslipidemia	30 (30)
Coronary atherosclerosis markers	
Coronary artery calcium score	280 (160–350)
CAC ≥400	11 (11)
Significant coronary stenosis >50%	15 (15)
Coronary plaque presence	68 (69)
Non-calcified plaque	2 (2)
Calcified plaque	66 (67)
Multiple coronary plaques	25 (25)
Thyroid Doppler parameters	
Resistive index (RI)	0.55 ± 0.09
Peak systolic velocity (PSV), cm/s	16 ± 0.78
End-diastolic velocity (EDV), cm/s	7 ± 0.89
Pulsatility index (PI)	0.89 ± 0.13

Table 2 – Association of coronary atherosclerotic markers with thyroid Doppler parameters

CAC			
	CAC <400	CAC ≥400	*p*-value
RI	0.54 ± 0.0	0.58 ± 0.1	0.25
PSV	16 ± 0.7	15 ± 0.6	0.03
EDV	7 ± 0.8	7 ± 1	0.63
PI	0.9 ± 0.1	0.8 ± 0.1	0.07
Coronary stenosis severity			
	Stenosis <50%	Stenosis ≥50%	*p*-value
RI	0.54 ± 0.0	0.60 ± 0.1	0.04
PSV	16 ± 0.7	15 ± 0.8	0.38
EDV	7 ± 0.8	7 ± 1	0.48
PI	0.9 ± 0.1	0.8 ± 0.1	0.09
Coronary plaque presence			
	Without plaque	Plaque presence	*p*-value
RI	0.54 ± 0.0	0.55 ± 0.0	0.71
PSV	16 ± 0.8	16 ± 0.7	0.39
EDV	7 ± 0.8	7 ± 0.9	0.92
PI	0.8 ± 0.1	0.8 ± 0.1	0.88

Table 3 – Regression analysis*

CAC ≥400			
	Odd ratio	Confidence interval	*p*-value
PSV	0.3	0.1–0.8	0.03
Diabetes mellitus	5	1.3–15	0.01
Significant coronary stenosis >50%			
Age	1.3	1–1.6	<0.01
Diabetes mellitus	4	1–10	<0.01
Hypertension	5	2–12	<0.01

* Only variables with statistically significant associations are displayed in the **Table**.

disorders, such as atherosclerosis, and parenchymal thyroid dysfunction, such as inflammation or fibrosis.[13] Furthermore, PSV is widely used in the differential diagnosis of thyrotoxicosis and can provide valuable data about underlying thyroid functional status.[1,14,15] In the present study, the significant and independent association of superior thyroid artery PSV with CAC ≥400 may suggest that thyroid vascular resistance, as measured by Doppler ultrasound, may reflect the systemic atherosclerosis burden such as significant coronary calcification, particularly among patients with suspected coronary artery disease.

Studies of the association between thyroid vascular parameters and coronary atherosclerosis markers are sparse and have been inconsistent in the literature.

A significant positive association has been reported between thyroid hormones, even in the euthyroid range, and coronary calcification burden.[9,16] A study conducted by Y. Zhang et al. enrolled an apparently healthy young and middle-aged euthyroid population and reported a significant association between thyroid hormones and a higher prevalence of subclinical coronary artery disease and a greater degree of coronary calcification.[10] Furthermore, Gunduz et al. conducted a prospective study to assess the impact of internal carotid angioplasty and stenting on the superior thyroid artery Doppler parameters. They found that there was no significant correlation between superior thyroid artery Doppler flow parameters and the presence of coronary artery disease and other coronary risk factors such as increased age, hypertension, diabetes mellitus, smoking, or dyslipidemia.[1]

Another study conducted by Chekalina et al. found that PSV and RI of thyroid arteries were considerably higher among euthyroid patients with autoimmune thyroiditis and coronary artery disease than in healthy persons, suggesting that high values of thyroid Doppler parameters in patients with thyroiditis and CAD have been linked to endothelial dysfunction secondary to pro-inflammatory cytokines overproduction.[17]

Several limitations should be addressed when interpreting the findings of the present study. First, this was a single-center cross-sectional study including patients with suspected CAD. As a result, the findings may not be generalizable, and the causal relationship between thyroid vascular parameters and coronary atherosclerotic markers cannot be determined. Second, the possibility of residual confounding in an observational cross-sectional study design cannot be entirely excluded. Third, thyroid hormone measurements were not performed, and the likelihood of some patients having subclinical thyroid functional changes cannot be ruled out, despite a normal thyroid appearance on ultrasound examination. Also, the potential effect of thyroid hormones on the association between thyroid vascular parameters and coronary calcification cannot be adjusted. Fourth, we enrolled a relatively small sample size of the study population, which may limit the power of the study to detect a statistically significant association between some Doppler parameters and coronary atherosclerosis markers. Further large prospective studies are required to establish a causal relationship between coronary atherosclerotic markers and thyroid vascular resistance and explore the potential mechanism.

Conclusion

PSV and RI of the superior thyroid artery showed a significant association with CAC burden and significant coronary stenosis. These results may suggest a possible link between thyroid vascular resistance parameters assessed by Doppler ultrasonography and coronary atherosclerosis burden among patients with suspected CAD.

Conflict of interest
The authors declare that they have no conflict of interest.

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Ethical approval
Not applicable.

Informed consent

Verbal informed consent was obtained from all enrolled participants.

Availability of supporting data

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Přehledový článek | Review article

Kontinuální termodiluce – nová metoda přímého měření koronárního průtoku a rezistence

(Continuous thermodilution – a novel method for direct measurement of coronary flow and resistance)

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SOUHRN

Angina pectoris bez obstrukce koronárních tepen je častý nález u pacientů s bolestmi na hrudi, v jehož patofyziologii se uplatňují zejména dva mechanismy – strukturální nebo funkční poškození mikrocirkulace či funkční poškození epikardiálních tepen, případně jejich kombinace. Souhrnný článek se zabývá diagnostikou koronární mikrovaskulární dysfunkce se zaměřením na kontinuální termodiluci jako bezpečnou, jednoduchou, rychlou a na operatérovi nezávislou metodu. Popisuje teoretický základ i praktické aspekty s grafickými ukázkami měření.

ABSTRACT

Angina with non-obstructive coronary artery disease is a frequent finding in patients with chest pain. Its pathophysiology involves two main mechanisms: structural and functional dysfunction of microcirculation, functional dysfunction of epicardial arteries, and their combination. The review article focuses on the diagnostics of microvascular dysfunction, particularly continuous thermodilution, as a safe, easy, fast, and operator-independent method. It describes both theoretical background and practical aspects with graphical examples of measurements.

Úvod

Angina pectoris (AP) bez obstrukce koronárních tepen (ANOCA) je častý nález (30–70 %) u pacientů s bolestmi na hrudi referovaných k selektivní koronarografii (SKG), kdy až u 25–30 % je detekovatelná ischemie (INOCA).[1–3]

V patofyziologii se uplatňují zejména dva mechanismy – strukturální a funkční poškození, která mohou postihovat jak epikardiální tepny, tak tepny mikrocirkulace a zároveň se i kombinovat. Z klinického hlediska tudíž u ANOCA rozlišujeme **1) mikrovaskulární anginu (MVA)** na podkladě **strukturálního** poškození mikrocirkulace (koronární mikrovaskulární dysfunkce [CMD] – snížená koronární průtoková rezerva [CFR] a/nebo zvýšená rezistence) nebo **funkčního** mikrovaskulárního vazospasmu (angina a EKG změny bez epikardiálního vazospasmu při acetylcholinovém testování) a **2) epikardiální vazospastickou anginu (VSA)** – angina, EKG změny a vazospasmus při acetylcholinovém testování (viz **tabulku 1**).[1,2,4]

Klinická manifestace ANOCA zahrnuje široké spektrum symptomů snižujících kvalitu života, které jsou často chybně diagnostikovány, léčeny a nezřídka vedou k opakovaným hospitalizacím a invazivním vyšetřením. Zároveň mají pacienti s MVA i VSA horší dlouhodobou prognózu.[1,5,6]

Přímé zhodnocení odpovědi koronární mikrocirkulace na vazodilatační podněty a diagnostika vazomotorických poruch jsou klíčové ke správné stratifikaci a volbě léčebné

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Tabulka 1 – Klinické endotypy ANOCA	
Mikrovaskulární angina (MVA)	FFR > 0,80, iFR > 0,89
- Mikrovaskulární dysfunkce (CMD)	CFR < 2,0 (2,5), IMR > 25, MRR < 2,1
- Mikrovaskulární vazospasmus (dynamická arteriolární obstrukce)	Angina + změny EKG + **< 90% epikardiální** spasmus při Ach testování
Vazospastická angina (VSA)	
- Epikardiální vazospasmus	Angina + změny EKG + **> 90% epikardiální** spasmus při Ach testování

Ach – acetylcholin; CFR – koronární průtoková rezerva; CMD – koronární mikrovaskulární dysfunkce; EKG – elektrokardiogram; FFR – frakční průtoková rezerva; iFR – instant wave-free ratio; IMR – index mikrocirkulační rezistence; MRR – rezerva mikrovaskulární rezistence; MVA – mikrovaskulární angina; VSA – vazospastická angina. Upraveno dle Vrints et al., 2024.[1]

strategie pacientů s ANOCA, což vede k redukci závažnosti anginy a lepší kvalitě života oproti standardní péči.[7,8]

Komplexní invazivní koronární funkční vyšetření (CFT) je v současné době jediná diagnostická metoda k určení definitivní diagnózy a charakterizaci specifického endotypu ANOCA, což je podpořeno i aktuálními doporučenými postupy.[1,2]

Cílem tohoto sdělení je představit metodu přímého měření koronárního průtoku a mikrovaskulární rezistence pomocí kontinuální termodiluce, která při srovnání se stávajícími metodami (bolusová termodiluce či dopplerovské měření) vyniká nezávislostí na operatérovi a výbornou reprodukovatelností.

Koronární průtok a koronární mikrocirkulace

Koronární tepennou cirkulaci si lze představit jako model dvou kompartmentů. **Epikardiální kompartment** tvoří tepny o průměru větším než 0,4 mm, zajišťují transport krve, jsou viditelné při koronarografii a mohou být postiženy aterosklerózou. K evaluaci hemodynamické významnosti zúžení epikardiálních tepen slouží hyperemické (např. FFR) nebo klidové indexy (např. iFR). **Mikrocirkulaci** tvoří cévy o průměru menším než 0,4 mm (malé arterie a arterioly), jsou to odporové cévy, které regulují koronární průtok. **Kapiláry** vytvářejí síť, jsou tvořeny jednou či dvěma vrstvami endoteliálních buněk a jsou v přímém kontaktu s myofilamenty, které zásobují. Kapilární síť nepřispívá k rezistenci mikrocirkulace.[9]

Cévy mikrocirkulace významně přispívají k cévní rezistenci a k regulaci koronárního průtoku (CBF). Jsou zodpovědné za udržování koronárního perfuzního tlaku nad 40 mm Hg. Tento tlak je považován za dolní hranici tlaku nezbytného k prevenci ischemie myokardu. Pod touto hranicí jsou subendokardiální cévy plně dilatované a kompenzatorní možnosti udržení nezbytného průtoku jsou vyčerpány. Tato schopnost udržovat konstantní CBF se nazývá **autoregulace**. Mezi vnější faktory ovlivňující CBF patří srdeční frekvence, krevní tlak a kontraktilita levé komory. Za normálních okolností se může koronární průtok vazodilatací zvýšit čtyřikrát až pětkrát nad klidové hodnoty (označováno jako koronární průtoková rezerva, CFR).[10]

Vyšetření koronární mikrocirkulace

CMD je charakterizována zvýšenou cévní rezistencí a sníženou odpovědí na vazodilatační podněty vedoucí k snížení koronární průtokové rezervy (CFR, tj. průtok za maximální hyperemie / klidový průtok).[1,2,4]

Vyšetření CMD může být prováděno neinvazivně nebo invazivně. Mezi neinvazivní metody patří metody nukleární kardiologie, magnetická rezonance nebo dopplerovská transtorakální sonografie. K invazivní diagnostice CMD se využívá intrakoronární dopplerovská sonografie nebo termodiluční metody – bolusová či kontinuální.[1,2]

Měření CFR pomocí nukleárních metod – pozitivní emisní výpočetní tomografie (PET) nebo jednofotonová emisní výpočetní tomografie (SPECT) – jsou pro svou přesnost a reproducibilitu považována za zlatý standard, ale klinické používání je limitováno cenou a dostupností vyšetření.[11,12]

Transtorakální dopplerovská sonografie průtoku v ramus interventricularis anterior (RIA) v klidu a během zátěžové echokardiografie má prognostická data, ale její provedení je limitováno technickou náročností a často vyšetřitelností pacientů.[13–16]

Z invazivních metod jsou k dispozici termodiluce nebo intrakoronární dopplerovské sonografie. Zásadní limitací dopplerovské metody je stabilita a kvalita intrakoronárního signálu,[2] proto se v klinické praxi aktuálně používá výhradně intrakoronární termodiluce, která využívá dedikovaný tlakově-teplotní katétr PressureWire™ X Guidewire (AbbottLaboratories, LibertyvilleTownship, IL, USA) a software Coroventis CoroFlow (Coroventis, Uppsala, Švédsko).

Parametry užívané při invazivním vyšetření CMD

1. Koronární průtok určený termodilučně (**bolusové měření** – *„mean transit time" [T_{mn}]* jako hodnota dobře korelující s průtokem; **kontinuální měření** – *absolutní hodnota průtoku [Q])* nebo pomocí dopplerovského měření.
2. Koronární průtoková rezerva (CFR).
3. Koronární rezistence (**bolusová termodiluce** – *index mikrocirkulační rezistence [IMR]* – relativní hodnota určená s pomocí „mean transit time" a distálního intrakoronárního tlaku; **kontinuální termodiluce** – *absolutní hodnota rezistence [R]* určená z průtoku zjištěného kontinuální termodilucí; *rezerva mikrovaskulární rezistence [microvascular resistance reserve, MRR]).*

Koronární průtok

Koronární průtok je nezbytný pro správnou funkci myokardu. Mikrovaskulární rezistence trvale přizpůsobuje koronární průtok potřebám myofilament (autoregulace).[9]

Hyperemické a klidové indexy (např. FFR, iFR) odvozené z měření tlaků určují podíl epikardiálních stenóz na

změnách myokardiální perfuze, a proto se používají jako referenční standard pro vedení „revaskularizace“ epikardiálních stenóz.[1]

Naopak posouzení koronární mikrocirkulace vyžaduje měření koronárního průtoku a mikrovaskulární rezistence. Index mikrocirkulační rezistence, metoda založená na odhadu koronárního průtoku pomocí bolusové termodiluce, se ukázala jako užitečná pro předpověď klinického výsledku pacientů bezprostředně po akutním infarktu myokardu.[17] Dlouhou dobu nebyla zavedena žádná přímá invazivní metoda, která by kvantifikovala funkci mikrocirkulace v absolutních hodnotách. To se změnilo s nástupem a validací termodiluční metody založené na kontinuálním měření, která umožňuje kvantifikaci absolutní hodnoty koronárního průtoku (ml/min) a absolutní mikrovaskulární rezistence (mm Hg/l/min nebo ve Woodových jednotkách [WU]).[18–20]

Termodiluce pomocí bolusu

Po prudkém vstříknutí bolusu fyziologického roztoku (o teplotě nižší než je teplota krve) zaváděcím katétrem zaznamenáváme pomocí teplotního čidla v distální části tepny křivku tvaru „V“ znázorňující změnu teploty krve v průběhu času. Obvykle pozorujeme rychle klesající první části křivky a pomaleji stoupající druhou část křivky (viz **obr. 1**).[9,21]

Z křivky lze odhadnout průtok podílem objemu cévy *V* a střední doby přenosu indikátoru krví (T_{mn}):

$Q = V / T_{mn}$

Objem cévy sice není znám, ale je po celou dobu konstantní, proto je T_{mn} nepřímo úměrné Q:

$Q \approx 1 / T_{mn}$

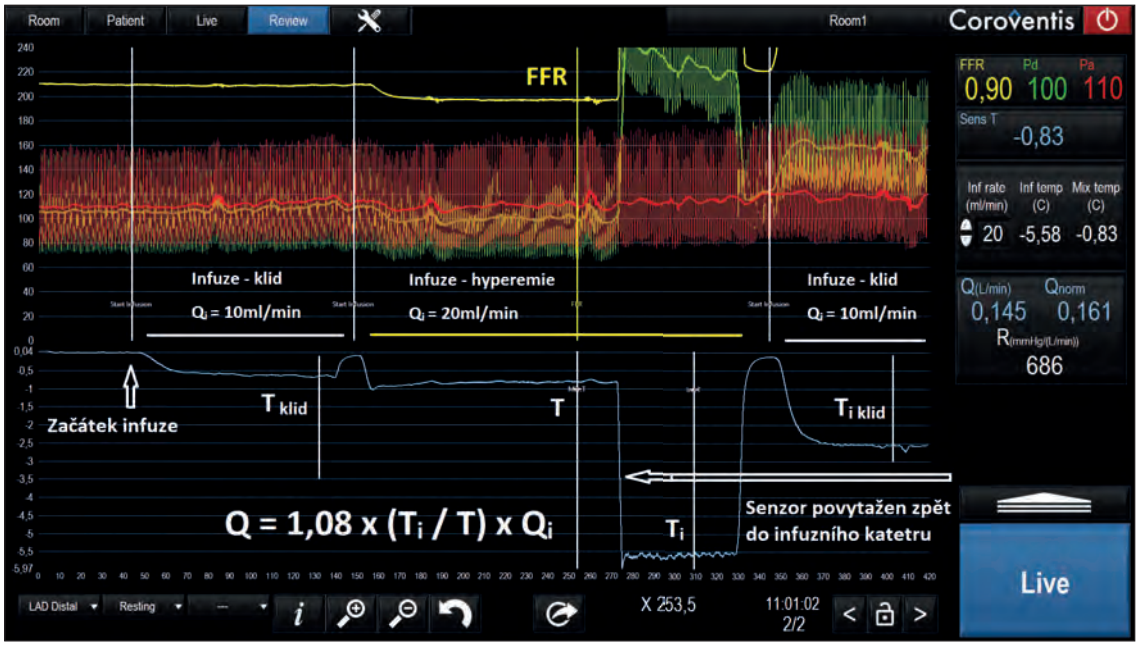
Bolusovou termodilucí tedy nezískáme absolutní hodnotu průtoku, ale můžeme využít T_{mn} jako ukazatel průtoku (čím je menší T_{mn}, tím je větší Q a naopak) a také k určení CFR a indexu rezistence mikrocirkulace (IMR) (viz dále). Pro tyto výpočty je nutné provádět bolusové měření za podmínek klidového průtoku a poté při navozené maximální hyperemii – standardně tři bolusy 3–4 ml FR přes 6F zaváděcí katétr v klidu a tři bolusy při hyperemii (při variabilitě větší než 30 % se doporučuje provést více měření), které se průměrují, a získáme tedy zvlášť T_{mn} za klidového průtoku ($T_{mn,klid}$) a poté T_{mn} při hyperemii ($T_{mn,hyper}$) (viz **obr. 1**). Stabilní maximální hyperemie se navozuje většinou pomocí kontinuální, minimálně 30sekundové intravenózní infuze adenosinu, s čímž mohou být spojeny nežádoucí příznaky jako bradykardie, pocity dušnosti, hypotenze. Na některých pracovištích se proto využívá intrakoronární injekce papaverinu.[9]

Termodiluce stanovená při kontinuálním měření

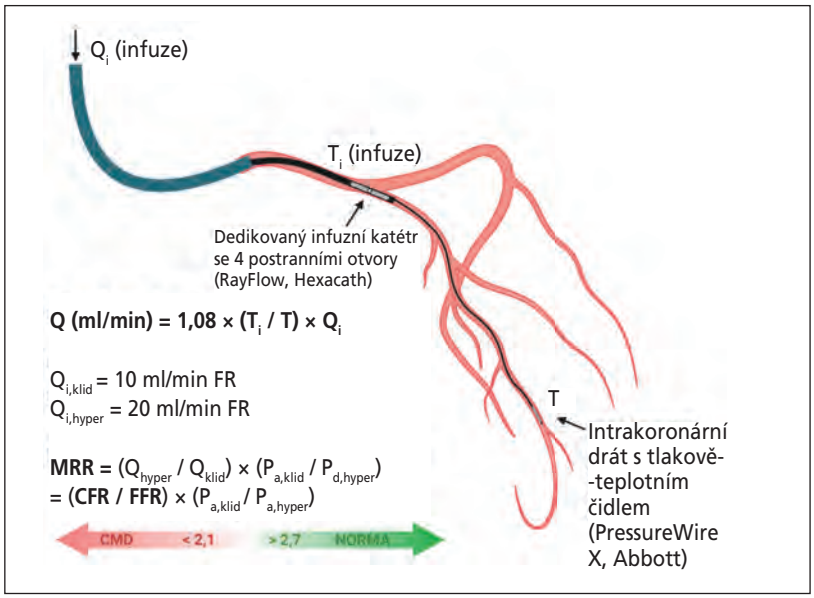
Při kontinuální termodiluci se klidový a maximální průtok měří stejným tlakově-teplotním katétrem jako u bolusové metody, ale při kontinuální infuzi FR do proximální části měřené koronární tepny (nejčastěji RIA) pomocí specifického katétru se čtyřmi otvory na distálním konci – např. katétr RayFlow (Hexacath, Rueil-Malmaison, Francie), který je napojen na infuzní pumpu s regulovatelným průtokem v ml/min.[19,20,22] Otvory v mikrokatétru zajišťují optimální promíchání FR s krví.

Vyšetření začíná klidovým měřením při průtoku FR rychlostí 10 ml/min, kdy po přibližně 2 minutách infuze dojde ke stabilnímu poklesu teploty v distální části koronární tepny oproti začátku měření (přibližně o 0,4–0,5 °C) (T_{klid}). Po tomto ustálení teploty se navodí hyperemie zvýšením průtoku FR na rychlost 20 ml/min, čímž dosáhneme výraznějšího poklesu teploty v distální části tepny s ustálením opět přibližně po 2 minutách (T_{hyper}). Poté povytáhneme tlakově-teplotní katétr z distální části měřené tepny proximálně k vyústění katétru RayFlow ke změření teploty FR vstupujícího do koronární tepny při průtoku

Obr. 1 – Měření bolusovou **termodilucí.** CFR – koronární průtoková rezerva; IMR – index mikrocirkulační rezistence; P_d – distální tlak; $T_{mn,hyper}$ – hyperemický mean transit time; $T_{mn,klid}$ – klidový mean transit time.



Obr. 2 – Měření kontinuální termodilucí. FFR – frakční průtoková rezerva; FR – fyziologický roztok; P_a – aortální tlak; P_d – distální tlak; Q – průtok; Q_i – průtok infuze; T – teplota změřená v distální části; T_i – teplota infuze.



Obr. 3 – Schematické znázornění měření kontinuální termodilucí.
CFR – koronární průtoková rezerva; FFR – frakční průtoková rezerva; FR – fyziologický roztok; MRR – rezerva mikrovaskularni rezistence; $P_{a,klid}$ – klidový aortální tlak; Q – průtok; Q_i – průtok infuze; $Q_{j,hyper}$ – rychlost infuze FR k navození maximální hyperemie; $Q_{j,klid}$ – rychlost infuze FR k navození klidového průtoku; Q_{hyper} – maximální průtok; Q_{klid} – klidový průtok; $P_{d,hyper}$ – distální tlak za maximální hyperemie; $P_{a,hyper}$ – aortální tlak za maximální hyperemie; T – teplota změřená v distální části; T_i – teplota infuze. Upraveno dle de Vos et al., 2023.[31] Vytvořeno v BioRender.com.

20 ml/min ($T_{i,hyper}$) a po ustálení snížíme průtok zpět na 10 ml/min ke změření teploty FR vstupujícího do koronární tepny při tomto průtoku ($T_{i,klid}$) (viz **obr. 2** a **3**).

Mechanismus maximální a stabilní hyperemie navozené průtokem 20 ml/min přes katétr RayFlow je dán zejména mírnou hemolýzou erytrocytů či jejich deformací vedoucí k uvolnění lokálních vazodilatačních působků jako adenosintrifosfátu (ATP) a oxidu dusnatého (NO), které působí jak nezávisle na endotelu (ATP přes receptory A_2 na hladkosvalových buňkách a NO přímo vazodilatačně), tak závisle na endotelu (NO produkované ATP aktivovanou endotelovou NO syntetázou).[19] Takto navozená krátká a lokální hemolýza nevede k významnému poklesu hemoglobinu, hyperkalemii ani nezvyšuje riziko postprocedurálního akutního renálního poškození.[18,19,23,24] Při průtoku 10 ml/min k těmto jevům nedochází, naopak vyšší než 20 ml/min již nevedou k výraznější hyperemii. Dalším významným předpokladem je průtok přes specifický mikrokatétr se čtyřmi bočními otvory na konci (RayFlow), protože bylo prokázáno, že aplikace kontinuálního FR pouze jedním koncovým otvorem, byť o vyšších rychlostech, nevede k navození hyperemie.[19]

Výhodou kontinuální termodiluční metody je stanovení absolutních hodnot průtoku i rezistence. Základní princip je relativně jednoduchý – za předpokladu minimální výměny tepla se stěnou tepny a že indikátor (FR) je homogenně rozptýlen v krvi ve známém a konstantním objemu, lze určit hodnotu průtoku „trojčlenkou“:

$Q = 1{,}08 \times (T_b - T_i/T_b - T) \times Q_i$
Q_i = rychlost infuze FR pokojové teploty (obvykle 8–25 ml/min)
T = teplota směsi indikátoru a krve distálně v koronární tepně
T_b = teplota krve
T_i = teplota FR v místě vstupu do koronární tepny (tj. proximálně)
Pokud T_b určíme jako výchozí („nulovou“) hodnotu, T_i a T pak odpovídají změnám teploty proti výchozí hodnotě a vzorec můžeme zjednodušit na:
$Q = 1{,}08 \times (T_i/T) \times Q_i$

Koronární průtoková rezerva (CFR)

CFR představuje náhradní ukazatel možnosti zvýšit prokrvení myokardu a posuzuje jak epikardiální, tak mikrovaskulární kapacitu. Je definována jako poměr maximálního a klidového koronárního průtoku. CFR tedy uvádí, kolikrát lze zvýšit koronární průtok při zátěži oproti klidu.[9]

Průtok koronární tepnou lze měřit pomocí intrakoronárního vodiče schopného detekce dopplerovského signálu nebo pomocí intrakoronární termodiluce. Obě metody spolu dobře korelují.

Hodnota CFR pod 2,5 získaná a validovaná intrakoronární dopplerovskou sonografií je považována za patologickou s negativními prognostickými daty, hraniční hodnota 2,0 je více specifická, ale méně senzitivní a zmiňuje se zejména při termodilučních metodách (viz **tabulku 2**).[1,20]

Koronární rezistence

Index mikrocirkulační rezistence (IMR)

IMR je parametrem mikrocirkulace, který je získán bolusovou termodilucí a nezávislý na hemodynamice epikardiálních cév. Inverzní hodnota střední doby přenosu indikátoru krví (T_{mn}) významně koreluje s absolutním průtokem. IMR se získá vydělením distálního koronárního tlaku (P_d) inverzní hodnotou T_{mn} (tzn. vynásobením T_{mn}), což je ukazatel koronárního průtoku. Teoreticky je tento parametr nezávislý na epikardiální anatomii, protože distální tlak i průtok klesají v případě významných epikardiálních koronárních lézí. T_{mn} musí být získán ve stavu stabilní maximální hyperemie (většinou kontinuální intravenózní infuzí adenosinu, viz výše), během níž je dosaženo minimální mikrovaskulární rezistence. Měření IMR je závislé na vzdálenosti tepelného čidla od místa podání FR.[2,25]

IMR vychází z Ohmova zákona, udává, že absolutní minimální rezistence mikrocirkulace se rovná podílu tlaků diference v dané oblasti a hyperemického průtoku v této oblasti:
$R = (P_d - P_v) / Q$
P_d = tlak v distální části koronární tepny; P_v = žilní koronární tlak
Protože P_v je zanedbatelný ve srovnání s P_d a za předpokladu, že $Q \approx 1 / T_{mn}$, můžeme předcházející rovnici zapsat jako:
$R \approx P_d / 1 / T_{mn,}$ resp. **$IMR = P_d \times T_{mn}$**
T_{mn} je bezrozměrné číslo, které dobře odráží skutečnou rezistenci mikrocirkulace.

Klinický význam

Normální hodnoty IMR odvozené od měření u zdravých jedinců jsou < 25 (viz **tabulku 2**).[1] U pacientů s infarktem myokardu s elevacemi úseku ST (STEMI) léčených přímou perkutánní koronární intervencí (PCI) byly hodnoty IMR > 40 asociovány s rizikem mikrovaskulární obstrukce, velikostí infarktového ložiska a kombinovaným ukazatelem kardiovaskulárních (KV) příhod (závažných nežádoucích KV příhod, MACE) během 30 dní po infarktu myokardu.[17] U pacientů s chronickým koronárním syndromem (CHKS) byly zvýšené hodnoty IMR před i po PCI asociovány s vyšším výskytem postprocedurálního poškození myokardu. U pacientů s angiograficky hraničním postižením a s FFR > 0,80 byly nízká hodnota CFR a zvýšená IMR asociovány s vyšším výskytem KV příhod.[7] Farmakoterapie u pacientů s ANOCA řízená podle výsledku vyšetření mikrocirkulace vedla k významnému symptomatickému efektu ve studii CORMICA.[7,8]

Význam hodnot IMR 25–40 je méně prozkoumán, při jejich posuzování je třeba zohlednit klinický stav pacienta a vyloučit možnost nepřesného měření.[17,26]

IMR má lepší reprodukovatelnost než CFR, protože není významně ovlivňován hemodynamickými výkyvy v závislosti na srdeční frekvenci, krevním tlaku a kontraktilitě.[9]

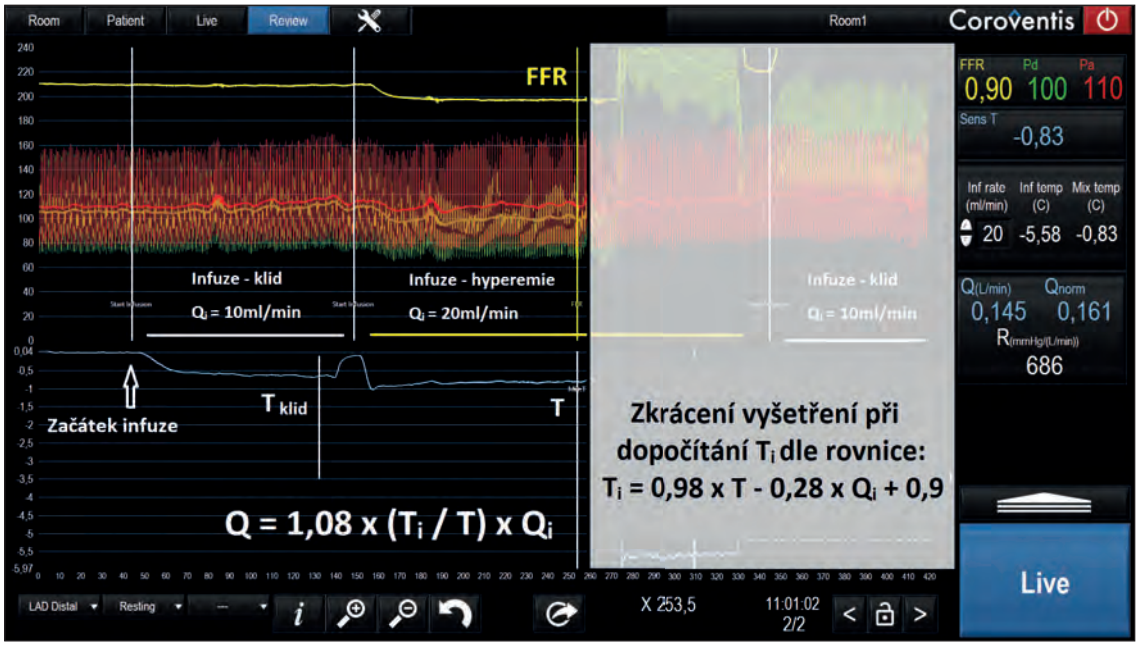
Absolutní hodnota rezistence (R)

Hodnota určená z průtoku zjištěného kontinuální termodilucí. Opět vychází z Ohmova zákona, může být vypo-

Tabulka 2 – Invazivní parametry používané u ANOCA

Zkratka	Parametr	Metoda měření	Patologie	Výpočet
CFR	Koronární průtoková rezerva	Intrakoronární dopplerovské monitorování, termodiluce	< 2,0–2,5	Dopplerovské monitorování: APV_{hyper}/APV_{klid} Bolus. termodiluce: $T_{mn,klid}/T_{mn,hyper}$ Kont. termodiluce: Q_{hyper}/Q_{klid}
IMR	Index mikrocirkulační rezistence	Bolusová termodiluce	> 25	$P_d \times T_{mn}$ při hyperemii
MRR	Rezerva mikrovaskulární rezistence	Kontinuální termodiluce	< 2,1	$(CFR/FFR) \times (P_{a,klid} / P_{a,hyper})$ $(Q_{hyper} / Q_{klid}) \times (P_{a,klid} / P_{d,hyper})$
R_{mikro}	Absolutní rezistence	Kontinuální termodiluce	> 500 Wj	P_d / Q

APV – average peak velocity; CFR – koronární průtoková rezerva; FFR – frakční průtoková rezerva; IMR – index mikrocirkulační rezistence; MRR – rezerva mikrovaskulární rezistence; P_d – distální tlak; Q – průtok; P_a – aortální tlak; R_{mikro} – absolutní rezistence; T_{mn} – mean transit time, Wj – Woodovy jednotky. Upraveno dle Smilowitz et al., 2023.[3]



Obr. 4 – Měření kontinuální termodilucí po zjednodušení dopočtením T_i. FFR – frakční průtoková rezerva; FR – fyziologický roztok; P_a – aortální tlak; P_d – distální tlak; Q – průtok; Q_i – průtok infuze; T – teplota změřená v distální části; T_i – teplota infuze.

čtena pro dané teritorium (R_{tot}), pro zvolený epikardiální segment (R_{epi}) nebo pro zvolenou oblast mikrocirkulace (R_μ; mikrovaskulární rezistence):

$R_{tot} = P_a / Q$

P_a = střední aortální tlak na špičce zaváděcího katétru

$R_{epi} = (P_a - P_d) / Q$

P_d = střední tlak v distální části koronární tepny

$R_\mu = P_d / Q$

Mikrovaskulární rezistence charakterizuje rezistenci oblasti myokardu v povodí měřené koronární tepny distálně od špičky infuzního katétru.

Klinický význam

Na rozdíl od IMR hodnoty absolutní rezistence určené kontinuální termodilucí nebyly dosud klinicky validovány u pacientů s ANOCA. Referenční hodnoty Q a R byly studovány u jedinců bez aterosklerózy, kde celkový hyperemický průtok srdcem byl stanoven na 670 ml/min a celková rezistence R_{tot} 160 WU. Byla však zaznamenána velká variabilita v hodnotách Q a R mezi pacienty.[20]

Normální hodnoty absolutní rezistence v RIA jsou do 400 WU (viz **tabulku 2**).[18,21]

Rezerva mikrovaskulární rezistence (MRR)

I když je měření absolutního hyperemického průtoku a rezistence pomocí kontinuální termodiluce přesné, je zatíženo významnou interindividuální variabilitou, což znesnadňuje klinické využití těchto parametrů, pokud nejsou tyto hodnoty vztaženy na masu myokardu perfundovaného teritoria (viz výše).[20]

Ideální parametr, jenž popisuje funkci mikrocirkulace, by měl být specifický pro mikrocirkulaci, měl by být nezávislý na operatérovi, na autoregulaci, na epikardiální rezistenci, na mase myokardu a měl by být odvozen od absolutních hodnot průtoku a rezistence.

Rezerva mikrovaskulární rezistence (MRR) je poměr „skutečné" klidové rezistence ku hyperemické ($R_{\mu,klid}$ / $R_{\mu,hyper}$). Udává, kolikrát se může klidová R_μ snížit v hypotetické situaci zcela normální epikardiální koronární arterie (analogie k FFR). Je třeba si uvědomit, že klidová R_μ je ovlivňována přítomností epikardiální stenózy. Epikardiální stenóza způsobuje kompenzatorní mikrovaskulární vazodilataci na podkladě autoregulace. V takovém případě naměřená hodnota R_μ není „skutečnou" klidovou R_μ, ale sníženou díky kompenzatorní vazodilataci. Skutečná R_μ může být naměřena pouze u „normální", tj. nepostižené koronární arterie.[22]

Při normální nebo minimálně postižené epikardiální tepně (FFR blízko 1) jsou hodnoty MRR a CFR podobné. S rostoucí epikardiální rezistencí (FFR < 1) se MRR začíná od CFR (CFR klesá) lišit v závislosti na hodnotě FFR. Tato skutečnost udává nezávislost MRR na epikardiální rezistenci.[22]

MRR je tedy nezávislá na epikardiální rezistenci, což svědčí o specificitě tohoto parametru pro mikrovaskulaturu (při absenci významné epikardiální nemoci se MRR a CFR rovnají). Při přítomnosti epikardiálního postižení dochází k aktivaci autoregulačních mechanismů a naměřená klidová R_μ již neodpovídá (je menší) skutečné R_μ, jaká by byla při nepostižené epikardiální tepně. MRR tedy odpovídá CFR po zohlednění FFR (jedná se o mikrocirkulační důsledek FFR), a je nezávislá na mase myokardu.[22]

MRR = (CFR / FFR) × ($P_{a,klid}$ / $P_{a,hyper}$)

($P_{a,klid}$ / $P_{a,hyper}$ se u kontinuání termodiluce pomocí FR rovná 1, což neplatí u hyperemie navozené adenosinem, kde může být rozdíl i 10–30 %.)

Klinický význam

Při měření kontinuální termodilucí hodnota MRR ≥ 2,7 prakticky vylučuje přítomnost CMD, zatímco hodnota MRR < 2,1 její přítomnost potvrzuje (viz **tabulku 2** a **obr. 3**).[21]

Zjednodušení metody kontinuální termodiluce

Recentně bylo popsáno a validováno další významné zjednodušení a zrychlení této metody spočívající v odvození vstupní teploty T_i výpočtem ze změřených hodnot, tudíž bez nutnosti posunutí tlakově-teplotního čidla zpět do katétru RayFlow (viz **obr. 4**). Toto vede prakticky k eliminaci vlivu operatéra na měření, a činí tak z tohoto postupu diagnostiky CMD nejméně závislou na operatérovi.[27]

Validovaný vzorec k výpočtu T_i:
$T_i = 0{,}98*T - 0{,}28*Q_i + 0{,}90$

Porovnání bolusové a kontinuální termodiluce

Několik studií se zaměřilo na přímé porovnání bolusové a kontinuální termodiluce v rámci diagnostiky CMD.

Jansen a spol. ukázali, že CFR odvozená bolusovou termodilucí byla vyšší než absolutně změřená pomocí kontinuální termodiluce (2,6 ± 1,0 versus 3,5 ± 1,8; $p < 0{,}001$) a že spolu jen středně silně korelovaly. Absolutně změřená MRR kontinuální termodilucí byla také nižší než vypočtená z bolusové metody (3,1 ± 1,1 versus 4,2 ± 2,5; $p < 0{,}001$) se slabou korelací. Navíc CFR ani MRR odvozené bolusovou termodilucí nekorelovaly s anginou a kvalitou života, kdežto absolutní CFR a MRR kontinuální metodou korelovaly s oběma parametry silně.[21]

Gallinoro a spol. se zabývali reprodukcibilitou bolusové vs. kontinuální termodiluce. Celkem 102 pacientů s ANOCA bylo vyšetřeno pomocí obou metod v rámci jednoho sezení, randomizovaně k jedné z metod jako první, následované druhou. Jejich výsledky potvrdily předchozí zjištění, a to nižší absolutně změřenou CFR kontinuální metodou oproti odvozenému bolusovou metodou (2,63 ± 0,65 vs. 3,29 ± 1,17; $p < 0{,}001$), bolusová CFR zároveň prokázala výrazně vyšší variabilitu měření čili nižší reprodukcibilitu (variabilita: 31,26 ± 24,85% bolus vs. 12,7 ± 10,4 % kontinuální; $p < 0{,}001$). MRR měřená kontinuální termodilucí byla více reprodukcibilní než IMR z bolusové termodiluce (variabilita 12,4 ± 10,1% kontinuální vs. 24,2 ± 19,3% bolus; $p < 0{,}001$) a hodnoty MRR a IMR spolu zcela nekorelovaly.[28,29]

V subanalýze studie EDIT-CMD s opakovaným termodilučním měřením Jansen a spol. také prokázali vyšší reprodukcibilitu absolutních měření CFR a MRR kontinuální termodilucí oproti CFR a IMR odvozeným bolusovou metodou.[30]

Pokud jde o praktické rozdíly při provádění bolusové a kontinuální termodiluce, je důležité vyzdvihnout rychlost a jednoduchost kontinuálního měření, téměř úplnou nezávislost na operatérovi a zejména pohodlnost a příjemnost pro pacienta bez nutnosti kontinuálního podávání intravenózního adenosinu. Naopak z technického hlediska je nutné mít pro kontinuální termodiluci k dispozici specifický katétr RayFlow a infuzní pumpu schopnou přepínat mezi 10 a 20 ml/min – např. Medrad Mark 7 Arterion (Bayer, Leverkusen, Německo).

Závěr

Nemocní s anginou pectoris a s normálním koronárním nálezem nebo s nálezem hemodynamicky nevýznamné ateromatózy na koronární angiografii tvoří významnou část vyšetřených pacientů. V současné době nelze bez invazivního vyšetření určit přesnou příčinu obtíží a podle převládající patofyziologie nastavit optimální léčbu či naopak vyloučit kardiální původ obtíží. Pro zařazení invazivního komplexního vyšetření koronární fyziologie je klíčová jeho jednoduchost a dobrá reprodukovatelnost minimálně závislá na operatérovi. Přímé měření koronárního průtoku a mikrocirkulační rezistence pomocí kontinuální termodiluce nabízí metodu, která by mohla napomoci standardizaci provádění evaluace mikrovaskulární dysfunkce v rutinní praxi.

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Přehledový článek | Review article

Detekce a terapie arytmií u pacientů s transthyretinovou srdeční amyloidózou

(Detection and treatment of arrhythmias in patients with transthyretin cardiac amyloidosis)

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SOUHRN

Poruchy srdečního rytmu jsou velmi častým projevem transthyretinové srdeční amyloidózy. Přehledový článek se zabývá mechanismy, které vedou ke vzniku fibrilace síní, převodních poruch srdečních a komorových tachykardií, jejich incidencí a prevalencí. Je zaměřen na možnosti využití externích a implantabilních monitorovacích zařízení v detekci arytmií. Shrnuje moderní možnosti v terapii s důrazem na radiofrekvenční katetrizační ablaci a využití přímých perorálních antikoagulancií u pacientů s fibrilací a flutterem síní. Zmíněna jsou úskalí přístrojové terapie bradykardií a prevence náhlé srdeční smrti.

ABSTRACT

Arrhythmias are a very common manifestation of transthyretin cardiac amyloidosis. The review article focuses on the mechanisms that lead to the development of atrial fibrillation, cardiac conduction disorders, and ventricular arrhythmias, as well as their incidence and prevalence. It emphasizes the possibilities of using external and implantable monitoring devices in the detection of arrhythmias. It summarizes modern therapeutic approaches with particular attention to radiofrequency catheter ablation and the use of direct oral anticoagulants in atrial fibrillation and flutter. It mentions the challenges of cardiac pacing and prevention of sudden cardiac death.

Úvod

Transthyretinová amyloidóza (TTR-amyloidóza) je získané či hereditární onemocnění vznikající v důsledku akumulace transthyretinových amyloidních fibril. Následkem ukládání těchto patologických komponent v myokardu vzniká kardiomyopatie způsobená transthyretinovou amyloidózou (ATTR-CM), která se u postižených jedinců často manifestuje ve formě srdečního selhání. V časných fázích choroby se jedná o srdeční selhání se zachovanou ejekční frakcí levé komory. Obvyklé jsou rovněž převodní poruchy, síňové i komorové arytmie (**obr. 1**).[1,2]

Fibrilace síní, flutter síní a síňová tachykardie

Prevalence fibrilace síní se pohybuje okolo 40–76 % u pacientů se získanou srdeční wild-type TTR-amyloidózou (wtATTR-CM), a představuje tak nejběžněji detekovanou arytmii v této kohortě (**obr. 1**).[3–5] U pacientů s hereditární formou amyloidové kardiomyopatie (mATTR-CM), která vzniká na podkladě depozice mutovaného transthyretinu, zjišťovaná prevalence fibrilace síní široce kolísá mezi 11–54 %.[4,5] Diagnóza fibrilace síní předchází potvrzení amyloidové kardiomyopatie až ve 33 % případů (**obr. 2**).[4]

Předpokládají se multifaktoriální vlivy vyvolávající vznik arytmie.[6] Kromě mechanismů uplatňujících se při srdečním

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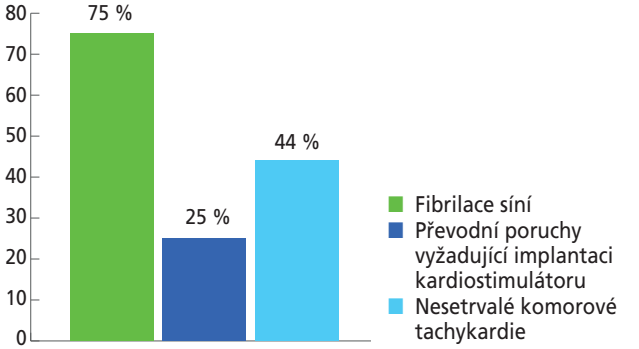
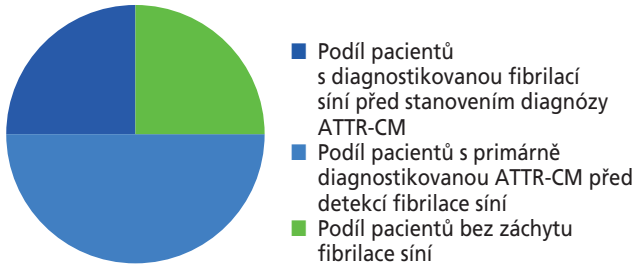


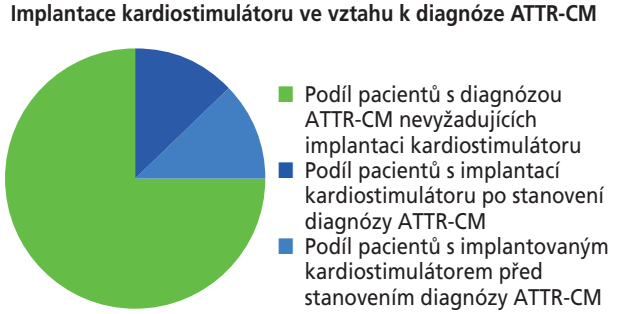
Obr. 1 – Graf znázorňující prevalenci jednotlivých typů arytmií u pacientů s transthyretinovou srdeční amyloidózou.

selhání a těžších poruchách diastolické funkce se na něm mohou podílet i specifické faktory v důsledku ukládání amyloidu v síních.[7] Kombinuje se tedy zřejmě jak působení zvýšeného plnicího tlaku a následná dilatace levé síně, tak sekundární strukturální remodelace z depozice amyloidu (**obr. 3**).[6]

Fibrilace síní je asociována s vyšším stupněm diastolické dysfunkce, nezdá se však být asociována se zvýšenou mortalitou ve skupině pacientů s TTR-amyloidózou.[5,8] Ztráta síňového příspěvku při plnění komor při diastolické dysfunkci a tachykardie často vedou ke zhoršení hemodynamické situace, dekompenzaci srdečního selhání až kardiogennímu šoku. Udržení srdečního výdeje je u těchto pacientů značně závislé na srdeční frekvenci.[9,10]

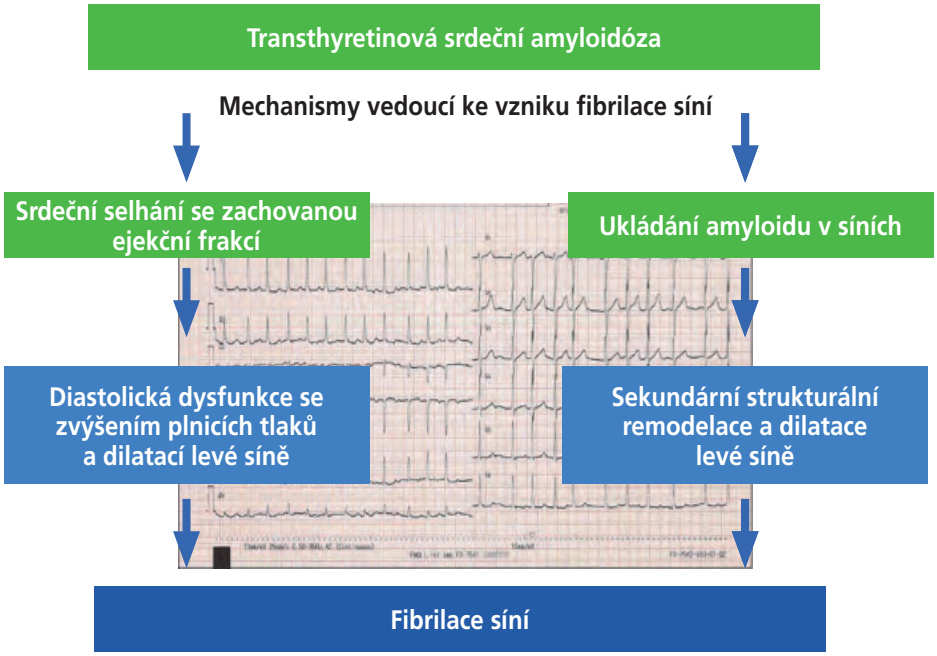
Pacienti s ATTR-CM jsou ohroženi vznikem intrakardiální trombózy i při sinusovém rytmu.[11] ATTR-CM představuje prediktor vzniku tromboembolismu nezávisle na skóre CHA_2DS_2VA (C – kardiální selhání, H – hypertenze, A_2 – věk 75 let a více, D – diabetes mellitus,





Obr. 2 – Graf znázorňující podíl pacientů s primární detekcí fibrilace síní ve vztahu k diagnostice transthyretinové srdeční amyloidózy a podíl pacientů s primární implantací kardiostimulátoru ve vztahu k diagnostice transthyretinové srdeční amyloidózy.

S_2 – tranzitorní ischemická ataka/cévní mozková příhoda, V – vaskulární onemocnění, A – věk 65–74 let), koncentraci kreatininu v séru a indexovaném objemu levé síně.[12] Bez ohledu na ostatní rizikové faktory je tedy antikoagulace při fibrilaci síní silně doporučena, protože



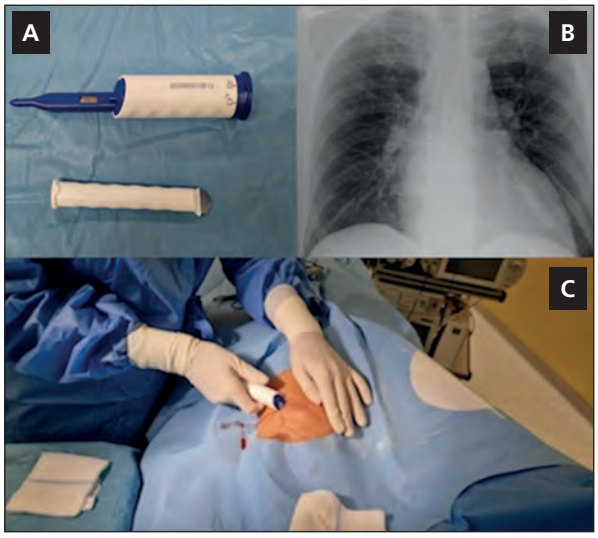
Obr. 3 – Schematické znázornění hlavních faktorů vedoucích ke vzniku fibrilace síní u pacientů s transthyretinovou srdeční amyloidózou.

arytmie přináší další zvýšení rizika tromboembolismu u ATTR-CM.[13,14]

Detekce fibrilace síní předchází diagnóze amyloidové kardiomyopatie až v jedné třetině případů, u ostatních pacientů je nutné po arytmii cíleně pátrat (**obr. 2**). V tomto ohledu může být přínosný nejen EKG screening během pravidelných klinických kontrol, ale také některé z metod umožňujících dlouhodobé sledování srdečního rytmu jak u symptomatických, tak i zcela asymptomatických pacientů. Bruce a spol. prokázali na menším vzorku 38 pacientů s ATTR-CM přínos dvoutýdenní vzdálené externí „patch" monitorace. Skupina pacientů s ATTR-CM měla vyšší záchyt fibrilace a flutteru síní ve srovnání s pacienty v kontrolní skupině (26,3 % vs. 5,3 %).[15]

Dale a spol. prezentovali observační studii, do níž bylo zařazeno 84 pacientů s ATTR-CM. Fibrilaci síní mělo 73 % ze sledované kohorty. U 34 % nemocných byly fibrilace či flutter síní diagnostikovány nově po dříve potvrzené ATTR-CM, u více než poloviny z těchto nově diagnostikovaných byla arytmie zjištěna díky pravidelnému monitorovacímu programu. Tento program zahrnoval kontroly srdečních implantabilních elektronických zařízení (CIED) každých šest měsíců u pacientů s implantovaným CIED nebo cílenou ambulantní monitoraci v šestiměsíčních intervalech. U většiny pacientů s prokázanou arytmií byla zahájena antikoagulační terapie.[16]

Značný podíl pacientů s ATTR-CM a zdánlivě trvajícím sinusovým rytmem tedy může mít silentní paroxysmální fibrilaci síní. Přínos implantabilních smyčkových záznamníků (ILR) u ATTR-CM je ještě méně zmapován než využití externích zařízení (**obr. 4**). Abbasi a spol. prezentovali malou pilotní studii zahrnující 24 pacientů s wtATTR-CM, kteří podstoupili šestiměsíční monitoraci pomocí ILR Biotronik Biomonitor 3, 18 z nich mělo anamnézu fibrilace síní. U deseti pacientů byla zaznamenána porucha srdečního rytmu, síňová fibrilace pak u devíti, u sedmi symptomatická, pouze u dvou však s novým začátkem a asymptomatická. U asymptotických pacientů s primodiagnózou síňové fibrilace byla vzhledem k dříve prodělané cévní mozkové příhodě zahájena antikoagulační terapie.[17]



Obr. 4 – (A) Implantabilní Biomonitor nejnovější generace využitelný k detekci arytmií u pacientů s transthyretinovou srdeční amyloidózou. (B) Implantovaný Biomonitor v předozadní rentgenové projekci. (C) Implantace Biomonitoru. Fotografie z archivu MUDr. Mariána Fedorca, Ph.D., I. interní klinika – kardiologická, Fakultní nemocnice Olomouc.

Terapie síňové fibrilace představuje u ATTR-CM rovněž výzvu. Zatímco strategie kontroly frekvence je častěji volenou strategií, nemusí být tolerována až u 80 % pacientů.[18] Snížení srdeční frekvence navozené betablokátory, blokátory kalciových kanálů či digoxinem může vést ke snížení srdečního výdeje, který je u těchto pacientů kriticky závislý na udržení dostatečné tepové frekvence. Tyto léky je tedy možné použít s opatrností.[6]

Výsledky starších studií naznačovaly, že strategie kontroly rytmu je účinná jen u menšiny takto léčených, může být efektivnější v počátečních fázích choroby, a to ať už se jedná o farmakologickou kontrolu rytmu, elektrickou kardioverzi, či radiofrekvenční katetrizační ablaci.[4,18,19] Recentně prezentovali Kanazawa a spol. retrospektivní observační studii zahrnující 233 pacientů s wtATTR-CM, z nichž 159 mělo síňovou fibrilaci, flutter či síňovou tachykardii. U 42 pacientů byla provedena radiofrekvenční ablace pro síňovou fibrilaci, u 33 pro flutter síní – s prokázaným makroreentry a u 18 pro síňovou tachykardii s fokálním zdrojem. Po jednom roce bylo bez rekurence arytmie 70,1 % pacientů, po dvou letech 57,6 % a po pěti letech 44 %, a to i po opakovaných reablacích. Celková mortalita, mortalita z kardiovaskulárních příčin a hospitalizace pro srdeční selhání byly procedurou nejpříznivěji ovlivněny u nemocných s arytmií, kteří byli symptomatičtí a měli exacerbace srdečního selhání. Katetrizační ablace by tedy mohla zlepšit prognózu a snížit hospitalizace pro srdeční selhání právě u těchto jedinců. Velmi nízkou efektivitu však měla ve skupině s komplexním flutterem síní, nezávislým na kavotrikuspidálním istmu, a u multifokální síňové tachykardie vznikající mimo atrioventrikulární anulus nebo crista terminalis.[19]

Radiofrekvenční ablace tedy představuje metodu kontroly rytmu s přijatelným rizikem periprocedurálních komplikací, která může u dobře vybraných pacientů snižovat mortalitu a hospitalizace pro srdeční selhání.[19–21]

Antikoagulační terapie je v případě ATTR-CM a fibrilace síní indikována nezávisle na skóre CHA_2DS_2VA.[22] Toto stratifikační skóre neidentifikuje správně pacienty ve zvýšeném riziku tromboembolismu, ať už jde o jedince s ATTR-CM s fibrilací síní, nebo se sinusovým rytmem.[23]

V nedávné metaanalýze zahrnující čtyři studie se prokázal nižší výskyt trombotických příhod a žádný rozdíl, pouze nesignifikantní trend ke snížení velkých krvácení při srovnání pacientů léčených přímými perorálními antikoagulancii (DOAC) a antagonisty vitaminu K (VKA). Vzhledem k úskalí, která přináší terapie warfarinem, mohou být DOAC optimálnější volbou v antikoagulační strategii těchto nemocných.[24]

Převodní poruchy

Ukládání amyloidu do intersticiálního prostoru myokardu vede k dezorganizaci srdeční tkáně s narušením přenosu elektrických impulsů převodním srdečním systémem. Svou roli hraje pravděpodobně také cytotoxicita a časná sympatická srdeční denervace.[1,25–27]

V době stanovení diagnózy wtATTR-CM může mít převodní poruchu s nutností předchozí implantace kardiostimulátoru 10–13 % pacientů a u dalších až 12 % se tato převodní porucha vyvine v průběhu dalšího sledování (**obr. 1, 2**).[28,29] Implantace kardiostimulátoru je spojena s nutností volby optimálního stimulačního režimu. Progrese převodní poruchy v průběhu času vede k vyššímu procentu pravokomorové stimulace, která je u pacientů s ATTR-CM spojena se zhoršením ve třídě NYHA (New York Heart Association), zhoršením závažnosti mitrální regurgitace a poklesem ejekční frakce levé komory.[30,31] Naopak biventrikulární stimulace je spojena se zlepšením ve třídě NYHA, mitrální regurgitace i vzestupem ejekční frakce levé komory, a měla by tedy být zvážena při nutnosti stimulace z bradykardické indikace.[31,32]

Ve studii Abbasiho a spol. byla převodní porucha pomocí ILR detekována u čtyř z 24 pacientů, pouze tři vykazovali symptomy během ataky arytmie (únava, točení hlavy, synkopa), tři byli léčeni implantací dvoudutinového kardiostimulátoru (PM), jeden pak vzhledem ke snížené ejekční frakci a záchytu asymptomatické kompletní atrioventrikulární (AV) blokády pomocí srdeční resynchronizační léčby PM (CRT-PM). Implantace ILR by tedy mohla být výhodná jak u asymptomatických pacientů, tak při nutnosti korelace symptomů a arytmie (**obr. 4**).[17]

Komorové arytmie

Prevalence setrvalých komorových arytmií u ATTR-CM a zejména význam implantace implantabilního kardioverteru-defibrilátoru (ICD) v prevenci náhlé srdeční smrti zůstávají předmětem diskusí. V observační studii 30 pacientů s familiární amyloidovou polyneuropatií s mutací *Val30Met* byla prokázána incidence komorových tachykardií 17 % na základě 24hodinové holterovské monitorace.[33] Knoll a spol. prezentovali studii, jež zahrnula 72 pacientů s wtATTR-CM, u kterých byla provedena 24hodinová holterovská monitorace EKG. Alespoň jedna epizoda nesetrvalé komorové tachykardie byla zaznamenána u 44 % sledovaných (**obr. 1**). U žádného pacienta pak nebyla potvrzena setrvalá komorová tachykardie.[34] Naopak ve studii Browna a spol. byla setrvalá komorová tachykardie zaznamenána v 5 % případů a komorová fibrilace ve 2 %.[35] V již zmiňované studii Abbasiho a spol. byla komorová tachykardie manifestující se námahovou synkopou detekována u jednoho z 24 pacientů s implantovaným ILR, u kterého byla následně provedena implantace jednodutinového ICD (1D-ICD).[17]

Prozatím nebyl prokázán příznivý mortalitní efekt 1D-ICD implantovaného z primárněpreventivní indikace u pacientů s ATTR-CM a sníženou EF LK.[35–38] Adekvátní terapie ICD mohou nastat ve 25–75 % případů.[35,38] Naproti tomu inadekvátní terapie je prováděna až ve 26 % případů.[37,38] Příčina úmrtí je v této skupině pacientů většinou nearytmická, způsobená progresí chronického srdečního selhání.[36] Implantace ICD v primární prevenci by tedy mohla být smysluplná u selektované skupiny pacientů a u pacientů s již dříve prokázanou maligní komorovou arytmií. Prediktory zvýšeného rizika náhlé srdeční smrti u ATTR-CM je potřeba dále analyzovat.[38,39] Hamon a spol. nezjistili ve studii se 45 pacienty se srdeční amyloidózou žádné klinické, biochemické či echokardiografické prediktory komorových arytmií. Zaznamenán byl trend k vyšší incidenci komorových arytmií u pacientů s lepším dvourozměrným globálním longitudinálním strainem. To by mohlo naznačovat vyšší riziko komorových arytmií u méně pokročilého srdečního postižení.[40]

Závěr

Závěrem lze říci, že detekce a terapie arytmií u pacientů s ATTR-CM zůstává oblastí ne zcela zmapovanou. Limitací dosavadních studií jsou zejména retrospektivní charakter a malé a heterogenní populace pacientů, jež zahrnují jak pacienty s wtATTR-CM, tak s mATTR-CM, či dokonce s amyloidózou z depozice lehkých řetězců (AL-amyloidózou). S ohledem na dostupnost specifické léčby tafamidisem, která redukuje celkovou mortalitu, počet hospitalizací z kardiovaskulárních příčin a zlepšuje dlouhodobé přežití u pacientů s ATTR-CM, bude nutno incidenci a prevalenci arytmií i výskyt náhlé srdeční smrti v této populaci dále sledovat.[41–43] Zatím se zdá, že by terapie tafamidisem mohla snižovat incidenci fibrilace síní u ATTR-CM. Zapotřebí jsou ale další, zejména prospektivní studie.[44]

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Přehledový článek | Review article

Spontaneous Coronary Artery Dissection in Patients with COVID-19: A Systematic Review of Published Case Reports

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SOUHRN

Kontext: Spontánní disekce koronární tepny (spontaneous coronary artery dissection, SCAD) představuje unikátní medicínskou výzvu vzhledem k nutnosti rychle stanovit diagnózu a zahájit léčbu; vyžaduje přitom velmi dobrou znalost základních mechanismů. Cílem tohoto systematického přehledového čllánku je nabídnout komplexní přehled případů SCAD u pacientů s diagnózou onemocnění covid-19.
Metody: Dne 3. června 2023 jsme provedli systematický přehled článků v databázích včetně PubMed, ScienceDirect a Cochrane. Do přehledu jsme zahrnuli případy SCAD u pacientů s onemocněním covid-19, v nichž byly uvedeny údaje jednotlivých pacientů.
Výsledky: Studie analyzovala 12 kazuistik; u všech pacientů byla potvrzena diagnóza onemocnění covid-19, byli ve věku s mediánem 49 let, jednalo se převážně o ženy (58,3 %). Většina pacientů vykazovala klasické symptomy onemocnění covid-19 (66,7 %), přičemž těžké projevy byly pozorovány u pacientek s těhotenstvím v anamnéze. Často byly zaznamenány vysoké hodnoty troponinů (83,3 %) stejně jako změny na EKG záznamu, hlavně abnormality v úseku ST a vlně T. Hlavním diagnostickým nástrojem byla koronagrafie (91,7 %), přičemž nečastějším místem disekce byla přední sestupná větev levé věnčité tepny (50 %). Ve čtyřech případech byla zjištěna snížená ejekční frakce levé komory, ale po léčbě nebyly zaznamenány žádné kardiovaskulární komplikace.
Závěr: Tato studie popisuje charakteristiky SCAD u pacientů s infekčním onemocněním covid-19; zároveň byly pozorovány vhodné diagnostické postupy a léčebné strategie.

Keywords:
COVID-19
Diagnosis
Spontaneous coronary artery dissection
Treatment

ABSTRACT

Background: Spontaneous coronary artery dissection (SCAD) presents a unique challenge due to its prompt diagnosis and treatment requirements, demanding an in-depth understanding of its underlying mechanisms. This systematic review aims to provide a comprehensive summary of the SCAD cases in patients diagnosed with COVID-19.
Methods: We performed a systematic search across databases, including PubMed, ScienceDirect, and Cochrane, on June 3, 2023. We included reported cases of SCAD in COVID-19 patients that described individual patient data.
Results: The study analyzed 12 case reports, revealing that all patients were confirmed COVID-19 cases with a median age of 49, predominantly female (58.3%). Most exhibited classic COVID-19 symptoms (66.7%), with severe presentations observed in those with a pregnancy history. High HS troponin levels were common (83.3%), as were ECG changes, namely ST and T abnormality. Coronary angiography was the primary diagnostic tool (91.7%), with the left anterior descending artery (LAD) being the most common site of dissection (50%). Four cases had reduced ejection fraction, but no cardiovascular complications occurred post-management.
This study elaborates on the characteristics of SCAD in COVID-19 patients, and appropriate modalities and treatments were observed.

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Background

In late 2019, coronavirus disease (COVID-19) emerged, presenting numerous challenges to global healthcare systems. While the primary respiratory symptoms of respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are well-documented, increasing evidence suggests that the virus can affect multiple organ systems, including the cardiovascular system. Spontaneous coronary artery dissection (SCAD) as a rare but emerging complication and potentially life-threatening condition has garnered attention. SCAD is defined as a nontraumatic separation of the layers of the coronary artery wall by intramural hemorrhage, generating restricted blood flow to the heart muscle.[1] This condition primarily affects young women without traditional coronary artery disease risk factors.[2] COVID-19-related SCAD presents a unique clinical challenge, as it requires prompt diagnosis and treatment and necessitates a comprehensive understanding of the underlying pathophysiological mechanisms. In COVID-19 patients, SCAD develops from the interaction between the pro-inflammatory state induced by the viral infection, the direct endothelial injury, and potential hypercoagulability related to COVID-19.[3] A systematic review of case reports is crucial to gain further insights into the relationship between COVID-19 and SCAD. This systematic review aims to provide an exhaustive summary of the reported cases of SCAD in patients diagnosed with COVID-19. Consolidating the available evidence will contribute to the growing knowledge surrounding this unique cardiovascular complication. The findings may help clinicians recognize and manage SCAD promptly in COVID-19 patients, improving outcomes and potentially saving lives.

Methods

The present review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for 2020[4]. Ethical approval was not required since no patients were directly involved in this study, and only published data were utilized.

Eligibility criteria

We systematically searched for SCAD case reports in patients with COVID-19, focusing on individual patient data. SCAD is defined as an emergency condition characterized by a tear in the wall of a coronary artery. Studies reporting SCAD in patients without COVID-19 were excluded. Additionally, studies involving animals as subjects, those not available in full text, and those written in languages other than English were also excluded. Duplicate articles were resolved before the title and abstract screening.

Search strategy and study selection

Systematic studies were retrieved from PubMed, ScienceDirect, and Cochrane on June 3, 2023. A manual or bibliography search was conducted to ensure comprehensive coverage of sporadic cases. The keywords used for the search included "spontaneous coronary artery dissection" and "COVID-19". We independently screened titles and abstracts of articles to identify potentially eligible studies, followed by a full-text review. Any discrepancies during the screening process were resolved through discussion with senior authors.

Data extraction

We extracted the following information from the included studies: author, year of publication, country, age, gender, presenting symptoms and signs, comorbidities and medical history, predisposing factors, diagnostic imaging, electrocardiogram (ECG) changes, high sensitivity (HS) troponin I level, timing about COVID-19 infection and severity, corticosteroid use, location of vessel dissection, ejection fraction, cardiac motion, management, complications, and outcomes. A structured and standardized form was meticulously used for data extraction. Any disagreement observed during the extraction process was resolved through discussion with senior authors.

Quality assessment

The risk of bias in the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports. The results were presented as a checklist rather than an accumulated score.[5] In cases where there were differing assessments or judgments during the quality assessment, these discrepancies were resolved through thorough discussions involving senior authors.

Statistical analysis

A meta-analysis could not be performed because this systematic review focuses on an extremely rare disease based on published cases. Narrative synthesis was the primary data synthesis method used in this review. However, quantitative analysis of extracted data was conducted using descriptive statistics. Similar findings for variables, such as clinical presentation, ECG findings, HS troponin I level, location of vessel dissection, and mortality, were grouped to assess their frequency. For instance, we compiled reported sites of vessel dissection, such as left anterior descending artery (LAD), right coronary artery (RCA), and left circumflex artery (LCx).

Results

Study selection

Out of the initial 388 records retrieved in the search, 155 were identified as duplicates and were consequently excluded. After thoroughly screening titles and abstracts, an additional 227 articles were excluded. Six published articles were included in this systematic review following this screening process, as determined through a comprehensive full-text assessment.[6–17] The PRISMA flow diagram visually presents the study's selection process and the rationales for exclusion (**Fig. 1).**

Quality assessment

All included case reports were assessed using a JBI critical appraisal checklist for case reports. Upon summarizing the critical appraisal checklist, it became evident that the overall risk of bias in these case reports was generally low. However, it's important to note that we did not establish

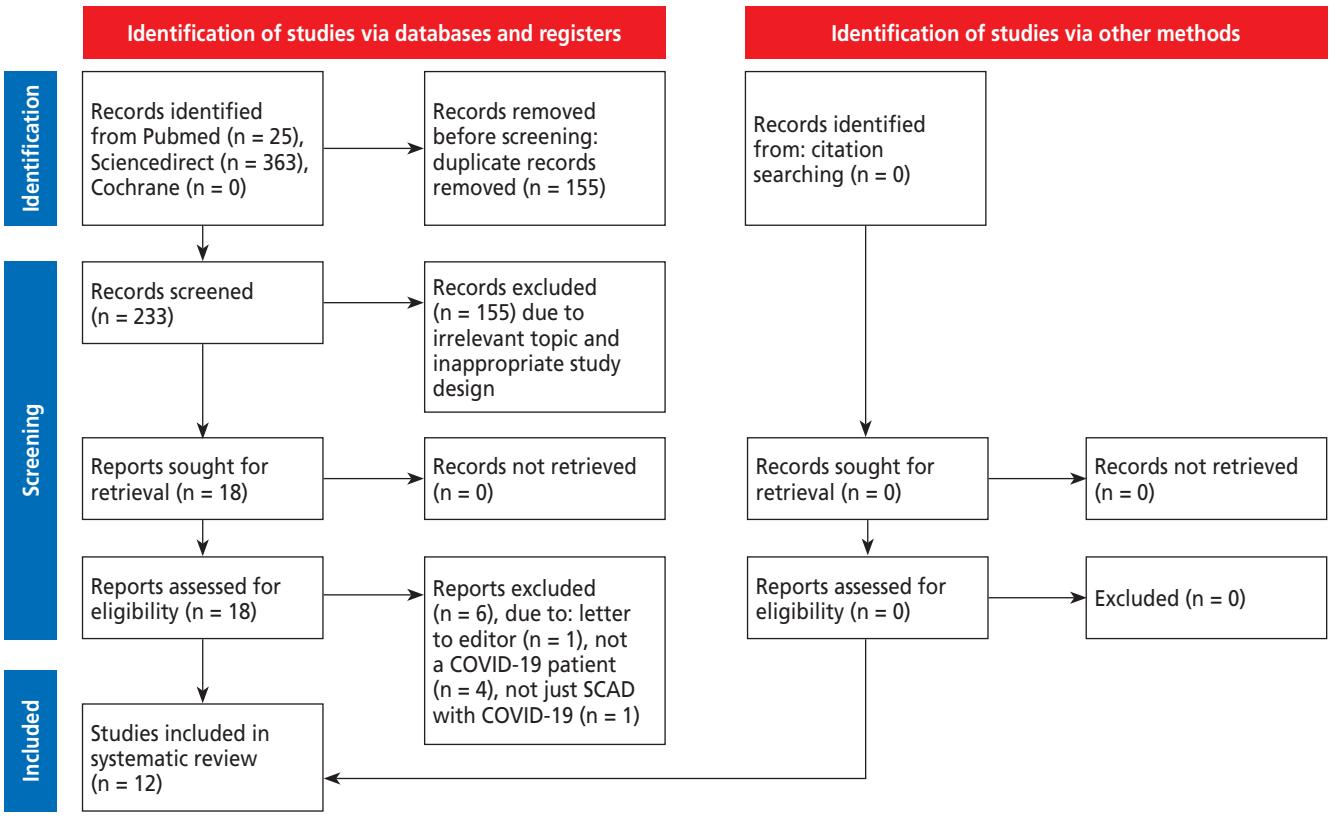

Fig. 1 – PRISMA flow of study selection.

specific criteria for categorizing a study as having a low risk of bias based solely on the total score obtained from the checklist (**supplementary file**).

Study characteristics

This systematic review of published cases included 12 case reports (**Table 1**).[6,7,9–18] The year of published case reports ranged from 2020 to 2022. Most published cases are from America[9,10,16,17,19] and Europe (5 cases each),[6,12–15] followed by Asia (2 cases).[7,11]

Clinical characteristics

The age of the patients ranged from 35 to 70 years, with a median age of 49. The data on age distribution suggests that SCAD in patients with COVID-19 is most common in adults and the elderly, with no instances reported in pediatric patients (**Table 1**). All cases were confirmed through COVID-19 testing, with five male patients for every seven female patients.

Cardiovascular symptoms, such as chest pain, palpitation, and dyspnea, are present in all cases.[6,7,9–18] Classic symptoms of COVID-19, such as shortness of breath, fever, coughing, and anosmia, were found in 6 cases.[6,9,11–13,15] One case presented with a syncopal episode due to ventricular fibrillation and required a defibrillation.[16] The time when SCAD symptoms appear varies. It can be at the same time as the diagnosis of COVID-19 or weeks after recovering from COVID-19. Five cases[9,13,14,17,19] were diagnosed with COVID-19 on the same day as the SCAD diagnosis, and two cases[12,15] were diagnosed two days after the SCAD diagnosis. Meanwhile, the other five cases[6,7,10,11,16] have a history of or have been hospitalized due to COVID-19, varying from 7 days to 3 months post-COVID-19.

The comorbidities of the patients varied among the cases. Five cases[10,11,13,14,17] did not have special medical terms, and five cases[6,7,12,15,19] had comorbidities or risk factors related to coronary artery disease, such as smoking, overweight, hyperlipidemia, hypertension, diabetes, and peripheral artery disease (PAD). There are two comorbidities related to pregnancy: pregnancy itself and postpartum cardiomyopathy.[9,16] A history of corticosteroid use was also reported in two cases,[6,10] with one of them in a case that had no risk factors for coronary artery disease or comorbidities except being a woman.

The HS troponin I levels were elevated in most cases (9 out of 10) that underwent examination. At the same time, there was no mention of HS troponin I levels in the other 2 cases.[11,17] Abnormal ECG changes were consistently observed in all cases reporting ECG examination results (11 of 12 cases), commonly presenting ST elevation and T inversion (**Table 1**).[6,7,9–14,16–18] However, the study by Courand et al. did not provide information on ECG examinations.

Coronary angiography is the most common primary imaging modality to diagnose SCAD (11 of 12 cases), followed by echocardiography,[7,9,11,13–16,19] coronary magnetic resonance (CMR),[7,14] CT angiography,[9] and myocardial perfusion imaging (MPI).[11] The location of the vessel's dissection is frequently found in the LAD (6 cases),[9,10,12–14,19] followed by the RCA (4 cases)[6,11,15,17] and LCx (2 cases).[7,16] The echocardiographic examination that was carried out showed that four patients experienced a decrease in the ejection fraction below 50%.[10,12,16,19] Meanwhile, the most

Table 1 – Demographics, presentation, comorbidities, COVID-19 infection status, and diagnosis of SCAD

No	Author/Year of publication	Country	Age (year), sex	Signs and presenting symptoms	Medical history and comorbidities	Imaging diagnosis	ECG abnormalities	Troponin I level	Timing according to COVID-19 infection, severity	History of corticosteroid use
1	Kireev et al./2020	Russia	35, M	Chest pain, weakness, fever, nasal congestion, anosmia, dry cough, chest congestion	Smoker, overweight, no autoimmune disease	Coronary angiography	Right precordial leads: slight ST elevations	Increase	Approximately 18 days post COVID-19, mild	Methylprednisolone
2	Kumar et al./2021	USA	48, F	Chest pain	Migraine, hyperlipidemia, FMD was ruled out	Coronary angiography, echocardiography, renal ultrasonography	Lead III and aVF: submillimeter ST elevations Lead V_3–V_5: biphasic changes	Increase	Covid test (+) at admission, NA	None
3	Alemzadeh et al./2022	Iran	58, F	Chest pain,	Severe thrombocytopenia, hyperlipidemia, hormone replacement therapy and physical/emotional stress was ruled out	Echocardiography, CMR, coronary angiography	Lead I and aVL: Q waves; lead V_5–V_6: inverted T	Increase	2 months post COVID-19, NA	None
4	Pettinato et al./2022	USA	43, F	Chest pain, palpitations, nausea, hypotensive, tachycardic	None	Coronary angiography	Lead V_2–V_4: ST elevation and T inversion	Increase	2 months post COVID-19, NA	Yes
5	Emren et al./2021	Turkey	50, M	Cough, fever, chest pain	None	Echocardiography, MPI, coronary angiography	Inferior leads: Q and inverted T waves	NA	7 days post COVID-19, Mild	None
6	Albiero and Seresini/2021	Italy	70, M	Chest pain, fever	Smoker, hypertension, diabetes	Coronary angiography	Precordial leads: ST-T abnormalities	Increase	1 day after coronary angiography, mild	None
7	Gasso et al./2020	Spain	39, M	Fever, cough, myalgia, chest pain, dyspnea	None	Echocardiography, coronary angiography	Lead II, III, aVF, and V_4–V_6: mild ST-elevation; lead V_1–V_4: appearance of a dominant R wave; lead II, III, aVF, and V_5–V_6: Q wave	Increase	Covid test (+) at admission, severe	None
8	Cannata et al./2020	UK	45, F	Chest pain	FMD was ruled out	Coronary angiography, echocardiography, CMR	Anterolateral leads: ST elevation	Increase	IgG covid test (+) at admission, NA	None

Pokračování na další straně

Table 1 – Demographics, presentation, comorbidities, COVID-19 infection status, and diagnosis of SCAD *(Dokončení)*

No	Author/Year of publication	Country	Age (year), sex	Signs and presenting symptoms	Medical history and comorbidities	Imaging diagnosis	ECG abnormalities	Troponin I level	Timing according to COVID-19 infection, severity	History of corticosteroid use
9	Ahmad et al./2021	USA	43, F	Cardiac arrest, hypothermia, bilateral decreased breath sounds	AF during pregnancy	Echocardiography, coronary angiography	AF with rapid ventricular	Normal	12 weeks post COVID-19, mild	None
10	Courand et al./2020	France	55, M	Cough, febrile, dyspnea, chest pain	Peripheral artery disease	Echocardiography, coronary angiography	NA	Increase	Moderate crazy pavy pattern in the lung in 48 hours after test result	None
11	Lewars et al./2022	USA	51, F	Chest pain, dyspnea	Anxiety, postpartum cardiomyopathy	Echocardiography, CT angiography	T wave inversion	Increase	COVID test (+) at admission, NA	None
12	Ali et al./2022	USA	53, F	Chest pain	NA	Coronary angiography	Inferior leads: ST elevation	NA	COVID test (+) at admission, NA	None

Table 2 – Artery dissection location, cardiac function, complication, management, and outcomes

No.	Author/Year of publication	Location of vessel's dissection	Ejection fraction	Cardiac motion	Management	Complication	outcome (survived/death)
1	Kireev et al./2020	RI, RCA	NA	NA	PCI, dual antiplatelet anticoagulation	None	Survived
2	Kumar et al./2021	LAD	45–50%	Distal anteroseptal and apical segments akinesis	Dual antiplatelet, nitroglycerin, fentanyl, beta blocker, amiodarone	None	Survived
3	Alemzadeh et al./2022	LCx	50%	Akinesia in the mid to apical lateral wall	Dual antiplatelet, metoprolol, lisinopril, statin	None	Survived
4	Pettinato et al./2022	LAD	45–49%	Basal to apical anterior, septal, and apical lateral segments of the left ventricle (LV) hypokinesis	Dual antiplatelet, nitroglycerin, heparin, morphine, ondansetron, atorvastatin, beta blocker, metoprolol, spironolactone, lisinopril, warfarin	None	Survived
5	Emren et al./2021	RCA	55%	Inferior and inferoseptum abnormality	PCI, dual antiplatelet anticoagulation, atorvastatin, metoprolol	None	Survived
6	Albiero and Seresini/2021	LAD	40–45%	Akinesis in LCx, severe hypokinesis in LAD	PCI, clopidogrel, bisoprolol, ASA, atorvastatin, metformin, pantoprazole	None	Survived
7	Gasso et al./2020	OM, LAD	50–55%	Hypokinesis of the severe basal, middle inferoseptal, inferolateral, and inferior wall; and hypokinesis of the basal inferior and lateral right ventricle	Conservative	None	Survived
8	Cannata et al./2020	LAD	NA	Hypokinesia of the anterior wall with moderate left ventricular systolic impairment	Dual antiplatelet, beta blocker, ACE inhibitor	None	Survived
9	Ahmad et al./2021	LCx	20%	New-onset global hypokinesis	Impella device, methylprednisolone	None	Survived
10	Courand et al./2020	RCA	60%	None	Conservative, ASA, statin, beta blocker	None	Survived
11	Lewars et al./2022	LAD	Normal	Dyskinetic apex	Nitroglycerine, aspirin, heparin, PCI	None	Survived
12	Ali et al./2022	RCA	NA	NA	PCI	None	Survived

common abnormal heart wall movements were hypokinesis (5 cases)[10,12–14,16] and akinesis (3 cases).[7,12,19] No complications related to the heart and blood vessels were found after management in all cases (**Table 2**).

A total of 5 cases underwent percutaneous coronary intervention (PCI) as the main therapy,[6,9,11,12,17] and no cases underwent coronary artery bypass graft (CABG). The remaining cases were administered conservative therapy with drugs.[7,10,13–16,19] Most cases reported receiving dual-antiplatelet therapy,[6,7,10–12,14,19] and two cases received aspirin alone.[9,15] Anticoagulant therapy was also given in 4 cases[6,9–11] as heparin or warfarin. Some cases also received beta-blocker therapy, ACE inhibitors, and statins. Statins are administered regardless of whether there is a history of hyperlipidemia. Methylprednisolone was administered in one case due to myocarditis as a late inflammatory sequela of COVID-19.[16] Due to an ejection fraction of 20% with new onset global hypokinesis, the patient in that case also received an impella device, which was then replaced with veno-arterial extra corporeal membrane oxygenation (VA-ECMO).[16] Despite all the characteristics and therapy provided, no cases experienced complications or mortality.

Discussion

Epidemiology and pathophysiology

Spontaneous coronary artery dissection, or SCAD, frequently occurs in young females under 50. SCAD was also reported in older and postmenopausal women and less than 10 % to 15 % of cases in men.[20] In this study, women younger than 50 have been reported by Kumar et al., Pettinato et al., Cannata et al., and Ahmad et al. Meanwhile, Alemzadeh et al., Lewars et al., and Ali et al. have reported SCAD cases in women older than 50. On the other hand, SCAD in men was only reported by Kireev et al., Emren et al., Albiero and Seresini, Gasso et al., and Corand et al.

Several studies have found that one of the risk factors for SCAD is pregnancy (pregnancy-related spontaneous coronary artery dissection or P-SCAD), and its incidence is approximately 1.81 per 100,000 pregnancies.[21,22] P-SCAD cases were found during pregnancy and three months of the postpartum period, and the most common incidences occur during the first month of the postpartum period and in the first week of the postpartum period.[22,23] Ahmad et al. reported atrial fibrillation in pregnancy as a comorbidity in a 43-year-old woman suffering cardiac arrest, whose ECG showed ventricular fibrillation and cardiogenic shock. Lewars et al. reported a 51-year-old woman with postpartum cardiomyopathy.

A tear of the tunica intima wall made blood enter and separate the coronary artery wall's layer, creating a false lumen filled with intramural hematoma in the medial layer. The external compression caused by the enlarging hematoma restricted coronary blood flow, which increased the pressure of the false lumen, leading to coronary artery insufficiency.[24–26] Another hypothesis is intramural hematoma accumulation from a spontaneous hemorrhage in vasa vasorum without a tear in the tunica intima.[27] Furthermore, more research about the pathophysiology of SCAD, specifically in patients with COVID-19 and its complications, is still required.

Clinical presentation and diagnostic approach

Phenotypically, SCAD exhibits consistent similarities with the atherothrombotic of acute coronary syndrome (ACS).[28] SCAD's primary manifestations, reported by the prior studies, were chest pain followed by an increase in specific cardiac enzymes, closely resembling ACS in general.[29–31] Hence, a definitive diagnosis of SCAD presents significant challenges and requires advanced diagnostic modalities, such as invasive intracoronary angiography, performed by experienced operators.[28] Presumptive diagnosis, however, can be considered by observing typical ACS clinical presentations in middle-aged women without traditional atherothrombotic risk factors like diabetes, hypertension, and dyslipidemia.[28,32] Additionally, additional comorbidities such as connective tissue diseases, arteriopathy, genetic predisposition, pregnancy, systemic inflammation, and precipitating factors like emotional stress and intense exercise in patients presenting with ACS support the suspicion of SCAD.[28]

COVID-19-associated SCAD's clinical manifestations did not appear significantly different from those in the general population. Importantly, SCAD was observed to occur in patients with varying temporal associations with COVID-19, ranging from during active infection to several months after recovery. Our study population primarily consisted of middle-aged females (median age of 49 years old), consistent with the demographic profile of non-COVID-19-associated SCAD patients.[28,33,34] Most patients had no pre-existing cardiovascular comorbidities. Nevertheless, we did observe a patient, a 70-year-old man, with risk factors of atherothrombosis, including hypertension, diabetes, and smoking, a 55-year-old male patient with peripheral artery disease, and another patient presenting with anxiety and postpartum cardiomyopathy. Chest pain was reported in all cases, with several patients also experiencing symptoms such as dyspnea and palpitations and one patient suffering from cardiogenic shock and arrest (the patient had a history of atrial fibrillation during pregnancy). This further confirms the similarity in clinical presentation between SCAD and other entities of ACS. Distinguishing factors may rely on coinciding signs and symptoms of associated comorbidities, such as COVID-19, which in our cases included flu-like syndrome and respiratory symptoms.

Furthermore, nine of the ten patients who underwent high-sensitivity troponin testing exhibited increased levels of this cardiac enzyme.[6,7,9,10,12–15,19] Six of the reported eleven EKG findings were characterized by ST elevation.[6,10,13,14,17,19] As mentioned earlier, differentiating atherothrombotic ACS from SCAD poses a distinct diagnostic challenge. For a definitive diagnosis of SCAD, the test of choice remains by invasive coronary angiography. Invasive coronary angiography remains the test of choice for the definitive diagnosis of SCAD.[28] Angiographic findings indicated that the majority of SCAD cases in COVID-19 patients was observed in LAD (50%), followed by RCA and LCX. These findings align with previous research highlighting the predisposition of SCAD in the LAD.[35,36] Moreover, coronary tortuosity and the absence of intraluminal thrombus were suggested as notable clues favoring the diagnosis of SCAD.[37,38] However, our findings noticed a case where SCAD diagnosis was made using non-invasive coronary computed tomography angiogra-

phy (or CTA), suggesting the potential role of noninvasive diagnostic modalities in detecting SCAD, especially when invasive coronary angiography was not feasible.[9]

Management and outcomes

Conservative therapy is preferred over other treatments in stable SCAD patients without ongoing ischemia and patients with occlusion of distal vessels or distal branches for which PCI is not routinely performed.[32] In a cohort study at Vancouver General Hospital, 79 patients who underwent repeat CTA or angiogram after 26 days showed complete healing from SCAD. In nine patients who did a repeat examination for less than 20 days, recovery did not occur. This indicates that the SCAD healing process depends on time.[39] Compared with conservative therapy, patients treated with PCI are at higher risk of complications and suboptimal outcomes. PCI is also at risk of requiring emergency CABG because of the failure of the procedure.[32,40] Coronary angiography causing iatrogenic dissection is rare (0.02-0.09%)[41,42]. However, in SCAD, the affected coronary arteries have a weak structure, which puts them at risk for iatrogenic dissection and dissection expansion due to PCI. The PCI procedure's wire can get into the false lumen, and the true lumen can be clogged. Additionally, SCAD frequently affects the distal coronary segment, which is not large enough for stent placement – field.[32,43] The incidence of iatrogenic dissection during diagnostic angiography and PCI was 4.7% in SCAD patients, according to a retrospective observational study.[44]

In SCAD cases, CABG is another option for therapy in patients with proximal or left main stem dissection, patients with failed PCI, patients with complications due to PCI, or refractory ischemia despite attempted conservative treatment.[32] In a retrospective study of 15 bypass grafts, 11 were occluded on follow-up angiography. This emphasizes that long-term protection against the effects of recurrent native coronary artery dissection is not provided by the CABG.[40] In high-risk patients with ongoing ischemia, left main artery dissection, or hemodynamic instability, conservative therapy is inappropriate. Therefore, the treatment for each SCAD patient is left to interventionists because there is no guideline for managing SCAD. Interventionists must consider coronary anatomy, operator skill, and facility availability in determining the best therapy.[32,45]

Relieving symptoms, improving short-term and long-term outcomes, and preventing recurrent SCAD are the main therapy goals for SCAD. Evidence of the benefit of using dual-antiplatelet in SCAD patients without coronary intervention is still limited.[32] The advantage of aspirin in large ACS populations is likely greater than the risk, which is why low-dose aspirin is considered.[46] No studies have compared the risk of bleeding or short-term and long-term outcomes using dual-antiplatelet or aspirin alone in the SCAD.[32] Since most SCAD involves prothrombotic intimal tears, empirically dual antiplatelet administration would be helpful. By using antiplatelet agents to reduce the false lumen thrombus burden, the true lumen compression could be reduced.[27] A retrospective Italian series examining long-term outcomes among patients with SCAD treated with dual-antiplatelet therapy in both PCI and conservative therapy patients found no bleeding complications and similar long-term outcomes for the two groups.[47]

Anticoagulation for SCAD is still controversial, with the risk of dissection extension balanced by the potential benefit of resolving overlying thrombus and improving true lumen patency, so heparin administration must be discontinued when SCAD is proven by angiography to prevent intramural hematoma extension. Beta-blockers can reduce arterial shear stress, which is expected to reduce coronary arterial wall stress.[27] Some experts recommend the routine use of SCAD based on its benefits for atherosclerotic MI or aortic dissection. In contrast, others recommend selective use because of the effect of vasospasm or symptomatic hypotension.[32]

Angiotensin-converting enzyme inhibitors are routinely administered to MI patients complicated by LV systolic dysfunction. This drug is also an option for patients with hypertension.[27,32] Statins should not be given routinely to SCAD patients but only to patients with hyperlipidemia as primary prevention of atherosclerosis and patients with concomitant atherosclerotic disease or diabetes mellitus[32,46] because less than 50% of SCAD patients had a prior diagnosis of hyperlipidemia.[45] In addition, statins were reported to be higher in patients with recurrence of SCAD.[32]

Conclusion

This study explained that SCAD in patients with COVID-19 had similar clinical presentation and complications to ACS, and they had different comorbidities and medical histories. Appropriate modalities to diagnose and treatments were chosen. Further research on SCAD with COVID-19 is still required.

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Conflict of interest
All the authors declare that there are no conflicts of interest.

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Ethical statement
Not required.

Underlying data
All data are available in the manuscript and separated files as supplementary.

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Přehledový článek | Review article

Minimally Invasive Management of Cystic Adventitial Disease in the Popliteal Artery: A Case Report and Review

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Hybridní výkony

SOUHRN

Kontext: Cystická degenerace adventicie (cystic adventitial disease, CAD) je vzácnou příčinou stenózy tepen, které postihuje převážně popliteální tepnu.
Kazuistika: K lékaři se dostavil 46letý muž s náhlou bolestí v pravém lýtku. Fyzikální vyšetření a CT angiografie odhalily významnou stenózu pravé popliteální tepny. Protože se nepodařilo iniciální trombektomií odstranit trombotický materiál, bylo rozhodnuto provést hybridní výkon zahrnující PTA a implantaci stentu. Vyšetření MR potvrdilo CAD a při kontrole po 24 měsících nebyly u pacienta zjištěny žádné příznaky.
Diskuse: Etiologie CAD je stále předmětem diskuse, přičemž byly předloženy teorie o místním poranění a synoviální/ganglionové cystě. Tradiční léčba byla chirurgická, nicméně tato kazuistika prokazuje účinnost minimálně invazivního přístupu.
Závěr: Minimálně invazivní endovaskulární léčba může být v případě CAD účinná; po výkonu je pro zajištění dlouhodobé průchodnosti tepny nezbytné pacienta pečlivě sledovat.

Keywords:
Cystic adventitial disease
Endovascular treatment
Hybrid surgery

ABSTRACT

Background: Cystic adventitial disease (CAD) is a rare cause of arterial stenosis, primarily affecting the popliteal artery.
Case presentation: A 46-year-old male presented with sudden right calf pain. Physical examination and CT angiography revealed significant stenosis of the right popliteal artery. Initial thrombectomy failed to remove thrombotic material, prompting a hybrid approach with PTA and stent implantation. MRI confirmed CAD, and the patient remained asymptomatic at 24-month follow-up.
Discussion: The etiology of CAD is debated, with theories including local trauma and synovial/ganglion origin. Traditional management has been surgical, but this case demonstrates the efficacy of a minimally invasive approach.
Conclusion: Minimally invasive endovascular treatment may be effective for CAD, with close monitoring needed to ensure long-term patency.

Introduction

Cystic adventitial disease (CAD) is a rare but well-documented form of nonatherosclerotic arterial stenosis. While it predominantly affects the popliteal artery (PA), it can also involve other arteries or veins.[1] The incidence of CAD is estimated to be 1 in 1,200 cases of claudication and 1 in 1,000 femoral angiograms, with a notable male predominance of 15 : 1. Approximately 85% of CAD cases are localized in the popliteal region.[2] Patients typically present as young, otherwise healthy individuals with no signs of multilevel atherosclerosis. Due to the rarity of the condition and the limited literature, primarily consisting of case reports, the management of CAD remains individualized and patient-specific.

Case presentation

A 46-year-old male presented with a sudden onset of pain in the right calf following prolonged squatting while gardening. The symptoms began seven days prior to admission. Unlike classic claudication, he was able to walk approximately one kilometer without pain, but experienced pain onset when ascending stairs. The patient had no

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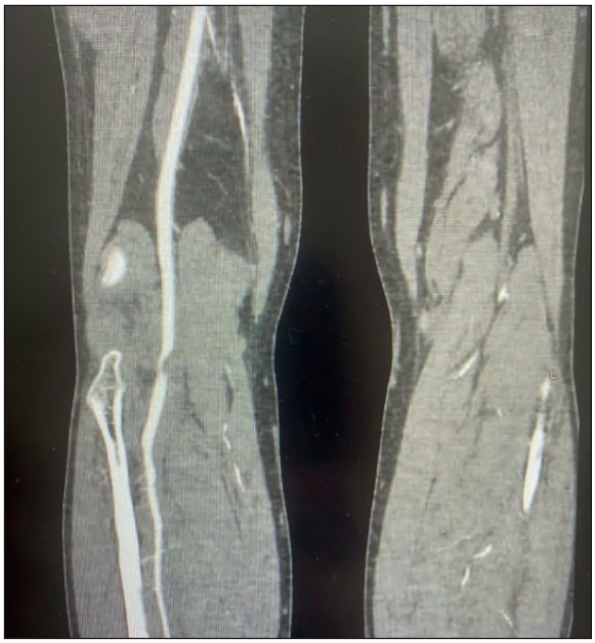

Fig. 1 – Sagittal view of a subtotal occlusion of the right popliteal artery.

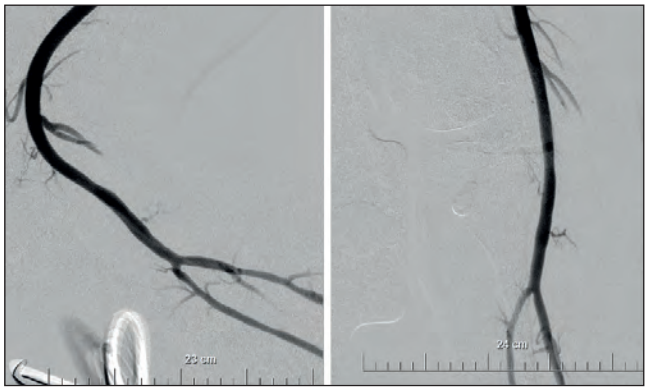

Fig. 2 – Post-thrombectomy angiography with flexed knee on the left and extended knee on the right. The angio suprisingly shows no residual stenosis.

comorbidities and had undergone arthroscopic cruciate ligament repair of the right knee five years earlier due to trauma.

Physical examination revealed the absence of pulsations in the anterior and posterior tibial arteries of the right leg, while the popliteal artery pulse remained palpable. An ankle-brachial index (ABI) was measured, showing significant discrepancies between the two legs, with an ABI of 0.5 on the right compared to 1.0 on the left.

The patient underwent a computed tomography angiography (CT-Angio), which revealed a significant 90% isolated stenosis of the right popliteal artery without an apparent underlying cause (**Fig. 1**).

Taking in consideration the sudden onset of symptoms and the high probability of fresh thrombus formation, we initially opted for an open thrombectomy of the popliteal artery via a femoral incision using a 4Fr Fogarty catheter. No thrombotic material was evacuated, prompting us to proceed with a hybrid approach. Our angiography post thrombectomy surprisingly showed no residual stenosis and excellent distal runoff (**Fig. 2**). Our hypothesis is that the outward force exerted by balloon of the Fogarty catheter itself was enough to push back the cystic formation.

Those findings prompted us to use IVUS which showed homogenous stenosis on the back wall of the PA. This involved percutaneous transluminal angioplasty (PTA) of the popliteal artery using a drug-eluting balloon. Follow-up angiography revealed no residual stenosis but a slight hint of a dissection flap leading to the decision to implant a short self-expandable stent. The final angiography showed excellent results – three patents below the knee arteries runoff, with palpable pulses restored in the anterior and posterior tibial arteries (**Fig. 3**)

Post-operative magnetic resonance imaging (MRI) revealed a cystic formation on the posterior wall of the popliteal artery in the previously stenosed area, confirming the pathogenesis of the lesion. The stent remained widely patent with no signs of residual stenosis (**Fig. 4**).

The patient has started on clopidogrel 300 mg loading dose immediately post procedure and 75 mg once daily. Following the intervention, the patient experienced

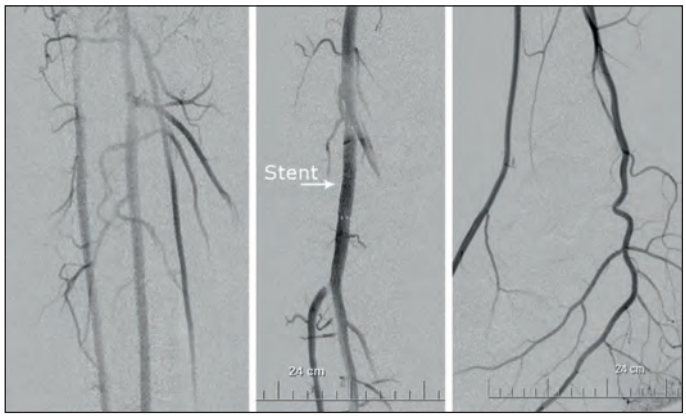

Fig. 3 – Post operative angiographies showing a patent popliteal stent in the middle, and three below the knee arteries run-off.

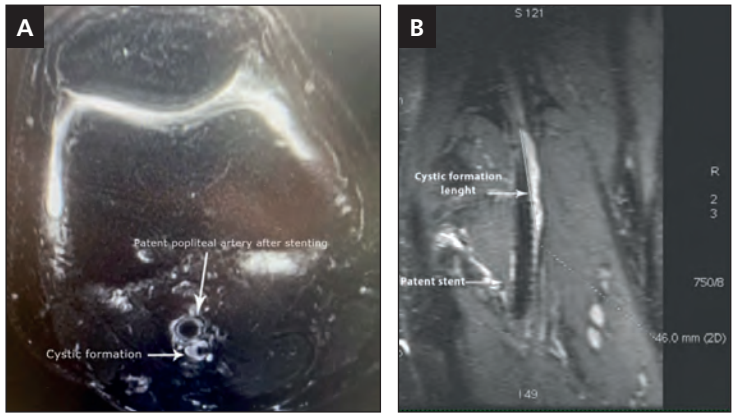

Fig. 4 – MRI of the right popliteal artery showing a cystic formation on the back artery wall with patent stent and no sign of compression. (A) Transversal view. (B) Sagittal view.

relief of claudication symptoms and remained asymptomatic at the 12-month follow-up. A noninvasive Doppler ultrasound examination confirmed patency of the stent. The ankle-brachial index at the 12-month follow-up was normal at 1.0.

At the 24-month interview, the patient reported remaining asymptomatic and continued to tolerate exercise well.

Discussion

The etiology of cystic adventitial disease (CAD) remains controversial, with several potential theories proposed, including: 1) repetitive local trauma, 2) systemic disease, 3) synovial/ganglion origin, and 4) embryological development.[3,4]

The repetitive local trauma theory postulates that vessels located near joints are subject to repetitive microtrauma, leading to disruption of the adventitia from the media. This disruption can result in intramural bleeding and subsequent cyst development due to enzymatic activity within the vessel wall.[2] There have been reports of trauma induced cysts; however, this theory is controversial as CAD can occur in children and is rare in athletes.[4]

Linquette et al. proposed the systemic disease theory, suggesting that CAD is related to a generalized disorder of myxomatous degeneration. However, this theory has failed to gain adequate support, as patients did not show systemic lesions on follow-up.[2] The synovial/ganglion theory and the embryological theory have recently gained more favor in the etiology of CAD. The synovial/ganglion theory proposes that adventitial cysts develop due to migration of synovial ganglions from the adjacent joint capsule or tendons, along vascular branches to the adventitia.[5] The synovial/ganglion theory seems to fit best in our case keeping in mind the fact that he had previous surgical repair in the knee joint. The embryological theory hypothesizes that during development, mesenchymal cells are incorporated into the adventitia from adjacent joint tissue. These cells then secrete mucin over a number of years giving rise to adventitial cysts which have the potential to encroach on the arterial lumen.[2,4] Because there is no single unifying theory able to account for the pathogenesis of all clinical cases, CAD may be better explained by a combination of multiple theories.

Management of CAD has predominantly been surgical[6,7] involving either cyst drainage to allow full arterial lumen expansion or arterial reconstruction via bypass. Results generally favor arterial reconstruction, although evidence has been primarily derived from case reports and occasional small series. A minimally invasive approach using percutaneous cyst drainage[8] has been described but has shown mixed results. Endovascular techniques have been infrequently utilized, typically involving balloon angioplasty or focusing on secondary interventions.[9–11]

Due to the location of the cyst beneath the adventitia, balloon angioplasty is likely to be ineffective. Unless there is disruption of the intima, media, or adventitia allowing drainage of the cyst contents either into the artery or towards the popliteal space, the cystic lesion is expected to remain unchanged or potentially refill with fluid over time.

At the time of the procedure, there was suspicion of CAD in this particular patient. However, we were surprised to observe a near-excellent result following Fogarty thrombectomy. This outcome is puzzling because significant force would theoretically be required to maintain artery patency if there were indeed compressions in this segment.

This observation led us to consider that stent placement alone might suffice, offering the potential for long--term patency with minimal surgical trauma, as it was the case ultimately.

The rationale behind deploying a bare-metal, self-expanding stent is to utilize its radial force to induce remodeling of the arterial wall. This mechanism theoretically involves "pushing" the contents of the cyst out of the adventitia, potentially utilizing anatomical connections similar to those described with the knee joint. This process aims to collapse the cystic cavity and stimulate an inflammatory reaction that could lead to cyst sealing. However, proving this concept is challenging definitively.[12]

Intimal hyperplasia and restenosis are significant concerns with this procedure. Minimizing arterial injury by avoiding balloon angioplasty before or after stent deployment is crucial. Close patient follow-up is essential, with re-intervention if necessary. Given the impracticality of directly intervening on the cyst, a short bypass graft would be considered as the primary option.

Conclusion

Cystic adventitial disease of the arteries presents a challenging diagnostic and therapeutic dilemma, characterized by cystic formations within the adventitial layer, predominantly affecting the popliteal artery. Management has traditionally been surgical, with options ranging from cyst drainage to arterial reconstruction. Our case highlights the efficacy of a minimally invasive approach using bare-metal, self-expanding stents, which leverages their radial force to potentially remodel the arterial wall and address the underlying pathology without the need for extensive surgical trauma.

However, the management of CAD remains complex, with considerations including the risk of intimal hyperplasia and restenosis post-stent placement. Close monitoring and prompt reintervention are essential to ensure long-term patency and symptom relief. Further research is warranted to elucidate the optimal treatment strategies and long-term outcomes of endovascular interventions in CAD.

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Ethical statement
Our institution does not require an ethical approval for reporting individual cases or case series.

Informed consent

Verbal informed consent was obtained for anonymized patient information to be published in this article.

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Přehledový článek | Review article

Persistent Severe Bradyarrhythmia Following Donepezil Discontinuation in Dementia Patient: A Case Report and Literature Review

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Kazuistika
Vysazení

SOUHRN

Kontext: Donepezil je inhibitor acetylcholinesterázy používaný v péči o nemocné s Alzheimerovou chorobou. Uvedená látka sice zmírňuje klinické symptomy, ale nese s sebou riziko vzniku ortostatické hypotenze a bradykardie. Pozornost je třeba věnovat nepříliš častému vzniku těžké bradyarytmie po vysazení donepezilu. Dosud nebyly publikovány žádné kazuistiky na téma těžkých bradyarytmií po vysazení donepezilu.
Popis případu: Uvádíme případ 33leté ženy s opakovanými mdlobami v anamnéze; trpí demencí a pravidelně užívá donepezil. Prodělala epizodu těžké bradyarytmie s hodnotou 45 úderů za minutu při aplikování dopaminu v dávce 5 μg/kg/min, která neodpovídala na podání atropinu. Vysazení donepezilu nevedlo k vymizení asymptomatické bradykardie. Protože použití dočasné kardiostimulace stav pacientky zlepšilo, byl jí implantován trvalý kardiostimulátor.
Závěry: Tento případ jednoznačně ukazuje na souvislost mezi užíváním donepezilu a těžkou bradyarytmií u pacientů s demencí. Kazuistika zdůrazňuje náročnost zvládání nežádoucích účinků a vyplývá z ní, že vysazení donepezilu a zahájení anticholinergní léčby nemusí vždy postačovat; v takovém případě je nutno pacientovi implantovat kardiostimulátor.

Keywords:
Bradyarrhytmia
Case report
Dementia
Discontinuation
Donepezil

ABSTRACT

Background: Donepezil is an acetylcholinesterase inhibitor used in Alzheimer's disease management. It improves clinical symptoms but carries risks of orthostatic hypotension and bradycardia. Uncommon severe bradyarrhythmias post-discontinuation deserve attention. In addition, there have been no previous case reports regarding severe bradyarrhythmias post donepezil discontinuation.
Case presentation: We report a case of a 33-year-old woman with a history of recurrent fainting. She has dementia and regularly takes donepezil. She experienced severe bradyarrhythmia with heart rate of 45 beats per minute regular on dopamine 5 μg/kg/min and unresponsive to atropine. The discontinuation of donepezil did not improve asymptomatic bradycardia. The use of temporary pacemaker (TPM) improved the patient's condition, then permanent pacemaker (PPM) was implanted.
Conclusions: This case report highlights donepezil's link to severe bradyarrhythmia in dementia patients. It stresses the challenges in managing adverse effects, suggesting that stopping donepezil and anticholinergic therapy may not always be sufficient and pacemaker implantation may be required.

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Background

Donepezil is a commonly prescribed acetylcholinesterase inhibitor used in the management of Alzheimer's disease.[1] Its primary function is to enhance cholinergic neurotransmission by inhibiting the breakdown of acetylcholine, thereby improving cognitive function in patients with dementia.[2] The adverse reactions commonly experienced by more than 10% of individuals taking donepezil include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. On the other hand, less common adverse effects, occurring in 1–10% of cases, encompass insomnia, emesis, gastritis, hypertension, syncope, bradycardia, chills, generalized coldness, pain, dizziness, abnormal gait, confusion, fatigue, diaphoresis, abdominal pain, bloating, and constipation.[3] This case report highlights an unusual and previously unreported manifestation of donepezil-related adverse effects, involving the development of persistent severe bradyarrhythmia in a dementia patient following drug discontinuation.

Case presentation

A 33-year-old woman, referred from a local government hospital, came to the emergency room with complaints of frequent weakness for the last 5 months. The patient had a history of recurrent fainting. Prior to fainting, she experienced dizziness. The patient had never previously had similar symptoms. There were no complaints of shortness of breath, typical chest pain, palpitations, or similar previous episodes. The patient did not experience dyspnea on exertion (DOE), paroxysmal nocturnal disease (PND), orthopnea, or swelling. She had dementia and regularly took donepezil 5 mg, with no other medications. BMI was measured at 25.39, indicating overweight. The patient denied having hypertension, diabetes mellitus, heart disease, or neurological conditions. While at the referring hospital, the patient received 2 ampoules of Sulfas Atropine, but there was no change in the patient's heart rate and clinical conditions.

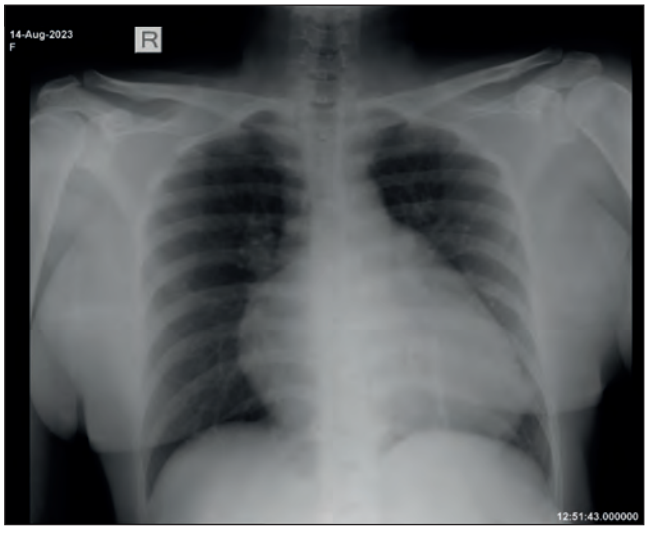

Fig. 1 – Chest X-ray on initial presentation showing prominent CTR 68%. CTR – cardiothoracic ratio.

On presentation, the patient had a GCS of 456, blood pressure of 111/67 mmHg, heart rate of 45 beats per minute regular on dopamine 5 µg/kg/min, respiratory rate of 18 breaths per minute, SpO_2 of 99% on room air, and a temperature of 36.5 °C. Upon auscultation of the heart, single regular S1 and S2 were heard, and no murmurs or gallops were found. Laboratory test results of the patient upon arrival at the emergency room are provided in **Table 1**.

The chest X-ray showed a prominent cardiothoracic ratio of 68% and no infiltrates were found (**Fig. 1**). The EKG results from the referring hospital revealed sinus arrest with junctional escape rhythm at 51 beats per minute, normal axis, and clockwise rotation with horizontal axis (**Fig. 2**). Transthoracic echocardiography (TTE) examination revealed dilatation in the left atrium and right atrium. Valve examination revealed qualitatively mild aortic

Table 1 – Laboratory work-up

Laboratory parameter	Patient's results	Normal range
Hb	14.7 g/dl	13–18
WBC	7.76 k/µL	4–11
Thrombocyte	221 k/µL	140–440
Natrium (Na)	140 mmol/l	135–145
Kalium (K)/potassium	3.2 mmol/l	3.5–5.0
Chloride (Cl)	107 mmol/l	98–107
Calcium (Ca)	9.1 mg/dL	8.5–10.5
Magnesium (Mg)	2.2 mg/dL	1.8–2.4
BUN	6.3 mmol/L	2.1–8.5
Creatinine	0.6 mg/dL	0.6–1.1
Random blood sugar	191 mg/dL	<200
SGOT	34 U/L	5–40
SGPT	14 U/L	7–56
Albumin	4.3 g/dL	3.4–5.4
CRP	1.16 mg/dL	<0.3
TSH	0.7530 µUI/mL	2–12 years: 0.64–6.27 12–18 years: 0.51–4.94 >18 years: 0.55–4.78
Free T4	0.99 ng/mL	1–23 months: 0.94–1.44 2–12 years: 0.86–1.4 13–20 years: 0.83–1.43
T3	0.63 ng/mL	0.35–1.93
Procalcitonin	0.02 ng/mL	<0.05: healthy ≥0.05 – <0.5: local infection ≥0.5 – <2: systemic infection ≥2 – <10: severe sepsis ≥10: septic shock
Blood sedimentation rate	9 mm	0–20
ANA test	15.7 AU/mL	<40.0: negative ≥40.0: positive
Anti ds.DNA	0.5 IU/mL	<30.0: negative ≥30.0: positive

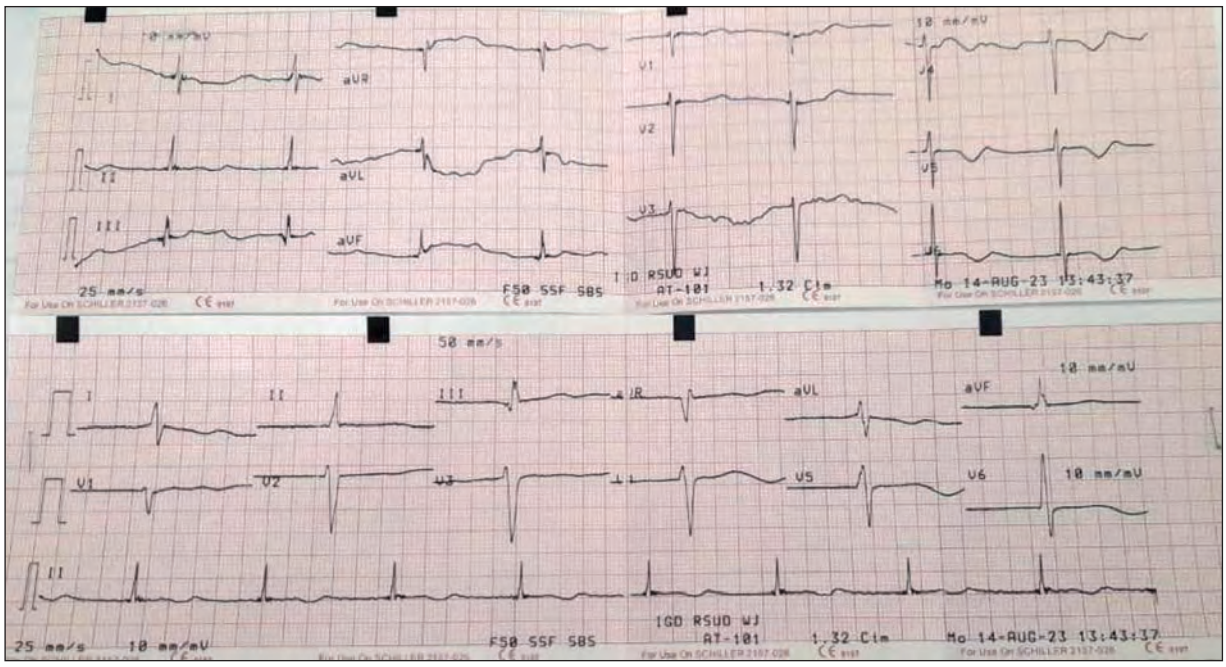

Fig. 2 – ECG on initial presentation.

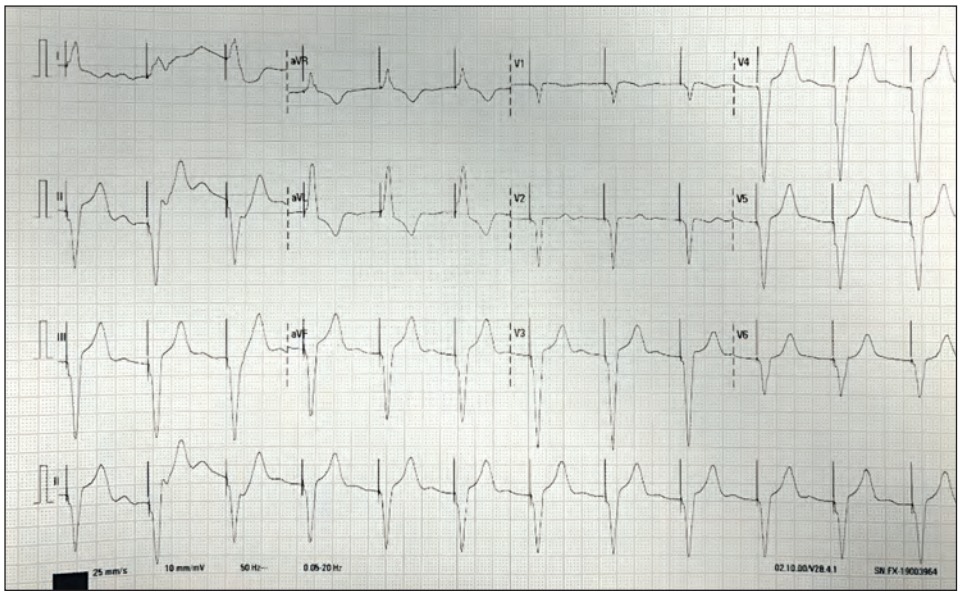

Fig. 3 – ECG after TPM installation.

regurgitation, trivial tricuspid regurgitation, and trivial pulmonary regurgitation. No signs of effusion or congestion were found.

The patient was diagnosed with symptomatic bradycardia, atrial fibrillation with slow ventricular response, and hypokalemia (3.1 mmol/l). The consumption of donepezil was also stopped and supervised by a nurse. A KCl drip of 40 mEq/100 cc over 3 hours via a central venous catheter (CVC) was administered to correct hypokalemia, but symptoms were still present. A temporary pacemaker (TPM) was implanted, and the dopamine pump was discontinued. After the TPM was placed, vital signs in normal limits with pacemaker rhythm, the patient had no symptoms and was under observation (**Fig. 3**).

However, asymptomatic bradycardia is persistent after 72 hours of donepezil discontinuation. After 72 hours of discontinuing donepezil consumption, the patient's heart rate did not change significantly. When attempting to remove the TPM, an EKG showed sinus arrest with junctional escape rhythm at 45 beats per minute, normal frontal axis, clockwise rotation of the horizontal axis, T-wave inversion in leads V_3–V_6 with prominent U wave (**Fig. 4**). The patient's potassium level became 3.7 mmol/l (normal). The patient experienced a weight loss of 10 kg

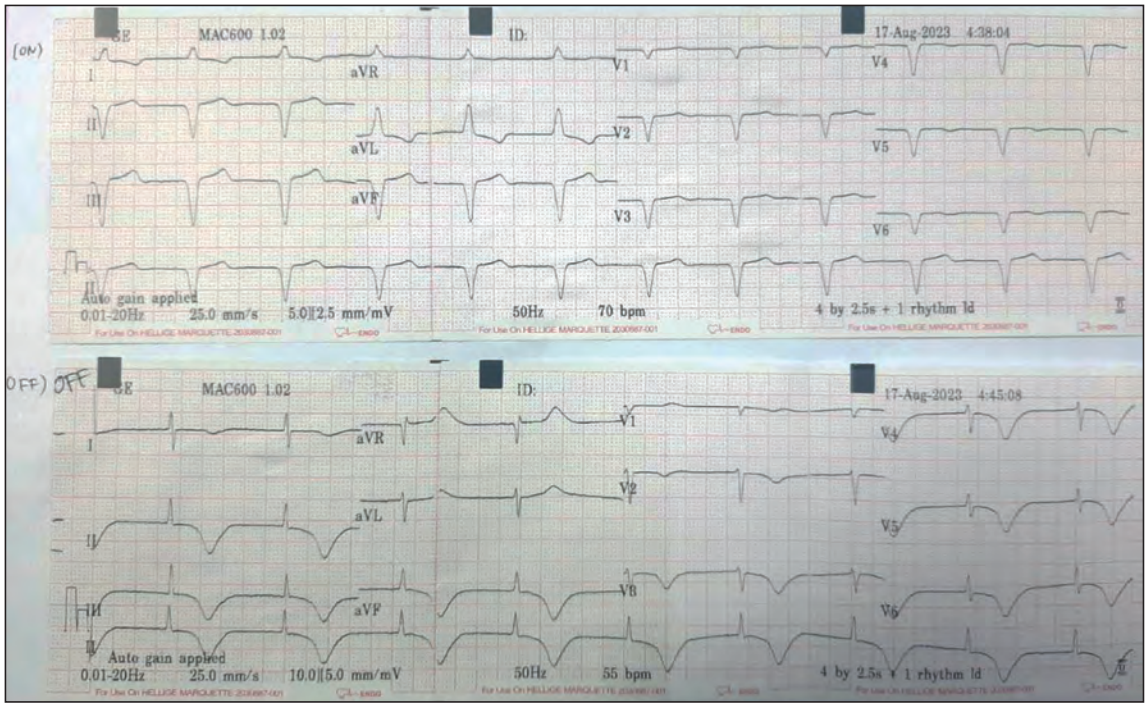

Fig. 4 – Comparison of ECG during TPM installation and TPM removal.

Table 2 – Similar published casereports

Number of cases or sex/age	Sign and symptoms	Donepezil dose	Treatment	Outcomes	Case link
Female/79	Letargy, vomiting, HR 56 bpm, pale skin, diaphoretic	50 mg	3 mg of atropine injection	Returned to baseline by day two in the hospital	Donepezil overdose: a tenfold dosing error - PubMed (nih.gov)[6]
Male/84	Nausea, vomiting, diarrhea, fatigue, excessive sweating, disorientation, HR 50 bpm, QTc prolongation	35 mg	0.5 mg of atropine injection	The patient's bradycardia and QTc prolongation resolved, and the patient returned home after six days in the hospital	Cardiotoxic overdose treated with intravenous fat emulsion and high-dose insulin in the setting of hypertrophic cardiomyopathy - PubMed (nih.gov)[7]
Female/74	Nausea, vomiting, drowsiness, flushing, diarrhea	45 mg	No treatment	Returned to baseline after stopping donepizil	Donepezil overdose - PubMed (nih.gov)[8]
Male/90	HR 36 bpm, advanced 2 : 1 atrioventricular block and QT prolongation	5–10 mg	The patient's donepezil was discontinued and 30 mg of orciprenaline was administered	By the fifth day, the patient's ECG and other symptoms had normalized	Donepezil-induced adverse side effects of cardiac rhythm: 2 case reports of atrioventricular block and Torsade de Pointes - PubMed (nih.gov)[9]
Female/87	Syncope, nausea, vomiting, HR 40 bpm, QT prolongation		30 mg of orciprenaline	On the fifth day, the donepezil was discontinued, and her heart rate increased to 55 BPM. On day 18, the QT prolongation resolved	Encephalopathy from unintentional donepezil and memantine ingestion - PubMed (nih.gov)[10]
Female/96	Difficult to awaken, diaphoretic, altered mental status, abdominal pain, HR 64 bpm	5–10 mg	Electrolyte correction, ciprofloxacin and metronidazole for colitis, 3 mg of glucagon injection	The patient was discharged on day six with two more days of antibiotic therapy (ciprofloxacin and metronidazole) and complete resolution for her symptoms	Suspected donepezil toxicity: A case report - PMC (nih.gov)[11]

(BMI 21.48). The patient was finally put on PPM because she remained symptomatic even though donepezil was discontinued. This decision took into consideration the patient's good quality of life and other health conditions. Patient was discharged from the hospital and had routine check-ups at the polyclinic in good condition for 2 months later.

Discussion

Bradyarrhythmias are characterized by an abnormally slow heart rate, fewer than 60 beats per minute (bpm).[4] Bradyarrhythmias can reflect normal physiologic responses, as in sleeping, or reveal a number of rhythm disorders, including sinus node dysfunction and AV conduction disturbances.[5] Common causes of bradyarrhythmias encompass intrinsic cardiac diseases, electrolyte imbalances, autonomic dysfunction, and pharmacological influences.[4] Although rare, bradyarrhythmias may occur in dementia patients taking donepezil at toxic and therapeutic doses, and all of them are elderly patients (>60 years) (**Table 2**). Bradycardia in older patients can occur due to the influence of an unstable autonomic nervous system so that donepezil causes bradycardia more easily in geriatrics, but uniquely in this case it occurred at a young age (33 years). This opens up insight that this condition can also occur at a young age.

The pathophysiological mechanisms underlying bradyarrhythmias in dementia patients following donepezil discontinuation remain elusive. It is postulated that donepezil's cholinergic enhancement may influence cardiac conduction pathways, potentially leading to abnormal rhythm disturbances.[12] The patient's bradycardia did not change even though donepezil had been stopped for 72 hours. The half-life of donepezil is 70 hours.[13] The altered pharmacodynamics of aging can cause up to a 17% decrease in clearance of donepezil in older adults and result in higher serum levels of donepezil.[14] In a randomized, open-label, real-world comparative trial, adverse effects accounted for 73.1% of discontinuations of donepezil, galantamine, and rivastigmine.[9] The adverse events listed as cardiovascular (CV) were "fast or slowed heart rate", and "irregular heartbeat", and the total CV adverse effects ranged from 6.5% for galantamine to 12.2% for rivastigmine. Other adverse events listed under other categories may have had, at least in part, an unrecognized CV contribution. Examples include fainting, dizziness, falls, and fatigue. The overall rates of discontinuation after the 18-week trial were 38.8% for donepezil, 53% for galantamine, and 58.7% for rivastigmine.[10]

Donepezil, by inhibiting acetylcholinesterase, increases synaptic levels of acetylcholine, thereby enhancing cholinergic signaling throughout the body. In dementia patients, this augmentation of cholinergic activity might exert a compensatory effect on cardiac autonomic regulation, potentially mitigating the occurrence of bradyarrhythmias. Conversely, abrupt cessation of donepezil could lead to a sudden decline in cholinergic tone, predisposing individuals to bradyarrhythmias. Cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without underlying cardiac conduction abnormalities.[10] Additionally, potential interactions with other drugs commonly used in dementia management, such as antipsychotics or antiarrhythmic agents, could exacerbate the risk of bradyarrhythmias.[11] The patient did not complain of abdominal pain, but experienced weight loss. The weight loss and potential decrease in nutrition may have resulted in an increase in serum concentrations of donepezil as this medication has a large volume of distribution and is 96% protein bound.[3]

The patient was found to have low potassium levels (3.1 mmol/l). Potassium ions play a crucial role in maintaining the resting membrane potential and action potential of cardiac myocytes. Reduced extracellular potassium levels can lead to membrane hyperpolarization, which in turn prolongs the duration of the cardiac action potential. This prolongation can manifest as delayed depolarization of cardiac cells, resulting in slowed conduction through the cardiac conduction system and predisposing individuals to bradyarrhythmias.[12] However, after correction for potassium, bradycardia was still persistent.

Donepezil overdose has been shown to result in profound sinus bradycardia, which is reversible with atropine.[13] However, in this patient bradycardia still occurred after injection of 2 ampoules of atropine and potassium correction. So a TPM was installed with a regular heart rate of 70×/minute. The patient was treated for four days. When the TPM was removed, an ECG showed sinus arrest with junctional escape rhythm at 45 beats per minute, normal frontal axis, clockwise rotation of the horizontal axis, T-wave inversion in leads V_3–V_6 with prominent U wave. The use of TPM is continued to keep the patient's heart rate stable. Because the understanding of the development of bradycardia, syncope, and other adverse effects of AChE inhibitor use is incomplete, there are few guidelines regarding the management of patients on or being considered for placement on these agents.[14] The suggestions for managing possible AChE inhibitor CV side effects include monthly pulse checks and symptom monitoring. If bradycardia is noted (<50 bpm) or if syncope or seizures are reported, the investigation of all possible causes is recommended before attributing these signs to AChE inhibitors.[15]

This study has a limitation. It is important to note that study's findings are based on a single patient, limiting its generalizability to broader populations of dementia patients or those discontinuing donepezil therapy.

Conclusion

This case report highlights the relationship between donepezil consumption and the incidence of severe bradyarrhythmia in a young patient without any cardiovascular risk disease and risk factors, that are persistent even after discontinuation of donepezil. Permanent pacemaker (PPM) installation should be considered in cases with persistent severe symptoms. Further research is needed to understand better the mechanisms and improve treatment strategies for adverse events related to donepezil in dementia patients.

Conflict of interest
Nothing to declare

Funding
None

Ethical statement
None.

Informed consent
The authors hereby grant permission to reproduce materials from our work for the purpose of dissemination, distribution, and academic or educational use. We have obtained consent from the patient to publish this information anonymously.

Availability of data and material
The authors confirm that the data supporting the findings of this study are available within the article.

Authors' contributions
OWF and BBD were responsible for drafting, literature review, and editing of the manuscript. RJ, CFA, PBT, and EP were responsible for literature review and editing. All authors approved the final version of paper.

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PCSK9i DOPORUČUJÍ ESC/EAS GUIDELINES

Snížení LDL-C přípravkem Repatha® je rychlé*, přetrvává po celou dobu léčby a redukuje KV riziko u pacientů v sekundární prevenci včetně těch, kteří nedávno prodělali IM a užívají maximální tolerovanou dávku statinů a případně ezetimibu.[1-3]

* Snížení LDL-C o přibližně 55-75 % bylo při léčbě evolokumabem dosaženo již v 1. týdnu a během dlouhodobé léčby přetrvávalo.[2].

Reference: **1.** Sabatine MS, et al.; Circulation. 2018;138:756-66. **2.** SPC Repatha březen 2023. **3.** Giugliano RP, et al. Lancet. 2017;390:1962-71.

Zkrácená informace o léčivém přípravku REPATHA
Název léčivého přípravku: Repatha 140 mg injekční roztok v předplněném peru. **Kvalitativní a kvantitativní složení**: Jedno předplněné pero obsahuje evolocumabum 140 mg v 1 ml roztoku. **Léková forma**: Injekční roztok (injekce) v předplněném peru (SureClick). **Terapeutické indikace**: Primární hypercholesterolemie (heterozygotní familiární a nefamiliární) nebo smíšená dyslipidemie u dospělých a heterozygotní familiární hypercholesterolemie u pediatrických pacientů ve věku 10 let a starších jako přídavek k dietě, a to: 1. v kombinaci se statinem nebo statinem a s dalšími hypolipidemiky u pacientů, u kterých není dosaženo cílových hladin LDL-C maximální tolerovanou dávkou statinu, nebo 2. v monoterapii nebo v kombinaci s dalšími hypolipidemiky u pacientů, kteří netolerují statin nebo u kterých je statin kontraindikován. Homozygotní familiární hypercholesterolemie v kombinaci s dalšími hypolipidemiky u dospělých a pediatrických pacientů ve věku 10 let a starších. Prokázané aterosklerotické kardiovaskulární onemocnění u dospělých ke snížení kardiovaskulárního rizika, a to 1. v kombinaci s maximální tolerovanou dávkou statinu s dalšími hypolipidemiky nebo bez nich, nebo 2. v monoterapii nebo v kombinaci s dalšími hypolipidemiky u pacientů, kteří netolerují statin nebo u kterých je statin kontraindikován. **Dávkování a způsob podání:** Podává se subkutánně do břicha, stehna nebo do horní oblasti paže. *Primární hypercholesterolemie a smíšená dyslipidemie (včetně heterozygotní familiární hypercholesterolemie) dospělí a pediatričtí pacienti (ve věku 10 let a starší)/ Prokázané aterosklerotické kardiovaskulární onemocnění u dospělých:* Doporučená dávka je 140 mg 1x za dva týdny nebo 420 mg 1x měsíčně. Obě dávky jsou klinicky ekvivalentní. *Homozygotní familiární hypercholesterolemie u dospělých a pediatrických pacientů ve věku 10 let a starších:* Úvodní doporučená dávka je 420 mg 1x měsíčně. Pokud nebylo po 12 týdnech dosaženo klinicky významné odpovědi na léčbu, frekvenci dávek je možné zvýšit na 420 mg 1x za 2 týdny. Pacienti na aferéze mohou zahájit léčbu dávkou 420 mg 1x za 2 týdny, aby toto schéma odpovídalo cyklu aferézy. **Kontraindikace:** Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku. **Zvláštní upozornění a opatření pro použití:** Sledovatelnost: Má se přehledně zaznamenat název podaného léčivého přípravku a číslo šarže. Porucha funkce jater: Pacienti s těžkou poruchou funkce jater (Child-Pugh C) nebyli studováni a evolokumab se má používat s opatrností. Suchý přírodní kaučuk: Kryt skleněné předplněné injekční stříkačky je vyroben ze suchého přírodního kaučuku (derivát latexu), který může vyvolávat závažné alergické reakce. **Interakce s jinými léčivými přípravky a jiné formy interakce:** Nebyly provedeny žádné studie interakcí. V klinických studiích byla hodnocena farmakokinetická interakce mezi statiny a evolokumabem. Při použití kombinace statinu a evolokumabu není nutná úprava dávky statinu. **Fertilita, těhotenství a kojení:** Údaje o podávání těhotným ženám jsou omezené nebo nejsou k dispozici. V těhotenství lze použít pouze tehdy, když klinický stav ženy vyžaduje léčbu evolokumabem. Není známo, zda se evolokumab vylučuje do lidského mateřského mléka. Riziko pro kojené novorozence/kojence nelze vyloučit. Na základě posouzení prospěšnosti kojení pro dítě a prospěšnosti léčby pro matku je nutno rozhodnout, zda přerušit kojení nebo ukončit/přerušit podávání přípravku Repatha. Nejsou k dispozici žádné údaje o vlivu evolokumabu na fertilitu u člověka. **Nežádoucí účinky:** Nejčastěji hlášené nežádoucí účinky při podávání doporučených dávek jsou nasopharyngitis (7,4 %), infekce horních cest dýchacích (4,6 %), bolest zad (4,4 %), artralgie (3,9 %), chřipka (3,2 %) a reakce v místě vpichu injekce (2,2 %). **Zvláštní opatření pro uchovávání:** Uchovávejte v chladničce (2 °C – 8 °C). Chraňte před mrazem. Uchovávejte v původním obalu, aby byl přípravek chráněn před světlem. **Držitel rozhodnutí o registraci:** Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, Nizozemsko. **Registrační číslo:** EU/1/15/1016/003. **Datum revize textu:** 30. března 2023.
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Raritní porucha rytmu u pacientů s hypertrofickou obstrukční kardiomyopatií během endokardiální radiofrekvenční katétrové ablace septální hypertrofie

(Rare rhythm disorder in patients with hypertrophic obstructive cardiomyopathy during endocardial radiofrequency ablation of septal hypertrophy)

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SOUHRN

Hypertrofická obstrukční kardiomyopatie (HOKMP) je charakterizována ztluštěním stěn a zvětšením masy myokardu nedilatované levé komory srdeční bez vysvětlujících hemodynamických příčin a přítomností gradientu ve výtokovém traktu levé komory (LVOTG). U pacientů s maximální farmakologickou terapií HOKMP je indikována invazivní metoda terapie. V minulosti metodou volby k redukci septální hypertrofie byla chirurgická myektomie, kterou vystřídala alkoholová septální ablace (ASA), nyní jde o všeobecně užívanou metodu v redukci septální hypertrofie. V posledních letech se objevila nová nefarmakologická metoda, a to radiofrekvenční ablace mezikomorového septa – v literatuře uváděná jako endocardial radiofrequency ablation of septal hypertrophy (ERASH). Cílem naší kazuistiky je popsat první zkušenosti s touto metodou. Jedná se o třiačtyřicetiletého pacienta s diagnostikovanou HOKMP, významným LVOTG a maximální farmakologickou terapií, který podstoupil v roce 2019 alkoholovou septální ablaci pouze s přechodným efektem na regresi LVOTG, a zároveň s nově vzniklou blokádou pravého Tawarova raménka (RBBB). V roce 2021 u pacienta při kontrolní echokardiografii perzistuje vysoká LVOTO až 127 mm Hg a progredující symptomatologie. Proto byla pacientovi navržena ERASH, se kterou souhlasil. Během výkonu byl mapován a označen převodní systém a hranice ztluštění septa s maximem v blízkosti předního cípu mitrální chlopně s patrným dopředným pohybem předního cípu mitrální chlopně v systole (SAM). Převodní systém byl označen v anatomické mapě body, aby se předešlo jeho poškození. Radiofrekvenční ablace byla zahájena ve střední části ztluštění septa v dostatečné vzdálenosti od převodního systému. Během ablace ale došlo k intermitentní atrioventrikulární blokádě III. stupně, následně ke střídaní bifascikulární blokády charakteru preexistujícího RBBB a levého předního a zadního hemibloku, s následnou restitucí do atrioventrikulární (AV) blokády Wenckebach 3 : 2, ablace byla pro riziko poškození převodního systému ukončena. Po výkonu bylo provedeno kontrolní měření LVOTG, který dosahoval 3,1 mm Hg, po komorové extrasystole 84,4 mm Hg. Během následujících hodin došlo k restituci AV vedení, 12 hodin po výkonu byl na povrchovém EKG patrný sinusový rytmus s AV blokádou I. stupně a RBBB bez převodní poruchy vyššího stupně, na dalších kontrolách po současnost je pacient bez převodních poruch rytmu a s trvajícím nízkým gradientem v LVOT. Pacienti s RBBB po předchozí ASA se jeví jako suboptimální kandidáti ERASH vzhledem k vysokému riziku vzniku blokády levého Tawarova raménka během výkonu ERASH a následné kompletní AV blokády. Při ERASH v terénu předchozí ASA mohou vznikat bizarní poruchy AV převodu jako v níže popsané kazuistice.

ABSTRACT

Hypertrophic obstructive cardiomyopathy (HOCMP) is characterized by abnormal thickening or enlargement of the left ventricular myocardium mass of non-dilated left ventricle not explained solely by loading conditions and presence of obstruction in outflow tract of left ventricle. Surgical septal myectomy was the first choice method of invasive treatment of septal hypertrophy in the past which was replaced by alcohol septal ablation in the nineties of the 20th century and nowadays it is still worldwide used, safe, and effective

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Tento článek prosím citujte takto: Doležalová K, Stárek Z, Honek T, et al. Raritní porucha rytmu u pacientů s hypertrofickou obstrukční kardiomyopatií během endokardiální radiofrekvenční katétrové ablace septální hypertrofie. Cor Vasa 2025;67:67–72.

method in reduction of septal hypertrophy. Nowadays there is a new method of non-pharmacological treatment of septal hypertrophy which is endocardial radiofrequency ablation of septal hypertrophy (ERASH).
Main goal of our case report is to describe first experiences with ERASH method in our department. A forty--three-year-old patient with diagnosed HOCMP and severe left ventricle outflow tract gradient (LVOTG) despite maximal pharmacological treatment who underwent alcohol septal ablation (ASA) in 2019, only with transient effect on LVOTG, and the new onset of right bundle branch block (RBBB). In 2021, there was still high LVOTG present on echocardiography – 127 mmHg and progressive symptomatology. The patient agreed to undergo ERASH. Hypertrophic part of septum and conduction system have been mapped and marked to avoid destruction. Radiofrequency ablation was started in the middle part of septal hypertrophy in safe distance from conduction system, however, during ablation there was a sudden onset of atrioventricular block of third degree, forwarded with alternating bifascicular block RBBB and left anterior or posterior hemiblock, with restitution to AV block of the second degree 3 : 2. Ablation was terminated at this point because of risk of harming conduction system. Immediate measurements straight after procedure were LVOTG 3.1 mmHg at rest and 84.4 mmHg after ventricle extrasystole. In next hours there was a restitution of conduction system to AVB of the first degree with preexisting RBBB. Nowadays the patient is without any conduction disorders of higher degree and low LVOTG still lasts.
The patients after alcohol septal ablation with preexisting RBBB seem to be inappropriate candidates for ERASH procedure due to high risk of conduction disorders of higher degree as was seen in our case report.

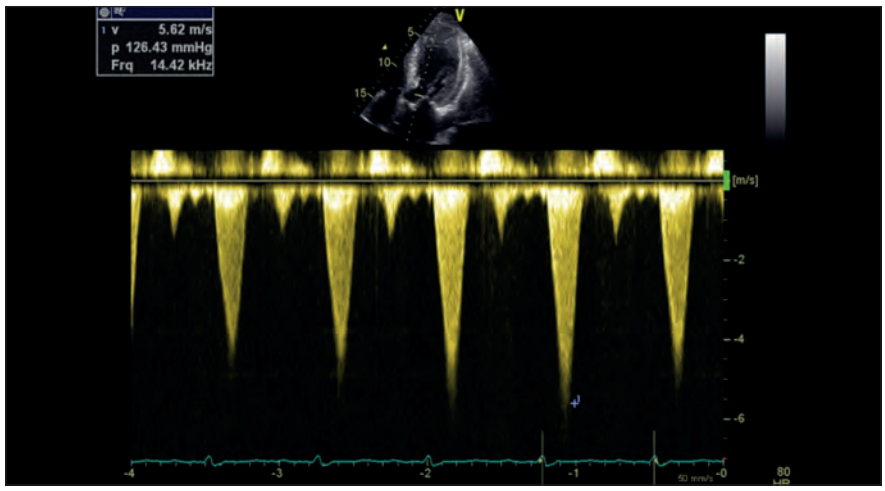
Keywords:
Endocardial radiofrequency ablation of septal hypertrophy
Left ventricle outflow tract gradient
NYHA classification
Periprocedural AV block

Úvod

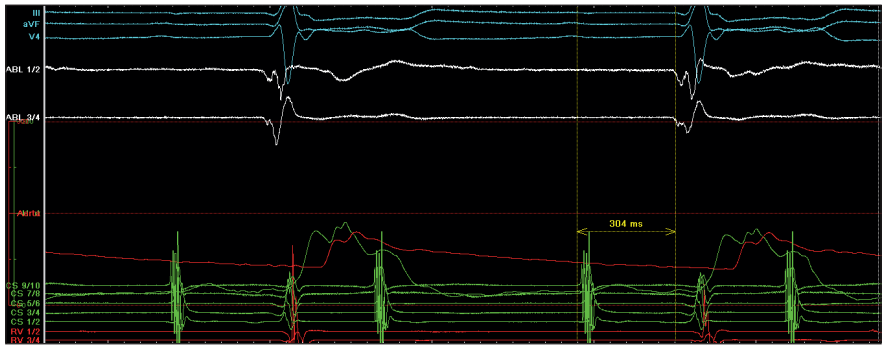
Hypertrofická obstrukční kardiomyopatie (HOKMP) je charakterizována ztluštěním stěn a zvětšením masy myokardu nedilatované levé komory srdeční bez vysvětlujících hemodynamických příčin a přítomnosti obstrukce ve výtokovém traktu levé komory. Typickou známkou je paradoxní pohyb předního cípu mitrální chlopně (SAM) při transtorakální echokardiografii.[1] V minulosti byla invazivní nefarmakologickou metodou volby k redukci septální hypertrofie chirurgická myektomie,[2] kterou v devadesátých letech vystřídala alkoholová septální ablace (ASA), nyní všeobecně užívaná, bezpečná a účinná metoda v redukci septální hypertrofie.[3] V posledních letech se objevila nová nefarmakologická metoda v léčbě HOKMP. Jedná se o radiofrekvenční ablaci (RFA) mezikomorového septa (IVS) – v literatuře uváděna jako „endocardial radiofrequency ablation of septal hypertrophy (ERASH)".[4] Metoda spočívá v RFA hypertrofického septa pomocí standardního proplachového ablačního katétru většinou z levé komory retrográdním či transseptálním přístupem za podpory 3D elektroanatomického mapovacího systému. Pokles gradientu ve výtokovém traktu levé komory (LVOTG) po provedení ERASH je dle publikovaných malých sérií pacientů srovnatelný s ASA. Dle publikovaných souborů pacientů se jedná o bezpečnou[5] terapii s minimálním rizikem poškození koronárních tepen, s nižším rizikem poškození převodního systému srdečního a s možností opakování výkonu. Na našem pracovišti byl tento výkon proveden poprvé v roce 2018 s dobrým bezprostředním i dlouhodobým efektem (výrazný pokles klidového i provokovaného gradientu v prvním a šestém měsíci po výkonu) srovnatelný s ASA a následně do dnešního data výkon podstoupilo dalších pět pacientů. U jednoho pacienta navzdory udávané bezpečnosti výkonu stran poruch vedení v oblasti atrioventrikulárního (AV) uzlu došlo k zajímavé poruše rytmu. Tento pacient je předmětem této kazuistiky.

Kazuistika

Jedná se o třiačtyřicetiletého pacienta, původně došetřovaného cestou plicní ambulance pro asi tři čtvrtě roku trvající námahovou dušnost. Během kardiologického vyšetření byla pomocí echokardiografie srdce diagnostikována HOKMP s obstrukcí a významným LVOTG (klidový 102 mm Hg, 159 mm Hg po Valsalvově manévru), s dobrou ejekční frakcí levé komory. Dne 31. 5. 2019 pacient podstoupil diagnostickou koronarografii v rámci vyloučení ischemické choroby srdeční, kde byly invazivně změřeny LVOTG – klidový 40 mm Hg, po Valsalvově manévru 85 mm Hg, po komorové extrasystole 105 mm Hg. Ramus septalis levé koronární tepny, jehož okluze je podkladem ASA, byl gracilní, nicméně relativně vhodný k provedení alkoholové septální ablace. Přes veškerou farmakologickou léčbu docházelo ke zhoršování funkčního stavu pacienta, progresi dyspnoe do funkční třídy NYHA III, proto byla pacientovi navržena nefarmakologická invazivní léčba pomocí alkoholové septální ablace. Pacient byl předveden na indikační komisi naší kardiologické kliniky a následně u něj byla indikována alkoholová septální ablace. Výkon byl proveden 17. 9. 2019, alkoholová septální ablace s uzávěrem ramus septalis 2 byla provedena s dobrým efektem, bezprostředně po okluzi tepny byly měřeny tyto tonometrické parametry – LVOTG v klidu 38 mm Hg, po komorové extrasystole 90 mm Hg, při Valsalvově manévru 70 mm Hg. Během výkonu byl pacient pod echokardiografickou kontrolou, kde před ASA byl popsán výrazný SAM, tloušťka septa do 20 mm, dobrá systolická funkce LK, difuzní hypertrofie, při echokardiografii po podání kontrastní látky do ramus septalis při ASA byla zaznamenána přítomnost kontrastu selektivně v midseptu směrem k bazi, samotná baze septa byla bez kontrastu, při insuflaci balonku bylo po chvíli patrné zlepšení ve smyslu poklesu gradientu. SAM byl méně výrazný, klidový gradient do 25 mm Hg. Pacient byl po výkonu stabilní, hospitalizován a monitorován na naší klinice celkově od 17. 9. do 22. 9. 2019. Před dimisí byla provedena kontrolní echokardiografie, kde se zobrazovala těžká hypokineze bazální části IVS, SAM s dotykem septa v oblasti šlašinek, mitrální regurgitace jen stopová a opětovně vysoký dynamický klidový LVOTG 100–110 mm Hg, po Vaslalvově manévru 115 mm Hg, celkový efekt alkoholové septální ablace byl uzavírán jako pouze přechodný, pravděpodobně pro suboptimální anatomii koronárních tepen. Dále byla po



Obr. 1 – Klidový LVOTG. LVOTG – gradient ve výtokovém traktu levé komory.



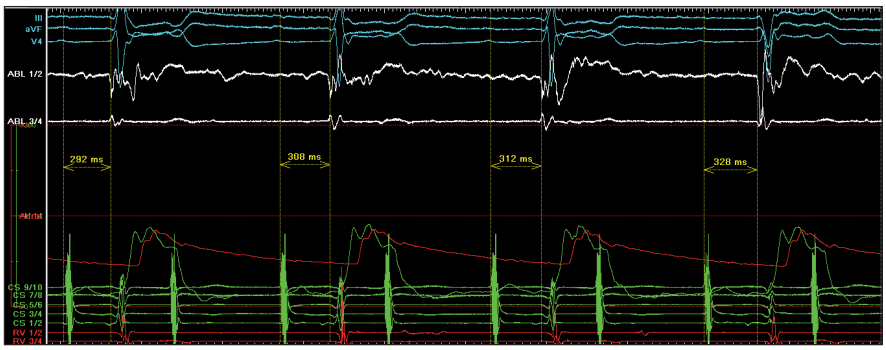
Obr. 2 – AVB II. stupně 2 : 1 – intrakardiální EKG. AVB – atrioventrikulární blokáda.

ASA nově na EKG zachycena blokáda pravého Tawarova raménka (RBBB). Pacient byl propuštěn ve stabilním stavu do ambulantní péče. Dne 14. 2. 2021 byl pacient na kontrolní echokardiografii, kde perzistoval vysoký LVOTG až 127 mm Hg (**obr. 1**), subjektivně přetrvávala výrazná námahová dušnost i při chůzi po rovině, NYHA III–IV, proto byla pacientovi navržena endokardiální radiofrekvenční ablace septální hypertrofie, se kterou souhlasil.

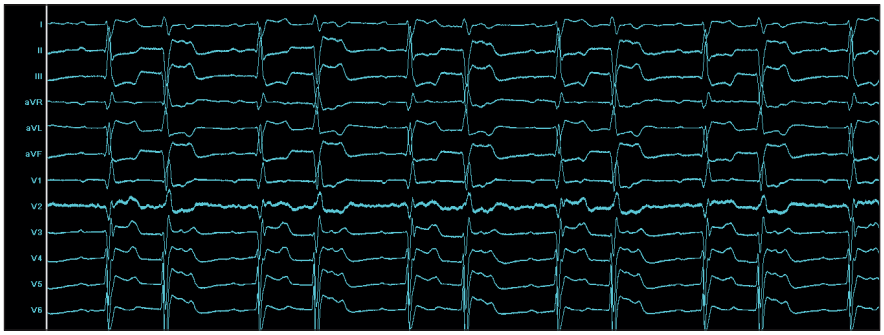
Dne 20. 5. 2021 byl pacient přijat na arytmologické oddělení, a ještě v ten den podstoupil výkon. Na vstupním EKG byla atrioventrikulární blokáda (AVB) I. stupně s intervalem PQ 240 ms, RBBB s QRS 160 ms.

Při katetrizaci byly do třísel zavedeny dva 7F sheathy a řiditelný transseptální sheath Agilis Large Curl (Abbott Laboratories, Abbott Park, IL, USA) a do arteria femoralis l. sin. 8F sheath. Poté byl zaveden diagnostický katétr do koronárního sinu a další katétr do hrotu pravé komory a bylo provedeno základní elektrofyziologické vyšetření. Na intrakardiálním EKG byly zaznamenány intervaly AH 120 ms, HV 30 ms, Wenckebachův bod 135/min, RBBB. Poté byla provedena transseptální punkce a pomocí řiditelného sheathu Agilis byl zaveden ablační katétr TactiCath Quartz 75 (Abbott Laboratories, Abbott Park, IL, USA). Retrográdně byl do levé komory (LK) zaveden pigtail katétr Cordis se dvěma lumen (Langston Dual Lumen Catheters), s jehož pomocí bylo prováděno invazivní měření tlaků. Průměrný klidový LVOTG počítaný ze tří hodnot byl 6,3 mm Hg, průměrný LVOTG po komorové extrasystole činil 38,85 mm Hg a průměrný LVOTG při Valsalvově manévru dosahoval 3,9 mm Hg.

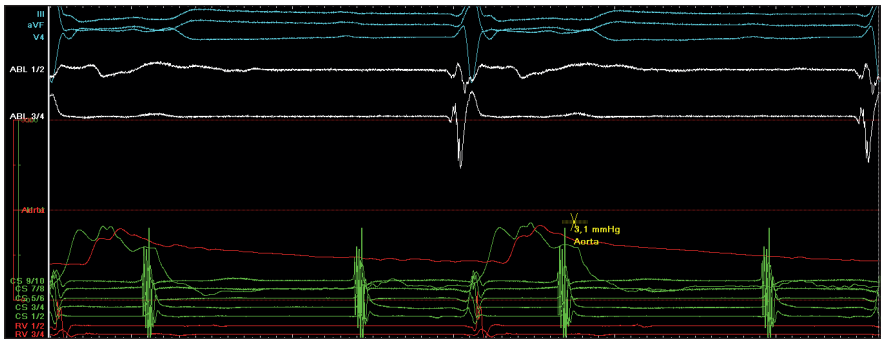
Pomocí ablačního katétru, za podpory 3D elektroanatomického mapovacího systému EnSite Precision (Abbott Laboratories, Abbott Park, IL, USA) a intrakardiálního ultrazvuku byla vytvořena anatomická mapa LK se znázorněním hypertrofického septa. Poté byl mapován a označen převodní systém a hranice ztluštění septa s maximem v blízkosti předního cípu mitrální chlopně s patrným SAM. Převodní systém byl vyznačen v anatomické mapě body, aby se předešlo jeho poškození. Radiofrekvenční ablace (RFA) byla zahájena ve střední části ztluštění IVS v dostatečné vzdálenosti od převodního systému. Během RFA po 6,7 s došlo ke vzniku chvilkové AVB III. stupně s pauzou 3 s, poté se porucha AV vedení stabilizovala do AVB II. stupně 2 : 1 (**obr. 2**), zpočátku 20 s morfologicky RBBB + levý přední hemiblok (LAH), pak stabilizace do RBBB + levý zadní hemiblok (LPH), pouze po komorových extrasystolách byly patrné jednotlivé převedené stahy s RBBB + LAH. Poté byla provedena druhá RFA, po 4 s došlo k prodlužování AV intervalu (**obr. 3**) až AVB II. stupně 2 : 1 se změnou morfologie komplexu QRS z RBBB + LPH na RBBB + LAH. RFA byla po 12 s ukončena. Po 50 s došlo k návratu morfologie komplexu QRS zpět na morfologii RBBB + LPH při trvající AVB II. stupně 2 : 1. Po salvách KES při manipulaci katétrem v komoře docházelo k opakovaným změnám morfologie z RBBB + LPH na RBBB + LAH a zpět (**obr. 4**). Během několika minut došlo k částečné úpravě poru-



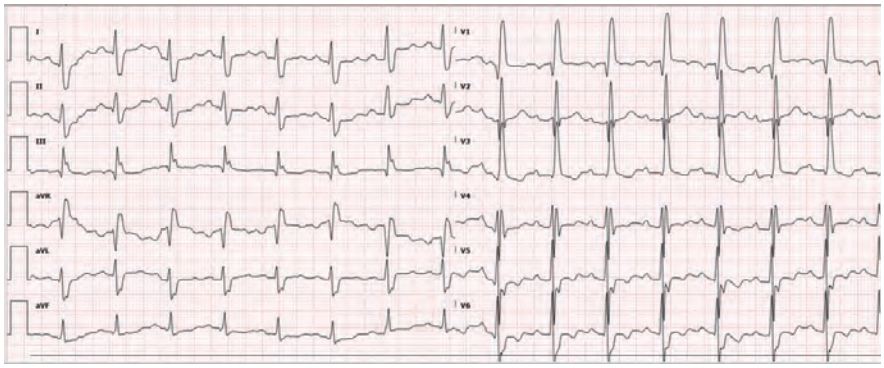
Obr. 3 – Postupné prodlužování AV intervalu během RFA – intrakardiální EKG. AV – atrioventrikulární; RFA – radiofrekvenční ablace.



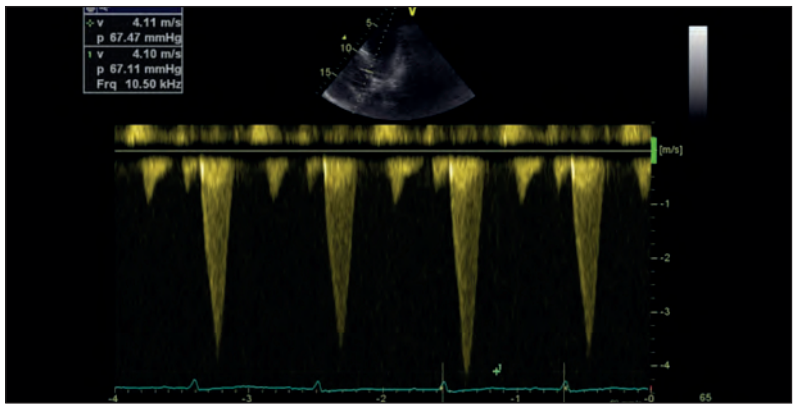
Obr. 4 – Střídaní RBBB + LPH a RBBB + LAH při AVB II. stupně – povrchové EKG. AVB – atrioventrikulární blokáda; LAH – levý přední hemiblok; LPH – levý zadní hemiblok; RBBB – blokáda pravého Tawarova raménka.



Obr. 5 – Výsledný gradient po RFA 3,1 mm Hg. RFA – radiofrekvenční ablace.



Obr. 6 – EKG po výkonu RBBB s LPH a AVB I. stupně. AVB – atrioventrikulární blokáda; LPH – levý zadní hemiblok; RBBB – blokáda pravého Tawarova raménka.



Obr. 7 – Klidový LVOTG po výkonu. LVOTG – gradient ve výtokovém traktu levé komory.

chy AV vedení a do konce výkonu trvala AVB II. stupně Wenckebachova typu 3 : 2 s alternující bifascikulární blokádou charakteru RBBB + LPH a RBBB + LAH. Po 15 min čekání bylo zachyceno intermitentní zlepšení AV vedení charakteru AVB I. stupně s bifascikulární blokádou RBBB + LPH. Poté bylo provedeno kontrolní měření gradientů – klidový LVOTG 3,1 mm Hg, po komorové extrasystole 84,4 mm Hg (**obr. 5**). Vzhledem k riziku vzniku trvalého poškození atrioventrikulárního vedení byl po seznámení pacienta s riziky výkonu a zvážení symptomatologie výkon ukončen. Po výkonu byl pacient hemodynamicky stabilní, bez záchytu dalších arytmií, byl propuštěn do ambulantní péče druhý den. Během následujících hodin došlo k restituci AV vedení, druhý den ráno, 12 hodin po výkonu byl na povrchovém EKG sinusový rytmus s AVB I. stupně a RBBB bez převodní poruchy vyššího stupně (**obr. 6**).

Dne 4. 9. 2020 pacient absolvoval kontrolní echokardiografii, kde došlo k snížení LVOTG na 43 mm Hg v klidu, provokovaného na 92 mm Hg se subjektivním zlepšením stavu, nadále je pravidelně sledován v ambulanci srdečního selhání. Od výkonu absolvoval již pět kontrol, kde aktuálně perzistuje klidový LVOTG 67 mm Hg (**obr. 7**) a na 24hodinové EKG holterovské monitoraci je zachycen sinusový rytmus s AVB I. stupně, bez AV blokády vyššího stupně, bez významných pauz. Opakovaně byly zachyceny komorové extrasystoly i s krátkým během nesetrvalé komorové tachykardie do šesti komplexů QRS.

Diskuse

Cílem naší kazuistiky bylo popsat raritní převodní poruchy zaznamenané během výkonu u pacienta podstupujícího ERASH. Všechny intervenční výkony redukující septální hypertrofii jsou zatíženy rizikem vzniku poruchy AV převodu vyššího stupně. U chirurgické septální myektomie je uváděna nutnost implantace kardiostimulátoru 4 %.[6]

Vznik AV blokády vyššího stupně po ASA je popsán v literatuře u 12 % pacientů – multicentrická studie EURO ASA registr.[7] U pacientů podstupujících ERASH z dosud publikovaných studií potřebovalo trvalou kardiostimulaci 8 % pacientů, nicméně soubor pacientů podstupujících ERASH je zatím relativně malý, doposud publikované studie zahrnují celkem 100 pacientů. Charakter výkonu s možností lokalizace převodního systému při mapování LVOT dává předpoklad nižšího rizika poškození AV převodu. Největší incidence trvalé AV blokády byla zaznamenána ve studiích, které zahrnovaly pacienty s předchozí ASA, nicméně ne ve všech těchto retrospektivních studiích je možné explicitně dohledat, zda AV blokády vyššího stupně souvisejí s předchozí ASA. Z těchto dat a z naší zkušenosti s naším souborem pacientů podstupujících ERASH vyplývá, že pacienti po předchozí ASA s preexistující RBBB mají vyšší riziko kompletní AV blokády.

Závěrem je potřeba zmínit, že s dostupností mavacamtenu, nového inhibitoru myozinu zaměřeného na základní příčinu mnoha symptomů souvisejících s HKMP, se farmakologická léčba této choroby stává účinnější, proto je do budoucna možné očekávat snížení četnosti nutnosti intervenční léčby pacientů s HOKMP.

Závěr

Endokardiální radiofrekvenční ablace mezikomorového septa u pacientů s hypertrofickou obstrukční kardiomyopatií se jeví jako proveditelná, bezpečná a účinná metoda léčby obstrukce u těchto pacientů. Nicméně je nutná vysoká opatrnost při ablaci hypertrofického septa v blízkosti převodního systému vzhledem k vysokému riziku vzniku AV blokády vyššího stupně. Pacienti s blokádou pravého Tawarova raménka po předchozí ASA se jeví jako suboptimální kandidáti ERASH vzhledem k vysokému riziku vzniku blokády levého Tawarova raménka během výkonu ERASH a následné kompletní AV blokády. Při ERASH v terénu předchozí ASA mohou vznikat bizarní poruchy AV převodu jako ve výše popsané kazuistice.

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The Role of Oral Calcium and Vitamin D in Hypocalcemia-Associated Cardiomyopathy: A Case Report

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Hypoparatyreóza
Kalcium
Srdeční selhání

SOUHRN

Hypokalcemií indukovaná kardiomyopatie je vzácné, avšak závažné onemocnění, náročné z hlediska diagnostiky i léčby. Těžká hypokalcemie na podkladě hypoparatyreózy může vyvolat vzácnou, nicméně potenciálně reverzibilní, formu dilatační kardiomyopatie. Tato kazuistika popisuje případ 31leté ženy se srdečním selháním vyvolaným hypoparatyreózou po tyreoidektomii. Přes klasickou léčbu srdečního selhání přetrvával u pacientky její závažný stav až do úpravy hypokalcemie. Léčba zahrnovala suplementaci kalcia a terapii vedenou podle příslušných doporučených postupů; následně došlo k významnému zlepšení. Proto je pro dosažení zlepšení – pokud byla klasická léčba srdečního selhání neúčinná – naprosto nezbytné monitorovat hodnoty kalcia v séru, zvláště u pacientů s tyreoidektomií v anamnéze. Při léčbě srdečního selhání je třeba být ostražitý a mít neustále na paměti možnou přítomnost hypokalcemie jako reverzibilní příčinu uvedené komplikace.

Keywords:
Calcium
Dilated cardiomyopathy
Heart failure
Hypoparathyroidism

ABSTRACT

Hypocalcemia-associated cardiomyopathy, a rare but serious condition, presents challenges in diagnosis and management. Severe hypocalcemia resulting from hypoparathyroidism can precipitate rare yet reversible cases of dilated cardiomyopathy. This case report reported a 31-year-old woman with heart failure precipitated by hypoparathyroidism following thyroidectomy. Despite conventional heart failure treatments, her condition persisted until correction of hypocalcemia. Treatment involved calcium supplementation and guideline-directed heart failure therapy. Significant improvement was observed then. Hence, monitoring serum calcium levels is imperative when conventional heart failure therapies fail to yield improvement, particularly in patients with a history of thyroidectomy. Sustaining clinical awareness and vigilance concerning hypocalcemia is crucial in managing heart failure, considering its possibility as a reversible cause.

Introduction

Calcium plays a pivotal role in both systolic contraction and diastolic relaxation of myocardium. Upon depolarization, calcium influx via voltage-sensitive L-type calcium channels initiates myocardial contraction, complemented by calcium release from the sarcoplasmic reticulum. This cascade of events involves calcium binding to specific proteins, facilitating contraction, and subsequent relaxation occurs as calcium is reabsorbed into storage sites.[1] Hypocalcemia, characterized with low levels of circulating calcium, profoundly disrupts myocardial contraction, potentially leading to ventricular dysfunction and subsequent heart failure. Although hypocalcemia contributes to cardiomyopathy, additional mechanisms underlying this condition remain to be fully elucidated. Recent research underscores the similar impact of vitamin D and parathy-

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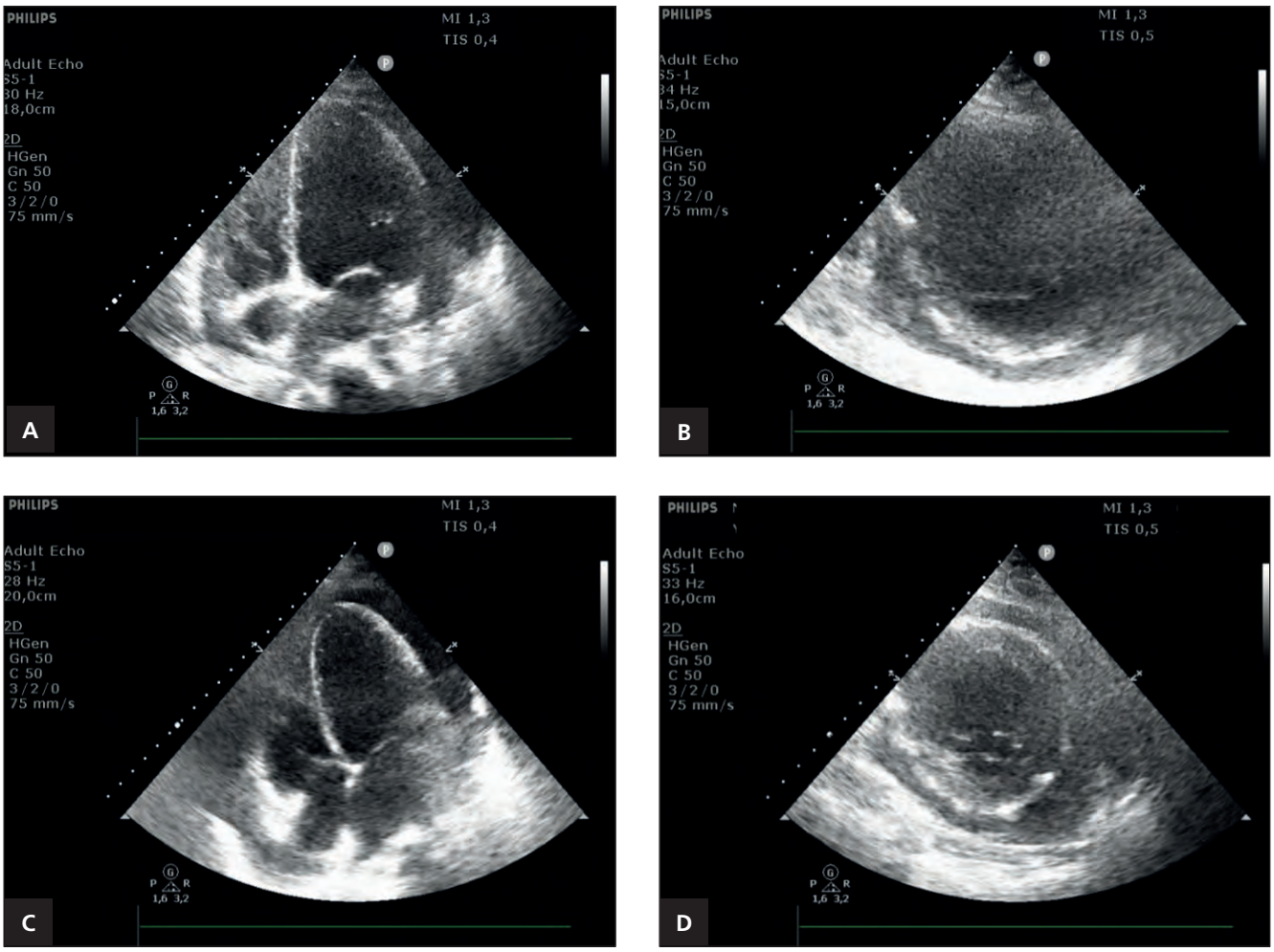

Fig. 1 – Changes in the pre-treatment (A, B) and post-treatment (C, D).

Table 1 – Evaluated laboratory parameters

Parameters	Normal range	Pre-treatment	Post-treatment (D + 4)
Creatinine (mg/dL)	0.7–1.4	1.3	N/A
Albumin (g/dL)	3.2–5.5	3.58	N/A
Calcium (mg/dL)	8.5–10.5	4.0	7.9
Magnesium (mmol/L)	0.8–1.2	1.2	1.9
TSH (mIU/L)	0.5–5.0	13.828	N/A
QT interval (mS)	360–460	662	441
Ejection fraction (%)	> 50	29.4	33.3

roid hormone (PTH) on myocardial function, suggesting broader implications beyond calcium regulation.[2]

Dilated cardiomyopathy (DCM) is a cardiac condition characterized by structural and functional abnormalities in the heart muscle, unrelated to other etiologies. Various factors can lead to DCM, including primary familial causes and secondary factors like myocarditis, toxins, autoimmune disorders, neuromuscular conditions, and endocrine issues. Among these, hypocalcemia has been identified as a reversible contributor to DCM.[3] Hypocalcemia-induced cardiomyopathy is typically characterized by a reduced ejection fraction (EF), often resistant to conventional heart failure therapy regimens. Despite resistance to conventional treatments, correcting the underlying cause of low calcium levels can rapidly improve the condition.[2,4] In this paper, we present a case report reporting heart failure precipitated by hypocalcemia, concomitant with hypoparathyroidism. By elucidating this case, we aim to advance understanding and refine management strategies for similar clinical presentations, contributing to prompt diagnosis and appropriate treatment of this case.

Case description

A 31-year-old woman presented to the emergency unit with shortness of breath, accompanied with cramps and body aches. She had a history of thyroidectomy for hypothyroidism two years prior and cataract surgery one year ago. During the physical examination, she weighed 80 kg and measured 156 cm in height. Her blood pressure was 90/67 mmHg while on 50 µg of norepinephrine and 5 µg of dobutamine, with a heart rate of 71 beats per minute. Fine wet crackles were noted in the basal third of both lungs. The electrocardiogram examination indicated a sinus rhythm at 73 beats per minute, slow R wave progression in leads V_1–V_3, and a prolonged QT interval (QTc with Bazett formula 662 ms).[5] Laboratory tests revealed an HB level of 11.1 g/dL, creatinine at 1.3 mg/dL, albumin 3.58 g/dL, calcium at 4.0 mg/dL, magnesium 1.2 mg/dL, TSH at 13.8 mIU/L, and FT4 at 0.94.

Treatment was initiated with norepinephrine 50 µg and dobutamine 5 µg, raising her blood pressure to 105/57 mmHg. Parenteral calcium was administered to address symptoms of hypocalcemia, along with correction for hypomagnesemia. After symptom improvement, therapy was switched to oral calcium 3000 mg/day and calcitriol 0.25 mg/day, and levothyroxine 250 mg/day was prescribed for her hypothyroidism. The transthoracic echocardiogram (TTE) revealed reduced left ventricular systolic function (ejection fraction with Simpson's biplane method 29.4%), global left ventricular hypokinesis, left ventricular dilation with eccentric hypertrophy, diastolic dysfunction, and moderate pericardial effusion. Treatment included spironolactone 50 mg daily, ivabradine 10 mg/day, and intravenous furosemide. Beta-blockers and ACE inhibitors/ARNIs were postponed due to ongoing support with norepinephrine and dobutamine.

Four days later, her symptoms of dyspnea, cramps, and aches had diminished following normalization of her calcium levels, allowing cessation of norepinephrine and dobutamine. Consequently, bisoprolol 2.5 mg/day and ramipril 5 mg/day were introduced. A follow-up ECG showed a sinus rhythm and a corrected QT interval of 441 ms, while a repeat echocardiogram showed an improvement in ejection fraction to 33% and left ventricular systolic function nearing the lower normal limit.

Discussion

This case report highlights a case of reversible heart failure precipitated by hypoparathyroidism following thyroidectomy surgery. The patient exhibited rapid improvement after receiving a combination of guideline-directed medication of heart failure and calcium replacement.

Dilated cardiomyopathy (DCM) is a condition marked by the enlargement and dilation of one or both ventricles, coupled with reduced contractility, typically indicated by a left ventricular ejection fraction (LVEF) under 40%.[6] Causes of reversible DCM include alcoholism, postpartum cardiomyopathy, and hypoparathyroidism.[7] Parathyroid hormone (PTH) plays a crucial role in calcium homeostasis, influencing bone resorption by osteoclasts, enhancing intestinal calcium absorption, and activating vitamin D in the kidneys. Additionally, PTH can exert a positive inotropic effect on the heart by increasing myocardial contraction through the stimulation of B-adrenergic receptors and promoting calcium influx into myocardial cells.[8] Deficiency in PTH, primarily resulting from surgical procedures on the neck, can lead to hypocalcemia, which is the most common cause of hypoparathyroidism. Other causes include radiation therapy, autoimmune conditions, and genetic mutations.[9] Severe and prolonged hypocalcemia can impair myocardial contractions, potentially leading to ventricular systolic dysfunction and heart failure with reduced ejection fraction. Fortunately, DCM-related hypocalcemia usually has a favorable prognosis, with systolic function typically normalizing between three to twelve months.[2]

Calcium also plays a fundamental role in myocardial contraction, particularly intracellular calcium concentration. During the depolarization, activation of voltage-sensitive L-type calcium channels facilitates calcium influx into the cell, alongside contributions from exchanges like Na+–Ca2+ exchange.[10] This influx triggers calcium release from the sarcoplasmic reticulum, leading to calcium binding with cytosolic buffers, notably troponin C, activating myofilaments for contraction. Conversely, during diastole or relaxation, the decline in intracellular calcium concentration allows for calcium dissociation from troponin C, halting contraction and enabling relaxation, facilitated by various transporters.[11] This intricate process underscores the pivotal role of calcium in both systolic contraction and diastolic relaxation of myocardium, with hypocalcemia potentially precipitating severe cardiac dysfunction and heart failure. However, additional mechanisms contributing to cardiomyopathy in hypocalcemia remain unclear.[12]

In the case we present, the patient developed heart failure symptoms due to DCM triggered by chronic, untreated hypocalcemia following iatrogenic hypoparathyroidism from thyroid surgery. The combination of heart failure management and calcium supplementation led to significant improvement in the patient's heart function and symptoms. Furthermore, patients with chronic hypocalcemia may experience non-specific symptoms such as fatigue, muscle weakness, and cramps, complicating the diagnosis in the absence of tetany. Notably, the presence of cataracts, especially in younger patients, can also indicate hypoparathyroidism, underscoring the need for increased vigilance among ophthalmologists for earlier diagnosis.[13,14] While acute coronary syndrome can manifest similarly to heart failure with reduced EF, distinguishing between the two is crucial. Typically, the diagnosis is supported by changes in cardiac biomarkers.[15] However, in our case, the improvement in left ventricular EF following calcium therapy confirmed that the heart failure was due to hypocalcemia rather than myocardial infarction. Hence, calcium levels should always be monitored in HF patients and the underlying causes of low calcium levels should be investigated. Beyond the guideline-directed medication of heart failure, it is crucial to include calcium supplementation in the treatment regimen of these patients.

Conclusions

Severe hypocalcemia resulting from hypoparathyroidism can trigger an uncommon yet potentially reversible case of dilated cardiomyopathy. This case report reported a 31-year-old woman with heart failure precipitated by hypoparathyroidism following thyroidectomy. Despite conventional heart failure treatments, her condition persisted until correction of hypocalcemia. Treatment involved calcium supplementation and guideline-directed heart failure therapy. Significant improvement was then observed. Hence, monitoring serum calcium levels is imperative when conventional heart failure therapies fail to yield improvement, particularly in patients with a history of thyroidectomy. Sustaining clinical awareness and vigilance concerning hypocalcemia is crucial in managing heart failure, considering its possibility as a reversible cause.

Conflict of interest
The authors declare no competing interests.

Funding
We disclose any potential conflicts of interest, financial or otherwise, that might be perceived as influencing the content of this study.

Ethical statement and informed consent
We declare that the case report has been conducted in accordance with applied ethical standards and guidelines; the Declaration of Helsinki. Appropriate permissions including written informed consent were obtained.

Availability of data and material
We agree to make the relevant data and materials of the case report available to the journal and readers, upon reasonable request, to ensure transparency and reproducibility.

Authors' contributions
We confirmed that we have contributed significantly to this study. All listed authors have reviewed and approved the final version of the manuscript, also agreed to the submission.

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High-Sensitivity Cardiac Troponin T Elevation and Paroxysmal Supraventricular Tachycardia. Is it Always Acute Coronary Syndrome?

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Paroxysmální supraventrikulární tachykardie
Srdeční troponin měřený vysoce senzitivní metodou

SOUHRN

Kontext: Paroxysmální supraventrikulární tachykardie (PSVT) je běžnou formou arytmie, která se často projevuje symptomy připomínajícími akutní koronární syndrom (AKS).
Popis případu: Popisujeme případ 58letého muže s PSVT doprovázenou bolestí na hrudi a zvýšenými hodnotami troponinu naměřenými vysoce senzitivní metodou (high-sensitivity troponin, hs-Tn). Koronarografické vyšetření prokázalo pomalý průtok krve koronárními tepnami v nepřítomnosti obstrukčního postižení. Pacientovy symptomy vymizely spontánně a echokardiografické parametry měly při jeho propouštění normální hodnoty.
Závěry: Popisovaný případ ukazuje diagnostickou náročnost rozpoznávání AKS a upozorňuje na přechodné zvýšení hodnot troponinu při PSVT, možná v důsledku ischemie myokardu na podkladě rychlé srdeční frekvence. Při rozhodování o léčbě, zvláště v nepřítomnosti významné ischemické choroby, je nezbytné opřít se o klinické korelace a použít doplňkové diagnostické metody.

Keywords:
Acute coronary syndrome
Chest pain
High-sensitive cardiac troponin
Myocardial ischemia
Paroxysmal supraventricular tachycardia

ABSTRACT

Background: Paroxysmal supraventricular tachycardia (PSVT) is a common arrhythmia often presenting with symptoms mimicking acute coronary syndrome (ACS).
Case presentation: We present a case of a 58-year-old man with PSVT accompanied by chest pain and elevated high-sensitivity troponin (hs-Tn) levels. Coronary angiography revealed slow coronary flow in absence of obstructive disease. The patient's symptoms resolved spontaneously, and echocardiographic findings normalized upon discharge.
Conclusions: This case underscores the diagnostic challenge of individuating ACS and highlights the transient troponin elevation seen in PSVT, potentially due to myocardial ischemia secondary to rapid heart rates. Clinical correlation and adjunctive diagnostic modalities are crucial in guiding management decisions, especially in the absence of significant coronary artery disease.

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Background

Paroxysmal supraventricular tachycardia (PSVT) is one of the most common tachyarrythmias and it encompasses a heterogeneous group of arrhythmias with different characteristics. It has a prevalence of 2.25/1000 and an incidence of 35/100000 people per year;[1–6] it is more common between the ages of 40 and 50 and predominantly affects females. PSVT refers to a rhythm disorder originating above the His bundle, which typically causes heart rates in excess of 150 per minute with regular and narrow QRS complex. The symptoms it presents with are often hardly distinguishable from acute coronary syndromes and include palpitations, chest pain, dyspnea, exertional intolerance, and syncope. The diagnosis is made through the recording of a 12-lead electrocardiogram during the arrhythmic episode.[7–11] It is generally a benign arrhythmia that resolves after vagal maneuvers or pharmacological therapy in most cases. The role of myocardial-specific marker measurement, particularly troponin, is not entirely clear. According to some studies, it has no correlation with coronary artery disease (CAD) in patients without cardiovascular risk factors, while it may indicate ischemic events in patients previously undergoing revascularization procedures.[12–21]

Case report

A 58-year-old man presented with palpitations and chest pain for about two hours. Due to the persistence of symptoms, the patient contacted emergency services and was taken to the nearest emergency department. The patient's medical history revealed hypertension, smoking habit, and diabetes mellitus,[22–26] with no history of cardiovascular diseases or prior revascularization. On arrival, the patient's vital signs were as follows: heart rate 150 bpm, oxygen saturation 96% with no supplementation of oxygen, respiratory rate 21 breaths per minute. Physical examination showed an accelerated but mostly regular heart rhythm with no further abnormalities noted. A 12-lead electrocardiogram showed atrial flutter with a ventricular rate of 150 bpm and ventricular repolarization alterations secondary to the high heart rate (**Fig. 1**).

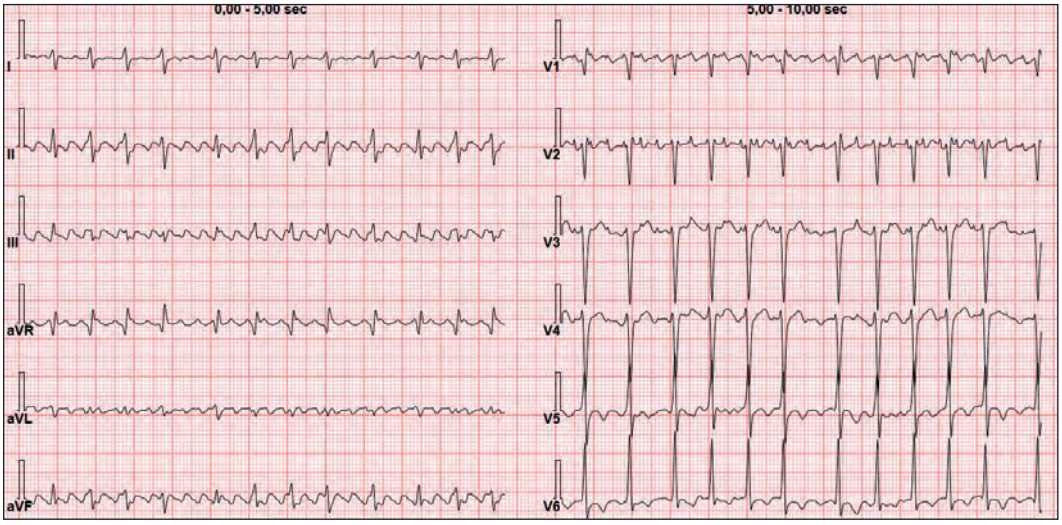

Fig. 1 – The ECG shows atrial flutter at a frequency of 150 bpm.

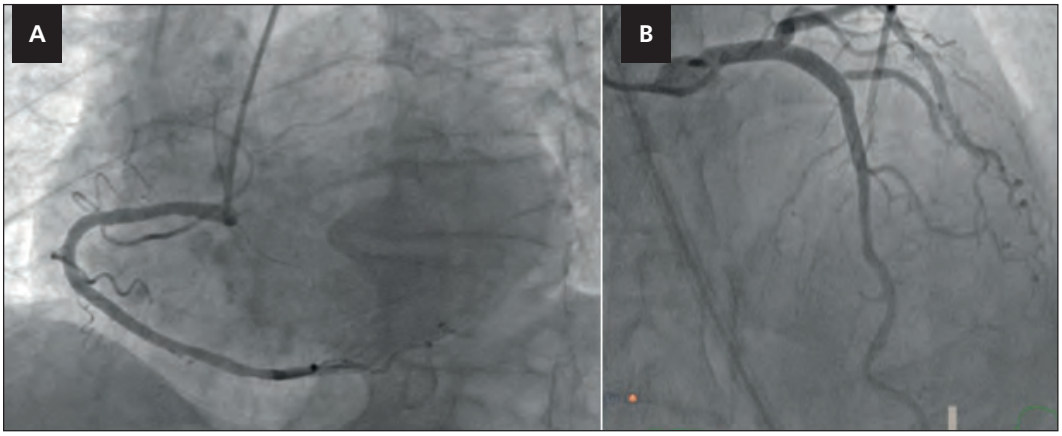

Fig. 2 – (A, B) The image depicts coronary angiography revealing sluggish and delayed flow of contrast material through the coronary arteries, characteristic of slow flow phenomenon. This phenomenon indicates impaired perfusion despite the absence of significant obstructive lesions in the arteries and is associated with conditions affecting coronary microcirculation.

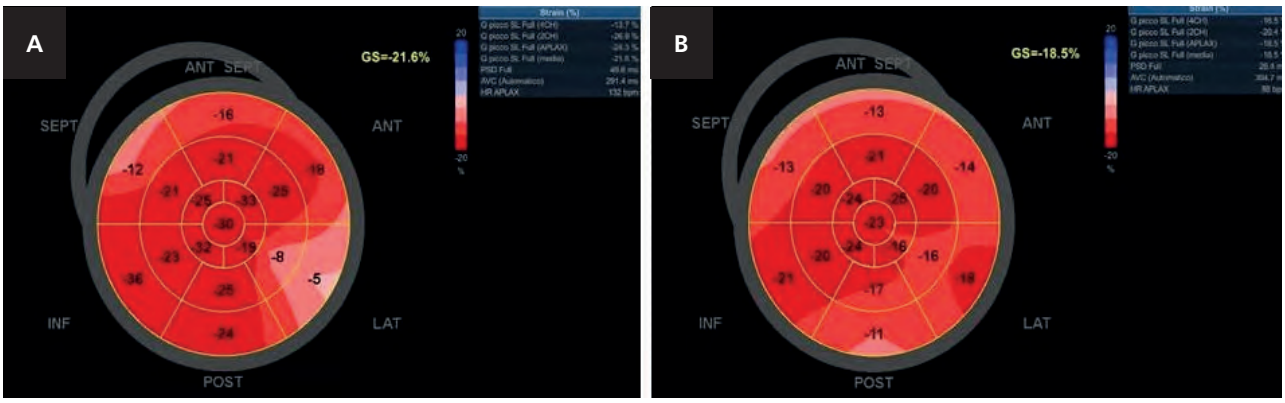

Fig. 3 – The figure illustrates the myocardial strain distribution represented as bull's eyes during and after the episode of paroxysmal supraventricular tachycardia (PSVT). (A) In the first image, the bull's eye plot of global longitudinal strain (GLS) during PSVT reveals regional abnormalities with decreased strain in the interventricular septum and lateral segments. (B) The bull's eye plot of GLS after resolution of PSVT, illustrates an improvement of strain in the interventricular septum and lateral segments. However, overall strain value remains preserved due to the hyperkinesia of the segments caused by supraventricular tachycardia.

Hematological tests including complete blood count, renal function, and myocardial-specific enzymes were performed. An echocardiogram revealed alterations in segmental kinetics and speckle tracking analysis showed normal global longitudinal strain (GLS) with hyperkinesis of apical segments and reduced GLS at the interventricular septum. The initial troponin Hs level was within normal limits (TropHS 10 ng/dl), but a subsequent control showed an approximately thirtyfold increase in the value (TropHS 300 ng/dl). The patient subsequently underwent coronary angiography, which showed no significant obstructive coronary artery disease but a condition of slow flow in all epicardial vessels (**Fig. 2**).

Spontaneous cardioversion occurred, and chest pain slowly subsided. Considering a CHA_2DS_2-VASc score >2, long-term anticoagulant therapy was initiated. A follow-up echocardiogram before discharge showed complete resolution of segmental kinetic abnormalities, and GLS analysis showed improved values in previously affected segments but with slightly lower global strain values compared to those during tachycardia (**Fig. 3**). The remaining anti-ischemic therapy was intensified, a calcium channel blocker and ranolazine were added for suspected microvascular disease, and lipid-lowering therapy was adjusted to achieve LDL targets. The patient experienced further episodes of tachycardia, albeit at a reduced frequency, and no further episodes of chest pain.[17,18,27–36]

Discussion

Paroxysmal supraventricular tachycardias are extremely common arrhythmias; the clinical presentation may vary from asymptomatic or perception of palpitation to severe chest pain or syncope. In the literature, there is widespread consensus on the close correlation between supraventricular tachycardia (SVT) and increased serum troponin levels.[37,38] However, the mechanism underlying troponin elevation in PSVT is not yet fully understood, but there are several hypotheses.[39] The most widely accepted mechanism is as follows: the increase in heart rate, even exceeding 150 bpm, on one hand, leads to an increased demand for oxygen, while on the other hand, it reduces the diastolic phase of the cardiac cycle considerably and coronary perfusion consequently. The mismatch between increased oxygen demand and reduced nutrient supply leads to a transient condition of ischemia that can result in oxidative stress, free radical release, cellular damage, and subsequent troponin release. In fact, troponin positivity has been reported in up to 30% patients with PSVT.[40–43] The transient increase in circulating myocardial necrosis enzymes is often unrelated to evidence of significant stenosis on coronary angiography and resolves once sinus rhythm is restored. Unnecessary coronary angiography carries potential risks and may add costs.[44–48] In fact, in the retrospective study by Dorenkamp, troponin levels were elevated in 14 out of 114 patients with PSVT. Out of these, 13 underwent coronary angiography, with none demonstrating significant coronary stenosis. According to this study, a positive exercise stress test performed in sinus rhythm was the best predictor of coronary artery disease and subsequent revascularization.[47] However, pre-existing pathological conditions such as intermediate stenosis or microvascular disease, which do not generate symptoms at rest, can manifest during tachycardia.[48] In a study conducted by Ben Yedder et al. on 73 patients with SPVT, one-third exhibited an elevation in troponin levels. Among these patients, only one had a significant coronary stenosis requiring revascularization intervention.[44] In another retrospective five-year study conducted by Huseyin Ede et al. involving 85 hospitalized patients with supraventricular tachycardia (SVT) associated with elevated high-sensitivity troponin, only two patients had obstructive coronary artery disease. Both patients were over 60 years old and had a high pretest probability of coronary artery disease.[49] Therefore, although significant coronary stenosis is uncommon in patients with PSVT, a comprehensive history (including cardiac risk factors), a physical examination and an interpretation of serial electrocardiograms (with particular attention to markers of myocardial ischemia, such as ST-segment depressions) are required to detect such cases. While the correlation

between troponin elevation and acute coronary syndrome remains unproven, several studies concur on the association between elevated troponin levels during supraventricular tachycardia and worsened prognosis, with an increased risk of future mortality, myocardial infarction, or hospital readmission.[50]

Conclusions

Troponin is a sensitive and specific biomarker of cardiac damage and plays an important role in the diagnosis of patients with acute coronary syndromes (ACS). A high troponin level however is not synonymous to ACS.[51–55] It is known that troponin elevation can occur in various situations such as myocarditis, chronic kidney disease, anemia, pulmonary embolism, stroke, sepsis, and not rarely, even during high heart rates.[44,45] Therefore, clinical correlation, history, ST-segment changes on ECG, and segmental kinetics on echocardiography are useful.

Some authors argue that it is also useful to subject the patient to coronary CT after arrhythmia resolution to avoid invasive procedures,[56] but the definitive test for diagnosing acute coronary artery disease remains coronary angiography. Improvements in non-invasive diagnostic techniques in the future will certainly lead to a more rapid and less invasive diagnosis.

Conflict of interest
None.

Funding body
None.

Ethical statement
We declare that the case report has been conducted in accordance with applied ethical standards and guidelines; the Declaration of Helsinki.

Informed consent
Appropriate permissions including written informed consent were obtained.

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ČESKÁ KARDIOLOGICKÁ SPOLEČNOST
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Centra sportovní kardiologie

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Úvod

Srdce sportovce se v mnohém liší od srdce obvykle posuzovaného v kardiologické ambulanci. Představuje fyziologickou adaptaci srdce na intenzivní pohybovou aktivitu.

Adaptační změny srdce na trénink se ale mnohdy překrývají s iniciálními fázemi rozvoje kardiomyopatií a intenzivní sportovní aktivita s nedostatečnou regenerací na hranicích adaptability s tlakem na výsledky může vést k tvorbě arytmického substrátu a spouštění arytmií, a tím zvyšovat riziko náhlé srdeční smrti. I sportovci s již diagnostikovaným kardiovaskulárním onemocněním chtějí pokračovat ve sportovní aktivitě.

Sportovní kardiologie se stará o sportovce-pacienty a pacienty-sportovce ve čtyřech modelových situacích:

1. Sportovní kardiologie řeší podezření na kardiovaskulární patologii sportovce, která je odhalena při preparticipačním screeningu.
2. Vyšetření symptomatického sportovce.
3. Diferenciální diagnostika mezi adaptačními změnami a počínajícími kardiomyopatiemi.
4. Preskripce pohybu, volba vhodné sportovní aktivity u sportovců s diagnostikovaným kardiovaskulárním onemocněním.

Sportovní medicína a sportovní kardiologie je s námi již od dob starého Řecka, i když jako podobor kardiologie se začala etablovat až koncem 20. století.

Historie sportovní kardiologie

Za otce sportovní medicíny je považován Herodikus z Thrákie (5. století př. n. l.), který byl spolu s Hippokratem velkým propagátorem pohybové aktivity. Ze stejné doby se traduje i legenda o Feidippidovi, který dle legendy běžel 42 km a 200 m z Maratonu do Atén a se slovy: „Zvítězili jsme," padl mrtev, zda pouhým vyčerpáním nebo na maligní arytmii, zůstane zahaleno tajemstvím.[1]

Feidippides byl voják a také první označení adaptačních změn na extrémní fyzickou zátěž bylo „srdce vojáka".[2] Až v pozdější době s rozvojem sportu se začalo používat a vžilo se označení atletické srdce (resp. srdce sportovce). Pojem atletické srdce byl poprvé použit v roce 1899, kde švédský lékař Salomon Eberhard Henschen popsal dilataci a hypertrofii srdce jakožto adaptační změny na sportovní aktivitu.[3]

Za přelomovou lze z pohledu sportovní kardiologie vnímat 16. konferenci v Bethesdě konanou v roce 1985, dále o 20 let později vydané doporučení ESC o způsobilosti k závodnímu (výkonnostnímu/vrcholovému) sportu. Významný byl také vývoj interpretace EKG u sportovce, kde postupným zpřesňováním hodnoticích kritérií se snížila falešná pozitivita na přibližně 2–3 % u posledních, tzv. International criteria.[4]

Sportovní kardiologie je mladou subspecializací kardiologie. První kongres zaměřený výhradně na sportovní kardiologii se konal v Římě koncem 70. let a navázalo na něj založení Italské společnosti sportovní kardiologie.

Až v roce 2002 byla oficiálně ustanovena Pracovní skupina sportovní kardiologie v rámci Evropské kardiologické společnosti (ESC), která byla zařazena pod Pracovní skupinu kardiovaskulární rehabilitace a zátěžové fyziologie ESC.[5]

V Evropě byly a jsou na poli sportovní kardiologie aktivní hlavně skupiny okolo prof. S. Sharma a A. Pelliccia. V Itálii D. Corrado začátkem 90. let zřídil registr případů náhlé srdeční smrti u sportovců.

Sportovní kardiologie se v evropském kontextu etablovala v rámci Evropské asociace preventivní kardiologie jako její samostatná sekce. V tomto okamžiku má vlastní vzdělávací curriculum[6] a od roku 2020 i vlastní doporučené postupy.[7]

Ve Spojených státech amerických vznikla Sekce cvičení a sportovní kardiologie při American College of Cardiology (ACC) v roce 2011.[8,9]

Sportovní kardiologie v České republice

Hodnocení kardiovaskulárního systému (minimálně klidové srdeční frekvence a změření krevního tlaku) bylo součástí tělovýchovných prohlídek již dlouho. Od roku 2005 je kardiovaskulární screening součástí sportovní prohlídky sportovce, kde rozsah a kompetence jsou definovány ve vyhlášce 391/2013 Sb. (vyhláška o zdravotní způsobilosti k tělesné výchově a sportu).

Sportovní kardiologie se začala objevovat na workshopech, v jednotlivých sděleních a sekcích na kongresech, např. blok sportovní kardiologie na kongresu České společnosti tělovýchovného lékařství v Ostravě v roce 2017.

V roce 2018 se konal v Praze Workshop sportovní kardiologie jako jeden z prvních cele věnovaných sportovní kardiologii. Workshop pokračoval ještě o rok později paralelně se sympoziem Srdce a sport, konaným v Ostravě. Od roku 2020 se sympozium Srdce a sport koná každoročně a nepřerušila jej ani covidová pandemie.

Okolo kardiologů a tělovýchovných lékařů se zájmem o sportovní kardiologii vznikla v rámci České společnosti tělovýchovného lékařství Pracovní skupina sportovní kardiologie v roce 2019. O rok později v rámci nově vznikající České asociace preventivní kardiologie rovnou vznikla Sekce sportovní kardiologie. Obě tyto sekce/pracovní skupiny spolu spolupracují a snaží se pole sportovní kardiologie propojovat mezi kardiology a tělovýchovnými lékaři.

Obr. 1 – Aktuálně fungující centra sportovní kardiologie.

Organizace sportovní kardiologie v ČR

V návaznosti na odborné skupiny sportovní kardiologie vznikla při komplexních kardiocentrech v roce 2020 jako pilotní projekt čtyři centra sportovní kardiologie pro dospělé sportovce: v Komplexním kardiocentru v Podlesí-Třinci, ve Fakultní nemocnici Olomouc, Všeobecné fakultní nemocnici v Praze a pro dětské sportovce při Dětském kardiocentru Fakultní nemocnice v Motole v Praze (viz **obr. 1**).

Protože se centralizovaná péče osvědčila i při péči o výkonnostní a vrcholové sportovce, byly vypracovány podmínky pro vznik dalších center, které předkládáme v tomto čísle *Cor et Vasa*. Snahou je, aby byla zajištěna odpovídající úroveň péče (znalosti nejen z kardiologie, ale i tělovýchovného lékařství a zátěžové fyziologie).

Kardiologická péče o sportovce by měla být stratifikována, kde primární péči zajišťuje praktický lékař nebo praktický lékař pro děti a dorost spolu s tělovýchovným lékařem. Základní kardiologické vyšetření sportovce spadá do kompetence ambulantních kardiologů. Centra sportovní kardiologie pak mají roli superkonziliární. V centrech sportovní kardiologie by pak mělo být dostupné i erudované multimodalitní zobrazení (magnetická rezonance srdce, CT koronarografie, zátěžová echokardiografie apod.), zároveň by měla být zajištěna spolupráce s klinickým genetikem s dostatečnou erudicí v interpretaci i hraničních výsledků. Důležitým aspektem je také vzájemná spolupráce a konzultace hraničních případů, zejména u vrcholových sportovců, kterých s kardiovaskulárními problémy naštěstí v Česku není mnoho.

Výhled do budoucna

Po pilotním úspěšném ověření a přijetí fungování center sportovní kardiologie by bylo dobré, kdyby sportovněkardiologická péče byla dostupná rovnoměrně po celé České republice. Ideálním stavem by bylo v každém kraji po jednom centru sportovní kardiologie, které by těsně spolupracovalo s komplexním kardiocentrem a mělo vytvořenou síť spolupracujících ambulantních kardiologů a tělovýchovných lékařů.

Na poli sportovní kardiologie vývoj směřuje od binárního rozhodování schopen/neschopen závodního sportu k mnohem širší paletě možností a rozhodování s čím dál větší vahou názoru sportovce/pacienta. To ale také vyžaduje dostatek zkušeností a centralizace sportovněkardiologické péče by k tomu měla napomoci.

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Centra sportovní kardiologie: odborné stanovisko

Vladimír Tuka, Bogna Jiravská Godula, Otakar Jiravský, Peter Kubuš, Eliška Sovová

Poslání center sportovní kardiologie: zajištěním terciární superkonziliární komplexní kardiologické péče o sportovce snižovat riziko zdravotních komplikací sportovců.

Vize center sportovní kardiologie

Existující národní síť center sportovní kardiologie zajišťuje adekvátní diagnosticko-terapeutickou péči o sportovce v oboru kardiologie a přispívá ke komplexní posudkové péči o sportovce. Tato síť navazuje na plošnou práci praktických a tělovýchovných lékařů a jejich spádových kardiologů.

Důvody pro vznik/existenci center sportovní kardiologie

- Dlouhodobě se zvyšuje počet jedinců ve společnosti, kteří se věnují sportovní/závodní činnosti intenzivně.
- Existují vědecká data potvrzující pozitivní přínos pohybové aktivity a je třeba ji systematicky ve společnosti podporovat.
- Náhlá srdeční smrt je u vysoce aktivních sportovců častější než u rekreačně sportující či nesportující veřejnosti, a proto je legislativně zakotvený systematický preparticipační screening.
- Preparticipační screening, stejně tak jako periodická reevaluace zdravotního stavu sportovce, vede k identifikaci jedinců, kteří vyžadují následné kardiologické dořešení.
- Kardiologická péče o sportovce je specifická existencí změn kardiovaskulárního aparátu vlivem dlouhodobého tréninku. Ty mohou imitovat kardiovaskulární onemocnění. Sportovec pak může být zbytečně zbaven způsobilosti ke sportovní činnosti. Neadekvátní vyhodnocení změn kardiovaskulárního aparátu sportovce, jako změny náležející atletickému srdci, může naopak sportovce vystavit riziku vážných zdravotních komplikací či smrti. Kardiolog ošetřující sportovce pak musí být nutně specificky znalý kardiovaskulární problematiky sportovců. Zvláště pak indikace a interpretace diagnostických postupů u sportovců – EKG i zobrazovacích metod.
- V intenzivní sportovní/závodní činnosti je možné pokračovat u některých kardiovaskulárně nemocných sportovců. Znalost problematiky způsobilosti k sportovní činnosti je důležitou komponentou znalostí kardiologa pečujícího o sportovce.
- Preskripce kardiovaskulárních farmak se u sportovců řídí nejen základním onemocněním, ale volba přípravků může být ovlivněna i jejich účinky na sportovní výkon a antidopingovými předpisy.

Organizace kardiologické péče o sportovce

- Kardiologická péče o sportovce by ideálně měla být trojstupňová
  1. stupeň – tělovýchovný lékař / praktický lékař
  2. stupeň – sportovní kardiolog (spolupracující s centrem sportovní kardiologie)
  3. stupeň – centra sportovní kardiologie
- Sportovní prohlídky a základní vyšetření symptomatického sportovce jsou v gesci registrujících praktických lékařů a praktických lékařů pro děti a dorost nebo tělovýchovných lékařů. V jejich gesci je i rutinní preparticipační screening včetně rutinního EKG u výkonnostních a vrcholových sportovců.
- V případě zjištěné patologie kardiovaskulárního systému je indikováno kardiologické vyšetření sportovním kardiologem, ideálně spolupracujícím s centrem sportovní kardiologie nebo přímo v centru sportovní kardiologie.
- Centra sportovní kardiologie plní funkci superkonziliární.

Zařazení do sítě center sportovní kardiologie

O schválení statutu centra sportovní kardiologie, a tím i o zařazení do sítě center sportovní kardiologie je možné žádat souběžně výbor České společnosti tělovýchovného lékařství (ČSTL) a České asociace preventivní kardiologie (ČAPK) České kardiologické společnosti (ČKS). Žadatel čestným prohlášením potvrdí splnění minimálních personálních a přístrojových požadavků. K tomuto čestnému prohlášení je připravený oficiální formulář. K zařazení do sítě je nutná kontrasignace obou výše zmíněných společností. Seznam center je uveden na webu ČSTL a na webu ČKS (pod sekcí Sportovní kardiologie České asociace preventivní kardiologie).

Pracoviště sportovní kardiologie

- **Náplň práce**
  - Sportovněkardiologické vyšetření sportovce – superkonziliární služba.
  - Poradní služba pro účely sportovních prohlídek.
  - Dlouhodobá kardiologická dispenzarizace sportovců s kardiovaskulárním onemocněním (arteriální hypertenze, málo významné chlopenní vady apod.) nevyžadující specializovanou centrovou péči.
- **Personální zajištění**
  - Kardiolog s erudicí ve sportovní kardiologii
  - Střední zdravotnický personál
- **Technické vybavení**
  - EKG
  - Ergometrie
  - Echokardiografie
  - EKG holterovské monitorování
  - 24hodinové monitorování krevního tlaku

Centra sportovní kardiologie

- **Náplň práce**

- ° Sportovněkardiologické vyšetření sportovce – superkonziiární služba
- ° Posudková činnost „Způsobilost ke sportu z kardiologického hlediska“
- ° Dlouhodobá kardiologická dispenzarizace sportovců s kardiovaskulárním onemocněním
- ° Edukace odborné veřejnosti ve sportovní kardiologii
- ° Vědecko-výzkumná činnost

• **Personální zajištění – minimální**
- ° Kardiolog s erudicí ve sportovní kardiologii
- ° Tělovýchovný lékař
- ° Střední zdravotnický personál

• **Personální zajištění – fakultativní**
- ° Psycholog – pomoc při vypořádání se s ukončením kariéry při diagnóze např. arytmogenní kardiomyopatie
- ° Fyzioterapeut
- ° Nutriční terapeut / specialista
- ° Klinický genetik

• **Technické vybavení – možno mít nasmlouváno**
- ° EKG
- ° Ergometrie
- ° Spiroergometrie
- ° Základní spirometrie
- ° Echokardiografie
- ° Zátěžová echokardiografie nebo jiná metoda zátěžové zobrazovací metody (např. SPECT)
- ° EKG holterovské monitorování / EKG monitorování
- ° 24hodinové monitorování krevního tlaku
- ° CT srdce / CT koronarografie
- ° Magnetická rezonance srdce
- ° Katetrizační sál invazivní kardiologie
- ° Elektrofyziologický sál

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Zemřel prof. MUDr. Jiří Fodor, CSc., FRCPC, FAHA (28. 10. 1927–10. 12. 2024)

10. prosince se uzavřel bohatý život profesora Jiřího Fodora, významného epidemiologa kardiovaskulárních chorob a preventivního kardiologa, který strávil většinu svého profesního života v Kanadě.

Jiří Fodor se narodil 28. října 1927 v Užhorodě v rodině dobře situovaného maďarského obchodníka se dřevem. Vyrůstal ve čtvrti Malá Praha, kde bydlela většina českých úředníků tehdejšího Československa a od jejich dětí se Jiří naučil dobře česky již v předškolním věku. Rodiče mu prokázali velkou službu, neboť ho dali zapsat do české školy. Tím si ovšem znepřátelili na zbytek života své maďarské příbuzné. Protože se oženil až v pozdějším věku, měl ke svým rodičům velmi úzký vztah. Jeho otec byl i předmětem vydírání tehdejší StB a matku vzal Jiří později, po otcově smrti, s sebou do emigrace.

Po maturitě na gymnáziu v Michalovcích se rozhodl studovat medicínu na Karlově univerzitě v Praze (1946–1951). Po promoci pracoval nejprve v Ústavu patologické fyziologie UK u prof. Hepnera. Na pozvání profesora Fejfara přešel v roce 1952 do tehdejšího Ústavu pro choroby oběhu krevního v Praze-Krči. Pracoval ve skupině pro výzkum ateroskleózy a publikoval první práce o endogenním heparinu a vlivu na tzv. clearing factor, který byl později nazván lipoproteinovou lipázou. Již tehdy se zabýval otázkou postprandiální lipemie, které je v poslední době opět věnována pozornost.

Na popud profesora Fejfara přešel od patofyziologie k epidemiologii kardiovaskulárních chorob, nově vznikající vědní disciplíně. Zásadní význam pro něj mělo stipendium Světové zdravotnické organizace (WHO) na Jamajce v Epidemiologické jednotce Britské výzkumné rady W. Mialla (MRC Epidemiological Research Unit). Po návratu z Jamajky inicioval epidemiologické studie v Praze 2 a 4 (spolu s Helenou Geizerovou a Zdeňkem Hejlem). Rovněž provedl srovnávací studii s Göteborgem (publikováno ve Švédsku). Kontakty získané na Jamajce vedly i k tomu, že Praha přistoupila ke známé studii WHO s klofibrátem (WHO Cooperative Trial on primary prevention of ischaemic disease using clofibrate to lower serum cholesterol: mortality follow-up, Lancet 1980;2(8191):379–385).

V pohnutých srpnových dnech roku 1968 Jiří Fodor opustil Československo. Jeho cesta vedla nejprve do Vídně a později do Göteborgu, kde pracoval společně s Larsem Werkö na prvním registru infarktu myokardu ve Švédsku. V roce 1971 přijal nabídku z Kanady a stal se jedním ze spoluzakladatelů nové lékařské fakulty v hlavním městě nejvýchodnější kanadské provincie St. John's, Newfoundland. Kromě výuky na lékařské fakultě (v letech 1981–1994 zastával funkci proděkana) se věnoval i výzkumu. Jako první zahájil v Kanadě epidemiologické studie hypertenze a ICHS. Založil a stal se prvním prezidentem Canadian Hypertension Society. Rovněž založil a byl prvním předsedou Canadian Coalition for High Blood Pressure Prevention and Control. Jiří Fodor prosadil sepsání prvních kanadských guidelines pro léčbu hypertenze. Později inicioval i první kanadská lipidová guidelines a organizoval národní edukační kampaň pro léčbu dyslipidemie.

V roce 1994 se Jiří Fodor přestěhoval do Ottawy, kde až do svého odchodu do důchodu (2014) zastával místo ředitele výzkumu v Centru prevence a rehabilitace Ottawského kardiologického ústavu (Ottawa Heart Institute). V období posledních 20 let byl hlavním investigátorem řady mezinárodních projektů orientovaných na prevenci kardiovaskulárních chorob ve střední a východní Evropě a také hlavním investigátorem multicentrické, randomizované klinické studie HOPE TOO v Ottawa Heart Institute.

Po roce 1989 se mu podařilo navázat kontakty v Čechách i na Slovensku a býval častým hostem na našich akcích. Já jsem měla možnost pracovat pod jeho vedením jako postdoctoral fellow déle než dva roky na Memorial University v St. Johns'. Od té doby nás pojilo úzké přátelství s jeho rodinou.

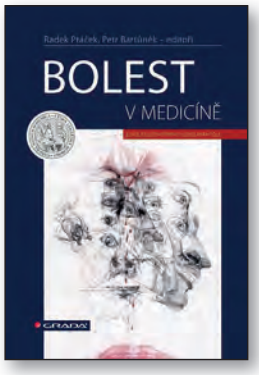
Pro svou laskavost a osobitý humor se Jiří těšil velké oblibě u svých studentů a kolegů. Byl oddán své profesi.

Od roku 2015 žil Jiří Fodor se svou manželkou v Praze. S nadhledem pozoroval politické dění u nás i ve světě. Stále si udržoval přehled o nejnovějších klinických studiích v oblasti hypertenze a kardiovaskulární prevence. Hodně četl a užíval si kulturních a gastronomických nabídek Prahy. Až do pozdního věku si zachoval svůj osobitý humor.

Za zásluhy o prevenci kardiovaskulárních chorob obdržel ceny Kanadské společnosti pro hypertenzi National Health Scientist Award a Distinguished Scientist Award a Segal Award za zásluhy o prevenci kardiovaskulárních chorob udělenou Canadian Cardiovascular Society. V roce 2001 se Canadian Coalition for High Blood Pressure Prevention and Control rozhodla vyhlásit „George Fodor Award" za zásluhy o kontrolu hypertenze. Publikoval více než 250 prací a bylo mu uděleno čestné členství České společnosti pro aterosklerózu, České společnosti pro hypertenzi, České kardiologické společnosti, Slovenské kardiologické společnosti a Slovenské společnosti pro aterosklerózu.

Loučíme se s mimořádnou osobností československé a kanadské preventivní kardiologie s díky za vše, co pro ni vykonal. Zařadil se mezi úspěšné absolventy Karlovy univerzity, kteří se mezinárodně prosadili. Vzpomínáme s úctou, čest jeho památce!

Prof. MUDr. Renata Cífková, CSc.



Radek Ptáček, Petr Bartůněk (editoři): Bolest v medicíně

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Recenzovaná kniha je třináctým dílem edice Etika a komunikace v medicíně, vydávané Českou lékařskou komorou. Stejně jako u předešlých dílů jsou jejími editory † prof. PhDr. et PhDr. Radek Ptáček, Ph.D., MBA, a doc. MUDr. Petr Bartůněk, CSc. Bohužel profesor Radek Ptáček se vydání tohoto dílu nedožil.

Tento knižní cyklus byl vysoce hodnocen a získal mimo jiné cenu rektora Univerzity Karlovy. Tak jako u předešlých dílů byl výběr některých kapitol prezentován na konferenci, která se konala 11. prosince 2024 v Domě lékařů v Praze.

Předmluvy napsali: Její Magnificence rektorka Univerzity Karlovy prof. MUDr. Milena Králíčková, Ph.D., děkan 1. lékařské fakulty Univerzity Karlovy prof. MUDr. Martin Vokurka, CSc., prezident České lékařské komory MUDr. Milan Kubek a editor doc. MUDr. Petr Bartůněk, CSc.

Autory vybírali ještě oba editoři. Oslovili především naše špičkové odborníky. Obsah monografie tvoří 45 samostatných kapitol různého rozsahu. Psali je nejen lékaři různých oborů, ale i psychologové, psychoterapeuti, etici, biologové, filozofové, osoby církevní denominace, právníci i laici.

Obsah je rozdělen do šesti částí. První část je věnována Bolesti pohledem klinických oborů (128 s.), 2. část Bolesti pohledem psychologie a psychoterapie (42 s.), 3. část Bolesti pohledem etiky, bioetiky a biologie (66 s.), 4. část Bolesti pohledem teologie (82 s.), 5. část Bolesti pohledem právních věd (13 s.). Poslední, 6. část je věnována Bolesti pohledem publicistiky (12 s.). Textovou část uzavírá dvousloupcový rejstřík (5 s.), český souhrn a anglické summary (po 1 s.). Literatura (různě rozsáhlá i různě aktuální) je uváděna za textovou částí jednotlivých kapitol. Do textu je vloženo několik jednoduchých černobílých obrázků a několik tabulek.

Jednotlivé kapitoly jsou různě dlouhé, na různé odborné úrovni, která závisí na rozdílných zkušenostech jednotlivých autorů. Tematicky nemohly být ani při 42 kapitolách zcela vyčerpány, ale zásadní problematika byla uvedena. Jako celek je publikace velmi kvalitní. Tato kniha je poslední v edici Etika a komunikace v medicíně, vydávané Českou lékařskou komorou po dobu 12 let. Bude také součástí materiálů pro delegáty příštího celostátního sjezdu České lékařské komory.

Komu knihu doporučit?

Protože bolest může být průvodním příznakem většiny chorob, najdou v ní „své kapitoly“ lékaři téměř všech specializací.

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