Bogatyreva F.M., Kaplunova V.Yu., Kozhevnikova M.V.,
Shakaryants G. A., Khabarova N. V., Privalova E.V., Belenkov Yu.N.
I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

Assessment of the structural and functional state of blood vessels in patients with hypertrophic cardiomyopathy

Aim — To evaluate the structural and functional condition of the vasculature using fingertip photoplethysmography and computerized videocapillaroscopy in patients with hypertrophic cardiomyopathy (HCMP).

Material and methods — The study included patients with HCMP (n=48; 28 (57%) men; age, 54.3±13.6 years) and healthy volunteers (control group, n=33, 15 (45%) men; age, 58.2±8.8 years). Standard laboratory and instrumental examination (blood count and biochemistry, electrocardiography, echocardiography, Holter electrocardiogram monitoring) were performed for all HCMP patients. The condition of vascular wall at various levels of the vasculature was evaluated by fingertip photoplethysmography (apparatus Angioscan-01) and computerized nail-fold videocapillaroscopy (apparatus Capillaroscan-01). The photoplethysmography study analyzed structural parameters, including the arterial wall stiffness index (aSI) of large blood vessels and the resistance index (RI) of small muscular arteries. Endothelial dysfunction was evaluated by the occlusion index (OI) and phase shift (PS). The capillaroscopy study assessed structural parameters, including the resting capillary density (rCD) and the capillary density following venous occlusion (voCD), and functional parameters, including the percentage of perfused capillaries (PPC), the percentage of restored capillaries (PRC), and the capillary density after the reactive hyperemia test (rhCD).

Results — The study showed increases in aSI (8.8 [6.8; 12.2] and RI (32.5 [17.4; 47.9] in the HCMP group. The OI was significantly lower in the HCMP group (1.3 [1.1; 1.5]) than in the control group (1.8 [1.5; 2.7], p<0.001). Also, PS values were significantly decreased in the HCMP group (4.4 [2.3; 8.6]) compared to the control group (8.4 [5.1; 12.1]. p=0.018). Disorders of structural and functional capillary indexes were observed in HCMP patients compared to the control group; rCD and voCD were decreased in the HCMP group (60 [52.6; 68] and 88 [75; 90], respectively) compared to the control group (75.8 [60; 87] and 90 [73; 101]), however, no intergroup difference reached a statistical significance. The rhCD, PPC, and PRC values were decreased in the HCMP group (66.3 [55; 72], 86.7 [70.9; 104.2] and 1.7 [– 6.95; 20.3], respectively) compared to the control group (86 [68.6; 100], 103 [96; 114] and 18.4 [8.1; 27.4], respectively); PPC and PRC values were significantly different (p<0.005 and p<0.004, respectively).

Conclusion — In patients with HCMP, fingertip photoplethysmography and computerized videocapillaroscopy showed increased wall stiffness in both large blood vessels and microvasculature, pronounced endothelial dysfunction, and decreases in capillary density and percentage of restored capillaries following respective tests.

Keywords — Hypertrophic cardiomyopathy; fingertip photoplethysmography; videocapillaroscopy; endothelial dysfunction; microcirculation; vascular stiffness

For citations — Bogatyreva F.M., Kaplunova V.Yu., Kozhevnikova M.V., Shakaryants G.A., Khabarova N.V., Privalova E.V. et al. Assessment of the structural and functional state of blood vessels in patients with hypertrophic cardiomyopathy. Kardiologiia. 2021;61(12):16–21. [Russian: Богатырева Ф.М., Каплунова В.Ю., Кожевникова М.В., Шакарьянц Г.А., Хабарова Н.В., Привалова Е.В. и др. Оценка структурного и функционального состояния сосудов у пациентов с гипертрофической кардиомиопатией. Кардиология. 2021;61(12):16–21]

Corresponding author — Bogatyreva F.M.. E-mail: fam505@yandex.ru

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic diseases of the myocardium, whose prevalence varies from 0.2% to 1.4% with no clear geographical, ethnic or sex distribution patterns [1, 2]. With the exception of stress-induced variants, around 20–30% of patients having left ventricular (LV) hypertrophy of more than 1.5 cm are likely to have sarcomere mutations [3, 4]. The annual mortality rate is 0.3–0.4% [3]. Although the symptoms of HCM can appear at any age, onset before the age of 40 increases the risk of adverse outcomes (life-threatening heart rhythm disorders, atrial fibrillation, chronic heart failure, stroke, death) compared to onset at

ISSN 0022-9040. Kardiologiia. 2021;61(12). DOI: 10.18087/cardio.2021.12.n1718

60 years [5]. The additional presence of sarcomere mutations causes a twofold increase in the risk of death [3]. However, the hypothesis that only sarcomere mutations are relevant cannot fully explain all clinical and pathophysiological features of HCM [6].

Analysis of histopathological findings in patients with HCM has demonstrated an abnormal structure of the coronary microvasculature – namely, arteriolar narrowing and intima-media hypertrophy, as well as a decreased number of capillaries and capillary density [7, 8]. Abnormal intramural arterioles are likely to constitute the main morphological substrate contributing to microvessel dysfunctions, such as violated dilation, which presumably make them responsible for the microvascular ischemia of the myocardium [6]. Coronary microvascular dysfunction is a predictor of adverse LV remodeling, systolic dysfunction and mortality in patients with HCM [9, 10]. However, it is unclear whether these abnormalities are attributed only to the coronary arteries or are generalized in patients with HCM.

Thus, it is of great interest to study endothelial dysfunction, as well as genetic regulation, which leads to early vascular remodeling (and, therefore, myocardial remodeling) and increased fibrogenesis processes causing electrical instability of the myocardium. However, due to their cost and complexity, it is difficult to perform histopathological studies as part of routine practice for the patients in this cohort. Thus, researchers are challenged to find effective, simple and non-invasive methods for real-time evaluation of the structural and functional state of the vasculature in patients with HCM.

Endothelial dysfunction can be evaluated using various plasma biomarkers and non-invasive methods, such as nailfold capillaroscopy (NFC) and finger photoplethysmography (PPG) tests. Since these methods have been shown to be effective for determining the extent of the damage of the coronary microvasculature in diffuse connective tissue diseases, they are included in the guidelines for managing patients with systemic scleroderma [11]. Accordingly, using these methods under other conditions involving microcirculation violations appears promising.

Increased stiffness and decreased elasticity of large and small arteries play an important role in the pathogenesis of cardiovascular diseases (CVDs) involving functional and structural abnormalities. In the systematic review by Ciaffi et al. [12], patients with diabetes mellitus type 2 – especially those with poor glycemia control or long-term

target organ involvement (retinopathy, polyneuropathy) – had decreased capillary density, avascular areas and giant capillaries; moreover, the same abnormalities were observed in patients with hypertension [12–15]. However, there have been no similar studies of microcirculation and endothelial dysfunction in patients with HCM using PPG and NFC. Such methods can be useful for improved understanding of the pathophysiology of clinical manifestations of HCM, contributing to improved treatment approaches based on endothelial function.

Objective

To assess the structural and functional state of the vasculature using finger PPG and NFC in patients with HCM and compare them with the control group (healthy volunteers).

Material and Methods

The study was carried out following the Helsinki Declaration and was approved by the Ethics Committee of I.M. Sechenov First Moscow State Medical University. All patients signed informed consent to participate in the study.

The study included patients with HCM (n=48; 28 (57%) male patients); the median age was 54.3±13.6 years. The control group included patients without CVDs (n=33; 15 (45%) male patients). The median age was 58.2±8.8 years. Patients with malignant neoplasms or severe dysfunctions of the liver, kidney and lung were excluded from the study. All patients with HCM included in the study underwent laboratory and clinical examination (complete blood count, biochemical blood test, electrocardiography, echocardiography, Holter monitoring). The vascular wall was evaluated in different parts of the vasculature using finger PPG (Angioskan-01, RF) and NFC (Kapillaroskan-01, RF).

Photoplethysmography

Pulse wave velocity (PWV) was measured at the first stage of PPG. Based on subsequent processing of the signal, structural changes of the walls of large vessels (brachial artery) and microvasculature were evaluated: stiffness index of the large vessel wall (ASI) and resistance index of small muscle arteries (RI). Endothelial dysfunction was assessed by reactive hyperemia test: an increase in the pulse wave amplitude was evaluated in the brachial artery (occlusion index – OI) after 5-minute occlusion using a sphygmomanometer (lag time or phase shift – PS).

Nailfold capillaroscopy

Prior to conducting NFC tests, the subject sits freely on a chair for 15 to 20 minutes at room temperature (22–25 °C). Patients were asked to refrain from smoking and caffeine for 4 hours before the test. NFC was not performed in patients who had undergone cosmetic procedures on the nail bed area within the previous two weeks. The following structural parameters were estimated using NFC on the dorsal surface of the right second finger: capillary density at rest (CDr) determined by counting the number of capillaries per area unit (capillaries/mm^2) in the nailfold; capillary density venous occlusion test (CDvo) with a wrist cuff pressure of 60 mmHg for 2 minutes. Functional parameters were as follows: capillary density after reactive hyperemia test (CDrh); percentage of perfused capillaries (PPC); percentage of capillary recovery (PCR). The latter two were calculated using the formulas:

$$PPC=(CDrh/\ CDvo) \times 100\%;$$
$$PCR=(CDrh - CDr)\ /\ CDvo \times 100\%.$$

Statistical processing of the data was performed using the Statistica 12.0 software suite. Normally distributed quantitative data are presented as means (M) and standard deviations (σ); non-normally distributed data are expressed as medians (Me) and interquartile ranges [Q1; Q3]. Student's t-test was used to evaluate the intergroup differences of normally distributed quantitative data. Non-normally distributed quantitative data were analyzed using the Mann – Whitney U-test, while qualitative data were analyzed using the chi-square test. Differences were statistically significant if p was less than 0.05.

Table 1. Demographic characteristics of the subjects

Parameter	HCM group (n=48)	Control group (n=33)	p
Male, n (%)	28 (57)	15 (45)	0.33
Age, years	54.3±13.6	58.2±8.8	0.55
BMI, kg/m^2	28.8±5.1	26.05±3.9	0.02

HCM – hypertrophic cardiomyopathy; BMI – body mass index; p – significance of differences assessed using Student's t-test and the chi-square test.

Results

The demographic characteristics of the subjects are presented in Table 1. Both groups were comparable in sex and age. Patients with HCM had higher body mass index. According to echocardiographic data, non-obstructive HCM prevailed (75% of patients); adverse myocardial remodeling was observed, namely concentric hypertrophy; LV outlet pressure gradient was 14.2 [8.2; 26.6] mmHg; left ventricular ejection fraction (LVEF) was 60 [54; 63] %. Seven patients (14%) had a history of myoectomy. Atrial fibrillation and chronic heart failure NYHA functional class II–III were established in 30% of patients with

ISSN 0022-9040. Kardiologiia. 2021;61(12). DOI: 10.18087/cardio.2021.12.n1718

Table 2. Intergroup differences in the structural and functional parameters of vessels according to PPG

Parameter	References	HCM group	Control group	p*
ASI, m/s	< 8	8.8 [6.8; 12.2]	7.7 [6.6; 9.1]	0.09
RI, %	< 30	32.5 [17.4; 47.9]	31.4 [19.2; 44]	0.95
Reactive hyperemia test (occlusion test)				
Occlusion index	> 2.0	1.3 [1.1; 1.5]	1.8 [1.5; 2.7]	< 0.001
Phase shift, ms	> 10	4.4 [2.3; 8.6]	8.4 [5.1; 12.1]	0.018

PPG – photoplethysmography; HCM – hypertrophic cardiomyopathy; ASI – stiffness index of large conductive arteries;
RI – resistance index of small muscle arteries; *the statistical significance of the intergroup difference was assessed using the Mann–Whitney test.

Table 3. Intergroup differences in the structural and functional parameters of vessels according to videocapillaroscopy

Parameter	References	HCM group	Control group	p*
Structural parameters				
CDr, cap/mm^2	53	60 [52.6; 68]	75.8 [60; 87]	0.4
CDvo, cap/mm^2	87	88 [75; 90]	90 [73; 101]	0.16
Functional parameters:				
CDrh, cap/mm^2	59	66.3 [55; 72]	86 [68.6; 100]	0.05
PPC, %	92.5±5.3	86.7 [70.9; 104.2]	103 [96; 114]	0.005
PCR, %	16.5±7.1	1.7 [-6.95; 20.3]	18.4 [8.1; 27.4]	0.004

HCM – hypertrophic cardiomyopathy; CDr – capillary density at rest; CDvo – capillary density following venous occlusion;
CDrh – capillary density after reactive hyperemia; PPC – percentage of perfused capillaries; PCR – percentage of capillary recovery;
*the statistical significance of the intergroup difference was assessed using the Mann-Whitney test.

HCM; among them, 8 (22%) patients had a history of cerebrovascular accidents. Syncope was observed in 17% of patients with HCM; 50% of patients were exposed to a high risk of sudden cardiac death; 3 (8%) patients had a pacemaker; 2 (5%) patients had a cardioverter-defibrillator. More than 50% of patients with HCM received beta-blockers and calcium channel blockers.

Structural and functional abnormalities of vessels in the study groups

Intergroup differences in the structural and functional parameters of large vessels and microvasculature shown by PPG are presented in Table 2. Although ASI and RI were increased in the HCM group compared to the control group (8.8 [6.8; 12.2] and 32.5 [17.4; 47.9] versus 7.7 [6.6; 9.1] and 31.4 [19.2; 44], respectively), the intergroup differences were not statistically significant. Thus, increased stiffness of both large vessels and coronary microvasculature vessels was observed in the HCM group. The functional parameters were evaluated: the occlusion index (OI) was statistically significantly lower in the HCM group than in the control group (1.3 [1.1; 1.5] versus 1.8 [1.5; 2.7]; p < 0.001). Phase shift (PS) was lower in the HCM group compared with the control group (4.4 [2.3; 8.6] versus 8.4 [5.1; 12.1]; (p=0.018).

The results of the assessment of intergroup differences in the structural and functional parameters of the microvasculature are shown in Table 3. The study found a marked capillary dysfunction in patients with HCM resulting in a decrease in structural and functional indicators as compared with the control group: a decrease in CDr, CDvo (60 [52.6; 68] and 88 [75; 90] versus 75.8 [60; 87] and 90 [73; 101], respectively); a decrease in CDhr, PPC and PCR (66.3 [55; 72], 86.7 [70.9; 104.2] and 1.7 [–6.95; 20.3] versus 86 [68.6; 100], 103 [96; 114] and 18.4 [8.1; 27.4], respectively); a statistically significant difference was achieved in the levels of PPC and PCR (p<0.005 and p <0.004, respectively).

Discussion

Finger PPG showed increased stiffness of the vessels of various sizes in patients with HCM and significant endothelial dysfunction, as confirmed by a statistically significant decrease in OI and PS. These data are consistent with the findings by Fernlund et al. [16]. However, it should be noted that endothelial dysfunction was evaluated using laser Doppler flowmetry with a pharmacological challenge (acetylcholine, sodium nitroprusside). Increased stiffness of vessels is a hallmark of vascular aging, which in turn progressively induces endothelial dysfunction even in the absence of CVDs or modifiable cardiovascular risk factors [17, 18]. However, despite the available evidence of oxidative damage of the endothelium associated with vascular aging, it remains unclear what triggers the strengthening of this process [17].

By assessing finger skin microvasculature in patients with HCM using NFC we were able to detect a statistically significant decrease in the indicators showing

structural and functional abnormalities. Significantly, the assessment of the peripheral coronary microvasculature show abnormalities in the coronary microcirculation in several studies of different CVDs [19, 20]. Moreover, the evaluation of the nailfold capillaries using NFC in patients with systemic scleroderma is significantly associated with coronary microvascular dysfunction identified by transthoracic echocardiography as reduced coronary flow reserve [21]. Coronary flow reserve is decreased in patients with HCM [7], which comprises a substrate for myocardial ischemia that often occurs in asymptomatic patients with HCM [7, 9, 22, 23]. The degree of coronary microvascular dysfunction is a strong and independent predictor of worsening clinical condition and death [9, 10]. Thus, abnormalities in the peripheral coronary microvasculature identified by NFC and PPG may be indicative of coronary endothelial dysfunction. Moreover, such methods can be used to inform the start of timely treatment aimed at improving endothelial function.

It should be noted that this study is limited by a relatively small sample of examined patients. Moreover, endothelium-independent dilatation was not evaluated. Therefore, it is possible that patients with HCM may have a primary vasomotor abnormality of smooth musculature, which contributes to vasodilation disturbance.

Conclusion

Microvascular dysfunction and increased vascular stiffness are important pathophysiological factors of hypertrophic cardiomyopathy. In this study, structural and functional abnormalities were demonstrated in peripheral vessels of various sizes. These abnormalities in the peripheral microvasculature in patients with hypertrophic cardiomyopathy are likely to reflect abnormalities developing in the coronary arteries. Thus, nailfold capillaroscopy and finger photoplethysmography can be used to perform an inexpensive, non-invasive and straightforward evaluation of endothelial dysfunction. Despite the current abundance of data on microcirculation disturbance, further research is required to determine the link between microvascular dysfunction, ischemia, fibrosis and prognosis, since these processes are treatable.

No conflict of interest is reported.

The article was received on 15/06/2021

REFERENCES

1. Ministry of Health of Russian Federation. Clinical Recommendation. Hypertrophic cardiomyopathy. I42.1/I42.2. 2020. Av. at: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_Kardiomiopatiya.pdf. [Russian: Министерство здравоохранения Российской Федерации. Клинические рекомендации. Гипертрофическая кардиомиопатия. I42.1/I42.2. 2020. Доступно на: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_Kardiomiopatiya.pdf]
2. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020;142(25):e533–57. DOI: 10.1161/CIR.0000000000000938
3. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW et al. Heart Disease and Stroke Statistics–2021 Update: A Report From the American Heart Association. Circulation. 2021;143(8):e254–743. DOI: 10.1161/CIR.0000000000000950
4. Bick AG, Flannick J, Ito K, Cheng S, Vasan RS, Parfenov MG et al. Burden of Rare Sarcomere Gene Variants in the Framingham and Jackson Heart Study Cohorts. The American Journal of Human Genetics. 2012;91(3):513–9. DOI: 10.1016/j.ajhg.2012.07.017
5. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D et al. Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights From the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation. 2018;138(14):1387–98. DOI: 10.1161/CIRCULATIONAHA.117.033200
6. Maron BJ, Maron MS, Maron BA, Loscalzo J. Moving Beyond the Sarcomere to Explain Heterogeneity in Hypertrophic Cardiomyopathy. Journal of the American College of Cardiology. 2019;73(15):1978–86. DOI: 10.1016/j.jacc.2019.01.061
7. Konst RE, Guzik TJ, Kaski J-C, Maas AHEM, Elias-Smale SE. The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions. Cardiovascular Research. 2020;116(4):817–28. DOI: 10.1093/cvr/cvaa009
8. Johansson B, Mörner S, Waldenström A, Stål P. Myocardial capillary supply is limited in hypertrophic cardiomyopathy: A morphological analysis. International Journal of Cardiology. 2008;126(2):252–7. DOI: 10.1016/j.ijcard.2007.04.003
9. Olivotto I, Girolami F, Sciagrà R, Ackerman MJ, Sotgia B, Bos JM et al. Microvascular Function Is Selectively Impaired in Patients With Hypertrophic Cardiomyopathy and Sarcomere Myofilament Gene Mutations. Journal of the American College of Cardiology. 2011;58(8):839–48. DOI: 10.1016/j.jacc.2011.05.018
10. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary Microvascular Dysfunction and Prognosis in Hypertrophic Cardiomyopathy. New England Journal of Medicine. 2003;349(11):1027–35. DOI: 10.1056/NEJMoa025050
11. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Annals of the Rheumatic Diseases. 2013;72(11):1747–55. DOI: 10.1136/annrheumdis-2013-204424
12. Ciaffi J, Ajasllari N, Mancarella L, Brusi V, Meliconi R, Ursini F. Nailfold capillaroscopy in common non-rheumatic conditions: A systematic review and applications for clinical practice. Microvascular Research. 2020;131:104036. DOI: 10.1016/j.mvr.2020.104036
13. Sirufo MM, Bassino EM, De Pietro F, Ginaldi L, De Martinis M. Nailfold capillaroscopy: Clinical practice in non-rheumatic conditions. Microvascular Research. 2021;134:104122. DOI: 10.1016/j.mvr.2020.104122
14. Safonova J.I., Kozhevnikova M.V., Danilogorskaya Yu.A., Zheleznykh E.A., Zektser V.Yu., Shchendrygina A.A. et al. Positive Effects of Perindopril on Microvascular Vessels in Patients With Chronic Heart Failure. Kardiologiia. 2020;60(8):65–70. [Russian: Сафонова Ю.И., Кожевникова М.В., Данилогорская Ю.А., Железных Е.А., Зекцер В.Ю., Щендрыгина А.А. и др. Положительное влияние периндоприла на сосуды микроциркуля-

ISSN 0022-9040. Kardiologiia. 2021;61(12). DOI: 10.18087/cardio.2021.12.n1718

торного русла у больных с хронической сердечной недостаточностью. Кардиология. 2020;60(8):65-70]. DOI: 10.18087/cardio.2020.8.n1216
15. Zhito A.V., Iusupova A.O., Kozhevnikova M.V., Shchendrygina A.A., Privalova E.V., Belenkov Yu.N. E-Selectin as a Marker of Endothelial Dysfunction in Patients with Coronary Artery Disease Including Those with Type 2 Diabetes Mellitus. Kardiologiia. 2020;60(4):24–30. [Russian: Жито А.В., Юсупова А.О., Кожевникова М.В., Щендрыгина А.А., Привалова Е.В., Беленков Ю.Н. Е-селектин как маркер дисфункции эндотелия у пациентов с ишемической болезнью сердца, в том числе в сочетании с сахарным диабетом 2-го типа. Кардиология. 2020;60(4):24-30]. DOI: 10.18087/cardio.2020.4.n1066
16. Fernlund E, Gyllenhammar T, Jablonowski R, Carlsson M, Larsson A, Ärnlöv J et al. Serum Biomarkers of Myocardial Remodeling and Coronary Dysfunction in Early Stages of Hypertrophic Cardiomyopathy in the Young. Pediatric Cardiology. 2017;38(4):853–63. DOI: 10.1007/s00246-017-1593-x
17. Laina A, Stellos K, Stamatelopoulos K. Vascular ageing: Underlying mechanisms and clinical implications. Experimental Gerontology. 2018;109:16–30. DOI: 10.1016/j.exger.2017.06.007
18. Dall'Olio L, Curti N, Remondini D, Safi Harb Y, Asselbergs FW, Castellani G et al. Prediction of vascular aging based on smartphone acquired PPG signals. Scientific Reports. 2020;10(1):19756. DOI: 10.1038/s41598-020-76816-6
19. Katunaric B, Cohen KE, Beyer AM, Gutterman DD, Freed JK. Sweat the small stuff: The human microvasculature and heart disease. Microcirculation. 2021;28(3):e12658. DOI: 10.1111/micc.12658
20. Sheikh AR, Difiore D, Rajendran S, Zeitz C, Beltrame J. 1346Laser doppler assessment of dermal microcirculatory endothelial function in patients with angina and non-obstructive coronary arteries. European Heart Journal. 2018;39(Suppl 1):1346. DOI: 10.1093/eurheartj/ehy565.1346
21. Zanatta E, Famoso G, Boscain F, Montisci R, Pigatto E, Polito P et al. Nailfold avascular score and coronary microvascular dysfunction in systemic sclerosis: A newsworthy association. Autoimmunity Reviews. 2019;18(2):177–83. DOI: 10.1016/j.autrev.2018.09.002
22. Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivotto I et al. Hypertrophic Cardiomyopathy Phenotype Revisited After 50 Years With Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology. 2009;54(3):220–8. DOI: 10.1016/j.jacc.2009.05.006
23. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: Pathologic evidence of myocardial ischemia. Human Pathology. 2000;31(8):988–98. DOI: 10.1053/hupa.2000.16659