From Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) to Chronic Coronary Syndrome: Clinical Diagnostic Use of Laser Doppler Flowmetry in Coronary Microvascular Dysfunction

Kristina Selthofer-Relatić
Marko Stupin
Ines Drenjančević
Ivica Bošnjak

Corresponding Author:
Kristina Selthofer-Relatić, e-mail: selthofer.relatic@gmail.com

Conflict of interest:
None declared

Patient:
Male, 40-year-old

Final Diagnosis:
Microvascular coronary artery disease

Symptoms:
Chest pain

Medication:
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Clinical Procedure:
Coronary angiography • echocardiography • laser Doppler flowmetry

Specialty:
Cardiology

Objective:
Unusual clinical course

Background:
MINOCA is defined as myocardial infarction with non-obstructive coronary changes, or the absence of atherosclerotic coronary plaques (less than 50%). The long-term prognosis of these patients is as poor as for those with obstructive coronary disease. Possibilities for treatment follow-up and improvement are still lacking. This case report provides a retrospective analysis of a case of MINOCA that transformed into chronic coronary syndrome (CCS).

Case Report:
A 40-year-old patient had acute coronary syndrome without atherosclerotic changes in the great epicardial coronary arteries, but with slow coronary flow in the left anterior descending coronary artery in 2011 and 2014. Two-dimensional transthoracic echocardiography showed no echocardiographic impairment of myocardial contractility. The comorbidities were visceral obesity, dyslipidemia, and smoking history. After the addition of a calcium channel blocker and trimetazidine to standard therapy, there were no anginal symptoms. In 2019, during a regular health check-up, contrast echocardiography showed a slow rinse of contrast in the apical and medial/distal anterolateral segment with reduced longitudinal strain in the same myocardial segments. Laser Doppler flowmetry (LDF) showed impaired microcirculatory function in the skin microcirculation.

Conclusions:
This case report highlights: 1) use of the non-invasive, inexpensive, and easy-to-use LDF technique for microcirculatory dysfunction confirmation; 2) follow-up of MINOCA to CCS transition; 3) visceral obesity as a risk factor for MINOCA and CCS; and 4) the role of trimetazidine in CCS.

MeSH Keywords:
Obesity, Abdominal • Microcirculation • Laser-Doppler Flowmetry • Acute Coronary Syndrome

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Background

Myocardial perfusion is tightly regulated by dynamic changes in the epicardial and intramyocardial coronary vasculature and microcirculation. During resting conditions, 75% of the oxygen is extracted from the blood by the myocardium. Any increase in oxygen consumption/cardiac metabolism leads to increased oxygen demand, which can only be matched by an increase in myocardial blood flow (MBF) [1]. In this complex process, coronary microcirculation (CM), with precisely regulated and interconnected physiological processes, has a key role in matching local blood flow to myocardial metabolic demands [2]. CM changes include mechanisms connected with vascular, extravascular, and vasostructural changes in responses to metabolic, neural, and mechanical factors. Standard cardiovascular comorbidities and risk factors such as dyslipidaemia, diabetes mellitus type II and arterial hypertension are associated with epicardial coronary artery atherosclerosis and/or with CM dysfunction, with incompletely understood underlying mechanisms [2,3]. In addition to standard risk factors for coronary atherosclerosis and CM dysfunction, obesity and aging should be considered as parts of the clinical presentation and aspects for further treatment [4]. Cardiac visceral obesity is a special phenotype that plays the most important role, leading to complex pathophysiology of the coronary artery, especially functional changes of microvascular arteries and cardiac steatosis development [5]. The main pathological characteristics of CM dysfunction in various forms of cardiomyopathies are genetic factors, immunology, systemic processes, inflammation, and aging [6].

There is currently a critical missing link between the use of most appropriate diagnostic tests of complete (epicardial and microvascular) coronary artery function, therapy, and health outcomes of patients with MINOCA [7]. Morphologic and functional changes of the great epicardial coronary arteries cannot be detected solely with coronary angiography (CA) because of low interobserver agreement and limitations of the assessment of myocardial ischemia in a variety of settings such as intermediate, eccentric, or diffuse coronary stenosis, or in angiographically normal or mildly diseased coronary arteries in patients with angina or myocardial infarction [8,9]. Invasive methods for coronary blood flow and reserve (CFR) measurement like Doppler-velocity and thermodilution coronary blood flow measurement with induced hyperemia (papaverine, nitroglycerine, or adenosine) and microvascular resistance have their own limitations, such as estimation of vessel cross-sectional area or internal volume, the need for surgeon experience, and adverse effects of the drugs [9]. Positron emission tomography (PET) is the most studied non-invasive imaging modality for the quantification of MBF. It offers enhanced image quality and better spatial resolution, and it results in lower radiation exposure. However, the relatively high cost associated with PET imaging means that it has limited clinical application because of the requirement for either onsite/nearby cyclotrons or expensive generators [1]. Other methods that could serve as good diagnostic tools for obstructive and non-obstructive coronary disease visualisation and MBF reserve are adenosine stress magnetic resonance imaging (MRI) with measurement of fractional flow reserve [10], and transthoracic Doppler echocardiographic CFR measurement with adenosine or dipyridamole in the left anterior descending (LAD) coronary artery flow [1,11]. Further studies are needed to assess whether non-invasive and invasive quantitative assessment of CFR can be applied for monitoring disease progression in these patient populations and to evaluate the clinical impact of early diagnosis and therapy facilitated by non-invasive and invasive coronary flow quantification [1,12]. There is also still a lack of adequate biomarkers for microcirculatory dysfunction detection and follow-up [13,14]. Biomarkers of endothelial cell activation are very diverse, ranging from biochemical/metabolic to functional biomarkers [15].

Laser Doppler flowmetry (LDF) is a technique enabling the monitoring of skin microvascular blood flow that reflects responses in other vascular beds. It is a non-invasive, easy-to-use, and cost-effective technique to assess endothelial microvascular function. It offers the unique opportunity to test various pathways of vascular response [16,17].

Functional and morphologic micro- and macro-vascular changes in coronary arteries lead to chronic multidimensional deformation, without good diagnostic tools for detection. In this case report, LDF was used as a method of assessment of subclinical levels of microcirculatory cardiac disease that started with acute coronary syndrome/repeated MINOCA, with a transition to chronic coronary syndrome [2,13,14,17–19].

Case Report

First hospitalization – MINOCA

In 2011, a 40-year-old, obese male patient with a body mass index (BMI) of 34.5 kg/m² (visceral type), who was also a smoker (10 cigarettes per day for 10 years), experienced chest pain which spread into his left arm after physical therapy for a traumatic injury and surgery on the left clavicle. He was admitted to the coronary unit because of acute coronary syndrome (ACS) with an elevated troponin level. There were slight electrocardiographic (ECG) changes during chest pain, shown as the slow depression of the ST segment in anterolateral leads (Figure 1). The patient was normotensive (110/70 mmHg) and normofrequent (67 beats per min), without other pathological physical findings. Two-dimensional transthoracic echocardiography (2D TTE) showed regular segmental and global myocardial...
contractility. The TIMI risk score was 3. CA showed slow coronary flow of the LAD coronary artery, without atherosclerotic plaques (intravascular ultrasound was not available in 2011) (Figure 2A). An additional comorbidity was dyslipidaemia (total cholesterol level of 8.03 mmol/L, LDL of 6.07 mmol/L). There were no significant data from family and earlier personal history. He was discharged with recommendations for dietary and lifestyle modifications, weight reduction, and physical activity. In addition, he was prescribed nitrates with prolonged activity, bisoprolol, acetylsalicylic acid, rosvastatin, ramipril,

Figure 1. Electrocardiographic (ECG) changes during chest pain and at rest: (A) Slight depression of ST-T* segment in anterolateral leads in the first hospitalization. (B) Without ST-T* segmental changes in second hospitalization. * ST-T segment – the part of ECG record where the ischemic changes are manifested.

Figure 2. Coronary angiography performed during hospitalizations because of acute coronary syndrome – both times slow rinse of contrast, without atherosclerotic plaques: (A) Hospitalization in 2011. (B) Hospitalization in 2014.
and polyunsaturated fatty acids. Most of the time he felt well, but sometimes he had dyspnea during physical activity. He reduced his body weight by 10 kg, quit smoking, and stopped taking nitrates because of headaches.

Second hospitalization – MINOCA

In 2014, at the age of 42, he was again admitted to the coronary unit because of repeated ACS. He had prolonged chest pain after physical activity, without significant ECG changes (Figure 1B), and with an increased troponin level. CA was performed again (MSCT coronaryography was not available in 2014), and the coronary flow was again slow in all the great epicardial coronary arteries (Figure 2B). 2D TTE again found no segmental contractile impairment, with normal global systolic function. He had a normal NTproBNP level, total cholesterol was 6.0, and LDL was 3.07 mmol/L. He was discharged with the same dietary lifestyle recommendations and therapy as 2 years ago. Nitrates were replaced with trimetazidine, ramipril into a calcium channel blocker, and the dose of rosuvastatin was increased.

Both times he was discharged from the hospital with a diagnosis of ACS with microcirculatory dysfunction (slow coronary flow). Antiphospholipid syndrome and thrombophilia disorders were excluded [12]. He did an exercise test, with good cardiac metabolic capacity, after hospitalization. After 2014, he did not have symptoms of angina, he had reduced his body weight by an additional 5 kg (BMI 30 kg/m²), he achieved target lipid levels, and he took his medication regularly.

Regular health check-up visit – CCS

At the end of 2019 at a regular health visit, contrast 2D TTE was performed because of bad image quality. A slow rinse of contrast in apical and distal anterolateral segment of left ventricular cavity; (B) strain 2D TTE showing reduced longitudinal strain in left ventricular apical and medial/distal anterolateral segment. of LV (Figure 3B). Invasive diagnostic CA was not repeated because there was no clinical indication: the patient was asymptomatic, he had reduced his risk factors (achieved target lipid levels, reduced body weight, quit smoking) and twice had “clean” epicardial coronary arteries without atherosclerotic changes.

Laser Doppler flowmetry measurement

To confirm the microcirculatory dysfunction, laser Doppler flowmetry (LDF) was performed at rest. LDF is a commonly used, non-invasive technique for the assessment of peripheral microvascular function [20,21]. To assess an overall change in peripheral (forearm) microvascular function, a post-occlusive reactive hyperaemia (PORH) test was performed by inducing vascular occlusion of the brachial artery. LDF measurements were performed in a quiet and temperature-controlled room (mean±SD temperature=23.5±0.5°C). Data collection started after 30 min of acclimatization during which subjects were resting in a supine position to avoid temperature-related and sympathetic-related changes of blood flow. All LDF measurements were performed by a single well-trained and experienced operator. LDF measurements were taken before, during, and after the release of 1-min vascular occlusion. Time-domain analysis of LDF data was used. The microcirculatory blood flow was expressed in arbitrary perfusion units (PU), values of blood flow were averaged over a specific time period (1 min), and were determined by software calculating the area under the curve (AUC) during baseline flow (AUC B), occlusion (AUC O), and reperfusion (AUC R). The results are expressed as the difference between the percentage of flow change during reperfusion [R%=(AUC R/AUC B)×100] and occlusion [O%=(AUC O/AUC B)×100] in relation to the baseline (R−O% increase). We compared, both numerically and visually, the PORH test of the patient with the PORH test of a healthy young individual. The microcirculatory flow was expressed in arbitrary perfusion units (PU), values of blood flow were averaged over a specific time period (1 min), and were determined by software calculating the area under the curve (AUC) during baseline flow (AUC B), occlusion (AUC O), and reperfusion (AUC R). The results are expressed as the difference between the percentage of flow change during reperfusion [R%=(AUC R/AUC B)×100] and occlusion [O%=(AUC O/AUC B)×100] in relation to the baseline (R−O% increase). We compared, both numerically and visually, the PORH test of the patient with the PORH test of a healthy young individual. The R-O percentage in the patient at rest was 65% and was 235% in the healthy young subject, indicating that the young, healthy individual had 3.6 times better skin microvascular reactivity in response to vascular occlusion than the patient. Furthermore, the maximal value of

Regular health check-up visit – CCS

At the end of 2019 at a regular health visit, contrast 2D TTE was performed because of bad image quality. A slow rinse of contrast in apical and distal anterolateral segment of left ventricular cavity; (B) strain 2D TTE showing reduced longitudinal strain in the same segments

![Figure 3. Two-dimensional transthoracic echocardiography (2D TTE) performed in 2019: (A) Contrast 2D TTE showing slow rinse of contrast in apical and distal anterolateral segment of left ventricular cavity; (B) strain 2D TTE showing reduced longitudinal strain in left ventricular apical and medial/distal anterolateral segment.](image-url)
blood flow achieved in the patient during hyperemia was 42 PU, and in the healthy subject it was 121 PU, which also represents an almost 3 times higher microvascular response in the healthy subject than in the patient. When visually comparing the shape of the microvascular reperfusion curve, it was evident that a healthy individual reaches a sharp peak very quickly during reperfusion, after which the flow is rapidly reduced to basal values. In addition to being characterized by significantly lower flow values in general, the reperfusion curve in the patient was much broader, with a longer time required for maximum reperfusion to occur, as well as for the flow to return to approximately basal values (Figure 4).

Discussion

The coronary microcirculation is far more extensive than the epicardial coronary vasculature, but adequate imaging techniques for use in everyday clinical practice are lacking, which limits the ability to detect abnormalities. Evidence indicates that both structural and functional coronary microvascular abnormalities can lead to myocardial ischemia, often comparable to atherosclerotic obstructive coronary artery disease. Impaired arteriole vasodilatation and a marked increase in coronary microvascular resistance can impair coronary blood flow and trigger anginal symptoms in acute and chronic conditions,
with ischemic ECG changes and myocardial perfusion defects, and lead to left ventricular dysfunction in patients who otherwise have patent epicardial coronary arteries [14,22]. These patients have a poor prognosis, with higher rates of hospitalization and increased rates of adverse cardiovascular events (including myocardial infarction, congestive heart failure, and sudden cardiac death) [23].

According to the latest research and MINOCA recommendations, these patients can be diagnosed according to a coronary angiography-derived morphologic and functional assessment in the absence of significant obstructive stenosis [14], but there are still no adequate tests for microvascular change detection. The LDF technique is non-invasive, easy-to-perform, and cost-effective, but it is not yet approved for clinical practice. Khan et al. [24] demonstrated that peripheral measurements of skin blood flow with LDF are representative of generalized microvascular function, including that of the coronary circulation in healthy subjects. In an experimental animal study, von Ahn et al. [25] showed that LDF can present adequate measurement of myocardial perfusion in an arrested porcine heart [25]. With the LDF technique, Yamamoto-Suganuma et al. [26] showed that the PORH index in diabetic patients may be the most sensitive indicator of micro- and macrovascular disease. Kruger et al. [27] compared LDF results to conventional risk factors for endothelial dysfunction in end-stage renal disease and showed that patients with abnormal LDF parameters have increased cardiovascular mortality and had risk assessments (Framingham, Cardiorisk, C reactive protein, and homocysteine) similar to those with unimpaired LDF tracings. The researchers concluded that LDF parameters of microvascular reactivity offer a sensitive way to test for endothelial dysfunction, which may improve cardiovascular risk assessment through incorporation into the Framingham or Cardiorisk algorithm. Papadogeorgos et al. [28] found severely impaired skin microvascular reactivity in diabetic patients with acute coronary syndrome, with the conclusion that diabetes mellitus has a major influence on microvascular dysfunction. This conclusion agrees with our results. In our case, repeated acute coronary syndrome in an obese patient caused chronic microvascular coronary disease; therefore, obesity is a major risk factor for microvascular dysfunction [3]. Azman-Juvan et al. [29] came to the important conclusion that reduced microvascular reactivity can occur after acute myocardial infarction as a result of an activated neurohumoral system.

In the present study, after 9 years of follow-up, microvascular impairment was confirmed in a patient with recurrent MINOCA after using the LDF technique for diagnosing a chronic condition. Our literature search found no studies on the use of the LDF technique in chronic coronary syndrome diagnosis. This case highlights the need for an easy-to-use and non-invasive technique for use in everyday clinical practice for coronary microvascular dysfunction detection. Also, this case report confirms the clinical benefit of trimetazidine administration in chronic coronary syndrome as recommended in recent guidelines on CCS [14]. The limitation of our study is the need for LDF technique validation and comparison with PET and cardiac stress MRI, although these techniques also have some clinical limitations in diagnosing CM dysfunction.

Conclusions

This case presentation raises several clinical and scientific questions about MINOCA and chronic coronary syndrome that highlight the need for better understanding of coronary microvascular pathophysiology, as well as the need for biomarkers and easier-to-use diagnostic tools for coronary microvascular disease detection. We present the use of the non-invasive, inexpensive, and easy-to-use LDF technique for detection of microcirculatory dysfunction, provide insight into coronary microvascular pathophysiology, with obesity as a risk factor for coronary microvascular disease, discuss the clinical use of trimetazidine in chronic coronary syndrome, and describe treatment follow-up.

Department and Institution where work was done

Department of Heart and Vascular Medicine, University Hospital Centre Osijek; Department of Physiology and Immunology, Faculty of Medicine Osijek, University Josip Juraj Strossmayer Osijek, Osijek, Croatia

Conflict of interest

None.
