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# CONTEMPORARY DIAGNOSIS OF CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

# SAVREMENA DIJAGNOSTIKA DISFUNKCIJE KORONARNE MIKROCIRKULACIJE KOD BOLESNIKA SA AKUTNIM INFARKTOM MIOKARDA

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## Abstract

Coronary microvascular dysfunction (CMD) is encountered in up to 50% of patients presenting with ST-segment elevation acute myocardial infarction (STEMI) and treated with primary percutaneous coronary intervention (PCI). The current reference standard to diagnose microvascular injury in this setting is cardiac magnetic resonance (CMR) imaging. The extent of microvascular injury, termed microvascular obstruction (MVO) on CMR, increases over time after recanalization of the infarct-related artery (IRA), until it reaches its peak around day 3, and it subsides by day 10. Most of the current research evaluated MVO on CMR on days 2 - 7 after primary PCI, and showed its association with cardiac death and heart failure independently of the infarct size. As microvascular injury becomes a new therapeutic target in STEMI, given the plateauing mortality curves despite widespread access to timely reperfusion, the question of early diagnosis of CMD grows in importance. To this end, invasive coronary microcirculation assessment in the recanalized IRA immediately after primary PCI, has been tested in terms of its association with MVO and infarct size on CMR, as well as its ability to predict adverse clinical outcomes. Both invasive thermodilution- and Doppler wire-derived indices of microvascular resistance were successful in stratifying patients according to the risk of cardiac death and heart failure in the follow-up. Recently, a coronary angiography-based method, which unlike thermodilution and Doppler derives indices of microvascular resistance from a computational dynamics software and does not require additional wiring of the epicardial artery, has demonstrated the ability to predict adverse clinical outcomes. The described diagnostic tools for stratification of patients according to the risk of CMD and consequently impaired prognosis after STEMI, still remain a subject of on-going research, in terms of both the most relevant cut offs for different indices and the optimal time point of assessment.

**Keywords:**
coronary microcirculation, acute myocardial infarction



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## Sažetak

Disfunkcija koronarne mikrocirkulacije dokumentovana je kod oko 50% bolesnika sa akutnim infarktom miokarda sa elevacijom ST-segmenta, koji su lečeni primarnom perkutanom koronarnom intervencijom (PCI). Prihvaćeni standard za dijagnozu povrede koronarne mikrocirkulacije predstavlja kardijalna magnentna rezonanca. Stepen povrede mikrocirkulacije na magnetnoj rezonanci, koji se naziva mikrovaskularna opstrukcija (MVO), povećava se tokom prvih nekoliko dana, dok ne dostigne vrhunac oko trećeg dana nakon infarkta, i zatim se smanjuje do desetog dana. U najvećem broju studija magnetna rezonanca rađena je od drugog do sedmog dana nakon primarne PCI, a prisustvo MVO bilo je povezano sa povećanim rizikom od smrti i srčane slabosti, nezavisno od veličine infarkta. Kako mikrovaskularna povreda postaje terapijski cilj kod bolesnika sa infarktom miokarda, pitanje pravovremene dijagnoze postaje relevantno sa stanovištva rane stratifikacije bolesnika i iniciranja terapije. U ovu svrhu, invazivne metode za procenu funkcije koronarne mikrocirkualcije, uključujući termodilucionu i dopler metodu, testirani su u pogledu njihove povezanosti sa MVO i veličinom infarkta na magnetnoj rezonanci, te mogućnosti da predvide kliničke ishode. Obe ove dijagnostičke metode, koje podrazumevaju plasiranje intrakoronarne žice u infarktnu arteriju nakon rekanalizacije, stratifikovale su uspešno bolesnike na kraju primarne PCI procedure prema riziku od smrti i nastanka srčane slabosti tokom praćenja. Nova istraživanja pokazala su da je procena funkcije koronarne mikrocirkulacije u sali za kateterizaciju pouzdana i putem softvera za analizu dinamike fluida, koji, na osnovu samo angiografske slike, i bez plasiranja intrakoronarne žice, računa indekse mikrovaskularne rezistencije. Opisane dijagnostičke metode i dalje su predmet istraživanja, gde je potrebno precizirati granične vrednosti i optimalno vreme merenja.

**Ključne reči:**
koronarna mikrocirkulacija, akutni infarkt miokarda

## Introduction

In patients with acute ST-segment elevation myocardial infarction (STEMI), current guidelines recommend a strategy of immediate referral to the nearest catheterization laboratory with an aim of providing timely mechanical recanalization of the occluded infarct-related coronary artery (IRA) by means of primary percutaneous coronary intervention (PCI) (1). Despite the widespread establishment of primary PCI networks offering timely reperfusion to patients with an acute myocardial infarction (AMI), mortality rates have plateaued at around 11% to 13% at 1 year across different real-world registries over the last decade (2,3), and the incidence of heart failure was reported to be up to 20% following an anterior wall infarction (4,5). Hence, the focus of the ongoing research has been how to further improve prognosis of patients with myocardial infarction, beyond the timely reperfusion, and coronary microcirculation has been identified as the new therapeutic target (5-7). The concept of inadequate reperfusion at the level of microcirculation, despite the recanalization of a major, epicardial artery, has entered into clinical arena as a no-reflow phenomenon, whereby it was early recognized that microvascular dysfunction increases the risk of adverse left ventricular remodeling (8). As the diagnostic capability to detect myocardial under-perfusion at the microvascular level has evolved, it became clear that angiographic measures of no-reflow, such as Thrombolysis In Myocardial Infarction (TIMI) flow grade, TIMI frame count, TIMI perfusion grade and myocardial blush grade, may underestimate no-reflow, as compared with contrast echocardiography and cardiac magnetic resonance (CMR) imaging (9). Early clinical data demonstrated impaired microvascular function on myocardial contrast echocardiography in up to 50% of patients with AMI and timely and successful epicardial flow restoration (10). Contemporary imaging protocols, which are CMR-based, also find impairment of coronary microcirculation in 50 - 60% of reperfused AMI patients (11). Most of the studied imaging protocols take place within 2-7 days after primary PCI. Therefore, if a therapeutic intervention targeting microvascular dysfunction at an early stage of its development post-reperfusion is envisaged, diagnostic tools in the catheterization laboratory would be needed. To this end, invasive Doppler wire- and thermodilution-derived methods to assess coronary flow velocity and to estimate coronary microvascular function after primary PCI, have been shown to correlate well with CMR-based microvascular injury and infarct size (12).

The aim of this review article is to address the current status in the diagnosis of coronary microvascular dysfunction (CMD) in patients presenting with AMI, while describing both invasive and non-invasive techniques. This is clinically important as the efforts to develop tailored therapeutic approaches that would target coronary microcirculation in patients with AMI may largely depend on accurate and timely identification of patients under high risk of CMD.

## Microvascular obstruction on cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) is at present considered to be the standard reference test for detection of coronary microvascular injury in patients with STEMI (5,13). Contrast enhancement provides an opportunity to study the distribution of an intravenously injected contrast agent (e.g. gadolinium) within different areas of myocardium. Hypointense, dark zones within hyper enhanced areas of infarcted myocardium were termed microvascular obstruction (MVO), as this term signified an impediment to contrast uptake within the infarct territory (14). Microvascular obstruction can be detected after 1 minute (early) or 15 minutes (late) of gadolinium injection. Whereas early MVO is sensitive to small changes in microvascular function, late MVO is a surrogate of advanced microvascular injury and is associated with clinical outcomes (13). A comprehensive CMR assessment in patients after STEMI showed that both infarct size and MVO are predictive of future cardiovascular events, including death and heart failure, in both observational analysis (15) and a pooled data set from randomized clinical trials (16). Importantly, although there seems to be an incremental increase in the risk of death and heart failure with the greater extent of MVO, mere presence of any extent of MVO (i.e. analyzed as a dichotomous variable) also independently predisposes AMI patients to a higher risk of death and heart failure during 5 years of follow-up (17). Since MVO and infarct size correlate with each other, it was important to document that MVO is associated with adverse prognosis after AMI, independently of infarct size (11,18), thus making it an independent therapeutic target, distinct from infarct size, as pathophysiology of the latter may also entail factors such as ischemia and reperfusion injury at the level of cardiomyocytes. Of note, intramyocardial hemorrhage (IMH) has been reported to concur with MVO in some patients, and to provide additional prognostic information beyond infarct size and MVO (19). Importantly, IMH appears to be detected only in the presence of MVO, whereas MVO is not always associated with IMH (5). The pathophysiological link between MVO and IMH is thought to be bidirectional (5). The damage to the microvasculature predisposes to erythrocyte accumulation in the intramyocardial space in some patients. The other way around, IMH exerts extravascular pressure on the microcirculation, thus aggravating MVO.

In terms of the practical applicability to diagnose microvascular injury with CMR in patients with AMI, there are at least the following two open issues, apart from infrastructural constraints hampering widespread CMR use for this indication. First, the timing of CMR acquisition. The described evidence base refers to CMR being done on days 3 - 7 after primary PCI (13). However, temporal evaluations by CMR showed a dynamic progression of hemorrhage and edema up to day 3 and subsequent regression until day 10 (13,20). Second, the MVO cut off value. Different studies associated different levels of MVO with adverse clinical outcomes, ranging from any MVO to ≥ 2.6% of the LV (17). In order to make the diagnosis of MVO actionable, future research may need to address more closely both points, standardizing the optimal timing and cut off value of CMR-derived microvascular injury.

## Invasive assessment of coronary microcirculation

Invasive, intracoronary wire-derived indices of microvascular function have been shown to correlate with the CMR-assessed MVO and infarct size. The benefit of invasive microcirculation assessment is its immediate availability in the catheterization laboratory, following primary PCI, thus making early therapeutic intervention possible. There are two currently available invasive methods to assess coronary flow, by measuring peak velocity with a Doppler-tipped wire (Doppler method) (21) or by estimating mean transit time (Tmn) of injected saline by calculating temperature difference across the coronary tree with a thermistor-equipped wire (thermodilution method) (22), both of which, together with the simultaneous distal coronary pressure measurement, quantify coronary flow reserve and the degree of microvascular resistance.

## Coronary flow reserve

The ability of baseline coronary flow to increase under the conditions of stress or upon pharmacological stimulation (e.g. with intracoronary injections of adenosine or papaverine), is termed coronary flow reserve (CFR). Both Doppler and thermodilution method have been used to invasively asses CFR in patients with AMI. Doppler-derived CFR correlated better with the gold standard [$^{15}$O] $H_2O$ PET-derived CFR (23) and most of the early evidence associating low CFR in the recanalized artery post primary PCI with adverse LV remodeling after STEMI derives from the studies which utilized intracoronary Doppler wire measurements (24). Moreover, Doppler wire-derived CFR ≤ 1.3 immediately following reperfusion in the IRA was associated with the risk of heart failure (25). In another study, CFR < 1.5 was associated with a trend towards higher 10-years mortality (26). More recent thermodilution data associated post-primary PCI CFR ≤ 1.6 in the infarct-related artery with the presence of MVO on CMR (27).

The described association of low CFR with adverse LV remodeling after STEMI notwithstanding, comparative analyses showed a stronger association of indices of microvascular resistance with both MVO and IMH, when contrasted with CFR (28,29). This was possibly due to a variability in baseline coronary flow depending on heart rate, blood pressure and LV contractility, which ultimately may impact CFR values (30). Moreover, by principle of its calculation, CFR simultaneously takes into account flow impedance both at the epicardial and at the microvascular level, thus being impacted by epicardial disease.

## Index of microcirculatory resistance

Thermodilution-derived index of microcirculatory resistance (IMR) is calculated as mean transit time multiplied by distal coronary pressure under hyperemic conditions. Therefore, it is a measure of microvascular function, beyond epicardial conductance, and is to a lesser degree affected by changes in coronary hemodynamics (31, 32). An analysis pooling observational data from 6 studies that included 288 patients showed close association of IMR > 41 in the IRA following primary PCI with CMR-assessed MVO (33). This coincides with the clinical data suggesting an increased risk of death of heart failure over 2.8 years of follow-up after STEMI, if IMR > 40 was recorded in the IRA at the end of primary PCI (34). More recently, the IMR cut off > 40, as a tool do diagnose poor functional status of coronary microcirculation following primary PCI, was associated with MVO and large infarct size on CMR, as well as with death or heart failure over 1 year follow-up (35). Since microvascular injury is of multifactorial and dynamic nature, there is an expected discordance between both assessments performed at different time points after primary PCI and different modalities to diagnose microvascular injury. A discordance in about a third of patients was noted between IMR (with a cut off > 40 and measured immediately after primary PCI) and MVO on CMR (measured on day 2 after primary PCI) (36). If MVO on CMR was paired with invasive IMR > 40, it predisposed patients to a marked increase in infarct size compared to those with MVO on CMR but IMR < 40 (36). These data showed the complementarity of the early invasive and the later CMR-based method to diagnose microvascular injury after STEMI, highlighting the fact that different diagnostic tools likely target different pathophysiological axes (37). However, in terms of practical applicability to early stratify patients according to the risk of CMD and therefore guide adjunctive therapies after STEMI, the immediately post- primary PCI available IMR seems to provide actionable information (38). This notion was reaffirmed by the recent evidence from the hitherto largest pooled analysis of 6 studies with individual-level data from 1265 patients, associating post-primary PCI IMR with both heart failure and cardiac death over 5 years follow-up (39). Although IMR cut off of 40 was shown to successfully discriminate between patients with and without cardiac events, the optimal threshold to predict cardiac death was IMR > 70 (39).

Apart from the index of microcirculatory resistance for which the evidence base is the strongest, several other thermodilution-derived indices of microcirculatory function have been described (7). Resistive reserve ratio (RRR), which quantifies the difference in microcirculatory resistance at baseline (resting distal coronary pressure multiplied by resting Tmn) and during hyperemia (i.e. IMR), was shown to predict MVO and infarct size on CMR, as well as heart failure after STEMI (35, 40). Temperature derived recovery time (TRT), represents the time needed from the nadir of the temperature curve during hyperemia until the temperature recovers at 20% from the baseline. It was associated with MVO on CMR following STEMI, independently of other thermodilution-derived indices such as IMR, CFR and thermodilution waveform (41). In addition, TRT was associated with death and heart failure over 5 years of follow-up (41). A wide or bimodal pattern of thermodilution curves during hyperemia have also been recognized as a predictor of adverse events after STEMI despite epicardial flow restoration in the infarct-related artery (42).

Of note, all of the above described thermodilution-derived parameters rely on repeated manual bolus intracoronary injection of saline through a guiding catheter, which inherently introduces uncontrolled variability at least in terms of the position of the guiding catheter and the forward pushing force exerted by the operator. A continuous thermodilution technique to measure absolute coronary flow, which is based on saline infusion through a dedicated intracoronary microcatheter, has been recently validated against the gold standard [$^{15}$O] $H_2O$ PET-derived CFR (43). So obtained absolute flow can then be used, together with distal coronary pressure, to calculate microvascular resistance. However, the prospective investigation of this method to assess coronary microcirculation in patients with AMI is still pending.

## Hyperemic microvascular resistance

Unlike the bolus thermodilution method, which estimates coronary flow based on temperature difference following saline injection/infusion, a Doppler-equipped intracoronary guidewire can be used to directly measure coronary flow velocity by the Doppler method. Hyperemic microvascular resistance (HMR) is calculated by dividing distal coronary pressure by average peak velocity (APV), both measured by the Doppler wire during hyperemia. The correlation between HMR and IMR is modest (44). Hyperemic microvascular resistance obtained at the end of primary PCI, was associated with both the occurrence of MVO and adverse clinical outcomes such as death and heart failure over 8 years after STEMI, with the corresponding cut off values of 2.5 mmHg/cm/s and 2.8 mm Hg/cm/s, respectively (45, 46).

Further to HMR, simultaneous recording of the distal coronary pressure and flow velocity by the Doppler wire has been used to generate additional indices of microvascular function, such as instantaneous hyperemic diastolic flow velocity-pressure slope (IHDVPS) and pressure at zero flow (PzF) (30). Whereas both IHVDPS and PzF were associated with structural damage to coronary microcirculation, such as rarefication of capillaries and microvascular lumen obliteration (47), PzF has been identified as predictor of CMR-based MVO (46). Pressure at zero flow is obtained from a regression line that relates pressure (x-axis) with flow velocity (y-axis) from the Doppler wire measurement. It gives a hypothetical point where this line would intersect the x-axis, thus amounting to a distal coronary pressure at which coronary flow would cease (30). In other words, PzF should in addition to impaired

vasoreactivity also account for extravascular compression as impedance to coronary flow. This may explain the results of a comparative analysis, which showed better capability of PzF (AUC = 0.94) vs. HMR (AUC = 0.74) and IMR (AUC = 0.54), to predict large infarct size (≥ 24% of the left ventricle) (48). The PzF cut off was > 42 mm Hg to predict infarct size ≥ 24% of the LV, which by itself was found to predispose to higher mortality (16).

## Coronary angiography-derived index of microvascular resistance

Recently, computational fluid dynamics analysis software were introduced to estimate pressure and flow gradient across the epicardial artery, thus opening a window of opportunity for producing angiography-based surrogates of wire-derived indices, which had previously been associated with clinical outcomes, such as fractional flow reserve (FFR) and index of microcirculatory resistance (49). In the setting of STEMI, coronary angiography-derived index of microcirculatory resistance (Angio-IMR) measured in the recanalized IRA at the end of primary PCI, was shown to correlate well with its invasive counterpart, i.e. IMR measured in the same vessel and at the same time point (r = 0.778) (50). Moreover, in all patients with invasive IMR > 40, angio-IMR was found to be above that cut point as well, and angio-IMR > 40 was associated with cardiac death or heart failure during 10 years of follow-up (50).

## Transthoracic Doppler echocardiography-derived coronary flow reserve

Transthoracic Doppler echocardiography (TTDE) has been used to estimate the flow in the LAD artery at baseline and under conditions of hyperemia, thus obtaining TTDE-derived CFR, which correlated well with the CFR values obtained by the established Doppler wire-based method (51). In patients with AMI, several studies showed the ability of TTDE-derived indices of microvascular function, such as CFR, reversal of systolic flow and diastolic deceleration time to predict adverse LV remodeling or perfusion defects on SPECT (52-54). However, contemporary comparative studies evaluating TTDE-derived CFR against Doppler wire-based indices of microvascular function with the state-of-the-art assessment of infarct size on CMR are lacking.

## Conclusion

The standard reference for the diagnosis of microvascular injury after STEMI is the contrast enhanced cardiac magnetic resonance imaging. In order to obtain early information on the risk of microvascular injury, invasive techniques in the catheterization laboratory are used to assess microvascular resistance in the recanalized infarct-related artery, which include thermodilution- and Doppler-based methods utilizing an intracoronary guidewire, or more recently coronary angiography-derived computational fluid analysis. Invasive methods have been linked to

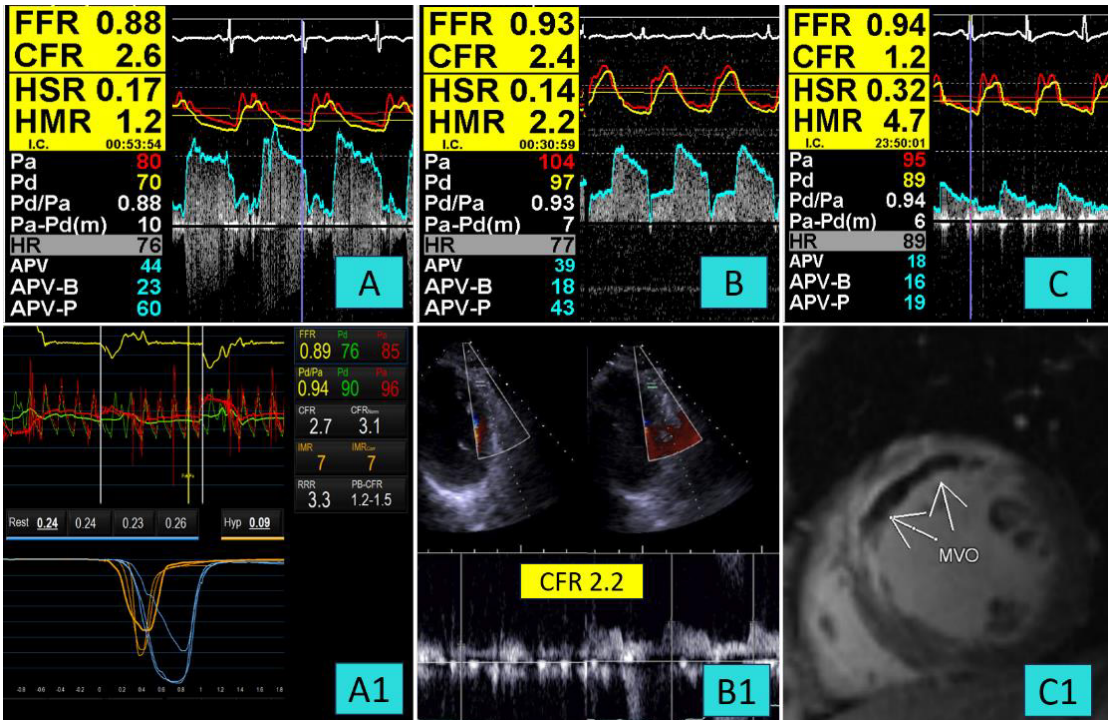


**Figure 1.** Different diagnostic tools to detect microvascular injury in patients with acute myocardial infarction

Doppler wire-derived coronary flow reserve (CFR) of 2.6 and hyperemic microvascular resistance (HMR) of 1.2 on day 4 after primary PCI (Panel A), with corresponding values of CFR of 2.7 and IMR of 7 derived by thermodilution in the same patient (Panel A1). Doppler wire-derived CFR of 2.4 (Panel B) coinciding with the transthoracic doppler echocardiography (TTDE)-derived CFR of 2.2 in the same patient (Panel B1). Doppler wire-derived HMR of 4.7 indicating poor functional status of coronary microcirculation after primary PCI (Panel C) with the corresponding image of extensive microvascular obstruction (MVO) on cardiac magnetic resonance (CMR) imaging in the same patient (Panel C1)

both microvascular injury on CMR and to clinical outcomes such as cardiac death and heart failure after STEMI, and can therefore be used to early stratify patients treated with primary PCI according to the residual risk of adverse events despite timely epicardial coronary flow restoration. Although described diagnostic tools are related to each other (**figure 1**), the multifactorial and dynamic nature of microvascular injury mandates further research to define optimal time point of assessment and appropriate cut off values to describe a clinically relevant CMD with an outlook to finding appropriate and timely treatment.

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