

# Perfusion cardiovascular magnetic resonance as the first-line technique in patients with stable chest pain

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## KEY WORDS

cardiovascular magnetic resonance, coronary artery disease, myocardial perfusion, perfusion cardiovascular magnetic resonance, stable chest pain

## ABSTRACT

Perfusion imaging with cardiovascular magnetic resonance is a noninvasive test free of ionizing radiation recommended by the latest European Society of Cardiology guidelines as one of the functional tests for coronary artery disease (CAD) detection. It has been demonstrated in numerous studies that perfusion imaging with cardiovascular magnetic resonance is highly accurate, provide strong prognostic data, and reduce the number of unnecessary invasive angiographies in patients with stable chest pain. Implementation of this method as the first-line technique in patients with stable chest pain provides an important refinement of the current concept for the assessment of CAD and in a unique way extends the diagnostic workup beyond simply ruling in or out myocardial ischemia.

**Introduction** According to the 2019 European Society of Cardiology (ESC) guidelines, stable chest pain is one of the 6 most frequently encountered clinical scenarios of chronic coronary syndromes (CCS).<sup>1</sup> However, the high rate of negative invasive coronary angiographies (ICAs) among patients with suspected coronary artery disease (CAD) demonstrates that an approach limited to ruling in or out CAD is insufficient.<sup>2</sup> Thus, evaluation of a patient with stable chest pain should go beyond CAD assessment and instead of simply answering the question whether the patient has CAD or not, should rather provide information on the cause of patient's symptoms, the best therapeutic strategy, and finally, the patient's modifiable risk factors. Only then, the patient's prognosis can be improved, and their individual optimal therapy can be guided.

Perfusion imaging with cardiovascular magnetic resonance (perfusion-CMR) is a noninvasive test free of ionizing radiation, recommended by the latest ESC guidelines as one of the functional tests for CAD detection.<sup>1</sup> Implementation of this method as the first-line technique in patients with stable chest pain provides

an important refinement of the current concept for the assessment of patients with CAD and in a unique way extends the diagnostic workup beyond ruling in or ruling out myocardial ischemia.

## Perfusion imaging with cardiovascular magnetic resonance technique

For a long time, evaluation of myocardial perfusion has been a domain of nuclear imaging and stress echocardiography. Relatively recently, perfusion-CMR has become a top imaging modality for the assessment of myocardial perfusion.<sup>3</sup> Myocardial perfusion CMR technique with adenosine- or regadenosone-induced hyperemia is a highly accurate and standardized method to detect significant CAD.<sup>1,3-8</sup> This CMR technique is based on tracking the first pass of an intravenous bolus of gadolinium-based contrast agent (GBCA) as it circulates through the myocardium during pharmacologically obtained maximal vasodilation (stress perfusion). In the presence of a hemodynamically significant coronary lesion, myocardial hypoperfusion is observed as a subendocardial, or less frequently, as transmural,

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Received: February 19, 2020.

Accepted: February 20, 2020.

Published online:

February 25, 2020.

Kardiolog Pol. 2020; 78 (2): 98-104

doi:10.33963/KP.15204

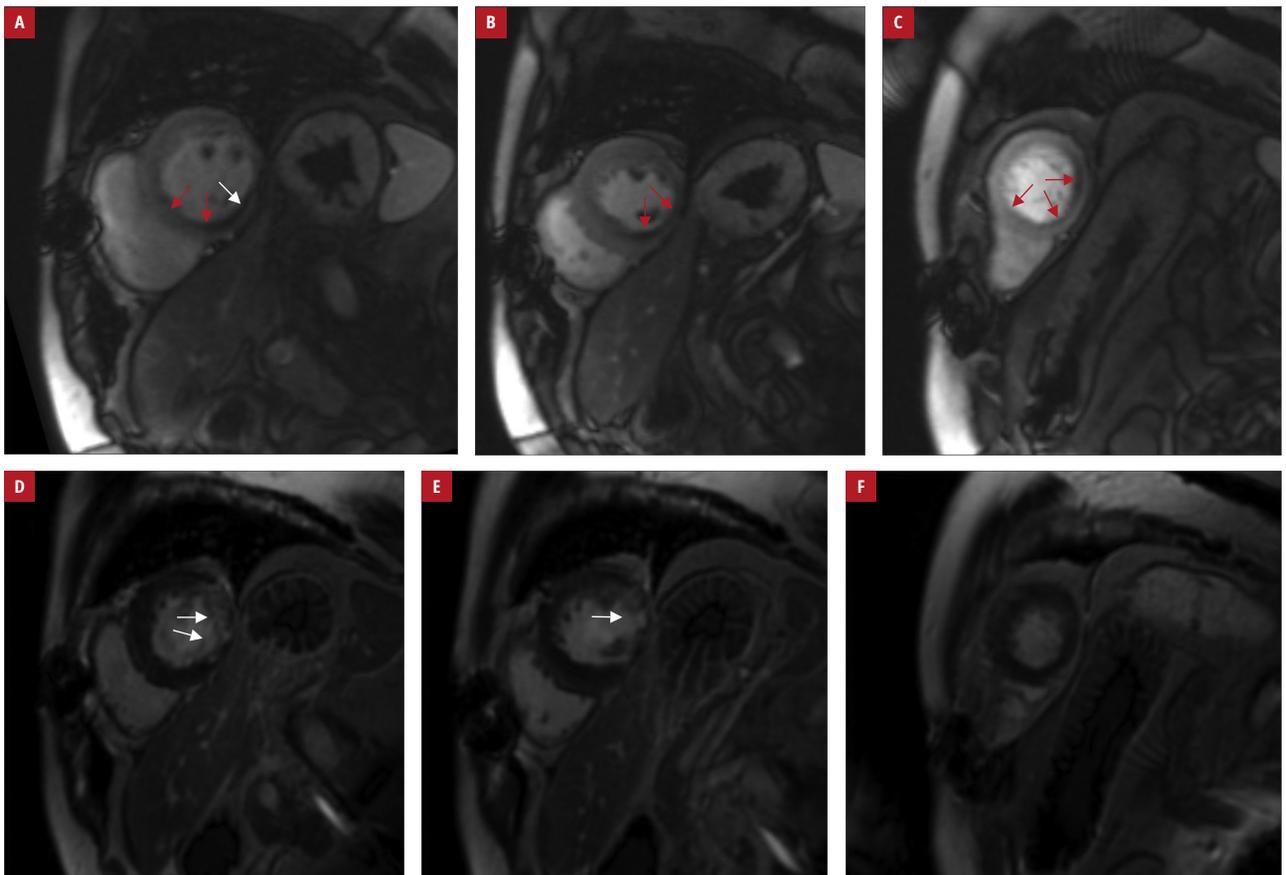
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hypointense areas in the territory supplied by the stenotic coronary artery. Presence of a perfusion defect is usually analyzed visually. It is also possible to use one of the semiquantitative or quantitative methods of perfusion assessment.<sup>3</sup> Interpretation of perfusion defects is performed in the context of detection of any myocardial infarction using the late gadolinium enhancement (LGE). This method is based on the assessment of myocardium in the late phase of GBCA enhancement. This sequence is usually performed 10 to 15 minutes after first pass perfusion and does not require additional injection of contrast agent. Areas of increased accumulation of GBCA (LGE areas) reflect myocardial damage, fibrosis, and infarction and provide information on myocardial viability.<sup>9</sup> Stress perfusion images are always reviewed in comparison to LGE images. The most typical perfusion defects scenarios and corresponding LGE are shown in FIGURES 1 and 2 and Supplementary material, *Figures S1* and *S2*. Myocardial hypoperfusion is regarded as prognostically relevant if stress perfusion defects are detected in at least 2 of 16 segments (or 4 of 32 subsegments) corresponding to an ischemic burden of more than 10% of the myocardium. In patients with previous myocardial infarction, any

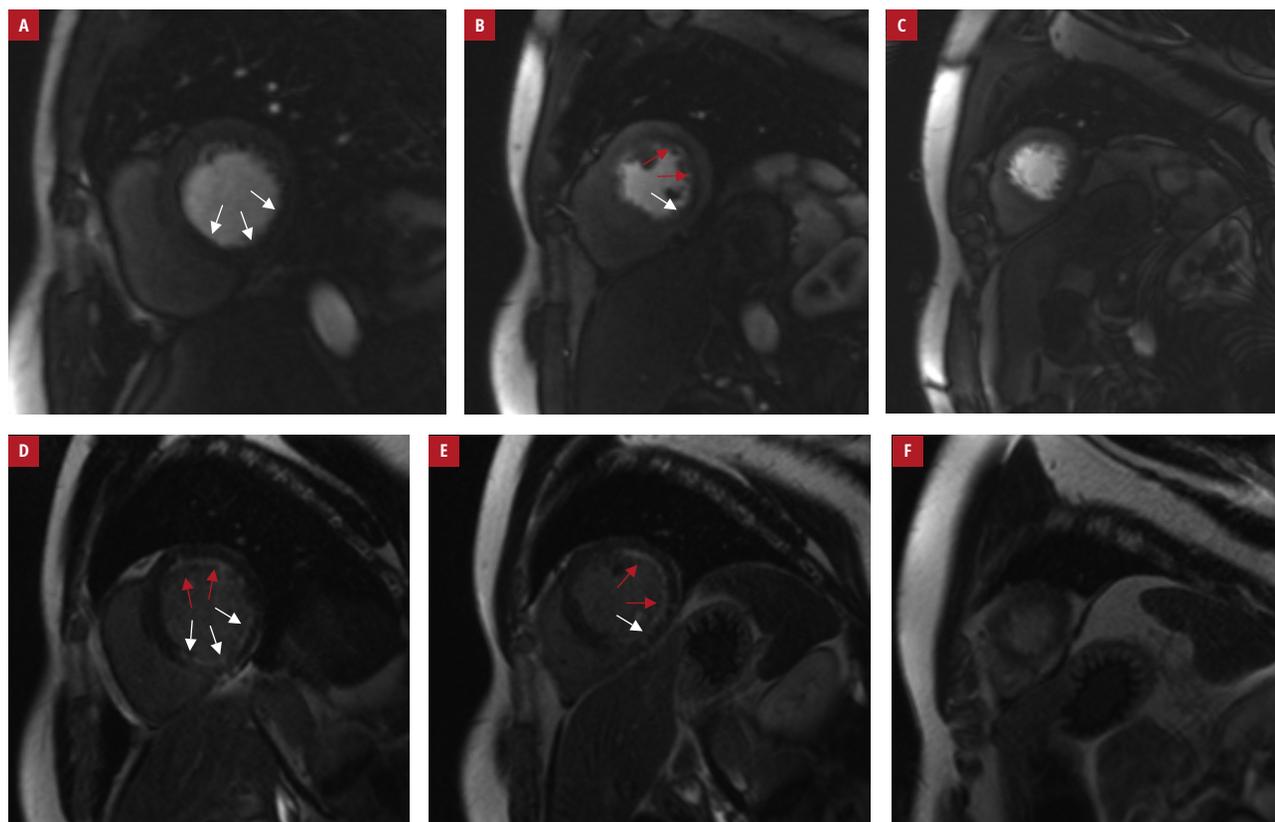
peri-infarct ischemia is considered as prognostically significant.<sup>1,10</sup>

For a long time, perfusion-CMR sequence was technically very difficult and prone to artefacts, because the whole data set has to be acquired every single heartbeat. To differentiate perfusion defects from artefacts, it was important to perform perfusion-CMR sequence without vasodilatation (rest perfusion). Presence of hypoperfusion in both rest- and stress-perfusion sequences with no LGE in corresponding areas suggested artefacts. Acquisition of rest perfusion sequence requires additional time and second dose of GBCA. Technical progress improved quality of stress perfusion imaging, reduced number of artefacts, and downgraded importance of rest perfusion. Current standard protocol recommended by the Society for Cardiovascular Magnetic Resonance placed rest perfusion as optional technique.<sup>11</sup>

Perfusion-CMR offers much more than assessment of myocardial ischemia. Its uniqueness lies in a comprehensive and highly accurate evaluation of patients with stable chest pain, which is not limited to the diagnostic workup of hemodynamically significant CAD. On the one hand, it allows for a more comprehensive assessment of patients with CAD and



**FIGURE 1** Perfusion imaging with cardiovascular magnetic resonance (CMR) during regadenoson stress in basal (A), medial (B), and apical (C) slice and corresponding CMR scar imaging (late gadolinium enhancement) in basal (D), medial (E), and apical (F) slice showing ischemic scar in the left circumflex artery territory (white arrows) and significant ischemia beyond the scar in the right coronary artery territory (red arrows)



**FIGURE 2** Perfusion imaging with cardiovascular magnetic resonance (CMR) during regadenoson stress in basal (A), medial (B), and apical (C) slice and corresponding CMR scar imaging (late gadolinium enhancement) in basal (D), medial (E), and apical (F) slice showing ischemic scar in the left anterior descending artery (red arrows) and right coronary artery territory (white arrows). There is no significant ischemia beyond the scar.

previous myocardial infarction. As a reference standard, CMR provides precise information on cardiac volume and function. Late gadolinium enhancement allows excellent assessment of myocardial viability.<sup>9</sup> Novel T1 and T2 mapping techniques are extremely useful in further tissue characterization and provide information on myocardial edema, inflammation or diffuse fibrosis.<sup>12-18</sup> Importantly, CMR hugely facilitates identification of complications related to CAD, including thrombus or postinfarction ventricular aneurysm.<sup>19-22</sup> Accurate detection of the cardiac thrombus is important in patients undergoing stress tests, because safety of such procedure in the presence of thrombus is unknown.<sup>23,24</sup> Perfusion-CMR allows to detect cardiac thrombus with higher sensitivity than transthoracic echocardiography.<sup>20,25</sup> In contrary to dobutamine stress echocardiography, vasodilators used in perfusion-CMR do not exert positive inotropic effect, which reduces potential risk of thromboembolic complications. Besides, perfusion-CMR with vasodilators, unlike dobutamine tests, does not cause real ischemia, and thus, adverse effects due to ischemia are avoided.<sup>26,27</sup>

On the other hand, in patients with chest pain without significant coronary stenoses, perfusion-CMR in one single modality allows identification of various noncoronary pathologies and

leads to the personalized management strategy. Specifically, CMR provides identification of inflammation-related diseases—such as pericarditis and myocarditis—which may cause chest pain.<sup>13-15</sup> Perfusion-CMR enables also to explain symptoms related to microvascular obstructive disease.<sup>28</sup> Perfusion-CMR is extremely beneficial in the assessment of patients with systemic diseases, for example lupus and diabetes, as it allows evaluation of microvascular disease as well as other abnormalities including fatty infiltration, diastolic dysfunction, and diffuse myocardial fibrosis.<sup>14,29</sup> It may explain symptoms in patients with hypertrophic cardiomyopathy. It also helps to differentiate hypertrophic cardiomyopathy from hypertensive heart disease and provides prognostically relevant information on LGE extent.<sup>30-32</sup> Perfusion-CMR with LGE assessment helps also to diagnose Takotsubo cardiomyopathy and allows identification of patients with myocardial infarction and nonobstructive coronary arteries.<sup>33,34</sup> Moreover, perfusion-CMR enables detection of extracardiac findings, which also may change patient management.<sup>35</sup>

In addition to absolute contraindications to CMR (eg, non-MR safe implants), there are only a few additional conditions related to vasodilators, when perfusion-CMR cannot be performed, including sinus node disease, second- or third-degree atrioventricular ventricular

disease.<sup>11</sup> While adenosine may cause side effects in patients with severe asthma or severe chronic obstructive pulmonary disease, these are much less pronounced with regadenoson. In general, with both vasodilators, there has been a tendency towards raising the threshold for not performing a CMR study over the last years as the observed significant adverse events were very rare.

In comparison with ICA or computed tomography coronary angiography (CTCA), perfusion-CMR, has not only ability to identify causes of chest pain other than CAD, including pericarditis, myocarditis, or microvascular disease, but is also safer in patients with chronic kidney disease (CKD), when macrocyclic contrast agents are used. Current state of knowledge and formal recommendations for minimizing risk of nephrogenic systemic sclerosis allows the diagnostic use of macrocyclic agents in the lowest possible dose across all CKD stages.<sup>36,37</sup> In our center (DZHK Centre for Cardiovascular Imaging, Goethe University Hospital Frankfurt, Germany), gadobutrol (Gadovist, Bayer, Leverkusen, Germany) is used at a reduced dose of 0.075 mmol per kilogram of body weight in all patients including those with CKD.<sup>5</sup> Hemodialysis patients undergo dialysis on the same day that a CMR scan with GBCA was performed.

#### Diagnostic accuracy, prognostic value, and cost-effectiveness of perfusion imaging with cardiovascular magnetic resonance technique

Recent data demonstrated that pure anatomical approach to CAD is inadequate to predict hemodynamic relevance of coronary stenoses and improved outcomes have been observed among patients undergoing functional tests.<sup>38-40</sup> However, it remains debated which functional test is more effective in terms of accuracy, clinical outcome, and cost-effectiveness.

Perfusion-CMR has been demonstrated to be highly accurate in numerous studies, provide

strong prognostic data, and reduce the number of unnecessary invasive angiographies in patients with stable chest pain.<sup>41-52</sup> Meta-analysis, in which diagnostic accuracy of noninvasive functional tests, including perfusion-CMR has been compared with the ICA with or without fractional flow reserve (FFR) as a reference standard, showed that perfusion CMR may serve as an efficient gatekeeper to invasive assessment of CAD.<sup>42,46,49</sup> A recent study confirmed usefulness and high diagnostic accuracy of perfusion-CMR also in stable symptomatic patients with positive coronary artery calcium score.<sup>53</sup> Interestingly, perfusion CMR had higher diagnostic performance in 3 Tesla field compared with studies performed in 1.5 Tesla.<sup>48</sup> A considerable amount of data, including results of 2 large randomized trials (MR-IMPACT II [Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial] and CE-MARC [Cardiovascular Magnetic Resonance and Single-photon Emission Computed Tomography for Diagnosis of Coronary Heart Disease]) confirmed superiority of perfusion-CMR over single-photon emission computed tomography (SPECT) in terms of diagnostic accuracy (TABLE 1).<sup>42-46,49,54</sup> However, patients with implantable devices (pacemakers, implantable cardioverter-defibrillator) and significant artefacts in perfusion-CMR, may still benefit from evaluation with SPECT.

Current assessment of noninvasive imaging modalities is shifting to an evaluation of their impact on clinical outcomes rather than of their diagnostic accuracy. Based on literature data, perfusion-CMR has excellent prognostic value.<sup>3</sup> A meta-analysis of 11 636 patients with a mean follow-up of 32 months showed that negative perfusion-CMR study was associated with a very low risk of cardiovascular death and myocardial infarction.<sup>55</sup> The results of the recent randomized clinical effectiveness trial (MR-INFORM [Myocardial Perfusion CMR versus Angiography and FFR to Guide the Management

**TABLE 1** Selected studies comparing diagnostic accuracy of perfusion imaging with cardiovascular magnetic resonance versus single-photon emission computed tomography

Study	Reference	Perfusion-CMR sensitivity	Perfusion-CMR specificity	SPECT sensitivity	SPECT specificity
Jaarsma et al <sup>42</sup>	ICA	89	76	88	61
Greenwood et al <sup>44</sup>	ICA	86.5	83.4	66.5	82.6
Schwitzer et al <sup>45</sup>	ICA	67	61	59	72
Takx et al <sup>46</sup>	Invasive FFR	87	91	61	84
Pontone et al <sup>49</sup>	Invasive FFR	81	91	64	82

Data are presented as percentage.

Abbreviations: CMR, cardiovascular magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography; SPECT, single-photon emission computed tomography

of Patients with Stable Coronary Artery Disease]) dispelled all doubts about high prognostic value of perfusion-CMR. The study demonstrated in patients with stable angina and risk factors for CAD that perfusion-CMR is as safe and effective as ICA supported by FFR to guide the management of patients with stable chest pain with respect to the primary outcome of major adverse cardiac events at 12 months. Interestingly, the use of perfusion-CMR was associated with a significantly lower incidence of ICA and coronary revascularization than was the use of FFR-based strategy.<sup>5</sup> Similarly, a strong prognostic power of perfusion-CMR has been demonstrated in a multicenter retrospective study, which included 2349 patients followed for a median of 5.4 years (SPINS [Stress CMR Perfusion Imaging in the United States Study]). Results of these analyses showed that patients without myocardial ischemia in CMR or LGE experienced lower incidence of cardiac adverse events, had lower need for coronary revascularization, and lower average annual cost spent on ischemia testing during follow-up.<sup>56</sup> Interestingly, first data from the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial demonstrated that routine invasive therapy in comparison with optimal medical therapy do not reduce major adverse cardiac events in patients with stable ischemic heart disease and moderate to severe ischemia on noninvasive stress testing.<sup>57</sup>

Information on cost-effectiveness of perfusion-CMR are not entirely complete. While cost analysis from MR-INFORM study is still not available, previous data, including results from CEMARC and STRATEGY (Stress Cardiac Magnetic Resonance Versus Computed Tomography Coronary Angiography for the Management of Symptomatic Revascularized Patients) study as well as from the European CMR registry, shows that using CMR is also a cost-effective strategy.<sup>58-60</sup>

### **Current place of perfusion imaging with cardiovascular magnetic resonance in the European Society of Cardiology guidelines**

Perfusion-CMR is an established noninvasive imaging method for detecting inducible myocardial perfusion deficits. The latest ESC guidelines for the diagnosis and management of CCS recommend perfusion-CMR as one of the first-line noninvasive functional tests for the assessment of CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical evaluation alone (class IB recommendation).<sup>1</sup> Decision which initial noninvasive functional test should be selected depends on local expertise, the availability of tests, patients characteristics, and most importantly, on the clinical likelihood of CAD (class IC recommendation). Current guidelines changed the approach to the clinical

assessment of CAD risk. Clinical likelihood of CAD is related to pretest probability of CAD, based on age, sex, and the nature of symptoms. However, additional features, including cardiovascular disease risk factors, abnormalities on electrocardiography and of left ventricular function, as well as coronary calcium assessed by computed tomography can further modify clinical likelihood of CAD. According to the guidelines, ICA is only indicated in a minority of cases as an alternative initial test in patients with high clinical likelihood and severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk (class IB recommendation).<sup>1</sup> Functional imaging for myocardial ischemia is also recommended in cases when CTCA is not diagnostic or has shown CAD of uncertain functional significance (class IB indication). In addition, CMR may be used in low pretest likelihood patients as alternative to CTCA.<sup>1</sup>

### **Cardiovascular magnetic resonance versus computed tomography in perfusion imaging**

Recently, novel computed tomography-based methods of myocardial perfusion have emerged: stress myocardial computed tomography perfusion (stress-CTP). Stress-CTP is a newly developed technique that, if combined with CTCA, provides both anatomical and functional evaluation of CAD in a single imaging modality. Several small studies have validated this technique against the anatomical reference method (cardiac catheterization) and functional methods, including SPECT and invasive FFR, showing high sensitivity and specificity of stress-CTP in detecting flow-limiting coronary stenosis.<sup>46,61-63</sup> A large multicenter study (CTP-PRO [Impact of Stress CT Myocardial Perfusion on Downstream Resources and Prognosis]) on the assessment of the usefulness of stress-CTP combined with CTCA in intermediate to high-risk patients for suspected CAD is still ongoing.<sup>64</sup> Of note, there are only few studies, mostly retrospective, which compare usefulness of stress-CMR versus stress-CTP.<sup>65-67</sup>

**Summary** Perfusion-CMR plays a pivotal role in the work-up of patients with stable chest pain. Novel ESC guidelines for the diagnosis and management of CCS strengthen perfusion-CMR position in CAD assessment. Importantly, perfusion-CMR is useful as the first-line technique in patients with stable chest pain, replacing invasive strategy of patient management. Due to its broad diagnostic spectrum and high prognostic value, perfusion-CMR can also be implemented into diagnostic workup of patients with low clinical likelihood of CAD to exclude CAD and evaluate non-coronary pathologies responsible for chest pain.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at [www.mp.pl/kardiologiapolska](http://www.mp.pl/kardiologiapolska).

## ARTICLE INFORMATION

**NOTE** This study was presented at the 23rd International Congress of the Polish Cardiac Society; September 27, 2019; Katowice, Poland.

**CONFLICT OF INTEREST** None declared.

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**HOW TO CITE** Gawor M, Nagel E. Perfusion cardiovascular magnetic resonance as the first-line technique in patients with stable chest pain. *Kardiol Pol*. 2020; 78: 98-104. doi:10.33963/KP.15204

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