Magnetic resonance imaging perfusion to assess transmural flow distribution

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Abstract
Cardiovascular magnetic resonance (CMR) is increasingly used to assess non-invasively the presence and the extent of myocardial ischemia. CMR perfusion has been shown to be superior to nuclear perfusion imaging, allows high-resolution quantitative assessment of myocardial perfusion reserve, has been validated against invasive reference standards and microspheres and therefore has the potential to become the non-invasive and radiation-free test of choice to guide patients’ clinical decision making. The higher spatial resolution of CMR is thought to be one the key factors explaining the superior diagnostic capabilities of CMR visual assessment when compared with other ischemia imaging techniques.

Keywords: Adenosine; coronary disease; fractional flow reserve; high-resolution quantification; magnetic resonance imaging; perfusion.

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Introduction
Cardiac magnetic resonance (CMR) perfusion imaging is increasingly used to diagnose non-invasively the presence of coronary artery disease (CAD) and to plan revascularization procedures [1].

The main advantages of CMR perfusion are the lack of radiation exposure, the excellent safety profile of the contrast agents and the capability of CMR perfusion to provide dynamic images of myocardial perfusion with a far better spatial resolution compared with other imaging modalities [2]. CMR perfusion has been shown to be superior to nuclear perfusion imaging [3], has been validated against microspheres [4–6] and invasive reference standards such as fractional flow reserve (FFR) [7–9], and therefore has the potential to become the non-invasive test of choice to guide patients’ clinical decision making.

Among the other advantages of CMR perfusion, the superior spatial resolution in particular plays an important role, and is thought to be the key factor explaining the superiority of CMR perfusion over nuclear perfusion imaging. Due to the complex interactions between coronary vasculature and myocardium, myocardial ischemia arises from and affects more severely the subendocardial layers of the left ventricular myocardium in comparison with the outer epicardial layers (Figure 1) [10, 11]. CMR perfusion is capable of an independent visualization of multiple left ventricular layers [7, 12, 13], and therefore allows the identification of ischemia at its on-
set from the endocardium. This might conversely be missed by lower spatial resolution techniques due to partial volume effects (Figure 2).

Regardless of the specific technical parameters used for the acquisition of the images, CMR perfusion allows a spatial resolution comparable or superior to nuclear medicine techniques. In recent years, older sequences based on echo planar imaging, turbo gradient echo or steady state free precession have been progressively replaced by more advanced sequences that exploit jointly the spatial and temporal k-space data correlations. One of these methods in particular, $k$-$t$ sensitivity encoding, allows a net increase in the efficiency of acquisition and enables a considerable improvement in spatial resolution [14], particularly at 3 Tesla (Figure 3).

In comparison with standard perfusion sequences, high-resolution $k$-$t$ CMR perfusion results in significantly improved image quality, signal-to-noise and contrast-to-noise, and a significant reduction in the extent...
and transmurality of subendocardial dark-rim artifacts, supporting the use of advanced perfusion sequences for clinical perfusion imaging [15].

**Analysis of high-resolution CMR perfusion**

**Visual assessment**

Visual assessment of CMR perfusion is currently regarded as the reference standard for the evaluation of the scans, and is mainly based on the spatial and temporal information of the CMR perfusion images. Several features in the images improve the confidence of the operators in visual diagnosis and in particular the identification of ischemic areas, which are predominantly subendocardial and the characteristic epicardial wash-in of the contrast agent during first pass in areas of abnormal perfusion (Table I).

A recent meta-analysis of the literature [17] demonstrated an elevated diagnostic accuracy of CMR perfusion with a sensitivity of 0.91 and specificity of 0.81 at a patient level. More recently, the CE-MARC study [3], the largest clinical study on CMR published so far (752 patients) comparing a combined CMR protocol (stress and rest perfusion, functional analysis, late gadolinium enhancement and CMR coronary angiography) for the assessment of patients with suspected CAD versus single photon emission computed tomography and coronary angiography, demonstrated a sensitivity and specificity of the CMR approach of 87% and 83%, respectively.

**Quantification**

A potential limitation of CMR visual assessment, however, is the presence of balanced ischemia in patients with three-vessel disease, in which the absence of normal reference segments can cause false negative results [18]. To overcome this limitation, quantitative analysis has been developed and validated [2, 19, 20]. Myocardial perfusion reserve (MPR) can be assessed in an objective [18] and reproducible way [21] using specific contrast agent injection schemes [22] in combination with signal deconvolution [19]. Quantitative

<table>
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<th>Diagnostic criterion</th>
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<td>1. Delayed wash-in of the contrast agent in one or more left ventricular segments</td>
<td>Strictly dependent on the elevated temporal resolution of CMR perfusion and the possibility to visualize a dynamic series of the first-pass</td>
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<tr>
<td>2. TPG during wash-in of the contrast agent, with more delayed and reduced perfusion affecting the inner left ventricular layers</td>
<td>Strictly dependent on the spatial resolution of CMR perfusion enabling the visualization of multiple independent left ventricular transmural layers</td>
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<td>3a. Exclusion of subendocardial dark-rim artifacts</td>
<td>The presence and severity of these artifacts is inversely proportional to the spatial resolution of the sequence</td>
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<td>3b. Exclusion of subendocardial dark-rim artifacts</td>
<td>Dark-rim artifacts usually appear when contrast agent arrives in the left ventricular cavity and before any signal increase in the left ventricular myocardium. This feature allows the identification of the artifacts from true perfusion defects and is based on the temporal resolution of CMR perfusion</td>
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**Table 1** Visual assessment diagnostic criteria for CMR perfusion series, in view of the spatial and temporal resolution of CMR perfusion.
analysis has been validated against microspheres [5] and FFR [7], and has recently been shown to allow an accurate assessment of patients with suspected CAD, providing comparable quantitative results to positron emission computed tomography [15].

However, until very recently, quantitative analysis has been used to analyze full-thickness myocardial segments or to quantify MPR in the subendocardial half of the myocardial wall, potentially neglecting important information about the localization and the extent of myocardial ischemia. This restriction is responsible for an important limitation to the overall accuracy of quantitative analysis when compared with visual assessment [23].

In order to overcome these limitations, methods for high-resolution voxel-wise quantification have recently been developed and validated by our group [23], using a novel hardware CMR perfusion phantom [24] and patients’ data (on advanced high-resolution k-t scans) and by others [6] (on standard resolution turbo gradient echo scans) in comparison to microsphere experiments in dogs and clinical data. Voxel-wise quantitative analysis allows the quantification of MPR while preserving the information about the extent, localization, and transmurality of ischemia (ischemic burden; Figure 4). Combining the advantages of visual (high spatial resolution) and quantitative (more objective and reproducible) assessment, voxel-wise quantification has the potential to allow an improvement in the accuracy of detection of CAD, as well as to provide novel and valuable information on the severity and extent of ischemia.

Transmural perfusion gradient analysis

In an attempt to exploit the full diagnostic information provided by high-resolution k-t perfusion scans to visualize the presence and extent of subendocardial ischemia, we have recently developed and validated a novel diagnostic technique for the identification of hemodynamically significant CAD, based on the spatial and temporal distribution of ischemia in the left ventricular myocardium and on the identification of differences in perfusion between the left ventricular layers. Transmural perfusion gradient (TPG) analysis is based on a two dimensional, “gradientogram” representation, which displays the evolution of the transmural gradient in left ventricular myocardial perfusion (contrast uptake) over time (Figure 5). Several new measurements of subendocardial ischemia are defined on the gradientogram (maximum and mean intensity of the TPG, temporal persistence and radial extent of the TPG), revealing a clear distinction between normal perfusion and areas of inducible ischemia and a good correlation with invasive coronary angiography [25]. As FFR is considered the invasive reference standard for the assessment of the functional significance of CAD, the optimal TPG diagnostic criterion has recently been defined and independently validated in two distinct populations of patients with suspected CAD versus FFR [26].

A transmural redistribution of myocardial perfusion of 20% (TPG 20%) was the best diagnostic criterion for the identification of FFR hemodynamically significant CAD, with a sensitivity of 0.78 and a specificity of 0.94 for a per-vessel analysis and a sensitivity of 0.89 and a specificity of 0.83 on a per-patient analysis. Moreover, TPG correlated well with the degree of severity of the coronary lesions as assessed with FFR.

While TPG analysis had a similar diagnostic accuracy to expert visual assessment, it is a fully automated analysis method, which analyzes the perfusion CMR data based on the expected spatial distribution and temporal evolution of myocardial ischemia. TPG analysis has several advantages over quantitative perfusion assessment, as it does not require the acquisition of rest
scans or any specific scheme for the administration of the contrast agent. Moreover, TPG analysis is more robust to image inhomogeneities and can potentially be used retrospectively on pre-existing datasets.

**Future perspectives**
Decisions regarding revascularization based on the assessment of the presence of ischemia with FFR have shown improved event-free survival in patients with stable CAD [27–29]. Despite the proof of an excellent diagnostic accuracy of CMR perfusion versus FFR, the best pathway for the non-invasive management of patients with a high risk of CAD has not yet been determined. An ongoing clinical trial (MR-INFORM) [30] will assess in a prospective, multicenter, randomized controlled non-inferiority, outcome setting whether an initial strategy of CMR perfusion is non inferior to invasive angiography and FFR measurements to guide the management of patients with stable CAD. The primary endpoint will be the occurrence of major adverse cardiac events (death, myocardial infarction and repeat revascularization) at 1 year.

Non-inferiority of CMR perfusion imaging to the current invasive reference standard (FFR) would establish CMR perfusion imaging as an attractive non-invasive alternative to current diagnostic pathways.

**Conclusion**
CMR perfusion is rapidly emerging as the method of choice for the assessment of ischemia in patients with suspected CAD. The capability to visualize subendocardial perfusion abnormalities with spatial and temporal resolution, the excellent diagnostic accuracy of visual assessment, as well as the increasing availability of post-processing methods to allow an objective assessment of the presence and extent of ischemia anticipate a bright future for this technique in the years to come.

**Fig. 5** Transmural perfusion gradient analysis (modified with permission from Hautvast et al [25]). (a) High-resolution k-t sensitivity encoding perfusion image of the mid-ventricular slice showing a perfusion defect in the territory of the right coronary artery. (b) Bull’s eye graph representing the peak gradient in each radial position over three slices. (c) Gradientogram plot. The intensity of the transmural perfusion gradient is represented by the grey level in each radial segment (Y-axis) and for each temporal dynamic (X-axis). Increasing endocardial to epicardial gradients are represented with a darkening grey level, so that an endocardial perfusion defect generates a dark area in the gradientogram. (d) The gradientogram can be segmented at different percentage thresholds of the gradient’s amplitude. In this case, an intensity threshold of 20% identifies a significant transmural perfusion gradient (green area).
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