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Contemporary Issues in Quantitative Myocardial Perfusion CMR Imaging

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Abstract

Purpose of Review This review highlights the development and application of quantitative myocardial perfusion by cardiac magnetic resonance (CMR) and discusses recent innovations in this area.

Recent Findings First pass, contrast-enhanced CMR can accurately quantify myocardial perfusion in order to diagnose obstructive coronary artery disease and microvascular dysfunction. Quantitative analysis conveys additional prognostic information beyond other CMR findings. New, fully automated techniques may aid standardization of methods across centers.

Summary CMR quantitative perfusion has robust performance for the diagnosis of obstructive coronary disease and microvascular dysfunction and conveys prognostic information. Adoption of automated post-processing and standardized protocols will further strengthen CMR in its position as the modality of choice for the evaluation of possible myocardial ischemia.

Keywords Cardiac magnetic resonance · Myocardial perfusion imaging · Myocardial blood flow · Myocardial ischemia · Microvascular disease · Coronary artery disease

Introduction

Coronary heart disease is a major cause of morbidity in the USA today [1]. To that end, considerable resources are dedicated to the detection, characterization, and treatment of coronary artery disease (CAD), the primary driver of cardiovascular mortality [1–3]. Furthermore, measuring the extent of inducible ischemia can be a critical factor in assessing the severity of stable CAD [4]. It is with this goal in mind that cardiac magnetic resonance (CMR) techniques have been developed which are capable of producing high-quality myocardial perfusion images. Clinically, qualitative analysis has been the primary analytic approach to date and is well validated for clinical use, but quantification offers potential advantages and may become the preferred approach in the future. This review will highlight the justification and development of these quantitative techniques, their current status in clinical care, and future potential.

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First Pass Contrast-Enhanced Perfusion

In the late 1990s, rapid CMR techniques for first pass perfusion during vasodilator stress were developed. Investigators utilized a fast T1-weighted gradient echo technique to visualize myocardial enhancement by the initial entry of a bolus of gadolinium-based contrast—the CMR analog of the myocardial blush [5]. Employed under hyperemic conditions to accentuate relative differences, so-called first-pass perfusion imaging has become the mainstay of perfusion CMR [6, 7]. Like nuclear techniques, perfusion CMR relies on visualizing differences in myocardial enhancement which are then reported according to a segmental model. While this has typically been a variant of the American Heart Association 17 segmental model (usually omitting segment 17), some have employed a 32 segmental model, taking advantage of the high spatial resolution of CMR [8, 9, 10]. Perfusion CMR during vasodilator stress visualizes relatively hypoperfused myocardial territories. Resting perfusion imaging can aid in the identification of artifacts, though inclusion of resting perfusion is not universal [11].

Measuring changes in myocardial signal intensity over time lends itself to the quantification of myocardial blood flow (MBF) at rest and stress (see below). This in turns allows for determination of myocardial perfusion reserve (MPR), calculated as the ratio of stress flow to rest flow. MPR is interpreted as the non-invasive analog of coronary flow reserve (CFR), or the reserve capacity of a coronary bed to augment MBF [12]. Given the logistical barriers to fully quantitative analysis, including manual, time-intensive processing offline (see below), various investigators have proposed semi-quantitative measures of myocardial perfusion, derived from tracking the myocardial signal intensity as a function of time (Fig. 1). A commonly used semi-quantitative criterion is the area under the myocardial signal intensity curve, up until the peak signal in the arterial input. This "initial area" assessment correlates well with microsphere measurement of MBF [13, 14]. Another proposed semi-quantitative method is taken from the maximal slope of the ascending limb of the signal intensity curve, termed the "upslope," [15, 16]. Using the upslope method, a relative perfusion index can be calculated as the ratio of the stress parameter to the resting parameter. Despite good performance and favorable comparisons with invasive measures and positron emission tomography (PET) in some circumstances, the upslope perfusion index should not be thought of as a non-invasive correlate of CFR [13]. Even when normalizing against arterial input, thresholds for abnormal perfusion are not well established and they lack critical data about resting and stress MBF to provide context for any abnormal perfusion reserve [17].

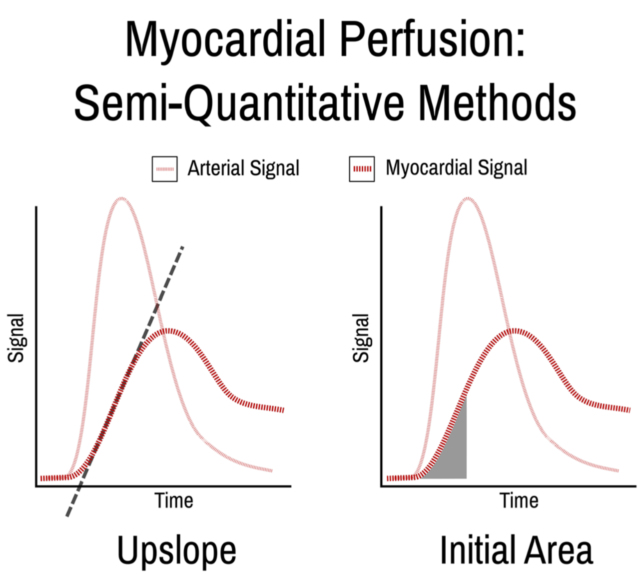

Fig. 1 Semi-quantitative methods of estimating myocardial blood flow (MBF). Among the semi-quantitative parameters used to estimate myocardial blood flow (MBF) are the upslope method (left) and the initial area method (right). The upslope method uses the maximum upslope of the myocardial signal intensity curve, typically normalized against the arterial input. Stress upslope is divided by resting value to provide a relative perfusion index. The initial area method involves taking the area under the myocardial signal intensity curve, up until the peak of arterial input

Full Quantification of Myocardial Blood Flow by First Pass Perfusion

Over the past several decades, substantial work has been done to enable absolute quantification of MBF. While the various methodologies and technical aspects are beyond the scope of this article, it is useful to bear in mind the considerations involved in arriving at flow quantification. Myocardial signal intensity curves are crucial, but they do not by themselves allow for the determination of MBF. Determining flow requires understanding how contrast arrives at the tissue of interest and how it traverses the tissue. Arrival of contrast occurs by arterial transit. The "arterial input function" models arterial contrast delivery (Fig. 2). Traversal is less intuitive. This involves conceptualizing the response of a system to an impulse, i.e., how an instantaneous bolus of contrast would traverse the various capillaries and exit the system, gradually decreasing in concentration with time. The model of the contrast residue is known as the "residual function." The residual function contains information about the properties of the system, including absolute blood flow [18]. The convolution of these two functions—the arterial input function and the residual function—models the appearance of contrast in the myocardium, referred to as the "tissue function."

The arterial input function and tissue function can be derived from signal intensity curves in the artery and myocardium, respectively. Obtaining residual function, and from it MBF, requires the complex process of deconvolving the effect of the arterial input function on the tissue response curve to fit the residual function. Among the easiest and best-established options for deconvolution involves constraining the residual function to the expected behavior of an intravascular tracer [13]. One solution adapted by Leon Axel in 1983 to computed tomography perfusion uses a Fermi function to model the residual function and is widely used for perfusion CMR today [19]. Conveniently, the initial amplitude of this function is proportional to the MBF. Other approaches, including multi-compartment modeling and distributed parameter models, have also been used [20, 21].

Prior to deriving the residual function and MBF, the measured signal intensities within the myocardium and the blood pool (arterial input) must be converted to correspond to the concentrations of gadolinium-based contrast. This operation requires accounting for the non-linear relationship between signal intensity and contrast concentration at higher

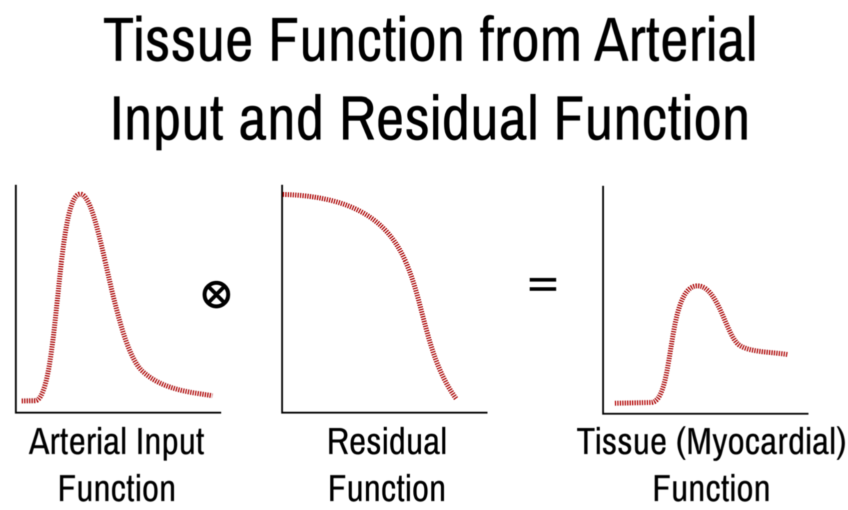

Fig. 2 Relationship between arterial input function, residual function, and tissue function. The tissue (myocardial) function results from the convolution of the arterial input function with the residual function. The arterial input function models arterial contrast delivery. The residual function is a model of the course of contrast through tissue capillaries and out of the system (impulse response)

gadolinium concentrations due to T1 saturation and T2* effects, uncertainty about the extent of residual magnetization after the saturation pulse (i.e., saturation efficiency), and variation in receive-coil sensitivities [13, 22]. Care must be taken to either use very low contrast doses where the signal intensity is proportional to the contrast concentration, or model the relationship between the signal intensity and gadolinium concentration. Once this conversion to concentrations has been performed, then the arterial input function and tissue function may be deconvolved to fit a residual function and then determine MBF. The basic steps involved in quantifying myocardial perfusion are laid out in Fig. 3. An example of fully quantitative perfusion is shown in Fig. 4 [23].

Why Quantify Myocardial Blood Flow

Diagnostic Performance

The reliance of single-photon emission tomography (SPECT) MPI on a region of normal myocardium as a comparator renders it prone to missing global reductions in perfusion, such that it is least sensitive to the greatest degree of ischemia [24]. Even without quantification of MBF, the high spatial resolution of CMR is less susceptible to missing balanced ischemia. At present, standard, non-quantitative, perfusion CMR is a thoroughly vetted diagnostic test with high overall performance, incorporated into major society guidelines for testing of stable ischemic heart disease [25–27]. Moreover, initial data from the multi-center MR-INFORM trial, comparing perfusion CMR visual analysis and invasive fractional flow reserve-guided care, demonstrate equivalent outcomes [28].

The addition of MBF quantification to perfusion CMR is intended to secure potential improvements in diagnostic accuracy. True to this intent, quantitative analysis appears to more accurately identify the extent of ischemia in patients with multi-vessel CAD. In a study of 30 patients undergoing invasive angiography, visual, compared with quantitative analysis, diagnosed the presence of any obstructive CAD with similar accuracy. However, quantitative analysis was able to detect a higher ischemic burden in patients with 3-vessel obstructive disease [29]. In a subset of patients with left main or equivalent CAD from the CE-MARC study, CMR had a higher diagnostic accuracy compared with SPECT [30]. Interestingly, quantitative analysis was no better than visual MPI by CMR, though all patients with any abnormal CMR perfusion had abnormal visual analysis, confirming that perfusion CMR is less susceptible to balanced ischemia.

Artifacts can also be more reliably addressed. MBF can help distinguish the dark rim artifact from inducible ischemia. Parsing the myocardium into three segments (subendocardium, midmyocardium, and subepicardium), dark-rim artifacts demonstrated reduced MBF exclusively in the subendocardium. Conversely, true perfusion defects extended into additional layers and involved more severe reductions in MBF [31]. There are other contributions to the evaluation of CAD as well. Quantitative analysis also appears to increase inter-observer agreement [29]. The higher spatial resolution of CMR—relative to nuclear techniques—has also lent itself to a more granular assessment than wall segments: perfusion differences within the myocardial wall itself. Whereas endocardial blood flow is typically slightly higher than epicardial blood flow at rest, ischemia is associated with a relative reduction in endocardial to epicardial MBF [32, 33]. The measurement of flow ratios between endocardium and epicardium appears to improve the diagnostic accuracy of CMR quantitative perfusion [34]. While full quantification is not strictly necessary for evaluation of transmural perfusion gradients (e.g., a ratio of semi-quantitative parameters could be performed, or even visual analysis in a 32 segmental model), there is currently no standardized method for their evaluation and our understanding of how this changes in CAD has

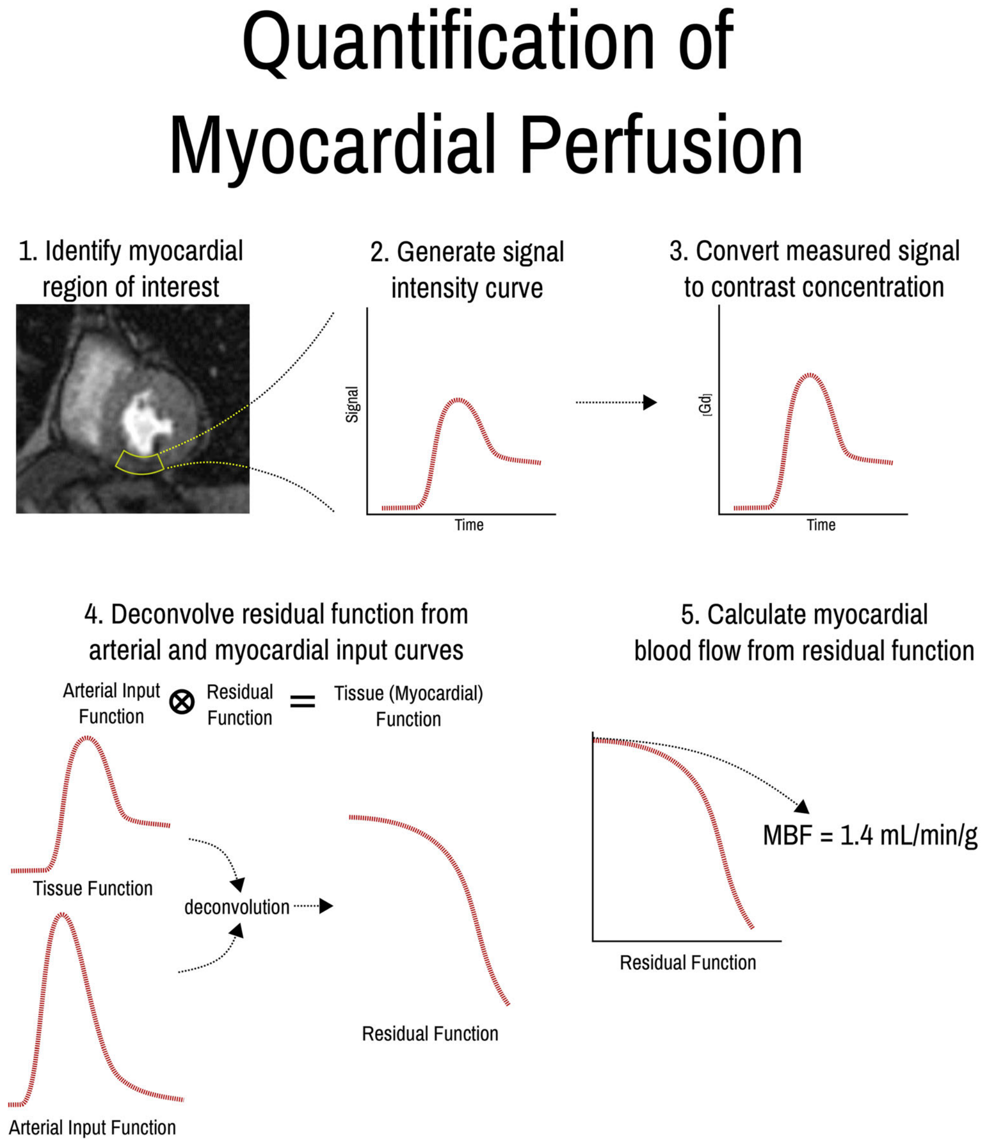

Fig. 3 Steps involved in quantification of myocardial blood flow (MBF) by CMR. After identifying a myocardial region of interest (step 1), a signal intensity curve for that corresponding region may be obtained (step 2). The signal intensity must be converted to gadolinium concentration (step 3), which requires accounting for the non-linearity of this relationship, as well as variations in saturation efficiency and receive-coil sensitivities. The most complex process (step 4) involves deconvolution of the arterial input function and tissue function to yield the residual function, often via the Fermi function. Finally, MBF can be extracted from the residual function (step 5)

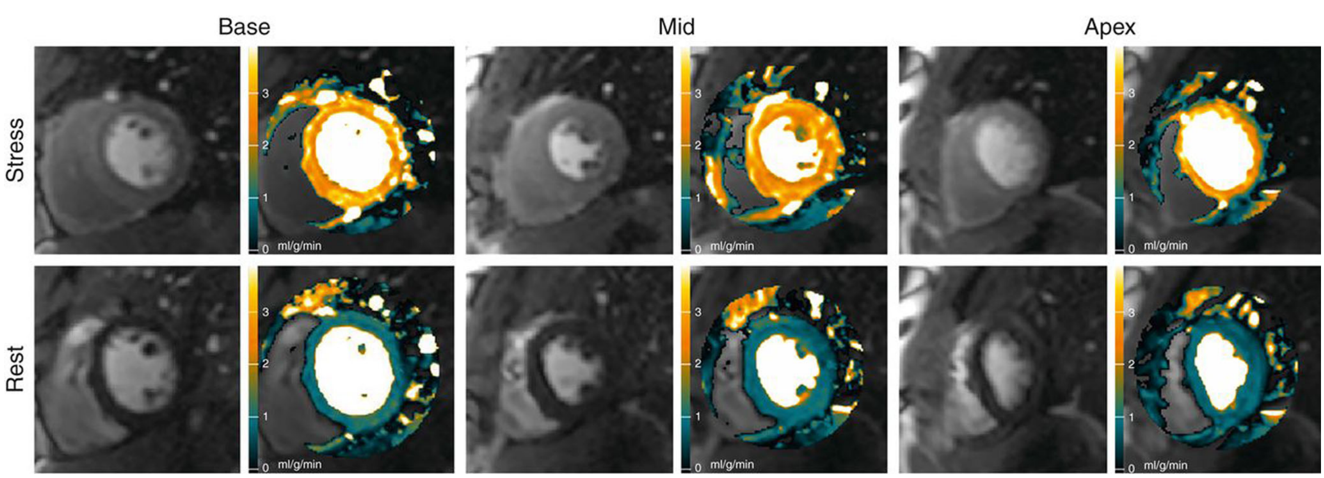

Fig. 4 Quantitative myocardial perfusion map. Example of pixel maps demonstrating quantitative myocardial perfusion with vasodilator stress and at rest (reproduced from: JACC: Cardiovascular Imaging 2018;11(5):697–707; https://doi.org/10.1016/S0140-6736(16)00618-8; Creative Commons user license https://creativecommons.org/licenses/by/4.0/) [23]

not yet completely matured. Accordingly, the most complete technique will provide the greatest flexibility as various methodologies are compared. Presently, this technique is pixelwise quantification of MBF, which provides the most granular spatial detail and a unit with intrinsic physiologic significance.

Microvascular Dysfunction

Quantitative MBF analysis has broadened our view of coronary disease from obstructive stenoses in the large epicardial vessels to the entire coronary tree. An abnormally low MPR in the absence of epicardial CAD can be taken as evidence of microvascular dysfunction (MVD). A recent study demonstrated an average MPR of 2.21 in patients with typical angina and risk factors for MVD, compared with MPR of 2.93 in healthy controls [35]. Another study using catheter-based criteria of index of microvascular resistance ≥ 25 and FFR ≥ 0.8 (to exclude obstructive epicardial disease) found a mean MPR of 1.8 in patients with MVD, compared to 2.6 without [36]. Taken together, these data indicate that MBF quantification can establish the diagnosis of MVD and could also be performed serially to monitor treatment efficacy for patients with MVD.

Prognosis

There is also substantial information on the prognostic utility of CMR quantitative perfusion [37]. Perhaps the best validated negative prognostic marker in CMR is late gadolinium enhancement [38]. In order to evaluate whether MBF quantitation could offer additional prognostic information, a group of investigators followed 395 patients who underwent quantitative and visual analysis MPI. In a model to predict adverse cardiovascular events, $\geq 10\%$ myocardial ischemia (≥ 2 AHA wall segments) by quantitative analysis improved the predictive performance, even after inclusion of late gadolinium enhancement [10]. While visual analysis is also capable of providing extent of ischemia on a segmental basis, discordant quantitative and visual MPI was predictive of adverse events only when quantitative analysis indicated ischemia. In the aggregate, these findings suggest that ischemia detection by CMR quantitative perfusion is prognostically significant beyond the information provided by late gadolinium enhancement and that it outperforms visual MPI.

Limitations

Despite multiple advantages, there are some limitations related to the quantification of myocardial perfusion. Many of these are process-related. There are no widely available or vendor-supported in-line systems for MBF quantification. As such, this often requires that the determination of flow rates must be performed manually, off-line, and typically with custom software packages (Fig. 3). The process may be intensive in time, resources, and experienced personnel. The conversion of signal intensity (arbitrary units) to contrast concentration can be done in several ways, such as using low contrast doses and assuming a linear relationship, or using Bloch equations to model gadolinium concentration as a function of T1, and utilizing proton density-weighted images [39]. Care must be taken with these strategies, to avoid introducing additional error. Technical considerations for MBF quantification are laid out in Table 1.

Future Advances

CMR quantitative perfusion is maturing into a well-vetted and increasingly disseminated adjunct to visual MPI. Furthermore, additional developments are pending that are expected to solidify the role of quantitative analysis within perfusion CMR and CMR at the forefront of non-invasive ischemic cardiac testing (Fig. 5).

Whole Heart Coverage

A frequently cited limitation of perfusion CMR in relation to nuclear MPI is its limited spatial evaluation for ischemia, typically consisting of three or four short-axis slices of left ventricular (LV) myocardium. Improving the three-dimensional coverage of perfusion sequences can both enhance the diagnostic assessment of ischemic extent and potentially reduce scan time by alleviating the burden of careful slice planning [40, 41]. Extending spatial coverage of perfusion sequences to include the entire LV myocardium may represent an important step forward in perfusion CMR that is synergistic with the goals of quantitative perfusion.

High Spatial Resolution

Synchronous with the development of whole heart coverage has come the drive to increase spatial resolution. Typical perfusion CMR in-plane resolution has been 2–3 mm for conventional methods, with < 2 mm resolution often defined as high

Table 1 Technical requirements for myocardial perfusion quantification

Protocol and technique to accurately measure the arterial input function and tissue function
(Dual bolus or Dual sequence)
Method to convert signal intensity from arbitrary units into gadolinium contrast concentration
Methods to perform constrained deconvolution to derive flow measurements
Software capable of manual or automatic image registration
Software capable of manual or automatic myocardial segmentation

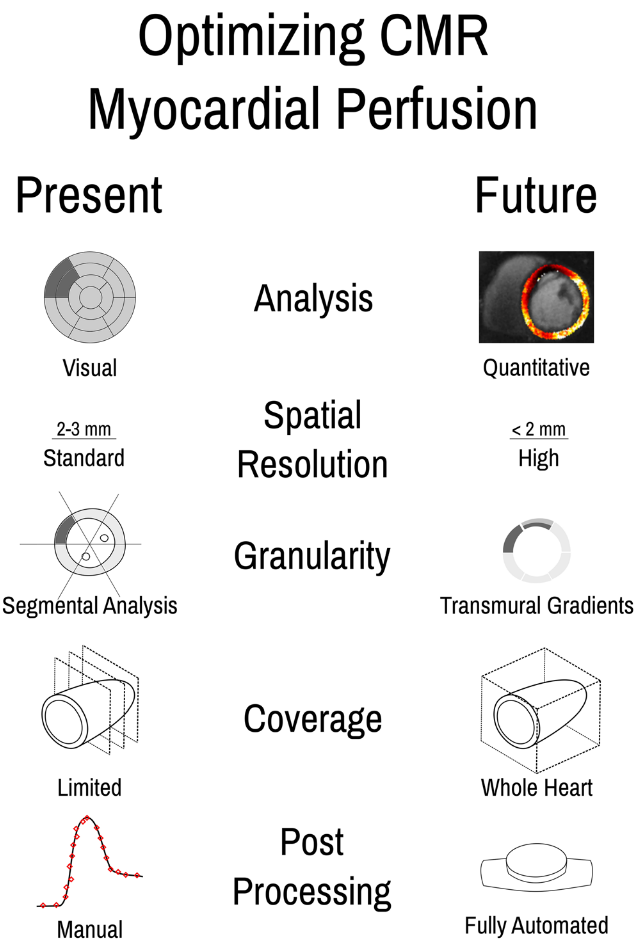

Fig. 5 Optimizing CMR myocardial perfusion. In addition to the standardization of full quantitation of myocardial blood flow, impending advances in CMR myocardial perfusion include high spatial resolution, interrogation of transmural perfusion gradients, whole heart coverage, and fully automated post-processing

resolution [42]. As discussed above, the high spatial resolution of CMR is responsible for many of its technical advantages. Additional high-resolution sequences can be accomplished with radial or spiral trajectories, which bring other advantages as well: these non-Cartesian patterns are less susceptible to dark-rim-causing motion [42, 43]. Together with high in-plane resolution and a reduction in dark rim artifacts, such sequences may meaningfully improve our ability to assess transmural perfusion gradients. Given this, ideal CMR perfusion techniques will provide perfusion quantification, include broad or whole heart coverage, and maintain high enough spatial resolution to allow measurement of transmural perfusion gradients.

Standardization in Techniques

As much as CMR has benefitted from a large network of committed investigators, the breadth of contributions has delayed necessary standardization. Quantitative MBF analysis is no exception. For example, despite its broad appeal, the Fermi function is not the universal standard for residual function deconvolution [13]. Recently, some have also questioned whether MBF could be more accurately determined with a distributive parameter model [44]. Additional comparative studies are needed in order to arrive at a consensus deconvolution method for clinical practice.

Lack of standardization has plagued other elements. There is also no universal location for the arterial input function. Options have included the LV cavity, left atrium, and aorta, each of which generates a different estimate of MBF in PET studies [45]. Even something as straightforward as transmural perfusion gradients has lacked consensus. One method involves the comparison of endocardial and epicardial MBF within the same myocardial segment, whereas others have calculated the ratio using the endocardium of each segment, divided by the median epicardial flow for the entire slice [9, 34]. Again, the ideal approach is not clear. A recent meta-analysis attempting to catalog the diagnostic accuracy of semi-quantitative and fully quantitative CMR perfusion concluded that the clinical value of these techniques was uncertain owing to "extensive" variation between studies, including "acquisition protocols, reference standards and methods of assessment," [46].

Full Automation

At present, quantitative analysis requires significant time and manual input for post-processing, which is a major limitation. For example, the work of manual contouring alone required 1 h per patient in a recent study [47]. Any attempts at broader implementation of quantitative analysis should also include efforts toward automation [48]. Meaningful progress is already being made in this regard. One group has developed a fully automated system comprising detection and correction of heart motion, correction of surface coil sensitivity variation, detection of the arterial input function and myocardial regions of interest, generation of signal intensity curves, and deconvolution to generate pixel-based maps of quantitative MBF [23]. Automated quantification compared well with those generated manually and showed acceptable diagnostic performance, using invasive angiography as a reference. Another fully automated, inline MBF quantification protocol that included free breathing motion correction recently demonstrated good intra-study and inter-study variability [49•]. There is reason to be optimistic that the utility of quantitative myocardial perfusion CMR will be buoyed by efficient and cost-effective automated post-processing.

Stress T1 Imaging

Arising from the limitations inherent in using exogenous contrast agents such as gadolinium chelates and the idea that measurement of MBF may not capture the entire range of changes involved in myocardial ischemia, increasing attention is being paid to non-contrast methods of evaluating for obstructive coronary stenoses. Particularly intriguing is the proposed use of T1 mapping with vasodilator stress. T1 mapping indirectly assesses myocardial water volume, by virtue of its prolongation of T1 relaxation times. Native T1 is elevated in ischemic myocardium at baseline due to vasodilation and capillary recruitment downstream from an epicardial coronary stenosis [50]. The normal increase in myocardial water volume from vasodilator stress is blunted in obstructive CAD, allowing for a comparison of stress and rest T1. The percent change from resting to stress T1 is referred to as the T1 reactivity. Comparison of resting and stress myocardial T1 maps can distinguish between normal, remote, and ischemic myocardium [51]. Correlation with invasive measures of coronary artery function, including fractional flow reserve, suggested an impressive diagnostic performance for stress T1 mapping. A threshold of $\leq 1.5\%$ T1 reactivity detected obstructive epicardial stenosis with a sensitivity of 93% and specificity of 95% [36]. By comparison, normal myocardial segments demonstrated a T1 reactivity of 6.2%, placing the absolute difference in T1 reactivity between normal and ischemic myocardium at 4.7%. Validation of these results at other centers is needed prior to widespread adoption of this technique.

Conclusion

MBF quantification is an important developing addition to the CMR armamentarium. Together with PET, CMR is one of only two modalities capable of high fidelity MBF quantitation [52]. However, CMR also has unrivaled spatial resolution among functional testing techniques, allowing interrogation of transmural perfusion gradients. Awaiting only a few technical refinements and further standardization, quantitative perfusion CMR is poised to strengthen its position as an emerging modality for diagnosis, prognosis, and monitoring of chest pain, epicardial CAD, and microvascular dysfunction.

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Compliance with Ethical Standards

Conflicts of Interest Austin A. Robinson declares no conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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