ARTICLE TITLE

Automated Quantitative Stress Perfusion in a Clinical Routine

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DISCLOSURE STATEMENT

No conflict of interest.

KEYWORDS

Myocardial perfusion, stress, ischemia, magnetic resonance imaging, cardiovascular magnetic resonance, quantification, automation.

KEY POINTS

1. Cardiovascular magnetic resonance (CMR) perfusion can assess ischemia with high accuracy and has been assessed against different modalities in well-designed randomized clinical trials.

2. Non-invasive quantification of ischemia has a potential clinical impact in management of patients with coronary artery disease beyond qualitative evaluation.

3. Quantitative CMR perfusion techniques have significantly developed over the years and have shown robust accuracy in comparison to PET studies or invasive measurements of coronary flow.

4. Automated quantitative CMR perfusion allows for rapid and accurate creation of pixel-based myocardial blood flow (MBF) maps with in-line processing and improvement in clinical workflow.

5. The use of automated CMR MBF maps in clinical routine may allow for more accurate diagnosis of coronary artery disease as well as evaluation of the different phenotypic expression of atherosclerosis in both epicardial arteries and microvascular vessels.

SYNOPSIS

Cardiovascular magnetic resonance (CMR) perfusion imaging has evolved into a robust non-invasive technique to evaluate ischemia in patients with coronary artery disease (CAD). While qualitative and semi-quantitative methods have shown that CMR has high accuracy in diagnosing flow-obstructing lesions in CAD, quantitative ischemic burden is an important variable used in clinical practice for treatment decisions. Quantitative CMR perfusion techniques have evolved significantly since their initial development with accuracy comparable to both Positron Emission Tomography and microsphere evaluation. Routine clinical use of these quantitative techniques has been facilitated by the introduction of automated methods that accelerate the workflow and rapidly generate pixel-based myocardial blood flow maps.

Introduction

Coronary heart disease (CHD) is the most common cause of morbidity and mortality globally.[1] It is caused by the atherosclerotic narrowing of the coronary arteries and is amenable to treatment with medical therapy and revascularization.[2-4] However, the suitability of a lesion to intervention depends on its functional significance. Coronary stenoses of hemodynamic significance are amenable to percutaneous intervention but intervening on those that are not "flow-limiting" may confer a worse prognosis.[5-7]. Furthermore, the amount of ischemia is important. Sub-group analysis of the COURAGE trial has shown that patients with greater than 10% LV ischemia benefit from revascularization over medical therapy alone.[8] The gold standard assessment for suspected coronary artery disease (CAD) is coronary angiography but this is invasive and therefore associated with risks,[9] and exposes patients to ionizing radiation.[10] Therefore, high quality assessment of ischemia and the functional significance of CAD is required to appropriately manage patients.[11-13]

There are various non-invasive techniques to assess ischemia including stress echocardiography, Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Computed Tomography (CT) with Fractional Flow Reserve (FFR) and Cardiovascular Magnetic Resonance (CMR).[14-20] There are advantages to each and they have high sensitivities and specificities for the detection of coronary heart disease.[14-20] CMR does not use ionizing radiation and is the gold standard for cardiac structure, function and tissue characterization[21, 22] giving extra useful information to the clinician.

In clinical practice perfusion CMR is a qualitative technique. Typically, three left ventricle (LV) short axis images (base, mid and apex) are acquired per heartbeat during the first pass of a gadolinium-based contrast agent under conditions of vasodilator stress and rest.[23] An

experienced observer compares the images and looks for areas of relative hypoperfusion at stress which corresponds to a functionally significant coronary stenosis. Clinical decisions are then made based on this qualitative assessment. However, truly “balanced” ischemia due to disease in all 3 of the coronary artery arteries could cause a global flow reduction that could be missed. Coronary microvascular dysfunction, a cause of chest pain and a common feature in cardiomyopathy, is not well characterized, and visual quantification may have reduced accuracy and reproducibility.[24] Therefore, it is desirable to fully quantify myocardial perfusion and bring this into clinical practice.

Advanced imaging techniques can now quantify myocardial perfusion, the myocardial blood flow (MBF, ml/g/min) at stress and at rest. The myocardial perfusion reserve (MPR, referred to as the coronary flow reserve, CFR, in PET studies) is the ratio of the stress MBF to rest MBF. Relative flow reserve can also be measured by dividing the stress MBF of different myocardial segments. The majority of the evidence for quantitative perfusion to date is from the PET literature but quantifying perfusion is also possible with CMR and recent advances have brought this to practice.

In this review we discuss the benefits of the non-invasive quantification of perfusion, discuss the methods of quantifying perfusion with CMR and suggest how through automating the process it is possible to introduce quantitative CMR into clinical practice.

The importance of quantitative perfusion in clinical practice

CMR quantitative perfusion has historically been time-consuming and difficult which has kept it out of the realms of clinical practice and meant that the majority of the evidence for

quantitative perfusion is in PET studies. Early evidence that MBF could be measured noninvasively came from the initial studies from Gould et al showing the value of quantification to detect significant coronary stenosis.[25] From those initial studies, quantification evolved to show its capability to characterize different levels of CAD severity in a more accurate way than qualitative analysis, especially identifying single- versus three-vessel disease and microcirculatory involvement. Patients with three-vessel CAD had more extensive perfusion abnormalities on fully quantitative assessment than patients with single vessel disease.[26] Similarly, in a small CMR study of 41 patients with suspected coronary artery disease, fully quantitative perfusion was able to reliably discriminate between single vessel and triple vessel disease which was not possible with qualitative perfusion.[27] In one PET study which enrolled 104 patients at moderate risk of CAD, absolute quantification had a significantly higher positive predictive value, negative predictive value and accuracy for the detection of obstructive disease compared to qualitative perfusion.[28] Furthermore, the inter-observer variability of perfusion assessment was lower for the quantitative method. All these findings have important clinical implications where the extent of ischemia influences treatment choices.

Quantitative perfusion also gives additional information over qualitative analysis. Absolute stress perfusion and CFR are prognostic. In one study 256 patients including 150 with known CAD underwent ammonia PET evaluation and were followed up for 5.5 years.[29] Those with impaired CFR (<2) had higher rates of death and major adverse cardiovascular events (MACE) than those with normal CFR (>2). CFR was additive to risk determined by qualitative clinical read. Those with perfusion defects and abnormal CFR had worse clinical outcomes than those with normal CFR.

In patients with impaired LV function myocardial perfusion is also important. Neglia et al. enrolled 67 patients with LV impairment with dipyridamole stress PET and followed them up for 45 months.[30] Patients with severely depressed stress ($\leq$ 1.36 ml/g/min) and rest perfusion ($\leq$ 0.65ml/g/min) had a relative risk of death or the progression of heart failure of 3.5 and 3.3 respectively compared to those with normal perfusion. On multivariate regression analysis, only stress MBF, resting heart rate and end diastolic dimensions were independently prognostic - 5-year event free survival was 35.8% in patients with stress MBF $\leq$ 1.36 ml/g/min compared to 79% in those with MBF > 1.36ml/g/min.

Perfusion may also be impaired in non-ischemic cardiomyopathies. Patients with hypertrophic cardiomyopathy (HCM) often present with chest pain and have ischemic features on electrocardiogram thought related to microvascular dysfunction.[31] Ischemic damage (both acute-subacute and chronic) is seen at autopsy[32] and ischemia detected by SPECT is associated with ventricular tachycardia.[33] Patient with HCM have impaired stress perfusion compared to healthy controls (even in non-hypertrophied segments) and this is associated with increasing wall thickness and fibrosis.[34] In a prospective cohort study of 51 patients and 12 controls with atypical chest pain the degree of perfusion impairment was an independent predictor of death and adverse cardiovascular events.[35] Other cardiomyopathies with hypertrophy, for example Fabry disease and amyloidosis also have impaired perfusion. In Fabry, this has been used to evaluate treatment efficiency.[36] In amyloidosis, microvascular dysfunction has been shown using PET even in the absence of epicardial CAD and with lower stress and rest absolute perfusion values compared to patients with hypertensive LV hypertrophy.[37] Using CMR, semi-quantitative perfusion has

been shown to differentiate amyloidosis from normal patients and to identify patients with normal and lower LV function.[38]

In summary, fast, efficient quantitative perfusion for clinical practice and research would have advantages for disease identification and characterization, adding prognostic information and increasing reliability and adding the ability to characterize microvascular disease in CAD and cardiomyopathies, potentially aiding therapeutic drug development and treatment monitoring.

Qualitative and semi-quantitative perfusion CMR

The "baseline" technique, qualitative stress perfusion CMR is sensitive and specific for CAD detection[16] and a "normal" CMR scan confers a good prognosis.[39, 40] Using the AHA 17 (or 16) segment model, ischemia extent can be evaluated[24] and used to target revascularisation[8] with either 10% or 1.5 ischemic segments defining patients with a worse prognosis.[41] To improve on this, semi-quantitative assessment has been used. This uses time-signal intensity curves in each myocardial segment to estimate the myocardial perfusion, Figure 1. There are various different methods that may be used for estimating perfusion including contrast enhancement ratio (CER), myocardial-to-LV upslope index ratio and upslope integral ratio.[42] The CER is calculated from $(SI_{peak} – SI_{baseline}) / SI_{baseline}$ where SI_{peak} is the maximum signal intensity (SI) in the region of interest and $SI_{baseline}$ is the mean baseline SI. The myocardial to LV upslope method is calculated by dividing the initial upslope of the myocardial time-signal intensity curve by the initial upslope of the LV blood pool myocardial time-signal intensity curve.[43] The upslope integral ratio is the area under the

curve for the myocardial time-SI curve once the baseline has been adjusted for.[44] The diagnostic accuracy of semi-quantitative perfusion has been compared with PET, to absolute MBF using animal models and microspheres[42] and invasive coronary angiography.[43, 45] Compared to absolute MBF as measured using animal models and microspheres, at low flows there is a linear relationship between semi-quantitative perfusion and MBF. However, as the absolute flow increases (hyperemic flow), the semi-quantitative methods all significantly underestimate flow. The CER and the LV to myocardial upslope method begin to underestimate absolute MBF from 1ml/g/min. Of the three, the most linearly associated method is the upslope integral ratio, but even with this method the linearity fell with flows over 3ml/g/min.

Schwitter et al. found that semi-quantitative perfusion had a sensitivity, specificity and area under the curve (AUC) of 91%, 945 and 93% respectively for the detection of CAD with PET as the gold standard but lower compared to quantitative angiography (diameter stenosis >50%) - 87%, 85% and 91% respectively.[43] Not all studies are so positive, for example Mordini et al. compared each of the semi-quantitative methods to quantitative coronary angiography[45] finding CER (57%, 91% and 78%), LV to myocardial upslope method (87%, 68% and 82%) and the upslope integral ratio (83%, 68% and 75%).

Overall the non-linear relationship between semi-quantitative perfusion and absolute MBF with the underestimation of hyperemic flow make semi-quantitative assessment of perfusion only modestly incremental for accuracy to qualitative approaches for routine clinical practice, a benefit at best marginal given the associated time penalty of the analysis.

Quantitative CMR Perfusion

Standardized full quantification is desirable for more accurate measurements of CMR perfusion but has been hard. The steps involved can be described as below:

a) Precise measurement of the arterial input function – AIF
b) Precise measurement of myocardial enhancement
c) Sufficient temporal-spatial resolution to detect disease
d) The ability to convert signals above into contrast concentrations [Gd]
e) A model of blood myocardium contrast behavior.
f) The computing power to solve the model to derive myocardial blood flow
g) The ability to do the above with sufficient accuracy, low time penalty and in a generalizable way to be useful for clinical care.

To perform the above, requires further capabilities. To convert MR signal to Gd concentration requires deep MRI sequence knowledge (eg gradient performance, understanding of prepulse limitations, coil performance, contrast non-linearity and signal clipping); the ability to image fast (every heartbeat, pixels across the myocardium, number of slices); the ability to motion correct images (at the varying contrast concentrations present); the ability to segment the blood pool and therefore the myocardium. For clinical utility, this needs to be automated – but in a way that permits quality control overview by the reporting physician (ie the display of quality control outputs) and display in a standardized format for clinicians. During first pass, gadolinium is very concentrated in the blood pool, resulting in T1, T2 and T2* effects not present when diluted during passage into the myocardium. A single measurement (read-out) technique cannot be optimized for both. Two approaches are used: a *dual bolus approach* (stress and rest perfusion done twice,

initially with a low dose (eg 10x lower) of Gd for blood AIF, repeated at normal dose for myocardium; or *a dual sequence approach* (full coverage optimized for myocardium, one slice repeated optimized to measure blood with its high Gd concentrations – this can be low resolution).[46] There are a variety of different models of blood myocardial contrast exchange, and a variety of different ways to solve these.[47] Increasing model sophistication requires increasing computational power but supplies more potential accuracy. This domain is not yet standardized and a variety of approaches are available.[48] A more comprehensive review on the models and approaches used for the quantification methods can be found in chapter 6 of this issue.

To assess the performance of such models requires both animal and human experimentation with increasingly robust gold standards ranging from microsphere experiments (animal models), comparator non-invasive testing (PET) and invasive testing based on coronary angiography, which needs to either quantitate luminal narrowing (3D quantitative coronary angiography, or via intracoronary wires with intravascular ultrasound or optical coherence tomography) or by measure intracoronary hemodynamics (fractional flow reserve, FFR or instantaneous wave-free ration IFR). A summary of quantitative CMR studies using different approaches is listed on Table 1. The first studies in 1993 and followed-up in 1998 compared MRI measurements to microspheres in a dog model.[49, 50]. These used a dual-bolus technique and compared to microsphere data with good correlation within a range of flow up to 5.0 mL/min/g both at rest and under pharmacological stress.[51] The first human studies compared quantitative perfusion to functional assessment of stenosis using invasive FFR as the gold standard demonstrated good sensitivity of 92.9% but low specificity of 56.7% using an MPR cutoff of 2.04.[52] Using a

high-resolution sequence at 3.0T, there was an improvement in the accuracy of quantitative MPR versus FFR using a cutoff of 1.58 with a sensitivity of 0.80 and an improved specificity of 0.89.[53] An example of a normal quantitative stress CMR perfusion exam is shown in Figure 2. Other authors have also shown that quantitative perfusion may outperform qualitative and semi-quantitative approaches with different techniques, either comparing the results to quantitative coronary angiography or invasive FFR as the gold standard.[45, 54-58] When compared to PET studies, CMR demonstrated similar accuracy for the detection of significant coronary lesions but the absolute myocardial flow values were only weakly correlated, with mean CMR MBF values slightly different than the ones obtained with PET both for stenotic and non-stenotic territories with the methods used.[59-62] Given the higher spatial resolution provided by CMR, analysis of differences in perfusion between the endocardial and epicardial layers can now be assessed more accurately and quantified as shown in Figure 3 in a patient with a severe left anterior descending artery proximal lesion. This assessment of transmural perfusion gradients quantitatively may become one of the unique applications made possible by CMR as it depends on high-resolution maps for correct analysis.[63]

Fully automated Quantitative CMR Perfusion

Recent developments in all aspects of CMR with advances in computational power have permitted full automation of quantitative perfusion either offline, or, most recently on-the-fly, generating perfusion maps on the scanner as DICOM images with each pixel color coded in mL/g/min. Kellman et al first developed a dual sequence approach integrated within the

Gadgetron framework[64] that allows all reconstruction and processing of images to be done in-line and fully automated with results available within up to two minutes after acquisition using a Blood Tissue Exchange Model (BTEX) solved by partial differential equations. The output includes the source signal-intensity first-pass images with and without motion correction plus a gadolinium-concentration image and an MBF map.[65] Additional quality control outputs provide the RR intervals through the acquisition, the blood pool segmentation and the arterial input function curve. Figure 4 shows motion-corrected first-pass images, LGE and the calculated MBF maps in a patient investigated for obstructive CAD with a reversible inferior-wall defect. An advantage of this approach is that the Gadgetron framework is open source and potentially deployable by all scanner manufacturers raising the possibility of a standardized approach to image reconstruction/analysis across healthcare systems.

This automated method has been validated against PET with good agreement between the two approaches for global/regional perfusion, rest/stress states and absolute/relative values.[66] The reproducibility of this approach has also been shown to be within the needs for clinical application with within-subject coefficients of variation between 8-12%, lower than the reported coefficients described for PET studies between 9.6-21%.[67, 68]

Similar automation processes have also been proposed by other authors showing similar results compared to manual steps for calculating arterial input function signal and MBF values.[69] From this framework, Hsu et al demonstrated that the full automated approach provided similar accuracy than the manual quantification and allowed for high diagnostic performance in detecting significant CAD both at a patient and vessel level against QCA and CTA.[70]

Clinical applications of CMR quantitative perfusion

With the wider adoption and ease of use of the newer automated techniques to perform routine CMR perfusion quantification, the increase in clinical applications of this method should increase significantly. Initial data suggested that the diagnostic accuracy of quantitative perfusion would outperform both semiquantitative and qualitative methods of analysis (AUC 92% versus 82% for semiquantitative methods versus 78% for qualitative, $P<0.001$ for both).[45] However, this notion has been challenged more recently using data from the CE-MARC trial where authors did not identify a difference between visual analysis and the quantitative approach.[71] While this may indicate that a qualitative approach is sufficient for clinical use, one has to take into account that the visual diagnosis was carried out by experienced users and only manual CMR quantification was used, with definite evidence for or against the superior accuracy of quantifying perfusion still not established, especially with the develop newer automated techniques.[72] One example of how quantification can improve the assessment of perfusion defects over visual analysis is demonstrated in a study where authors showed that MBF is much lower in true perfusion defects versus in areas with dark rim artifacts, allowing for easier distinction between these frequent confounding entities.[73] The example shown in Figure 3 also illustrates this point as the subendocardial layers had significantly lower MBF values during stress, facilitating the diagnosis of a true perfusion defect. Another example of the use of quantitative CMR perfusion is shown in Figure 5 in a patient with apical hypertrophic cardiomyopathy where subendocardial hypoperfused areas can sometimes be misinterpreted given the location of these defects.

Three-vessel disease CAD is a known situation where quantitative perfusion has demonstrated an increased diagnostic threshold in comparison to qualitative analysis when PET is compared to SPECT.[26] While no focused studies with similar comparisons have been made with CMR, individual cases have already been described.[65] One example of such situation is shown in Figure 6 where a woman with known three-vessel CAD was evaluated with CMR to determine the best treatment strategy given her poor overall clinical status and need to determine where an invasive approach would derive the best results.

Besides the assessment of diagnostic accuracy, quantitative CMR perfusion has been shown to add prognostic value over visual assessment alone with the measurement of ischemic burden either as a continuous variable or using a threshold of MPR < 1.5 affecting an area > 10% of the myocardium significantly increasing both the AUC for cardiovascular events at 2 years and improving the net reclassification index.[74] Besides that, microvascular disease assessment is also another clinical use where quantitative CMR seems to have a clear diagnostic advantage. In a group of patients without obstructive CAD but positive risk factors for atherosclerosis, reduced MPR and MBF were identified in these subjects versus healthy volunteers using quantitative CMR.[75] Interestingly in this study, no differences were observed regarding native T1 or ECV values and perfusion values remained significantly different even after adjusting for ventricular mass, age and gender. The ability to monitor changes in microvascular disease with quantitative perfusion in the absence of obstructive disease and beyond traditional clinical and other imaging markers is a unique feature of CMR that may prove even more useful in future studies.

Conclusions

In conclusion, CMR quantitative perfusion has evolved rapidly in the recent years from a tool used only in large research centers to an applicable feature that can be used in a routine clinical environment. Accuracy and reliability of CMR perfusion quantification have been validated against many different standards, with evidence pointing to true gains over qualitative techniques and laborious semi-quantitative approaches. Automation of processes involved in acquisition and analysis are crucial to the more widespread dissemination of these techniques, opening many opportunities for new discoveries in the pathophysiology of coronary circulation with potential novel treatment goals.

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Figure Legends

Figure 1: Semi-quantitative perfusion analysis of a patient with a perfusion defect in the inferolateral wall. A – endocardial and epicardial contours are drawn for each slice and for each measurement and the superior RV insertion point is identified. B – Signal intensity is plotted against time for an area of ischemic myocardium (blue) and remote myocardium (yellow). Subsequent analysis can be performed to calculate perfusion in a semi-quantitative fashion.

Figure 2: Myocardial blood flow (MBF) maps during stress with 0.56mg/kg of dipyridamole (A-C) and rest (E-F). The calculated MBF at stress was 2.23 mL/min/g versus the rest MBF of 0.61 mL/min/g. The myocardial perfusion reserve (MPR) was normal at 3.7. First-pass perfusion images (not shown) were also considered normal, without any visual perfusion deficits. Rest and stress slices are in a slightly different location due to patient movement between acquisitions.

Figure 3: Stress (A) and rest (B) myocardial blood flow (MBF) maps from a patient with severe left anterior descending coronary artery. During stress, the endocardial MBF in the antero-septal wall fell from 0.70 to 0.30mL/min/g a significant reduction compared to the epicardial layer where the MBF almost did not change. The relative perfusion reserve (RPR) during rest was 0.88 but fell significantly to 0.36 during stress, quantitatively showing the predominance of ischemia affecting the subendocardial layers.

Figure 4: Stress (A) and rest (B) perfusion in a patient with a severe stenosis of the right coronary artery. There is an adenosine induced perfusion defect demonstrated in the basal to mid inferior wall (white arrows). Late gadolinium enhancement (LGE) images (C) show no associated infarction. Perfusion mapping basal, mid and apical short axis views are shown at stress (D) and rest (E). Perfusion is quantified automatically and inline at the scanner at a voxel level. There is an area of hypoperfusion in the basal and mid inferior wall (0.7ml/g/min compared to 2.7ml/g/min in the remote myocardium). The rest flow in the inferior wall is 1.0 ml/g/min.

Figure 5: Stress (A) and rest (B) perfusion in a patient with apical hypertrophic cardiomyopathy. There is an adenosine induced perfusion defect demonstrated in the hypertrophied apex at stress (white arrows). Perfusion mapping in the same patient in basal, mid, apical short axis and horizontal long axis views at stress (C) and rest (D). Perfusion is quantified automatically and inline at the scanner at a voxel level. There is an area of hypoperfusion in the apex at stress (0.5ml/g/min compared to 2.2ml/g/min in the remote basal myocardium). The flow in the apex actually falls at stress (a perfusion reserve <1) with flows of 1ml/g/min measured at rest.

Figure 6: A woman with known three-vessel CAD was evaluated with CMR to determine the best treatment strategy. Qualitative first pass perfusion images (A) and late gadolinium enhancement (B) did not show any significant changes. When quantitative analysis was performed using the myocardial blood flow (MBF) maps (stress in basal and mid slices in C and E; rest in D and F), global stress MBF was significantly reduced at 1.12mL/min/g. The relative flow reserve showed a more pronounced reduction in flow in the inferior wall (MBF

of 0.75 to 0.86 mL/min/g) in comparison to the anterior wall values (MBF of 1.1 to 1.2 mL/min/g) and a percutaneous intervention was indicated to selectively treat the inferior wall ischemia in order to minimize the invasive procedure.

Acknowledgements

We thank Dr Peter Kellman (Medical Signal and Image Processing Program; National Heart, Lung, and Blood Institute; NIH, USA) for his valuable comments and suggestions to improve the manuscript and overall support on implementing some of the sequences used in the figures.

Table 1 – CMR Perfusion Quantification Studies

Study	Field Strength (T)	AIF	Calculation Model	Automation	Software Used	Validation
Costa, 2007[52]	1.5	Single bolus	Fermi deconvolution	No	in-house development	FFR
Lockie, 2011[53]	3.0	Single bolus	Fermi deconvolution	No	in-house development	FFR
Hsu, 2012[58]	1.5	Single bolus, dual-sequence	Model-constrained deconvolution	Semi-automated; pixel-wise quantification	in-house development	Microspheres (dogs); Visual invasive coronary angiography (human studies)
Huber, 2012[54]	1.5	Single bolus	Model-independent deconvolution	No	in-house development	QCA+FFR
Morton, 2012[59]	1.5	Dual-bolus	Fermi deconvolution	No	ViewForum Software	PET
Miller, 2014[62]	1.5	Single bolus	Fermi, truncated singular valued, Tikhonov regularization	No	in-house development	PET
Mordini, 2014[45]	1.5	Dual-bolus	Fermi deconvolution	No	in-house development	QCA

Motwani, 2014[55]	3.0	Single bolus	Fermi deconvolution	No	in-house development	QCA
Papanastasiou, 2016[56]	3.0	Single bolus	Fermi and 1-barrier, 2 region distributed parameter	No	in-house development	FFR
Chung, 2016[57]	3.0	Single bolus	Flexible tissue homogeneity and adiabatic tissue homogeneity	No	in-house development	Visual invasive coronary angiography
Kellman, 2017[65]	1.5	Single bolus, dual-sequence	Fermi + Blood Tissue exchange (BTEX)	Yes	Gadgetron framework	Phantom, PET
Qayyum, 2017[61]	1.5	Single bolus	Tikhonov regularization	No	in-house development	PET
Hsu, 2018[70]	1.5	Single bolus, dual-sequence	Model-constrained deconvolution		in-house development	QCA and CTA