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REVIEW ARTICLE－FOCUS ISSUE: MBF ESTIMATION USING MULTI-MODALITY

Quantitative Myocardial Perfusion MR Imaging: Saturation Correction of Arterial Input Function for the Accurate Quantification

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Abstract

Myocardial perfusion can be assessed with dynamic cardiovascular magnetic resonance imaging (MRI) during the passage of contrast agent bolus. Myocardial perfusion MRI has been evaluated qualitatively or semi-quantitatively. However, fully-quantitative myocardial perfusion MRI permits more objective assessment of coronary artery disease and evaluation of diffuse microvascular disease. Advances in acquisition and image analysis of cardiac magnetic resonance have enabled absolute myocardial perfusion quantification, previously only achievable with positron emission tomography. Absolute quantification of myocardial blood flow (MBF) requires knowledge of the amount of contrast agent in the myocardial tissue and the arterial input function (AIF) driving the delivery of contrast agent. However, accurate quantification of MBF is challenging due to lack of linearity between the measured blood signal and high blood contrast concentration during first pass, because sequences for perfusion MRI have been developed to optimize the contrast between normal and ischemic myocardium. Saturation correction of AIF response curve is required for the perfusion quantification. This review article will discuss saturation correction of AIF for accurate MBF measurements in perfusion MRI.
Keywords: Input function, Magnetic resonance, Myocardial perfusion, Quantification, Saturation correction
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Perfusion imaging uses dynamic contrast-enhanced acquisition to observe the first-pass dynamics of contrast agent delivery in the tissue of interest over time. Stress perfusion MRI is increasingly used for evaluation of myocardial ischemia (1–3). Myocardial perfusion MRI is most commonly evaluated qualitatively with visual assessment. Perfusion MRI may be analyzed semi-quantitatively, by evaluating upslope of myocardial and blood time-intensity curves. Although myocardial perfusion reserve index (MPRI) can be calculated by the semi-quantitative approach, MPRI can be substantially influenced by bolus profile of the arterial input function (AIF). Fully-quantitative analysis would be much more desirable. Recent technological advances in MRI acquisition and analysis permit absolute quantification of MBF and myocardial perfusion reserve. Previous studies demonstrated the quantitative assessment of stress perfusion MRI can provide high diagnostic performance for detecting flow-limiting coronary artery disease (4–7). However, for the accurate quantification of MBF with dynamic contrast-enhanced MRI, we should take into account various technical aspects, such as the optimization of myocardial perfusion MRI sequences, image acquisition parameters and contrast injection protocols, and the selection of tracer kinetic models. Among those issues, this review will focus on saturation correction of AIF for accurate perfusion quantification in contrast-enhanced MRI.

Saturation effect on quantitative myocardial perfusion MRI

Myocardial perfusion MRI is based on T1-weithted pulse sequences where interactions of paramagnetic gadolinium with surrounding water molecules provide lower T1 relaxation

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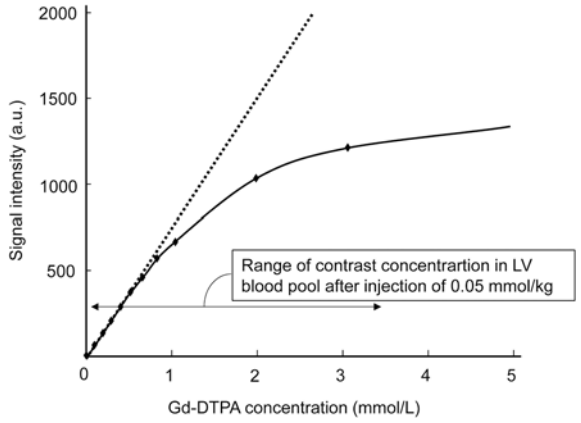

Figure 1 The relationship between gadolinium-based contrast concentration and signal intensity in the blood pool.

At lower contrast concentration, the relationship of signal intensity and contrast concentration is linear. However, at higher contrast concentration, the signal intensity shows a non-linear dependence on the contrast concentration. This deviation from the linear dependence is referred to as saturation effect.

times of the protons involved, resulting in signal enhancement on the T1-weighted image that reflects the distribution of gadolinium in tissue (8, 9). Contrast medium used for perfusion MRI is small molecule (<1kDa, typical particle diameters of 0.82 nm for gadolinium dimeglumine) that distributes to the interstitial space and generally do not enter the intracellular space (9).

In general, a linear relationship between contrast enhancement and contrast concentration facilitates absolute perfusion quantification in contrast enhanced imaging. The linearity between contrast enhancement and contrast concentration is present in CT iodine-based contrast agents regardless of their concentrations, but in MRI gadolinium-based agents only up to a certain concentration limit (8). The limited linearity of contrast enhancement to contrast concentration is one of the major challenges in quantitative perfusion MRI.

There are several approaches to obtain T1-weighted MR images, including a short repetition time gradient echo (GRE) imaging for perfusion imaging of tumors, an inversion recovery (IR) approach for late gadolinium enhanced MRI of myocardial infarction, and saturation recovery (SR) approach for myocardial perfusion MRI. Myocardial perfusion MRI is designed to optimize the contrast between normal and ischemic myocardium, by using the delay time (TI) between 90 degree saturation pulse and image acquisition of 50 ms to 150 ms. For myocardium, the relationship between contrast enhancement and tissue gadolinium concentration remains approximately linear. However, gadolinium concentration in the blood is much higher than that in myocardial tissue during the first pass after bolus administration of gadolinium contrast medium, resulting in the saturation or non-linearity of the blood AIF.

The relationship of signal intensity and gadolinium contrast concentration on typical myocardial perfusion MRI is shown in Figure 1. At lower contrast concentration, the relationship of signal intensity and gadolinium contrast concentration is linear (10). However, at higher contrast concentration, the signal intensity shows a non-linear dependence on the contrast concentration (10). The difference of observed signal intensity from the expectation occurs mainly due to T1- saturation effect. The T1- saturation effect is observed in the blood pool of left ventricle (LV), where one measures the AIF.

AIF is the first-pass contrast dynamics at the respecting supplying artery. It is important to measure AIF accurately for perfusion quantification in first-pass contrast-enhanced MRI. The typical AIF acquisition site for myocardial perfusion is the LV cavity in MRI. If the T1- saturation effect in AIF is neglected, the contrast enhancement in the myocardium would appear to be larger relative to the arterial contrast enhancement, and then myocardial perfusion would be overestimated. Therefore, the saturation correction of AIF is required for accurate myocardial perfusion quantification.

If we use short TI between 90 degree saturation pulse and image acquisition, <10 ms for example, both blood and myocardial time intensity curves become linear, and there is no need for saturation correction. However, the image quality of perfusion MRI are suboptimal with much lower signal-to-noise and contrast-to-noise ratios.

Implementation of AIF saturation correction in myocardial perfusion MRI

For saturation correction of AIF in perfusion MRI, there are two major approaches; dual-bolus method and dual-sequence method. Both approaches are performed to correct the non-linearity between signal intensity and contrast concentration.

Dual-bolus method uses the pre-bolus image data to correct AIF in the main bolus. In this approach, injection of a diluted bolus of contrast medium is performed prior to the main bolus in perfusion MRI. The points for the dual-bolus protocol are 1) both the main-bolus of neat gadolinium contrast agent and the pre-bolus of diluted contrast solution should be of equal volume and administered at the same flow rate, and 2) each bolus should be followed by a saline flush to maintain a compact contrast agent bolus in the LV chamber (11–15). The diluted contrast medium (e.g. 0.005 mmol/kg of gadolinium contrast) shows linear relationship with signal intensity in the LV blood pool (16). Saturation correction of AIF in dual-bolus approach is performed as follows. First, the blood time-signal intensity curve in the LV cavity without saturation effect is obtained by using perfusion MRI with the diluted contrast medium. Then, the blood time-signal intensity curve in main neat bolus is corrected by using the pre-bolus blood time-signal intensity curve (Figure 2A) (10). Example of

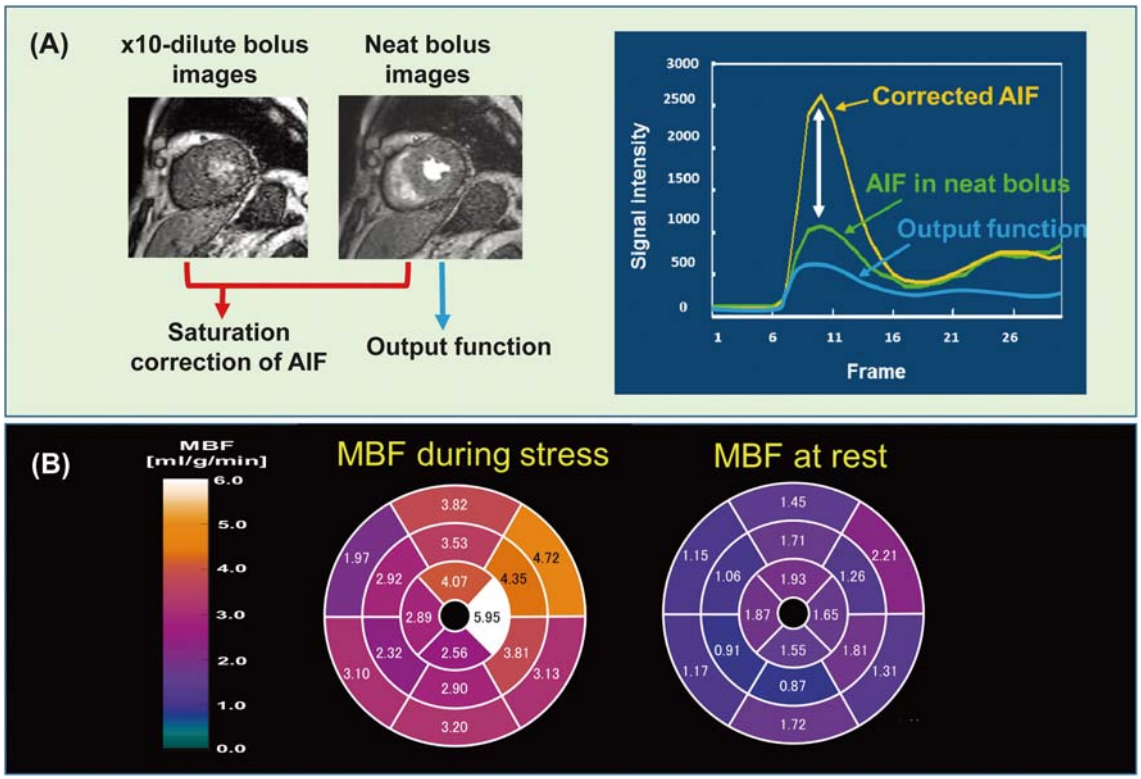

Figure 2

(**A**) Dual-bolus approach for saturation correction of arterial input function (AIF). In this approach, 10-times dilute bolus and neat bolus are used to correct for T1 saturation of contrast medium in LV blood pool. AIF in neat bolus is converted to saturation-corrected AIF by using blood–signal intensity curve on dynamic images with10-times dilute bolus.

(**B**) Example of stress and rest myocardial blood flow (MBF) bull's eye maps using dual-bolus approach for AIF saturation correction in a patient with suspected coronary artery disease. Mean stress flow was approx. 3.5 mL/g/min and mean rest flow was approx. 1.5 mL/g/min in this case.

myocardial perfusion maps is shown in Figure 2B. The dual-bolus protocol has shown to be robust for accurate quantification of myocardial blood flow in perfusion MRI (15, 17). The position statement of SCMR in 2013 refers to the dual-bolus method as a technique to reduce saturation effects in the blood pool (18).

Dual-sequence method is another promising approach for AIF correction. This method uses a combination of two different type of image acquisition in a single scan (19). In this approach, short saturation recovery image with low spatial resolution for AIF correction is combined by long saturation recovery image with high spatial resolution acquisitions for myocardial signal (Figure 3) (19). As previously explained, T1-weithting for myocardial perfusion MRI is achieved by applying a saturation pulse before each image. A long TI (time between saturation pulse and image acquisition) is necessary to obtain high contrast between normal and ischemic myocardium. However, a long saturation delay can cause non-linearity of the AIF which exhibits much higher contrast concentration during the first pass. For accurate measurement of AIF, it is necessary to use saturation pulse with short TI. There is an opposing requirement between the need for a long saturation delay for good myocardial response and a short saturation delay for accurate measurement of AIF. Dual-sequence method is an approach to solve the issue by using separate pulse sequences optimized for AIF and myocardial tissue in a single scan. Compared to dual-bolus method, a benefit of this approach is that simultaneous measurement of the AIF and myocardial signals avoids physiological variation between bolus injections such as those due to differences in respiration which can be the source of errors for the perfusion quantification. Recently, the dual sequence approach was optimized for generating a fully automatic in-line pixel-wise MBF mapping (20). The feasibility of this dual-sequence method for MBF quantification has shown to be demonstrated (21). Although the dual-sequence method is not yet available as a clinical sequence at this point, this approach seems to be easily incorporated into a clinical workflow in near future.

Conclusions

Saturation correction of AIF is important for accurate measurement of myocardial blood flow in contrast-enhanced perfusion MRI. Dual-bolus and dual-sequence method are robust techniques to correct the non-linearity between signal

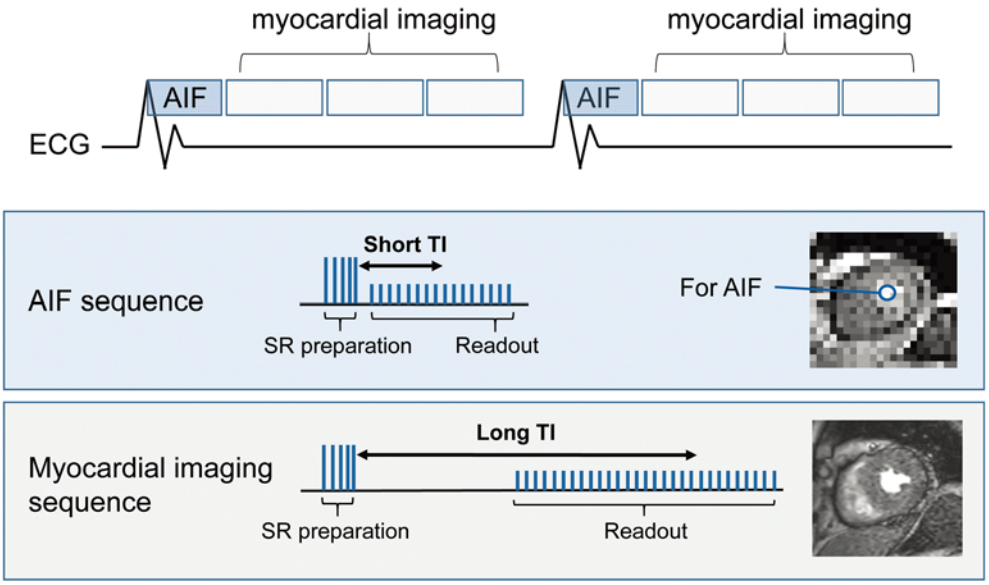

Figure 3 Overview diagram of dual-sequence method for multi-slice saturation recovery (SR).
Each image has an SR preparation followed by single shot image readout. Low spatial resolution AIF image is acquired with short saturation delay (TI) at the R-wave triggered, and high spatial resolution myocardial perfusion imaging is acquired with long TI.

intensity and contrast concentration of AIF on quantitative myocardial perfusion MRI.

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Conflicts of interest

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