Repeatability of quantitative first-pass perfusion MRI in the mouse myocardium

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Introduction

Recently, first-pass perfusion MRI of the mouse myocardium was demonstrated[1,2]. This technique is of considerable interest for the quantification of perfusion in preclinical models of cardiac disease. The repeatability of this method to quantify mouse myocardial perfusion has not been studied and still needs to be proven. Therefore, the main **aim** of this study was to evaluate the repeatability of quantitative, first-pass perfusion MRI in the healthy mouse heart.

A dual-bolus approach was used for accurate determination of the arterial input function (AIF), while a Fermi constraint deconvolution model was used to quantify perfusion[3,4]. First, we proved that the use of a pre-bolus allows for measuring an AIF that is not saturated, as would be the case for the second full bolus, by establishing linearity of AIF signal intensity with Gd-DTPA concentration. Secondly, repeatability of quantitative myocardial perfusion values was demonstrated by measuring a group of 9 mice at two time points.

Methods

All MR images were acquired using a 9.4T small animal MRI scanner. Mice were anesthetized with isoflurane in medical air. An infusion pump (flow rate: 2 ml/min) was used to ensure reproducible infusion of Gd-DTPA in 0.9% NaCl in the tail vein. First-pass perfusion images (**Fig. 1**) were acquired using an optimized ECG triggered FLASH sequence[1]. *Experiment 1: C57BL/6 mice* (♂, age 11 weeks, n=10) underwent up to 3 MRI sessions. To assess linearity of the AIF signal with Gd-DTPA concentration, at each session one 25 µl pre-bolus of Gd-DTPA (15, 30, 40 or 60 mM) was infused. *Experiment 2: C57BL/6 mice* (♂, age 11 weeks, n=9) underwent two MRI sessions with a one-week interval. At each session first-pass perfusion images were acquired of a pre-bolus (25 µl, 40 mM) and a full bolus (100 µl, 40 mM). Left ventricular (LV) function and mass were quantified from Cine MRI using an ECG triggered and respiratory gated FLASH sequence[5]. *Data analysis:* SI time curves from the LV blood pool and the myocardium were obtained using dedicated segmentation software. For experiment 1, a γ-variate function was used to fit the LV lumen SI time curves, from which the mean transit time (MTT) and the area under the curve (AUC) were determined[4]. For experiment 2, the AIF was defined from a series of four time-shifted γ-variate fits of the pre-bolus data, as described previously[3]. Next, myocardial tissue perfusion (ml/min/g) was quantified using a Fermi constraint deconvolution of the AIF and the myocardial tissue response from the full bolus using home-build software in Matlab[4]. Finally, repeatability was assessed in terms of the coefficient of variation (CV)[6].

Results and Discussion

Experiment 1: The maximum LV lumen signal increased with Gd-DTPA concentration (**Fig. 2a**). An excellent linear correlation (r=0.99) was found between the AUC and the pre-bolus Gd-DTPA concentration (**Fig. 2b**). The average MTT for the pre-bolus injection was 1.5±0.5s (n=28). The MTT was found to be equal for the pre-boluses with varying Gd-DTPA concentrations (one-way ANOVA, p>0.05), showing that there was no influence on the shape of the AIF curve with varying Gd injection dose. These results provide important justification for derivation of the AIF from the pre-bolus data.

Experiment 2: No significant differences were detected in respiratory rate and cardiac parameters (heart rate, LV end diastolic and end systolic volume, stroke volume, cardiac output, and LV mass) that could have biased repeatability of the quantification of mouse myocardial perfusion (p>0.05 in all cases, paired two-sided *t*-test). **Fig. 3** shows representative examples of two SI time curves of the pre-boluses and full boluses in one mouse for the repeated measurements. Perfusion values of individual mice at both time points are plotted in **Fig. 4a**. The average perfusion values in experiment 1 and 2 were 6.6±1.5 and 5.7±1.0 ml/min/g, respectively. Bland-Altman analysis (**Fig. 4b**) showed good limits of agreement between both measurements. Inter-animal CVs were found similar for the first (CV = 23%) and second (CV = 17%) measurement. Between-session CV of week 1 and 2 was 11%.

Conclusion

In this study an excellent, linear correlation (r=0.99) was obtained between the pre-bolus AIF signal intensity and the Gd-DTPA concentration. This provides direct experimental evidence that the pre-bolus approach results in an unsaturated AIF, which can be used for quantification of mouse myocardial perfusion. The between-session CV for myocardial perfusion values was 11%, which is low enough to detect pathological changes in perfusion. Therefore, this method is well suitable for longitudinal studies in various mouse models of cardiac pathologies, such as those of myocardial infarction and heart failure induced by transverse aortic constriction.

It is therefore concluded that repeatable, quantitative perfusion values can be obtained in the mouse myocardium with first-pass perfusion MRI, using a dual-bolus approach in combination with a Fermi constraint deconvolution model.

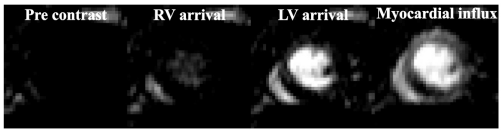

Fig. 1. Myocardial first-pass perfusion images of a full bolus at 4 time points.

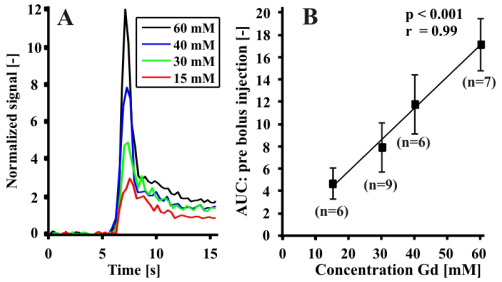

Fig. 2. SI time curves of the pre bolus with varying concentration Gd-DTPA (A) and the AUC, as measure for maximal SI, as function of the Gd-DTPA concentration (B). Error bars indicate SD.

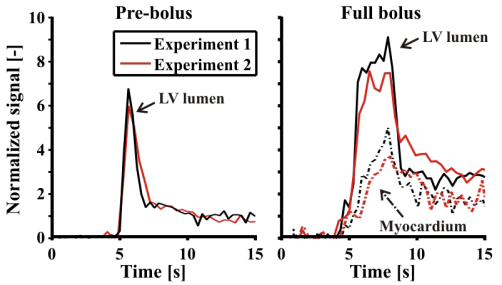

Fig. 3. Example of two SI time curves in the lumen (-) and myocardium (-.) of the pre-bolus and full bolus infusion in one mouse. There is excellent agreement between the different MRI experiments.

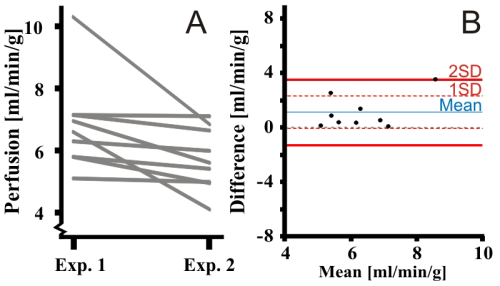

Fig. 4. Myocardial perfusion values (ml/min/g) of all mice for both experiments (A) illustrating good repeatability of the method, and the corresponding Bland-Altman plot (B).

Acknowledgement

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References

1) Coolen *et al.* MRM, **2010** (64), p1658. 2) Makowski *et al.* MRM, **2010** (64), p1592. 3) Köstler *et al.* MRM, **2004** (52), p296. 4) Jerosch-Herold *et al.* Med Phys, **1998** (25), p73. 5) Heijman *et al.* JMRI, **2008** (27), p86. 6) Bland & Altman. Lancet, **1986** (1), p307.