Towards a synergistic application of multimodal MR/PET myocardial perfusion imaging: Measuring capillary transit time heterogeneity with MRI and blood flow with simultaneous N-13 Ammonia PET

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Introduction: Despite efforts to validate quantitative measurements of myocardial blood flow (MBF) and myocardial stress/rest perfusion ratio (MPR) derived from dynamic contrast enhanced (DCE-) MRI using MBF/MPR estimates from established PET-based approaches, the potential of exploiting the inherent differences in data structure between PET and MR cardiac perfusion data remains underappreciated. With the advent of integrated MR/PET systems, those differences pertaining to different indicator/tracer kinetics and time resolutions between both modalities become crucial when shifting the paradigm in multimodality imaging from validation to the creation of synergies. It is the purpose of this study to present a first example of a synergistic MR/PET evaluation of myocardial perfusion imaging. For that, N-13 PET data is evaluated to yield reliable estimates of MBF/MPR while simultaneously acquired DCE-MRI perfusion data provides complementary information about microvascular hemodynamics, which is not accessible within the limited time resolution of clinical PET. Building on recent research on the role of capillary transit time heterogeneity (CTH) and mean transit time (MTT) in the regulation of myocardial oxygen extraction efficacy,[1] we hypothesize that MR-based assessment of CTH and a newly defined CTH reserve (CHR) adds incremental value to the assessment of MBF/MPR with N-13 Ammonia PET.

Methods: N-13 Ammonia PET and Gd-DTPA MRI myocardial perfusion data were acquired on an integrated 3T MR/PET scanner (mMr Biograph, Siemens, Erlangen) in 23 patients with suspected coronary artery disease (CAD) or suspected microvascular disease (MVD). Simultaneous acquisition of MR/PET stress (adenosine) and rest perfusion data was performed with an acquisition scheme and sequence parameters as previously reported.[2] An ECG-gated SR-FLASH sequence with dual sequence design for dedicated measurement of the arterial input function (AIF) was applied in three left ventricular short axis slices on the MR side and an ungated Listmode acquisition was used on the PET side. PET MBF was computed from N-13 Ammonia time-activity curves using a four-parameter three-compartment model with spillover correction.[3] Signal to concentration modeling for Gd-DTPA was performed according to Cernicanu et al.[4] Model constrained deconvolution[5] (MCD) was performed on the parts of the perfusion curves covering the first pass of the Gd-DTPA bolus. The distribution of vascular transit frequencies h was modeled as a Gaussian, resulting in a vascular residue function R given by the complementary error function (ERFC = 1 - ERF). To account for interstitial leakage a constant loading term I representing the interstitial volume as a fraction of the whole Gd-DTPA distribution volume is added to R, neglecting potential washout of Gd-DTPA during the first pass. After multiplication with an amplitude parameter F and constraining the mean of the distribution to be equal to 3 times its standard deviation (to include >99% of transit frequencies), the impulse response function R is given by:

$$R(t,F,\sigma,I) = F \cdot \left[(1-I)\cdot\left[1 - \frac{1}{\sigma\sqrt{2\pi}}\cdot\int_{-\infty}^{t} e^{\frac{(\tau-3\sigma)^2}{2\sigma^2}} d\tau\right] + I\right] = F\cdot[(1-I)\cdot ERFC(t,\sigma) + I]$$

Figure 1 shows examples of rest and stress tissue curves (TC) visualizing the MCD analysis for one case. The standard deviation of vascular transit frequencies σ was chosen to represent CTH,[1] CHR was defined as the ratio of σ-values from stress and rest scans.

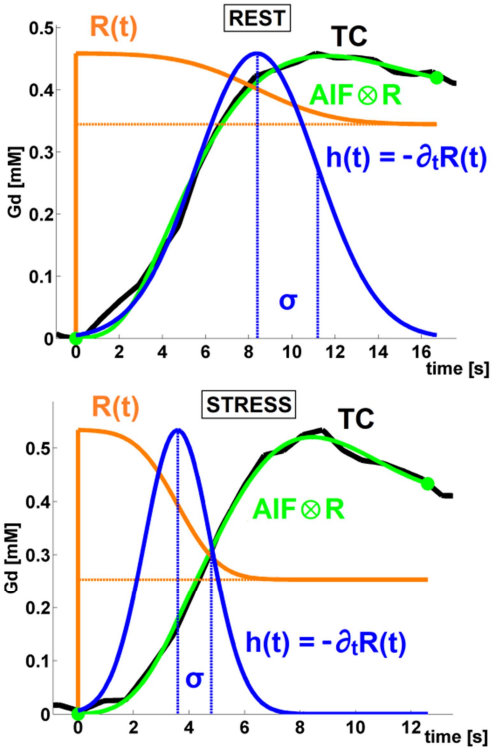

Fig. 1: Visualization of MCD and the calculation of σ

Results: Slice average MRI-derived CHR was compared to PET-derived MPR for one mid-ventricular short axis slice per patient as shown in figure 2. There is a continuous spectrum in the deviations of CHR from MPR, with CHR values being lower or equal to MPR values, but never less than one. Average values ± standard deviation for rest and stress CTH were 2.87±0.81 and 1.83 ±0.46 seconds respectively, average CHR was 1.62±0.46 seconds.

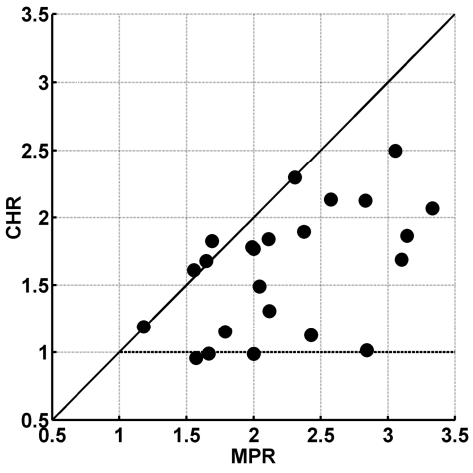

Fig. 2: MRI-derived CHR vs PET-derived MPR

Discussion: The results indicate that the proposed method to quantify CHR is able to open a new perspective on the concept of MPR with respect to the microvasculature. The data shown in Fig. 2 suggest that CHR, or more accurately the respective underlying physiological process, can be interpreted as a contributor to the full perfusion reserve as assessed with PET. By quantifying the involvement of the microvasculature in the overall reaction to stress, it may thus be possible to detect a given microvascular disorder despite non-pathologic overall MPR. Although this is a dedicated MR/PET study, it is not inconceivable that simultaneous CTH and MBF quantification is feasible with MR perfusion imaging alone. However, one great advantage of this study is that MRI data is used to extract only time/frequency-related perfusion parameters. Thereby, several assumptions necessary in the calculation of volume-related parameters such as MBF are avoided, e.g. global/microvascular hematocrit and water exchange conditions.[6] To assess indicator CTH or MTT, so far several approaches based on gamma-variate functions have been proposed to model the distribution of transit times.[1,6] In this study however, introducing additional parameters to include capillary lag times was waived in favor of fit stability.

Conclusion: This study shows for the first time that the assessment of capillary transit time heterogeneity with DCE-MR perfusion imaging using the proposed method adds incremental value to the estimation of MBF/MPR, possibly enabling the assessment of MVD in the absence of flow-limiting CAD. Especially in the context of MR/PET multimodality imaging, such synergistic approaches have the potential to expand our knowledge of cardiac microvascular dysfunction as well as the capability to assess it clinically.

References: **1.** Østergaard et al., Basic Res Cardiol (2014) 109-409 **2.** Zhang et al., Proc ISMRM (2013) 0576 **3.** Hutchins et al., JACC (1990) 15:1032-1042 **4.** Cernicanu et al., Acad Radiol (2006) 13:686-693 **5.** Jerosch-Herold et al., Med Phys (1998) 25:73-84 **6.** Lombardi et al., JMRI (1999) 9:402-408