Myocardial microvascular function at rest and under adenosine stress measured with dynamic contrast-enhanced MRI

D. L. Buckley[1], J. D. Biglands[1], A. Larghat[2], S. P. Sourbron[1], A. Radjenovic[3], J. P. Greenwood[2], and S. Plein[2]
[1]Division of Medical Physics, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, West Yorkshire, United Kingdom, [2]Division Cardiovascular & Neuronal Remodelling, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, West Yorkshire, United Kingdom, [3]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, West Yorkshire, United Kingdom

Introduction. Dynamic contrast-enhanced (DCE) MRI has been used to estimate myocardial perfusion (F_b) for some time [1] yet very little work has been published on MRI measurement of related myocardial microvascular characteristics such as blood volume (v_b), permeability-surface area product (PS) and interstitial volume (v_e). This may be related to the relatively small size of MRI contrast agents; nutritional flow to the myocardium by small solutes can become perfusion-limited at resting flows [2], and conventional measures of contrast agent transport (e.g. K^{trans}) are likely to reflect F_b rather than PS [3]. This concept is supported by the tracer kinetics analysis of Jerosch-Herold et al [4] that suggested PS was unreliably estimated using an extracellular agent (Gd-DTPA). Conversely, a recent study by Li et al [5] assumed Gd-DTPA uptake was permeability limited (i.e. K^{trans} ~ PS) and that PS increased under stress in proportion to changes in F_b; this increase was interpreted as reflecting capillary recruitment. The current study was designed to assess the potential of estimating microvessel characteristics in a group of normal volunteers at rest and under adenosine stress and to address the question, is delivery of an extracellular MRI contrast agent to the myocardium perfusion-limited?

Methods. We enrolled 16 healthy volunteers (9 males, 7 females, mean age 34 ± 8 years). Informed consent was taken from all volunteers in accordance with a study protocol approved by the local Ethics Committee. Perfusion imaging was performed at 1.5 T (Intera; Philips Medical Systems, Best, The Netherlands) using a flexible 5–element cardiac phased array receiver coil and in a single mid-ventricular short axis slice during systole. The sequence used was a SR-TFE with twofold SENSE, TR/TE/TI/flip 2.7 ms/1.0 ms/150 ms/15°, typical FOV 380x380 mm, Image matrix 160x160, slice thickness 10 mm. A first perfusion scan was performed during maximal vasodilatation, followed by a second scan about 15 min later at rest. Maximal vasodilatation was obtained by injection of adenosine at a dose of 140 µg/min/kg for 4 minutes. For each perfusion acquisition a contrast injection at a dose of 0.05 mmol/kg Gd-DTPA was administered by power injector at 5 ml/s followed by a 20-ml saline flush. All perfusion imaging was carried out during a single breath-hold at end expiration.

Endo- and epicardial contours were manually traced and corrected for respiratory motion when required. The arterial input function (AIF) was derived from a region of interest placed within the left ventricular cavity, avoiding the papillary muscles. Transmural signal intensity-time courses were converted to tracer concentration-time courses using the known relationship between SR-TFE signal and blood & tissue T_1. An average literature value for the T_1 of blood (1435 ms) was used [6] to estimate concentration-time courses in the AIF. By assuming the same signal calibration factor applies to the myocardium and blood, this relationship allows the calculation of concentration-time courses in the myocardium [6]. The concentration-time data were analyzed using the adiabatic approximation to the tissue homogeneity (AATH) model [7] to arrive at estimates of F_b, v_b, PS and v_e.

Results. AATH fits were completed in all 32 concentration-time courses. Adenosine induced significant increases in F_b (from 1.2 ± 0.3 ml/min/ml tissue to 3.5 ± 0.9 ml/min/ml tissue; myocardial perfusion reserve (MPR), 2.9 ± 0.9), v_b (8 ± 5% to 12 ± 4%), and PS (1.5 ± 0.8 ml/min/ml tissue to 2.1 ± 1.2 ml/min/ml tissue) while having negligible effect upon v_e (stable at 17 ± 3%).

Discussion. Our data suggests that transport of Gd-DTPA in the resting myocardium was close to perfusion limited. The first pass extraction fraction, E, was estimated to be 0.82 ± 0.12, approaching complete first-pass extravasation. Transport in the myocardium under adenosine stress was not perfusion limited; E decreased to 0.62 ± 0.15. While our data lack definitive validation our estimates of perfusion and MPR lie within the range of previous results [8] and our estimates of v_b and v_e are similar to figures reported in other studies [4,9].

Taking the results obtained at rest and stress, what do they tell us about the effect of adenosine on myocardial microvascular function in healthy volunteers? Myocardial perfusion increases almost 3-fold, while interstitial volume is unaffected. The total blood volume, v_b - a mixture of large and small vessels, increases by 55%. It has been suggested that adenosine only causes relaxation of the larger vessels [9] but it may be that capillary recruitment is also contributing to the v_b increase [2,5]. The 45% increase in nutritional flow, PS, measured in the current study could be explained by an increase in P, the flow across each unit surface area of capillary wall (simply due to the increase in myocardial perfusion and/or due to changes in leakiness of the capillaries), or by an increase in capillary surface area, S (capillary recruitment). Further work is required to elucidate these mechanisms.

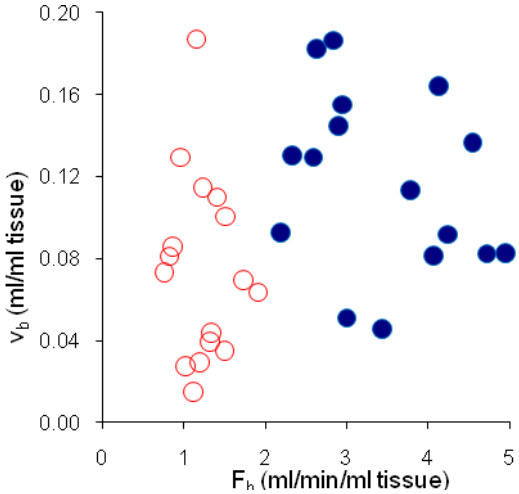

Fig. 1 Effect of adenosine on F_b and v_b. Open circles, rest; filled circles, stress.

Acknowledgments. Supported, in part, by the British Heart Foundation (RG/05/004). Thanks to John Ridgway and Stephen Ball for their input.

References.

[1] Wilke N et al, *Magn Reson Q* 1994;10:249; **[2]** Overholser KA, Harris TR, *J Pharmacol Exp Ther* 1984;229:148; **[3]** Vallee JP et al, *Magn Reson Med* 1997;38:981; **[4]** Jerosch-Herold M et al, *Int J Card Imaging* 1999;15:453; **[5]** Li X et al, *NMR Biomed* 2009;22:148; **[6]** Biglands J et al, ISMRM, Stockholm, 2010; **[7]** St Lawrence KS, Lee TY, *J Cereb Blood Flow Metab* 1998;18:1365; **[8]** Pack NA, DiBella EV, *Magn Reson Med* 2010;64:125; **[9]** Crystal GJ et al, *Am J Physiol* 1981;241:H194.