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A Quantitative Pixel-Wise Measurement of Myocardial Blood Flow by Contrast-Enhanced First-Pass CMR Perfusion Imaging

Microsphere Validation in Dogs and Feasibility Study in Humans

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OBJECTIVES The aim of this study was to evaluate fully quantitative myocardial blood flow (MBF) at a pixel level based on contrast-enhanced first-pass cardiac magnetic resonance (CMR) imaging in dogs and in patients.

BACKGROUND Microspheres can quantify MBF in subgram regions of interest, but CMR perfusion imaging may be able to quantify MBF and differentiate blood flow at a much higher resolution.

METHODS First-pass CMR perfusion imaging was performed in a dog model with local hyperemia induced by intracoronary adenosine. Fluorescent microspheres were the reference standard for MBF validation. CMR perfusion imaging was also performed on patients with significant coronary artery disease (CAD) by invasive coronary angiography. Myocardial time-signal intensity curves of the images were quantified on a pixel-by-pixel basis using a model-constrained deconvolution analysis.

RESULTS Qualitatively, color CMR perfusion pixel maps were comparable to microsphere MBF bull's-eye plots in all animals. Pixel-wise CMR MBF estimates correlated well against subgram (0.49 ± 0.14 g) microsphere measurements ($r = 0.87$ to 0.90) but showed minor underestimation of MBF. To reduce bias due to misregistration and minimize issues related to repeated measures, 1 hyperemic and 1 remote sector per animal were compared with the microsphere MBF, which improved the correlation ($r = 0.97$ to 0.98), and the bias was close to zero. Sector-wise and pixel-wise CMR MBF estimates also correlated well ($r = 0.97$). In patients, color CMR stress perfusion pixel maps showed regional blood flow decreases and transmural perfusion gradients in territories served by stenotic coronary arteries. MBF estimates in endocardial versus epicardial subsectors, and ischemic versus remote sectors, were all significantly different ($p < 0.001$ and $p < 0.01$, respectively).

CONCLUSIONS Myocardial blood flow can be quantified at the pixel level (~32 μl of myocardium) on CMR perfusion images, and results compared well with microsphere measurements. High-resolution pixel-wise CMR perfusion maps can quantify transmural perfusion gradients in patients with CAD. (J Am Coll Cardiol Img 2012;5:154–66) © 2012 by the American College of Cardiology Foundation

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First-pass gadolinium-enhanced cardiac magnetic resonance (CMR) perfusion imaging is effective in detecting and diagnosing coronary artery disease (CAD) in patients (1–11). Several studies have used semiquantitative approaches to measure first-pass CMR perfusion images. Although these methods are generally simple, semiquantitative perfusion estimates compress the effects of vasodilation into a narrower range of perfusion values compared with fully quantitative estimates (12,13). Myocardial blood flow (MBF) can be estimated from first-pass CMR perfusion images (12,14–18). These validation studies showed that fully quantitative MBF estimates from CMR correlated well with absolute MBF as measured by microspheres. However, these studies were performed on a sector-by-sector basis to improve signal-to-noise ratio and to mitigate motion artifacts. This approach inherently downgrades the resolution of CMR perfusion information to significantly larger regions of interest.

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The aim of this study was to evaluate whether first-pass CMR perfusion imaging has sufficient spatial resolution to estimate fully quantitative MBF at the pixel level. We developed a computer-based method for pixel-wise MBF quantification from CMR perfusion images. The results of the fully quantitative pixel-wise CMR MBF estimates were compared with absolute MBF as determined by microsphere measurements in canines. The heterogeneity of pixel-wise CMR perfusion MBF estimates was studied within myocardial sectors. To evaluate the feasibility of this method in a clinically relevant model, pixel-wise CMR perfusion maps were examined in patients with significant coronary stenosis as determined by invasive coronary angiography to determine whether endocardial to epicardial perfusion gradients could be detected.

METHODS

Experimental preparation. The study protocol was reviewed and approved by the Animal Care and Use Committee of the National Heart, Lung, and Blood Institute (NHLBI). Seven healthy mongrel dogs weighing between 10 and 22 kg were used in this study. The animals were anesthetized with 1% to 2% isoflurane during the experiment. Instrumentation of each animal included 2 femoral arterial lines for blood pressure monitoring and microsphere blood sample withdrawals, a left atrial catheter for microsphere injection, and a catheter in a right ventricular branch of the left anterior descending coronary artery (LAD) for a local adenosine infusion.

Approximately 5 million 15-μm fluorescence-labeled microspheres (Interactive Medical Technologies, Irvine, California) were administered during reference blood sampling (10 ml/min for 3 min) to measure absolute MBF (in ml/min/g) at baseline and during adenosine infusion. Adenosine was infused at 20 μg/kg/min and diluted with normal saline to provide an intracoronary injection rate of 1 ml/min to produce a local hyperemic zone. Microspheres and CMR perfusion imaging was performed within 5 to 10 min during the same adenosine infusion.

CMR perfusion imaging. The CMR perfusion images were acquired with a 1.5-T scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) using a steady-state free precession sequence with saturation recovery magnetization preparation (19). A dual-bolus technique (12) was used that consisted of 2 doses of gadolinium diethylenetriamine pentaacetic acid (DTPA) (Magnevist; Berlex Laboratories, Wayne, New Jersey) at 0.005 mmol/kg and 0.05 mmol/kg diluted into equal volumes and injected at 2 ml/s followed by a 20-ml saline flush. Two or 3 short-axis images were collected every R-R interval for 60 heartbeats for each bolus during a breath-hold by transiently stopping a mechanical ventilator.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CMR = cardiac magnetic resonance
CV = coefficient of variation
LAD = left anterior descending coronary artery
LV = left ventricular
MBF = myocardial blood flow
NS = not statically significant

Typical imaging parameters included a 90° composite saturation preparation pulse, 50° readout pulse, saturation recovery time = 90 ms, repetition time = 2.6 ms, echo time = 1.3 ms, field of view = 260 × 179 mm, acquisition matrix = 128 × 80, image matrix = 256 × 176 after interpolation, slice thickness = 7 mm. Each voxel represents approximately 32 μl of myocardium (or 33 mg/voxel). Parallel imaging with an acceleration factor of 2 was used. Two proton density–weighted images were also acquired to allow correction of surface coil B_1-field inhomogeneity.

Microsphere processing. After perfusion imaging, the animals were euthanized with potassium chloride while under anesthesia. The heart was removed and placed in agar to facilitate cutting into 3.5-mm short-axis slices. The papillary muscles and right ventricular walls were excluded before microsphere processing. A pair of adjacent pathological slices was matched to a 7-mm short-axis CMR perfusion image based on anatomic landmarks. The pair of