JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE®
Vol. 6, No. 2, pp. 499–507, 2004

PERFUSION IMAGING

Regional Heterogeneity of Myocardial Perfusion in Healthy Human Myocardium: Assessment with Magnetic Resonance Perfusion Imaging[#]

Olaf M. Muehling, M.D.,[1,*] Michael Jerosch-Herold, Ph.D.,[1] Prasad Panse, M.D.,[3] Andrey Zenovich,[1] Betsy V. Wilson, R.N.,[2] Robert F. Wilson, M.D., F.A.C.C.,[2] and Norbert Wilke, M.D.[2]

[1]Section of Cardiovascular MRI of the Department of Diagnostic Radiology and [2]Cardiovascular Division of the Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota, USA
[3]Department of Radiology, University of Florida, Jacksonville, Florida, USA

ABSTRACT

The knowledge of myocardial perfusion in healthy volunteers is fundamental for evaluation of patients with ischemic heart disease. The study was conducted to determine range, regional variability, and transmural gradient of myocardial perfusion in normal volunteers with Magnetic Resonance Perfusion Imaging (MRPI). Perfusion was assessed in 17 healthy volunteers (age: 20–47 yr, 11 males) at rest and adenosine-induced hyperemia using a 1.5 T MR scanner. Perfusion was quantified (mL/g/min) for the transmural myocardium and separately for the endo- and epimyocardium in the anterior, lateral, posterior, and septal left ventricular wall using the Fermi model for constrained deconvolution. Regional variabilities for resting, hyperemic perfusion, and perfusion reserve were 22 ± 8%, 21 ± 10%, and 35 ± 18%. Mean resting, hyperemic perfusion, and perfusion reserve were 1.1 ± 0.4 mL/g/min, 4.2 ± 1.1 mL/g/min, and 4.1 ± 1.4. Perfusion in the septum was higher at rest (1.3 ± 0.3 mL/g/min vs. 1.0 ± 0.3 mL/g/min, $p<0.05$) and lower during hyperemia (3.6 ± 0.8 mL/g/min vs. 4.5 ± 1.1 mL/g/min, $p<0.03$), resulting in a reduced perfusion reserve (PR) (3.2 ± 0.9 vs. 4.5 ± 1.4, $p<0.01$) in the septum vs. the combined anterior, lateral, and posterior segments. Resting (0.9 ± 0.3 mL/g/min vs. 1.4 ± 0.5 mL/g/min, $p<0.01$), but not hyperemic perfusion, was lower in the epi- vs. endomyocardium, resulting in a higher

[#]This paper was presented in part at the Annual Meeting of the Society of Magnetic Resonance Imaging 2003.
[*]Correspondence: Dr. Olaf M. Muehling, Medical Hospital and Clinics I, Großhadern Hospital, University of Munich, Marchioninistr. 15, 81377 Munich, Germany; Fax: 011-49-89-7095-2224; E-mail: omuehlin@helios.med.uni-muenchen.de.

DOI: 10.1081/JCMR-120030570
1097-6647 (Print); 1532-429X (Online)

epimyocardial PR (4.8±1.8 vs. 3.5±1.4, $p<0.01$) in all regions but the septum, where endo- and epimyocardial perfusion and perfusion reserve were not different. A considerable regional variability of myocardial perfusion was confirmed with MRPI. The exceptional anatomical position of the septum is reflected by the lack of a perfusion gradient, which was demonstrated in all other regions but the septum.

Key Words: Perfusion imaging; Regional perfusion; Transmural perfusion; Healthy humans.

INTRODUCTION

Assessment of myocardial perfusion is highly sensitive for diagnosing coronary artery disease. Recent technical advances in magnetic resonance imaging (MRI) and increasing spatial resolution have made it possible to assess not only transmural but also endo- and epimyocardial differences of myocardial perfusion (Panting et al., 2002; Schwitter et al., 2001). In addition, magnetic resonance first-pass imaging (MRPI) has been validated as a noninvasive tool for absolute quantification of myocardial perfusion (Jerosch-Herold et al., 1998; Wilke et al., 1997).

Exclusive reliance on a qualitative evaluation of images might be inadequate because of the natural heterogeneity of regional myocardial blood flow. This heterogeneity might lead to contradictory reports, such that blood flow in hibernating myocardium is within normal limits (Gerber et al., 1996), while others report a reduced perfusion (Rahimtoola, 1985) compared to its normal range. The heterogeneity of contrast enhancement due to inhomogeneous MRI receiver coil sensitivities (Klocke and Wittenberg, 1969) will add further inaccuracy to sole, qualitative assessment of myocardial perfusion.

Thus, with the ongoing development and increasing applicability of MRPI in clinical practice, it is necessary to determine the normal range of myocardial perfusion and the physiological heterogeneity of myocardial perfusion assessed with MRPI. This would improve interpretation of perfusion data in patients with coronary artery disease or other forms of heart disease.

In the present study, we assessed myocardial perfusion in the anterior, lateral, posterior, and septal myocardium in a group of healthy volunteers. Transmural differences between endo- and epimyocardial perfusion also were determined.

Besides a transmural gradient and a considerable variability of regional myocardial perfusion, a considerable difference between the perfusion in the septum and the left ventricular free wall has been described (Ramanathan et al., 1988). We hypothesize that perfusion of the septum differs from the remaining myocardial regions. Based on its anatomical position, the myocardial septum is exposed not only to the left but also to the right ventricular intracavitary pressure. In addition, septal perfusion is provided by intramural branches of the coronary arteries, but not directly from branches arising from the epicardial coronary arteries as in the remaining regions. If differences in myocardial perfusion exist, they need to be accounted for in the judgment of pathological myocardial perfusion, and normal values are invaluable.

MATERIAL AND METHODS

Study Population and Protocol

Seventeen healthy volunteers (age range 20–47 years, mean 34±9 years, 11 men) were enrolled to undergo Magnetic Resonance Perfusion Imaging (MRPI). For all subjects, written informed consent was acquired in accordance with the requirements of the Institutional Review Board for Protection of Human Subjects at the University of Minnesota. All volunteers were asked to abstain from caffeine-containing beverages 24 hours prior to the scan. All volunteers gave no history of cardiac or pulmonary disease, hypertension, hyperlipidemia, smoking, or diabetes. None of the subjects were on any kind of chronic medication. All had a normal resting electrocardiogram and a normal exercise tolerance. Based on these findings, all participants had a low probability of coronary artery disease (Diamond and Forrester, 1979). None of the subjects had contraindications for MR imaging such as metal implants or severe claustrophobia.

Image Acquisition

T1-weighted imaging tailored to a quantitative evaluation of myocardial perfusion was performed on a commercially available, 1.5 T whole body system (VISION, Siemens Medical Systems, Erlangen, Germany) using a four-channel, phased-array, body coil. Multislice imaging with three slices in a double-oblique,

short-axis orientation was performed using a snapshot-FLASH sequence with linear k-space ordering. The in-plane resolution was $\sim 2 \times 3$ mm^2 with an acquisition time of 160–235 ms/slice. The sequence was set to the following: TR 2.5 ms/phase encoding step, TE 1.2 ms, flip angle α of 18°, matrix size $60-90 \times 128$ (phase encodings $\times$ readout points), a rectangular field of view of 280×330 mm^2, a slice thickness of 10 mm, and an inter-slice gap of 3–5 mm. Studies were obtained during a 0.03 mmol/kg body weight antecubital bolus injection of 0.5 mmol/l-Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) contrast medium. The low dosage of Gd-DTPA was used, because MR contrast agents show a linear relation between contrast concentration and signal intensity only in a dose range of 0.2 to 2.0 mmol/L (Koenig et al., 1986; Strich et al., 1985). The preloaded contrast bolus was flushed through the IV line with 15 mL normal saline at a rate of 7 mL/sec using a power injector (Medrad, Pittsburgh, PA). Image acquisition was started 3–4 heartbeats before injection of the contrast material, and 40–60 images per slice were obtained to follow the contrast bolus through the circulation. Image acquisition was ECG-gated, and signal acquisition started 10 ms after the end of a nonselective saturation-recovery magnetization preparation that was triggered by the detection of an R-wave. The ECG gating allowed acquisition of images at a fixed time point in the cardiac cycle, and the myocardial wall motion appeared frozen. Hyperemia was induced by increasing doses (70–100–140 μg/kg/min) of intravenous adenosine over a period of 4 min and constant monitoring with consecutive image acquisition. Perfusion scans during rest and hyperemia were performed within a minimum of 15 minutes between the two scans to allow for contrast agent clearance between the two perfusion measurements.

To assess myocardial function, cine imaging was performed before perfusion imaging, using an ECG-gated, segmented, turboFLASH cine sequence (TR/TE 40/4 ms, flip angle 20°). The image matrix was 128×256, the field of view 350 mm using oversampling. The slice thickness was 8 mm with a 2-mm gap. The entire heart was covered from base to apex.

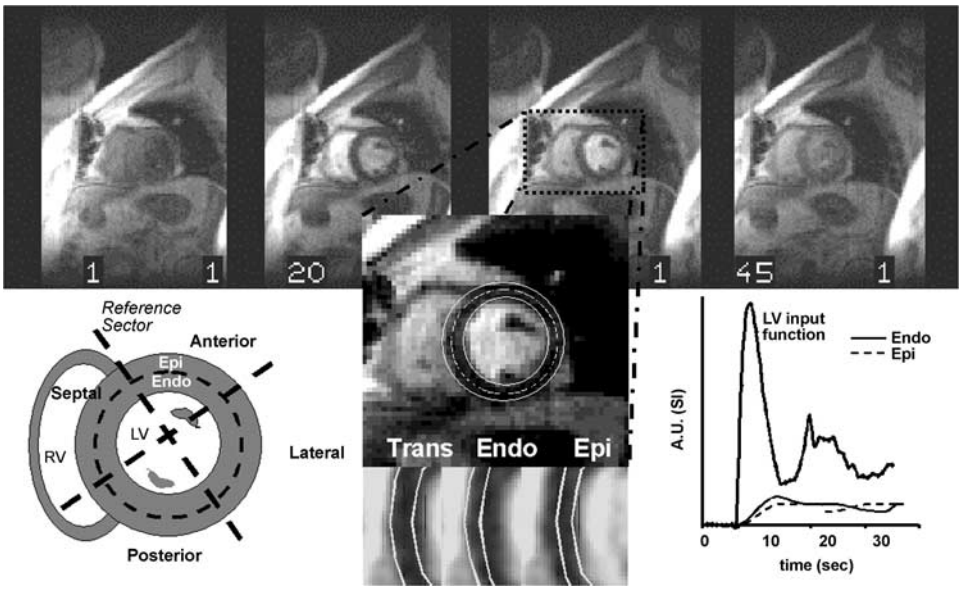

Figure 1. Perfusion analysis and generation of the Signal Intensity (SI) curves from the MR first-pass perfusion images. Upper row: The contrast bolus is traced through the heart [precontrast image (image on the left); maximum enhancement of the right ventricle (second image from the left); maximum enhancement of the left ventricle (second image from the right); enhancement of the myocardium (image on the right)]. The image with the brightest contrast enhancement in the left ventricular cavity is chosen and myocardial contours are manually drawn separately to determine the transmural, endo-, and epimyocardial region of interest (ROI). An automated edge detection algorithm applies the segmentation to the remainder of the image frames (not shown). The program calculates the signal/time-intensity values for the anterior, lateral, posterior, and septal region (figure in the lower left corner); and raw values (before applying the fitting algorithm) are plotted in the graph in the right lower corner. A ''reference sector'' was defined as the sector bordering the anterior junction of the epicardium of the LV and right ventricle. SI curves for Endo (thin solid line), Epi (thin dotted line), and left ventricle (thick solid line, LV input function).

Image Analysis

The studies were archived to an optical disk and transferred to a SPARC 10 Workstation (Sun Microsystems, Mountain View, CA). The studies were analyzed using the Argus Cardiac Image Analysis Software (Siemens, Iselin, NJ). The perfusion analysis was performed as outlined previously (Muehling et al., 2001). The analysis provides good intra- and interobserver agreement (Muehling et al., 2001).

The left ventricular (LV) myocardium was defined as one region of interest (ROI) by manually applying endo- and epimyocardial contours. A midmyocardial line was used to further separate the LV myocardial ROI into an endo- and epimyocardial layer. All contours were drawn only once and saved. The so-defined ROIs of the left ventricle were further subdivided into four (anterior, posterior, lateral, and septal) ROIs of equal size using the computer software. To standardize the subdivison, a reference sector was defined at the anterior junction of the epicardium of the left and right ventricles.

Consecutively, software-generated, spatially averaged, signal intensity (SI) values from each ROI were used to plot SI time curves. For further details see Fig. 1.

Model constrained deconvolution was used to calculate the maximum amplitude of the impulse response function from the SI bolus curves (Jerosch-Herold et al., 1998) of each ROI. This amplitude can be interpreted as a measure of flow (Clough et al., 1994). The method has been validated against radiolabeled microspheres in an animal model to quantify perfusion in mL/g/min (Muehling et al., 2002).

The MR cine image analysis was performed as described elsewhere (Holman et al., 1997). Ejection fraction (EF, %) was calculated from the computerized end-diastolic and end-systolic volumes. Muscle mass was determined from end diastolic images.

Statistical Analysis

Data are given as mean ± standard deviation (SD) unless outlined differently. The coefficient of variation (CV, %) was calculated as the mean of the standard deviation/mean regional perfusion per patient. The CV was used to demonstrate the degree of variability of regional myocardial perfusion. Data were analyzed using MedCalc for Windows Version 5 (MedCalc Software, Marinkerke, Belgium). For intra-subject comparison of regions, Analysis of Variance (ANOVA) was used. Bonferroni correction for multiple comparisons was applied where appropriate. Comparison between gender groups was done with a t-test for unpaired data. A p value of <0.05 was considered to be statistically significant.

RESULTS

Image acquisition was successfully performed in all volunteers. All subjects tolerated the imaging procedure, contrast, and adenosine administration well. Common side effects associated with adenosine such as hot flushes or the urge to breath deeply were experienced in five volunteers. None of the subjects reported chest pain suggestive of angina, or exhibited arrhythmias, suggestive of ischemia. Total study time per patient was 35–45 min. A total of three slices with four regions in 17 subjects = 204 regions were analyzed for each transmural, endo-, and epimyocardial perfusion.

Table 1. Mean ± SD and range of data for resting and hyperemic perfusion (mL/g/min) and perfusion reserve.

Myocardial region	Perfusion mL/g/min	Resting	Hyperemic[d]	Perfusion reserve
Anterior	Mean ± SD	1.1 ± 0.4	4.3 ± 0.9	4.6 ± 1.3
	Range	0.5–1.7	3.2–6.4	2.7–6.6
Lateral	Mean ± SD	1.0 ± 0.3	4.7 ± 1.1	4.7 ± 1.3
	Range	0.6–1.4	3.2–7.1	2.1–6.6
Posterior	Mean ± SD	1.0 ± 0.3	4.3 ± 1.3	4.2 ± 1.4
	Range	0.6–1.5	3.1–6.7	3.0–6.5
Septal	Mean ± SD	1.3 ± 0.3[a]	3.6 ± 0.8[b]	3.1 ± 0.9[c]
	Range	0.8–1.8	2.6–5.1	1.8–4.2
All	Mean ± SD	1.1 ± 0.4	4.2 ± 1.1	4.1 ± 1.4

[a] $p<0.05$.
[b] $p<0.03$.
[c] $p<0.02$ vs. combined other regions.
[d] $p<0.01$ vs. Resting.

Subject Variables

The body mass index in our population was 23.9±4.1. Left ventricular muscle mass per body surface area was 73±10 g/m^2. Ejection fraction was 65±3%. The mean resting heart rate was 64±9 beats/min and mean blood pressure was 95±9 mmHg. During maximum rate of adenosine infusion the heart rate increased significantly to 87±14 beats/min ($p<0.01$) and mean blood pressure decreased slightly 90±10 mmHg ($p<0.05$). The pressure rate product increased from 6137±967 to 7919±1862 mmHg/min ($p<0.01$).

Myocardial Perfusion at Rest and Hyperemia

Data on regional myocardial perfusion at rest are shown in Table 1 and Fig. 2. The mean variation of myocardial resting perfusion between regions in one subject was 22±8% with a maximum of 40%. The septum had a significantly ($p<0.03$) higher resting perfusion compared to the mean of the remaining regions. Women had an overall higher resting myocardial perfusion than men (1.2±0.5 vs. 0.9±0.3 mL/g/min, $p<0.05$).

Table 1 and Fig. 3 show the regional myocardial perfusion under hyperemic conditions. The mean variation of myocardial hyperemic perfusion between regions was 21±10%, with a maximum of 39% between two regions in one subject. The septum showed a significantly ($p<0.03$) lower hyperemic perfusion compared to the mean of the remaining regions.

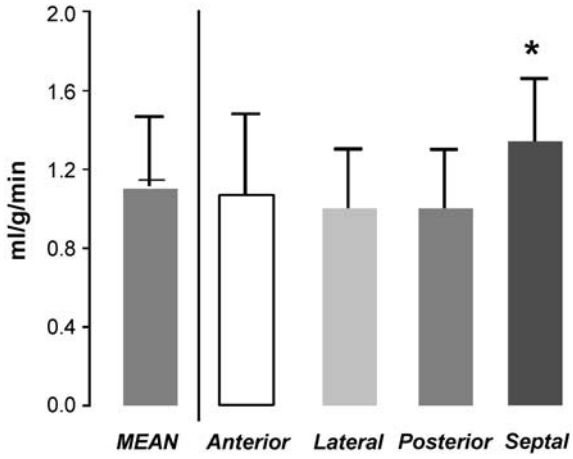

Figure 2. Overall and regional mean±SD of resting myocardial perfusion. *$p < 0.05$.

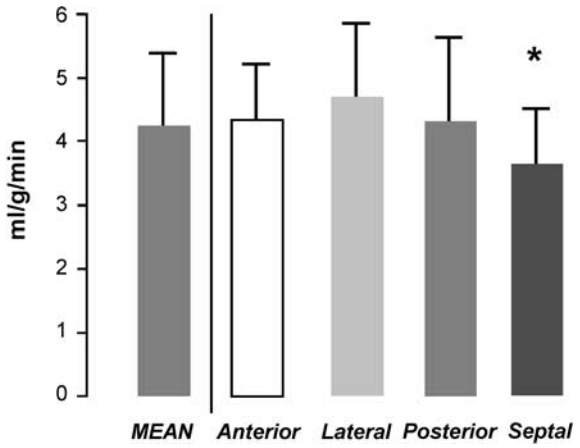

Figure 3. Overall and regional mean±SD of hyperemic myocardial perfusion. *$p < 0.03$.

Myocardial Perfusion Reserve

Values of myocardial perfusion reserve are shown in Table 1 and Fig. 4. The mean variation of myocardial perfusion reserve between regions was 35±18% with a maximum of 65% between two regions in one subject. The septum showed a significantly ($p<0.01$) lower perfusion reserve when compared to the mean of the remaining regions.

Myocardial Perfusion in the Endo- and Epimyocardium

Endo- and epimyocardial perfusion at rest and hyperemia and perfusion reserve are shown in Table 2 and in Fig. 5. Mean myocardial resting perfusion in the endomyocardial layer of the left ventricle was significantly ($p<0.01$) higher compared to the perfusion in the epimyocardium. The endo/epi gradient, determined as endomyocardial perfusion divided by epimyocardial perfusion for the perfusion at rest, was approximately 46%. The perfusion reserve in the endomyocardium was significantly ($p<0.01$) lower than in the epimyocardium, with a gradient of approximately 31%. In the septum, endo- and epimyocardial perfusion and perfusion reserve were not different (see Table 2).

DISCUSSION

In the present study we assessed perfusion in healthy volunteers with a low probability of coronary artery disease, to define normal myocardial perfusion. According to previous studies assessing perfusion

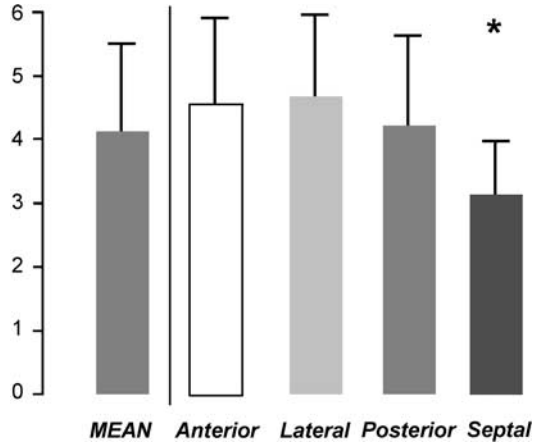

Figure 4. Overall and regional mean±SD of myocardial perfusion reserve. *$p < 0.02$.

reserve with invasive or noninvasive methods (Chareonthaitawee et al., 2001; Wilson et al., 1990), we found an adenosine-induced perfusion reserve of ~4 in healthy human myocardium using magnetic resonance first-pass imaging. There is a considerable variation of myocardial perfusion reserve among the myocardial regions within one individual. This results from a variation of myocardial perfusion at rest and adenosine-induced hyperemia. Therefore, comparison between two myocardial regions, e.g., stenosis-dependent and remote myocardium, is not trivial. The heterogeneity of regional blood flow in mammalian hearts has been described earlier, although flows in near-neighbor regions correlate strongly (Beard and Bassingthwaighte, 2000). The closest relationship appears to be between blood flow and mechanical function. However, it is not clear whether this is directly related to energy metabolism or metabolic reactions such as intracellular calcium flux (Bassingthwaighte et al., 2001). Although our study population was small and conclusions might be preliminary, our results confirm that baseline perfusion in women is higher than in men (Chareonthaitawee et al., 2001; Duvernoy et al., 1999). This has been explained in part by the effects of estrogens on vascular tone (Collins et al., 1995) and needs to be taken into account when ischemia is assessed in women.

The limited spatial resolution of other noninvasive imaging modalities results in a lack of a gold standard for the assessment of transmural myocardial perfusion in healthy humans. However, several findings support the hypothesis of an endo/epimyocardial perfusion gradient as demonstrated in our study. It is known that autoregulatory vascular resistance in the endomyocardium is lower, to overcome the higher compressive force from the left ventricular chamber. This results in a physiologically lower vasodilatator reserve in the endomyocardium. Furthermore, there are studies suggesting a higher capillarity or recruitment of capillaries in the endomyocardium with a transmural gradient of up to 40% (Myers and Honig, 1964), which is similar to our results. Animal studies support the hypothesis of a transmural gradient (Bache and McHale, 1977; Bergelson et al., 1996) of the left ventricular myocardium. In addition, histological and electrophysiological differences between the endo- and epimyocardial layer have been described (Klocke, 1976). In patients with myocardial hypertrophy, the image resolution of

Table 2. Mean±SD and range of data for resting and hyperemic perfusion (mL/g/min) and perfusion reserve in the endo- and epimyocardial layer.

		Resting		Hyperemic[b]		Perfusion reserve	
Region	Perfusion mL/g/min	Endo	Epi	Endo	Epi	Endo	Epi
Anterior	Mean±SD	1.4±0.5	0.9±0.4[a]	4.8±1.6	4.6±1.6	3.8±1.1	5.0±2.0[a]
	Range	0.6–2.1	0.4–1.5	3.0–7.4	3.1–7.1	2.5–5.5	3.6–7.3
Lateral	Mean±SD	1.4±0.6	0.9±0.4[a]	4.9±1.9	5.2±1.7	3.6±1.3	5.7±1.7[a]
	Range	0.8–2.4	0.4–1.5	3.1–7.2	3.8–8.7	2.0–5.6	3.8–7.7
Posterior	Mean±SD	1.4±0.5	0.9±0.3[a]	4.9±2.2	4.5±1.5	3.6±1.8	5.2±0.9[a]
	Range	0.7–2.3	0.5–1.4	3.2–7.5	3.5–6.6	2.1–6.5	3.9–7.1
Septal	Mean±SD	1.3±0.4	1.2±0.4[c]	3.7±1.2[c]	3.5±0.7[c]	3.1±1.1	3.2±1.1[c]
	Range	0.6–2.0	0.6–1.8	2.2–6.1	2.5–4.5	1.7–5.2	2.0–4.6
ALL	Mean±SD	1.4±0.5	0.9±0.3[a]	4.8±1.6	4.9±1.9	3.5±1.4	4.8±1.8[a]

[a]$p < 0.01$ vs. Endo.
[b]$p < 0.01$ vs. Resting.
[c]$p < 0.01$ vs. combined other regions.

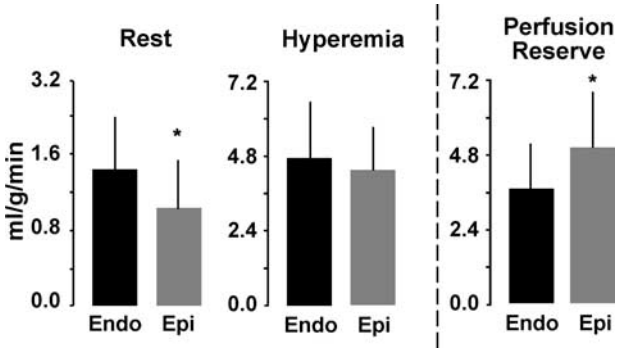

Figure 5. Separate endo- and epimyocardial perfusion at rest and hyperemia and perfusion reserve. Mean overall myocardial regions. Perfusion reserve is lower in the endomyocardium due to a higher resting perfusion. *$p < 0.01$.

positron emission tomography is sufficient to determined a transmural gradient. In a study by Choudhury et al. (1999), a transmural gradient of >10% in patients with hypertrophic cardiomyopathy was shown. In a study by Parodi et al. (1993), the transmural perfusion in explanted human hearts was assessed by radiolabled microspheres, the experimental gold standard for the assessment blood flow. The transmural gradient for patients with dilated cardiomyopathy was approximately 15%. The lower transmural gradients in these studies compared with the gradient in our healthy population are likely explained by endomyocardial hypoperfusion. This is common in LV hypertrophy (Choudhury et al., 1999) or an increased, left ventricular end-diastolic pressure as present in dilated cardiomyopathy (Parodi et al., 1993).

In our study, the exceptional anatomical position of the interventricular septum is reflected by a minor perfusion reserve and a lack of transmural gradient in endo- and epimyocardial perfusion in contrast to the remaining anterior, lateral, and posterior sections. The missing transmural gradient and the smaller perfusion reserve in this region might be explained by the fact that the epimyocardial layer of the septum is the ''endomyocardium'' of the right ventricle. In addition, there are no epicardial blood vessels as in the remaining regions, where the coronary arteries run on the surface of the heart and branch before reaching the endomyocardial layer. In contrast, septal branches rise from the LAD and branch a second time intramurally before they reach into the endomyocardial layers of the left and right ventricles. The particular perfusion of the septum has been supported by data that showed that ischemia of the septum not only affects left ventricular, but also right ventricular function and geometry (Jerzewski et al., 1999). Resting (22%), as well as hyperemic (21%) perfusion, has a smaller interregional variability than perfusion reserve (35%). This important finding supports the concept that absolute hyperemic perfusion is more sensitive in detecting an abnormal perfusion than a ratio, like perfusion reserve. Thus, a higher variability in the normal values requires a greater absolute difference between normal and pathological values to detect abnormality. Therefore, absolute quantification of myocardial perfusion, which is feasible with the presented method, has an advantage over methods determining relative perfusion values [i.e., a perfusion reserve index (Al Saadi et al., 2000; Panting et al., 2002)].

Limitations

Analysis of myocardial perfusion on the basis of MR images using the Fermi model and constrained deconvolution is a time consuming process. This limits the application of this approach in daily clinical practice. A new, model-free approach has recently been presented (Jerosch-Herold et al., 2002). Due to propagation of a faster and easier method, the approach of absolute quantification of myocardial perfusion will find greater acceptance and might enter the clinical arena.

Using only short-axis slices, as presented in this study, perfusion in the tip of the apex was not determined. Qualitative evaluation of apical perfusion and subsequent evaluation of short- and long-axis slices is possible with the currently available MR hardware and software. However, a real quantitative approach in the apex might be limited by the velocity of the longitudinal movement of the tip of the heart and the thinner transmural myocardial mass at the apex.

Determination of endo- or epimyocardial perfusion in subjects with a thin LV wall (i.e., after transmural myocardial infarction or dilative cardiomyopathy) might be cumbersome with the image resolution currently available. However, the available resolution assesses a transmural gradient of myocardial perfusion in subjects with normal or increased LV wall thickness. In our subjects, LV wall thickness was ≥ 7 mm and resolution was $\sim 2 \times 3$ mm^2 in-plane. Therefore, we did not face problems with image resolution.

We cannot exclude the possibility that the high signal intensities observed during the first pass of the contrast through the left ventricular blood pool may have contributed in part to higher signal intensities in the endocardial layer. This can be partially due to the limited spatial resolution, i.e., partial volume effects, and may also result from any inaccuracies in the

tracing of the endocardial contours. However, during hyperemia epimyocardial perfusion was higher than endomyocardial perfusion, despite this possible signal contamination from the LV blood pool into the endomyocardium. If there is a signal contamination in the endomyocardium from the LV blood pool, it seems limited. We also like to point out that the adapting perfusion values between the endo- and epimyocardium of the septum are not related to a signal contamination from the right ventricular blood pool into the epimyocardial septum. The signal enhancement in the right ventricle has fallen approximately by 80% from its peak value when the signal intensity reaches a peak in the LV.

CONCLUSION

Magnetic resonance first-pass perfusion imaging allows quantitative evaluation of myocardial perfusion. This is the first study defining quantitative myocardial perfusion and transmural perfusion values with MRPI in a normal population. There is a high inter-subject and intra-subject, interregional variability of myocardial perfusion. These results confirm the heterogeneity of myocardial blood flow in healthy subjects and highlight the difficulty in establishing the limits of normal blood flow. In addition, the high variability of myocardial perfusion demonstrates the need for an accurate method to distinguish healthy from pathological myocardial perfusion. Its high spatial resolution gives MR a unique position in the assessment of selective endo- and epimyocardial perfusion. The data demonstrate a transmural perfusion gradient from the epi- to the endomyocardium. The intraventricular septum seems to have a distinguished transmural perfusion with a reduction of its regional perfusion reserve and transmural perfusion gradient, in accordance with its particular anatomical position.

These data serve as a reference for future clinical trials and eventually standard clinical evaluation of quantitative myocardial perfusion in patients with ischemic heart disease.

ACKNOWLEDGMENTS

Olaf Muehling was supported by a grant from the ''Deutsche Forschungs-Gemeinschaft'' (MU 1570/1-1) as a postdoctoral research fellow. The author would like to acknowledge the work of Michael J. Kleindl, R.T. (R.M.R.), for continuous support in data acquisition and patient care.

REFERENCES

Al Saadi, N., Nagel, E., Gross, M., Bornstedt, A., Schnackenburg, B., Klein, C., Klimek, W., Oswald, H., Fleck, E. (2000). Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. *Circulation* 101(12):1379–1383.

Bache, R. J., McHale, P. A., Greenfield, J. C. Jr. (1977). Transmural myocardial perfusion during restricted coronary inflow in the awake dog. *Am. J. Physiol.* 232(6):H645–H651.

Bassingthwaighte, J. B., Beard, D. A., Li, Z. (2001). The mechanical and metabolic basis of myocardial blood flow heterogeneity. *Basic Res. Cardiol.* 96(6):582–594.

Beard, D. A., Bassingthwaighte, J. B. (2000). The fractal nature of myocardial blood flow emerges from a whole-organ model of arterial network. *J. Vasc. Res.* 37(4):282–296.

Bergelson, B. A., Yu, T. K., Ruocco, N. A. (1996). Effects of hypercholesterolaemia on physiological recruitment of coronary vascular reserve in swine. *Clin. Sci. (Colch.)* 90(4):261–268.

Chareonthaitawee, P., Kaufmann, P. A., Rimoldi, O., Camici, P. G. (2001). Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc. Res.* 50(1):151–161.

Choudhury, L., Elliott, P., Rimoldi, O., Ryan, M., Lammertsma, A. A., Boyd, H., McKenna, W. J., Camici, P. G. (1999). Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. *Basic Res. Cardiol.* 94(1):49–59.

Clough, A. V., al Tinawi, A., Linehan, J. H., Dawson, C. A. (1994). Regional transit time estimation from image residue curves. *Ann. Biomed. Eng.* 22 (2):128–143.

Collins, P., Rosano, G. M., Sarrel, P. M., Ulrich, L., Adamopoulos, S., Beale, C. M., McNeill, J. G., Poole-Wilson, P. A. (1995). 17 beta-Estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. *Circulation* 92(1):24–30.

Diamond, G. A., Forrester, J. S. (1979). Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N. Engl. J. Med.* 300(24): 1350–1358.

Duvernoy, C. S., Meyer, C., Seifert-Klauss, V., Dayanikli, F., Matsunari, I., Rattenhuber, J., Hoss, C., Graeff, H., Schwaiger, M. (1999). Gender differences in myocardial blood flow dynamics: lipid profile

and 23hemodynamic effects. *J. Am. Coll. Cardiol.* 33(2):463–470.

Gerber, B. L., Vanoverschelde, J. L., Bol, A., Michel, C., Labar, D., Wijns, W., Melin, J. A. (1996). Myocardial blood flow, glucose uptake, and recruitment of inotropic reserve in chronic left ventricular ischemic dysfunction. Implications for the pathophysiology of chronic myocardial hibernation [see comments]. *Circulation* 94(4):651–659.

Holman, E. R., Buller, V. G., de Roos, A., van der Geest, A. J., Baur, L. H., van der Laarse, A., Bruschke, A. V., van der Wall, E. E. (1997). Detection and quantification of dysfunctional myocardium by magnetic resonance imaging. A new three dimensional method for quantitative wall-thickening analysis. *Circulation* 95(4):924–931.

Jerosch-Herold, M., Wilke, N., Stillman, A. E. (1998). Magnetic resonance quantification of the myocardial perfusion reserve with a Fermi function model for constrained deconvolution. *Med. Phys.* 25(1): 73–84.

Jerosch-Herold, M., Swingen, C., Seethamraju, R. T. (2002). Myocardial blood flow quantification with MRI by model-independent deconvolution. *Med. Phys.* 29(5):886–897.

Jerzewski, A., Steendijk, P., Pattynama, P. M., Leeuwenburgh, B. P., de Roos, A., Baan, J. (1999). Right ventricular systolic function and ventricular interaction during acute embolisation of the left anterior descending coronary artery in sheep. *Cardiovasc. Res.* 43(1):86–95.

Klocke, F. J. (1976). Coronary blood flow in man. *Prog. Cardiovasc. Dis.* 19(2):117–166.

Klocke, F. J., Wittenberg, S. M. (1969). Heterogeneity of coronary blood flow in human coronary artery disease and experimental myocardial infarction. *Am. J. Cardiol.* 24(6):782–790.

Koenig, S. H., Spiller, M., Brown, R. D. III, Wolf, G. L. (1986). Relaxation of water protons in the intra- and extracellular regions of blood containing Gd(DTPA). *Magn. Reson. Med.* 3(5):791–795.

Muehling, O., Dickson, M., Zenovich, A., Huang, Y., Wilson, B., Wilson, R. F., Anand, I. S., Seethamraju, R. T., Jerosch-Herold, M., Wilke, N. (2001). Quantitative magnetic resonance first-pass perfusion analysis: inter- and intraobserver agreement. *J. Cardiovasc. Magn. Reson.* 3(3):247–256.

Muehling, O., Wang, Y., Panse, P., Jerosch-Herold, M., Cayton, M., Wann, S., Mirhoseini, M., Wilke, N. (2002). Transmyocardial laser revascularization preserves regional myocardial perfusion: an MRI first pass perfusion study. *Cardiovasc. Res.* 57(1):63–70.

Myers, W. W., Honig, C. R. (1964). Number and distribution of capillaries as determinants of myocardial oxygen consumption. *Am. J. Physiol.* 207:653–658.

Panting, J. R., Gatehouse, P. D., Yang, G. Z., Grothues, F., Firmin, D. N., Collins, P., Pennell, D. J. (2002). Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N. Engl. J. Med.* 346(25): 1948–1953.

Parodi, O., De Maria, R., Oltrona, L., Testa, R., Sambuceti, G., Roghi, A., Merli, M., Belingheri, L., Accinni, R., Spinelli, F. (1993). Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplantation. *Circulation* 88(2):509–522.

Rahimtoola, S. H. (1985). A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. *Circulation* 72(6 Pt. 2):V123–V135.

Ramanathan, K. B., Wilson, J. L., Mirvis, D. M. (1988). Effects of coronary occlusion on transmural distribution of blood flow in the interventricular septum and left ventricular free wall. *Basic Res. Cardiol.* 83(3):229–237.

Schwitter, J., Nanz, D., Kneifel, S., Bertschinger, K., Buchi, M., Knusel, P. R., Marincek, B., Luscher, T. F., von Schulthess, G. K. (2001). Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. *Circulation* 103(18):2230–2235.

Strich, G., Hagan, P. L., Gerber, K. H., Slutsky, R. A. (1985). Tissue distribution and magnetic resonance spin lattice relaxation effects of gadolinium-DTPA. *Radiology* 154(3):723–726.

Wilke, N., Jerosch-Herold, M., Wang, Y., Huang, Y., Christensen, B. V., Stillman, A. E., Ugurbil, K., McDonald, K., Wilson, R. F. (1997). Myocardial perfusion reserve: assessment with multisection, quantitative, first-pass MR imaging. *Radiology* 204(2):373–384.

Wilson, R. F., Wyche, K., Christensen, B. V., Zimmer, S., Laxson, D. D. (1990). Effects of adenosine on human coronary arterial circulation. *Circulation* 82(5):1595–1606.

Received May 16, 2003
Accepted September 3, 2003