Magnetic Resonance–Based Assessment of Global Coronary Flow and Flow Reserve and Its Relation to Left Ventricular Functional Parameters

A Comparison With Positron Emission Tomography

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Background—Measurement of coronary sinus blood flow (CSF) by phase-contrast magnetic resonance (PC-MR) imaging at rest and during hyperemia may allow noninvasive assessment of global coronary hemodynamics.

Methods and Results—Sixteen healthy volunteers (age, 22 to 32 years) were examined with MR and PET in random order within 1 to 2 days. At rest and during hyperemia (dipyridamole 0.56 mg/kg), CSF was measured by a cine PC-MR technique (temporal resolution, 40 ms; spatial resolution, 1.25×0.8 mm²), and myocardial blood flow (MBF) was measured by [13 N]NH₃ PET. PET and MR agreed closely for coronary flow reserve (CFR; mean difference, 2.2±14.7%; Bland-Altman method). CSF divided by either total left ventricular mass or an estimate of drained myocardium (LVMdrain) correlated highly with PET flow data (r=0.93 and 0.95, respectively) and with measures of oxygen demand, ie, heart rate, afterload-corrected fiber shortening, and peak systolic stress determined by MR (overall correlation coefficients, 0.81 and 0.87, respectively, multivariate analysis). CSF/LVMdrain did not differ significantly from PET-derived MBF (difference, 3.6±16.6%). In orthotopic heart transplant recipients (n=9), CFR was reduced and blood supply-demand relationships at rest were shifted toward higher flows (P<0.0001).

Conclusions—This integrated MR approach allows comprehensive assessment of autoregulated and hyperemic coronary flow and is suitable for serial measurements in patients. In transplanted hearts, elevated resting flow is the major cause of reduced CFR. (Circulation. 2000;101:2696-2702.)

Key Words: magnetic resonance imaging ■ tomography ■ circulation ■ transplantation

In the past decade, there has been increasing interest in the use of coronary flow reserve (CFR) measurements to investigate coronary pathophysiology.¹ The introduction of intracoronary Doppler wires and PET considerably improved our understanding of how coronary hemodynamics are affected by physiological²,³ and pathological conditions.³⁻⁴ However, far fewer studies have addressed the reversibility of alterations in coronary hemodynamics.⁶ This fact may reflect the need for noninvasive methods for coronary blood flow quantification that ideally can be repeated in patients without restrictions.

Phase-contrast magnetic resonance (PC-MR) techniques have emerged recently as an attractive tool for noninvasive quantification of blood flow.⁷⁻⁹ In disease states that affect most of or the entire coronary circulation, flow measurements might be most sensitive for detection of coronary flow alterations when performed in the coronary sinus (CS), which drains a large portion of the left ventricular (LV) myocardium.¹⁰,¹¹ With this in mind, we optimized a PC-MR sequence for this vessel to quantify flow at rest and during drug-induced hyperemia. The present study was designed to assess the accuracy of CFR determinations by PC-MR technique in comparison with PET.¹² Furthermore, we hypothesized that MBF (mL·min⁻¹·g⁻¹) can be quantified from PC-MR data if CS flow is related to the amount of myocardium drained by the CS and its tributaries. In addition, various determinants of oxygen demand, ie, indexes of contractility and ventricular loading, were derived from the MR data to characterize blood supply-demand relationships in normal hearts and in hypertrophied hearts of orthotopic heart transplant (OHT) recipients.¹³,¹⁴

Methods

Study Population and Protocol

For the PET-MR comparison, 16 healthy volunteers (8 men; mean age, 28±3 years) without a history of cardiovascular disease, with a

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normal physical examination, and with normal 12-lead ECGs at rest and during dipyridamole infusion were studied with both MR and PET in random order within 1 to 2 days. During both PET and MR studies, blood pressure (BP) and heart rate (HR) were acquired at 2-minute intervals, and ECG was monitored continuously. All data were compiled, analyzed, and stored without knowledge of the findings obtained during the other procedure.

In addition, 10 male OHT recipients were examined by MR imaging 11±4 months after transplantation. The control group (matched to donors’ ages and sexes) comprised 15 healthy male subjects (8 also had a PET study). In all OHT recipients, coronary angiography (performed within 6 months of the MR study) and endomyocardial biopsies (performed within 12±16 days of the MR study) revealed absence of transplant coronary artery disease and rejection (ISHT grading 2), respectively. Immunosuppressive therapy included cyclosporine (CsA), prednisone, and mycophenolate mofetil in all patients plus azathioprine in 5 patients. CsA was withheld for 12 hours before the study; all other drugs were continued. Before the MR examination, blood was drawn for CsA determination (Sandoz Pharmaceutical). Study protocols were approved by the local ethics committees, and written informed consent was obtained from all subjects. All study participants refrained from ingesting caffeinated beverages or food 24 hours before examinations.

MR Examination

Data Acquisition

Each subject was imaged in the supine position in a 1.5-T system (Horizon Echospeed, GE Medical Systems) with a 2-coil phased array (GP-Flex Coils, GE) as a radiofrequency receiver. For LV volume and mass measurements, short-axis gradient echo images covering the entire LV were acquired. On a localizer depicting the CS in plane, the site of flow measurement was defined by an imaging plane transecting the center of both the left atrium and the aortic valve, thereby cutting the CS perpendicularly (Figure 1a). Imaging parameters were as follows: repetition time/echo time, 20/7.4 ms; flip angle, 15°; retrospective ECG gating; 2 excitations averaged; respiratory compensation (respiratory ordered-phase encoding); field of view, 20×20 cm² with a matrix of 256×160 (linearly interpolated before display yielding a spatial resolution of 0.8×0.8 mm²); and velocity encoding, ±0.80 and ±1.40 m/s for baseline and hyperemic conditions, respectively. CS flow measurements were performed twice during baseline conditions (at an interval of 5 minutes to determine short-term reproducibility) and were repeated 4 minutes after dipyridamole administration (0.56 mg/kg IV over 4 minutes, Perfusor VI).

Data Analysis

CS blood flow (mL/min) was calculated by summing the flow per cardiac phase over the cardiac cycle and multiplying by the mean HR during the measurement. Flow per cardiac phase equals mean velocity at that phase times vessel area determined manually on the magnitude images (whereby border pixels were included in the area measurement). Phase offset errors were minimized for each cardiac phase by subtracting phase shifts averaged from 2 regions of stationary tissue (chest wall and skeletal muscle of the back). CFR was defined as the ratio of hyperemic to baseline CS flow. For calculation of CFR, baseline flows were corrected for differences in rate-pressure product (RPP) (see below).

LV mass and volumes were calculated from Simpson’s rule. In a first approach, a measure of MBF (mL·min⁻¹·g⁻¹) was obtained by dividing CS flow by total LV mass. Because the inferior third of the interventricular septum is almost exclusively drained by the middle cardiac vein10,11 that enters the CS distal to the site of MR flow measurement (see Figure 1a) and the inferoposterior wall of the heart is typically drained by 1 to 3 posterior veins,10,11,12 LV mass that drains into the CS (LVM intraventricular septum and inferior third of the interventricular septum minus the inferoposterior segment) was defined as total LV mass minus the inferior third of the interventricular septum (Figure 1b).

Indexes of Contractility and Loading

As an index of LV contractility, midwall circumferential fiber shortening (cFS) was calculated from the MR data14 by applying a 2-shell cylindrical model.16 cFS was negatively correlated with circumferential end-systolic wall stress (cSWS) (see Results section), and the slope of the regression equation was used to correct cFS for differences in cSWS (cFS norm ) by calculating cFS at the mean cSWS of all volunteers. Systolic wall thickening and LV ejection fraction were calculated as described earlier.13,14

In the formulas for calculations of end-systolic circumferential17 and meridional18 LV wall stresses, cuff systolic BP was substituted for end-systolic BP as proposed by Reichek et al. For estimation of peak systolic stress indexes, LV dimensions and wall thicknesses were obtained at a point one third of ejection21 by linear interpolation between end diastole and end systole. Furthermore, cuff systolic BP was substituted for systolic LV pressure.

PET Examination

Dynamic PET measurements were performed with a whole-body PET scanner (Advance, GE Medical Systems). Images were reconstructed with filtered back projection (Hanning filter; cutoff, 5 mm transaxial, 8.5 mm axial) and a 128×128-pixel output matrix. Beginning with the intravenous bolus administration of 700 to 800 MBq [13 N]NH₃, serial images were acquired for 15 minutes. After a delay time of ≥50 minutes to allow for ¹³ N decay (physical half-life, 9.9 minutes), hyperemia was induced by dipyridamole (same regimen as for the MR study), and the flow measurement was repeated. Finally, a 20-minute transmission scan was acquired for attenuation correction.

On reformatted short-axis views, 8 regions of interest (ROIs) were placed in 8 slices each as demonstrated in Figure 1c. From all 64 ROIs, regional myocardial tissue time-activity curves were obtained. The arterial input function was derived from an ROI in the LV blood pool. As a direct estimator of MBF, Ki (mL·min⁻¹·g⁻¹) was calculated from the time-activity curves with a previously validated 2-compartment model (Ki = kᵢ, spillover correction).12 In analogy to the LVM intraventricular septum as defined on the MR data set, MBF values of ROIs 1 through 3, 7, and 8 of all 8 slices were averaged (see Figure 1c). This analysis was performed for baseline and hyperemic flow states.

Both MR and PET baseline flows correlated with the RPP (see Results section), and the slope of the regression equation was used to...
correct flows for differences in the RPP by calculating their values at the mean RPP of all subjects (pooled MR and PET data).

**Statistical Analysis**

Values are given as mean±SD. Limits of agreement between PET- and MR-derived flow and flow reserve measurements are reported as mean±2 SD of differences calculated from paired PET and MR measurements. Additionally, a repeated-measures ANOVA was performed (2 within factors: MR versus PET and baseline versus hyperemia), followed by paired t tests and Bonferroni’s correction (P<0.05/4 is significant because of 4 comparisons). Correlations of oxygen demand and MBF data were sought through univariate and stepwise linear regression analysis. Intraobserver and interobserver variabilities and short-term reproducibility of MR flow measurements are reported as mean±2 SD of differences of paired analyses. Comparisons between OHT recipients and control subjects were performed with unpaired Student’s t tests. We considered P<0.05 to be statistically significant.

**Results**

In 1 OHT recipient and 1 healthy volunteer, CS flow could not be measured by MR because of dipyridamole-induced nausea and for technical reasons, respectively. Representative examples of MR images of the CS and corresponding flow profiles are given in Figures 2 and 3, respectively.

**Comparison of MR and PET results**

The hemodynamic data for the PET-MR comparison are given in Table 1. Figure 4 demonstrates the close agreement of the 2 techniques for measurements of CFRnorm (mean difference, 2.2%; limits of agreement, −27.2% to 31.6%).

CS flow in these healthy volunteers increased from 68.8±16.1 mL·min⁻¹ at baseline to 290.2±70.2 mL·min⁻¹ during hyperemia (P<0.0001). MBF calculated as CS flow divided by total LV mass correlated highly with PET flow data; however, the slope was considerably less than unity (Figure 5a and Table 1). If CS flow was divided by LVMdrain, the slope approached unity (Figure 5b and Table 1). Resting MBF correlated with RPP (slope, 7×10⁻³ mL·g⁻¹·mm Hg⁻¹, r=0.61, P<0.001; pooled PET and MR data). The difference for RPP-corrected MR and PET flow data at baseline was 3.4±12.8% and was similar for hyperemic condition (3.9±20.2%, P=NS versus baseline; Figure 6).

<table>
<thead>
<tr>
<th>TABLE 1. Systemic and Coronary Hemodynamics: PET-MR Comparison</th>
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<td></td>
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<tr>
<td>HR, bpm</td>
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<tr>
<td>BPsys, mm Hg</td>
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<tr>
<td>BPdiast, mm Hg</td>
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<tr>
<td>RPP, mm Hg/min</td>
</tr>
<tr>
<td>MBF, mL·min⁻¹·g⁻¹</td>
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<tr>
<td>MR: CSF/LVMtotal</td>
</tr>
<tr>
<td>MR: CSF/LVMmin</td>
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<tr>
<td>CFRnorm</td>
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</table>

Syst indicates systolic; diast, diastolic.

*P<0.0001 vs baseline; †P<0.0003 vs MR; ‡P<0.008 vs MR; ANOVA for repeated measures with 2 within factors and post hoc paired t tests with Bonferroni correction (P<0.05/4 is significant because of 4 comparisons).
For the intraobserver variability of CS flow and CFR, the mean difference (with 95% CI in parentheses) was −0.3% (−19.7% to 19.1%) and 2.4% (−15.6% to 18.4%), respectively. For the interobserver variability, the results were 5.0% (−9.8% to 19.8%) and −1.6% (−19% to 15.8%), respectively. The short-term reproducibility for baseline CS flow measurements was 1.3% (−29.7% to 32.3%).

Determinants of Coronary Flow in Healthy Volunteers
LV anatomical and functional data of the study population are given in Table 2. The negative correlation between cFS and cFSnorm (slope, −0.07, r = −0.76, P < 0.001) was used for calculation of cFSnorm. Both measures of MBF (CS flow divided by total LV mass and by LVMdrain) were positively correlated with HR (r = 0.76, P < 0.001 and r = 0.77, P < 0.001, respectively), cFSnorm (r = 0.54, P < 0.05 and r = 0.70, P < 0.005, respectively), and mS peak (r = 0.51, P < 0.05 and r = 0.58, P < 0.03, respectively; univariate analysis; Figure 7a through 7c). No correlations were found for systolic BP, cSES, and mSak. In a stepwise regression analysis, HR and cFS norm were identified as independent predictors of baseline MBF (CS flow divided by LVM total) and together explained 67% (adjusted R²) of autoregulated MBF (r = 0.85, P < 0.0001; Figure 7d).

Blood Supply-Demand Relationship in OHT Recipients
OHT recipients exhibited a marked concentric LV hypertrophy, along with a reduction in LV systolic loading and reduced indexes of contractility (Table 2). Nevertheless, MBF (CS flow/LVM total) per heart beat was increased in these patients (0.011±0.001 versus 0.008±0.002 mL · g⁻¹ · beat⁻¹ in control subjects, P < 0.002). Because HR and cFS norm were identified as independent predictors of blood flow in normal hearts (see above), this blood supply-demand relationship (represented by the equation MBF=0.0086×HR+0.29×cFS norm−6.67) was applied to control and transplanted hearts, yielding MBFpredicted (MBF predicted by HR and cFS norm). In the control hearts, MBFpredicted closely matched MBFmeasured (slope, 0.997; intercept, −0.00363 mL · min⁻¹ · g⁻¹; mean difference, 0.001±0.047 mL · min⁻¹ · g⁻¹; P = 0.92 versus 0; Figure 8). However, in transplanted hearts, MBFmeasured was substantially higher than MBFpredicted (difference, 0.378±0.123 mL · min⁻¹ · g⁻¹, P < 0.0001 versus 0; Figure 8). This difference, reflecting the degree of blood supply-demand imbalance, was positively correlated (r = 0.72, P = 0.026) with blood CsA (trough levels on the day of MR examination). No relations were found for azathioprine dose, prednisone dose (mg/kg), type of antihypertensive treatment, LV mass, and time after transplantation. Similar results were obtained for CSF divided by LVMdrain with MBFmeasured higher than MBFpredicted (1.23±0.16 versus 0.87±0.21 mL · min⁻¹ · g⁻¹, P < 0.002) and the difference correlating with CsA levels (r = 0.74, P = 0.024).

CFR was reduced in transplanted patients compared with control subjects (Table 3). Further analysis revealed a weak negative correlation between hyperemic MBF and LV mass index (r = −0.56, P < 0.005; n = 24).

Discussion
The major findings in the present study are as follows: (1) the presented MR approach allowed noninvasive measurement of global CFR in healthy volunteers and patients and yields absolute units of MBF (mL · min⁻¹ · g⁻¹) by relating CS flow to estimates of drained myocardium, and

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Comparison of PET and MR measurements of global CFR (Bland-Altman analysis). Differences are given in absolute values (a) and as percentage (b). CFRnorm is ratio of hyperemic to baseline CSF with baseline flow normalized for RPP.

![Figure 5](https://example.com/figure5.png)

**Figure 5.** Correlations between estimates of MBF (mL · min⁻¹ · g⁻¹) derived from PET (x axis) and MR (y axis) measurements. For both MR-derived measures of MBF, ie, CSF divided by total left ventricular mass (LVMtotal; a) and divided by drained myocardium (LVMdrain; b), correlations with PET flow data are high. For CSF divided by LVMtotal, slope of regression line approximates unity (dashed line).

![Figure 6](https://example.com/figure6.png)

**Figure 6.** Comparison of MBF as measured by PET and MR (CSF divided by drained myocardium) with baseline flows normalized for RPP (Bland-Altman analysis). Mean differences between PET and MR measurements during baseline (3.4±12.8%) and hyperemia (3.9±20.2%) were not significantly different.
TABLE 2. LV Anatomic and Functional Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>OHT Male Recipients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=15)</td>
<td>Women (n=6)</td>
</tr>
<tr>
<td>Age, y</td>
<td>28±3</td>
<td>26±3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76±11</td>
<td>63±10*</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.91±0.18</td>
<td>1.72±0.14*</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>69±10</td>
<td>66±5</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>25±4</td>
<td>23±6</td>
</tr>
<tr>
<td>CI, L/min</td>
<td>2.9±0.4</td>
<td>3.0±0.6</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>78±10</td>
<td>70±8</td>
</tr>
<tr>
<td>LVEDV/LVM ratio, mL/g</td>
<td>0.89±0.11</td>
<td>0.96±0.18</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>64±5</td>
<td>65±7</td>
</tr>
<tr>
<td>%WT, %</td>
<td>59.5±14.7</td>
<td>62.2±12.1</td>
</tr>
<tr>
<td>cFS, %</td>
<td>22.3±3.7</td>
<td>24.0±2.5</td>
</tr>
<tr>
<td>cFSnorm, %</td>
<td>22.3±2.2</td>
<td>23.4±2.1</td>
</tr>
<tr>
<td>cSES, kdyne/cm²</td>
<td>185±42</td>
<td>169±25</td>
</tr>
<tr>
<td>mSES, kdyne/cm²</td>
<td>81±31</td>
<td>60±12</td>
</tr>
<tr>
<td>cSpeak, kdyne/cm²</td>
<td>296±43</td>
<td>298±27</td>
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<tr>
<td>mSpeak, kdyne/cm²</td>
<td>131±22</td>
<td>138±17</td>
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</table>

BSA indicates body surface area; LVEDVI and LVESVI, LV end-diastolic and end-systolic volume index, respectively; CI, cardiac index; LVMi, LV mass index; LVEF, LV ejection fraction; %WT, percent systolic wall thickening; cFS, circumferential fiber shortening; cFSnorm, normalized cFS; cSES, circumferential end-systolic wall stress; and mSpeak and mSpeak, circumferential and meridional peak-systolic wall stress, respectively.

*P<0.05 vs men (unpaired t tests).

(2) it determines coronary blood supply-demand relationships and in chronically denervated hearts demonstrated an increased resting flow in relation to major determinants of oxygen demand.

Figure 7. Blood supply-demand relationships in normal hearts derived from MR data. MBF (CSF flow divided by drained myocardium) was positively correlated with HR (bpm; a), afterload-corrected midwall cFS (cFSnorm; b), and peak systolic meridional wall stress (mSpeak; c). HR and cFSnorm were used to calculate MBFpredicted and explained 67% (adjusted R²) of variability in baseline flow (d).

Figure 8. In control subjects, MBF predicted by heart rate and afterload-corrected midwall circumferential fiber shortening (MBFpredicted) correlated highly with measured MBF (slope=0.997; r=0.92, P<0.0001; dotted lines represent 95% CI). In OHT recipients, MBFmeasured exceeded MBFpredicted (difference, 0.37±0.123 mL·min⁻¹·g⁻¹, P<0.0001 vs 0), suggesting alterations in coupling of blood supply and oxygen demand in transplanted hearts.

CFR Measurements by Means of Cine PC-MR Technique

PET with [¹³N]NH₃ is well established as an accurate method for blood flow quantification. The agreement between PC-MR and PET measurements of CFR was excellent, with a difference of 2.2±14.7% over a wide range of flow reserves, and the limit of agreement of ±29.4% is acceptable if one considers the reproducibility of PET for CFR measurements of approximately ±30% (estimated from the method of Nagamachi et al). PC-MR techniques accurately measured blood flow in the coronary arteries and CS. Extensive in-plane motion of the cardiac contours made an accurate determination of CFR challenging. Therefore, it was decided to use PC-MR techniques to calculate CFR even though they were not part of the clinical protocol. The PC-MR techniques estimated CFR in the range of ±15%.

TABLE 3. Comparison of Hemodynamics in Control Subjects and OHT Recipients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>OHT Male Recipients</th>
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<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>60±8</td>
<td>85±11†</td>
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<tr>
<td>BPsys, mm Hg</td>
<td>120±8</td>
<td>136±12</td>
</tr>
<tr>
<td>BR, mm Hg</td>
<td>73±10</td>
<td>85±9*</td>
</tr>
<tr>
<td>RPP, mm Hg · min⁻¹</td>
<td>7258±1398</td>
<td>11 533±1719†</td>
</tr>
<tr>
<td>CSF, mL/min</td>
<td>73±18</td>
<td>179±29†</td>
</tr>
<tr>
<td>MBF, mL · min⁻¹ · g⁻¹</td>
<td>0.50±0.12</td>
<td>0.89±0.10†</td>
</tr>
<tr>
<td>CSF/LVM, RPP corrected</td>
<td>0.73±0.20</td>
<td>1.23±0.16†</td>
</tr>
<tr>
<td>CSF/LVM, RPP corrected</td>
<td>0.73±0.15</td>
<td>0.84±0.19</td>
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</table>

Hyperemia

<table>
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<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>OHT Male Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>85±12</td>
<td>99±15*</td>
</tr>
<tr>
<td>BPsys, mm Hg</td>
<td>125±12</td>
<td>139±6†</td>
</tr>
<tr>
<td>BR, mm Hg</td>
<td>72±11</td>
<td>87±7†</td>
</tr>
<tr>
<td>RPP, mm Hg · min⁻¹</td>
<td>10 807±2248</td>
<td>13 756±1837†</td>
</tr>
<tr>
<td>CSF, mL/min</td>
<td>271±184</td>
<td>348±70*</td>
</tr>
<tr>
<td>MBF, mL · min⁻¹ · g⁻¹</td>
<td>1.89±0.74</td>
<td>1.75±0.48</td>
</tr>
<tr>
<td>CSF/LVM, RPP corrected</td>
<td>2.56±0.98</td>
<td>2.49±0.67</td>
</tr>
<tr>
<td>CFR</td>
<td>3.9±1.4</td>
<td>2.0±0.4†</td>
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Abbreviations as in Table 1.

*P<0.05, †P<0.005 vs control subjects.
CS during the cardiac cycle and the highly pulsatile flow pattern necessitate high temporal resolution of flow data acquisition. In the present study, this was achieved by acquisition of $k$ lines without segmentation. Furthermore, recent improvements in scanner hardware and software allowed us to shorten the acquisition time to assess coronary hemodynamics not only during autoregulation but also during pharmacological stimulation. Prolonged breath holds may affect the hemodynamics of the right atrium and hence could change flow dynamics in the CS. This source of error was avoided in the present study by the non–breath hold approach. Furthermore, in hemodynamically compromised patients, data acquisition without breath holding might be advantageous.

Assessment of Myocardial Blood Supply-Demand Relationship in Control Hearts

Blood supply to the heart was assessed by measuring CS outflow. Both estimates of MBF, ie, CS flow divided by total LV mass or LVM$_{\text{drain}}$, correlated highly with PET flow data ($r=0.93$ and $r=0.95$, respectively), indicating that both measures of MBF are useful for assessing blood supply. Further, indexes of contractility and LV systolic loading derived from the MR data set correlated with both measures of MBF, indicating that the presented MR technique provides all components necessary to establish blood supply-demand relationships noninvasively.

It is advantageous to relate CS flow to LVM$_{\text{drain}}$ because it allows direct quantitative comparison between MR and PET data. The limits of agreement for the MR and PET measurements of MBF were $-29.6\%$ and $36.8\%$, which are in the range for the reproducibility of PET measurements of $\pm 25\%$ to $\pm 32.4\%$ (calculated from the methods of Nagamachi et al$^1$ and Czernin et al$^5$, respectively).

Uncoupling of Myocardial Blood Supply and Demand in Transplanted Hearts

In the present study, resting MBF (CS flow/LVM$_{\text{drain}}$) of OHT recipients was $1.23$ mL $\cdot$ min$^{-1} \cdot$ g$^{-1}$, which is in agreement with results of PET studies ranging from $0.94$ to $1.63$ mL $\cdot$ min$^{-1} \cdot$ g$^{-1}$.$^{22-25}$ In the present study, MBF of OHT recipients was significantly higher than in control subjects as demonstrated in several PET studies.$^{22-25}$ Despite this increase in resting MBF, indexes of contractility and systolic loading were reduced in these concentrically hypertrophied hearts. Accordingly, predicted MBF that reflects MBF dictated by oxygen demand was significantly less than measured MBF, supporting the notion that coupling between oxygen demand and blood supply is altered in human denervated myocardium. Furthermore, this study provides evidence that supply-demand uncoupling is modulated by CsA. Similarly, in rat hearts, coronary blood flow was increased during CsA treatment while contractile function was depressed.$^{26}$ One may speculate whether CsA-induced alterations in mitochondrial calcium handling$^{26,27}$ could be responsible for this observation.

Study Limitations

Regional assessment of myocardial flow and flow reserve is not achieved by the presented MR approach. However, progression of coronary artery disease is not limited to individual coronary arteries but is a generalized disease process of the coronary vasculature. Therefore, serial measurements of global CFR by the proposed technique might be useful for monitoring the progression of coronary artery disease and assessing the effects of drug interventions in these patients. Another disadvantage of the presented MR technique is its inability to assess flow and flow reserve in different myocardial layers, a limitation, however, that is shared by most other noninvasive techniques aimed at perfusion measurements in the heart. Whereas CFR measurements by means of the proposed MR technique are not affected by the anatomic variability of the coronary venous system, absolute flows (mL $\cdot$ min$^{-1} \cdot$ g$^{-1}$) depend on estimated mass of drained myocardium. Accordingly, alterations in absolute coronary flows may be inferred from appropriately sized patient populations rather than from a single measurement.

Implications and Conclusions

PC-MR imaging, as presented in this study, could become a valuable research tool thanks to its noninvasiveness and an integrated evaluation of coronary flow and LV function. To the best of our knowledge, this is the first report to demonstrate in humans the capability of an integrated MR approach to quantitatively measure MBF under resting and hyperemic conditions and to simultaneously provide quantitative estimates of major determinants of myocardial oxygen demand. Thus, the technique may be ideal for studying coronary hemodynamics in generalized diseases of the LV, such as hypertensive heart disease, valvular heart disease, cardiomyopathies, and others, and for assessment of therapeutic interventions in these disease states. In OHT recipients, the presented data suggest an uncoupling between blood supply and demand under resting conditions. Further studies are warranted to clarify the role of cardiac denervation and immunosuppressive therapy in this setting.

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References


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