Quantitative Evaluation of Myocardial Ischemia by Cardiac Magnetic Resonance Imaging

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Abstract

The aim of this study is to evaluate the significance of transmural perfusion gradient (TPG) method with 3.0T MRI to detect coronary artery disease (CAD). Traditional quantitative analysis of transmural myocardial perfusion neglects that subendocardium is more vulnerable to ischemia than subepicardium. In contrast, TPG and relative TPG reserve (TPGR) can take it in account and should be useful for CAD diagnosis. 44 patients (35 men, age 61.5 ± 7.8 years) with known or suspected CAD underwent adenosine-stress CMR scan. Quantification of myocardial perfusion was based on exponential model by deconvolution technique. Quantitative coronary angiography (QCA) ≥ 70% stenosis was considered as anatomically significant. TPG and relative TPGR showed significant difference between ischemia and normal territories (TPG 0.72 ± 0.14 vs. 0.95 ± 0.18, stenosis vs. normal, respectively, P < 0.0001; relative TPGR 0.82 ± 0.13 vs. 1.09 ± 0.11, P < 0.0001). Area under curve (AUC) was 0.87 for TPG and 0.94 for relative TPGR. Relative TPGR yielded significantly better sensitivity and specificity of CAD diagnosis compared to myocardial blood flow (MBF), relative myocardial perfusion reserve (MPR) and TPG (P < 0.0001) and appeared to be the most meaningful parameter to detect anatomically significant CAD.

1. Introduction

Cardiac magnetic resonance imaging (CMR) has recently established itself as an accurate and valuable tool to evaluate coronary artery disease (CAD).[1] Most of the previous studies focused on the transmural myocardial perfusion analysis, such as myocardial blood flow (MBF) and myocardial perfusion reserve (MPR).[2] As recent study has revealed that myocardial ischemia affects the subendocardial layers of the left ventricular myocardium earlier and more severely than the subepicardial layers,[3] traditional MBF and MPR analysis might overlook the early appearance of myocardial ischemia.

The objective of this study is to assess the differences of transmural perfusion gradient (TPG) and relative transmural perfusion gradients reserve (relative TPGR) between normal and ischemia perfusion territories and also to probe the diagnosis abilities of TPG and relative TPGR with CMR quantitative perfusion analysis compared with quantitative coronary angiography (QCA). In our study, we find that TPG analysis has higher diagnosis value than conventional perfusion analysis.

2. Methods

2.1. Patient population and study design

Patients with typical chest pain suspected as CAD were recruited and underwent CMR perfusion imaging scan before invasive coronary studies. CMR data were acquired with a 3.0-T system (MAGNETOM Verio, Siemens Medical Solutions, Erlangen, Germany). Perfusion imaging consisted of 3 LV short-axis slices using T1-weighted saturation recovery turbo flash sequence. Adenosine-induced stress imaging preceded rest by 15 min. The duration of the scan was 50 cardiac cycles. Late gadolinium enhancement images were acquired 10 min after contrast administration.

2.2. Catheter laboratory protocol

X-ray coronary angiography was performed within 7-14 days of CMR exam. QCA was calculated for all arteries. Coronary territories subtended by a coronary artery with ≥ 70% stenosis were classified as stenosis territories, and all other territories were classified as remote or reference normal territories.

2.3. CMR image analysis

The implementation of high resolution signal intensity (SI) analysis in this study was preprocessed by registration to avoid respiratory and cardiac motion. Perfusion was quantified in 16 standard American Heart

Association segments.[4] Subendocardial and subepicardial borders were outlined and manually corrected where required. The region of interest was placed in the LV cavity [Fig 1.].

Deconvolution technique was applied to yield the SI vs. time curves and provided a parameterized myocardial blood flow measurement. Spatially averaged SI values were used to plot SI vs. time curves of the whole myocardial circumference and the region of interest in the center of LV blood pool, based on the Central Volume Principle suggested by Zierler. [5] The exponential model was used to match the residual function as $R(t) = P \cdot e^{-t/\tau}$, where we calculated MBF. Relative MPR was calculated by dividing the values of the MBF of impairment perfusion territory irrigated by stenosis coronary artery to remote normal territory.

The subendocardial and subepicardial SI curves were obtained from the inner and outer halves of the LV myocardium [Fig 1.]. The TPG was defined as the ratio of MBF in the subendocardial and subepicardial layers. Relative TPGR was defined as the ratio of TPG in impairment perfusion territory to remote normal territory as relative MPR did. All parameters were assigned to a coronary perfusion territory on the basis of the standardized LV segmentation and compared with CAG.

2.4. Statistical analysis

The IBM SPSS Statistics (version 21.0, SPSS, Chicago, Illinois) and Medcalc software (Med-calc, Mariakerke, Belgium) were used. Data are presented as mean ± SD, except where stated. Group means were compared using paired or unpaired Student *t* test. Receiver-operating characteristic (ROC) analysis was used to assess the diagnostic accuracy of TPG and relative TPGR and to determine their threshold with the greatest sensitivity and specificity to detect coronary disease at a QCA cut-off of 70%. Optimal cutoffs were determined by the maximum Youden Index. ROC curves were compared using the DeLong test.

3. Results

3.1. Study population

44 patients completed the study protocol. Angiography was performed within 2 weeks after the CMR scan. Basic information of patients as well as the results of CMR and angiography are shown in Table 1.

Table 1. Baseline demographics of patient cohort.

Parameter	Data (n = 44)
Age (y)	61.5 ± 7.8
Male, n (%)	35 (79.5)
CMR data	
Ejection fraction (%)	57 ± 12
Late gadolinium enhancement, n (%)	
Full thickness	0
Partial thickness	2 (4.5)
Angiographic data	
Time from CMR scan, days	12.1 ± 7.8
Patients with coronary disease (≥ 70% QCA stenosis), n (%)	32 (72.7)
Vessels with QCA≥ 70%, n (%)	50 (37.9)
Left anterior descending, n (%)	22 (44)
Circumflex, n (%)	10 (20)
Right coronary artery, n (%)	18 (36)
One-vessel disease, n (%)	18 (40.9)
Two-vessel disease, n (%)	10 (18.2)
Three-vessel disease, n (%)	4 (9.1)

Data are n (%) or mean ± SD unless otherwise indicated.

3.2. Quantitative analysis

Quantitative analysis was available for all territories (Table 2). In the analysis of subendocardial and transmural myocardium, the stress MBF_{endo} and relative MPR_{endo} in the 50 ischemic territories (stenosis ≥ 70% in QCA) were 1.41 ± 0.42 and 0.69 ± 0.24 respectively. The stress MBF_{trans} and relative MPR_{trans} were 1.67 ± 0.49 and 0.76±0.24. In the 82 normal reference territories (stenosis < 70% in QCA), the corresponding parameters were 1.90 ± 0.36 ($P < 0.01$) and 1.02 ± 0.23 ($P < 0.0001$) for subendocardium and were 1.98 ± 0.36 ($P < 0.05$) and 0.98 ± 0.23 ($P < 0.01$) for transmural myocardium. In the analysis of subepicardium, the MBF_{epi} and relative MPR_{epi} were not significantly different from stenosis territories and non-stenosis territories.

In ROC analysis, the area under the receiver-operating curve (AUC) to detect significant CAD was 0.69 for stress MBF_{endo} and 0.85 for relative MPR_{endo}. Sensitivity and specificity against QCA were: stress $MBF_{endo} \leq 1.28$: 53.57% and 83.61%; and relative $MPR_{endo} \leq 0.88$: 79.31% and 76%. The AUC of stress MBF_{endo} and relative MPR_{endo} were significantly higher than that of stress MBF_{trans} ($P < 0.01$) and relative MPR_{trans} ($P < 0.001$), respectively, on a vessel basis for QCA ≥ 70%.

Table 2. Quantitative perfusion data and comparison between coronary artery stenosis with QCA < 70% and QCA ≥ 70%.

	QCA < 70% (n = 82)	QCA ≥ 70% (n = 50)	*P* value
Stress MBF			
MBF_{endo}	1.9 ± 0.4	1.4 ± 0.4	**0.002**
MBF_{epi}	2.0 ± 0.4	2.0 ± 0.6	0.687
MBF_{trans}	2.0 ± 0.4	1.7 ± 0.5	**0.038**
RelativeMPR			
$RelativeMPR_{endo}$	1.0 ± 0.2	0.7 ± 0.2	**< 0.0001**

Relative MPR_{epi}	1.0 ± 0.3	0.8 ± 0.3	0.127
Relative MPR_{trans}	1.0 ± 0.2	0.8 ± 0.2	**0.001**

3.3. Gradient analysis

All quantitative analysis data were available for gradient analysis (Table 3.). The stress TPG and relative TPGR in the 50 ischemic territories were 0.72 ± 0.14 and 0.82 ± 0.13, respectively. In the 82 reference territories, the parameters were 0.95 ± 0.18 ($P < 0.0001$) and 1.09 ± 0.11 ($P < 0.0001$). In ROC analysis, the AUC to detect significant CAD was 0.87 for stress TPG and 0.94 for relative TPGR. Sensitivity and specificity against QCA ≥ 70% were: stress TPG ≤ 0.79: 82.14% and 81.15%; and relative TPGR ≤ 0.95: 89.66% and 92.00%.

In ROC analysis, the AUC for TPG analysis was significantly higher for transmural myocardium perfusion analysis (stress TPG vs. stress MBF_{trans}: $P < 0.001$; relative TPGR vs. relative MPR_{trans}: $P < 0.01$) while did not show superiority compared with subendocardium perfusion analysis (relative TPGR vs. relative MPR_{endo}: $P = 0.1513$) except stress TPG (stress TPG vs. stress MBF_{endo}: $P = 0.0147$). Relative TPGR yielded significantly better sensitivity and specificity of CAD diagnosis compared to stress TPG ($P < 0.0001$).

Table 3. TPG analysis data and comparison between coronary artery stenosis with QCA < 70% and QCA ≥ 70%

	QCA < 70% (n = 82)	QCA ≥ 70% (n = 50)	*P* value
Stress TPG	1.0 ± 0.2	0.7 ± 0.1	**< 0.0001**
Rest TPG	1.0 ± 0.3	1.0 ± 0.2	0.616
Relative TPGR	1.1 ± 0.1	0.8 ± 0.1	**< 0.0001**

4. Discussion

The main findings of our study are: 1)TPG and relative TPGR are better than traditional transmural myocardium perfusion analysis to detect anatomically significant CAD; 2) Relative TPGR ≤ 0.95 is an optimal threshold for the detection of significant CAD; and 3) Subendocardium is more vulnerable to ischemia injury than subepicardium.

Due to higher workload and oxygen consumption in subendocardium than in subepicardium, blood flow favors the subendocardium. [6] The ratio of subendocardial to subepicardial blood flow is about 1.15:1 in normal perfusion area, while it is often less than 1:1 in ischemic area, especially under stress. [7] Therefore, the appearance of subendocardial ischemia is considered to be a useful hint for early diagnosis of myocardial blood supply impairment. [8]

Previous studies have validated the value of MBF and MPR in CAD detection. [2] New developments in high field (3 Tesla) CMR, with sufficient spatial and temporal resolution, have made it possible to detect more subtle evidence of regional myocardial ischemia. [5]

Early studies have described the transmural perfusion gradient in healthy subjects [9] and in CAD patients. [10] Most of previous studies analyzed TPG merely under rest or stress state. This is the first study, to our knowledge, to define the diagnosis values of TPG and relative TPGR to determine regional myocardial ischemia based on CMR perfusion imaging.

Anatomical significance of coronary stenosis was assessed by QCA in this study. In our study, transmural MBF under adenosine stress state is consistent with previous studies. [11] We then subdivided the transmural myocardium segment into subepicardial and subendocardial parts (Fig. 1) and found a significant decrease in the subendocardial MBF but not in the subepicardial one, where perfusion impairment existed, especially under stress state. Diagnostic accuracy for subendocardial perfusion analysis was superior to transmural perfusion analysis based on ROC analysis. It confirms that subendocardium is more vulnerable to ischemia as we discussed before. Moreover, there might be some inevitable and unknown errors in quantification analysis methodologically and physiologically. Fortunately, the calculation of TPG might remove these errors as they influenced both subepicardial and subendocardial perfusion values similarly.

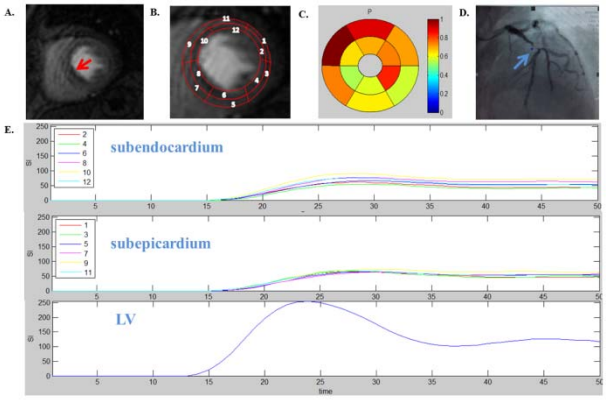

Figure 1. Example CMR perfusion image study; 56-year-old man with angina pectoris. This detected a stress-induced hypoperfusion in the anterior and septal subendocardium (red arrow) (A). The subendocardial and subepicardial time-signal intensity curves were from the inner and outer halves of the LV myocardium (E). A significant perfusion gradient was found in the corresponding area (C). Perfusion imaging consisted of 3 LV short-axis slices (basal, mid-papillary and apical) covering 16 of the American Heart Association segments with apex segment excluded. Each segment was subdivided into subendocardial and subepicardial parts. (B) Example of mid-papillary slice. Angiography revealed a severe 90% stenosis in LAD (blue arrow) (D).

Other studies have showed that MPR, the ratio of stress and rest MBF, is superior to MBF in detecting the impaired perfusion area.[11] Later studies found that MPR might be influenced by resting hemodynamics.[12] Therefore, the relative MPR, defined as the ratio of hyperemic blood flow with stenosis to the remote, eliminates such influence and becomes more stable than MPR.[5] We applied the relative MPR theory into TPG analysis and tried to find out whether taking into account the hyperemic flow induced by adenosine stress would improve the result over TPG as relative MPR does over MBF.

In our study, based on ROC analysis, MBF and relative MPR of both transmural myocardium and subendocardium showed high sensitivity and specificity to predict stenosis ≥ 70%, while the corresponding parameters of subepicardium did not reveal such results. Relative TPGR was significantly lower in ischemic myocardial segments as compared with reference normal myocardium. The results of the AUC also indicated the accuracy of TPG and relative TPGR to detect anatomical significant CAD (QCA ≥ 70% stenosis). Under linear regression analysis, relative TPGR correlate inversely with QCA data significantly.

To our knowledge, it is the first study to analyze TPGR and relative TPGR in the diagnosis of CAD. They take into account the influence of hyperemia and the vulnerability of subendocardium, which magnify the extent of myocardial perfusion impairment and improve the diagnosis accuracy. Relative TPGR excludes the effects of the varied resting hemodynamics variation and assesses hemodynamic significance of coronary artery stenosis more precisely.

Due to the complexity of blood vessel distribution, the 17 standard myocardial segments cannot represent real blood vessel distribution precisely. The integration of magnetic resonance angiography and myocardial perfusion imaging in the future study might improve the diagnosis accuracy of CAD.

5. Conclusion

TPG and relative TPGR yield high diagnostic accuracy of coronary artery stenosis compared with the invasive reference standard QCA.

References

[1] Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. J Am Coll Cardiol 2007;50:1343-53.

[2] Lockie T, Ishida M, Perera D, Chiribiri A, De Silva K, Kozerke S, Marber M, Nagel E, Rezavi R, Rewood S, Plein S. High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. J Am Coll Cardiol 2011;57:70-75.

[3] Algranati D, Kassab GS, Lanir Y. Why is the subendocardium more vulnerable to ischemia? A new paradigm. Am J Physiol Heart Circ Physiol 2011;300:H1090-100.

[4] Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS, American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the cardiac imaging committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105: 539-542.

[5] Warren JM, Dudley JP. Cardiovascular magnetic resonance. Second edition. Philadelphia: Saunders Elsevier, 2010:57

[6] Arai AE, Grauer SE, Anselone CG, Pantely GA, Bristow JD . Metabolic adaptation to a gradual reduction in myocardial blood flow. Circulation 1995;92:244-252.

[7] Canty IJ, Piotrowski B, Klocke F. Relative reductions in subendocardial and full-thickness flow during pharmacologic vasodilation as an index of functional stenosis seventy.J Am Coll Cardiol 1990;15:182A

[8] Muehling OM, Wilke NM, Panse P, Jerosch-Herold M, Wilson BV, Wilson RF, Miller LW. Reduced myocardial perfusion reserve and transmural perfusiongradient in heart transplant arteriopathyassessed by magnetic resonance imaging. J Am Coll Cardiol 2003;42:1054-60.

[9] Muehling OM, Jerosch-Herold M, Panse P, Zenovich A, Wilson BV, Wilson RF, Wilke N. Regional Heterogeneity of Myocardial Perfusion in Healthy Human Myocardium: Assessment with Magnetic Resonance Perfusion Imaging. J Cardiovas Magn Reson 2004;6:499-507.

[10] Chiribiri A, Hautvast GL, Lockie T, Schuster A, Bigalke B, Olivotti L, Redwood SR, Breeuwer M, Plein S, Nagel E. Assessment of Coronary Artery Stenosis Severity and Location: Quantitative Analysis of Transmural Perfusion Gradients by High-Resolution MRI Versus FFR. JACC Cardiovasc Imaging 2013;6:600-609.

[11] Morton G, Chiribiri A, Ishida M, Hussain ST, Schuster A, Indermuehle A, Perera D, Knuuti J, Baker S, Hedstrom E, Schleyer P, O'Doherty M, Barrington S, Nagel E. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. J Am Coll Cardiol 2012;59:E1064.

[12] Schwitter J, DeMarco T, Kneifel S, von Schulthess GK, Jorg MC, Arheden H, Ruhm S, Stumpe K, Buck A, Parmley WW, Luscher TF, Higgins CB. 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. Circulation 2000;101:2696-2702.

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