

The delay of contrast arrival in magnetic resonance first-pass perfusion imaging: A novel non-invasive parameter detecting collateral-dependent myocardium

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MR imaging for the detection of collateral-dependent myocardium

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ABSTRACT

Objectives: To establish the regional delay of contrast arrival in magnetic resonance perfusion imaging (MRPI) for the detection of collateral-dependent myocardium in patients with coronary artery disease.

Design and Setting: observational study, case series; single center, university hospital.

Patients: 30 patients with coronary artery disease and collateral-dependent myocardium and 17 healthy volunteers.

Methods: Resting and hyperemic (adenosine) MRPI was used to determine delay time (Δt_d) of contrast arrival between the left ventricle and collateral-dependent or antegradely-perfused myocardium, and myocardial perfusion (MP, ml/g/min).

Results: In healthy volunteers Δt_d at rest and during hyperemia were 0.8 ± 0.4 and 0.3 ± 0.3 sec., and MP was 1.14 ± 0.21 and 4.23 ± 1.12 ml/min/g. Δt_d in antegradely-perfused vs. collateral-dependent myocardium was 0.9 ± 0.7 vs. 1.7 ± 1.0 sec. at rest ($p < 0.001$) and 0.4 ± 0.3 vs. 1.1 ± 0.6 sec ($p < 0.001$) during hyperemia. MP was 1.12 ± 0.11 and 0.98 ± 0.28 ml/min/g ($p = \text{n.s.}$) at rest and 2.46 ± 0.85 vs. 1.86 ± 0.91 ml/min/g ($p < 0.01$) during hyperemia. ROC analysis showed best sensitivity and specificity of 90% and 83% for hyperemic Δt_d of > 0.6 sec (AUC=0.89) to detect collateral-dependent myocardium, while resting Δt_d (AUC= 0.77) or perfusion (AUC = 0.69 at rest or 0.70 during hyperemia) were less accurate.

Conclusions: MRPI derived hyperemic delay of contrast arrival detects collateral-dependent myocardium with high sensitivity and specificity. Perfusion was less sensitive, emphasizing the clinical role of Δt_d for non-invasive detection of collateral-dependent myocardium.

Key Words: collateral circulation; magnetic resonance imaging; perfusion

INTRODUCTION

The impact of coronary collaterals on prognosis and their protective role in patients with coronary artery disease has been described [1,2]. Detection and the assessment of coronary collaterals is the domain of invasive coronary angiography [3] since clinical and electrocardiographic responses during exercise testing failed to show a correlation with the presence of collateral circulation [4]. Prospective, non-invasive detection of collateral perfusion is cumbersome since perfusion might be normal if collateralisation is sufficient.

Quantitative MR first-pass perfusion (MRPI) imaging has been used to assess collateral flow in animals [5]. Pearlman et al. [6] used MRI and determined a delay time measured from the appearance of the contrast in the left ventricle (LV) to the time when the signal reaches a tissue region. Recent animal data suggest that MRPI imaging might be able to detect collateral-dependent myocardium by an increased delay time of contrast arrival [7].

The purpose of this study was to assess the delay time of contrast arrival with magnetic resonance first-pass perfusion imaging as a novel parameter to detect collateral-dependent myocardium in patients. In a population of patients with one total chronically occluded coronary artery we assessed regional delay of contrast arrival to distinguish antegradely-perfused and collateral-dependent myocardium. We aimed to define a threshold value for the delay parameter, to distinguish collateral-dependent from antegradely-perfused myocardium. We hypothesized that despite a similar myocardial perfusion, the arrival of contrast may be delayed in collateral-dependent myocardium and therefore better distinguishes it from antegradely-perfused myocardium.

METHODS

Thirty patients (mean age 63 ± 11 years, 20 men) with collateral-dependent myocardium due to a chronic total coronary occlusion of one main coronary artery (LAD $n=8$, LCx $n=12$, RCA $n=10$) were enrolled. The remaining coronary arteries including the feeding vessel of the collateral-dependent myocardium had less than 50% diameter stenosis. Clinical history, 12-lead electrocardiogram and serum Troponin I level were used to exclude acute or recent (<3 month) myocardial infarction. Patients underwent MRI within 48 hours of their coronary angiogram. Antianginal medication was discontinued at least 24 hours prior to testing. MRI was also performed in 17 healthy volunteers (mean age 34 ± 9 years, 11 men). At the time of the study all patients were in stable clinical condition. Subjects with contraindications to MR imaging, such as metal-implants, and patients with prior coronary bypass surgery were not enrolled. All subjects gave written informed consent in accordance with requirements of the local institutional ethics committee.

Coronary Angiography. Coronary angiography was performed using standard Judkins's technique. Coronary collaterals were graded according to Rentrop's classification [8] (0 = no filling of the distal vessel, 1 = small side branches filled, 2 = major side branches filled and 3 = main epicardial vessel filled). Quantitative coronary angiography was performed to exclude $> 50\%$ diameter stenosis of the collateral feeding vessels using the ACOM software package (Siemens Medical Solutions, Erlangen/Germany).

MR Image Acquisition. A 1.5T MR scanner (Siemens Medical Solutions) with eight receiver channels and a 12-element phased-array body coil was used. Myocardial function was assessed in the short axis plane covering the entire left ventricle from base to apex using a segmented single-slice cine sequence (TR/TE 3.0/1.5 ms, flip angle 50° , slice thickness 8 mm, FoV 280×380 mm, matrix size 190×256). Perfusion imaging was performed with a single-shot gradient-echo technique with saturation-recovery preparation for T1-weighting (repetition time/echo time/flip angle of 2.4/1.2 ms/ 18° , acquisition of 1 image/slice/heart beat, spatial resolution 2-3 mm, slice thickness 10 mm). Sixty images per slice were acquired. Patients were asked to hold their breath as long as they comfortably could. This reduces breathing motions, which hamper post processing of the images. Perfusion was determined in three LV short axis slices: one slice located close to the base of the heart just below the aortic outflow tract, a second in the middle of the LV, a third close to the apex just below the base of the papillary muscles. Perfusion imaging was performed first during adenosine-induced hyperemia then at rest, with an interstudy delay of a minimum of 10 minutes. An i.v.-bolus of 0.05 mmol/kg body weight gadolinium-DTPA (Magnevist®, Schering) injected at a rate of 6 ml/sec was applied for perfusion imaging. An additional 20 ml saline flush was given after contrast injection. Adenosine was given for a minimum of 4 minutes with a dose of $140 \mu\text{g}/\text{kg}/\text{min}$. Heart rate and cuff-blood pressure (at rest and during adenosine infusion) were recorded.

Although a dose of 0.05 mmol/kg BW Gd-DTPA can result in some signal saturation in the left ventricle, we found it best for visual assessment of the images, while maintaining the possibility for quantitative analysis with the imaging protocol outlined above. To ascertain whether there was signal saturation in the blood pool, we compared the peak amplitudes and the width at half height of the first pass peak. In all case the peak signal intensity was higher in the right and lower in the left ventricle, in proportion to the dispersion of the bolus between RV and LV. We

concluded that signal saturation effects were if at all relatively minor in these studies, although we can not completely exclude the possibility of overestimating blood flow. For the delay parameter, any saturation of the signal in the left ventricle will not have any material effect on the delay estimation, as the delay pertains to the lag between contrast enhancement in the LV and the myocardium, but not the degree of contrast enhancement itself.

Following perfusion imaging, a third contrast injection with 0.1 mmol/kg body weight gadolinium-DTPA was given. After ten minutes, delayed contrast-enhanced images were acquired in the short axis view according to the orientation of the perfusion images, using an inversion-recovery TurboFLASH sequence (TR/TE 11/4.4ms, TI set to 260-290 ms (adjusted to null the myocardial signal), slice thickness 10 mm FoV 280x340 mm², matrix 166x256).

Image Analysis. MR image analysis was performed by definition of collateral-dependent myocardium based on the assessment of the coronary angiogram, the individual anatomy, size, dominance, and location of the occluded vessel (see figure 1 A and C). Regions which appeared only partially collateral-supplied were assigned to antegradely-perfused myocardium.

Image analysis was performed blinded to the clinical status and the coronary angiogram. Cine and perfusion studies were analyzed using a dedicated Software (ARGUS, Siemens Medical Solutions). LV ejection fraction (EF, %) was calculated from the endsystolic and enddiastolic volumes derived from the short axis cine study. For perfusion imaging the short axis images were automatically divided into six sectors of equal size, with the reference sector defined at the anterior junction of the left and right ventricle (see figure 1 C). Spatially averaged, baseline corrected signal intensity (SI) values from each region were used to plot SI versus time curves from the perfusion images (see figure 2 and [9]). The software interpolated the curves automatically to 100 data points, resulting in an interpolated resolution equal to 60% of the RR interval. An additional ROI in the center of the LV cavity was used to obtain the arterial input. An impulse response was calculated by deconvolution of each measured tissue curve with the arterial input [10] using custom-written software (Matlab 6.5.1, Mathworks Inc.). A tissue response was calculated from this impulse response. The software allows the calculation of delay time and perfusion in a one step approach. The delay parameter was defined as the delay time (t_d , in seconds) between contrast arrival in a myocardial ROI and the LV input (see figure 2). The software adjusted the delay for best agreement with the measured SI curve, i.e. the intersection of a regression line of increasing flow vs. time shift over the range in which flow remains constant [7].

According to our experience in an animal model [7] the t_d had to be corrected for the dependence of the delay time on the distance of the short axis slices from the base of the heart (corrected delay time (Δt_d) = delay time of the individual sector (t_d) - minimum delay in that slice).

Myocardial perfusion in ml/min/g was determined from the maximum amplitude of the impulse response curve [10]. Myocardial perfusion was normalized to the rate pressure product (RPP, mmHg/min*10000) as an index of cardiac work [11].

Infarct was identified by a signal intensity greater than two standard deviations above the signal intensity in antegradely-perfused myocardium ten minutes after contrast injection [12] in the delayed contrast enhanced images. Where applicable, transmural extent of infarction (% TEI) was determined by planimetry using the scanner software. TEI was calculated as the contrast enhanced area in collateral-dependent myocardium (mm²) x 100 / total area of collateral-dependent myocardium (mm²) per region.

Statistics. Data were analysed using SPSS (Release 13, SPSS Inc., Chicago, USA). Students t-test for paired samples was used to test levels of significance between antegradely-perfused and collateral-dependent regions in one patient. Two-way analysis of variance (ANOVA) was used to test levels of significance between regions in patients and volunteers. If significance was indicated by ANOVA, a Bonferoni correction was used as a post-hoc test for multiple pair-wise comparisons. Threshold values were determined by receiver operating characteristics (ROC) and the area under the curve. Association between Rentrop grade and Δt_d or perfusion were evaluated by Spearman's rank correlation coefficient. Continuous data are expressed as mean \pm standard deviation. A p-value of <0.05 was considered significant.

RESULTS

Demographic characteristics and hemodynamic data of patients and volunteers are shown in table 1.

	Patients n=30	Volunteers n=17	p
Age (years)	61±11	34±9	p<0.001
Male	67%	65%	p=n.s.
Ejection Fraction (%)	52±14	65±3	p<0.05
Heart Rate (min⁻¹)			
at Rest	65±12	64±9	p=n.s.
during Hyperemia	76±13*	87±14*	p=0.05
Pressure Rate Product (mmHg/min)			
at Rest	6373±1445	6137±967	p=n.s.
during Hyperemia	7531±1774*	7919±1862*	p=n.s.
Occluded Vessel			
LAD	27%	-	
LCx	40%	-	
RCA	33%	-	
Risk factors			
Smoking	62%	No	
Hyperlipidemia	80%	No	
Diabetes	7%	No	
Hypertension	80%	No	

p<0.01 vs. resting measurement

In the group of volunteers a total of 306 regions (6 regions x 3 slices x 17 volunteers) were analysed. In patients 135 regions were assigned to collateral-dependent and 405 regions to antegradely-perfused myocardium. Uncorrected resting delay time (t_d) was 1.6 ± 1.0 and 1.7 ± 0.7 sec. in antegradely-perfused and myocardium of healthy volunteers. Table 2 shows mean resting and hyperemic data of the slice-corrected delay time (Δt_d) and perfusion in collateral-dependent and antegradely-perfused myocardium and myocardium of healthy volunteers.

	<i>Patients</i>		<i>Volunteers</i>	<i>p</i>	
	<i>Antegradely-perfused</i> n=405	<i>Collateral-dependent</i> n=135	<i>Normal myocardium</i> n=306		
Regions (n)					
Δt_d	<i>Rest</i>	$0.9\pm 0.7^*$	1.7 ± 1.0	$0.8\pm 0.4\#$	* $p < 0.01$ and # $p < 0.001$ vs. collateral-dependent
	<i>Hyperemia</i>	$0.4\pm 0.3\#$	1.1 ± 0.6	$0.3\pm 0.3\#$	
p<0.001 rest vs. hyperemia in all groups					
Perfusion	<i>Rest</i>	1.12 ± 0.11	0.98 ± 0.28	1.14 ± 0.21	* $p < 0.0001$ vs. patients # $p < 0.01$ vs. antegradely-perfused
	<i>Hyperemia</i>	2.46 ± 0.85	$1.86\pm 0.91\#$	$4.23\pm 1.12^*$	
p<0.001 rest vs. hyperemia in patients p<0.0001 rest vs. hyperemia in volunteers					

Data of the slice corrected delay time in individual patients and volunteers in collateral-dependent, antegradely-perfused and normal myocardium is shown in figures 3 (at rest) and 4 (during hyperemia).

The results of a prospective analysis of a regional based ROC analysis detecting collateral dependent myocardium by the delay of contrast arrival or myocardial perfusion are shown in table 3.

Parameter	<i>Cut-off value</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>AUC</i>	<i>CI</i>
$\Delta t_{d \text{ rest}}$	> 1.0 sec.	77	67	0.77	0.66 to 0.88
$\Delta t_{d \text{ hyperemia}}$	> 0.6 sec.	90	83	0.89	0.78 to 0.96
MP_{rest}	<1.0 ml/min/g	65	85	0.69	0.54 to 0.84
MP_{hyper}	<1.6 ml/min/g	55	93	0.70	0.52 to 0.84

Δt_d – slice corrected delay time

MP – myocardial perfusion

AUC – area under the curve

CI – confidence intervall

Relationship between extent of infarction, angiographic collateral vessel filling, myocardial perfusion and slice-corrected delay time

Δt_d was not significantly different in 43 collateral-dependent regions with $\geq 50\%$ TEI, compared to 92 regions with $< 50\%$ TEI (at rest: 1.8 ± 0.8 vs. 1.6 ± 0.8 sec., $p = \text{n.s.}$) or during hyperemia (1.2 ± 1.0 vs. 1.0 ± 0.4 sec., $p = \text{n.s.}$). By contrast, perfusion in collateral-dependent myocardium with $\geq 50\%$ TEI was significantly lower compared to regions with less than 50% TEI at rest (0.39 ± 0.12 and 1.12 ± 0.28 ml/g/min, $p < 0.001$) and during adenosine-induced hyperemia (0.93 ± 0.44 and 2.21 ± 0.73 ml/min/g, $p < 0.001$).

Δt_d in collateral-dependent myocardium was longer in 12 patients with Rentrop grades 0-1 (52 regions) compared to 18 patients with Rentrop grades 2-3 (83 regions) at rest (2.1 ± 0.9 vs. 1.4 ± 0.8 sec., $p < 0.04$) and during hyperemia (1.4 ± 0.7 vs. 0.8 ± 0.5 sec., $p < 0.03$). At rest no significant difference in perfusion of collateral-dependent myocardium was found in patients with Rentrop grades 2-3 compared to patients with Rentrop grades 0-1 (1.00 ± 0.25 compared to 0.96 ± 0.29 ml/min/g, $p = \text{n.s.}$), and a similar pattern during hyperemia (1.88 ± 0.86 for Rentrop grades 2-3, compared to 1.82 ± 0.81 ml/min/g for Rentrop grades 0-1, $p = \text{n.s.}$). Rentrop grades were not significantly different in patients with $\geq 50\%$ TEI, compared to those with $< 50\%$ TEI (1.7 ± 0.8 vs. 1.9 ± 1.1 , $p = \text{n.s.}$).

There was a significant inverse correlation between Rentrop grade and Δt_d in collateral-dependent myocardium at rest ($r = -0.49$, $p < 0.04$) and hyperemia ($r = -0.56$, $p < 0.03$) but not between Rentrop grade and perfusion (at rest: $r = 0.02$, $p = 0.94$, hyperemia: $r = 0.09$, $p = 0.72$).

DISCUSSION

This is the first study to show that collateral-dependent myocardium in patients with a chronic occluded coronary artery can be non-invasively detected using the delay of contrast arrival MR first pass perfusion imaging. The slice corrected delay time is a stronger predictor of collateral-dependent myocardium than myocardial perfusion. The uncorrected delay of contrast arrival in antegradely-perfused myocardium is 1.6-1.7 sec at rest in our study. Based on the Stewart-Hamilton principle and a flow of 1 ml/min/g, a theoretical estimate of the delay time between the LV and the myocardium is about 1.5 sec [7] at rest which compares well with our measured delay for antegradely-perfused myocardium. The higher sensitivity and specificity of the hyperemic over the resting delay for the detection of collateral-dependent myocardium demonstrated by the ROC analysis can be best explained by an increasing heterogeneity to the delay parameter in relation to the resistance of the microcirculation. The influence of the microcirculation on the delay parameter can be decreased by adenosine and results in a reduced data overlap between collateral-dependent and antegradely-perfused myocardium. This can be best perceived considering figures 3 and 4. In addition, there is a slightly smaller variability of the slice-corrected delay time during adenosine-induced hyperemia compared to the data at rest. Our findings are supported by an increasing variability of baseline, but not hyperemic coronary Doppler-flow velocity in response to adenosine with increasing atherosclerosis in an earlier study [13].

Advantage of the delay time over perfusion. Our data demonstrate that perfusion at rest may not be reduced in collateral-dependent myocardium, if significant stenosis of the coronary feeding vessel and extensive ($\geq 50\%$) transmural infarction are excluded. Hyperemic perfusion may be significantly lower in collateral-dependent compared to antegradely-perfused myocardium, however, this can be related to other pathologies, such as infarction, as demonstrated in our study, or coronary stenosis as demonstrated elsewhere [14]. Furthermore, hyperemic perfusion was similar in collateral-dependent compared to antegradely-perfused myocardium if transmural extent of infarction was limited ($<50\%$). This explains to some extent the higher sensitivity of the delay time compared to myocardial perfusion for the detection of collateral-dependent myocardium. Thus, perfusion, neither at rest nor under hyperemic conditions, is an adequate parameter to distinguish collateral-dependent from antegradely-perfused myocardium. Accordingly, we as well as others [15] believe that even quantification of myocardial flow or flow reserve may be inadequate for the detection of collateral-dependent myocardium.

Correlation between perfusion and angiographic collateral vessel filling. A weak correlation between perfusion and angiographic collateral vessel filling has been demonstrated earlier with echocardiography [16]. It was explained by the limited spatial resolution of a coronary angiogram, which only visualizes vessels of $>100 \mu\text{m}$ diameter [17]. Thus, many collateral vessels are smaller and not visualized by this technique. The delay of contrast arrival in collateral-dependent myocardium had an inverse relationship to the angiographic collateral vessel filling ('Rentrop grade'). An increase in Rentrop grade translates into a decrease in delay time, whereas myocardial perfusion did not allow a differentiation between regions with good and poor angiographic collateral vessel filling. In addition, and despite the significant difference in antegrade hyperemic perfusion the delay Δt_d was not significantly different between patients and

volunteers. For non-invasive assessment of myocardial blood flow it therefore becomes important to consider both flow and delays in contrast arrival together, rather than assuming a constant delay.

Limitations. Our patient population included only two diabetics. It is unknown how significant microcirculatory disease, e.g. in patients with diabetes, will influence the results. In this context, Seiler et al. recently reported identical collateral flow indices in diabetics and non-diabetics [3]. Furthermore, we can only speculate how a flow limiting stenosis of the collateral-feed vessel will affect the difference in delay time between antegradely-perfused and collateral-dependent myocardium. A previous MR study demonstrated that a hemodynamically significant epicardial stenosis does reduce perfusion reserve, but will not result in a noticeable delay of contrast arrival [18]. Patients with bypass vessels were not included in our study. Although this is speculative, with the relationship of the delay time to the length of the vessel we believe that a long bypass vessel will most likely increase delay time of contrast arrival.

Conclusion. Using the delay of contrast arrival during adenosine-induced hyperemia MRPI offers a novel non-invasive parameter to detect collateral-dependent myocardium with high sensitivity and specificity in patients without a flow limiting stenosis in the collateral feeding vessel and independent of the transmural extent of infarction. The delay of contrast arrival is related to angiographic collateral vessel filling but seems mostly independent of myocardial perfusion. Resting and hyperemic myocardial perfusion in collateral-dependent myocardium can be maintained, if significant stenosis of the coronary feeding vessel and extensive transmural infarction are excluded. In this context, the clinical impact of the delay time becomes evident since it allows distinguishing antegradely-perfused from collateral-dependent myocardium and therefore might be a useful parameter for further clinical decision making, e.g. interventional/surgical vs. conservative approach.

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Legends

Figure 1

A) The angiogram shows an occluded LAD (after the first diagonal branch) which is filled by Rentrop grade III collaterals from the RCA; the three rings indicate a basal, midventricular and apical short axis slices of the left ventricle as assessed by MR perfusion imaging. B) a representative MR first pass perfusion image in a midventricular slice position showing the peak enhancement in the left ventricle. For generation of the SI curves endocardial and epicardial borders are manually drawn in the image with the brightest contrast enhancement in the LV cavity. An automated edge detection algorithm is then applied for segmentation to the remainder of the image frames, with subsequent manual adjustment of the contours to avoid signal-spillover from the LV. The program then calculates the signal/time-intensity values in the six sectors; C) The schematic plot shows the three slices (basal, midventricular and apical short axis position) of the left ventricle divided into six regions; the black dots indicate collateral-dependent regions according to the angiogram.

Figure 2

The signal intensity curve for a left ventricular region of interest, used here as arterial input, is shown with tissue curves for a collateral-dependent and antegradely perfused myocardial regions, respectively. $td_{antegrade}$ is the time between the appearance of the contrast in the left ventricle and antegradely-perfused myocardium; $td_{collat.}$ is the time between the appearance of the contrast in the left ventricle and collateral-dependent myocardium.

Figure 3:

Analysis of slice corrected delay time at rest in antegradely-perfused and collateral-dependent myocardium per patient and in myocardium of healthy volunteers. The cut-off value for resting Δt_d of >1.0 sec. derived from ROC analysis and indicates best sensitivity and specificity to detect collateral-dependent myocardium (see text and table 3 for details).

Figure 4:

Per patient analysis of slice corrected delay time during hyperemia in antegradely-perfused and collateral-dependent myocardium per patient and in myocardium of healthy volunteers. The cut-off value for hyperemic Δt_d of >0.6 sec. derived from ROC analysis and indicates best sensitivity and specificity to detect collateral-dependent myocardium (see text and table 3 for details).

Figure 1

A



B



C

BASE

MID

APEX

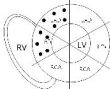


Figure 2

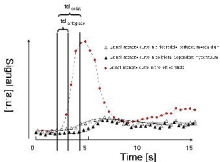


Figure 3

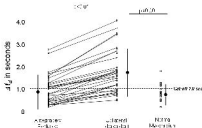
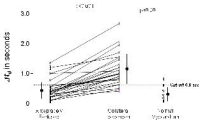


Figure 4





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