Assessment of effects of intravenous dipyridamole on regional myocardial perfusion in children with Kawasaki disease without angiographic evidence of coronary stenosis using positron emission tomography and $H_2{}^{15}O$

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Background: Positron emission tomography and $H_2{}^{15}O$ were used to characterize regional myocardial blood flow and distribution at rest and in response to dipyridamole in children with Kawasaki disease but without angiographic evidence of coronary stenosis.
Method: Patients were classified into two groups on the basis of the results of selective coronary angiography: subjects in group I had normal coronary angiograms (n=4): subjects in group II had aneurysms (n=5).
Results: Myocardial perfusion, assessed with $H_2{}^{15}O$, was homogeneous over all regions at rest and at peak flow in groups I and II. Dipyridamole infusion significantly reduced myocardial perfusion reserve in group II (average 3.56±1.03 fold versus 5.06±1.37 fold in group I, $P<0.001$).
Conclusion: Our results suggest that aneurysms associated with Kawasaki disease may reduce myocardial reserve. Non-invasive quantitative assessment of myocardial blood flow with positron emission tomography and $H_2{}^{15}O$ was useful in assessing the functional capacity of coronary artery lesions and the extent of myocardial damage in children with Kawasaki disease.

Coronary Artery Disease 1995, 6:555–559

Keywords: coronary artery disease, positron emission tomography, oxygen-15 labelled water ($H_2{}^{15}O$), myocardial blood flow, myocardial perfusion reserve

Introduction

Coronary angiography is used to assess accurately the involvement of the coronary arteries in patients with Kawasaki disease. However, the use of this shadowing technique is limited by the subjective interpretation of angiograms and the variable relationship between percent stenosis and coronary perfusion. Thus, improved methods are needed to assess the severity of functional impairment of coronary artery lesions in patients with Kawasaki disease.

The supply of oxygen to the myocardium is determined mainly by the volume of coronary blood flow; myocardial perfusion normally increases in proportion to work and hence oxygen demand. Therefore, measurement of coronary blood flow is a useful way of evaluating coronary lesions and myocardial ischaemia. Coronary sinus blood flow in children with Kawasaki disease has previously been measured using the continuous thermodilution method with a specially designed flow catheter [1,2]. However, measurement of coronary sinus blood flow may not reflect nutritive perfusion because of its inability

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Date received: 16 December 1995; revised: 21 April 1995; accepted: 28 April 1995.

to distinguish between regional alterations in flow. In addition, the thermodilution method cannot be performed frequently in the same patient.

Positron emission tomography (PET), which may provide a more accurate quantitative evaluation of regional myocardial perfusion, has been used to assess coronary artery disease *in vivo* [3,4].

In the present study, we used PET and $H_2{}^{15}O$ to assess regional myocardial blood flow distribution at rest and in response to dipyridamole infusion in children with Kawasaki disease without angiographic evidence of coronary stenosis.

Methods

By reviewing the records of the cardiac catheterization laboratory of the Children's Research Hospitals we retrospectively selected nine patients with Kawasaki disease (seven boys and two girls; mean age 17 years; range 13–23 years) without angiographic evidence of coronary stenosis.

The patients' mean age at disease onset was 4 years (range 3 months to 8 years); the time from disease onset to the present study ranged from 13 to 23 years. All subjects fulfilled the criteria for the diagnosis of Kawasaki disease. None of the patients showed evidence of ischaemia on electrocardiography or exercise ^{201}Th single photon emission tomography, or any history of myocardial infarction. No pathologic Q waves were observed on control ECGs. The average interval between coronary angiography and the PET study was 4 months (range 1–6 months).

Coronary angiography with multiple projections and contrast left ventriculography in the right and left oblique projections was performed in all patients. Patients were classified into two groups on the basis of the results of selective coronary angiograms: group I consisted of four patients with normal coronary angiograms; group II consisted of five patients with aneurysm of the left coronary artery.

The study protocol was discussed with the patients' parents, and written consent was obtained from both parents and subjects.

Positron emission tomography

Positron emission tomography (PET) imaging was performed using a Headytome-3 (Shimadzu Corporation, Kyoto, Japan) with continuously rotating and wobbling rings that provided three simultaneous tomographic imaging slices. A 10 min transmission scan was performed to correct attenuation using a 5 mCi (68 Ge–68 Ga) ring source with a diameter of 50 cm.

A 2 min scan was performed during the state of equilibrium after subjects inhaled ^{15}O labelled carbon monoxide (30 mCi) for calculation of blood volume. A dynamic PET study using ^{15}O labelled water was performed after administration of an intravenous bolus of $H_2{}^{15}O$ (10–15 mCi), with a scanning protocol of 12 s over a 5 min period.

Dipyridamole was administered intravenously to nine patients for 4 min (0.56 mg/kg total dose) with an infusion pump. The peak flow response was imaged 3 min after the end of the infusion. The imaging sequence was repeated after a second injection of $H_2{}^{15}O$.

Regional myocardial perfusion was assessed in three transverse slices (upper, middle and lower). The regions of interest (ROIs) were set in three areas of the myocardium (the septum, the anterior wall, and the lateral wall) by referring the autoradiographic myocardial blood flow image according to the segmentation by Schelbert and co-workers [5]. Regional blood flow values were calculated by ROI analysis and a modified single compartment model that incorporated the tissue fraction developed by Iida and colleagues [6]. The arterial input function was derived from the ROI in the left ventricular segments before and after peak. The input function obtained from analysis of the time–activity curve obtained from analysis of a left ventricular ROI was used.

ECGs were monitored continuously throughout the procedure. Serial 12-lead ECGs were recorded at baseline, before and after the first imaging sequence, and after infusion of dipyridamole. Blood pressure was monitored with a sphygmomanometer at 1 min intervals during imaging. Myocardial perfusion reserve was defined as the ratio of myocardial blood flow after dipyridamole infusion to myocardial blood flow at rest in the same region.

Statistical analysis

Results are expressed as mean ± standard deviation. Means were compared using the unpaired Student's t test. $P < 0.05$ was considered statistically significant.

Results

Haemodynamic and clinical changes before and after dipyridamole infusion

The mean interval between the beginning of dipyridamole infusion and the second injection of $H_2{}^{15}O$ was 6.5 ± 0.8 min for all subjects.

The haemodynamics and myocardial perfusion reserve are summarized in Table 1. Heart rate increased from 67 ± 8 to 89 ± 8 beats/min ($P < 0.01$) accompanied by a slight decline in diastolic pressure. Neither systolic nor diastolic blood pressure changed significantly.

Table 1. Haemodynamic parameters at rest and after dipyridamole infusion.

Patient	Coronary lesion		Rest					Dipyridamole					
No.	RCA	LCA	HR	SBP	DBP	PRP	MBF	HR	SBP	DBP	PRP	MBF	MPR
Group I (n=4) Patients with normal coronary angiograms													
1	N	N	61	100	92	6710	S1:0.96	92	111	58	10212	S1:4.48	4.66
							S2:0.95					S2:4.44	4.67
2	N	N	52	118	80	6136	S1:0.73	75	132	86	9900	S1:2.47	3.38
							S2:0.68					S2:2.16	3.18
3	N	N	72	132	82	8064	S1:0.82	96	132	76	11136	S1:5.25	6.40
							S2:0.79					S2:5.45	6.90
4	N	N	76	110	80	8360	S1:0.96	98	110	86	10176	S1:4.46	4.64
							S2:0.90					S2:4.98	5.63
Group II (n=5) Patients with aneurysms													
5	N	AN	75	112	80	9250	S1:1.48	87	126	72	10875	S1:4.17	2.82
		(5–6)					S2:1.32					S2:3.76	2.85
6	N	G-AN	65	110	76	7150	S1:0.78	89	116	66	10235	S1:3.22	4.13
		(5–6)					S2:0.80					S2:3.25	4.06
7	N	G-AN	71	118	70	8378	S1:0.86	99	112	60	11088	S1:4.10	4.77
		(5–6)					S2:0.88					S2:3.98	4.52
8	N	AN	83	108	82	9130	S1:1.01	92	108	76	9936	S1:2.55	2.52
		(5–6)					S2:1.00					S2:2.50	2.50
9	N	G-AN	61	116	60	7076	S1:0.76	81	126	60	10206	S1:3.29	4.33
		(5–6)					S2:0.89					S2:3.29	3.70
Group I			65±11	115±13	63±5	7317±1066	0.85±0.12	90±7	121±12	76±13	10356±538	4.21±1.23	4.95±1.19
Group II			71±9	112±4	73±9	8196±1044	0.98±0.24	90±7	118±8	67±7	10583±538	3.41±0.59	3.48±0.87†
All patients			67±8	113±9	78±9	7680±976	0.92±0.20	89±8*	119±10	71±10	10418±160*	3.77±0.98†	4.10±1.24

*$P<0.01$, †$P<0.001$. RCA, right coronary artery; LCA, left coronary artery; HR, heart rate (beats/min); SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); PRP, pressure rate product (mmHg); MBF, myocardial blood flow; MPR, myocardial perfusion reserve (magnitude of the flow response defined as the rate of hyperaemic to resting blood flow); N, normal coronary artery; S1, upper transverse slice; S2, middle transverse slice; AN, aneurysm (<8mm in diameter); G-AN, giant aneurysm (>8mm in diameter).

None of the patients experienced chest pain during or after infusion of dipyridamole, or exhibited ST-segment depression. The maximal myocardial load, reflected by the pressure–rate product (systolic blood pressure×heart rate), increased significantly ($P<0.01$) after dipyridamole infusion. There were no significant differences in systolic blood pressure and pressure–rate product after dipyridamole infusion between groups I and II.

Regional myocardial perfusion

Dipyridamole significantly increased the mean absolute resting myocardial blood flow in all patients (Table 1), although individual responses were variable (Fig. 1).

The mean value of the measured absolute resting myocardial blood flow in all patients was 0.92±0.20 ml/min/g; the flow response after dipyridamole loading was variable, but increased to 3.77±0.98 ml/min/g ($P<0.001$; Fig. 1).

Mean myocardial perfusion at rest was similar in the two groups (0.85±0.12 ml/min/g in group I and 0.98±0.24 ml/min/g in group II). After dipyridamole loading, however, mean peak perfusion was diminished in group II compared with that in group I (3.62±0.87 ml/min/g and 5.17±1.19 ml/min/g, respectively ($P<0.001$; Table 1)

No discrete perfusion defects were observed on composite tomographic images. There were no differences between groups I and II in perfusion among anterior, septal and lateral regions with regard to

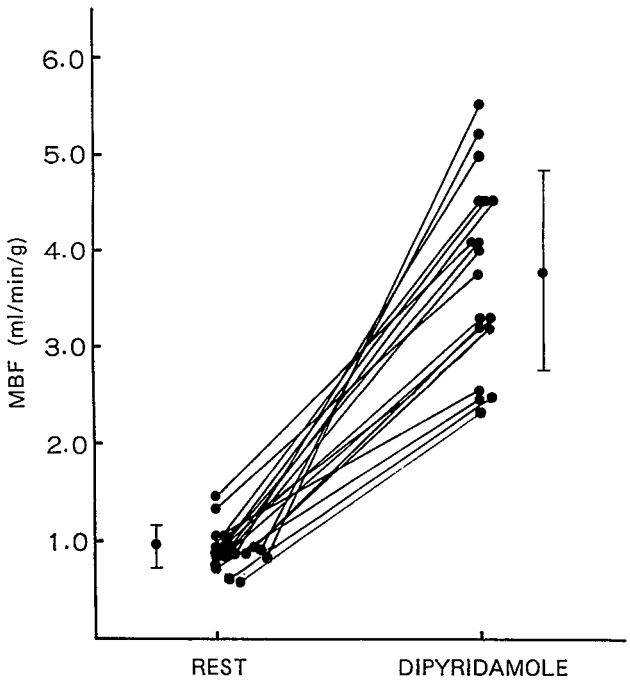

Fig. 1. Individual values for myocardial perfusion at rest and after dipyridamole infusion for all patients. Values indicated (●) are group means; bars indicate standard deviations. MBF, myocardial blood flow.

resting and peak flow after dipyridamole. Regional homogeneity, assessed by coefficient of variation of flow response, was similar in groups I and II (Fig. 2).

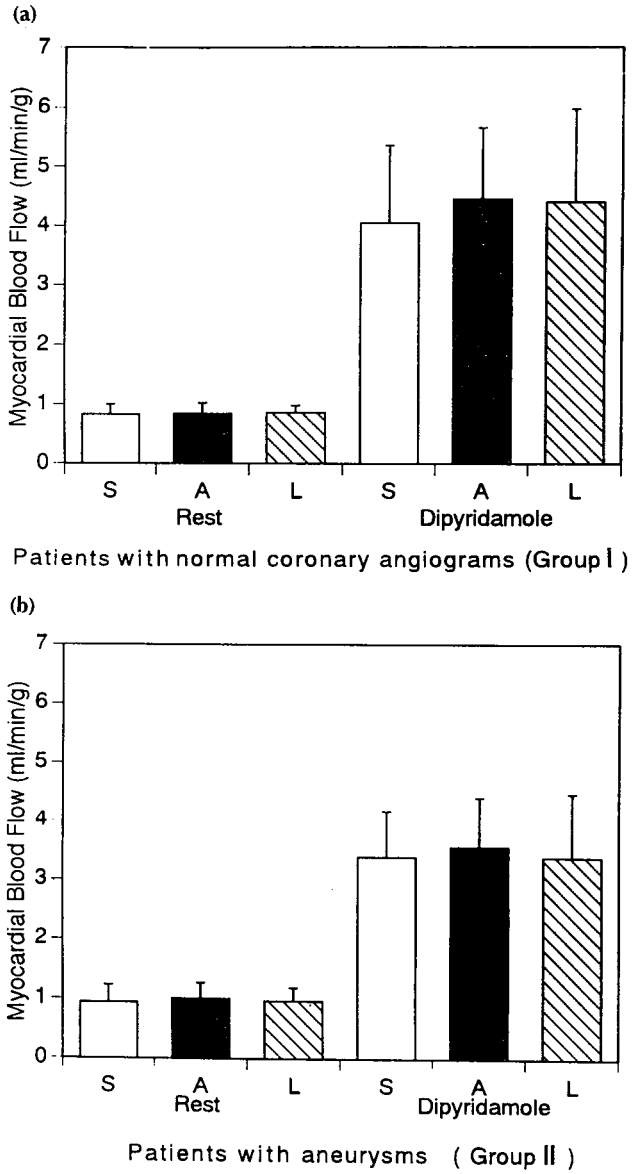

Fig. 2. Regional myocardial blood flow at rest and after intravenous dipyridamole in **(a)** group I and **(b)** group II showing regional homogeneity of flow at rest and homogenous increases in flow with pharmacologic coronary vasodilatation. After dipyridamole, mean myocardial blood flow in group II was lower than that in group I. S, septum; A, anterior; L, lateral.

Myocardial perfusion reserve, defined as average myocardial perfusion after dipyridamole administration divided by average myocardial perfusion at rest was slightly increased. The mean reserve in group I was significantly higher ($P<0.01$) than that in group II (Fig. 3): group II patients exhibited reduced functional capacity compared with group I (Fig. 3).

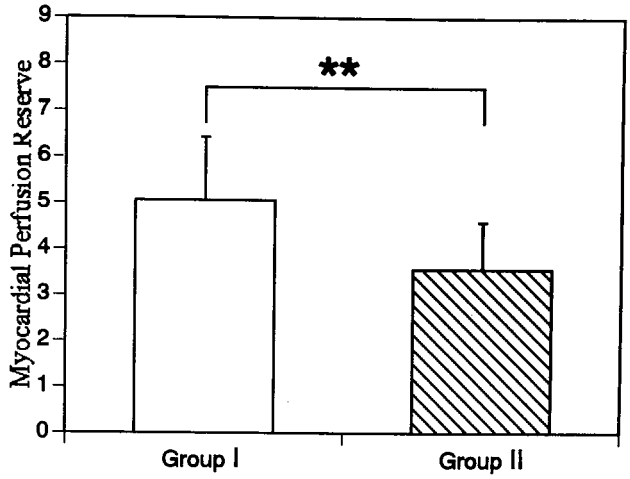

Fig. 3. Mean myocardial perfusion reserve in group I and group II. Bars indicate standard deviations; $^{**}P<0.01$, group I versus group II.

Discussion

Coronary artery lesions, ranging from transient slight coronary dilatation in the acute phase to giant coronary aneurysms [7], develop in approximately 20% of patients with Kawasaki disease, a condition first described in 1967 [8].

The prognosis of Kawasaki disease is related to the severity of the coronary artery lesions, which are the most serious complication of the illness. Thus, it is important clinically to determine the course of these lesions and the relationship between coronary artery disease and cardiac function [9].

Coronary angiography is the most accurate method for identifying coronary artery lesions in Kawasaki disease; however, it is difficult to assess the functional impairment of coronary artery lesions using this technique. Measurement of coronary blood flow is useful for the evaluation of coronary lesions and myocardial ischaemia, but may not reflect myocardial perfusion, in part because of the inability to distinguish regional alterations in flow [10].

Positron emission tomography (PET) with $H_2{}^{15}O$ provides a more accurate non-invasive characterization of myocardial perfusion than conventional single photon scintigraphy because of its greater quantitative ability. Previous studies have shown that myocardial perfusion can be measured accurately over a wide range of flow and metabolic conditions using PET with $H_2{}^{15}O$ [11,12].

In the present study, there was no significant difference in regional myocardial perfusion before or after dipyridamole infusion in group I. Absolute myocardial blood flow at rest was similar to that observed in adults in studies using PET [3,4].

Coronary artery reserve depends on the ability of the coronary vessels to increase blood flow in response

to oxygen demand, to compensate for decreased oxygen carrying capacity, or both. In the present study, we used a standard dose of dipyridamole which increases coronary blood flow without increasing myocardial oxygen demand. Coronary vascular reserve can be assessed after administration of dipyridamole without causing tissue damage that may occur with ischaemia, and without incurring the small but real risks associated with exercise stress in the presence of critical coronary stenosis that precludes hyperaemia. Previous studies have demonstrated the usefulness of dipyridamole-induced vasodilatation for assessment of coronary stenosis in Kawasaki disease [13].

Our results are consistent with those of previous studies that measured myocardial perfusion reserve invasively or non-invasively using intracoronary Doppler or PET. Two- to 5-fold increases were reported in blood flow after pharmacological vasodilatation in normal volunteers and in the normal myocardium of patients with coronary artery disease [14,15]. A previous study in healthy volunteers also failed to demonstrate a significant correlation between hyperaemic flow and age. There was a significant difference in hyperaemic flow only in subgroups of subjects younger and older than 50 years of age [16]. Our data showed that myocardial perfusion reserve in children with normal coronary angiograms with Kawasaki disease was greater than that in adults.

In the group with aneurysms, myocardial perfusion reserve was significantly reduced compared with subjects with normal angiograms but myocardial blood flow reserve in group II was similar to that in adults with normal coronary angiograms. Decreased reserve did not induce any clinical signs of myocardial damage. Thus, such patients are likely to be associated with minor coronary artery disease.

Conclusion

Our data suggest that children with coronary artery aneurysms associated with Kawasaki disease have reduced myocardial reserve compared with children having normal coronary arteries. Non-invasive quantitative assessment of myocardial blood flow using PET and $H_2{}^{15}O$ was effective in determining the functional capacity of coronary artery lesions.

References

1. Hamaoka K, Itoi T, Nakagawa M, Kamiya Y, Sawada T: **Coronary sinus cannulation via the femoral vein.** *Pediatr Cardiol* 1989, **10**:191–192.
2. Hamaoka K, Onouchi Z, Ohmochi Y: **Coronary flow reserve in children with Kawasaki disease without angiographic evidence of coronary stenosis.** *Am J Cardiol* 1992, **69**:691–692.
3. Bergman SR, Fox KAA, Rand AL, McElvany KD, Welch MJ, Markham J, *et al.*: **Quantification of regional myocardial blood flow *in vivo* with $H_2{}^{15}O$.** *Circulation* 1984, **70**:724–733.
4. Bergmann SR, Herrero FR, Markham J, Weineimer CJ, Walsh MN: **Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography.** *J Am Coll Cardiol* 1989, **14**:639–652.
5. Schelbert HR, Wisenberg G, Phelps ME, Gould KL, Henze E, Hoffman EJ, *et al.*: **Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation.** *Am J Cardiol* 1982, **49**:1197–1207.
6. Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Tkahashi K, *et al.*: **Measurement of absolute myocardial blood flow with $H_2{}^{15}O$ and dynamic positron emission tomography.** *Circulation* 1988, **78**:104–115.
7. Onouchi Z, Tomizawa M, Goto M, Nakata K, Fukuda M, Goto M: **Cardiac involvement and prognosis in acute mucocutaneous lymph node syndrome.** *Chest* 1975, **68**:297–301.
8. Kawasaki T, Kasaki F, Okawa S, Shigemuratu I, Yanagawa H: **A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan.** *Am J Dis Child* 1974, **130**:559–607.
9. Kato H, Ichinose E, Kawasaki T: **Myocardial infarction in Kawasaki disease: clinical analysis of 195 cases.** *J Pediatr* 1986, **108**:923–927.
10. Hamaoka K, Onouchi Z, Kamiya Y: **Coronary sinus blood flow and coronary haemodynamic function in children by the continunous thermodilution method with coronary sinus cannulation via femoral vein.** *Br Heart J* 1991, **65**:171–173.
11. Arujo LI, Lammertsma AA, Rhodes CG, McFalls EO, Iida H, Rechavia E, *et al.*: **Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography.** *Circulation* 1991, **83**:875–885.
12. Knamm RM, Fox KAA, Sobel BE, Bergman SR: **Characterization of the functional significance of subcritical stenoses with $H_2{}^{15}O$ and positron emission tomography.** *Circulation* 1985, **76**:1271–1278.
13. Kondo C, Hirose M, Nakanichi T, Takao A: **Detection of coronary in children with Kawasaki disease: usefulness of phamacologic stress 201Tl-myocardial tomography.** *Circulation* 1989, **80**:615–624.
14. Marcus M, Wright C, Doty D, Eastham C, Laughlin D, Krumm P, *et al.*: **Measurements coronary velocity and reactive hyperemia in the coronary circulation of humans.** *Circ Res* 1981, **49**:877–891.
15. Wilson RF, Laughlin DE, Ackell PH: **Transluminal subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man.** *Circulation* 1985, **72**:82–89.
16. Stennef M, Geltman EM, Bergman SR, Hartman J: **Noninvasive delineation of the effects of moderate aging on myocardial perfusion.** *J Nucl Med* 1991, **32**:2037–2042.