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Analysis of Arterial Endothelial Function Assessed by the Non-invasive Method of Flow-Mediated Dilatation in Patients with a History of Kawasaki Disease: A Review of the Literature

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Abstarct

Kawasaki disease, which was first reported by Kawasaki T, is an acute, febrile, pediatric illness that occasionally causes coronary artery lesions. Kawasaki disease is characterized by systemic vasculitis, although the etiology remains unknown. Whether Kawasaki disease is a risk factor for the early progression of atherosclerosis in adolescents and young adults has been discussed for a long time. Endothelial function has been studied in patients with a history of Kawasaki disease by many investigators. Measurement of the percentage of flow-mediated dilatation (%FMD) is a non-invasive method for evaluation of endothelial function. This review focuses on the 15 published articles found in our literature search pertaining to %FMD measurements in patients with a history of Kawasaki disease.

Keywords: Kawasaki disease; Endothelial function; Children

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Introduction

%FMD is a non-invasive method for evaluation of endothelial function

Endothelial dysfunction is one of the earliest changes identified to date during various types of vascular remodeling, including atherosclerosis [1]. Since Celermajer et al. first reported the method, endothelial function has been investigated noninvasively on the basis of systemic arterial reactivity in response to sphygmomanometer cuff occlusion [2]. To measure %FMD, the subject should fast at least 8-12 hours before the study. The substances such as caffeine, high-fat foods, tobacco should be avoided.

The subject is positioned supine in a quiet and temperature-controlled room. After the rest for 10-15 minutes, the brachial artery is imaged above the antecubital fossa in the longitudinal plane by high-resolution ultrasonic equipment. To create a flow stimulus, sphygmomanometric cuff placed forearm is inflated to supersystolic pressure (ranged 200-300 mmHg, or 20-50 mmHg above the resting systolic blood pressure) for 4-5 minutes. The image of the artery is recorded from 30 sec before to 90-180 sec after subsequent cuff deflation.

Increased blood flow causes increased shear stress on the target arterial wall, and subsequently nitric oxide, a strong vasodilator, is released from the endothelial cells of the vessel. Consequently, the vessel dilates. However, a vessel with endothelial dysfunction does not dilate as much as an intact vessel. Thus, the %FMD reflects endothelial function [2,3].

All 15 published articles used basically the same standard protocol to measure %FMD, although some reports used alternative method in minor part of the protocol. Sabri et al. used radial artery instead of brachial artery as a target artery, and Ghelani et al. placed cuff at upper arm instead of forearm. Although accurate scanning and assessment of brachial artery reactivity is technically challenging and the training for obtaining the technic should be necessary, this technic has been shown to be reproductive and reliable [4,5]. Celermajer et al. reported the reproducibility and repeatability of this method were 1.7 ± 1.4% and 2.8 ± 2.3%, respectively [2].

Controversies with regard to %FMD in patients with a history of Kawasaki disease

Is endothelial dysfunction of the systemic artery found in Kawasaki disease?

During the last two decades, many investigators have reported %FMD studies regarding patients with a history of Kawasaki disease **(Table 1)**. However, the results have not been consistent. According to Dhillon et al. systemic endothelial dysfunction exists in Kawasaki disease irrespective of coronary artery sequalae [6]. Deng et al. reported that %FMD as reduced in patients with Kawasaki disease. In addition, Deng et al. reported that endothelial dysfunction was not affected by early treatment with high-dose gamma globulin in the acute stage of Kawasaki disease, and also that the dysfunction improved after administration of vitamin C [7].

In contrast, Silva and McCrindle reported that no differences in %FMD were observed between children with a history of Kawasaki disease and control subjects [8,9]. Sabri et al. reported that there were no differences in baseline %FMD between Kawasaki patients and control subjects, and that control subjects had the better %FMD response after vitamin C administration [4]. Borzutzky et al. also reported that while there were no differences in baseline %FMD between Kawasaki disease and control groups, high-sensitivity CRP levels were higher in the former [10].

Interestingly, in the articles by Silva, Borzuzky and Sabri, mean values of %FMD in the control group ranged from 6.2% to 8.0%, which seem lower than those in the other reports; on the other hand, in the articles in which the authors reported reduced %FMD in the Kawasaki disease group, values in the control group ranged from 9.4% to 18.8% [4,9,10]. The discrepancy in the results for patients with Kawasaki disease might be attributable to the differences in %FMD values of the control group. Is this related to differences of ethnicity? Or is it related to dietary differences in the different regions? All articles from North and South America have shown no differences between control and patient with Kawasaki disease [8-10]. On the other hand, all reports from eastern Asia including Japan have shown differences between the two groups. The answers are still unclear.

Is the presence or absence of coronary artery lesions a relevant factor for impaired %FMD?

Ikemoto et al. classified coronary artery lesions into 4 groups, that is no CAL , mild, moderate, and severe, and reported that the %FMD values of Kawasaki disease patients with moderate to severe coronary artery lesions were significantly lower than those of control subjects, whereas those of patients with mild or no coronary artery lesions did not differ from those of the control group [11]. It has been reported reduced %FMD in Kawasaki disease patients and further reduction in patients with CAL during childhood **(Table 2)** [12-15].

The differences on %FMD between patients with and without coronary artery lesions were investigated in 7 articles (Table 2). Five of these 7 studies revealed reduced %FMD in patients with coronary artery lesions. While the remaining 2 articles reported no statistical differences in %FMD between Kawasaki disease patient with and without coronary artery lesions, %FMD in the patients with coronary artery lesions was lower than that in the patients without coronary artery lesions in both articles.

Therefore, the presence of endothelial dysfunction in Kawasaki disease patients with coronary artery lesions is a less controversial conclusion, whereas whether endothelial dysfunction exists in patients with a history of Kawasaki disease without coronary artery lesions remains unclear.

Is a febrile period during the acute phase of Kawasaki disease a relevant factor for impaired %FMD?

Ishikawa et al. investigated %FMD in younger children who were within 5 years after the onset of Kawasaki disease at the time of examination. They reported that %FMD was inversely correlated with the total duration of fever during the acute phase of Kawasaki disease [12].

Most recently, Mori et al. reported on the endothelial function of Kawasaki disease patients in an investigation of %FMD in nearly 100 children [16]. The mean duration from the onset of Kawasaki disease to examination was 7.5 years. In this report, the %FMD of children with a history of Kawasaki disease was significantly lower than that in the control subjects, and a febrile period >10 days during the acute phase of Kawasaki disease was an independent risk factor for endothelial dysfunction irrespective of presence of coronary artery lesions. Both of these reports suggest that protracted inflammation during the acute phase of Kawasaki disease may cause lingering vascular injury for several years.

It has become clear that the cytokine network is activated during the acute phase of Kawasaki disease and that various growth factors and cytokines are elevated at this time. Adhesion molecules also show increased expression, while hypercoagulation and reduced fibrinolysis have been reported [17]. These data suggest that endothelial cell damage occurs in the acute phase of Kawasaki disease.

Atherosclerotic lesions are thought to result from an excessive, inflammatory, fibroproliferative response to various forms of insult to the endothelium and smooth muscle of the arterial wall [18]. Thus, atherogenesis may result from inflammation during the acute phase of Kawasaki disease. A protracted febrile period means a longer duration of endothelial damage in the acute phase, which may cause endothelial impairment to persist for a long period after the onset of Kawasaki disease, even without causing coronary artery lesions. The data from Ishikawa's report may support these hypotheses, and Mori's data appear to suggest the lingering endothelial dysfunction lasts much longer than had been expected.

High-sensitivity C reactive protein as a marker of chronic inflammation in the patients with a history of Kawasaki disease

How long this endothelial dysfunction lasts is another concern. High-sensitivity C reactive protein (hs-CRP) is considered as one of the markers of the chronic low-grade inflammation of vascular injury. Persistent hs-CRP has been found in patients long after the onset of Kawasaki disease, both with and without reduced %FMD. In Borzutzky's report, hs-CRP levels

Table 1 %FMD studies regarding patients with a history of Kawasaki disease.

Author	published year	country	number of subjects	number of KD patients with CAL size				number of control	Age at examination (years)		duration from the oncet of KD (years)		mention of fasting/ caffene free substances	Differene (KD vs control)	Differene (KD CAL(+) vs CAL(-))
				CAL(-)	small-regress	moderate	giant		KD CAL(-)	KD (CAL(+)		control			
Liu	2009	China	63	20	15	0	6	22	7.3	7.0	3.8-5.0	8.4	< 5 years	-	yes	yes
Ishikawa	2013	Japan	46	15	9	0	0	22	6.1	7.2	3.3	7.9	< 5 years	+	yes	yes
Kadono	2005	Japan	65	9	9	4	2	41		8.3	5.8	10.7	5-15years	-	yes	yes
Ikemoto	2005	Japan	85	31	16	8	10	20	13.1	12.8(s),12.7(m),13.8(g)*	10.8-11.6	16.2	5-15years	+	yes	yes
Niboshi	2008	Japan	71	20	6	9		36		27.0	24.1	25.5	> 15 years	+	yes	yes
Deng	2002	China	56	33	6	0	0	17		7.1	3.4	7.0	< 5 years	-	yes	no
Mori	2015	Japan	95	57	4	6	0	28		9.7	7.5	8.6	5-15years	+	yes	no
Ghelani	2009	India	40	19	1	0	0	20		8.6	2.1	8.4	< 5 years	-	yes	
Dhillon	1996	England	40	17	3	0	0	20		13	11.3	15	5-15years	-	yes	
Huang	2008	Taiwan	22	0	no description of CAL size			11		12.9	10.8	13.0	5-15years	+	yes	
Noto	2009	Japan	70	0	0	22	13	35		20.5	18.6	19.6	> 15 years	+	yes	
Silva	2001	Canada	35	11		11	2	11		14.3	11.3	14.1	5-15years	-	no	
McCrindle	2007	Canada	112	30	16	6		60		15.5	11.2	14.9	5-15years	+	no	
Borzutzky	2008	Chile	22	10	1	0	0	11		10.6	8.1	10.4	5-15years	+	no	
Sabri	2015	Iran	35	11	no description of CAL size			19		12.1	5.8	12.6	5-15years	+	no	

KD: Kawasaki Disease, CAL: Coronary Artery Lesions.

increased in the Kawasaki disease group in spite of normal %FMD [10]. Huang et al. also reported that both reduced %FMD and increased hs-CRP improved in the Kawasaki disease patients with coronary artery lesions after administration of a statin [19]. Niboshi et al. reported that increased hs-CRP was observed in only Kawasaki disease patients with coronary artery lesions [15].

%FMD and time course of Kawasaki disease long after the onset

Among the 15 articles discussed earlier, 4 reports were on %FMD in children with a history of Kawasaki disease within 5 years after the onset. It is noteworthy that the %FMD of these patients was significantly lower than that of the control group in all 4 articles. %FMD also has been studied in children with a history of Kawasaki disease 5 to 15 years after the onset, as reported in 9 articles. The results are not consistent. In 5 studies, reduced %FMD was found in patients, while no differences with controls were observed in the other 4. Furthermore, young adults with a history of Kawasaki disease were investigated in 2 studies. Niboshi et al. investigated Kawasaki disease patients both with and without coronary artery lesions while Noto et al. studied endothelial function in only Kawasaki disease patients with coronary artery lesions. Both studies revealed reduced %FMD in Kawasaki disease patients [15,20].

Conclusion

In summary, endothelial dysfunction persists in children with a history of Kawasaki disease within 5 years after the onset, and the extent of inflammation during the acute phase may relate to endothelial function during that subsequent period. Whether the impaired endothelial function persists thereafter is controversial. In the majority of previous studies, presence of coronary artery lesions was likely the most relevant factor regarding endothelial function. Furthermore, 2 previous studies of young adults with a history of Kawasaki disease indicate that persistent endothelial dysfunction demonstrated with and without presence of coronary artery lesions. However, the sample sizes of these previous studies were small. Further investigations are needed, and longitudinal studies involving long-term follow-up of patients would be particularly helpful.

Table 2 The differences on % FMD between patients with and without coronary artery lesions.

Author	published year	country	% FMD control	% FMD KD (CAL(+))	% FMD KD (CAL(-))	Differene (KD CAL(+) vs CAL(-))	Valuables correlated with % FMD	Other findings
Dhillon	1996	England	9.4	NA			vessel size, KD history	
Silva	2001	Canada	6.2	NA			none	
Deng	2002	China	14.1	5.7	6.3	no		improved FMD with Vitamin C
Kadono	2005	Japan	11.7	-0.5	8.3	yes	CAL(+)	
Ikemoto	2005	Japan	18.8	19.5, 8.9, 4.2	19.4	yes	moderate severe CAL	no difference in IMT, stiffness
McCrindle	2007	Canada	NA	NA			TG, FAA	
Borzutzky	2008	Chile	8.0	NA				increased hsCRP in KD
Niboshi	2008	Japan	14.4	8.8	9.6, 11.5	yes		high TAT in KD, high hsCRP in CAL(+), high PWV in boy KD
Huang	2008	Taiwan	13.1		NA			improved FMD % hsCRP with statin
Noto	2009	Japan	13.3		NA		age at examination in KD	increased IMT, Ep in KD
Ghelani	2009	India	12.2	NA				
Liu	2009	China	12.1	4.5	9.5	yes	EPC in KD with CAL	increased SI in KD with CAL
Ishikawa	2013	Japan	11.1	4.4	9.1	yes	febrile period at acute KD	no difference in IMT
Sabri	2015	Iran	6.5					decreased IMT with Vitamin C
Mori	2015	Japan	13.1	8.1	10.4	no	febrile period at acute KD	

NA: Not Available; FAA: Free Fatty Acid; EPC: Endothelial Progenitor Cell; IMT: Intima-Media Thickness; TAT: Thrombin-Antithrombin III Complex; PWV: Pulse Wave Velocity; Ep: Elastic Modulus.

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