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ORIGINAL ARTICLE

# Transthoracic Echo-Doppler Assessment of Coronary Microvascular Function Late after Kawasaki Disease

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**Abstract** The goal of this study was to demonstrate that Doppler transthoracic echocardiography (TTE) may represent a valuable tool for the noninvasive demonstration of coronary microvascular dysfunction in children with previous Kawasaki disease (KD) by the measurement of coronary flow reserve (CFR) during cold pressor test (CPT). Twenty-five children with previous KD (mean follow-up, 4.6 ± 2.6 years) were included in the study—16 with no evidence of coronary artery lesions ($CALs^-$) by TTE and 9 with coronary aneurysms ($CALs^+$). Seventeen age-matched healthy subjects were also recruited. Diastolic peak velocity was measured by pulsed Doppler both at rest ($DPV_{Rest}$) and during CPT ($DPV_{CPT}$) in the anterior descending artery. CFR was calculated as $DPV_{CPT}$/$DPV_{Rest}$. KD patients demonstrated significantly higher values of $DPV_{Rest}$ (0.21 ± 0.05 vs 0.13 ± 0.01 cm/sec, $p < 0.0001$) and $DPV_{CPT}$ (0.33 ± 0.07 vs 0.27 ± 0.03 cm/sec, $p < 0.005$). CFR was reduced in KD compared to control subjects (1.5 ± 0.4 vs 2.1 ± 0.2, $p < 0.0001$). CFR was decreased in a similar manner in both $CALs^+$ patients (1.4 ± 0.4, $p = 0.002$ vs controls) and $CALs^-$ patients (1.6 ± 0.4, $p < 0.0001$ vs controls). Doppler TTE at rest and during CPT may represent a valuable modality for CFR evaluation in children with a history of KD. CFR is significantly reduced in KD patients independently of the presence of CALs.

**Keywords** Kawasaki disease · Coronary flow reserve · Doppler echocardiography

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Kawasaki disease (KD) is an acute self-limited vasculitis with a strong predilection for coronary arteries, occurring in children of all ages. Coronary artery aneurysms are a common sequaela of the vasculitis (20–25% of untreated children) and a significant percentage of these patients develop coronary stenosis and coronary artery disease at long-term follow-up [2, 3, 18]. Early diagnosis of KD is helpful since appropriate therapy can significantly reduce the incidence of coronary complications over time in these patients.

No clear picture has yet emerged about the potential complications of KD in patients with apparently normal coronary arteries during the acute phase. However, several findings suggest the existence of an impaired coronary endothelial function in this clinical setting. Serial intracoronary infusions of acetylcholine have demonstrated impaired endothelium-dependent relaxation in both affected and normal coronary arteries in patients with a history of KD [20]. Moreover, an impaired myocardial flow reserve has been described using positron emission tomography associated with cold pressor test (CPT), a recognized endothelial-dependent hyperemic stimulus, in both patients with and without coronary artery lesions (CALs) [7, 8].

In recent years, Doppler transthoracic echocardiography (TTE) has emerged as an easy and noninvasive technique

to assess coronary flow reserve (CFR) [16]. In patients with KD, it has already shown clinical usefulness in identifying the presence of significant epicardial coronary stenosis [14, 23]. However, it must be taken into account that in the absence of epicardial coronary stenosis, a decreased CFR may indicate a persisting functional impairment of coronary microcirculation [1, 10, 19].

In the current study, Doppler TTE was applied to evaluate CFR at the level of the distal left anterior descending coronary artery in a population of children with a history of KD, with and without evidence of CALs during a long-term follow-up, compared to a healthy control group. The aim of the study was to demonstrate that Doppler TTE, by measurement of coronary flow velocities at rest and during CPT, may represent a valuable tool for the noninvasive assessment of endothelial-mediated coronary microvascular dysfunction in patients with a previous episode of KD.

## Materials and Methods

### Study Population

From 1997 to 2004, 88 patients with a history of KD (mean age at the time of disease, 3.5 ± 1.9 years; range, 0.6–7.0) were referred to the KD center of the Santobono-Pausilipon Hospital and studied by TTE for evaluation of coronary involvement. At the time of acute KD, the diagnosis was ascertained on the grounds of clinical signs and serum markers values, and all patients underwent standard treatment including high-dose gamma-globulin and oral aspirin [22].

Parent's informed consent for the CFR study was obtained for 25 KD patients and 17 healthy children. At the time of inclusion in the study, the 25 children in the KD group (17 males; mean age, 7.7 ± 2.7 years) had been clinically followed for a mean period of 4.6 ± 2.6 years (range, 1–12) and they presented no evidence of myocardial ischemia (via ECG at rest and, when indicated, stress ECG and/or myocardium perfusion single-photon emission computed tomography). The control group included 17 children (10 males; mean age, 7.4 ± 2.9 years) with a low probability for cardiovascular disease (absence of risk factors and symptoms, and a normal resting ECG and complete TTE evaluation).

All the recruited patients underwent TTE-derived CFR evaluation after the acute febrile or inflammatory disease and in the presence of inflammatory serum markers within the normal range at the time of evaluation. A complete clinical assessment including weight, height, blood pressure, and heart rate measurements was performed. Body mass index was calculated as follows: weight/(height)$^2$ (kg/m$^2$).

Institutional review board approval for the procedures included in the study was obtained.

### TTE Study

All the recruited children underwent a one-session TTE evaluation, including complete coronary morphological study of the three main arteries and CFR assessment in the distal left anterior descending artery. TTE examinations were performed using the Aloka ProSound SSD-5500 system (Aloka, Tokyo).

#### *Coronary Morphological Study*

All patients were examined in the left lateral decubitus position and the three coronary arteries were carefully and systematically studied. By using a parasternal short-axis view, the proximal portion of the right coronary artery and the proximal and the medium portions of the anterior descending artery and the circumflex coronary artery were visualized [27]. The medium portion of the right coronary artery was investigated by directing the transducer to the right from the parasternal window [26] and by using a subcostal view when an optimal visualization could not be obtained [25]. The distal portion of the anterior descending artery was studied by using a modified two-chamber view obtained by sliding the transducer superiorly and medially from an apical two-chamber view, in order to obtain the best alignment to the anterior interventricular sulcus [4, 16]. Finally, the distal portion of the right coronary artery in the posterior interventricular sulcus was visualized using a two-chamber view with a 3-MHz transducer [32]. All coronary segments were evaluated for the presence of CALs, including aneurysms, stenoses, and thombi.

#### *CFR Determination*

Flow recording was performed at the level of the distal anterior descending artery by using a 5-MHz transducer with harmonic capability or, for younger children, 7-MHz commercially available transducers. The Doppler sample volume was placed on the color signal of the anterior descending artery and the characteristic biphasic flow pattern (with a large diastolic and a small systolic component) was recorded after 10 minutes at rest (baseline) and during hyperemia. CPT was performed with the subject's right hand immersed in ice water up to the forearm for 4 minutes and the coronary Doppler pattern was recorded after this time [34]. In all subjects, CPT was successfully completed with no need for sedation.

CFR was defined as the ratio between the maximum diastolic peak velocity (DPV) obtained during hyperemia ($DPV_{CPT}$) and at rest ($DPV_{Rest}$): $CFR = DPV_{CPT}/DPV_{Rest}$. In each subject, DPV measurements were obtained by averaging the three highest spectral Doppler signals. All images were recorded on a magneto-optical disk and subsequently analyzed off-line by an observer blinded to the subject's identity and to the clinical data. To evaluate the reproducibility of CFR measurements, two independent observers (M.G. and S.C.) performed the measurements on a sample of 10 subjects randomly selected, reporting an intraobserver variability (for measurements repeated by S.C. at least 2 weeks apart) of 3.6% and an interobserver variability of 4.4%.

### Statistical Analysis

The analyses were performed by SPSS for Windows version 12.0 (SPSS, Chicago, IL, USA). Data are presented as mean ± SD for continuous variables and proportions for categorical variables. After confirmation of the normal distribution of the testing variables, *t*-test for repeated measures was performed to compare hyperemic coronary flow velocities to baseline velocities. Children with KD were initially analyzed as pooled data and subsequently analyzed separately. *t*-test for unpaired data was used to assess differences between the two groups. One-factor analysis of variance was used to determine differences among controls and the $CALs^-$ and $CALs^+$ groups, with multiple comparisons by Scheffe' and Dunnett T3 post hoc tests. Differences were considered significant at $p < 0.05$.

## Results

### Characteristics of the Study Population

General characteristics of the patients with KD, including serum marker values at the time of acute illness, are listed in Table 1. Patients with a history of KD and controls had similar ages [7.4 ± 2.9 vs 7.7 ± 2.7 years, respectively; $p$ = not significant (NS)] and body mass index (17.9 ± 3.2 vs 15.7 ± 4.7 kg/m$^2$, respectively; $p$ = NS).

A complete morphological evaluation of the three main coronary arteries by TTE was successfully achieved in all patients. According to echocardiographic evidence of CALs, patients were divided in two subgroups: 16 (9 males; age, 8.3 ± 2.6 years) with no evidence for CALs, both at the time of acute illness and during follow-up ($CALs^-$ group), and 9 (7 males; mean age, 6.4 ± 2.4 years) with evidence of an aneurysm in the proximal anterior descending artery persisting at follow-up ($CALs^+$ group).

**Table 1** Characteristics of KD patients ($n$ = 25) at the time of acute illness

| Variable | Mean ± SD (range) or prevalence |
|---|---|
| Age (years) | 3.5 ± 1.9 (0.6–7.0) |
| Fever duration (days) | 12 ± 5 (5–20) |
| Changes in extremities (%) | 98 |
| Polymorphous exanthema (%) | 80 |
| Bilateral bulbar conjunctival injection (%) | 72 |
| Changes in lips and oral cavity (%) | 68 |
| Cervical lymphadenopathy (%) | 64 |
| Hemoglobin (g/dl) | 10 ± 1 (9.1–12.5) |
| Leukocytes/ml | 15 ± 5 (7.4–21.2) |
| Platelets/ml | 628 ± 226 (229–1073) |
| ESR (mm) | 85 ± 35 (3–132) |
| CRP (mg/L) | 61 ± 93 (2–293) |
| GOT (IU/L) | 66 ± 73 (9–199) |
| GPT (IU/L) | 60 ± 61 (7–186) |
| LDH (IU/L) | 420 ± 197 (207–812) |
| CPK (IU/L) | 285 ± 295 (28–548) |
| PT (in activity %) | 75 ± 31 (11–100) |
| aPTT (sec) | 36 ± 28 (22–98) |
| Fibrinogen (mg/dl) | 532 ± 167 (351–821) |

aPTT, activated partial thromboplastin time; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; LDH, lactate dehydrogenase; PT, prothrombin time

In the $CALs^+$ group, TTE evaluation revealed eight small aneurysms or dilatations (<4-mm diameter) and one giant aneurysm (>8-mm diameter), all localized at the mid/proximal level of the left anterior descending coronary artery. In none of the 25 patients there was TTE evidence for intraluminal thrombus.

### Coronary Flow Reserve

During Doppler TTE-derived CFR assessment, no significant differences in heart rate were observed between KD patients and controls both at baseline (85.7 ± 15.0 vs 86.3 ± 9.0 bpm, respectively; $p$ = NS) and during CPT (96.0 ± 17.6 vs 93.3 ± 11.2 bpm, respectively; $p$ = NS). Similarly, no differences in arterial blood pressure were found at rest (110/72 vs 108/70 mmHg, respectively; $p$ = NS) and during CPT (119/78 vs 120/79 mmHg, respectively; $p$ = NS). No adverse reactions occurred and no patients showed ST segment depression on electrocardiogram during the test and recovery.

$DPV_{Rest}$ was significantly higher in children with KD compared to controls (0.21 ± 0.05 vs 0.13 ± 0.01 cm/sec, $p < 0.0001$). During CPT, a significant increase in

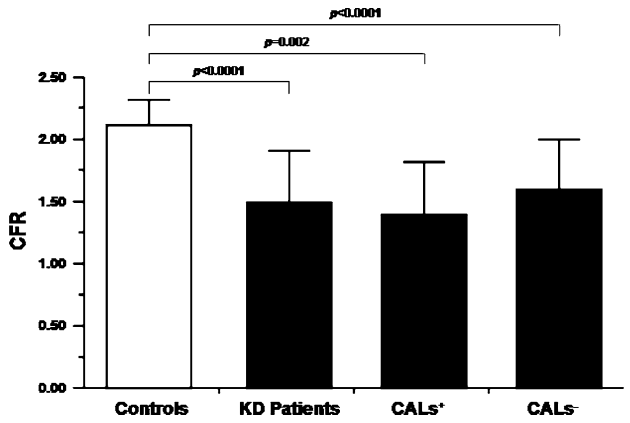


**Fig. 1** CFR values measured in the total KD population and in the $CALs^+$ and $CALs^-$ subgroups compared to controls

coronary DPV was registered in the overall population ($p < 0.0001$). $DPV_{CPT}$ values were higher in children with KD than in controls (0.33 ± 0.07 vs 0.27 ± 0.03 cm/sec, $p < 0.005$). Compared to controls, coronary CFR was significantly impaired in KD patients (2.1 ± 0.2 vs 1.5 ± 0.4, respectively; $p < 0.0001$; Fig. 1). An equivalent CFR reduction was observed in $CALs^+$ and $CALs^-$ patients (1.4 ± 0.4 vs 1.6 ± 0.4, respectively; $p$ = NS).

Figures 2 and 3 depict examples of coronary flow velocities obtained in a control subject and in a KD patient, respectively.

## Discussion

The major finding of our study is that in children with a history of KD evaluated late after the acute illness, Doppler TTE is able to reveal an impairment of CFR. The CFR impairment is unrelated to the presence of CALs and is accompanied by increased coronary flow velocities at rest (a sign of microvascular dysfunction itself) and by altered endothelial coronary vasomotion.

When epicardial coronary stenosis is not evident, the reduction of CFR can be attributed to coronary microvascular dysfunction [15]. Doppler TTE evaluation of CFR in the distal left anterior descending coronary artery has demonstrated the ability to detect alterations of coronary microcirculation [1, 9, 10].

### Resting Coronary Flow Velocities in KD Patients

In our study, children with a previous history of KD showed higher $DPV_{Rest}$ values in comparison with a control group of a comparable age. Several arguments can be proposed to justify this finding. Blood flow velocities measured in coronary arteries at rest are closely related to myocardial oxygen demand. Of interest, some important determinants of oxygen consumption, such as body mass index and hemodynamic parameters (e.g., heart rate and blood pressure measured at the time of CFR evaluation), were not significantly different in our population of KD patients in comparison to controls. In addition, some pathological aspects, such as increased intimal thickness and minimal vessel lumen narrowing, previously described in epicardial coronary arteries of patients with KD, may justify the elevated values of $DPV_{Rest}$ measured in the distal portion of the coronary arteries [6, 31]. These features can be considered compensatory mechanisms to maintain normal flow at rest in response to a minimal luminal loss that is not detectable by TTE [33]. Furthermore, high $DPV_{Rest}$ values may reflect delayed morphofunctional damage involving resistance coronary arteries in KD and accounting for an increased arteriolar vasomotor tone [19]. Finally, left anterior descending artery stenosis may be a reasonable justification for the finding of increased $DPV_{Rest}$ values in our KD population. However, to exclude the possibility of evaluating CFR in patients with coronary stenosis, we selected asymptomatic patients with no echocardiographic evidence of intraluminal thrombi and, when indicated, with negative stress test for myocardial ischemia. Moreover, high values of $DPV_{Rest}$ were recorded in both patients with and patients without CALs (data not shown), significantly reducing the probability that high values of resting velocity may be the result of recording stenosis-related flow acceleration.

### Cold Pressor Test for Noninvasive Coronary Flow Reserve Assessment in KD Patients

To the best of our knowledge, this is the first study to use CPT as an endothelial-dependent vasodilator stimulus during TTE Doppler evaluation of a coronary artery to obtain a noninvasive assessment of CFR. We applied this test to assess the late impact of KD on coronary microvascular endothelial function, in relation to the presence or absence of CALs. CPT represents an endothelial-dependent coronary vasodilating stimulus capable of identifying early atherosclerosis in the clinical setting [17, 34, 35]. By activating the sympathetic nervous system, CPT induces direct coronary vasodilation and increased coronary blood flow. This increased coronary blood flow in turn results in an increase in shear stress on endothelial cells, thus triggering the release of the endothelial-derived relaxing factor.

### Coronary Flow Reserve

CFR was significantly impaired in our population of patients with KD. In agreement with previous studies [7, 8,

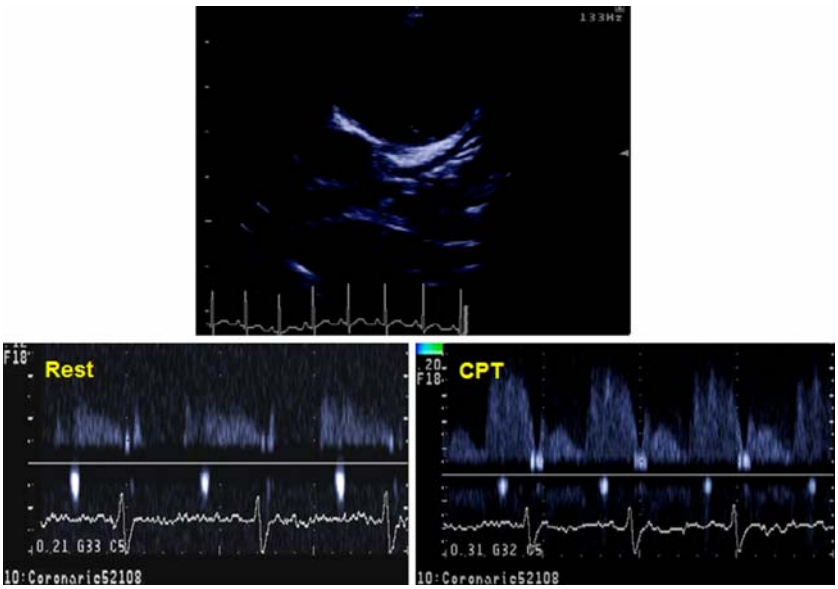


**Fig. 2** CFR measurement by Doppler TTE in a control child. (**Top**) Visualization of a normal left anterior descending coronary artery. (**Bottom**) Doppler-derived coronary flow profile at rest (*left*) and during CPT (*right*), showing a normal increment of coronary diastolic peak velocity (CFR = 2.1)

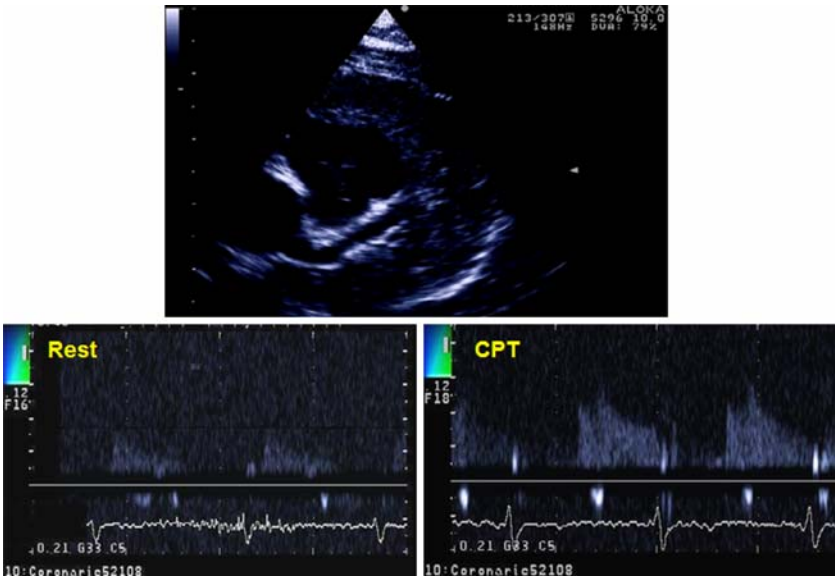


**Fig. 3** CFR measurement by Doppler TTE in a KD patient presenting with a fusiform aneurysm involving the proximal tract of left descending coronary artery. (**Top**) Visualization of fusiform aneurysm in the proximal tract of left anterior descending coronary artery. (**Bottom**) Doppler-derived coronary flow velocity at rest (*left*) and coronary flow velocities during CPT (*right*). A reduced increment of coronary diastolic peak velocity is observed (CFR = 1.5)

13, 21], this finding indicates the late-standing dysfunction of coronary microcirculation in patients with KD. Microcirculatory dysfunction may be justified in KD patients by the presence of anatomical damage consisting of intimal infiltration of inflammatory cells in the resistance arteries [19]. It has been demonstrated that active remodeling (intimal hypertrophy and endothelial dysfunction) can persist at the level of the epicardial coronary arteries for a long time after the acute phase of KD [29, 30]. Thus, it is conceivable that coronary arteriolar resistance vessels may be involved in these morphologic and functional changes, indicating long-lasting persistence of coronary microcirculation abnormalities.

Interestingly, similarly decreased CFR values were demonstrated in patients with and without CALs. Previous studies in patients with KD, performed by invasive evaluation of coronary reactivity during intracoronary acetylcholine infusion, revealed the presence of a paradoxical vasoconstriction not only in the affected arteries but also in the normal epicardial coronaries and in coronaries with regressed aneurysms, suggesting the presence of impaired endothelium-dependent vasomotion of the epicardial coronary arteries unrelated to CALs evolution [12, 20]. Using positron emission tomography, previous studies have reported on the critical role of the resistance arteries, demonstrating an impaired endothelial-dependent myocardial blood flow reserve in children with KD and normal epicardial coronary artery [8, 13, 21]. However, because of the ethical constraints concerning the administration of a radioactive agent to normal subjects, the control

groups of these studies were not of comparable age with the pathologic groups, raising the possibility of, at least in part, age-related findings. In our study, the ages of the diseased and normal groups were comparable; additionally, the method we used is noninvasive, easy to perform, and does not require drug administration.

### Study Limitations

In accordance with clinical guidelines [22], only the patient with a giant aneurysm underwent coronary angiography, which excluded the presence of epicardial coronary stenosis at the CALs level or the presence of CALs involving peripheral branches of the three main coronary arteries. Coronary angiography was not indicated in the remaining patients. However, in previous studies, TTE demonstrated excellent sensitivity and specificity in detecting coronary artery involvement in KD [5].

## Conclusion

The results of this study indicate that Doppler TTE of the distal left anterior descending artery using CPT as hyperemic stimulus is a feasible modality for the noninvasive evaluation of coronary flow velocities and CFR in patients with KD. Compared to controls, impaired CFR is demonstrable in KD patients with and without evidence of CALs by TTE.

In view of the recognized predictive role of impaired vascular response for subsequent development of atherosclerosis [11, 28], these findings suggest the predisposition to accelerated atherosclerosis of children with KD [24]. Further studies are needed to evaluate the possibility of improving CFR with appropriate therapy in children with a history of KD.

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