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### Title

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### Permalink

<https://escholarship.org/uc/item/6kf4f6qq>

### Journal

Journal of the American College of Cardiology, 62(12)

### ISSN

0735-1097

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### Publication Date

2013-09-01

### DOI

10.1016/j.jacc.2013.06.018

Peer reviewed

# Accepted Manuscript



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PII: S0735-1097(13)02532-1

DOI: [10.1016/j.jacc.2013.06.018](https://doi.org/10.1016/j.jacc.2013.06.018)

Reference: JAC 19047

To appear in: *Journal of the American College of Cardiology*

Received Date: 5 June 2013

Accepted Date: 13 June 2013

Please cite this article as: Burns JC, Daniels LB, Assessing vascular health after Kawasaki disease: A cautionary tale, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.06.018.

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**Assessing vascular health after Kawasaki disease: A cautionary tale**

Running Title: Assessing vascular health after Kawasaki disease

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Disclosures: None

Financial Support: This work was supported, in part, by a grant from the Macklin Foundation (JCB and LBD), and from the American Heart Association, National Affiliate (LBD).

Word count: 1798

Key Words: Kawasaki Disease, vascular health, endothelial function

Kawasaki disease (KD) is a self-limited, systemic vasculitis of children with the most profound effect on the coronary arterial bed (1). Without timely diagnosis and treatment with intravenous immunoglobulin, one in four children will develop coronary artery aneurysms with the attendant risks of thrombotic occlusion, myocardial infarction, and sudden death (2,3). Two major areas of controversy are emerging as this patient population ages. The first is whether or not patients will have long-term cardiovascular sequelae following KD and the second is whether or not these patients will develop accelerated atherosclerotic changes in the coronary arteries as a direct consequence of the arterial wall inflammation during their acute disease.

Common sense dictates that there will be long-lasting sequelae in children who suffered coronary artery aneurysms documented by echocardiography during the acute phase of the illness and this should not be a matter of controversy. Although no systematic, longitudinal studies have been reported, case series from Japan of young adults post-KD have catalogued the adverse outcomes in patients who developed coronary artery aneurysms during the acute illness (4-6). As one might expect, the outcomes appear to be worse in patients with the largest aneurysms, the so-called giant aneurysms measuring at least 8mm in diameter (7,8). In addition, studies have documented the paradoxical vasoconstriction response to intracoronary acetylcholine challenge in aneurysm patients long after KD, suggesting prolonged dysfunction of the endothelium in that arterial bed (9,10). Subsequently, investigators attempted to use flow-mediated dilation (FMD) of the brachial artery as a surrogate for direct interrogation of the endothelial cell function of the coronary arterial bed. This had obvious advantages in a young population for whom cardiac catheterization was not necessarily clinically indicated. However, in making this leap, investigators may have overlooked an important detail: the non-invasive

technique of FMD was developed following extensive correlation studies of intracoronary acetylcholine injection vs. FMD for assessment of endothelial cell function in atherosclerosis, a generalized, pathologic state of both peripheral and coronary arteries (11). No such studies have been performed in KD subjects. Therefore, one cannot assume that interrogating the response of the endothelium of the brachial artery in teenagers and young adults informs us about anything other than the health of that specific artery.

Similarly, the technique of ultrasound assessment of carotid intima-media thickness (IMT), another non-invasive procedure, was developed to refine risk assessment for future cardiovascular events (myocardial infarction and stroke) in patients at intermediate and high risk (12). In a different patient population, namely patients following KD in childhood, it is not clear whether thickening of the intima represents early atherosclerotic changes or rather the process known as luminal myofibroblastic proliferation that has been described in KD autopsy studies (1). It should be noted that in this extensive review of arterial pathology from 41 KD subjects, atherosclerosis, defined as lipid-laden macrophages and cholesterol clefts in the media of the arterial wall, was not a prominent finding, despite the fact that many of the subjects were adults. Similarly, reports from the forensic literature of adults who died suddenly of complications attributed to missed KD in childhood do not describe atherosclerotic changes (13). Further potential pitfalls come from assuming that images of a thickened media/intima complex generated by intravascular ultrasound (IVUS) are signs of atherosclerosis as opposed to the changes of KD vasculopathy (14).

In the work by Tierney et al. in this issue of JACC, the authors studied a cohort of 203 subjects ages 11-29 years with a history of KD at least 1 year prior to testing using Endothelial Pulse Amplitude Testing (Endo-PAT) as a more reliable and reproducible method of measuring

FMD of the brachial artery. They also assessed carotid IMT by ultrasound, C-reactive protein (CRP) levels, and fasting lipid profiles. Although the premise of the paper was to assess the vascular health of these subjects through these different modalities, confusion emerges as to whether the authors are testing to determine vascular health or to detect atherosclerosis. The major findings of the study are that, overall, measures of peripheral vascular health in individuals with a history of KD were not significantly different from controls. Although the pulsatility index of the carotid arteries appeared to be higher in KD patients than in controls, when the KD patients were grouped by coronary artery status, no meaningful trend or difference was apparent. A strength of the study is that most of the initial echocardiograms were performed at a single center with experience in assessing KD patients. Therefore, subjects could be confidently classified as having had normal, dilated, or aneurysmal coronary arteries. The single center design also introduces some potential biases, though. The KD population was predominantly white (80%), and may not be representative of the overall KD population in the United States where children of African American and Asian descent are disproportionately affected.

Previous studies have demonstrated decreased FMD in patients with persistent coronary artery aneurysms (15-17). The present study did not find any such differences, but due to the small number of subjects with persistent aneurysms (n=10) it may have lacked sufficient power to detect such a difference. Prior studies have also found abnormal levels of high sensitivity CRP in KD patients with persistent aneurysms (18). Although the present study did not find any significant differences in CRP levels, the use of a standard rather than a high sensitivity assay could be responsible for this since high sensitivity assays are needed to accurately quantify the low levels of CRP (<10 mg/L) seen in chronic inflammation states (19); standard CRP assays

would not be expected to detect any differences when the median CRP level is 1 mg/L, as in this study.

One of the major unanswered questions in this field is whether the long-term vascular health of KD subjects who never had coronary aneurysms, or who had only transient abnormalities, will be similar to that of a healthy control population. Unfortunately, the present study does not answer this question. First, the study provided little data comparing vascular measures specifically in this subgroup of individuals. Additionally, the median time from onset of KD to the tests performed in the current study was 12 years, however the authors included subjects whose KD was as recent as 1 year. One year (or even 5 years) is probably not nearly enough time for individuals to develop the long-term vascular sequelae of KD, especially if chronic inflammation plays a role. Previous studies evaluating the time course of coronary artery calcification after KD have shown that it may take at least 10 years for calcification to develop after KD (20,21); changes in the peripheral vasculature may not be any quicker to develop. Thus, the authors' conclusion, that individuals with a history of KD whose coronary arteries were either always normal or only mildly ectatic might not need further surveillance, may be premature.

This study provides a good starting point for understanding the long-term cardiovascular sequelae in children and young adults with a history of KD. It suggests that the majority of such individuals are likely to have minimal or no detectable changes in their peripheral vascular health. Future studies will be needed to determine whether these surrogate measures translate into real-life, event-free, healthy outcomes and a truly clean bill of health for KD patients with apparently normal coronary arteries.

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