Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 4, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.09.021

Long-Term Prognostic Impact of Dobutamine Stress Echocardiography in Patients With Kawasaki Disease and Coronary Artery Lesions

A 15-Year Follow-Up Study

Nobutaka Noto, MD, PhD, Hiroshi Kamiyama, MD, PhD, Kensuke Karasawa, MD, PhD, Mamoru Ayusawa, MD, PhD, Naokata Sumitomo, MD, PhD, Tomoo Okada, MD, PhD, Shori Takahashi, MD, PhD

Tokyo, Japan

Objectives This study sought to determine the prognostic value of dobutamine stress echocardiography (DSE) over a 15-year follow-up for predicting cardiac events in adolescent Kawasaki disease (KD) patients with coronary artery lesions (CALs).

Background Although DSE is an established technique for the detection of coronary artery disease, its prognostic value to predict cardiac events in adolescent KD patients with CALs is unknown.

Methods Fifty-eight adolescent KD patients, including 36 patients with CALs documented by coronary angiography, and 22 patients with normal coronary arteries documented by echocardiography who underwent DSE were reviewed at initial testing (mean age: 13.6 years) and at 15 years' follow-up. Follow-up events were tabulated as major adverse cardiac events (MACEs) that included cardiac death, nonfatal myocardial infarction, and revascularization.

Results During a mean follow-up of 14.7 years, there were 16 patients with MACEs (acute myocardial infarction: n = 1; old myocardial infarction: n = 7; coronary artery bypass grafting: n = 4; percutaneous coronary intervention: n = 4). Significant coronary artery disease (CAD) (>70% coronary stenosis) was detected in 31.0% of patients at initial testing and 42.1% at follow-up. However, there were no significant differences in wall motion score indices (WMSI) at peak DSE between initial testing and follow-up (p = 0.762). Five of 6 patients (85%) with false-positive DSE results (WMSI: ≥1.25) at initial testing, who had giant aneurysms without CAD, developed CAD with MACEs during follow-up. Cumulative event-free survival rate to 15 years was 25.0% in patients with WMSI ≥1.25 and 91.7% in patients with WMSI <1.25. Cox regression analysis showed the grade of peak WMSI at initial testing to be the only independent predictor of MACEs (relative risk: 3.28; 95% confidence interval: 1.73 to 6.20).

Conclusions DSE provided independent prognostic information up to 15 years in adolescent KD survivors. (J Am Coll Cardiol 2014;63:337–44) © 2014 by the American College of Cardiology Foundation

Kawasaki disease (KD) is a systemic vasculitis of unknown origin in young children. Although intravenous immunoglobulin infusion initiated at the acute phase reduces the morbidity of KD and the incidence of coronary artery lesions (CALs) such as coronary artery ectasia or coronary aneurysm (1,2), some patients still develop coronary aneurysms, leading to coronary artery disease (CAD, i.e., coronary artery stenosis or obstruction), which often induces myocardial infarction and cardiac death during the convalescent stage (3,4). The progression of a coronary aneurysm to a stenotic lesion is an important determinant of the prognosis of KD and CALs (5); however, little is known about the incidence of coronary stenotic lesions during follow-up in KD patients with CALs (6,7). Moreover, studies concerned with the prediction of cardiac events, including cardiac death, acute myocardial infarction (AMI), old myocardial infarction (OMI), and revascularization in adolescents and young adults with KD and CALs, have not been reported.

Dobutamine stress echocardiography (DSE) is a widely accepted and useful noninvasive test for the diagnosis, risk stratification, and prognosis of adult patients with suspected or known CAD (8,9). DSE has also been shown to provide valuable information for the detection of coronary artery stenosis in children and adolescents with KD (10). Although

From the Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 16, 2013; revised manuscript received July 25, 2013, accepted September 11, 2013.

Abbreviations and Acronyms

AMI = acute myocardial infarction
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CAG = coronary angiography
CAL = coronary artery lesion
CTCA = computed tomography coronary angiography
DSE = dobutamine stress echocardiography
HR = heart rate
KD = Kawasaki disease
MACE = major adverse cardiac event(s)
OMI = old myocardial infarction
PCI = percutaneous coronary intervention
WMA = wall motion abnormality
WMSI = wall motion score index

DSE is an established technique for the detection and prognostic stratification of CAD, the prognostic value of DSE in adolescents and young adults with KD and CALs for predicting cardiac events is unknown. This study was designed to determine the prognostic value of DSE involving a 15-year follow-up for predicting the cardiac events in adolescents and young adults with KD and CALs.

Methods

Subjects. Consecutive KD patients meeting the following criteria were recruited from our outpatient clinic between August 1996 and August 1998: 1) a diagnosis of KD; 2) an interval from initial onset of illness of ≥5 years; 3) KD patients who received periodic follow-up at our institution; and 4) KD patients who underwent DSE for the detection of CALs during that time period. In our institution, KD follow-up protocol includes annual DSE beginning 5 years after the initial onset of illness in patients with risk level IV (large or giant coronary aneurysm) or V (coronary artery obstruction) and biennial DSE in patients with risk level III (small-to-medium coronary aneurysm). Patients with risk level I (no coronary artery changes) or II (transitional coronary artery ectasia) undergo DSE only when they have an episode of atypical chest pain, resting electrocardiogram changes, and nondiagnostic or ambiguous exercise stress electrocardiogram results according to the risk stratification of American Heart Association guidelines (11). Subjects were excluded if they had a history of any cardiac events including nonfatal myocardial infarction and revascularization prior to 5 years from initial onset of illness. The study was approved by the human research ethics committee of our institution, and written informed consent for participation in this study was obtained from all subjects or their parents.

Follow-up and endpoints. Follow-up data, including medical records, DSE results, details of major coronary arteries by either quantitative coronary angiography (CAG) or computed tomography coronary angiography (CTCA) in KD patients with CALs and by two-dimensional echocardiography in KD patients without CALs, were reviewed during initial testing (I) (from 1996 to 1998). To investigate the incidence of CAD and the diagnostic accuracy of DSE in KD patients over time, the same variables were compared between (I) and at follow-up testing (F) (from 2010 to 2012). A follow-up period of 15 years was used when plotting survival curves. The endpoints were all-cause mortality and major adverse cardiac events (MACEs). MACEs, assessed individually and as a composite, were nonfatal myocardial infarction, including AMI and OMI; cardiac death; and revascularization. AMI was diagnosed in patients with symptoms of myocardial ischemia accompanied by an increase in a marker of myocardial necrosis. OMI was diagnosed in patients who had no subjective symptoms at the time when an abnormal Q-wave was observed on the electrocardiogram. Cardiac death was documented as death related to MI, congestive heart failure, sudden cardiac death, or arrhythmia. Revascularization included any percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). In our institution, PCI was considered in patients with ischemic symptoms, patients without ischemic symptoms but ischemia on stress tests, and patients without ischemia but with >75% stenosis in the left anterior descending coronary artery that could potentially result in sudden cardiac death. In addition, CABG was considered in patients with findings of ischemia for which PCI is contraindicated, including patients with a severe occlusive lesion of the left main coronary artery or left anterior descending coronary artery, with severe multivessel occlusive lesions and with jeopardized collateral according to the guidelines (12).

Dobutamine stress echocardiography protocol. Transthoracic echocardiography was performed with a 2.5-MHz or 3.75-MHz phased array transducer (model SSH 140A or SSH 880A, Toshiba Medical Systems, Tokyo, Japan). Images were obtained in standard parasternal long-axis and short-axis, apical 4-chamber, and 2-chamber views at baseline and after each incremental dose of dobutamine. An infusion of dobutamine was started at 5 μg/kg/min and increased every 3 min to 10, 20, 30, and 40 μg/kg/min until the target heart rate was achieved. Dobutamine infusion was terminated if the target heart rate (85% of the age-predicted maximal heart rate) was achieved; the protocol was completed; or for standard indications such as severe chest pain, ST-segment depression >2 mm, marked hypertensive response of >210 mm Hg systolic blood pressure, development of new or worsening regional wall motion abnormalities (WMA), or if requested by patients. Images were digitized and displayed in 4-quadrant views for side-by-side comparison of baseline, 10-μg, peak dose, and recovery images and stored on a magneto-optical disk for offline analysis.

DSE analysis. A normal response to dobutamine infusion was defined as a progressive increase in myocardial thickening and hyperdynamic wall motion from rest to peak dose of dobutamine infusion (negative DSE). An abnormal response to dobutamine infusion was defined as a reduction in myocardial thickening or wall motion at any stage of the dobutamine infusion compared with the previous stage (positive DSE). The wall motion of the left ventricle was assessed with a 16-segment model, which was scored according to a 4-point scale: 1 for normokinesia, 2 for