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Increased ^{99m}Tc-Sestamibi Washout Reflects Impaired Myocardial Contractile and Relaxation Reserve During Dobutamine Stress Due to Mitochondrial Dysfunction in Dilated Cardiomyopathy Patients

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Objectives This study investigated whether the technitium-99m sestamibi (MIBI) washout rate (WR) would predict mitochondrial damage and myocardial dysfunction in patients with dilated cardiomyopathy (DCM).

Background Myocardial mitochondrial damage reduces adenosine triphosphate production, resulting in myocardial dysfunction. Increased myocardial ^{99m}Tc-MIBI washout is reportedly caused by mitochondrial dysfunction.

Methods Twenty DCM patients (New York Heart Association functional class I–III) underwent myocardial ^{99m}Tc-MIBI scintigraphy and cardiac catheterization. Myocardial MIBI uptake was quantified as an early and delayed heart-to-mediastinum ratio, and WR was calculated. Maximum first derivative of left ventricular (LV) pressure (LV dP/dt_{max}) (an index of myocardial contractility) and LV pressure half-time ($T_{1/2}$) (an index of myocardial relaxation) were calculated by the left ventricular pressure curve at baseline and during dobutamine infusion (15 μg/kg/min at maximum). Endomyocardial biopsy specimens were obtained for quantitative mRNA analysis and electron microscopy. The patients were divided into two groups as follows: 1) group A of 10 patients showing a WR ≤24.3% (median value) and 2) group B of 10 patients showing a WR >24.3%.

Results WR was significantly correlated with the percentage changes in LV dP/dt_{max} (%LV dP/dt_{max}) (r: −0.59; p = 0.01) and $T_{1/2}$ (r: −0.57; p = 0.03) from baseline to peak dobutamine stress. The %LV dP/dt_{max} was significantly greater in group B than in group A. The abundance of mRNAs for mitochondrial electron transport–related enzymes was more significantly reduced in group B than in group A. Electron microscopy revealed significant correlations between WR and the severity of mitochondrial damage (r: 0.88; p = 0.048) and glycogen accumulation (r: 0.90; p = 0.044).

Conclusions Increased ^{99m}Tc-MIBI washout may predict mitochondrial dysfunction and the impairment of myocardial contractile and relaxation reserves during dobutamine stress in DCM patients. (J Am Coll Cardiol 2013;61:2007–17)

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) dilatation and myocardial systolic dysfunction (1,2). The recent advancement in pharmacological treatments, such as treatments with renin-angiotensin-aldosterone system inhibitors or beta-blockades, provides significant beneficial effects for patients with DCM. However, some DCM patients fail to show significant responses to these treatments, resulting in a poor prognosis. The prevalence of severe myocardial damage, including mitochondrial functional failure, is thought to be associated with a poor prognosis. Accordingly, it is important to clarify the underlying pathophysiological mechanisms involved in refractoriness to any treatments.

See page 2018

Myocardial technitium-99m–labeled sestamibi (MIBI) is commonly used as a myocardial perfusion imaging tracer for

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Abbreviations and Acronyms

BNP = brain natriuretic peptide

COX5B = cytochrome c subunit 5B

DCM = dilated cardiomyopathy

GAPDH = glyceraldehyde-3-phosphate dehydrogenase

H/M = heart-to-mediastinal ratio

α-KGDH = alpha-ketoglutarate dehydrogenase

LV = left ventricular

LV dP/dt_{max} = maximum first derivative of left ventricular pressure

LVEF = left ventricular ejection fraction

MIBI = sestamibi

mRNA = messenger ribonucleic acid

NADH = nicotinamide adenine dinucleotide

NDUFV3 = nicotinamide adenine dinucleotide dehydrogenase-ubiquinone flavoprotein 3

NYHA = New York Heart Association

RT-PCR = reverse transcriptase–polymerase chain reaction

SPECT = single photon emission tomography

$T_{1/2}$ = left ventricular pressure half-time

WR = washout rate

detecting significant coronary artery disease. Approximately 90% of myocardial MIBI is localized within a mitochondrial fraction. Myocardial MIBI uptake, which is positively charged electrically, depends on a strong negative charge in mitochondrial membranes (3,4). A lack of MIBI uptake has been reported in some experimental studies (5,6). In addition, an increased MIBI washout is thought to be related to impaired mitochondrial function coexisting with myocardial damage (7,8). An increased myocardial MIBI washout was often reported in patients with myocardial infarction (9,10) or cardiomyopathy (11–14). We previously reported that increased MIBI washout was associated with abnormal myocardial properties linked to myocardial mitochondrial damage in patients with nonobstructive hypertrophic cardiomyopathy (15,16).

In the present study, we investigated the relationship between myocardial MIBI washout, myocardial functional properties, mitochondrial messenger ribonucleic acid (mRNA) expression, and mitochondrial structural configuration in DCM patients.

Methods

Study population. A total of 20 DCM patients (11 men and 9 women; mean age: 50 ± 13 years; and mean LV ejection fraction [LVEF]: 34 ± 9%) were studied. DCM was diagnosed on the basis of clinical, electrocardiographic and echocardiographic findings according to previously proposed diagnostic criteria (17). Patients were excluded if they showed prior evidence of coronary artery disease, primary valvular disease, essential or secondary hypertension, chronic atrial fibrillation, or diabetes mellitus. All patients underwent coronary angiography to exclude those with significant coronary artery disease. An endomyocardial biopsy was also performed to assess the reverse transcriptase–polymerase chain reaction (RT-PCR) analysis, and electron microscopy was subsequently conducted. All patients underwent cardiac catheterization analysis at rest and under dobutamine stress, as well as myocardial MIBI scintigraphy at rest. The study protocol was approved by the ethics review board at the Nagoya University School of Medicine, and written informed consent was obtained from all patients.

Myocardial MIBI scintigraphy. Myocardial MIBI scintigraphy was conducted at rest. Six hundred megabecquerels of MIBI tracer was injected in each patient intravenously. The initial images were acquired 60 min after tracer injection, and the delayed images were initiated 4 h later. A Toshiba gamma triple-head rotation camera (GCA9300, Toshiba Inc., Tokyo, Japan) equipped with a low-energy, high-resolution collimator was used for single-photon emission computed tomography (SPECT) imaging. Projection images were obtained over a 360° arc at an acquisition time of 20 s per image. A 20% symmetric window centered at 140 KeV was applied. Projected image data were transferred to a dedicated computer using a 64 × 64 matrix size. For SPECT reconstruction, Butterworth filter served as prefilter and Ramp filter as back-projection filter, with a cutoff frequency of 0.32 cycles/pixel and an order of 8, were used without correction for attenuation or scatter. Tomographic slices were reconstructed relative to the anatomic axis of the left ventricle. The vertical and horizontal long-axis and short-axis slices were then generated.

For quantitative analysis, the early and delayed heart-to-mediastinal ratio (H/M) and global WR were calculated. The region of interest (ROI) on the planar imaging was manually set over the whole heart and a rectangular ROI on the upper mediastinum. The H/M was calculated as (Count density of the whole LV)/(Count density of the mediastinum). The global WR was also calculated on the planar image as [(Initial H–Initial M)–(Delayed H–Delayed M) × DC]/(Initial H–Initial M) × 100, where *H* indicates mean heart counts, *M* indicates mean mediastinal counts, and *DC* indicates decay coefficiency. The normal values of MIBI WR, early H/M, and delayed H/M of the age-matched control group (10 subjects; 9 men; age: 56 ± 9 years; LVEF: 70 ± 7%) were 11 ± 5%, 3.5 ± 0.3, and 3.1 ± 0.3, respectively.

Echocardiography. Echocardiography was performed using a Sonos 2500 ultrasound system (Hewlett-Packard, Andover, Massachusetts) equipped with a 2.5- to 3.5-MHz transducer. The LV end-diastolic dimension, LV end-systolic dimension, interventricular septal thickness, posterior wall thickness, and LVEF were measured on the M-mode of the long-axis image according to standard criteria recommended by the American Society of Echocardiography (18).

Cardiac catheterization and endomyocardial biopsy. Biventricular catheterization was performed using the standard techniques. In the left heart catheter, a 6-F fluid-filled pigtail catheter with a high-fidelity micromanometer (CA-61000-PLB Pressure-tip Catheter; CD Leycom, Zoetermeer, the Netherlands) was positioned in the left ventricle for the measurement of LV pressure. Micromanometer pressure signals and standard electrocardiograms were continuously recorded with a multichannel recorder online. The LV pressure signals were digitized at 3-ms intervals and