CASE REPORT

Vagal Enhancement Linking Abnormal Blood Pressure Response and Subendocardial Ischemia in Hypertrophic Cardiomyopathy

Tatsuya Kawasaki, M.D., and Hiroki Sugihara, M.D.

From the Department of Cardiology, Matsushita Memorial Hospital, Osaka, Japan

An abnormal blood pressure response to exercise has been reported to be associated with left ventricular subendocardial ischemia in patients with hypertrophic cardiomyopathy (HCM), but the underlying mechanism remains unclear. We report a case of HCM with an abnormal blood pressure response and subendocardial ischemia, in which the analysis of heart rate variability revealed exercise-induced vagal enhancement. The present case highlights the possible mechanism linking abnormal blood pressure response and left ventricular subendocardial ischemia in patients with HCM.

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hypertrophic cardiomyopathy; vagal nerve; blood pressure; subendocardial ischemia

Hypertrophic cardiomyopathy (HCM) patients often have unique clinical features, such as an abnormal blood pressure response to exercise^{1,2} or left ventricular subendocardial ischemia,^{3,4} in cases without epicardial coronary artery stenosis. Interestingly, an abnormal blood pressure response has been reported to be associated with subendocardial ischemia,⁵ but the underlying mechanism remains unclear. We report a case of HCM with an abnormal blood pressure response and subendocardial ischemia, in which exercise-induced vagal enhancement was likely to connect the two phenomena.

CASE REPORT

A 70-year-old woman, who had been diagnosed with nonobstructive HCM with asymmetrical septal and apical hypertrophy in the left ventricle, was referred to our hospital to undergo exercise scintigraphy. The medical history was unremarkable, with no history of hypertension, dyslipidemia, or diabetes mellitus. Coronary angiography reportedly showed no stenosis. The patient did

not smoke, drink alcohol, or use illicit drugs. Medications included verapamil (80 mg three times daily) and ubidecarenone (20 mg three times daily). Her son had HCM.

Maximal symptom-limited exercise scintigraphy with Tc-99m tetrofosmin was performed under drug-free conditions. The exercise workload began with 25 W and was increased by 25 W every 2 min using a sitting ergometer under continuous monitoring with the Mason-Likar lead system. Blood pressure was measured using arm-cuff sphygmomanometry at least every 2 min. The exercise ended due to physical exhaustion without any diagnostic ST-segment changes. Maximal workload and rate-pressure product were 75 W and 15,540, respectively. A diagnosis of an abnormal blood pressure response, defined as a failure to exhibit an increase ≥ 25 mmHg during exercise,⁵ was made (Fig. 1).

Tc-99m tetrofosmin of 370 MBq or 740 MBq was injected intravenously 1 min before the termination of exercise or 4 hours later. Images were obtained 30 min after tracer injections with a digital gamma camera equipped with a low-energy,

Address for correspondence: Tatsuya Kawasaki, M.D., Ph.D., Department of Cardiology, Matsushita Memorial Hospital, Sotojima 5-55, Moriguchi, Osaka 570-8540, Japan. Fax: +81-66992-4845; E-mail: js-k@wfb6.so-net.ne.jp

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Figure 1. Heart rate increases steadily during exercise (upper panel), but blood pressure almost fails to increase (middle panel). The coefficient of high-frequency component variance (lower panel, solid line) does not decrease after the start of exercise (arrowheads), notably increases before the peak heart rate (arrow), and remains high after exercise, indicating less vagal withdrawal and subsequent vagal enhancement. A dotted line shows changes in the mean of the coefficient of high-frequency component variance in 9 normal subjects recruited from our database.

high-resolution, and parallel-hole collimator on a matrix of 64×64 pixels, and were reconstructed as single-photon emission computed tomograms using a Hanning filter without correction for attenuation or scatter. Left ventricular subendocardial ischemia

was quantified using software that we had developed⁶ and modified appropriately.⁷ Briefly, the left ventricle was divided into 15 short-axis slices and 100 radii were generated at 3.6-degree intervals from the center of each image. An area surrounded by 100 points each displaying the maximum count on each radius was calculated automatically in the stress and rest images. Subendocardial ischemia was considered present if the stress to rest ratio in the sum of the 15 surface areas was >1.07 .⁷ The patient was diagnosed with left ventricular subendocardial ischemia because the stress to rest ratio was increased to 1.20, as shown in Fig. 2.

To examine the effect of the autonomic nervous system on the abnormal blood pressure response, RR intervals during exercise testing were derived from the archived data at a frequency of 500 Hz and heart rate variability was analyzed using commercially available software (MemCalc/Tarawa, GMS Co. Ltd., Tokyo, Japan).^{7,8} The coefficient of high-frequency component (0.15–0.40 Hz) variance, which is the square root of high frequency divided by the mean RR interval, was used in the estimation of vagal modulation from short-duration recordings.^{8,9} The coefficient of high-frequency component variance hardly decreased after the start of exercise, notably increased before the peak heart rate, and remained high after exercise (solid line in Fig. 1). The autonomic response to exercise in 9 normal subjects, who were recruited from the control database in our institute (six women and three men; 57–75 years of age; maximal workload of 75 W in all), is shown as a dotted line in Figure 1, in which the mean of the coefficient of high-frequency component variance steadily decreased during exercise and smoothly returned to the baseline level after the cessation of exercise.

DISCUSSION

An abnormal blood pressure response and left ventricular subendocardial ischemia developed during exercise in our patient with nonobstructive HCM. The analysis of heart rate variability showed less vagal withdrawal or enhanced vagal modulation during and after exercise. Thus, we may safely consider that exercise-induced vagal enhancement was the cause of the abnormal blood pressure response to exercise in this case. Our

Figure 2. Short-axis images of technetium-99m tetrofosmin myocardial scintigraphy show exercise-induced left ventricular cavity dilation, a finding suggestive of subendocardial ischemia.

speculation may be supported by our previous study, in which vagal enhancement after exercise (not assessed during exercise), compared with that before exercise, was associated with abnormal blood pressure response in HCM patients.⁷

The precise mechanism of exercise-induced vagal enhancement is unclear, but may be explained by the fact that vagal nerves are predominantly distributed in the left ventricular subendocardium.^{10–12} Cardiac receptors with vagal afferents are known to be activated by chemical stimuli due to myocardial ischemia (i.e., subendocardial ischemia in our case).¹³ Furthermore, mechanical stimuli may be an additional cause of activated vagal afferents because subendocardial ischemia has been reported to be associated with increased left ventricular end-diastolic pressure in patients with HCM.⁴

Vagal enhancement might not be consistent with the steady increase in heart rate during exercise, but we believe that the activation of sympathetic nerves, accompanied by vagal enhancement, increased heart rate to some extent (i.e., 72% of the maximal age-predicted heart rate). Simultaneous co-activation of sympathetic and vagal nerves has been known to occur in certain situations, including chemoreceptor and baroreceptor reflexes.^{14,15} In our case, enhanced sympathetic

modulation might have prevented hemodynamic collapse, which could develop in the situation of vagal enhancement during exercise, although simultaneous co-activation of both nerves seems to show unpredictable physiological responses.^{14,16}

In conclusion, the present case highlights the possible mechanism linking abnormal blood pressure response and left ventricular subendocardial ischemia in patients with HCM. Further studies are needed to determine whether our findings can be extrapolated to the general population of HCM patients.

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