Muscle Weakness Is Associated With an Increase of Left Ventricular Mass Through Excessive Blood Pressure Elevation During Exercise in Patients With Hypertension

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SUMMARY

Autonomic imbalance in hypertension induces excessive blood pressure (BP) elevation during exercise, thereby increasing left ventricular mass (LVM). Although muscle weakness enhances autonomic imbalance by stimulating muscle sympathetic activity during exercise, it is unclear whether muscle weakness is associated with an increase of LVM in patients with hypertension. This study aimed to investigate the relationships between muscle weakness, BP elevation during exercise, and LVM in these patients. Eighty-six hypertensive patients aged 69 ± 8 years with controlled resting BP (ie, $< 140/90$ mmHg) were recruited. Plasma brain natriuretic peptide (BNP), left ventricular mass index (LVMI), and knee extension muscle strength were measured. Changes in plasma noradrenaline (NORA) and brachial-ankle pulse wave velocity (ba-PWV) were assessed before and after an ergometer exercise test performed at moderate intensity (Δ NORA and Δ PWV, respectively). A difference between baseline and peak systolic BP during the exercise test was defined as BP elevation during exercise (Δ SBP). Relationships between muscle strength, Δ NORA, Δ PWV, Δ SBP, BNP, and LVMI were analyzed, and significant factors increasing LVM were identified using univariate and multivariate regression analyses. Muscle strength was negatively correlated with Δ NORA ($r = -0.202$, $P = 0.048$), Δ PWV ($r = -0.328$, $P = 0.002$), Δ SBP ($r = -0.230$, $P = 0.033$), BNP ($r = -0.265$, $P = 0.014$), and LVMI ($r = -0.233$, $P = 0.031$). LVMI was positively correlated with Δ PWV ($r = 0.246$, $P = 0.023$) and Δ SBP ($r = 0.307$, $P = 0.004$). Muscle strength was a significant independent factor associated with LVMI ($\beta = -0.331$, $P = 0.010$). Our findings suggest that muscle weakness is associated with an increase of LVM through excessive BP elevation during exercise in patients with hypertension. (Int Heart J 2017; 58: 551-556)

Key words: Arterial stiffness, Autonomic activity, Cardiac overload, Muscle strength

Long-lasting high blood pressure (BP) increases left ventricular mass (LVM) due to left ventricular pressure overload.¹⁻³⁾ Hypertension-related LVM increase leads to the progression of left ventricular dysfunction, which can result in chronic heart failure.⁴⁾ Left ventricular hypertrophy (LVH) is also known to be a strong risk factor for future cardiac events and mortality.⁴⁾ Therefore, the prevention of LVM increase is considered a promising therapeutic strategy, in addition to BP control, in patients with hypertension.

Patients with hypertension have been known to exhibit an autonomic imbalance even in ordinary activities of daily living (ADL), which indicates elevated sympathetic activity and reduced parasympathetic activity.^{5,6)} Accordingly, an unexpected increase in sympathetic activity can excessively elevate BP and/or heart rate (HR) during exercise, even at low or moder-

ate intensity.⁷⁾ One previous study reported that hypertensive patients who had increased sympathetic activity during exercise developed LVH more rapidly compared to those without autonomic imbalance.⁸⁾

Skeletal muscles are known to accumulate metabolites such as lactic acid during exercise.⁹⁾ These metabolites stimulate the rostral ventrolateral medulla, which is the center of the sympathetic system, via metabolite-sensitive receptors in skeletal muscle, thereby enhancing sympathetic activity.⁹⁾ Inactive and weak skeletal muscles are reported to enhance sympathetic activity during exercise more than active and powerful muscles, because those muscles release more metabolites.^{10,11)} Arterial stiffness varies based on autonomic and metabolic conditions during exercise, the change in which is evaluated as functional arterial stiffness.¹²⁾ Therefore, we considered that

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muscle weakness augmented functional arterial stiffness more easily in patients with hypertension, given that enhanced sympathetic activity during exercise increases peripheral vascular resistance. Augmented functional arterial stiffness can then evoke BP elevation and increase LVM. However, it is unclear whether muscle weakness augments functional arterial stiffness and excessively elevates BP during exercise, leading to the LVM increase. This study aimed to investigate the relationships between muscle weakness, BP elevation during exercise, and LVM in patients with hypertension.

METHODS

The study was approved by the Ethics Committee on Human Research at Kitasato University Hospital and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients after they received a detailed explanation of the study protocol.

Patients were eligible to participate if they received outpatient care for hypertension at the Cardiovascular Center of Kitasato University Hospital between April 2012 and March 2015, and their BP had been maintained below 140/90 mmHg with antihypertensives. Patients who had hypertrophic cardiomyopathy, atrial fibrillation, frequent ventricular arrhythmias, significant coronary stenosis, unstable angina pectoris, prior myocardial infarction, uncontrolled heart failure, end stage renal disease on hemodialysis, type 1 diabetes mellitus (DM), catastrophic complications of DM, malignancy, or significant malnutrition were excluded from the study. Patients were also excluded if they could not carry out exercise tests using a treadmill and cycle ergometer due to neurological diseases or orthopedic disorders, or if they showed an ankle brachial index of < 0.90. Consequently, 86 patients with hypertension participated in the present study.

Study protocol: After clinical characteristics were obtained from medical records or by interview, patients underwent fasting blood examination, an echocardiogram, and muscle strength measurements at study entry. Patients performed exercise tests using a treadmill and cycle ergometer to examine autonomic activity, functional arterial stiffness, and BP elevation during exercise. Tests were carried out in the order of treadmill exercise and cycle ergometer exercise at an interval of at least 2 days.

Clinical characteristics and blood examination: Age, gender, height, weight, body mass index (BMI), diagnosis, complications, systolic and diastolic BP (SBP and DBP), HR, estimated glomerular filtration rate (eGFR), left ventricular ejection function (LVEF), carotid intima-media thickness (cIMT), current smoking status, and medications were assessed. BMI was calculated as weight in kilograms divided by height in square meters. Resting SBP, DBP, and HR were measured with an automatic sphygmomanometer (FB-300, Fukuda Denshi, Tokyo). The eGFR was calculated from the age, sex, and serum creatinine level.¹³⁾ LVEF and cIMT were measured by ultrasonographic examination as indicators of cardiac function and atherosclerosis, respectively. Daily steps were counted for two weeks using an accelerometer (Kenz Lifecorder, SUZUKEN Co Ltd., Nagoya, Japan), the mean value of which was expressed as steps/day to assess daily physical activity. Plasma glucose, blood hemoglobin A1c (HbA1c), and serum levels of

triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured as indicators of glycolipid metabolism using blood samples obtained from the antecubital vein after an overnight fast.

Muscle strength: Maximum voluntary isometric knee extensor strength was measured twice in each leg with a hand-held dynamometer (μ -Tas; Anima, Tokyo) while patients sat on a chair with the hip and knee flexed at 90 degrees.^{14,15)} Muscle strength was obtained from the average of the right and left maximum isometric knee extensor strength divided by body weight and was expressed as a percentage of body weight (%BW).

Treadmill exercise test: Symptom-limited treadmill exercise testing was performed according to the Bruce protocol.¹⁶⁾ During the exercise test, HR and electrocardiogram (ECG) were continuously monitored using a stress test system (ML-6500; Fukuda Denshi, Tokyo), and BP was measured every minute with the cuff method using an automatic sphygmomanometer.

Cycle ergometer exercise test: Cycle ergometer exercise testing was performed using an upright cycle ergometer (Well Bike BE-360; Fukuda Denshi, Tokyo). Patients were instructed to pedal at 50 rpm during the exercise test. After resting for 15 minutes (resting phase), the patients started the exercise on a cycle ergometer at 15 watts for 3 minutes as a warm-up. The target HR was achieved within 3 minutes by increasing the workload and was maintained for another 10 minutes (exercise phase). The target HR was set at 75% of maximum HR measured during the treadmill exercise test. Patients cooled down at 15 watts for 3 minutes after the end of exercise and then rested in the supine position for 10 minutes (recovery phase). HR and ECG were continuously monitored using a stress test system (ML-1800; Fukuda Denshi, Tokyo) and BP was measured every minute throughout the exercise test.¹²⁾

Autonomic activity: Plasma concentration of noradrenaline (NORA) was measured at the end of the resting phase and end of the recovery phase in the cycle ergometer exercise test. The 10-minute recovery phase was sufficient to normalize elevated NORA and BP in healthy adults.^{17,18)} The change from NORA at the resting phase to that at the recovery phase (Δ NORA) was calculated to determine sympathetic activity.

Heart rate recovery (HRR) was assessed during the treadmill exercise test. HRR was defined as the HR decrease from maximum HR during the exercise test to that measured 1 minute after completion, and was used as an indicator of parasympathetic activity.^{19,20)}

Cardiovascular responses: The change from SBP at the resting phase to peak SBP during the exercise phase in the cycle ergometer exercise test was calculated as an indicator of BP elevation during exercise (Δ SBP).

Brachial-ankle pulse wave velocity (ba-PWV) was measured in the supine position using PWV/ABI (Fukuda Denshi, Tokyo) at the end of the resting phase and end of the recovery phase in the cycle ergometer exercise test. The change from ba-PWV at the resting phase to that at the recovery phase (Δ PWV) was calculated as an indicator of functional arterial stiffness, with a negative value indicating greater vascular compliance.¹²⁾

Plasma brain natriuretic peptide (BNP) was also measured as an indicator of left ventricular pressure overload.^{21,22)}

Assessment of left ventricular mass: Left ventricular end-di-

astolic dimension (LVDd), end-diastolic interventricular septum thickness (IVSd), and end-diastolic left ventricular posterior wall thickness (PWd) were measured in the supine position on an echocardiogram (Sonos 7500, Philips, Bothell, WA, USA). LVM was calculated using the formula of Devereux: $LVM (g) = 0.8 \times \{1.04 \times [(LVDd + IVSd + PWd)^3 - (LVDd)^3]\} + 0.6$.²³ LVM was normalized with body surface area to obtain the left ventricular mass index (LVMI).²³ Relative wall thickness (RWT) was also calculated as an indicator of LVH with left ventricular dilatation using the following formula: $RWT = (IVSd + PWd)/LVDd$.²⁴ Echocardiographic measurement was performed according to the recommendations of the American Society of Echocardiography by an observer who was blinded to the biochemical data.²⁵

Statistical analysis: Data are presented as the mean $\pm$ standard deviation (SD). Relationships between muscle strength, HRR, Δ NORA, Δ PWV, Δ SBP, BNP, and LVMI were analyzed using Spearman's correlation coefficient. Univariate and multivariate regression analyses were performed using LVMI as a dependent variable, and factors related to LVM increase as independent variables in order to clarify the relationship between muscle strength and LVMI. $P < 0.050$ was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 23.0 for Windows (IBM Corporation, NY, USA).

RESULTS

The clinical characteristics of the patients are summarized in Table I. The mean age of the patients was 69 ± 8 years, and 53.4% were male. Type 2 DM and dyslipidemia were detected in 34.9% and 43.0% of the patients, respectively, and 9.0% were smokers. Muscle strength ranged from 24.4 to 87.6%BW and the average was $56.9 \pm 12.6\%$ BW.

Figure 1 shows the relationships between muscle strength and autonomic activity. Δ NORA was negatively correlated with muscle strength ($r = -0.202$, $P = 0.048$). No significant relationship was observed between muscle strength and HRR.

Figure 2 shows the relationships between muscle strength

gth, functional arterial stiffness, and BP elevation during exercise. Δ PWV and Δ SBP were negatively correlated with muscle strength ($r = -0.328$, $P = 0.002$; $r = -0.230$, $P = 0.033$, respec-

Table I. Clinical Characteristics

Variable	
Number of patients (male/female) (n)	86 (46/40)
Age (years)	69 ± 8
Body mass index (kg/m^2)	24.3 ± 3.0
Resting systolic blood pressure (mmHg)	127 ± 11
Resting diastolic blood pressure (mmHg)	77 ± 8
Resting heart rate (/minute)	62 ± 9
Complications (%)	
Type 2 diabetes mellitus	34.9
Dyslipidemia	43.0
Current Smoking	9.0
Left ventricular hypertrophy	37.2
Medication (%)	
Ca channel blocker	70.5
Angiotensin II receptor blocker	80.1
Angiotensin-converting enzyme inhibitor	0.0
β Blocker	38.6
Diuretics	29.5
Insulin	9.1
Antidiabetic drugs	10.2
Antihyperlipidemic drugs	44.2
Glucose (mg/dL)	119 ± 27
Hemoglobin A1c (%)	6.3 ± 1.1
Triglycerides (mg/dL)	125 ± 85
Total cholesterol (mg/dL)	192 ± 43
Low density lipoprotein cholesterol (mg/dL)	119 ± 27
High density lipoprotein cholesterol (mg/dL)	62 ± 17
Estimated glomerular filtration rate (mL/minute/1.73m ²)	65.3 ± 15.9
Brain natriuretic peptide (pg/mL)	30.4 ± 27.1
Left ventricular ejection fraction (%)	66.4 ± 6.3
Interventricular septum thickness	8.8 ± 1.3
Posterior wall thickness	8.8 ± 1.1
Relative wall thickness	0.4 ± 0.1
Left ventricular mass index (g/m^2)	93.1 ± 17.5
Intima-media thickness (mm)	1.8 ± 0.8
Muscle strength (%BW)	56.9 ± 12.6
Daily steps (steps/day)	$7,046 \pm 2,802$

Data are shown as mean $\pm$ standard deviation.

Figure 1. Relationships between muscle strength, sympathetic activity, and parasympathetic activity. NORA indicates noradrenaline; Δ NORA, change from NORA at resting phase to NORA at recovery phase in the cycle ergometer exercise test; and HRR, heart rate recovery.

Figure 2. Relationships between muscle strength, functional arterial stiffness, and blood pressure elevation during exercise. PWV indicates pulse wave velocity; Δ PWV, change from PWV at resting phase to PWV at recovery phase in the cycle ergometer exercise test; SBP, systolic blood pressure; and Δ SBP, change from peak SBP during exercise phase to SBP at recovery phase in the cycle ergometer exercise test.

Figure 3. Relationships between functional arterial stiffness, blood pressure elevation during exercise, and left ventricular mass. PWV indicates pulse wave velocity; Δ PWV, change from PWV at resting phase to PWV at recovery phase in the cycle ergometer exercise test; SBP, systolic blood pressure; Δ SBP, change from peak SBP during exercise phase to SBP at recovery phase in the cycle ergometer exercise test; and LVMI, left ventricular mass index.

tively).

Figure 3 shows the relationships between functional arterial stiffness, BP elevation during exercise, and LVM. LVMI was positively correlated with Δ PWV and Δ SBP ($r = 0.246$, $P = 0.023$; $r = 0.307$, $P = 0.004$, respectively).

Figure 4 shows the relationships between muscle strength, left ventricular pressure overload, and LVM. BNP and LVMI were negatively correlated with muscle strength ($r = -0.265$, $P = 0.014$; $r = -0.233$, $P = 0.031$, respectively).

Table II shows the results of univariate and multivariate regression analyses for LVMI. HbA1c and muscle strength were significantly correlated with LVMI ($\beta = 0.265$, $P = 0.014$; $\beta = -0.304$, $P = 0.004$, respectively), and were identified as significant independent factors associated with LVMI ($\beta = 0.210$, $P = 0.047$; $\beta = -0.319$, $P = 0.012$, respectively).

DISCUSSION

This is the first report to demonstrate that muscle weakness is a significant independent factor increasing LVM in patients with hypertension.

Muscle strength was negatively correlated with Δ NORA, Δ PWV, Δ SBP, BNP, and LVMI. Moreover, multivariate regression analysis revealed that muscle strength was a significant independent factor for LVMI, in addition to HbA1c. Previous studies have reported that inactive skeletal muscles enhance more muscle sympathetic activity during exercise than active skeletal muscles in normal volunteers.^{11,26} Furthermore, inactive and weak muscles are known to produce less vascular endothelial growth factor, which stimulates angiogenesis, leading to a coarse capillary bed in the muscles.²⁷ Because oxygen supply is lower during exercise in those muscles, physically inactive patients reach the anaerobic threshold during exercise

Figure 4. Relationships between muscle strength, left ventricular overload, and left ventricular mass. BNP indicates brain natriuretic peptide; and LVMI, left ventricular mass index.

Table II. Results of Univariate and Multivariate Regression Analyses for Left Ventricular Mass Index

	Univariate Regression		Multivariate Regression	
	β	<i>P</i>	β	<i>P</i>
Age (years)	0.142	0.191	0.001	0.994
Gender (male/female)	0.035	0.752	0.158	0.205
Body mass index (kg/m ²)	0.202	0.062	0.124	0.291
Resting systolic blood pressure (mmHg)	0.035	0.752	0.016	0.884
Hemoglobin A1c (%)	0.265	0.014	0.210	0.049
Low density lipoprotein cholesterol (mg/dL)	-0.086	0.432	0.035	0.752
Estimated glomerular filtration rate (mL/minute/1.73m ²)	-0.144	0.186	-0.073	0.545
Muscle strength (%BW)	-0.304	0.004	-0.331	0.010

earlier than active patients.¹⁰ Consequently, it is considered that inactive and weak muscles accumulate more lactic acid, resulting in the stimulation of muscle sympathetic activity.¹¹ Therefore, the present study demonstrated that hypertensive patients who have weaker muscle strength showed higher functional arterial stiffness. This may lead to excessive BP elevation during exercise and thereby increase LVM.

HbA1c was also shown to be a significant factor associated with LVMI in the present study. Chronic hyperglycemia is well known to promote the formation of advanced glycation end products (AGEs) and reactive oxygen species.²⁸ AGEs were reported to enhance myocardial fibrosis by forming secure bridging of collagen fibers.²⁹ It was also reported that reactive oxygen species activated a protein synthesizer, transcription factor NF- κ B, in cardiomyocytes resulting in cardiac hypertrophy.³⁰ The present study showing that HbA1c was one of the significant factors associated with LVMI is considered to be consistent with the findings in these previous studies.

In the present study, the workload of the ergometer exercise test was set at 75% of maximum HR measured during the treadmill exercise test in order to avoid variations among patients. This workload was of moderate intensity and could be considered an ordinary workload tantamount to that carried out when people perform their ADLs, such as walking at a quick pace or walking up stairs.¹² We speculated that patients with muscle weakness had increased functional arterial stiffness and excessive BP elevation in their daily physical activities. The LVM increase was likely accelerated in these patients because

they suffered frequently from pressure overload in ordinary ADLs. One study reported that increased functional arterial stiffness predicted the severity of atherosclerosis one year later in patients with hypertension.³¹ Furthermore, we found that the increase in functional arterial stiffness was associated with LVM increase. Thus, cardiovascular condition should be monitored not only during rest, but also during exercise in order to prevent LVM increase in patients with hypertension, particularly in those who are older or are physically inactive.

This study has some limitations, the first of which is the cross-sectional design. We did not examine the protective effects of increasing muscle strength against LVM increase. Future prospective clinical studies should determine whether increasing muscle strength through exercise training can suppress the elevation of functional arterial stiffness and BP during exercise, and thereby protect patients from LVM increase. Second, we speculated that inactive and weak muscles accumulated more lactate and consequently stimulated more sympathetic activity during exercise, as compared with active and strong muscles, and that this led to LVM increase. However, we did not measure lactate levels in muscle. In future studies, it will be informative to compare lactate content in muscles and sympathetic activity during exercise between patients with weak muscles and those with strong muscles. Third, although patients were administered various kinds of antihypertensives, we did not assess the effect of each antihypertensive on BP elevation during exercise. Therefore, it will be important to evaluate the relationship between muscle weakness and LVM in-

crease in patients with hypertension who are treated with the same kinds of antihypertensives.

In conclusion, our findings suggest that muscle weakness is associated with an increase of LVM through increased functional arterial stiffness and excessive BP elevation during exercise in patients with hypertension.

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