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RELATIONSHIP BETWEEN WITHIN-VISIT BLOOD PRESSURE VARIABILITY AND SKELETAL MUSCLE MASS

K.-I. KIM[1], M.-G. KANG[1], S.-J. YOON[2], J.-Y. CHOI[1], S.-W. KIM[1], C.-H. KIM[1]

1. Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Republic of Korea; 2. Department of Internal Medicine, Kangwon National University Hospital, Republic of Korea. Corresponding author: Kwang-il, Kim, MD, PhD, Professor, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro, 173 Beon-gil, Bundang-gu, Seongnam-si, Kyeongi-do, 13620, Republic of Korea. E-mail: kikim907@snu.ac.kr; Telephone: +82-31-787-7032; Fax: +82-31-787-4052

Abstract: Sarcopenia, defined as loss of skeletal muscle mass and function with age, is an important health issue in aging society. We tried to investigate the relationship between blood pressure variability and skeletal muscle mass in nation-wide large population cohort. This cross-sectional study was based on data acquired in the Korea National Health and Nutrition Examination Survey (KNHANES), conducted from 2009 to 2011 by the Korean Centers for Disease Control & Prevention. We included 14,481 participants (age ≥ 20 years, male 6,302) for the analysis who had both blood pressure and whole-body dual energy X-ray absorptiometry (DXA) scan data. As an intra-individual within-visit blood pressure variability index, we calculated standard deviation (SD), coefficient of variation (CV), and maximum minus minimum BP difference (MMD) of systolic and diastolic blood pressure, which was measured 3 times. Appendicular skeletal muscle mass (ASM) was the sum of lean masses of both arms and legs. We adjusted ASM by body mass index. Significant inverse relationship was observed between blood pressure variability index (SD, CV, and MMD) and adjusted ASM. Blood pressure variability index were significantly higher in the lowest ASM quintile group both in male and female participants ($p<0.001$). In multivariate analysis, blood pressure variability index were significantly associated with ASM, even after adjusting confounding factors ($p<0.001$). In conclusion, hemodynamic influence may play an important role in the development of sarcopenia.

Key words: Blood pressure variability, cohort, skeletal muscle mass.

Introduction

Sarcopenia, defined as loss of skeletal muscle mass and function with age, is an important health issue. Especially, the clinical significance of sarcopenia will be greater in the near future due to the increase of aging population. Sarcopenia is associated with adverse outcomes such as falls, fracture, and disability (1, 2). Furthermore, sarcopenia, especially with central obesity, is associated with greater risk of cardiovascular disease (3).

Several mechanisms have been proposed for the underlying cause of sarcopenia. In other words, neuropathic, hormonal, immunological, nutritional and physical activity factors are reported to be involved in the development or progression of sarcopenia (4). However the exact mechanism of sarcopenia has not yet been clearly identified.

Adequate blood flow supply is essential for the skeletal muscle tissue. Accordingly, low skeletal muscle capillarization can be a contributing factor of sarcopenia or reduced exercise capacity in older adults by limiting diffusion of substrates, oxygen, hormones, and nutrients (5). In other words, inadequate blood flow supply to skeletal muscle might be associated with the progression of skeletal muscle mass loss with aging.

Blood pressure variability (BPV) is known to be an important prognostic factor for coronary heart disease, heart failure, stroke, and cardiovascular or all-cause mortality, independent of the mean blood pressure (BP) (6-8). However, the effect of BPV on the skeletal muscle mass or function has not been fully investigated. Increased BPV is associated with arterial stiffness, thus related with impairment of peripheral circulation. In other words, exaggerated fluctuations in systemic BP could result in repeated episodes of hypoperfusion causing tissue injury and cell death, particularly in vulnerable individual such as elderly people. Accordingly, there may be a relationship between BPV and skeletal muscle mass. Thus, we aimed to investigate the relationship between BPV and skeletal muscle mass in nation-wide large population cohort.

Methods

Study Population

This cross-sectional study was based on data acquired from the Korea National Health and Nutrition Examination Survey (KNHANES), conducted from 2009 to 2011 by the Korean Centers for Disease Control & Prevention. KNHANES have been conducted to assess the health and nutritional status of Koreans, monitor trends in health risk factors and the prevalence of major chronic diseases, and provide data for the development and evaluation of health policies and programs in Korea. Detailed information regarding KNHANES described elsewhere (9). We included 14,481 participants (age ≥ 20 years, 6,302 male) for the analysis who had both BP and whole-body dual energy X-ray absorptiometry (DXA) scan data. This study was approved by the Institutional Review Board of Seoul

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Table 1
Clinical and blood pressure characteristics of study population according to quintile group of axial skeletal muscle mass

(A) Male participants (N=6,302)						
	1Q (N=1213)	**2Q (N=1266)**	**3Q (N=1267)**	**4Q (N=1274)**	**5Q (N=1282)**	**P value**
Age (year)	60.8 (13.5)	54.5 (14.5)	49.0 (14.7)	45.6 (14.1)	38.1 (12.5)	<0.001
HT, n (%)	706 (58.9%)	582 (46.2%)	484 (38.4%)	405 (31.9%)	242 (18.9%)	<0.001
DM, n (%)	268 (22.9%)	172 (14.0%)	136 (11.1%)	89 (7.3%)	42 (3.4%)	<0.001
Current smoking, n (%)	386 (32.1%)	487 (38.7%)	577 (45.8%)	599 (47.2%)	632 (49.5%)	<0.001
Regular exercise, n (%)	133 (11.1%)	114 (9.1%)	160 (12.7%)	174 (13.7%)	205 (16.0%)	<0.001
Obesity, n (%)	604 (49.8%)	536 (42.3%)	487 (38.4%)	382 (30.0%)	264 (20.6%)	<0.001
Hypercholesterolemia, n (%)	197 (16.8%)	173 (14.1%)	135 (11.0%)	127 (10.4%)	55 (4.4%)	<0.001
Low HDL-cholesterolemia, n (%)	505 (42.8%)	452 (36.6%)	456 (37.1%)	410 (33.4%)	284 (22.8%)	<0.001
SBP (mmHg)	130.0 (17.2)	127.0 (16.4)	123.7 (16.0)	121.5 (14.8)	117.3 (12.7)	<0.001
DBP (mmHg)	80.7 (10.9)	81.6 (10.7)	81.2 (10.1)	80.8 (10.2)	78.9 (9.9)	<0.001
CV-SBP (mmHg)	3.2 (2.1)	3.2 (2.1)	3.0 (2.0)	3.0 (2.0)	2.8 (1.8)	<0.001
CV-DBP (mmHg)	3.5 (2.9)	3.2 (2.5)	3.1 (2.5)	3.2 (2.6)	3.0 (2.5)	<0.001
MMD-SBP (mmHg)	7.7 (5.1)	7.5 (5.0)	6.8 (4.7)	6.7 (4.6)	6.1 (4.2)	<0.001
MMD-DBP (mmHg)	5.2 (4.2)	4.7 (3.8)	4.6 (3.6)	4.6 (3.7)	4.3 (3.4)	<0.001
(B) Female participants (N=8,179)						
	1Q (N=1551)	**2Q (N=1643)**	**3Q (N=1654)**	**4Q (N=1659)**	**5Q (N=1672)**	**P value**
Age (year)	60.6 (14.0)	54.1(14.4)	49.4 (14.6)	44.5(14.4)	39.2 (13.0)	<0.001
HT, n (%)	834 (54.1%)	637 (39.1%)	452 (27.5%)	274 (16.6%)	182 (10.9%)	<0.001
DM, n (%)	244 (16.2%)	172 (10.7%)	142 (8.7%)	96 (6.0%)	40 (2.5%)	<0.001
Current smoking, n (%)	70 (4.6%)	83 (5.1%)	76 (4.6%)	103 (6.3%)	124 (7.5%)	0.001
Regular exercise, n (%)	201 (13.1%)	188 (11.5%)	196 (12.0%)	181 (11.0%)	232 (13.9%)	0.064
Obesity, n (%)	861 (55.5%)	610 (37.1%)	454 (27.4%)	317 (19.1%)	128 (7.7%)	<0.001
Hypercholesterolemia, n (%)	362 (24.0%)	326 (20.3%)	208 (12.8%)	138 (8.6%)	84 (5.2%)	<0.001
Low HDL-Cholesterolemia, n (%)	378 (24.9%)	329 (20.3%)	327 (20.0%)	278 (17.2%)	190 (11.6%)	<0.001
SBP (mmHg)	128.7 (18.6)	123.4 (19.2)	118.9 (17.9)	114.2 (16.3)	110.8 (14.7)	<0.001
DBP (mmHg)	78.2 (9.8)	77.3 (10.1)	75.6 (10.3)	73.8 (9.3)	72.3 (9.5)	<0.001
CV-SBP (mmHg)	3.3 (2.2)	3.3 (2.1)	3.2 (2.1)	3.2 (2.1)	3.0 (2.1)	0.007
CV-DBP (mmHg)	3.6 (3.0)	3.4 (2.7)	3.4 (2.8)	3.4 (2.7)	3.4 (2.8)	0.126
MMD-SBP (mmHg)	7.8 (5.3)	7.5 (5.0)	7.1 (4.8)	6.8 (4.6)	6.3 (4.6)	<0.001
MMD-DBP (mmHg)	5.1 (4.2)	4.7 (3.8)	4.7 (3.9)	4.5 (3.6)	4.5 (3.8)	<0.001

National University Bundang Hospital (IRB No: X-1703-388-905).

Subject Evaluation and Laboratory Study

Blood pressure was measured on the right arm, by trained nurses using a mercury sphygmomanometer (Baumanometer® Desk model 0320, Baum, USA) with an appropriately sized cuff after participants remained still for at least 5 minutes in a sitting posture. During the measurement period, participants were seated leaning against the back of a chair, while their feet remained flat on the floor. The right arm of participant was located at the middle of the cuff to be at the level of the heart. BP was measured 3 times, and the mean BP of the second and third measured value was used to determine the final systolic and diastolic blood pressure. Blood samples were collected from each participant during the survey. Body mass index (BMI) was calculated by dividing body weight (kg) by height^2 (m^2). Waist circumference was measured at the narrowest point from the lower border of the rib cage to the iliac crest.

Within-visit blood pressure variability

As an intra-individual within-visit blood pressure variability index, we calculated standard deviation (SD), coefficient of variation (CV), and maximum minus minimum BP difference

(MMD) of systolic and diastolic blood pressure, which was measured 3 times.

Skeletal muscle mass measurement

Appendicular skeletal muscle (ASM) measurements based on dual-energy X-ray absorptiometry (DXA, QDR 4800A; Hologic, Bedford, MA). ASM was the sum of lean masses of both arms and legs. We adjusted ASM by body mass index (10).

Definitions

Diabetes was defined as fasting blood sugar ≥ 7 mmol/L (126 mg/dL), taking an oral hypoglycemic agent or insulin, or diagnosed with diabetes by a medical doctor. Obesity was defined as BMI ≥ 25 kg/m^2 (11). Smokers were defined as those who smoked 5 packs of cigarettes in a lifetime or more, or they were current smokers. Exercise was defined as either 3 times or more per week of 20 minutes or longer strenuous physical activity, 5 times or more per week of 30 minutes or longer moderate physical activity or walking exercise.

Statistical analysis

All statistical analyses were performed using the SPSS version 19.0 statistical package (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation, and were compared by one-way analysis of variance (One-way ANOVA). Discrete variables were expressed as counts and percentages, and the proportions were compared by using the Chi-square test. We used linear regression analysis to estimate the unstandardized coefficients and 95% confidence intervals (CI), adjusting for factors that were considered to potentially influence the results. All statistical analyses were two-tailed, and P-values<0.05 were taken as statistically significant.

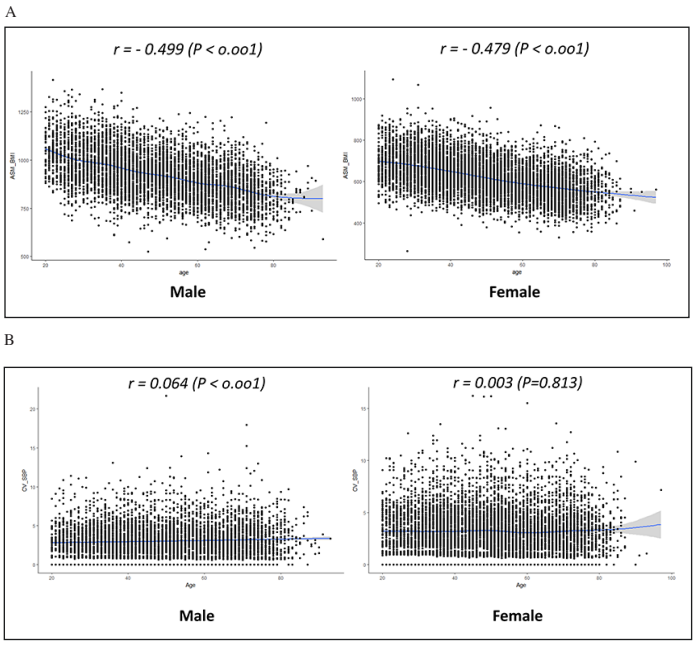
Results

Characteristic findings according to the quintile of skeletal muscle mass

Baseline characteristics of study participants according to skeletal muscle mass quintile group were presented in table 1. Skeletal muscle mass was significantly decreased as the increase of age both in male and female participants (Figure 1A). However, BP variability index were moderately associated with age, only in male participants (Figure 1B). In addition, skeletal muscle mass was inversely associated with prevalence of hypertension, diabetes mellitus, obesity, and hypercholesterolemia, but positively associated with smoking both in male and female participants. Regular exercise was positively associated with skeletal muscle mass in male participants, however, the association was non-significant in female participants.

Figure 1

The relationship between skeletal muscle mass/blood pressure variability and age. Skeletal muscle mass decreases as people get older both in male and female participants (A). But blood pressure variability index were moderately associated with age, only in male participants (B)



Association between skeletal muscle mass and blood pressure variability

Mean systolic and diastolic BP was negatively associated with skeletal muscle mass both in male and female participants (Table 1). Skeletal muscle mass tend to decrease as the increase of CV_SBP (Figure 2). In addition, BP variability index, such as CV and MMD of systolic and diastolic BP were also significantly inversely associated with skeletal muscle mass both in male and female participants (Figure 3).

Figure 2

Mean and 95% CI of body mass index adjusted skeletal muscle mass (ASM_BMI) according to coefficient of variation (CV)-SBP quintile group both in male and female participants

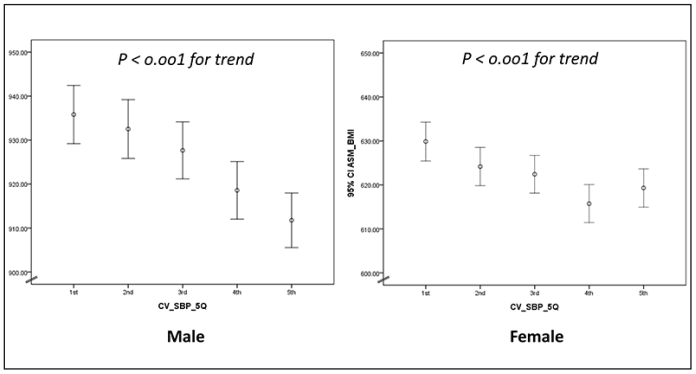


Table 2
Multiple linear regression analysis associated with skeletal muscle mass (ASM-BMI)

(A) Male participants (N=6,302)							
	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**Sig.**	**95% Confidence Interval for B**	
	B	**Std. Error**	**Beta**			**Lower Bound**	**Upper Bound**
Age	-.037	.001	-.421	-31.210	<0.001	-.040	-.035
Mean_SBP	-.005	.002	-.052	-2.960	0.003	-.008	-.002
Mean_DBP	.006	.002	.046	2.800	0.005	.002	.011
CV_SBP	-.016	.008	-.023	-2.001	0.045	-.032	.000
CV_DBP	-.037	.006	-.069	-5.970	<0.001	-.049	-.025
Smoking	.006	.031	.002	.184	0.854	-.055	.067
Exercise	.214	.045	.050	4.731	<0.001	.125	.302
DM	-.121	.024	-.059	-5.135	<0.001	-.167	-.075
HT	-.134	.029	-.079	-4.608	<0.001	-.192	-.077
Obesity	-.576	.030	-.215	-19.070	<0.001	-.636	-.517
Hypercholesterolemia	-.251	.048	-.056	-5.213	<0.001	-.345	-.157
Low HDL-cholesterolemia	-.126	.032	-.042	-3.878	<0.001	-.190	-.062
(B) Female participants (N=8,179)							
	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**Sig.**	**95% Confidence Interval for B**	
	B	**Std. Error**	**Beta**			**Lower Bound**	**Upper Bound**
Age	-.030	.001	-.336	-26.166	<0.001	-.032	-.027
Mean_SBP	.000	.001	-.006	-.334	0.738	-.003	.002
Mean_DBP	.003	.002	.021	1.429	0.153	-.001	.007
CV_SBP	-.025	.007	-.038	-3.867	<0.001	-.038	-.013
CV_DBP	-.024	.005	-.047	-4.741	<0.001	-.034	-.014
Smoking	.042	.058	.007	.718	0.473	-.072	.156
Exercise	.124	.040	.029	3.086	0.002	.045	.203
DM	-.016	.023	-.007	-.674	0.501	-.061	.030
HT	-.139	.028	-.085	-5.040	<0.001	-.193	-.085
Obesity	-.767	.026	-.292	-28.979	<0.001	-.819	-.715
Hypercholesterolemia	-.190	.040	-.047	-4.769	<0.001	-.269	-.112
Low HDL-cholesterolemia	.048	.035	.013	1.393	0.164	-.020	.117

Multivariate analysis affecting on the level of skeletal muscle mass

Because there was significant imbalance of age and other factors which can influence the association between skeletal muscle mass and BP variability, we performed multiple regression analysis to show the independent association between them. After adjusting other variables, BP variability index (CV-SBP & CV-DBP) were significantly associated with skeletal muscle mass both in male and female participants (Table 2).

Discussion

In the present study, we observed that within-visit BPV was related with skeletal muscle mass in national representative cohort. Interestingly, the relationship was significant after adjusting other confounding variables. Considering the effect of BPV on the adequate supply of blood flow to the peripheral tissue, the association between them might suggest the importance of circulatory influence on skeletal muscle loss with aging. However, further studies are required for this hypothesis.

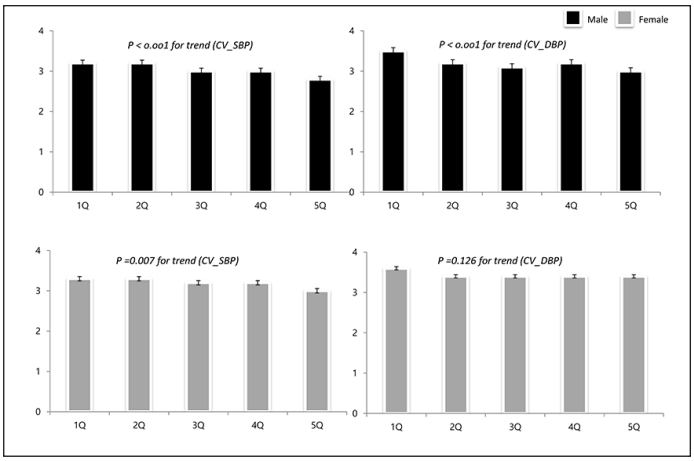
In this study, we measured within-visit BPV, however, there was heterogeneous data regarding the clinical significance of within-visit BPV. Schutte et al failed to show any significant association between within-visit BPV and cardiovascular or all-cause mortality (12). In contrast, Blood Pressure control rate and CArdiovascular Risk profile (BP-CARE) study demonstrated that within-visit BPV has an adverse clinical significance and even when limited to a single visit its assessment may help physicians to better

identify patients at increased cardiovascular risk who require a more intense treatment and a close follow-up (13). Also, a greater within-visit BPV was associated with an increase in the risk of stroke in a post-hoc analysis of the data obtained in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) (14) and correlated with cardiovascular risk profile of subjects representative of the general population of the Korean National Health and Nutrition Examination Survey (KNHNES) (15).

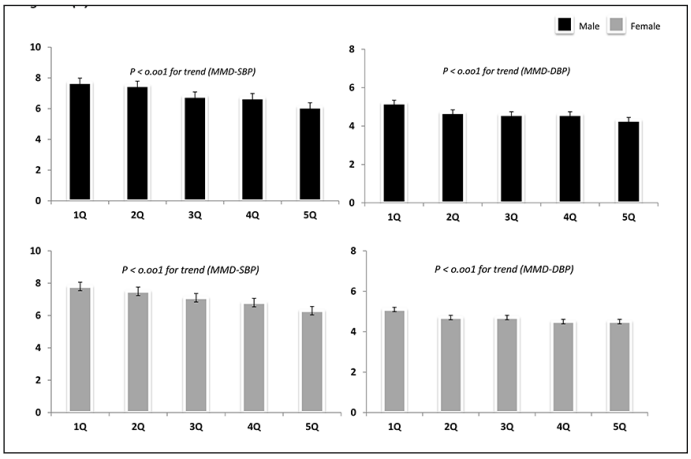
Figure 3

Coefficient of variation (CV) (A) and maximum minus minimum BP difference (MMD) of systolic and diastolic BP (B) according to skeletal muscle mass quintile group both in male and female participants

A



B



The underlying mechanisms linking between body composition and BP or BPV have not been fully investigated. Yano et al reported that excess visceral fat was associated with persistently higher short- and long-term mean BP levels and with lower long-term BPV (16). However, increased BPV is known to be associated with adverse outcome or (sub)clinical organ damage, the inverse relationship between fat deposition and BPV need to be confirmed.

This study has strengths and limitations. First, the study population was drawn from nationally representative samples of older adults in Korea. Therefore, the results of this study can be generalizable to Korean population. Second, statistically significant results were attained after adjusting for multiple covariates. Limitations of this study are as follows. First, causality was unknown because of the cross-sectional study design. Second, data from the KNHANES were based on self-reported questionnaires, which present the limitation of recall bias.

In conclusion, using the national representative database, we showed significant inverse relationship between within-visit blood pressure variability and skeletal muscle mass in Korean population. Considering the underlying mechanism of increased blood pressure variability, hemodynamic influence may play an important role in the development of sarcopenia.

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Conflict of interest: Kwang-il Kim, Min-gu Kang, Sol-Ji Yoon, Jung-Yeon Choi, Sun-wook Kim, and Cheol-Ho Kim declare that they have no conflict of interest.

Ethical standard: This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No: X-1703-388- 905).

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