Relationship Between Mitral Leaflet Size and Coaptation and Their Associated Factors in Patients with Normal Left Ventricular Size and Systolic Function
Real-Time 3D Echocardiographic Analysis

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Summary
Enlargement of the mitral valve (MV) has gained attention as a compensatory mechanism for functional mitral regurgitation (FMR). We aimed to determine if MV leaflet area is associated with MV coaptation-zone area and identify the clinical factors associated with MV leaflet size and coaptation-zone area in patients with normal left ventricle (LV) systolic function and size using real-time 3D echocardiography (RT3DE).

We performed RT3DE in 135 patients with normal LV size and ejection fraction. MV leaflet and coaptation-zone areas were measured using custom 3D software. The clinical factors associated with MV leaflet and coaptation-zone areas were evaluated using univariate and multivariate linear regression analyses.

There was a significant relationship between MV leaflet and coaptation-zone areas ($r = 0.499$, $P < 0.001$). MV leaflet area was strongly associated with body surface area (BSA) ($r = 0.905$, $P < 0.001$) rather than LV size and age. MV leaflet area/BSA was independently associated with male gender ($P = 0.002$), lower diastolic blood pressure ($P = 0.042$), and LV end-diastolic volume (LVEDV) index ($P = 0.048$); MV coaptation-zone area/BSA was independently associated with lower LVEDV index ($P = 0.01$).

In patients with normal LV systolic function and size, MV leaflet size has a significant impact on competent MV coaptation. MV leaflet area might be intrinsically determined by body size rather than age and LV size, and the MV leaflet area/BSA is relatively constant. On the other hand, some clinical factors might also influence MV leaflet and coaptation-zone area.

Key words: Mitral valve, Valve leaflet, Valve function, Body size, Standardization

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lation as reference data before examining patients with FMR who have increased stretch force on the mitral leaflets due to LV dilation. The goal of this study was to determine whether MV leaflet area is associated with MV coaptation-zone area and identify the clinical factors associated with mitral leaflet size and coaptation-zone area in patients with normal LV systolic function and size using real-time 3D echocardiography (RT3DE).

Methods

Study subjects: We consecutively acquired 3D echocardiographic volume data in subjects who underwent conventional echocardiography using iE33 (Philips, Andover, MA, USA) for screening or assessing heart disease. These subjects visited our hospital for medical care or suspicion of various kinds of disease. Out of the pooled 3D data set, we consecutively screened our study subjects according to our 2D echocardiographic screening criteria and added retrospective 3D echocardiographic analysis. Our 2D echocardiographic screening criteria was subjects with normal LV dimensions (an indexed LV end-diastolic diameter < 3.3 cm/m²) and systolic function (LV ejection fraction ≥ 50%) without regional LV wall motion abnormalities in a mixed clinical conditions. Consequently, the study enrolled 251 patients with normal LV dimension and ejection fraction. We excluded patients with cardiomyopathy, atrial fibrillation, and significant valvular heart disease, except FMR in which MV is structurally normal and ejection fraction as reference data before examining patients with FMR who have increased stretch force on the mitral leaflets due to LV dilation. The goal of this study was to determine whether MV leaflet area is associated with MV coaptation-zone area and identify the clinical factors associated with mitral leaflet size and coaptation-zone area in patients with normal LV systolic function and size using real-time 3D echocardiography (RT3DE).

Conventional echocardiography: Conventional echocardiography was consecutively performed in a prospective fashion. To screen for valvular stenosis or regurgitation, 2D and color Doppler imaging were performed. LV mass and left atrial (LA) volume index were measured with 2D echocardiography, according to the guidelines. We used the cube formula to calculate LV mass during end-diastolic period: LV mass (g) = 0.8 × 1.04 × [(IVST + LVID + PWT)³ − LVID³] + 0.6 (g) (IVST, interventricular septal wall thickness; LVID, LV internal diameter; PWT, posterior wall thickness). LA volume index was calculated as LA volume/body surface area (BSA). LA volume was measured using the biplane area-length method. LA volume index was calculated as LA volume/BSA. We obtained transmitral diastolic flow by pulsed-wave Doppler from the apical four-chamber view. Peak velocities of the early (E-wave) and late (A-wave) phases of the mitral inflow pattern from Doppler recordings were measured in the apical four-chamber view, and their ratio (E/A) was calculated. The peak early diastolic (e’) velocity of the septal mitral annulus was measured by pulsed tissue Doppler imaging in the apical four-chamber view. The ratio of the E-wave to the e’ velocity (E/e’) was calculated as an index of LV filling pressure. The severity of MR was semiquantitatively graded by color Doppler studies of the spatial distribution of the regurgitant jet, and the proximal isovelocity surface area method was applied to quantify the severity of MR only in cases assumed to have moderate or severe MR. Our echocardiographic machines and laboratory are maintained under the guidelines of the Japanese Society of Echocardiography.

3D echocardiographic data acquisition and LV volume measurement: We used an iE33xMATRIX system (Philips, Andover, MA, USA) equipped with a highly ergonomic X5-1 transducer for RT3DE acquisition. Transthoracic 3D images were taken from the apical window during a breath hold with the patient in the lateral decubitus position. Full-volume 3D volumetric data were obtained by combining four ECG-triggered, wedge-shaped sub-volumes. The recorded RT3DE data sets included the complete MV anatomic apparatus and the entire LV in the pyramidal data set. Frame rates (16-22 frames/second) were selected based on imaging depth (12-16 cm). The 3D images were digitally stored by experienced sonographers and then transferred to a workstation. We used commercially available Q-lab 3D computer software (Philips, Andover, MA, USA) to determine the LV end-diastolic and end-systolic volumes (LVEDV and LVEVS). The cavity of the LV in each image plane was manually traced, and the LV volume was calculated using the multiplanar Simpson method. Ejection fraction (EF%) was calculated as follows: EF% = 100 × (LVEDV − LVEVS) / LVEDV.

3D echocardiographic quantification of the mitral complex: Custom software (Realview, YD, NARA, Japan) was used to analyze the mitral complex geometry from the RT 3DE volume data, according to previous studies. Initially, the time of MV closure onset was identified. The 3D volumetric image was automatically cropped into 18 se-
The mean tenting height was calculated as the average distance between the annular plane and the tethered leaflets. Tenting volume was determined as the volume enclosed between the annular plane and the mitral leaflets. MV leaflet size was determined as the product of tenting height and tenting area. MV coaptation-zone area was calculated by subtracting the tenting area at the time of MV closure onset. MV coaptation-zone area was then automatically reconstructed by rotation of the MV annulus in the sagittal plane and MV leaflets in the frontal plane in each segmented image, and these images were used to quantify parameters of MV geometry at the onset of MV closure. The same images of the mitral apparatus at mid-systole, AL indicates anterolateral and postero medial papillary muscle. The timing of mid-systole was determined, and the MV coaptation-zone area was calculated by subtracting the MV tenting area at mid-systole from the MV tenting area at the closure onset (Figure 1A and B). To assess the reproducibility of 3D echo quantification of mitral leaflet size and coaptation-zone areas, two independent observers performed 3D echocardiographic measurements and one observer subsequently repeated the measurements in 10 cases. In addition, an observer repeatedly performed the same measurements using two images from different heartbeats in the same patients to assess the inter-beat (beat-by-beat) reproducibility.

**Statistical analysis:** All data were expressed as the mean ± SD for continuous variables and as percentages for categorical variables, and all statistical analyses were conducted utilizing SPSS24.0 software (SPSS Inc, Chicago, IL, USA). Pearson’s linear correlation analysis was used to determine the correlations between the MV parameters and the echocardiographic and clinical variables. Multivariate linear regression analysis was performed to assess the factors that determined the MV leaflet area and

![Figure 1](image-url)
coaptation-zone area. Variables with $P < 0.1$ in univariate analysis were incorporated into the multivariate linear regression model. Statistical significance was defined as a two-tailed $P$ value $< 0.05$.

**Results**

Of the 251 enrolled cases, 76 were considered to be inadequate for 3D echo analysis because of poor 3D echocardiographic images of MV. Consequently, we performed 3D echo analysis in 175 out of 251 cases (69.7%) in this study. Then, we excluded 40 cases without normal LV for 3D echo analysis because of poor 3D echocardiographic images of MV. Consequently, we performed 3D echo analysis in 175 out of 251 cases (69.7%). In univariate analysis, MV leaflet area/BSA was significantly associated with BSA, age, LV size, and LVEDV, and LVESV (Figure 3 and Table III), but these associations were weaker than the associations with MV leaflet area. In multivariate analysis, LVEDV was independently associated with MV leaflet area, whereas LVEDV had a greater influence on MV leaflet area, whereas LVEDV had a greater influence on MV coaptation-zone area.

In light of the close relationship between MV leaflet area and BSA in our results, we indexed MV leaflet area and coaptation-zone areas by BSA, and the associations between these indexed parameters and the clinical and echocardiographic parameters were examined by univariate and multivariate linear regression analyses (Table IV). In univariate analysis, MV leaflet area/BSA was significantly associated with male gender, lower diastolic blood pressure, LVEDV index, LVESV index, and LV mass index. MV coaptation-zone area/BSA was significantly associated with LVEDV index and LVESV index. In multivariate analysis, male gender, diastolic blood pressure, and LVEDV index were independently associated with MV leaflet area/BSA, and LVEDV index was independently associated with MV leaflet area/BSA.

**Discussion**

In this study, we found a significant relationship between MV leaflet and coaptation-zone areas in subjects who had preserved LV ejection fraction and no LV dilation. When we explored the clinical factors associated

| Table I. Patient Characteristics and Echocardiographic Parameters |
|---------------------------------------------------------------|
| Variables | $n = 135$ |
| Age (years) | $61 \pm 15$ |
| Male | $83 (61.5\%)$ |
| Body surface area (m$^2$) | $1.7 \pm 0.2$ |
| Body mass index (kg/m$^2$) | $24.4 \pm 4.2$ |
| Heart rate (bpm) | $70 \pm 2$ |
| Systolic blood pressure (mmHg) | $138 \pm 22$ |
| Diastolic blood pressure (mmHg) | $78 \pm 13$ |
| Comorbidities | |
| Hypertension | $64 (47.4\%)$ |
| Type II diabetes mellitus | $19 (14.1\%)$ |
| Dyslipidemia | $43 (31.9\%)$ |
| Coronary artery disease | $11 (8.1\%)$ |
| Ischemic stroke | $5 (3.7\%)$ |
| Chronic kidney disease | $18 (13.3\%)$ |
| Hemodialysis | $2 (1.5\%)$ |
| Smoking | $16 (11.9\%)$ |
| 3D echocardiography | |
| LVEDV index (mL/m$^2$) | $54.4 \pm 7.4$ |
| LVESV index (mL/m$^2$) | $8.7 \pm 3.8$ |
| LV ejection fraction (%) | $65.6 \pm 4.9$ |
| 2D echocardiography | |
| LV mass index (g/m$^2$) | $79.7 \pm 15.3$ |
| LA volume index (mL/m$^2$) | $28.6 \pm 9.4$ |
| E/A | $1.0 \pm 0.4$ |
| Septal e’ (cm/second) | $6.4 \pm 2.4$ |
| E/e’ | $11.7 \pm 4.0$ |

LVEDV indicates left ventricular end-diastolic volumes; LVESV, left ventricular end-systolic volumes; LV, left ventricular; and LA, left atrial.
Table II. Mitral Valve Geometrical Parameters at the Onset of MV Closure and Mid-Systole

| MV variables                        | At MV closure onset | At mid-systole |
|-------------------------------------|---------------------|----------------|
|                                     | Mean ± SD           | Range          | Mean ± SD | Range          |
| Annular area (cm²)                  | 8.8 ± 1.0           | 6.5-11.5       | 7.7 ± 1.0 | 5.4-10.3       |
| Annular circumference (mm)          | 105.7 ± 6.2         | 90.5-121.1     | 99.1 ± 6.5 | 82.9-114.5     |
| AP - diameter (mm)                  | 32.4 ± 2.1          | 28.1-38.1      | 30.3 ± 2.1 | 25.4-35.8      |
| ML - diameter (mm)                  | 34.2 ± 2.2          | 28.5-39.3      | 31.6 ± 2.2 | 26.9-36.4      |
| Annular height (mm)                 | 3.2 ± 0.6           | 1.0-4.9        | 4.0 ± 0.7 | 1.5-5.6        |
| Max tenting length (mm)             | 6.5 ± 1.8           | 3.0-11.2       | 4.8 ± 1.8 | 1.6-9.4        |
| Mean tenting length (mm)            | 3.2 ± 1.1           | 0.8-6.0        | 1.9 ± 1.2 | 0.0-5.4        |
| Tenting volume (cm³)                | 2.2 ± 0.9           | 0.6-5.0        | 1.2 ± 0.6 | 0.2-3.3        |
| Leaflet area (cm²)                  | 11.1 ± 1.6          | 7.5-15.3       | -         | -              |
| Basal-clear-zone area (cm²)         | -                   | -              | 9.3 ± 1.4 | 6.4-14.2       |
| Coaptation-zone area (cm²)          | -                   | -              | 1.8 ± 0.7 | 0.2-4.0        |

AP indicates anterior-posterior; MV, mitral valve; and ML, medial-lateral.

Figure 2. Correlation between mitral valvular leaflet and coaptation-zone areas. MV leaflet area was significantly associated with MV coaptation-zone area (A). This association was also observed when these parameters were indexed by BSA (B).

with MV leaflet area and coaptation-zone area, our major findings were as follows. (1) Body size was the strongest determinant of MV leaflet area in our population. The size of mitral leaflet area might be intrinsically determined by body size in subjects with normal LV size and EF. (2) MV leaflet area/BSA was relatively constant, regardless of differences in the clinical factors. However, LVEDV index or other clinical factors such as low diastolic blood pressure or gender may be associated with MV leaflet area. In particular, LVEDV index was an important determinant of MV leaflet area/BSA. (3) MV coaptation-zone area was also associated with BSA. However, it varied more widely compared with MV leaflet area and was mainly determined by LVEDV rather than BSA.

Previous investigations demonstrated that the measurement of MV annular, tenting, and papillary muscle parameters widely varied in individual patients. Ultrastructural and cellular changes in the mitral leaflets due to chronic mechanical loading have been reported. In addition, reduction in cellularity, disoriented collagen fibers, and increased elastin fibers with reduced mucopolysaccharides were seen in the MV of individuals over 60 years old. Furthermore, previous studies indicated that the MV leaflets were active living structures, with their own metabolic and compensatory mechanisms, and their structure could be modified by various clinical factors. In the MV, there are compensatory and intrinsic metabolism occurring within leaflets, named endothelial-mesenchymal trans-differentiation capacity. This capacity actively enlarges the size of the MV leaflets area and elicits a complex embryonic developmental pathway in leaflet tissue. Histologically, the endothelium cells in MV leaflets under the tethering stress stimulated by transforming growth factor-ß 1 become alpha-smooth muscle actin-positive cells, which results into fibroblast cell transformation and collagen fiber growth. The compensatory capacity and normal metabolism of MV leaflets can be weakened and can disappear when complicated with ischemic cardiac diseases through matrix metalloproteinase-2. However, unlike the aortic valve, structural changes in the MV leaflets related to age, atherosclerosis, and other clinical factors are not well understood.

As shown in this study, the MV leaflet area had a significant relationship with the MV coaptation-zone area, indicating the importance of MV leaflet size for proper MV closure in patients with normal LV size. A reduced
Figure 3. Correlations between mitral valvular leaflet area and body surface area (A), age (B), left ventricular end-diastolic volume (C), and left ventricular end-systolic volume (D). MV leaflet area was strongly associated with BSA than with age, LVESV, or LVEDV.

Table III. Univariate and Multivariate Analyses of the Relationship of MV Leaflet and MV Coaptation Areas with BSA, BMI, Age, and LV Volume

| Variables       | MV leaflet area (cm²) | MV coaptation-zone area (cm²) |
|-----------------|-----------------------|-------------------------------|
|                 | Univariate analysis   | Multivariable analysis        | Univariate analysis   | Multivariable analysis |
|                 | Correlation coefficient | Odds ratio          | P value  | Correlation coefficient | Odds ratio          | P value  |
| BSA (m²)        | 0.905                 | 0.735            | < 0.001 | 0.278               | 0.043            | 0.89     |
| BMI (kg/m²)     | 0.602                 | 0.056            | < 0.001 | 0.138               | 0.336            |          |
| Age (years)     | −0.34                 | −0.009           | < 0.001 | −0.219              | −0.141           | 0.123    |
| LVEDV (mL)      | 0.653                 | 0.337            | < 0.001 | 0.032               | 0.319            | 0.02     |
| LVESV (mL)      | 0.624                 | −0.04            | < 0.001 | 0.427               | 0.084            | 0.55     |

BSA indicates body surface area; BMI, body mass index; LVEDV, left ventricular end-diastolic volumes; and LVESV, left ventricular end-systolic volumes.

MV leaflet area even in patients with normal LV size could result in a reduced MV coaptation-zone area and the generation of FMR. Furthermore, MV leaflet area was associated with BSA, age, and LV size in univariate analysis, and the strongest association was with BSA. Although MV leaflet area slightly decreased with age, age was not independently associated with MV leaflet area in multivariate analysis. Thus, decreased MV area with aging might be mainly related to decreased body size with aging. It is known that LV size can be enlarged in those with acquired conditions that require high cardiac output, such as athletes, patients with anemia, or those on hemodialysis. However, our study suggests that the most important intrinsic determinant of mitral leaflet size might be body size. Our results suggest that it might be reasonable to index MV leaflet area by BSA for comparison among individuals with different clinical characteristics.

MV coaptation-zone area was also associated with BSA, but this association was weaker than the association of MV leaflet area with BSA. In addition, LVEDV index was the only independent determinant of MV coaptation-zone area/BSA, suggesting a close relationship between MV coaptation-zone area and LV size. As previous studies suggested, MV coaptation-zone area, which is an essential component of complete MV closure, is significantly influenced by tethering and the subvalvular appara-
Factors associated with MV leaflet size by RT3DE

Figure 4. Correlations between mitral valvular coaptation-zone area and body surface area (A), age (B), left ventricular end-diastolic volume (C), and left ventricular end-systolic volume (D). MV coaptation-zone area was significantly but weakly associated with BSA, age, LVESV, and LVEDV.

As previous study demonstrated, LV dilation causes MV tethering and the reduction of MV coaptation-zone area. Our results indicate that MV coaptation-zone area might be reduced according to LV size even in subjects with normal range of LV size and that the reduction of MV coaptation-zone area by LV dilation might occur earlier than the compensatory elongation of MV leaflet. On the other hand, MV tethering is associated with not only LV size but also regional LV wall motion abnormality and multiple clinical factors. This multifactorial aspect of MV tethering might account for the more wide variation of MV coaptation-zone area than MV leaflet size in the present study. However, further study is needed to address this issue.

To examine the influence of clinical factors on MV leaflet area, we explored the factors associated with MV leaflet area/BSA. A lower diastolic blood pressure was independently associated with a decreased MV leaflet area/BSA, and male gender and a larger LVEDV index were independently associated with a larger MV leaflet area/BSA. In particular, LVEDV index was strongly associated with MV leaflet area/BSA. Since LV size can change in response to acquired conditions or various heart diseases, the MV leaflet area could be stretched according to LV size, which is the most important factor among the acquired clinical factors, even in patients without significant LV dilation. As for the association between male gender and MV leaflet area/BSA, there might be intrinsic gender differences in MV leaflets size, as well as cardiac chambers. On the other hand, the associations between MV leaflet area/BSA and the clinical factors other than LV size were weak or not significant. We may conclude that MV leaflet size could be influenced by these clinical factors, but it was mainly determined by body size, and MV leaflet area/BSA should remain relatively constant as long as LV size remains within normal limits.

A lower diastolic blood pressure is recognized as a surrogate of increased arterial stiffness. In our study, in patients without significant aortic regurgitation, lower diastolic blood pressure was presumably associated with advanced atherosclerosis. We speculate that degenerative changes due to atherosclerosis, represented by decreased diastolic blood pressure, might be associated with degenerative changes in MV tissue and decreased MV leaflet area. In patients with advanced atherosclerosis, reduced MV leaflet area might be one of possible mechanisms for FMR. On the other hand, other atherosclerotic factors such as systolic blood pressure or the presence of hypertension, diabetes, dyslipidemia, CKD, or smoking did not have statistical significant correlations with MV leaflet area/BSA in the present study. Thus, further investigation is needed to disclose the pathophysiology underlying the association between lower blood pressure and MV leaflet size.

Limitations: Mitral leaflet area was calculated at the onset of mitral leaflet closure. However, it has been shown...
that the mitral leaflet stretches during systole.\textsuperscript{36} Accordingly, the mitral leaflet area that we measured could have been underestimated; thus, the coaptation-zone area could also have been underestimated. However, this should not have influenced the associations between the coaptation-zone area and the clinical factors. Since our study was conducted at a single center, there may have been selection bias in our study population. In this study, we utilized 3D echocardiography to evaluate MV geometry. Although the advancement of 3D echocardiography is remarkable, it still has limited spatial and temporal resolutions. Further advancement of 3D echocardiography or other imaging modalities may bring more novel and precise insight into our study theme. In this study, we examined the reproducibility of 3D measurements using the same data set by two investigators. However, the reproducibility might be decreased if 3D data sets are recorded by a different sonographer even in the same patients. Finally, our study patients did not include patients with significant FMR. Thus, further study is needed to discuss the relationship between MV leaflet area and the mechanisms for FMR. Nevertheless, our study is the first to provide insight into the clinical factors that can reduce MV leaflet coaptation-zone area, which might increase the risk of progressive FMR. Further advancement of 3D echocardiography or other imaging modalities may bring more novel and precise insight into our study theme. In this study, we examined the reproducibility of 3D measurements using the same data set by two investigators. However, the reproducibility might be decreased if 3D data sets are recorded by a different sonographer even in the same patients. Finally, our study patients did not include patients with significant FMR. Thus, further study is needed to discuss the relationship between MV leaflet area and the mechanisms for FMR. Nevertheless, our study is the first to provide insight into the clinical factors that can reduce MV leaflet coaptation-zone area, which might increase the risk of progressive FMR.

**Conclusions**

Even in patients with normal LV systolic function and size, MV leaflet size has a significant impact on competent MV coaptation. MV leaflet area might be intrinsically determined by body size rather than age and LV size, and the MV leaflet area/BSA is relatively constant. MV coaptation-zone area is mainly determined by LV LVEDV. On the other hand, some clinical factors might also influence MV leaflet and coaptation-zone areas.

**Disclosure**

**Conflicts of interest:** The authors declare that they have no relationship with any industry.

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**Table IV.** Univariate and Multivariate Analyses of MV Leaflet Area/BSA and MV Coaptation Area/BSA with the Clinical Factors

| Variables                        | MV leaflet area/BSA (cm\(^2\)/m\(^2\)) | MV coaptation-zone area/BSA (cm\(^2\)/m\(^2\)) |
|----------------------------------|--------------------------------------|-----------------------------------------------|
|                                  | Univariate analysis                  | Multivariate analysis                         | Univariate analysis | Multivariate analysis |
|                                  | Correlation coefficient | P value | Odds ratio | P value | Correlation coefficient | P value | Odds ratio | P value | Correlation coefficient | P value | Odds ratio | P value |
| Age (years)                      | -0.11                                | 0.203   | 0.239     | 0.002   | -0.126                  | 0.147   | 0.075      | 0.387   | 0.017      | 0.846   | 0.042     | 0.346   |
| Male                             | 0.188                                | 0.029   | 0.239     | 0.002   | 0.017                  | 0.846   | 0.042      | 0.346   | 0.042      | 0.346   | 0.042     | 0.346   |
| Heart rate (bpm)                 | -0.065                               | 0.458   | 0.147     | 0.042   | 0.082                  | 0.346   | 0.042      | 0.346   | 0.042      | 0.346   | 0.042     | 0.346   |
| SBP (mmHg)                       | 0.065                                | 0.458   | 0.147     | 0.042   | 0.082                  | 0.346   | 0.042      | 0.346   | 0.042      | 0.346   | 0.042     | 0.346   |
| DBP (mmHg)                       | 0.180                                | 0.036   | 0.147     | 0.042   | 0.082                  | 0.346   | 0.042      | 0.346   | 0.042      | 0.346   | 0.042     | 0.346   |
| Hypertension                     | -0.011                               | 0.902   |           |         | -0.029                  | 0.734   |           |         | -0.029      | 0.734   |           |         |
| Type II diabetes mellitus        | -0.052                               | 0.549   |           |         | -0.047                  | 0.586   |           |         | -0.047      | 0.586   |           |         |
| Dyslipidemia                     | 0.057                                | 0.512   |           |         | 0.02                   | 0.815   |           |         | 0.02        | 0.815   |           |         |
| Coronary artery disease          | 0.029                                | 0.739   |           |         | -0.137                  | 0.112   |           |         | -0.137      | 0.112   |           |         |
| Ischemic stroke                  | -0.021                               | 0.808   |           |         | -0.072                  | 0.408   |           |         | -0.072      | 0.408   |           |         |
| Chronic kidney disease           | -0.008                               | 0.922   |           |         | -0.043                  | 0.620   |           |         | -0.043      | 0.620   |           |         |
| Hemodialysis                     | 0.049                                | 0.573   |           |         | -0.033                  | 0.702   |           |         | -0.033      | 0.702   |           |         |
| Smoking                          | -0.058                               | 0.503   |           |         | 0.021                   | 0.813   |           |         | 0.021       | 0.813   |           |         |
| LVEDV index (mL/m\(^2\))         | 0.506                                | <0.001  | 1.076     | 0.048   | 0.363                  | <0.001  | 0.297     | 0.01    | 0.029      | 0.531   | 0.042     | 0.346   |
| LVESV index (mL/m\(^2\))         | 0.444                                | <0.001  | -0.845    | 0.298   | 0.289                  | <0.001  | 0.07      | 0.531   | 0.289      | 0.531   | 0.289     | 0.531   |
| LV ejection fraction (%)          | -0.161                               | 0.062   | -0.667    | 0.259   | -0.077                  | 0.376   |           |         | -0.077      | 0.376   |           |         |
| LV mass index (g/m\(^3\))       | 0.253                                | 0.003   | 0.083     | 0.267   | 0.165                  | 0.055   | 0.06      | 0.483   | 0.165      | 0.055   | 0.06      | 0.483   |
| E/e'                             | 0.033                                | 0.707   |           |         | -0.88                   | 0.310   |           |         | -0.88       | 0.310   |           |         |
| LA volume index (mL/m\(^2\))     | 0.063                                | 0.469   |           |         | -0.016                  | 0.854   |           |         | -0.016      | 0.854   |           |         |

BSA indicates body surface area; DBP, diastolic blood pressure; LVEDV, left ventricular end-diastolic volumes; LVESV, left ventricular end-systolic volumes; LA, left atrial; MV, mitral valve; and SBP, systolic blood pressure.
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