

Association of Cardiac Hemodynamic Factors With Severity of White Matter Hyperintensities in Chronic Valvular Heart Disease

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 Supplemental content

IMPORTANCE The cerebral white matter hyperintensity (WMH) is frequently noted in patients with chronic heart disease. Long-term alteration of cardiac hemodynamics might have an influence on the mechanism of cerebral WMH.

OBJECTIVE To investigate the association between chronically altered cardiac hemodynamics and severity of cerebral WMH in patients with chronic valvular heart disease.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional analysis identified 303 consecutive patients at a tertiary referral center between 2008 and 2016 who were 50 years or older, and diagnosed with severe chronic valvular heart disease and underwent cardiac catheterization, echocardiography, and received brain magnetic resonance imaging. Among these patients, 71 with other demonstrated cardiac disease, central nervous system disease, and/or without sufficient catheterization data were excluded, and the remaining 232 patients were included in further analyses.

EXPOSURES The site and mechanism of valve diseases, as well as clinical and medication profiles, were reviewed. Cardiac catheterization parameters such as right atrial (RA) mean pressure, right ventricular pressure, and aortic mean pressure were obtained. Comprehensive echocardiographic hemodynamic markers such as left ventricular (LV) ejection fraction, LV mass index, LV end diastolic volume, cardiac index, and E/e' ratio were also obtained.

MAIN OUTCOMES AND MEASURES White matter hyperintensity volume was quantitatively evaluated using volumetric analysis.

RESULTS This study included 232 patients (103 men [44.4%] and 129 women [55.6%]; mean [SD] (range) age, 65.6 [8.8] (51-88) years) in the final analysis. The mean (SD) WMH volume was 5.93 (7.14) mL (median [interquartile range], 4.33 [1.33-8.62] mL), and mean (SD) RA pressure was 10.0 (4.7) mm Hg. From the catheterization data, 147 patients (63.4%) were classified as having a disease involving the mitral valve; 93 (40.1%), aortic valve; 37 (15.9%), tricuspid valve; and 4 (1.7%), pulmonary valve. In multivariate linear regression analysis, adjusting the type and mechanism of valve disease and clinical, echocardiographic, and/or other catheterization parameters, WMH volume was linearly associated with mean RA pressure (B coefficient, 0.702; 95% CI, 0.373-1.031; $P = .001$), along with age (B coefficient, 0.145; 95% CI, 0.029-0.261; $P = .01$) and mean aortic pressure (B coefficient, 0.112; 95% CI, 0.034-0.190; $P = .005$).

CONCLUSIONS AND RELEVANCE Mean RA pressure was independently associated with the WMH volume in chronic valvular heart disease. Chronically altered RA hemodynamics might have a distinct influence on the pathomechanism underlying the development of WMH.

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Cerebral white matter hyperintensity (WMH) is a prevalent consequence of the aging process and has a substantial influence on various medical complications.¹⁻³ Chronic impairment of the fundamental systems for maintaining metabolic homeostasis in the brain, which are cerebral blood vessels and blood-brain barrier (BBB), has been recognized as the main mechanism underlying the development of WMH.^{1,4,5} Recently, impaired clearance of brain metabolites via the glymphatic system has been demonstrated as another major mechanism of WMH.^{3,6,7} Glymphatic system is the route where the cerebrospinal fluid (CSF) enters along the periaxonal space into the brain parenchyma, is mixed with the interstitial fluid, and is cleared out to the perivascular space of the venules, draining waste to perimeningeal lymphatic vessels, deep cervical lymph nodes, and finally to the right atrium (RA) via subclavian veins, jugular veins, or vertebral venous plexus.^{3,6-8}

Because the adequate pulsation of the cerebral penetrating arterioles is crucial for retaining the integrity of those systems, markers for vascular stiffness have been widely investigated in relation with the WMH severity.^{1,9-11} Meanwhile, as the arterial pulse is primarily generated by the left-sided cardiac chambers, their chronically reduced functions are also known to be associated with WMH pathophysiology.¹² However, the impact of chronic hemodynamic changes in right-sided cardiac chambers on the development of WMH have not been elucidated, although the perfusion in brain parenchyma, the integrity of BBB, and glymphatic clearance system are all dependent on the adequate drainage of cerebral veins and lymphatics to the RA, the common downstream pathway of those systems.

Valvular heart disease is a prevalent disorder in older patients and potentially presents multiple complications that require a surgical intervention.^{13,14} Given a valvular heart disease induces chronic alteration in cardiac hemodynamics, and that the detailed hemodynamic status is evaluated with cardiac catheterization and echocardiography under consideration of surgical interventions in most patients with severe valvular heart disease,^{13,14} evaluation of the hemodynamic changes in valve disease in association with the WMH severity may help us to elucidate the pathophysiological role of the heart in the development of WMH.

We hypothesized that various factors reflecting altered cardiac hemodynamics have different value as potential indices for mechanisms underlying WMH. In the current study, we obtained complete hemodynamic data from cardiac catheterization and echocardiography in patients with chronic valvular heart disease and investigated the association between various cardiac hemodynamic factors and the volume of WMH.

Methods

Study Population

All consecutive patients who were 50 years of age or older; diagnosed with valvular heart disease; admitted to a tertiary hospital between January 2008 and June 2016; and had undergone cardiac catheterization, transthoracic echocardiography, and brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) to evaluate whether the pa-

Key Points

Question Is long-term alteration of the cardiac hemodynamics in chronic valvular heart disease associated with on the development of cerebral white matter hyperintensity?

Findings In this cross-sectional study that included 232 consecutive patients with a severe chronic valvular heart disease, cerebral white matter hyperintensity volume was linearly associated with mean right atrial pressure on cardiac catheterization, along with age and mean aortic pressure.

Meaning Long-term elevation of right atrial pressure might be a distinct motive to disturb the cerebral metabolic homeostasis and aggravate the extent of the cerebral white matter hyperintensity.

tient was suitable for undergoing elective surgical intervention was reviewed.¹³ Magnetic resonance imaging were performed as a part of preoperative assessment in our institution to evaluate the risk of developing ischemic or hemorrhagic complications in the brain by the hemodynamic challenges during the surgical treatments.¹⁵ The diagnosis of valve disease was made by an echocardiographic evaluation per the criterion of defining severe valve disease.^{13,14} Patients who had disease durations of 1 year or longer from the initial diagnosis at the time of the catheterization, echocardiography, and MRI evaluations were included, and those studies were performed within 2-week intervals of each other.

Among the initially identified 303 patients, those who fulfilled the following criteria were included in the final study population: (1) had not had a demonstrated cardiac disease other than valve disease (eg, coronary artery disease, cardiomyopathy, pericarditis, or shunt disease); (2) had available complete hemodynamic data (including pressure data of the RA, right ventricle [RV], and aorta) in cardiac catheterization recordings; and (3) did not have a medical condition that may interfere with the exact measurement of WMH burden, such as an acute stroke (<30 days), brain tumor, vascular malformation, or other inflammatory or degenerative disorders involving the central nervous system. Cardiac diseases other than valve diseases were excluded because they might have potential biases on demonstrating the long-term effect of cardiac hemodynamic alteration on the WMH severity. For instance, cardiomyopathy and pericarditis usually have acute or reversible disease courses, and thus the alterations in cardiac parameters are not suitable to be interpreted as having a long-term effect. Coronary artery disease also has a relatively dynamic disease course and shares the risk factors with the systemic arteriolar stiffness. In intracardiac shunt disease, chronically altered arterial oxygen saturation might have a distinct impact on WMH.

According to these criteria, 31 patients with other demonstrated cardiac disease (26 patients demonstrated coronary heart disease; 3, cardiomyopathy or pericarditis; and 2, shunt disease), 5 patients did not have sufficient catheterization data, 28 patients had a recent stroke (<30 days), and 7 patients had a history of other central nervous system disease and were sequentially excluded. The remaining 232 individuals were included (eFigure in the Supplement). The design of this study was reviewed and approved by the institutional review board

of Seoul National University Hospital. Because patient information was anonymized and deidentified prior to our analysis, the requirement for informed consent was waived.

Acquisition of Clinical Data

Clinical profiles, including body mass index (calculated as weight in kilograms divided by height in meters squared), presence of hypertension, diabetes mellitus, hyperlipidemia, smoking in the past 5 years, atrial fibrillation, chronic stroke history, and regular use of medications such as angiotensin-converting enzyme inhibitor or aldosterone receptor blocker, calcium channel blockers, diuretics, and antithrombotic agents were obtained from patient medical records. Decompensated heart failure was defined as reduced left ventricle (LV) ejection fraction (<35%) in echocardiography with chronic clinical symptoms (≥ 6 months) of New York Heart Association functional class III-IV. A patient with evidence of atrial fibrillation from any electrophysiologic evaluations or a documented history of atrial fibrillation was regarded as having atrial fibrillation. Duration of valve disease was estimated with the date of initial diagnosis. History of open heart surgery was also reviewed. Glomerular filtration rate (GFR) was measured with serum creatinine levels.

Acquisition of Cardiac Catheterization Data

Cardiac catheterization was performed in all patients with a percutaneous approach via the femoral artery and vein using a 7.0F or 7.5F balloon-tipped catheter. From the catheterization data, we obtained parameters including RV peak systolic pressure, RV early diastolic pressure, RV end diastolic pressure, mean RA pressure, aortic peak systolic pressure, aortic end diastolic pressure, mean aortic pressure, cardiac index, and mean LV oxygen saturation.¹⁶ Coronary angiography was also performed in most cases (208 of 232 [89.7%]) to exclude a 50% or greater stenosis in the coronary arteries.¹⁴

Acquisition of Echocardiographic Data

A comprehensive 2-dimensional and Doppler echocardiographic examination was performed using commercially available echocardiography devices with a 2.5-MHz transducer by skilled echocardiographers following a standardized protocol.^{17,18} We obtained data including left ventricular end-diastolic diameters (LVEDD), end-diastolic interventricular septal thickness (IVSd), end-diastolic posterior wall thickness (PWD), and LV ejection fraction. Left ventricular end-diastolic volume (LVEDV) was calculated using LVEDD by the Teiholz formula. Left ventricular mass index (LVMI) was measured as: $(0.8 \times \{1.04[(LVEDD + IVSd + PWD)^3 - LVEDD^3]\}) + 0.6$ (g)/body surface area (g/m²). Early-diastolic peak mitral filling velocities (E), mean early septal-mitral-annulus velocity (e'), and the E/e' ratio were also obtained.¹⁷

Classification of Valve Disease

According to the echocardiographic and catheterization evaluations, presence of valve disease categorized as moderate or severe was defined per the previously demonstrated criteria.¹³ Patients were classified according to the presence of each type of valve disease as follows: mitral stenosis, mitral (steno) insufficiency, aortic stenosis, aortic (steno) insufficiency, tricus-

pid, and pulmonary valve disease. Mild or trivial valve disease incidentally found during the evaluations was not counted as significant.¹³ The etiology of valve disease was categorized into rheumatic or nonrheumatic based on the criteria using echocardiographic findings.¹⁹

Analysis of WMH Volume

Magnetic resonance imaging was performed using a 1.5-T scanner (Philips Ingenia) according to protocols that included T1-weighted or T2-weighted images, fluid-attenuated inversion recovery, gradient echo, intracranial time-of-flight angiography, and a contrast-enhanced neck MRA. Intracranial and neck MRA images were reviewed to evaluate whether the patient had a significant stenosis ($\geq 30\%$) in the internal carotid artery or the middle cerebral artery using the established methods for measuring intracranial and/or extracranial stenosis,^{20,21} and fluid-attenuated inversion recovery and gradient echo images to evaluate the presence of preexisting ischemic or hemorrhagic lesions, by a radiologist (Y. J. R.) with 6 years of experience and who was blinded to other clinical data.

For quantitative analysis of WMH volume, fluid-attenuated inversion recovery sequences were registered into an offline workstation. Using semi automated freeware NeuRoi (Nottingham University),^{11,22} WMH was manually identified by a neurologist (W. -J. L.) with 6 years of experience and who was blinded to other clinical data as a hyperintense lesion without central hypointensity in the white matter area excluding the cerebellum or brainstem, and regions of interest were semiautomatically drawn by manually adjusting the signal-intensity ranges. Regions of interest interconnected between the adjacent axial fluid-attenuated inversion recovery images and were combined into 1 object. The total WMH volume was automatically calculated by adding the volumes of each object.^{11,22}

Statistical Analysis

For all statistical analyses, SPSS 21.0 (SPSS Inc) was used. Data are reported as numbers (percentages), mean (SD), or median (interquartile range [IQR]). Pearson correlation coefficients were used to measure correlations between continuous variables and WMH volume. *t* Tests or Mann-Whitney *U* tests were used to compare the WMH volume between 2 subgroups divided by categorical variables. In univariate analyses, variables with *P* values less than .15 were included in a multivariate linear regression analysis. The variance inflation factor was used to assess a multicollinearity between variables in a linear regression analysis. For all analyses, *P* values less than .05 were considered statistically significant.

Results

In total, 232 individuals (103 men [44.4%] and 129 women [55.6%]; mean [SD] [range] age, 65.6 [8.8] [51-88] years) were included in the final analysis. Among the study population, mitral stenosis was present in 47 patients (20.3%), mitral (steno) insufficiency in 100 (43.1%), aortic stenosis in 50 (21.6%), aortic (steno) insufficiency in 43 (18.5%), tricuspid valve disease in 37 (15.9%), and pulmonary valve disease in 4 (1.7%), with a

median (IQR) disease duration of 60 (24-144) months. Patients were diagnosed with rheumatic valve disease in 89 cases (38.4%) and nonrheumatic valve disease in 143 cases (61.6%). The mean (SD) RA pressure was 10.1 (4.7) mm Hg, mean (SD) aortic pressure was 92.7 (13.1) mm Hg, and mean (SD) pulse pressure was 64.4 (22.5) mm Hg. In echocardiography, mean (SD) LV ejection fraction was 57.3% (9.3%), mean (SD) LV mass index was 109.9 (32.5), mean (SD) LVEDV was 138.8 (49.1) mL, and the mean (SD) E/e' ratio was 21.7 (12.7). Magnetic resonance imaging was performed (median [IQR] [range], 0.34 [-1.03 to 1.44] [-8 to 12] days) after catheterization, and most of the patients (131 of 232 [56.5%]) underwent MRI after cardiac catheterization. No patient in this study population exhibited clinical symptoms suggesting a procedure-related acute stroke after the catheterization. Mean (SD) WMH volume was 6.14 (7.20) mL and median (IQR) WMH volume was 4.33 (1.33-8.62) mL (Table 1). Reproducibility for measuring WMH volume, evaluated by reanalyzing 20 randomly allocated MRIs, was 0.999 (95% CI, 0.998-1.000).

Correlation analyses revealed that WMH volume was associated with increasing age ($r = 0.176$; $P = .01$), mean RA pressure ($r = 0.311$; $P < .001$), mean aortic pressure ($r = 0.281$; $P < .001$), RV peak systolic pressure ($r = 0.139$; $P = .04$), RV early diastolic pressure ($r = 0.154$; $P = .02$), and RV end diastolic pressure ($r = 0.156$; $P = .02$), but not with body mass index ($r = -0.027$; $P = .69$), GFR ($r = -0.129$; $P = .05$), aortic pulse pressure ($r = 0.114$; $P = .08$), cardiac index ($r = -0.004$; $P = .96$), LV ejection fraction ($r = -0.078$; $P = .24$), LVEDV ($r = 0.017$; $P = .80$), LVMI ($r = 0.072$; $P = .29$), E/e' ratio ($r = 0.132$; $P = .06$), or disease duration ($r = 0.046$; $P = .49$). Among the 3 RV pressure parameters, only the RV end diastolic pressure was included in the multivariate linear regression analysis, to minimize the effect of multiple colinearity.

For categorical parameters, the mitral (steno) insufficiency category of valve disease (mean [SD], 7.33 [8.86] mL vs 5.24 [5.48] mL; $P = .03$), atrial fibrillation (mean [SD], 7.10 [6.92] mL vs 5.01 [7.44] mL; $P = .03$), the presence of stenosis in the internal carotid artery/middle cerebral artery (mean [SD], 8.11 [2.72] mL vs 6.00 [7.39] mL; $P = .02$), and regular use of antithrombotic agents (mean [SD], 6.83 [7.69] mL vs 4.19 [5.17] mL; $P = .01$) were associated with higher WMH volume. However, none of the conventional vascular risk factors or history of open heart surgery were associated with higher WMH volume (Table 2).

In multivariate linear regression analyses, WMH volume was linearly associated with the mean RA pressure (B coefficient, 0.702; 95% CI, 0.373-1.031; $P = .001$), along with age (B coefficient, 0.145; 95% CI, 0.029-0.261; $P = .015$) and the mean aortic pressure (B coefficient, 0.112; 95% CI, 0.034-0.190; $P = .005$) (Table 3). Variance inflation factor values were less than 1.70 for every factor included in the linear regression analysis.

When the study population was divided into the tertiles of the mean RA pressures (lowest, ≤ 8.0 mm Hg; middle, 8.1-10.8 mm Hg; and highest, ≥ 10.9 mm Hg), age categories (≤ 60 , 61-70, and ≥ 71 years) of higher mean RA pressure appeared to be associated with larger WMH volumes in every age group (all, $P < .01$, Figure 1).

Table 1. Clinical, Catheterization, Echocardiographic, and White Matter Hyperintensity Profiles of the Study Population

| Clinical Profiles | No. (%) |
|--|------------------|
| Age, mean (SD), y | 65.6 (8.8) |
| Male | 103 (44.4) |
| Body mass index, mean (SD) ^a | 22.8 (3.3) |
| Types of valve disease | |
| Mitral stenosis | 47 (20.3) |
| Mitral (steno) insufficiency | 100 (43.1) |
| Aortic stenosis | 50 (21.6) |
| Aortic (steno) insufficiency | 43 (18.5) |
| Tricuspid valve disease ^b | 37 (15.9) |
| Pulmonary valve disease ^c | 4 (1.7) |
| Rheumatic valve disease | 89 (38.4) |
| Non-rheumatic valve disease | 143 (61.6) |
| Estimated disease duration, median (IQR), mo | 60 (24-144) |
| History of open heart surgery | 27 (11.6) |
| Decompensated heart failure | |
| Atrial fibrillation | 102 (44.0) |
| Hypertension | 107 (46.1) |
| Diabetes | 47 (20.3) |
| Hyperlipidemia | 20 (8.6) |
| Smoking in past 5 y | 30 (12.9) |
| Stroke history | 27 (11.6) |
| Stenosis in ICA/MCA ^d | 15 (6.5) |
| Glomerular filtration rate, mean (SD), mL/min | 72.2 (24.0) |
| Regular use | |
| ACEI/ARB | 114 (49.1) |
| Diuretics | 48 (20.7) |
| Calcium-channel blockers | 63 (27.2) |
| Antithrombotic agents | 171 (73.7) |
| Cardiac catheterization data profiles, mean (SD) | |
| RV peak systolic pressure, mm Hg ^e | 47.1 (16.6) |
| RV early diastolic pressure, mm Hg ^e | 12.9 (4.5) |
| RV end diastolic pressure, mm Hg ^e | 4.3 (4.2) |
| Mean RA pressure, mm Hg | 10.1 (4.7) |
| Mean aortic pressure, mm Hg ^f | 92.7 (13.1) |
| Aortic pulse pressure, mm Hg ^f | 64.4 (22.5) |
| Cardiac index, L/min/m ^{2g} | 2.19 (0.76) |
| LV oxygen saturation, % | 95.5 (6.5) |
| Echocardiographic data profiles, mean (SD) | |
| Ejection fraction, % | 57.3 (9.3) |
| LV mass index ^g | 109.9 (32.5) |
| LV end diastolic volume, mL | 138.8 (49.1) |
| E/e' ratio ^h | 21.7 (12.7) |
| Baseline WMH severity profile | |
| WMH volume, mean (SD), mL | 6.14 (7.20) |
| Median (IQR) | 4.33 (1.33-8.62) |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; ICA, internal carotid artery; IQR, interquartile range; LV, left ventricle; MCA, middle cerebral artery; RA, right atrium; RV, right ventricle; WMH white matter hyperintensity.

^a Calculated as weight in kilograms divided by height in meters squared.

^b All patients had tricuspid regurgitation.

^c Three patients with pulmonary stenosis and 1 with pulmonary regurgitation.

^d Five patients with bilateral ICA stenosis, 5 with unilateral MCA stenosis, and 5 with unilateral ICA stenosis.

^e Data set of 229 profiles available.

^f Data set of 230 profiles available.

^g Data set of 217 profiles available.

^h Data set of 204 profiles available.

Table 2. Univariate Analyses for Factors Associated With White Matter Hyperintensity Volume

| Characteristic | WMH Volume, Mean (SD), mL | | P Value |
|---|---------------------------|-------------------|---------|
| | No | Yes | |
| Male | 6.70 (8.37) | 5.43 (5.33) | .18 |
| Type of valve disease | | | |
| Mitral stenosis | 6.46 (7.66) | 4.84 (4.82) | .17 |
| Mitral (steno) insufficiency ^a | 5.24 (5.48) | 7.33 (8.86) | .03 |
| Median (range) | 3.07 (1.15-8.05) | 5.08 (1.70-9.65) | |
| Aortic stenosis | 6.37 (7.61) | 5.29 (5.38) | .35 |
| Aortic (steno) insufficiency | 6.03 (7.45) | 6.59 (6.02) | .65 |
| Tricuspid or pulmonary valve disease | 6.04 (7.44) | 6.63 (5.97) | .64 |
| Rheumatic valve disease ^a | 6.73 (8.34) | 5.19 (4.74) | .11 |
| Median (range) | 4.53 (1.23-8.78) | 3.98 (1.39-8.57) | |
| History of open heart surgery | 5.97 (7.66) | 6.23 (4.97) | .86 |
| Decompensated heart failure | 10.1 (4.7) | 12.1 (7.9) | .46 |
| Atrial fibrillation | 5.01 (7.44) | 7.10 (6.92) | .03 |
| Hypertension | 5.56 (7.92) | 6.52 (6.73) | .29 |
| Diabetes | 5.76 (7.30) | 7.64 (6.62) | .11 |
| Hyperlipidemia ^a | 5.93 (6.36) | 8.32 (13.26) | .44 |
| Median (range) | 4.39 (1.24-8.62) | 4.20 (1.42-10.80) | |
| Smoking in past 5 y | 6.37 (7.53) | 4.67 (4.18) | .17 |
| Stroke history | 6.15 (7.33) | 6.04 (6.29) | .94 |
| Stenosis in ICA/MCA | 6.00 (7.39) | 8.11 (2.72) | .02 |
| Regular use | | | |
| ACEI/ARB | 5.65 (6.59) | 6.74 (7.77) | .25 |
| Diuretics | 6.14 (7.53) | 6.13 (5.80) | .99 |
| Calcium-channel blockers | 5.94 (6.10) | 6.67 (9.57) | .49 |
| Antithrombotic agents | 4.19 (5.17) | 6.83 (7.69) | .01 |

Abbreviations: ACEI, angiotensin converting-enzyme inhibitor; ARB, aldosterone receptor-blocker; ICA, internal carotid artery; MCA, middle cerebral artery; WMH, white matter hyperintensity.

^a Because the equal variance was not assumed, median (interquartile range) was reported.

Table 3. Linear Regression Analyses for Factors Associated With White Matter Hyperintensity Severity^a

| Characteristic | B (95% CI) | β | P Value |
|--|-----------------------------|--------|---------|
| Constant variable | -15.356 (-27.551 to -3.162) | | .01 |
| Age, y | 0.145 (0.029 to 0.261) | 0.167 | .02 |
| Glomerular filtration rate | -0.012 (-0.052 to 0.027) | -0.043 | .54 |
| Mean RA pressure | 0.702 (0.373 to 1.031) | 0.469 | .001 |
| Mean aortic pressure ^b | 0.112 (0.034 to 0.190) | 0.194 | .01 |
| Aortic pulse pressure ^b | -0.277 (-0.601 to 0.046) | -0.177 | .09 |
| RV end diastolic pressure ^c | -0.046 (-0.121 to 0.029) | -0.103 | .23 |
| E/e' ratio ^c | 0.036 (-0.049 to 0.121) | 0.063 | .40 |
| Mitral (steno) insufficiency | 1.096 (-0.954 to 3.147) | 0.075 | .29 |
| Rheumatic valve disease | -0.796 (-2.888 to 1.296) | -0.053 | .45 |
| Atrial fibrillation | 0.100 (-2.252 to 2.452) | 0.007 | .93 |
| Diabetes mellitus | 1.036 (-1.360 to 3.432) | 0.058 | .40 |
| Stenosis in ICA/MCA | 2.888 (-0.695 to 6.470) | 0.106 | .11 |
| Regular use of antithrombotic agents | -0.513 (-3.082 to 2.056) | -0.032 | .69 |

Abbreviations: B, unstandardized coefficient; β, standardized coefficient; ICA, internal carotid artery; MCA, middle cerebral artery; RA, right atrium; RV, right ventricle.

^a R² = 0.263 and P < .001 for the linear regression equation.

^b Data set of 230 profiles available.

^c Data set of 229 profiles available.

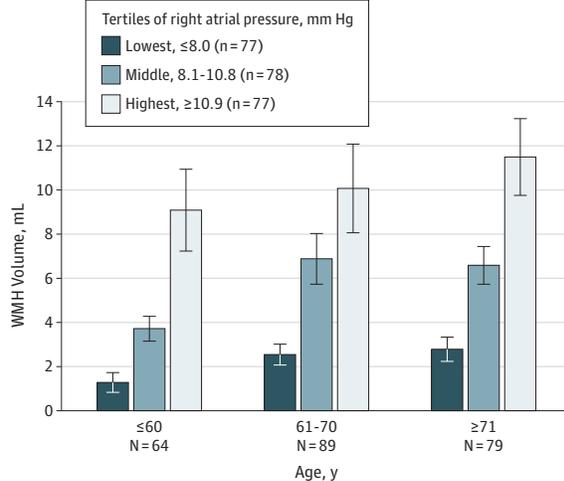
When the hemodynamic parameters, disease duration, and WMH severity were compared between the groups with or without the presence of each valve disease type, mean RA pressure was higher in the group with tricuspid or pulmonary valve disease (*P* = .03) and WMH volume was significantly high in the group with mitral (steno) insufficiency (*P* = .04) (eTable 1 in the Supplement). When multivariate analyses for the hemodynamic factors associated with WMH severity were performed in each valve disease type, mean RA pressure was associated with WMH volume only in the groups with mitral (steno) insufficiency and aortic stenosis (*P* = .002 and *P* = .008,

respectively). However, no marker for LV hemodynamics was significantly associated with the WMH severity (eTable 2 and eTable 3 in the Supplement).

Discussion

In the present study, we observed a linear relationship between the mean RA pressure and cerebral WMH volume in patients with chronic valvular heart disease. Notably, this association was valid after adjustment of the previously

Figure 1. Comparison of White Matter Hyperintensity (WMH) Volumes According to Age and Right Atrial Pressure



Patients were divided into 3 subgroups according to age (≤ 60 , 61-70, and ≥ 70 years) and tertiles of right atrial pressure. In each subgroup of age, the WMH volume increased in correlation with increasing right atrial (RA) pressure. Error bars denote standard errors.

recognized factors associated with arteriolar compliance and LV hemodynamic markers.^{1,9,10} Additionally, age and mean aortic pressure were independently associated with the severity of WMH, which is in concordance with the previous investigations.^{9,10}

Numerous studies²³⁻²⁵ have reported the frequent development of WMH in some pathologic conditions in which cerebral venous pressure (CVP) is elevated, including cerebral arteriovenous fistula and jugular venous reflux. In those studies,²³⁻²⁵ authors argued that elevated CVP may chronically reduce the cerebral perfusion pressure. However, the overt and localized elevation of CVP would more often provoke significant brain swelling and even venous-originated infarction, which are distinct phenomena from the WMH development.²⁶ On the other hand, chronic disorders in the upstream component of cerebral perfusion, such as decreased LV systolic function and intracranial and extracranial artery stenosis, have also been widely associated with cognitive dysfunction and WMH.^{12,27,28} However in the present study, RA pressure was consistently associated with WMH volume independently from the upstream components of cerebral circulation, such as aortic pulse pressure, mean aortic pressure, LV ejection fraction, cardiac index, E/e' ratio, or stenosis in the internal carotid artery/middle cerebral artery. Therefore, our study may provide a novel insight into the pathomechanisms underlying WMH, which is distinct from the traditional chronic hypoperfusion model.

The mean (SD) WMH volumes of the lowest and middle tertiles of RA pressure correspond to the mild degrees of WMH severity (2.23 [2.56] mL and 5.85 [5.53] mL, respectively), whereas the mean (SD) WMH volume in the highest tertile was mild to moderate (10.32 [9.32] mL).²⁹ Although

there is no established cutoff value in WMH volume to be clinically significant, a large cohort study has reported that a population with a WMH severity comparable with the highest mean RA pressure tertile has 10.5 per 100 person-years, incidence of disability and 2.1 per 100 person-years, incidence of death,² which might be a clinically considerable risk.

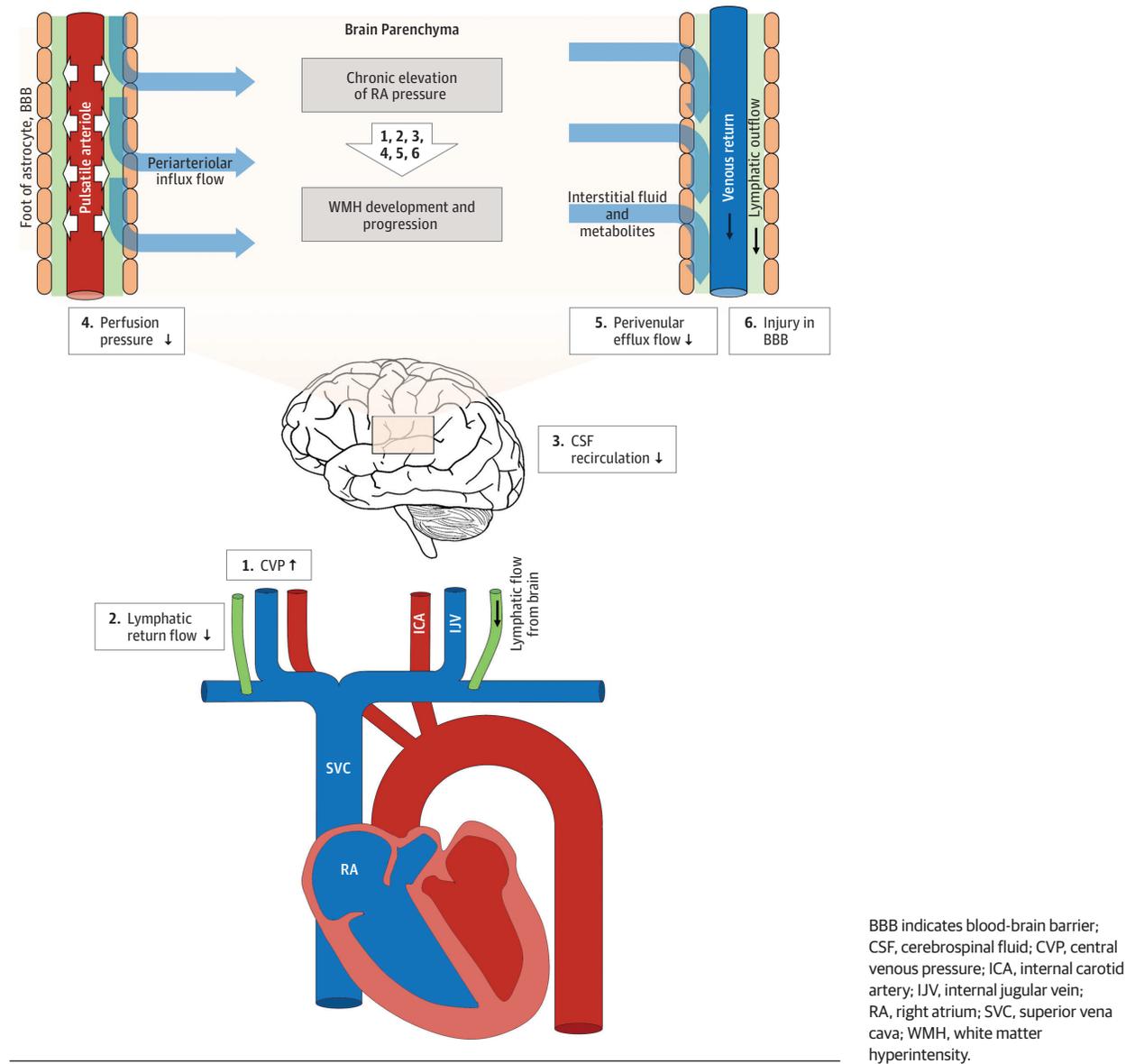
The mean RA pressure was higher than the reference value (2-6 mm Hg) in every type of valve disease,³⁰ indicating the significant influence of chronic valve dysfunction on the hemodynamics of RA. Additionally, no significant association was found between the markers for LV function and WMH severity in any specific type of valve disease. Although the negative associations might be due to the small populations in each valve disease type, it might imply that the association between the mean RA pressure and WMH might be at least partly independent from the type or severity of left-sided valve disease. Therefore, it can be argued that chronic elevation of RA pressure might be a distinct motive to aggravate the WMH severity.

The effect of mean RA pressure on cerebral WMH may be explained by the following pathophysiology. First, mean RA pressure may have multidirectional relationships with the recirculation of the glymphatic, CSF, and cerebral venous system. As the glymphatic flow is ultimately drained to the RA,⁸ an elevation of mean RA pressure may induce a stagnation of the lymphatic return. Moreover, because the mean RA pressure actually represents CVP,^{31,32} its elevation may interfere with the reabsorption of CSF to cerebral veins via the arachnoid villi,³³ disturb the recirculation of CSF, and consequently aggravate parenchymal solute accumulation. Additionally, exit of the parenchymal CSF and interstitial fluid to the glymphatic system may be motivated by the convection of cerebral venous flow. Given that cerebral venous return is affected by the RA pressure change during a pulse cycle,³⁴ chronically elevated mean RA pressure may reduce the cerebral venous return resulting in an inadequate drainage of the glymphatic fluid.^{31,32} Second, elevated RA pressure may chronically injure the BBB.^{31,32} Disturbance of the returning venous flow increases the expression of adhesion molecules such as intracellular adhesion molecule-1 in the vascular endothelium, induces loosening of the BBB, and provokes inflammatory response in the endothelium.^{35,36} Consequently, infiltrated inflammatory cells and swelling in brain parenchyma may facilitate further progression of WMH.^{4,35} Third, the elevation of CVP may reduce the perfusion pressure and result in chronic hypoperfusion of the brain.^{5,23-25} For these reasons, mean RA pressure may exhibit a close relationship to the underlying mechanisms of WMH (Figure 2).

Limitations

The present study has some limitations to be addressed. First, because we included patients with valvular heart disease under consideration for surgical treatment, the study result might not be interpreted as the main WMH mechanism in general geriatric population. Second, owing to the cross-sectional study design, this study did not establish the

Figure 2. Pathomechanistic Links Between Chronic Elevation of Right Atrial Pressure and Development of Cerebral White Matter Hyperintensity



causative effect of RA pressure on chronic progression of WMH. Third, this study did not evaluate the risk of consequent cerebrovascular events from the heart disease and cardiac interventions, as those events are affected by various clinical circumstances. These limitations may be resolved in future prospective cohort studies by applying a predefined evaluation protocol and performing follow-up MRI analyses for chronic progression of WMH.

Conclusions

Along with increasing age and mean aortic pressure, mean RA pressure may be associated with WMH burden in patients with chronic valvular heart disease. This finding may give novel insight into the pathomechanisms of cerebral WMH.

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