Major Non-Cardiac Surgery Is a Risk Factor for Rapid Hemodynamic Progression of Non-Rheumatic Aortic Stenosis

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Background: Inflammatory processes are suggested to play a pathogenic role in the development and progression of non-rheumatic aortic stenosis (AS). Major surgery causes an inflammatory reaction. With the increasing prevalence of non-rheumatic AS, the number of affected patients undergoing major surgery increases. We hypothesized that major non-cardiac surgery (MNCS) could accelerate the progression of non-rheumatic AS.

Methods and Results: We enrolled 218 consecutive patients with non-rheumatic AS who underwent transthoracic echocardiography (TTE) at least twice more than 6 months apart. Study patients were divided into the MNCS group and the non-MNCS group. The MNCS group consisted of patients who underwent MNCS during the TTE follow-up interval. At baseline, peak pressure gradient across the aortic valve (AVG) was similar between the groups. Also baseline clinical characteristics and TTE follow-up interval were similar. The annual rate of peak AVG increase was much higher in the MNCS group than in the non-MNCS group. The proportion of patients with rapid hemodynamic progression was much higher in the MNCS group than in the non-MNCS group. Multiple logistic regression analysis showed that MNCS was an independent predictor of rapid hemodynamic progression of non-rheumatic AS.

Conclusions: The present study indicates for the first time that MNCS is associated with the rapid progression of non-rheumatic AS. (Circ J 2015; 79: 867 – 872)

Key Words: Aortic valve stenosis; Echocardiography; Major non-cardiac surgery

Non-rheumatic aortic stenosis (AS) is the most common valve lesion in the elderly population. In general, the mean pressure gradient across the aortic valve (AVG) increases by 4–7mmHg and the aortic valve area decreases by 0.1cm² each year in non-rheumatic AS, but there is wide interindividual variability.1-4 Recent studies report that a history of hypertension, dilated left atrium, elevated pulmonary artery pressure, and low admission systolic blood pressure are associated with mortality in patients with severe AS.5-7 Previous studies have suggested that inflammatory processes are involved in the development and progression of non-rheumatic AS.8-11 The pathophysiology is in many ways similar to that of atherosclerosis.12,13 Recent studies in humans and mice have documented that acute myocardial infarction (AMI) aggravates preexisting atherosclerosis at a distance via increased inflammatory activity.14-16 Similarly to AMI, major surgery induces an acute major injury accompanied by a major inflammatory reaction, so it may also aggravate preexisting atherosclerosis; furthermore, it may exacerbate preexisting non-rheumatic AS. With the increasing prevalence of non-rheumatic AS, the number of affected patients undergoing major surgery increases. We hypothesized that major non-cardiac surgery (MNCS) could accelerate the progression of non-rheumatic AS and that MNCS could be an independent risk factor for rapid progression of non-rheumatic AS.

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Methods

Patients

We retrospectively selected consecutive patients with non-rheumatic AS who underwent transthoracic echocardiography (TTE) between November 2009 and June 2010 in the echocardiography laboratory of Nara Medical University hospital. Of the selected patients, we enrolled 218 patients who had under-
Exclusion criteria
- LVEF ≤ 50% (n = 11)
- Moderate or severe valvular disease except for AS (n = 17)
- Bicuspid aortic valve or subaortic stenosis (n = 3)
- Myxoma (n = 1)
- Previous CABG (n = 9)
- Previous MVR (n = 3)
- Previous PCI (n = 17)
- Infective endocarditis (n = 3)
- Rheumatic heart disease (n = 9)
- Thoracic radiation (n = 1)
- Pneumonia (n = 6)

**MNCS group n = 12**

**Non-MNCS group n = 126**

**Figure 1.** Patient selection flow chart. AS, aortic stenosis; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MNCS, major non-cardiac surgery; MVR, mitral valve replacement; PCI, percutaneous coronary intervention.

Echocardiography
TTE was performed using a commercially available ultrasound system with the patient in the left lateral decubitus position. All measurements and recordings were obtained according to the recommendations of the American Society of Echocardiography. Multiple transducer positions were used to record maximum aortic jet velocities. Peak AVG was calculated with a modified Bernoulli equation. TTE was performed by experienced sonographers. Echocardiographic measurements were performed by an experienced observer (R.M.).

AS Progression
For analysis of the hemodynamic progression of AS, the annual rate of peak AVG increase during the interval from baseline to follow-up TTE was calculated. Patients with an annual rate of peak AVG increase in the highest quartile were defined as having rapid hemodynamic progression.

Clinical and Laboratory Data
Clinical information, including MNCS, comorbidity, medications, and laboratory data, were obtained by review of the medical records. Chronic kidney disease was defined according to the National Kidney Foundation’s criteria.

Intra- and Interobserver Variability
Reproducibility of the measurement of peak AVG at both baseline and follow-up TTE was assessed in all patients. Intraobserver variability was assessed by a single observer (R.M.) who repeated the measurement of peak AVG. Interobserver variability was assessed by 2 independent observers (R.M. and experienced sonographer).

Statistical Analysis
Continuous data are expressed as mean±SD. Categorical data are expressed as a percentage. Differences between groups
were assessed by the unpaired Student’s t-test for continuous variables and the chi-square test for categorical variables. Multiple logistic regression analysis was used to assess the independent predictors of rapid hemodynamic progression of non-rheumatic AS. In addition to MNCS, clinical characteristics and echocardiographic measurements at baseline TTE were analyzed in the univariate analysis. Variables with P<0.1 on univariate analysis were incorporated into the multivariate analysis. Intra- and interobserver reproducibilities were evaluated by interclass correlation coefficient. Two-tailed P-values <0.05 were considered statistically significant. Statistical analyses were performed using the statistical software StatFlex version 5.0 (Osaka, Japan).

Results

Patients Characteristics
The patient selection flow chart is shown in Figure 1; 80 patients were excluded according to our criteria, so the final study population consisted of 138 patients: 12 patients in the MNCS group and 126 patients in the non-MNCS group. None had hypertrophic obstructive cardiomyopathy or sigmoid septum with significant pressure gradient across the left ventricular outflow tract, which affects the measurement of peak AVG. Atrial fibrillation was not detected in any of the study patients at either baseline or follow-up TTE or during the interval between each TTE. Surgical procedures in the MNCS group were as follows: lobectomy (n=1), mastectomy (n=2), partial colectomy (n=3), cystectomy (n=1), craniotomy (n=1), discectomy (n=2), implant arthroplasty (n=1), and abdominal aortic aneurysm repair (n=1). Baseline clinical characteristics were similar between the MNCS and non-MNCS groups, including comorbidities and medication use (Table 1). C-reactive protein (CRP) levels were also similar between the 2 groups. Baseline echocardiographic data are shown in Table 2. Peak AVG was not significantly different between the 2 groups. LVEF and stroke volume (SV), which affect AVG irrespective of AS severity, were similar between the 2 groups. Left atrial dimension was significantly greater in the MNCS group than in the non-MNCS group.

Table 1. Baseline Clinical Characteristics of Patients With Non-Rheumatic Aortic Stenosis

| Variable                        | MNCS group (n=12) | Non-MNCS group (n=126) | P value |
|---------------------------------|-------------------|------------------------|--------|
| Age, years                      | 74.3±8.0          | 73.7±9.4               | 0.784  |
| Male sex, n (%)                 | 7 (58.3)          | 62 (49.2)              | 0.546  |
| BMI                             | 23.8±3.8          | 22.6±3.7               | 0.327  |
| Comorbidities, n (%)            |                   |                        |        |
| Hypertension                    | 12 (100)          | 103 (81.7)             | 0.105  |
| Diabetes mellitus               | 6 (50.0)          | 39 (31.0)              | 0.179  |
| Dyslipidemia                    | 5 (41.7)          | 56 (44.4)              | 0.853  |
| Ischemic coronary artery disease| 5 (41.7)          | 35 (27.8)              | 0.311  |
| Cerebrovascular disease         | 1 (8.3)           | 18 (14.3)              | 0.567  |
| Peripheral vascular disease     | 1 (8.3)           | 9 (7.1)                | 0.879  |
| Chronic kidney disease          | 8 (66.7)          | 50 (39.7)              | 0.070  |
| Hemodialysis                    | 1 (8.3)           | 22 (17.5)              | 0.418  |
| Anemia                          | 2 (16.7)          | 41 (32.5)              | 0.257  |
| Obesity, n (%)                  | 4 (33.3)          | 26 (20.6)              | 0.308  |
| Ever or current smoker, n (%)   | 3 (unknown, n=4)  | 29 (unknown, n=39)     |        |
| Drug use, n (%)                 |                   |                        |        |
| ACEI                            | 4 (33.3)          | 32 (25.4)              | 0.550  |
| ARB                             | 6 (50.0)          | 61 (48.4)              | 0.916  |
| β-blocker                       | 2 (16.7)          | 35 (27.8)              | 0.406  |
| Statin                          | 3 (25.0)          | 51 (40.5)              | 0.294  |
| CRP (mg/dl)                     | 0.6±1.48          | 0.4±0.93               | 0.676  |

Values are mean±SD or total number (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CRP, C-reactive protein.

AS Progression
Echocardiographic data at follow-up TTE are shown in Table 2. At the time of follow-up TTE, all patients in MNCS group were in a stable state after surgery. Frequency of anemia, which can increase the peak AVG, was not significantly different between the 2 groups at the time of follow-up TTE (data not shown), similarly to the baseline TTE. There was no significant difference in the interval from baseline to follow-up TTE between the 2 groups. At follow-up TTE, peak AVG was significantly higher in the MNCS group than in the non-MNCS group. The annual rate of peak AVG progression was much higher in the MNCS group than in the non-MNCS group (16.9±11.3 mmHg/year vs. 4.6±7.1 mmHg/year, P=0.003) (Figure 2). The highest quartile of annual rate of peak AVG progression was 9.8 mmHg/year. The proportion of patients with rapid hemodynamic progression was much higher in the MNCS group than in the non-MNCS group (9 patients (75.0%) vs. 26 patients (20.6%), P<0.001).

Predictors of Rapid Hemodynamic Progression of AS
Multiple logistic regression analysis showed that MNCS was the strongest independent predictor of rapid hemodynamic progression of non-rheumatic AS (Table 3). Baseline peak AVG was also an independent predictor. Although the baseline left
atrial dimension was significantly greater in the MNCS group than in the non-MNCS group, it was not shown as a significant risk factor.

**Intra- and Interobserver Variability**

Intraobserver reproducibility at both baseline and follow-up TTE was excellent, with the interclass correlation coefficient being 0.994 and 0.996, respectively, for peak AVG. Similar results were obtained for interobserver reproducibility, with interclass correlation coefficient of 0.992 and 0.993, respectively, for peak AVG at baseline and follow-up TTE.

**Discussion**

The present study showed that MNCS is related to rapid hemodynamic progression of non-rheumatic AS and to the best of our knowledge, this is the first study to report this finding. A number of previous studies did not adopt MNCS as a candidate of risk factor, although they did hypertension, diabetes mellitus, hypercholesterolemia and hemodialysis. Taking the high odds ratio of 12.2, after adjustment for other risk factors, physicians should pay an attention to checking not only cardiac function but also aortic valve status when a patient is
undergoing major surgery. If there is non-rheumatic AS before the operation, the physician should carefully follow up AS after the operation. Although the baseline left atrial dimension was significantly greater in the MNCS group than in the non-MNCS group, it was not shown as a significant risk factor. Atrial fibrillation is one of major causes of dilatation of the left atrium, but was not detected in any of the study patients at either baseline or follow-up TTE or during the interval between each TTE. Therefore, it is unlikely that the presence of atrial fibrillation affected the results of this study. The incidence of AS increases with aging. Aged patients often have comorbidities such as malignancies, orthopedic diseases, and aortic diseases, many of which usually require major surgery. It is clinically important to diagnose AS before operation in aged patients. The mechanism responsible for the rapid progression of AS after MNCS is unclear at the present time. Dutta et al.\textsuperscript{14} reported that in experimental animals AMI, another major inflammatory condition, aggravates preexisting atherosclerosis at a distance. It was related to abundant monocyte recruitment by increased supply of hematopoietic stem and progenitor cells from bone marrow via activation of sympathetic activity. We also reported that AMI augments neointimal hyperplasia in a remote artery via activation of a proinflammatory cytokines network in a mouse model.\textsuperscript{15} In a human study, we observed stronger progression of atherosclerosis in the non-culprit coronary artery after emergency coronary intervention in AMI patients compared with after an elective coronary intervention in patients with stable angina.\textsuperscript{16} Thus pathological conditions that produce proinflammatory cytokines and activate sympathetic nervous activity possibly exaggerate atherosclerosis, furthermore non-rheumatic AS.\textsuperscript{8–13} It is likely therefore that MNCS progresses preexisting non-rheumatic AS via increased inflammatory activity in the degenerative aortic valve. Several previous studies revealed an association between increased CRP and progression of non-rheumatic AS,\textsuperscript{23–25} supporting our hypothesis.

### Study Limitations
First, the present study was a retrospective analysis of a small sample from a single center. We cannot exclude the possibility that a bias of small sample size affects our results. To confirm our findings, a large prospective multicenter study is needed. Second, we used AVG to evaluate AS progression, because the aortic valve area was not measured in some of the study patients. AVG decreases as LV contraction and SV reduce. However, we selected only the patients with LVEF >50% and no differences were present in LVEF and SV between the MNCS and non-MNCS groups. Third, the accuracy of measuring peak AVG has a major effect on the results. In this study, intra- and interobserver reproducibilities of the measurement of peak AVG were excellent. Therefore, we think it unlikely that an error in measuring peak AVG had a major effect in this study.

### Table 3. Predictors of Rapid Hemodynamic Progression of AS in Univariate and Multivariate Analyses

| Variable                              | P value  | OR      | 95% CI   |
|---------------------------------------|----------|---------|----------|
| **Univariate analysis**               |          |         |          |
| Age (per year)                        | 0.355    | 1.023   | 0.975–1.072 |
| Male sex                              | 0.206    | 0.605   | 0.278–1.318 |
| BMI (per 1 kg/m²)                     | 0.529    | 0.966   | 0.888–1.076 |
| Obesity                               | 0.773    | 0.870   | 0.337–2.247 |
| Hypertension                          | 0.341    | 1.753   | 0.553–5.560 |
| Diabetes mellitus                     | 0.490    | 0.744   | 0.322–1.721 |
| Dyslipidemia                          | 0.914    | 1.044   | 0.483–2.254 |
| Ischemic coronary artery disease      | 0.622    | 0.804   | 0.338–1.913 |
| Cerebrovascular disease               | 0.553    | 0.702   | 0.218–2.260 |
| Peripheral vascular disease           | 0.687    | 0.720   | 0.145–3.562 |
| Chronic kidney disease                | 0.563    | 0.792   | 0.360–1.744 |
| Chronic hemodialysis                  | 0.714    | 1.214   | 0.431–3.419 |
| Anemia                                | 0.567    | 1.270   | 0.561–2.875 |
| Use of ACEI                           | 0.699    | 1.185   | 0.503–2.793 |
| Use of ARB                            | 0.283    | 1.528   | 0.705–3.311 |
| Use of β-blocker                      | 0.303    | 1.545   | 0.675–3.535 |
| Use of statin                         | 0.984    | 1.008   | 0.461–2.206 |
| CRP (per 0.1 mg/dl)                   | 0.418    | 1.015   | 0.979–1.052 |
| Major noncardiac surgery              | <0.001   | 11.539  | 2.914–45.683 |
| Baseline peak aortic valve gradient (per 5 mmHg) | 0.022 | 1.107 | 1.015–1.207 |
| Baseline IVSth (per 1 mm)             | 0.753    | 1.034   | 0.841–1.269 |
| Baseline LVDD (per 1 mm)              | 0.457    | 0.975   | 0.912–1.042 |
| Baseline LAD (per 1 mm)               | 0.475    | 1.024   | 0.960–1.092 |
| Baseline LVEF (per 1 %)               | 0.350    | 1.027   | 0.971–1.085 |
| Baseline SV (per 1 ml)                | 0.852    | 0.998   | 0.978–1.019 |
| Baseline E/A (per 0.1)                | 0.454    | 0.937   | 0.791–1.111 |
| **Multivariate analysis**             |          |         |          |
| Major noncardiac surgery              | <0.001   | 12.184  | 3.031–48.978 |
| Baseline peak aortic valve gradient (per 5 mmHg) | 0.018 | 1.114 | 1.019–1.218 |

Abbreviations as in Tables 1,2.
Conclusions

The present study provides a new concept for rapid progression of non-rheumatic AS after MNCS. Patients with non-rheumatic AS should be followed carefully after MNCS, especially those with moderate or severe AS. A prospective large study is needed to confirm this hypothesis.

Disclosures

Yoshiki Saito has conflicts of interest to disclose as follows. Honoraria: MSD Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co, Daiichi Sankyo Company Ltd, Otsuka Pharmaceutical Co, Ltd, Pfizer Japan Inc. Research funding: Japan Heart Foundation, The Naito Foundation. Subsidies or donations: MSD Co, Ltd, Mitsubishi Tanabe Pharma Corporation, Daichi Sankyo Company Ltd, Takeda Pharmaceutical Co, Ltd, Novartis Pharma K.K., Shionogi & Co, Ltd. Astellas Pharma Inc, Astellas Pharma K.K., Astellas Pharma US Inc. Commercially, Yoichi Saito has conflicts of interest to disclose as follows. Honoria: MSD Co, Ltd, Kyowa Hakko Kirin Co Ltd. Endowed departments by commercial entities: MSD Co, Ltd.

Other authors have no financial conflicts of interest to disclose.

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