Influence of Left Ventricular Function on the “Aortic Regurgitation Index” Proposed for the Hemodynamic Assessment of Postprocedural Aortic Regurgitation

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Summary

The aortic regurgitation (AR) index, proposed as an objective indicator of postprocedural AR, decreases in proportion to AR severity, besides reportedly providing additional prognostic information. Meanwhile, left ventricular (LV) function has also been considered an essential prognostic factor. This study aimed to clarify whether LV function affected the AR index using cardiac catheterization data.

A retrospective study was performed in patients whose LV function was evaluated using a micromanometer-tipped catheter. Patients with grade 2 or higher AR were excluded to explore non-AR factors affecting the AR index value. The AR index was calculated as a ratio of the gradient between the aortic diastolic blood pressure (DBP) and the LV end-diastolic pressure (EDP) to the aortic systolic blood pressure (SBP): AR Index = [(DBP − LVEDP) / SBP] × 100.

A total of 64 patients [age, 62 (interquartile range: 48-70) years; LV ejection fraction, 19% (16%-26%)] were examined. AR index values ranged from 18.3 to 68.6. Despite having no AR, two patients displayed an AR index < 25, indicating significant AR. Multiple-regression analysis revealed that LV diastolic stiffness (β = −0.750, P < 0.001), LV max dP/dt (β = −0.296, P = 0.006), and heart rate (β = 0.284, P = 0.011) were independent determinants of the AR index value.

Patients with impaired LV diastolic function and preserved systolic function had low AR index values. The additional prognostic information of the AR index may be related to LV diastolic function.

Key words: LV max dP/dt, LV tau, LV diastolic stiffness, LV diastolic function

To date, several studies have demonstrated an association between postprocedural aortic regurgitation (AR) and poor prognosis after transcatheter aortic valve replacement (TAVR). Precise grading of paravalvular AR after valve deployment during TAVR is crucial for determining whether balloon post-dilatation would be necessary. However, paravalvular AR jets are often multiple, eccentric, and quite observer-dependent.

The AR index, calculated as the ratio of the gradient between the diastolic blood pressure (DBP) and the left ventricular (LV) end-diastolic pressure (EDP) to the systolic blood pressure (SBP) [AR Index = ([DBP − LVEDP] / SBP) × 100], had been proposed as an objective indicator of postprocedural AR. The AR index value decreases in proportion to AR severity, with an AR index < 25 indicating significant AR associated with poor prognosis. According to the report by Vasa-Nicotera, et al., the AR index can be used as a predictor of 1-year mortality risk, even after adjusting for postprocedural AR severity. The same researchers stated that the AR index provides additional prognostic information beyond echocardiographic assessment of postprocedural AR severity. No conclusions, however, have yet been reached with regard to what additional prognostic information is provided.

Although LV function has also been considered to be an essential prognostic factor for patients with heart disease, few available studies have investigated effects of LV function, particularly LV functional properties strictly assessed through cardiac catheterization, on the AR index. Micromanometer-tipped catheters, which consist of an ultra-miniature pressure sensor at the distal end of a catheter, provide high-fidelity LV pressure recordings and allow the highly accurate assessment of the hemodynamic function. Hence, this study aimed to clarify whether the LV function can affect the AR index using cardiac catheterization data in patients with no significant AR to eliminate the effects of AR.
Methods

Study subjects: We identified 97 patients with heart failure whose LV function was studied for cardiac resynchronization therapy using high-fidelity LV pressure recordings obtained using micromanometer-tipped catheters. Data regarding demographic and clinical characteristics, echocardiography, and cardiac catheterization were collected from hospital medical records and catheterization reports. The exclusion criteria were as follows: (1) grade 2 or higher AR; (2) moderate to severe aortic stenosis; (3) prior aortic valve replacement or cardiac surgery; (4) unavailability of LV high-fidelity pressure data; and (5) atrial fibrillation. Patients with an AR of grade ≥ 2 were excluded to explore non-AR factors affecting the AR index value. The Institutional Review Board of the National Cerebral and Cardiovascular Center approved this retrospective study (M29-051). The opt-out method was employed, and the need for individual written informed consent was waived. This study was conducted in accordance with relevant institutional guidelines and principles of the Declaration of Helsinki.

Echocardiography: All patients underwent comprehensive echocardiographic examination using a GE Vivid 7 ultrasound machine (GE Healthcare, Milwaukee, WI, USA), including two-dimensional and pulsed-wave, continuous-wave, tissue, and color flow Doppler echocardiography according to the guidelines. Data regarding LV dimensions, LV wall thickness, LV volumes, LV ejection fraction (LVEF), left atrial (LA) dimension, LA volume indexed to the body surface area (LAV index), peak E velocity, E-wave deceleration time, average of mitral annular septal and lateral velocities (e'), E/e', and severity of heart valve disease were extracted. AR severity was integratively graded on a semi-quantitative scale from 0 to 4. LV mass was calculated based on the formula of Devereux11 and was indexed to the body surface area (LV mass index). E/e’/LVEDV was calculated as the echocardiography-derived LV stiffness index.12

Cardiac catheterization: High-fidelity LV pressure waves obtained using a 5-Fr micromanometer-tipped catheter (Millar Mikro-Tip; Millar Instruments, Houston, TX, USA) were digitally stored using a polygraph system (RMC-3000; Nihon Kohden Corporation, Tokyo, Japan). The maximal value of the first derivative of the LV pressure trace (LV max dp/dt, an index of the contractile state) and the time constant of LV isovolumic relaxation (tau, an index of early diastolic relaxation) were calculated automatically from LV pressure waves. Tau was determined by applying monoeponential fitting with a zero asymptote to the LV pressure decay (Weiss formula).13 SBP and DBP were then recorded at the aorta by pulling out the catheter from the left ventricle. Right-sided heart catheterization was performed using a 7-Fr Swan-Ganz catheter (Edwards, Irvine, CA, USA). Cardiac output was determined using the direct Fick method. Oxygen consumption was measured using an expiration gas analyzer (Aeromonitor AE-300S; Minato Medical Science, Osaka, Japan). LV diastolic stiffness, an index of passive ventricular compliance, was evaluated as follows: LV diastolic stiffness = (LVEDP - LV minimum pressure) / stroke volume.14 Given the effects of aortic stiffness on both SBP and DBP, systemic arterial compliance (SAC) was determined as follows: SAC = (SBP − DBP) / stroke volume.15

Statistical analysis: Continuous variables are described as mean ± standard deviation when normally distributed or as median plus interquartile range (IQR) when not. The Shapiro-Wilk test was used to assess normality. Categorical variables are expressed as absolute and relative frequencies. Simple linear regression was applied to identify factors associated with the AR index. Furthermore, a multiple-linear-regression analysis was performed to investigate the effect of LV function on the AR index value. The multivariate model included selected variables, such as age, the heart rate, LV max dp/dt, LV tau, LV diastolic stiffness, and SAC. Statistical analyses were conducted using STATA 14.2 software (StataCorp LP, College Station, TX, USA), with a value of P < 0.05 indicating statistical significance.

Results

Subjects’ characteristics: A total of 64 patients (48 men and 16 women) with a median age of 62 years were ultimately included in this retrospective analysis (Figure 1). Table I summarizes their characteristics. Among the included patients, 39 (61%) had moderate to severe heart failure symptoms [New York Heart Association functional class III or IV]. The etiology of heart failure included non-ischemic cardiomyopathy in 31 (80%) patients and coronary artery disease in 13 (20%) patients. The median serum BNP level was 337.0 (IQR: 186.0-621.0) pg/mL. All patients had LV systolic dysfunction with a median LVEF of 19%. Their e’ value decreased along with LA dilatation, indicating that they also had LV diastolic dysfunction.

Hemodynamic parameters of cardiac function measured using catheterization: The median pulmonary artery wedge pressure (PAWP), systolic pulmonary artery pressure (PAP), SBP, and LVEDP were 6.5 (4.0-11.0), 23.0 (19.5-30.0), 92 (82-104), and 11.0 (8.0-14.5) mmHg, respectively. LV max dp/dt was 795 ± 178 mmHg/second, and LV tau was 58.7 (49.9-64.0) ms. The stroke volume was 54 (46-60) mL, yielding LV diastolic stiffness of 0.148 (0.102-0.177) mmHg/mL. The SAC was evaluated as 1.462 (1.187-1.706) mL/mmHg.

Aortic regurgitation index value: AR index values ranged from 18.3 to 68.6 (median, 46.2; mean, 45.3). Among the included patients, 55 (86%) had no AR, whereas the remaining 9 (14%) had AR grade 1+. As illustrated in Figure 2, the median AR index value was 46.4 in those without AR and 40.0 in those with AR grade 1+. Although not statistically significant, the AR index value was lower in those with AR grade 1+. Particular attention was paid to two patients who displayed an AR index < 25 despite having no AR (Figure 2).

Correlation between clinical parameters and the AR Index: Clinical factors associated with the AR index were identified by performing a simple regression analysis, as shown in Table II. Accordingly, the AR index value was negatively correlated with peak E velocity, E/e’/LVEDV, PAWP, systolic PAP, LVEDP, LV tau, and LV diastolic...
stiffness. Figure 3 presents the scatter plots for the AR index and parameters, showing a significant correlation between the AR index and E/e’/LVEDV, LV tau, and LV diastolic stiffness.

Table III presents results of the multiple-linear-regression analysis to select LV function parameters independently associated with the AR index value. The multivariate model (Table III) indicated that LV diastolic stiffness ($\beta = -0.750$, $P < 0.001$), LV max dP/dt ($\beta = -0.296$, $P = 0.006$), and the heart rate ($\beta = 0.284$, $P = 0.011$) were independent determinants significantly associated with the AR index.
Table II. Simple Linear Regression Analysis of the Relationship Between the AR Index and Clinical Parameters

| Parameters                               | Coefficient | Beta   | P      |
|------------------------------------------|-------------|--------|--------|
| Age, years                               | −0.084      | −0.134 | 0.290  |
| Body mass index, kg/m²                    | 0.209       | 0.085  | 0.504  |
| Cardiac catheterization                   |             |        |        |
| PAWP, mmHg                                | −0.745      | −0.469 | <0.001 |
| Systolic PAP, mmHg                        | −0.342      | −0.505 | <0.001 |
| Systolic blood pressure, mmHg             | −0.067      | −0.126 | 0.322  |
| LVEDP, mmHg                               | −0.933      | −0.693 | <0.001 |
| LV max dP/dt, mmHg/second                 | −0.008      | −0.166 | 0.189  |
| LV tau, ms                                | −0.328      | −0.401 | 0.001  |
| LV diastolic stiffness, mmHg/mL           | −59.965     | −0.536 | <0.001 |
| SAC, mL/mmHg                              | 4.020       | 0.188  | 0.137  |
| Stroke volume, mL                         | −0.136      | −0.198 | 0.116  |
| Heart rate, bpm                           | 0.185       | 0.137  | 0.279  |

AR indicates aortic regurgitation; LV, left ventricular; EF, ejection fraction; LAV, left atrial volume; E-DcT, E-wave deceleration time; e’, early diastolic mitral annular velocity; EDV, end-diastolic volume; PAWP, pulmonary artery wedge pressure; PAP, pulmonary artery pressure; EDP, end-diastolic pressure; SAC, systemic arterial compliance; and bpm, beats per minute.

Discussion

The major findings of this study are as follows: (1) Two patients exhibited an AR index < 25 despite having no AR, and (2) LV diastolic stiffness, LV max dP/dt, and the heart rate were identified as independent determinants of the AR index. To our knowledge, this is the first study to demonstrate that the AR index is affected by LV function, especially diastolic function, using a micromanometer-tipped catheter.

The aortic regurgitation index in heart failure: Prior two studies regarding postprocedural AR found AR index values of 31.7 ± 10.4 and 29.4 ± 6.3 in a subgroup of patients with no postprocedural AR. By contrast, AR index values obtained from our study patients were higher than those published in the aforementioned reports. Considering the difficulty of recording high-fidelity LV pressure waves during TAVI procedures, we focused on patients with heart failure as models in the current study. Therefore, our patients had a lower LVEF than those in the aforementioned studies. However, given that some patients with TAVI may exhibit LV dysfunction, we believe that our analysis in patients with low EF may also be of significance. This is significant when one considers that our analysis indicated that the AR index values tended to increase as LVEF decreased (Figure 3). Our multiple-regression analysis indicated that LV max dP/dt, a measure of LV contractility, was negatively correlated with the AR index (Table III). Thus, our results demonstrated that the reduced LV contractility promoted high AR index values.

Although our study patients had generally high AR index values, we note that two patients had an AR index < 25, indicating significant AR, despite having no AR. This observation is concrete evidence that any factor, other than AR, can decrease the value of the AR index. We, therefore, confirmed that the AR index should be interpreted together with various clinical factors, including LV function.

LV diastolic function and the aortic regurgitation index: Postprocedural AR can be characterized as a type of acute AR. When significant AR occurs after TAVR in patients with little preprocedural AR, the LV is suddenly exposed to the regurgitant flow. Elderly patients considering TAVR typically have impaired LV diastolic function due to long-standing pressure overload. In such cases, the LV cannot adapt effectively to the abrupt increase in regurgitant flow, thereby resulting in elevated LVEDP and decreased DBP. LVEDP is indeed included in the formula for calculating the AR index. When one considers that LVEDP increases with severe LV diastolic dysfunction, a decrease in the AR index can be easily predicted. This is thought to be a reason why the AR index reflects postprocedural AR. The e’ is relatively independent of loading state and is used to assess LV relaxation in echocardiography. Our results indicate that as the e’ value decreased, the AR index value showed a decreasing trend (Table II). Moreover, E/e’/LVEDV, which is LV stiffness index derived from echocardiography, was significantly correlated with the AR index value. LV tau and LV stiffness are both catheter parameters of LV diastolic properties. The multiple-regression analysis conducted herein finally dem-
Figure 3. Correlation between the AR index value and key parameters. The e’, LV tau, and LV diastolic stiffness are measures associated with LV diastolic function. AR indicates aortic regurgitation; e’, early diastolic mitral annular velocity; and LV, left ventricular.

Table III. Multiple Linear Regression Analysis of Independent Determinants of the AR Index

| Parameters                          | Coefficient | Beta  | P
|------------------------------------|-------------|-------|---
| Age, years                         | -0.070      | -0.112| 0.269
| Heart rate, bpm                    | 0.378       | 0.281 | 0.012
| LV max dp/dt, mmHg/second          | -0.014      | -0.266| 0.013
| LV tau, ms                         | -0.047      | -0.058| 0.656
| LV diastolic stiffness, mmHg/mL    | -79.061     | -0.707| <0.001
| SAC, mL/mmHg                       | 2.618       | 0.122 | 0.241

AR indicates aortic regurgitation; bpm, beats per minute; LV, left ventricular; and SAC, systemic arterial compliance.

onstrated that LV diastolic stiffness was one of the significant determinants of the AR index (Table III). Acute AR can be clinically severe, particularly in the presence of LV diastolic dysfunction, supporting our assertion that the AR index would display lower values in patients with more severe LV diastolic dysfunction.

After analyzing predictors of 1-year mortality following TAVR, Abdel-Wahab, et al.\textsuperscript{18) found that mortality increased by 15% for every 10 mmHg increase in systolic PAP. PAWP, systolic PAP, and LVEDP have all been identified as indicators of diastolic LV filling pressures, representing the LV diastolic property. Collas, et al.\textsuperscript{19} reported that the postprocedural AR index value correlated with LV hypertrophy and the preprocedural AR index value, sug-
gesting that pre-existing LV function affects the postprocedural AR index. We believe that the aforementioned studies indicate the involvement of LV diastolic function in the outcomes of TAVR. Given that the diastolic property generally affects the symptoms, functional capacity, and prognosis of patients with heart failure, the additional prognostic information provided by the AR index, advocated by Vasa-Nicotera, et al., could be exactly the LV diastolic function.

Aortic compliance and the AR index: When blood is ejected into the aorta, the aortic walls expand to accommodate the increased blood volume, acting as an elastic buffering chamber. However, aortic stiffening along with aging elevates the SBP and reduces the DBP. The low DBP can compromise coronary perfusion as the coronary driving pressure decreases, thereby contributing to impaired LV relaxation. Indeed, studies have associated low SAC with higher cardiovascular and all-cause mortality. We had initially thought that low SAC was also prognostic information provided by the AR index. However, our analyses did not demonstrate a close association between SAC and the AR index (Tables II, III), perhaps because the majority of our study participants were between 48 and 70 years old and had no severely calcified aorta.

Limitations: This study has some limitations worth noting. First, the association between the AR index and LV function was not investigated in TAVR patients. Therefore, subsequent studies should investigate actual TAVR patients. Second, no available data on long-term outcomes were available. Third, given the small number of study subjects included herein, the statistical power of multivariate analysis was limited. Therefore, further large-scale studies are certainly warranted.

Conclusions

The present study revealed that LV diastolic stiffness, LV max dp/dt, and the heart rate were independent determinants of the AR index. Patients with impaired LV diastolic function and preserved systolic function can have low calculated AR index values despite having no AR. In other words, poor outcomes in patients with low AR index values after TAVR may be attributed to pre-existing LV diastolic dysfunction, aside from significant postprocedural AR. Therefore, it is imperative for one to consider such effects when using the AR index in determining the severity of postprocedural AR.

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Disclosure

Conflicts of interest: The authors have no conflicts of interest directly relevant to the content of this article.

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