Sex Differences in Aortic Valve Calcification Measured by Multidetector Computed Tomography in Aortic Stenosis

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Background—Aortic valve calcification (A VC) is the intrinsic mechanism of valvular obstruction leading to aortic stenosis (AS) and is measurable by multidetector computed tomography. The link between sex and AS is controversial and that with A VC is unknown.

Methods and Results—We prospectively performed multidetector computed tomography in 665 patients with AS (aortic valve area, 1.05±0.35 cm²; mean gradient, 39±19 mm Hg) to measure A VC and to assess the impact of sex on the AVC–AS severity link in men and women. AS severity was comparable between women and men (peak aortic jet velocity: 4.05±0.99 versus 3.93±0.91 m/s, P=0.11; aortic valve area index: 0.55±0.20 versus 0.56±0.18 cm²/m²; P=0.46). Conversely, A VC load was lower in women versus men (1703±1321 versus 2694±1628 arbitrary units; P<0.0001) even after adjustment for their smaller body surface area or aortic annular area (both P<0.0001). Thus, odds of high-A VC load were much greater in men than in women (odds ratio, 5.07; P<0.0001). Although A VC showed good associations with hemodynamic AS severity in men and women (all r>|0.67|; P<0.0001), for any level of AS severity measured by peak aortic jet velocity or aortic valve area index, A VC load, absolute or indexed, was higher in men versus women (all P≤0.01).

Conclusions—In this large AS population, women incurred similar AS severity than men for lower A VC loads, even after indexing for their smaller body size. Hence, the relationship between valvular calcification process and AS severity differs in women and men, warranting further pathophysiological inquiry. For AS severity diagnostic purposes, interpretation of A VC load should be different in men and in women. (Circ Cardiovasc Imaging. 2013;6:40-47.)

Key Words: aortic valve calcification ■ aortic valve stenosis ■ Doppler echocardiography ■ multidetector computed tomography ■ sex differences

A ortic stenosis (AS) is common in elderly people, affecting 2% of the population ≥65 years old and 4.6% of population ≥75 years old based on Doppler echocardiographic or community studies.1,2 Nowadays, the most common cause of AS is degenerative, and aortic valve calcification (A VC) is the intrinsic mechanism of valvular stiffening and obstruction.3–6 Although degenerative AS has long been considered age related, recent studies have demonstrated that it is an active process involving biological pathways with many similarities to atherosclerosis.7,8 Epidemiological studies identified similar risk factors for calcific AS and coronary atherosclerosis such as age, smoking, elevated cholesterol levels, diabetes mellitus, metabolic syndrome, hypertension, and increase in lipoprotein-a levels.9 Male sex was also touted as an independent risk factor for AS similar to atherosclerosis,9 but studies linking valve tissue alterations10,11 and calcification to AS12 have not differentiated between men and women. Moreover, studies of aortic valve weight as a surrogate for calcification load showed discordant results with regard to sex,13,14 and clinically, guidelines do not differentiate between men and women for AS pathophysiology and management.6

However, the analogy to atherosclerosis suggests that there may be important, yet thus far undefined, sex-related differences in the development of A VC and the transition to AS. This issue can now be analyzed because cardiac computed tomography (CT) provides accurate and reproducible quantification of A VC load,15 and multidetector CT (MDCT) may prove to be a useful adjunct tool for the evaluation of AS severity. However, previous studies suggested a single set of cutoff values for detecting severe AS regardless of sex,16 so the impact of sex on the relation between aortic cusp calcification measured by MDCT and hemodynamic severity of AS remains uncertain. The aim of the present study was to determine the differential physiological relationship between A VC...
load and AS hemodynamic severity between men and women. We hypothesized that women reach thresholds for severe AS for lower calcification loads than men and that when MDCT is used for the diagnosis of AS severity, criteria of AVC load would need to be adjusted specifically for each sex.

Methods

Study Population

We prospectively enrolled patients with at least mild calcific AS in whom we performed noncontrast MDCT scan for the evaluation of AVC and comprehensive transesophageal echocardiography within 90 days of each other between 1999 and 2010 in 2 large academic centers: Mayo Clinic, Rochester (MN), and Hôpital Bichat, Paris (France). AS severity was defined as recommended in the guidelines;5 mild (aortic valve area [AVA] ≥1.5 cm²); mean gradient [MG] <25 mm Hg; or peak aortic jet velocity [VPeak] <3.0 m/s), moderate (AVA, 1.0–1.5 cm²; MG, 25–40 mm Hg; or VPeak, 3.0–4.0 m/s), or severe (AVA≤1.0 cm²; MG≥40 mm Hg; or VPeak≥4.0 m/s). The mean interval of time between echocardiographic and MDCT examination was 4±11 days (range, 0–68 days). Patients with overt rheumatic valve disease (defined as the calcium present on the valvular leaflets and annulus. The aortic valve was visualized in multiple planes to accurately exclude contiguous calcium in the mitral valve annulus or aortic wall. A VC load was as the average of 2 separate runs. Calcium scoring was performed by an investigator blinded to the echocardiographic data detecting AVC density (as independent variables) and AVC, AVCi, and AVCdensity (as dependent variables) were assessed with multiple regression models, and the equation providing the best fit was retained. The association between AVC and echocardiographic indexes of AS severity became linear after square root transformation of AVC. The impact of sex (as stratifying variable) was assessed by the interaction between sex and stenotic indexes in correlations using transformed and untransformed AVC. The impact of center or MDCT differences in these correlations was assessed by ANCOVA. Multivariable linear and logistic regressions were used to determine the associations between baseline characteristics and AVC load (as continuous variable, before and after square root transformation) or high AVC load (using the previously described AVC threshold of 1650 arbitrary units (AU)). The odds ratios (ORs) of high AVC load and their 95% confidence interval (in brackets) were calculated unadjusted and adjusted in logistic models. Clinically relevant variables with a value of P<0.05 on univariable analysis were included in multivariable models with the focus of adjusting for independent correlates of AVC and examining the independent role of sex in determining AVC load as the main aim of the study. The final model retained included only the independent determinants of AVC, but extensive verification that no other variable inclusion affected the result was conducted in multiple models. Values of P<0.05 were considered statistically significant. Statistical analyses were performed with JMP 9.0.0 and Table Curve version 5.01 software programs.

Results

Population

In our cohort of 665 patients (Mayo Clinic, 503; Bichat Hospital, 162), there were 238 women and 427 men, and their baseline characteristics are presented in Table 1. The men:women ratio was not different between centers (64%=36% men:women in both centers; P=0.99) or between scanners (65%=35% men:women in 16-detector CT and 63%=37% men:women in 64-detector CT; P=0.45). As expected, there were slight clinical differences between men and women with AS: Women were slightly older, had a smaller body surface area, and were more often severely symptomatic. Men presented more frequently with a history of coronary disease, of hyperlipidemia, and, in
a borderline proportion, of diabetes mellitus. The renal function analysis was contrasted because men had higher creatinine, which, in view of a larger body, corresponded nevertheless to higher creatinine clearance. Importantly, men and women have equivalent AS severity (Table 1), measured by VPeak (4.05±0.99 versus 3.93±0.91; P=0.11), MG (41±21 versus 39±18; P=0.09), or AVAi (0.55±0.20 versus 0.56±0.18; P=0.46).

AVC Load

AVC load was lower in women compared with men (1703±1321 versus 2694±1628 AU; P<0.0001). This difference remained significant even after accounting for the smaller body and heart size of women and normalizing the AVC load for body surface area (AVCi, 996±781 versus 1344±823 AU/m²; P<0.0001) and for cross-sectional aortic annulus area (AVC density, 502±384 versus 633±399 AU/cm²; P<0.0001; Table 1).

Characteristics associated with high AVC load (>1650 AU) in univariable analysis were age (OR, 1.35 [1.25–1.45] per 10-year increase; P<0.0001), male sex (OR, 3.06 [2.21–4.26]; P<0.0001), New York Heart Association functional class ≥III (OR, 2.97 [2.07–4.27]; P<0.0001), history of coronary artery disease (OR, 1.87 [1.35–2.59]; P=0.0001), history of atrial fibrillation (OR, 1.85 [1.24–2.76]; P=0.002), chronic obstructive pulmonary disease (OR, 1.55 [1.03–2.33]; P=0.03), body surface area (OR, 1.20 [1.12–1.28]; P=0.001), LVOT diameter (OR, 1.22 [1.17–1.27] per 0.1-cm increase; P<0.0001), AVAi (OR, 2.29 [2.14–2.46] per 0.1-cm² decrease; P<0.0001), MG (OR, 2.63 [2.43–2.85] per 10-mm Hg increase; P<0.0001), VPeak (OR, 5.57 [4.85–6.40] per 1-m/s increase; P<0.0001), left ventricular ejection fraction (OR, 1.35 [1.26–1.45] per 10% decrease; P<0.0001), and creatinine level (OR, 1.84 [1.48–2.29]; P=0.002).

After adjustment for age, LVOT diameter, VPeak, and AVAi as other independent determinants of AVC, men compared with women had higher odds of severe valve calcification (Table 2). Further adjustment for left ventricular ejection fraction, creatinine (or creatinine clearance), and history of coronary disease did not affect the independent determinants of severe AVC or the female sex–lower AVC link (both P<0.0001). The model was confirmed when MG replaced VPeak with similarly high OR of severe AVC attached to male sex (OR, 5.40 [2.94–10.19]; P<0.0001). The model was also confirmed with AVC as a continuous variable by using multiple linear regression models, showing that, adjusting for age, VPeak, LVOT diameter, and AVAi, women had independently lower AVC load than men (P<0.0001; Table 3). Moreover, the interaction term (ie, interaction between sex and AS severity documented by Doppler echocardiography) was highly significant (P<0.004 with or without the use of square root–transformed AVC; Table 3). Similarly, with the use of normalized AVC (AVCi or AVC density), women independently had lower normalized AVC load than men, adjusted for the same

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole Cohort (n=665)</th>
<th>Female (n=238)</th>
<th>Male (n=427)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>75±11</td>
<td>76±11</td>
<td>74±11</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3±6.1</td>
<td>28.6±7.8</td>
<td>28.1±5.0</td>
<td>0.31</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.91±0.24</td>
<td>1.73±0.22</td>
<td>2.01±0.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA functional class ≥III, n (%)</td>
<td>218 (33)</td>
<td>93 (39)</td>
<td>125 (29)</td>
<td>0.009</td>
</tr>
<tr>
<td>History of CAD, n (%)</td>
<td>279 (42)</td>
<td>71 (30)</td>
<td>208 (49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>453 (68)</td>
<td>171 (72)</td>
<td>282 (66)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>158 (24)</td>
<td>47 (20)</td>
<td>111 (26)</td>
<td>0.07</td>
</tr>
<tr>
<td>History of atrial fibrillation, n (%)</td>
<td>151 (23)</td>
<td>52 (22)</td>
<td>99 (23)</td>
<td>0.61</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>142 (21)</td>
<td>55 (23)</td>
<td>87 (20)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>444 (67)</td>
<td>148 (62)</td>
<td>296 (69)</td>
<td>0.07</td>
</tr>
<tr>
<td>Creatinine level, mg/dL</td>
<td>1.17±0.50</td>
<td>1.04±0.42</td>
<td>1.23±0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>66±28</td>
<td>58±28</td>
<td>70±28</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Echocardiographic data

| Peak aortic jet velocity, m/s | 3.97±0.94 | 4.05±0.99 | 3.93±0.91 | 0.11 |
| Mean gradient, mm Hg | 39±19 | 41±21 | 39±18 | 0.09 |
| Aortic valve area, cm² | 1.05±0.35 | 0.94±0.34 | 1.11±0.34 | <0.0001 |
| Aortic valve area index, cm²/m² | 0.55±0.19 | 0.55±0.20 | 0.56±0.18 | 0.46 |
| LV outflow tract diameter, cm | 2.2±0.2 | 2.1±0.1 | 2.3±0.2 | <0.0001 |
| LV ejection fraction, % | 60±13 | 62±12 | 59±13 | 0.002 |

MDCT data

| AVC, AU | 2339±1597 | 1703±1321 | 2694±1628 | <0.0001 |
| AVCi, AU/m² | 1220±825 | 996±781 | 1344±823 | <0.0001 |
| AVC density, AU/cm² | 586±398 | 502±384 | 633±399 | <0.0001 |

AVC indicates aortic valve calcification; AVCi, aortic valve calcification index to body surface area; AVC density, aortic valve calcification index to cross-sectional aortic annulus area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LV, left ventricular; MDCT, multidetector computed tomography; and NYHA, New York Heart Association.
background variables (all \( P<0.005 \)), and the interaction term remained significant (all \( P<0.01 \)). Adjusting the models further for serum creatinine level or creatinine clearance did not affect the significance of sex (all \( P<0.0001 \)) or interaction term (all \( P<0.009 \)) in the multivariable models of A VC, A VCi, and A VCdensity. Thus, regardless of the format of analysis, women have lower A VC, lower A VCi that accounts for smaller body size, and lower A VCdensity that accounts for smaller LVOT than men, warranting an analysis of the relation in A VC-hemodynamic severity of AS in both sexes.

### Contrasting Associations Between A VC and Hemodynamic Markers of AS Severity

In Figure 1, we plotted A VC (x-axis) versus VPeak (Figure 1A), MG (Figure 1B), and A VAi (Figure 1C). In all plots, A VC showed good associations with these hemodynamic markers of AS severity in men and in women (all \( r>0.67 \) and \( P<0.0001 \)). Despite these similar association strength, the regression curves in men and women separated, showing that for a higher but similar loads of calcium, hemodynamic severity of AS was worse in women than men. This difference in association between AS severity and A VC load remained significant when A VC was indexed to body surface area to account for lower body size in women (A VCi: all interaction \( P<0.005 \)) or to LVOT area to account for smaller heart size in women (A VCdensity: all interaction \( P<0.009 \)).

After patients were divided in to tertiles of normalized A VC (Figure 2), A VCi in Figure 2A, and A VCdensity in Figure 2B, women had a more severe AS, as documented by VPeak and A VAi in each tertile of normalized A VC (all \( P<0.01 \)).

### Discussion

The main findings of this prospective study are as follows.

1. Women, with similar AS severity as men, present with lower A VC load than men. Moreover, after taking into account that women have smaller bodies and smaller LVOT, A VC load normalization for body surface area and cross-sectional aortic annulus area shows that women present lower A VCdensity than men for similar AS severity.

2. The difference between sexes is related to a steeper slope of AS severity increase with any given A VC load or density increase in women than in men.

3. For diagnostic purposes, interpreting the A VC load link to severe AS should be different and lower for women as compared with men. Therefore, while valvular calcification is the mechanism of AS in both men and women, there are important pathophysiological differences between men and women that warrant specific clinical approaches and further research into disease mechanisms specific to each sex.

### A VC–AS Mechanism

The link between aortic valve accumulation of calcification (ie, anatomic lesion of the valve) and AS (ie, hemodynamic burden of the lesion) has been long demonstrated in autopsy studies,19–21 even at a very early stage of the disease.10 This anatomic link for AS calcification was confirmed in vivo casually during fluoroscopy22 and more recently quantitatively by using CT in previous small studies.13,23–25 In the present large, prospective, cross-sectional study with simultaneous CT scans and Doppler echocardiograms, we observed excellent correlations between hemodynamic severity of AS and severity of A VC load determined by MDCT.15,23,26,27 However, although the general mechanism of more calcification associated with more severe AS holds true, this large series of patients provides the power to detect for the first time that the relation between AS severity and A VC load in men and women is significantly different (Figure 1). As expected, in patients with mild A VC and less severe AS, the difference between sexes is smaller (Figure 2), and obviously, at that relatively benign end of the spectrum, A VC load, peak aortic velocity, mean gradient, and indexed aortic valve area should be equal in men and women with normal or minimally affected aortic valves. Thus, there is an expected overlap with mild AS, but inclusion of a wide range of AS severity allows demonstration of the strong impact of sex on A VC load and the lower odds of severe A VC load in women compared with men regardless of any adjustment. Remarkably, the hemodynamic severity of AS was similar between men and women, but direct comparison or interaction analysis of A VC load emphasized the lesser calcification in women. The explanation of this difference is not in the body habitus because normalization for body surface area and cross-sectional area of the aortic annulus showed the same results. Differences between men and women with AS generally emphasized the ventricular

### Table 2. Multivariable Predictors of an Aortic Valve Calcification >1650 AU

<table>
<thead>
<tr>
<th>Increment Category</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Estimate±SD</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>+10 y</td>
<td>1.71 (1.38–2.13)</td>
<td>0.54±0.11</td>
</tr>
<tr>
<td>Male sex</td>
<td>Yes</td>
<td>5.07 (2.78–9.46)</td>
<td>1.62±0.31</td>
</tr>
<tr>
<td><strong>Echocardiographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak aortic jet velocity</td>
<td>+1 m/s</td>
<td>4.59 (2.97–7.33)</td>
<td>1.52±0.30</td>
</tr>
<tr>
<td>Indexed AVA</td>
<td>−0.1 cm²/m²</td>
<td>1.79 (1.44–2.24)</td>
<td>0.58±0.11</td>
</tr>
<tr>
<td>LV outflow tract diameter</td>
<td>+0.1 cm</td>
<td>1.4 (1.22–1.65)</td>
<td>0.35±0.07</td>
</tr>
</tbody>
</table>

AV indicates aortic valve area; and LV, left ventricular.
response to the disease, with differing hypertrophy patterns. However, differences in the process of calcification have not been emphasized because doing so requires large series with simultaneous quantitative measurements in vivo. This new insight into the pathophysiology of AS development raises the question of its biological mechanism. Whether factors that have been cited as affecting AS and A VC progression such as vitamin D receptors or growth factors are different in women and may lead to more extensive fibrosis is unclear and requires further research. Regardless of the new observation that A VC load is different in men and women with AS, A VC load has important and immediate diagnostic implications.

A VC–AS Diagnosis

Doppler echocardiography remains the gold standard technique to assess AS severity. However, this technique has some significant limitations. Echocardiography can be challenging in patients with poor windows such as those suffering from obesity or chronic obstructive pulmonary disease. More important, assessment of AS severity can often be challenging in patients with low A VA (in the severe range) and low gradient (in the moderate range) with or without low flow or low ejection fraction. Affirming the severity of AS is crucial for clinical management and decision making. Doppler echocardiography at rest is not conclusive in such patients, requiring additional testing to differentiate truly severe from pseudosevere AS. Catheterization is often not helpful because of similar discrepancies in AS severity markers, whereas crossing the aortic valve also carries a significant risk of cerebral embolism, and stress Doppler echocardiography is not always conclusive. Hence, CT has emerged as an adjunct to Doppler echocardiography in the determination of AS severity. Indeed, although Doppler echocardiography quantifies the hemodynamic degree of AS, CT measures the intrinsic lesion of the valve and provides an additional parameter to evaluate calcified aortic valve disease severity. A VC measurement by MDCT is a fast, simple, noninvasive, highly feasible, widely available, and highly reproducible technique. In these studies, intraobserver and interobserver variabilities were <7%. Moreover, for visualization of calcification, CT does not require contrast and can be performed in patients with arrhythmias. A VC may also have other interest in AS evaluation because it has been shown in transcatheter aortic valve implantation to predict aortic regurgitation after the procedure. However, our study emphasizes the necessity to interpret differently the link between A VC load values and AS severity in men and women.

Limitation

In this study, the type and length of use of medication cannot be assessed for each patient; thus, it is possible that some medication may influence the calcification of the aortic valve.
valve. Nevertheless, no medication has been shown to differently modify AVC and hemodynamic severity, and because we focused on this relation, medication may have only a minor impact. Another limitation of the study is that the measurements were done in 2 institutions and with different echocardiographic and CT equipment. However, Doppler echocardiographic measurements are routinely used clinically, and methods of measurement are well defined. The MDCT quantification of calcification has been the subject of conventions in defining calcification of interest. As shown, variability is low, and ANCOVA showed that the slope of the regression of velocity–AVC is similar between institutions in men (P=0.40) and women (P=0.61) and between scanners used in men (P=0.34) and women (P=0.52). Thus, the multicenter and multisccanner nature of our study further reinforces our main result.

Conclusions

In this large prospective study of AVC by MDCT with simultaneous Doppler echocardiography–derived hemodynamics of AS, women reached similar AS severity as men for lower aortic valve calcium loads, even after normalization for lower body surface area and smaller aortic annulus area. The differences between sexes are related to a steeper slope of AS severity increase for any given AVC load (or density) increase in women compared with men. For diagnostic purposes, linking AVC load to severe AS should be different and lower for women compared with men. Therefore, although valvular calcification is the mechanism of AS in both men and women, important pathophysiological differences between men and women warrant specific clinical approaches and further research in disease mechanisms specific to each sex.

Acknowledgments

We thank Douglas W. Mahoney for statistical assistance.

Sources of Funding

The COFRASA and GENERAC studies are supported by a grant from the Assistance Publique-Hopitaux de Paris (PHRCnational 2005 and PHRCregional 2007, respectively). Dr Clavel holds a Vanier Canada Graduate Scholarship and a Michael Smith Foreign Study Supplements Scholarship, Canadian Institutes of Health Research, Ottawa, ON, Canada.

Disclosures

Dr Enriquez-Sarano reports receiving research grant from Edwards Lifesciences. Dr Messika-Zeitoun reports receiving modest consultant fees from Valtech Inc and Symetis Inc and modest consultant fees from Edwards Lifesciences. The other authors have no conflicts to report.

References


Aortic stenosis (AS) in the adult is attributed to calcific deposits in the aortic leaflets tissue by a process similar to atherosclerosis. Differences in atherosclerotic lesions between men and women are well known, but it is unclear whether such differences exist for aortic valve calcification (AVC) load. New insights can be obtained by quantifying AVC load using multidetector computed tomography. In our study, which uses Doppler echocardiography and multidetector computed tomography during the same episode of care, men and women presented with the same AS hemodynamic severity, but AVC load was higher in men compared with women. After taking into account the smaller body surface area and smaller left ventricular outflow tract area in women compared with men, the difference in AVC load remained significant. Moreover, for a similar AS severity as documented by Doppler echocardiography, men had a 5-fold-higher chance of being considered as having a severe AVC load. Thus, our study shows a considerable physiological difference between men and women with AS in that women reach severe hemodynamic AS with a much smaller AVC load, absolute or size adjusted, than men. This difference warrants mechanistic investigation to relate AVC load progression to AS progression in women compared with men. Clinically, for diagnosis purposes, the link between AVC load values and AS severity should be interpreted differently in men and women.
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_Circ Cardiovasc Imaging_. 2013;6:40-47; originally published online December 10, 2012; doi: 10.1161/CIRCIMAGING.112.980052
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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