Left Ventricular Diastolic Function Is Closely Associated With Mechanical Function of the Left Atrium in Patients With Paroxysmal Atrial Fibrillation

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Background: Left ventricular (LV) diastolic dysfunction may be a mechanism of left atrial (LA) electroanatomical remodeling in atrial fibrillation (AF). We evaluated the association between LV diastolic function and LA mechanical function in non-valvular paroxysmal AF (PAF).

Methods and Results: In 286 patients with PAF (males 73%, 57±11 years), LA size, indexed LA volume, LV diastolic function, and LA appendage flow velocity (LAA-FV) in sinus rhythm were measured using transthoracic echocardiography, transesophageal echocardiography and cardiac computed tomography. The LA voltage map was obtained using NavX contact mapping. Patients with impaired LA mechanical function (LAA-FV <58 cm/s, n=142) showed a higher E/Em ratio (10.3 vs. 9.2, \(P=0.034\)) and lower Em velocity (6.8 vs. 7.7 cm/s, \(P=0.004\)) than those with preserved function (LAA-FV ≥58 cm/s, n=144). The patient population displayed weak correlations of E/Em with LAA-FV (\(r=-0.19, P=0.003\)) and LA voltage (\(r=-0.23, P=0.004\)), but more significant association of E/Em and LAA-FV (\(r=-0.39, P<0.001\)) for age ≥55 years and LA diameter ≥40 mm. E/Em was an independent predictor of LAA mechanical function (\(\beta=-0.20, P=0.013\)) even after age, sex, LA size and comorbidities were controlled for.

Conclusions: In patients with non-valvular PAF, LA mechanical function is closely related to the degree of LA remodeling and LV diastolic function. Impaired LV diastolic function significantly contributes to LA electroanatomical remodeling in older patients with a larger LA. (Circ J 2013; 77: 697–704)

Key Words: Atrial fibrillation; Diastolic function; Electroanatomical remodeling; Left atrium; Left ventricle

Atrial remodeling, both structural and electrical, is a pathophysiological phenomenon observed in atrial fibrillation (AF). Over the years, various studies have shown that fibrillatory electrical activation causes progressive structural and electrical remodeling of the atria. Subsequently, remodeling impairs the function of the rest of the heart, and this partly explains why this arrhythmia is a major cause of population morbidity and mortality. The reverse seems to be also true: impaired function of the heart, especially that of the ventricles, debilitates the atria, because the left atrium (LA) and the left ventricle (LV) are intricately coupled. For instance, the LA during diastole is under the direct influence of pressure in the LV through the open mitral valve. Hence, it is not without reason to suspect that the function of the LV, or the lack thereof, would alter the LA in structure and function. Sure enough, many studies to date have come to the conclusion that the state of the LA reflects the diastolic function of the LV. In this context, LV diastolic dysfunction would be a major contributor to LA electroanatomical remodeling observed in paroxysmal AF (PAF). However, no studies so far have conclusively proved that the relationship between the LA and the LV exists in this arrhythmia. Employing a variety of diagnostic tests to obtain data on heart structure, function and electrophysiology of patients undergoing radiofrequency catheter ablation (RFCA), we hypothesized that electroanatomical remodeling of the LA is intimately connected to LV diastolic dysfunction in PAF. Hence, the aim of this study was to evaluate the association between LV diastolic function and LA mechanical function, and to characterize those individuals, in whom LV diastolic function significantly altered LA mechanical function.

Methods

Patient Selection

The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital, Yonsei University. All patients included in the study...
provided proper written informed consent. The study enrolled 286 patients (73% males, 57±11 years) who underwent RFCA for symptomatic drug-refractory PAF. The study’s exclusion criteria were as follows: (1) persistent or permanent AF; (2) AF at the time of transesophageal echocardiography (TEE); (3) LA anterior-posterior diameter >55 mm measured by trans-thoracic echocardiography (TTE); (4) the presence of intracardiac thrombi; (5) AF with significant valvular disease or structural heart disease; (6) previous AF ablation; and (7) history of cardiac surgery. All subjects underwent TEE, TTE, and cardiac computed tomography (CT) in preparation for the ablation procedure. All antiarrhythmic drugs were discontinued of body size on volume.

Table 1. Clinical Characteristics of the Patients With Non-Valvular PAF

| Age, years | 58.5±10.3 | 55.2±12.0 | 0.012 |
|----------------------|-----------|-----------|-------|
| LAA-FV <58 cm/s (n=142) | LAA-FV ≥58 cm/s (n=144) |
| Male sex, n (%) | 7 (4.9) | 8 (5.6) | 0.812 |
| Male sex, n (%) | 98 (69.0) | 109 (75.7) | 0.206 |
| BMI, kg/m² | 24.5±2.9 | 24.8±3.0 | 0.493 |
| Hypertension, n (%) | 72 (50.7) | 65 (45.1) | 0.346 |
| Diabetes mellitus, n (%) | 22 (15.5) | 13 (9.0) | 0.095 |
| Heart failure, n (%) | 10 (7.0) | 5 (2.8) | 0.092 |
| Stroke, n (%) | 19 (13.4) | 7 (4.9) | 0.012 |
| TIA, n (%) | 2 (1.4) | 1 (0.7) | 0.512 |
| Stroke + TIA, n (%) | 21 (14.8) | 8 (5.6) | 0.018 |
| CHADS2 Score | 1.08±1.19 | 0.74±0.90 | 0.008 |

*P<0.05 was considered statistically significant.

BMI, body mass index; LAA-FV, left atrial appendage flow velocity; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.

**Electrophysiological Mapping**

Intracardiac electrogroms were recorded using the Prucka Cardio Lab™ electrophysiology system (General Electric Medical Systems, Milwaukie, WI, USA). A 3D electroanatomical map (NavX, St. Jude Medical, Minnetonka, MN, USA) was generated by merging the NavX system-generated 3D geometry of the LA and PVs with the corresponding 3D spiral CT images. This map was then used to guide the RFCA procedure. A decapolar catheter (Bard Electrophysiology, Lowell, MA, USA) and a duo-decapolar catheter (St. Jude Medical) were inserted into the left femoral vein to map the high right atrium (RA), low RA, and the coronary sinus, and a quadripolar catheter was advanced and placed in the superior vena cava. To gain access to the LA, a double trans-septal puncture approach was taken, and multiview pulmonary venograms were obtained. Thereafter, using a long sheath (Schwartz left 1, St. Jude Medical), a circumferential PV mapping catheter (Lasso; Biosense-Webster, Diamond Bar, CA, USA) was also inserted. Intravenous heparin was injected in order to have systemic anticoagulation with an activated clotting time of 350–400 s. Using a multipolar ring catheter (Lasso, Johnson & Johnson, Diamond Bar, CA, USA), a 3D LA voltage map was generated from contact bipolar electrograms of 350–400 points on the LA endocardium during high RA pacing (pacing cycle length 500 ms). The bipolar electrograms were filtered at 32–300 Hz. Color-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage as previously described. However, when frequently re-initiating AF required more than 3 electrical cardioversions, the LA voltage map was not constructed. In the end, 171 of the 286 patients had a complete set of LA and LAA voltage data. For further comparisons, these 171 patients were divided again according to LA voltage and echocardiographic measurement.
LA Function vs. LV Diastolic Function

Table 2. Electroanatomical Remodeling, Pressures, and Voltage of the LA

|                        | LAA-FV <58 cm/s (n=142) | LAA-FV ≥58 cm/s (n=144) | P value* |
|------------------------|-------------------------|-------------------------|----------|
| TTE: 2D and Doppler parameters |                         |                         |          |
| LA diameter, mm        | 40.7±5.8                | 39.4±5.5                | 0.040    |
| LVEDD, mm              | 49.5±4.5                | 49.5±4.0                | 0.881    |
| LVESD, mm              | 32.2±4.7                | 32.3±4.1                | 0.836    |
| LVEF, %                | 62.3±9.0                | 63.4±8.0                | 0.267    |
| LV mass index, g/m²    | 97.0±18.7               | 95.2±20.3               | 0.451    |
| E velocity, cm/s       | 67.4±20.4               | 68.5±21.6               | 0.710    |
| Em velocity, cm/s      | 6.8±2.2                 | 7.7±2.3                 | 0.004    |
| E/Em                   | 10.3±4.4                | 9.2±3.6                 | 0.034    |
| TEE: Doppler parameters |                         |                         |          |
| LAA-FV, cm/s           | 40.8±11.8               | 75.1±13.5               | <0.001   |
| Right PV               |                         |                         |          |
| Systolic FV cm/s       | 41.3±17.2               | 50.1±22.5               | 0.001    |
| Diastolic FV, cm/s     | 50.0±17.8               | 46.6±13.8               | 0.064    |
| Systolic/diastolic ratio | 0.89±0.43              | 1.12±0.47               | <0.001   |
| Left PV                |                         |                         |          |
| Systolic FV, cm/s      | 48.7±18.4               | 55.5±16.8               | 0.004    |
| Diastolic FV, cm/s     | 46.7±18.7               | 41.0±13.2               | 0.008    |
| Systolic/diastolic ratio | 1.15±0.52              | 1.43±0.48               | <0.001   |
| CT: 3D indexed volume  |                         |                         |          |
| LA, ml/m²              | 65.0±18.0               | 59.6±18.2               | 0.013    |
| LAA, ml/m²             | 5.6±2.5                 | 4.9±2.4                 | 0.017    |
| LA voltage             |                         |                         |          |
| Mean LA, mV            | 1.38±0.63               | 1.55±0.64               | 0.047    |
| LAA, mV                | 2.54±1.46               | 3.17±1.43               | 0.003    |

*P<0.05 was considered statistically significant.

CT, computed tomography; E, mitral inflow early diastolic; Em, mitral annulus early diastolic; FV, flow velocity; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; PV, pulmonic vein; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Results

LA Mechanical Function and Electroanatomical Remodeling

Based on the LAA-FV obtained during sinus rhythm, the patients were divided into low LAA-FV (LAA-FV <58 cm/s, n=142) and high LAA-FV (LAA-FV ≥58 cm/s, n=144) groups; the median LAA-FV of 58 cm/s marks the point of separation between these 2 groups (Table 1). Compared with the high LAA-FV group, the patients with a low LAA-FV were significantly older (P=0.012), and showed a higher prevalence (P=0.012) and risk of stroke, estimated by the CHADS2 score (P=0.008). The parameters reflecting electroanatomical remodeling of the LA and invasive hemodynamic data are summarized in Table 2. Upon close analysis, the LA anterior-posterior diameter was found to be significantly greater among patients with a reduced LA function (Figure 1). In order to verify this finding, 3D spiral CT was performed to measure the volumes of the LAA and LA. Indeed, after having been corrected for the influence of BSA, the indexed LA volume (P=0.013) and LAA volume (P=0.017) were significantly greater among the patients with a diminished LAA-FV. As expected, the endocardial voltage measured in these areas revealed that the mean LA voltage (P=0.047) and LAA voltage (P=0.003) were lower in patients with a reduced LAA-FV when compared with those with a high LAA-FV (Figure 1). In other words, a functionally abated LA tended to be electrically remodeled as well.

Association of LA Mechanical Function and LV Diastolic Function

To gain insight into the association between the LA and the LV in our patient population, the LV diastolic parameters were
tomical remodeling, these 171 patients were categorized into 4 groups, using the LA anterior-posterior diameter measured with echocardiography and the LA voltage. Those whose LA diameter was <40 mm were categorized into the small LA group, and ≥40 mm was classified as large LA group. Those whose LA voltage was less than the median voltage value of the small (1.41 mV) and large LA groups (1.45 mV) were classified as displaying low voltage in their respective groups. These 4 groups were: (1) small LA/high voltage, (2) small LA/low voltage, (3) large LA/high voltage, and (4) large LA/low voltage (Table 4). The small LA/high voltage group represented the least remodeled stage and the large LA/low voltage group depicted the most extensively remodeled LA (4 group differences in ANOVA: P<0.001 for LA size, P=0.001 for LA volume index, P<0.001 for LA voltage; Table 4). What is striking about the comparisons of these 4 groups is that as remodeling of the chamber progressed, variables known to indicate LA mechanical function and LV diastolic function also changed accordingly. LAA-FV decreased (P=0.003), and E/Em increased dramatically (P<0.001) as remodeling progressed (Figure 3). The same can be said for 2 other indicators of diastolic function: left pulmonic vein systolic/diastolic ratio (P=0.007) and LA diastolic pressure (P=0.001).

LV Diastolic Function and LA Electroanatomical Remodeling

Of the 286 patients, high-density LA voltage mapping data were available for 171. To assess in detail the changes in various parameters in relation to the extent of LA electroanatomical remodeling, these 171 patients were categorized into 4 groups, using the LA anterior-posterior diameter measured with echocardiography and the LA voltage. Those whose LA diameter was <40mm were categorized into the small LA group, and ≥40mm was classified as large LA group. Those whose LA voltage was less than the median voltage value of the small (1.41 mV) and large LA groups (1.45 mV) were classified as displaying low voltage in their respective groups. These 4 groups were: (1) small LA/high voltage, (2) small LA/low voltage, (3) large LA/high voltage, and (4) large LA/low voltage (Table 4). The small LA/high voltage group represented the least remodeled stage and the large LA/low voltage group depicted the most extensively remodeled LA (4 group differences in ANOVA: P<0.001 for LA size, P=0.001 for LA volume index, P<0.001 for LA voltage; Table 4). What is striking about the comparisons of these 4 groups is that as remodeling of the chamber progressed, variables known to indicate LA mechanical function and LV diastolic function also changed accordingly. LAA-FV decreased (P=0.003), and E/Em increased dramatically (P<0.001) as remodeling progressed (Figure 3). The same can be said for 2 other indicators of diastolic function: left pulmonic vein systolic/diastolic ratio (P=0.007) and LA diastolic pressure (P=0.001).

compared between the 2 groups. The patients with a low LAA-FV showed a significantly lower Em velocity (6.8±2.2 vs. 7.7±2.3 cm/s, P=0.004) and a higher E/Em (10.3±4.4 vs. 9.2±3.6, P=0.034) than those with a high LAA-FV (Table 2). There also existed intriguing changes in a Doppler parameter of TEE: patients with a low LAA-FV revealed a diastolic dominant pattern in both pulmonic vein flow velocities. Therefore, in low LAA-FV patients, LV relaxation was more impaired and LV filling pressure was more elevated. When a simple correlation analysis was done, E/Em was found to be linearly correlated with LAA-FV (r=−0.19, P=0.003) and mean LA voltage (r=−0.23, P=0.004). These associations were even stronger for subjects who were ≥55 years of age and had a large LA diameter (≥40 mm) (LAA-FV r=−0.39, P<0.001; mean LA voltage r=−0.31, P=0.030; Figure 2). Subsequent multiple regression analyses found that E/Em was an independent predictor of LA mechanical function (β=−0.20, P=0.013) even after age, sex, indexed LA volume, LV mass index, LV ejection fraction and comorbidities were controlled for (Table 3).

LV Diastolic Function and LA Electroanatomical Remodeling

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LA Function vs. LV Diastolic Function

Our results shed light on the direct relationship between the mechanical function of the LA, LA electroanatomical remodeling, and LV diastolic function in PAF patients. Hence, we propose that in PAF patients, LV diastolic dysfunction is an independent predictor of LA mechanical function, which is itself closely associated with the degree of LA electroanatomical remodeling and events or risk of ischemic stroke. Moreover, 4 groups representing 4 progressive stages of electroanatomical remodeling of the LA showed drastic changes in LV diastolic function when evaluated using echocardiographic parameters or invasively measured LA pressure. In this regard, our study is, to the best of our knowledge, the first attempt to examine electroanatomical remodeling of the LA in patients with PAF through comprehensive interpretation of echocardiographic findings in combination with CT data and intracardiac electrograms.

LAA-FV and Electroanatomical Remodeling of the LA in AF
Various studies have proven LAA-FV to be a valuable means by which to predict the structure and function of the LA in fibrillation. More specifically, they have argued that larger LA and LAA sizes are associated with lower LAA-FV.\textsuperscript{13,14} What is more, as the contractility of the LA and LAA decreases, indicated by a low LAA-FV, blood stasis becomes a more common occurrence, and the risk of thrombosis and stroke increases.\textsuperscript{13-16} In addition to the mechanical function of the LAA, the degree of electroanatomical remodeling of the LA, as indicated by an increase in LA volume and a decrease in endocardial voltage, was found to be significantly associated with the risk or event of stroke in our previous study and in another study.\textsuperscript{17-20} In this study, we firstly defined the relationship between LA mechanical dysfunction as represented by a low LAA-FV on TEE and global electroanatomical remodeling of the LA in PAF patients through comprehensive interpretation of CT\textsuperscript{12} and intracardiac electrograms.\textsuperscript{21} Secondly, we found that the risk of stroke estimated by CHADS\textsuperscript{2} score and the prevalence of ischemic stroke or transient ischemic attacks were significantly higher in patients with a low LAA-FV.

Relationship Between LA Mechanical Function and LV Diastolic Function
LA and LV function are known to be interdependent.\textsuperscript{6-8,22} During the LV systolic phase, the LA works as a reservoir and its functionality can be evaluated by the right ventricular systolic pressure and the relaxation properties of the LA. During the early diastolic phase and diastasis, the LA acts as a conduit, and this aspect is mainly affected by LV diastolic function and pressure. Finally, in late LV diastole, the LA works as a pump, whereby LV compliance, pressure, and LA contractility modulate its effectiveness. Thus, we can speculate that LA function in PAF, as estimated by LAA-FV, may be altered by both LV diastolic function\textsuperscript{23,24} and LA myocardial function proper,\textsuperscript{25} which is associated with the degree of electroanatomical remodeling. However, some studies have put

### Table 3. E/Em as an Independent Predictor of Left Atrial Mechanical Function

|                          | β  | t    | P value |
|--------------------------|----|------|---------|
| LAA-FV, cm/s (R=0.286)   |    |      |         |
| Age                      | –0.13 | 0.003 |         |
| Male sex                 | 0.32  | 0.751 |         |
| BMI                      | 0.23  | 0.821 |         |
| Hypertension             | 0.66  | 0.511 |         |
| Diabetes mellitus        | –0.98 | 0.331 |         |
| LVEF                     | 1.48  | 0.141 |         |
| LV mass index            | 1.49  | 0.139 |         |
| LA volume index          | –2.13 | 0.034 |         |
| E/Em                     | –2.50 | 0.013 |         |

Abbreviations as in Tables 1, 2.
Table 4. Comparisons of Clinical, Electromechanical and Hemodynamic Characteristics of Patients Based on Size and Endocardial Voltage of the LA

|                        | Small LA          | Large LA          | P value |
|------------------------|-------------------|-------------------|---------|
|                        | High voltage (n=46) | Low voltage (n=45) |         |
| Age, years             | 53.5±10.3         | 57.9±13.1         |         |
| Male sex, n (%)        | 36 (78.3)         | 27 (60.0)         | 0.079   |
| CHADS2 Score           | 0.67±0.87         | 0.98±1.10         | 0.085   |
|                        |                   |                   |         |
| TTE: 2D and Doppler parameters |                   |                   |         |
| LA size, mm            | 35.8±3.8          | 36.2±3.3          | <0.001  |
| LV mass index, g/m²    | 64.9±7.6          | 64.8±7.4          | 0.965   |
| E velocity, cm/s       | 61.3±17.4         | 69.1±21.3         | 0.037   |
| Em velocity, cm/s      | 7.3±2.3           | 8.0±2.6           | 0.020   |
| E/Em                   | 8.7±2.6           | 9.7±4.0           |         |
|                        |                   |                   |         |
| TEE: Doppler parameters |                   |                   |         |
| LAA-FV                 | 61.4±23.1         | 61.4±16.2         | 0.003   |
| Right PV S/D ratio     | 1.23±0.39         | 0.97±0.49         | 0.015   |
| Left PV S/D ratio      | 1.49±0.49         | 1.29±0.54         | 0.007   |
| CT: 3D indexed volume  |                   |                   |         |
| LA, ml/m²              | 56.7±16.2         | 57.5±19.1         | 0.001   |
| LAA, ml/m²             | 5.0±2.6           | 4.9±2.3           | 0.855   |
| LA pressure            |                   |                   |         |
| Systolic, mmHg         | 21.3±7.7          | 20.3±7.1          | 0.489   |
| Diastolic, mmHg        | 2.5±3.7           | 4.4±3.1           | 0.001   |
| Mean, mmHg             | 11.0±4.6          | 11.9±4.7          | 0.178   |
| Pacing voltage         |                   |                   |         |
| LA, mV                 | 2.01±0.53         | 0.98±0.29         | <0.001  |
| LAA, mV                | 3.56±1.49         | 2.16±1.04         | <0.001  |

*P<0.05, compared with small LA/high voltage; †P<0.05, compared with small LA/low voltage; ‡P<0.05, compared with large LA/high voltage. S/D, systolic/diastolic. Other abbreviations as in Table 2.

Figure 3. Comparisons of left atrial (LA) mechanical function and left ventricular diastolic function based on atrial size and endocardial voltage. LAA, left atrial appendage.

Circulation Journal  Vol.77, March 2013
forth the argument that LV dysfunction develops in response to remodeling of the fibrillating atria.26,27 Our study proved that there exists a correlation between LAA-FV and E/Em in PAF, which was even more significant in older patients with a larger LA, and that the degree of electroanatomical remodeling affects the LAA-FV and E/Em in these patients. Hence, it appears that as LA pressure increases to compensate for impaired LV function and to maintain adequate filling, the overload on the LA first precipitates changes in endocardial voltage, which then evokes changes in the physical structure.6,8 Finally, progressive remodeling of the atrium increases the likelihood of developing AF. In this study, we systematically revealed the pathophysiological aspects of AF with comprehensive data that included echocardiography, CT, and electroanatomical voltage mapping. This is in contrast to the previous fragmentary studies that have attempted to prove the relationships of LAA-FV,28 LA remodeling,14,18 LV diastolic function,29 and LA thrombus formation or the events of isch-emic stroke. According to our study, among the diverse mechanisms leading to electroanatomical remodeling of the LA in PAF, LV diastolic dysfunction is a principal mechanism, especially in old patients with a large LA. Therefore, careful monitoring of heart rhythm and clinical events is mandatory in patients with PAF and LV diastolic dysfunction, because potentially deranged LA function with high E/Em is related to the risk of stroke. In subjects over 55 years of age with an enlarged LA (≥40 mm), LAA-FV reflecting LA mechanical function can be indirectly estimated by E/Em without TEE evaluation, which is a semi-invasive procedure for patients with PAF.

Study Limitations
This study was a retrospective observational study that included a highly selected group of patients referred for AF catheter ablation. In order for it to comprise only the data from patients whose LAA-FV was measured during sinus rhythm, patients with persistent AF were excluded. Although we found a close relationship to exist among LA function, LA remodeling, and LV diastolic function, we did not prove the nature of this relationship to be causal. Spontaneous termination of AF has been reported to be associated with stunning of the LA.30,31 Therefore, we cannot exclude that LA stunning affected the LAA-FV. Although the LAA-FV (TEE) and LA voltage (NavX) were measured in sinus rhythm, TTE or cardiac CT was not always done in sinus rhythm. Therefore, there might be some discrepancies between LA function and LA volume depending on rhythm status. Because the endocardial voltage was measured by point-by-point contact mapping, the values used to draw the voltage map may not have accurately represented a spatiotemporally homogeneous distribution of endocardial voltage. The 3D voltage map analysis was performed with 2D measurements.

Conclusions
LA mechanical function was closely related to the degree of LA remodeling and LV diastolic function in PAF patients, according to systematic analyses of LAA-FV, TTE parameters, 3D-CT, and electrogram-based voltage mapping. The contribution of LV diastolic dysfunction to LA electroanatomical remodeling was especially significant in older patients with a large LA diameter.

Acknowledgments
This work was supported by a grant (AO85136) from the Korea Health 21 R&D Project, Ministry of Health and Welfare, and a grant (2010-0010537) from the Basic Science Research Program of the National Research Foundation of Korea under the Ministry of Education, Science and Technology of the Republic of Korea.

Disclosure
No conflict of interest declared.

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