EFFECTS OF DIALYSIS ON LEFT VENTRICULAR DIASTOLIC FILLING IN PATIENTS WITH CHRONIC RENAL FAILURE

— Assessment with Radionuclide Ventriculography —

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To examine the effects of dialysis on left ventricular (LV) filling, gated radionuclide ventriculography was conducted in 15 patients with renal failure before and after dialysis. The LV regional function was assessed by subdividing the LV region of interest into 4 regions from which global and regional time-activity curves and their first-derivative curves were obtained. Early diastolic asynchrony was measured as the sum of the absolute values (total Δt) of the time differences (Δt) between the global peak LV filling rate (PFR) and that for each of the other 3 regions. Dialysis produced an increase in the peak LV ejection rate (PER), heart rate, total Δt and total Δt /diastolic time. It caused a delay or tendency to delay in the time to PFR without significant changes in the PFR either globally or regionally, and the PFR/PER ratio decreased both globally and regionally. These alterations indicated a failure of improvement of the global and regional LV filling, with more asynchronous filling occurring after dialysis despite the increases in PER and heart rate, both of which are expected to increase PFR and shorten the time to PFR. There was a negative correlation between the change in total Δt /diastolic time and the change in the PFR/PER ratio ($r = -0.62$, $p < 0.01$), with a greater increase in asynchrony occurring with the relative greater reduction in the relative global PFR compared with the global PER after dialysis.

Dialysis can produce early diastolic asynchronous filling, which will be associated with a failure of improvement of LV filling despite the increases in LV peak ejection rate and the heart rate. Thus, LV filling requires careful attention in patients undergoing dialysis, since the pattern and timing of the filling is altered, and the excessive water removal by dialysis may affect the LV diastolic filling.

CHRONIC renal failure and uremia can affect left ventricular (LV) function through hypertension, water retention, anemia, metabolic imbalance, myocardial damage and pericarditis. Many investigators have reported on the hemodynamic changes in LV systolic function following dialysis, using both invasive and noninvasive methods

of investigation, and have generally agreed that dialysis produces beneficial effects on LV systolic function.¹⁻⁹ Although there is widespread use of measurements of filling to describe LV diastolic function, there is little information available on how the LV filling characteristics are influenced by dialysis. Previous observations have suggested that LV filling is dependent on preload conditions,²¹ and that the preload reduction caused by hypovolemia¹⁸ or lower body

Key words:
Diastolic filling and hemodialysis

(Received November 16, 1989; accepted January 22, 1990)

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Fig.1. The LV region of interest was divided into basal, septal (SEP), apical (AX), and lateral (LAT) regions at the geometric center of the area. The background correction was estimated in each of the LV region of interest. The basal region was excluded from analysis. ED=end-diastole, ES=end-systole.

Fig.2. The first derivative curves (dV/dt). From top to bottom, GLB=global left ventricle, SEP=septal region, LAT=lateral region, AX=apical region, PER=peak ejection rate, PFR=peak filling rate, TPFR=time to peak filling rate, DT=diastolic time, Δt =time difference between the peak filling rate for the global left ventricle and that for each of the three regions.

negative pressure²⁸ is associated with impairment of LV filling. Routine dialysis is known to be accompanied by a preload reduction due to water removal and metabolic changes, and these alterations may affect LV diastolic filling.

The purpose of this study was to test the hypothesis that alteration of the loading con-

TABLE I METABOLIC PARAMETERS BEFORE AND AFTER DIALYSIS (n=15)

	Before	After	p value
Blood urea nitrogen (mg/dl)	104±31	45±22	<0.001
Creatinine (mg/dl)	14.6±2.6	6.9±1.8	<0.001
Potassium (mEq/dl)	5.1±0.6	3.7±0.4	<0.001
Sodium (mEq/dl)	138±4	135±2	<0.01
Chloride (mEq/dl)	100±4	94±3	<0.001
Phosphorus (mEq/dl)	5.7±1.7	3.2±0.7	<0.001
Calcium (mEq/dl)	5.3±1.7	6.2±2.1	<0.001
Uric acid (mg/dl)	8.1±1.8	3.1±1.0	<0.001

Values represent mean ± SD.

ditions caused by dialysis can have influence on the diastolic LV filling pattern. Radionuclide ventriculography and echocardiography were used in 15 patients with chronic renal failure on dialysis to investigate this hypothesis.

MATERIALS AND METHODS

Patient selection

Fifteen stable patients on maintenance dialysis who gave informed consent to the trial were the subjects. The mean age of the patients was 45 ± 12 years (age range 22 to 70 years) and the duration of dialysis prior to this study ranged from 0.3 to 10.5 years, the average duration being 3.6 ± 3.0 years. These patients were selected on the basis of their clinical stability and their suitability for precise radionuclide and echocardiographic measurements. Thus, patients with regional contraction abnormalities that might invalidate echocardiographic measurements of LV volume were excluded from the study. All patients were undergoing regular dialysis treatment three times a week at the Hemodialysis Unit of the National Hamada Hospital. The causes of renal failure were chronic glomerulonephritis (8), chronic pyelonephritis (2), hydronephrosis (2) and di-

abetic nephropathy (3). None of the patients had clinical evidence of coronary artery disease or hypertensive heart disease and none were taking cardioactive drugs. All patients were in sinus rhythm and none had conduction disturbances. The average time needed for each dialysis session was 3 h. Radionuclide ventriculography and echocardiography were performed both 30 min before and 30 min after dialysis. Patients were weighed and blood samples were withdrawn from the arterial line both immediately before and after dialysis, for determination of blood urea nitrogen, creatinine, calcium, phosphorus, potassium, sodium, chloride, and uric acid.

Gated radionuclide ventriculography

Multigated equilibrium blood pool imaging was performed both before and after dialysis using a conventional gamma camera (Ohio Nuclear Sigma 410S) equipped with a high-resolution, all-purpose, parallel-hole collimator. The technique used in this study has been reported previously.¹⁵⁻¹⁷ In brief, all patients were studied while resting supine. Each patient was injected with 20 mCi of technetium-99 m-labeled human serum albumin 10 min prior to the initial study (before dialysis), and an additional 10 mCi was given 10 min prior to the second study (after dialysis) to correct count decay. The camera was placed in the 40° to 60° modified left anterior oblique projection (15° caudal tilt), depending on the greatest separation of the right and left ventricles.

Images were stored on a magnetic disc of a computer system (Ohio Nuclear VIP 450). The average RR interval was separated into 25 equal frames, and cardiac cycles with RR intervals that were not within 10% of this average interval were rejected. Counts were acquired until the desired count density (200 counts/pixel) was reached in the first acquisition frame. Only those photoevents falling within a 20% window centered on the photopeak of technetium-99 m were recorded. Acquisition was completed within about 5 min in each study. Blood pressure was measured with a cuff sphygmomanometer and stethoscope during the study period.

Original multiple-gated mode data were collected with a 64 by 64 matrix. The background region of interest was traced manually with a light pen along the lateral, apical

and septal portions adjacent to and inside the end-diastolic perimeter that was applied to the end-systolic frame (Fig. 1). A computer program determined the geometric center of the area inside the end-diastolic perimeter of the left ventricle.¹⁶ The area was then subdivided into basal, septal, apical and lateral regions by 2 lines intersecting at an angle of 45° to the longitudinal axis of the left ventricle at the above-mentioned geometric center (Fig. 1). Background-corrected global and regional time-activity curves and their first-derivative curves (dV/dt) were generated after 3-point temporal smoothing using the fixed region of interest method, which is superior in reducing measurement variability and appears to be the preferred method for analyzing serial studies.²⁶ Global ejection fractions calculated by this technique correlated well with those determined by cineangiography ($r=0.92$, $p<0.001$, $n=24$).¹⁶ The maximum value of positive dV/dt in the first half of diastole was defined as the peak LV filling rate. End-systole was defined as the minimum volume at which the dV/dt value was zero. The minimum value of negative dV/dt during systole was defined as the peak LV ejection rate. Since the basal region of the left ventricle tended to overlie the regions of the mitral and aortic valves, aorta, left atrium and great vessels, this region was excluded from the study. Using the data thus obtained, the following indexes were derived both globally and regionally (Fig. 2).

Systolic phase indexes: (1) Ejection fraction (%) (2) Peak ejection rate normalized to end-diastolic counts (end-diastolic counts/s). (3) Time to end-systole (ms) and time to end-systole/R-R interval = the time interval between the electrocardiographic R wave and the end systole was defined as the time to end-systole, and the time interval was divided by the R-R interval to take into account the effect of heart rate.

Diastolic phase indexes: (1) Peak filling rate normalized to end-diastolic counts (end-diastolic counts/s). (2) Peak filling rate/peak ejection rate. This ratio was used to normalize peak filling rate for peak ejection rate and to cancel the influence of the end-diastolic counts on the peak filling and peak ejection rates,^{16,17} since peak filling rate closely parallels peak ejection rate and these rates

TABLE II ECHOCARDIOGRAPHIC PARAMETERS BEFORE AND AFTER HEMODIALYSIS (n=15)

	Before	After	p value
End-diastolic dimension (mm)	51±6	48±6	<0.001
End-systolic dimension (mm)	32±4	31±4	NS
End-diastolic volume (ml)	127±36	110±30	<0.001
End-systolic volume (ml)	41±13	38±15	NS
Ejection fraction (%)	67±7	66±9	NS
Stroke volume (ml)	86±28	73±24	<0.01
Cardiac output (L/min)	6.18±2.50	5.65±1.90	NS
Left atrial dimension (mm)	31±5	27±6	<0.01

Values represent mean±SD.

may be influenced by end-diastolic volume!¹⁰ (3) Time to peak filling rate (ms) and time to peak filling rate/diastolic time. The time elapsed from global end-systole to peak filling rate was defined as the time to peak filling rate. This was divided by the diastolic time to take into account the effect of heart rate!^{10,15} The time elapsed from global end-systole to the next global end-diastole was defined as the diastolic time.

Indexes of regional asynchrony: (1) Total Δt (ms) and total Δt /diastolic time=the sum of the absolute values of the time difference (Δt) from the peak positive dV/dt of the global left ventricle to that for each of the 3 other regions studied. It was defined as the total Δt and was divided by the diastolic time to take into account the effect of heart rate. Regional asynchrony has been shown to increase along with an increase in the values of these indexes!¹⁵⁻¹⁷

The reproducibility of the variables measured in this study has been reported and validated in patients both with and without regional wall motion abnormalities!^{15,16}

Echocardiography

The LV dimensions, volume and wall motion were evaluated by M-mode echocardiography with the aid of two-dimensional

echocardiography at the level of the distal mitral leaflets using a Toshiba SSH 40A. The LV end-diastolic diameter at the peak of the QRS complex, the LV end-systolic diameter at the point of maximum septal contraction, and the left atrial diameter at the point of maximum dilatation were measured for 3 consecutive cardiac cycles and then averaged. The LV volume was calculated using Teichholz's equation!²⁵ Special care was taken to make serial recordings at similar levels in the left ventricle both before and after dialysis.

Statistical analysis

All data are presented as the mean±standard deviation (SD). The paired t test was used to compare the values before and after dialysis. Simple correlation analysis was performed to determine which alterations in metabolic factors (before dialysis vs after dialysis) were related to changes in the radionuclide-derived parameters (before vs after). Linear regression analysis by the least-squares method was used to determine the relationship between changes in regional asynchrony (before vs after) and changes in the ratio of global peak LV filling rate to global peak LV ejection rate (before vs after). The level of statistical significance was set at $p<0.05$.

RESULTS

The data are summarized in Tables I to IV. Dialysis returned blood biochemical parameters towards normal, with the levels of blood urea nitrogen, plasma creatinine, potassium, sodium, chloride, uric acid and phosphorus all showing significant decreases following dialysis, while there was a concomitant increase in the serum calcium level (Table I). Body weight declined in all patients by 1.6 ± 0.8 kg (range from 0.5 to 2.8 kg) from an initial value of 53.8 ± 8.1 kg. Heart rate increased significantly from an initial value of 74 ± 12 to 79 ± 11 beats/min ($p<0.01$). There was a significant shortening of the R-R interval following dialysis (from 840 ± 147 to 776 ± 115 ms, $p<0.02$). This shortening mainly resulted from a significant decrease in the time to end-systole (from 414 ± 52 to 365 ± 35 ms, $p<0.001$), when it would be expected that the changing

TABLE III RADIONUCLIDE PARAMETERS BEFORE AND AFTER HEMODIALYSIS (n=15)

	Before	After	p value
<i>Heart rate (beats/min)</i>	74±12	79±11	<0.01
<i>Systolic blood pressure (mm Hg)</i>	123±39	122±25	NS
<i>Diastolic blood pressure (mm Hg)</i>	74±18	70±19	NS
<i>R-R interval (ms)</i>	840±147	776±115	<0.02
<i>Diastolic interval (ms)</i>	425±113	411±101	NS
<i>Ejection fraction (%)</i>			
<i>Global</i>	60±10	61±9	NS
<i>Septal</i>	62±9	58±11	NS
<i>Apical</i>	74±13	79±11	NS
<i>Lateral</i>	71±10	77±11	NS
<i>Peak ejection rate (end-diastolic counts/s)</i>			
<i>Global</i>	2.60±0.54	3.09±0.68	<0.01
<i>Septal</i>	2.80±0.56	2.99±0.66	NS
<i>Apical</i>	3.31±0.79	4.09±0.88	<0.01
<i>Lateral</i>	2.98±0.70	3.86±0.91	<0.001
<i>Time to end-systole (ms)</i>			
<i>Global</i>	414±52	365±35	<0.001
<i>Septal</i>	397±51	358±30	<0.01
<i>Apical</i>	422±52	376±39	<0.001
<i>Lateral</i>	427±58	383±43	<0.001
<i>Time to end-systole/R-R interval</i>			
<i>Global</i>	0.50±0.05	0.48±0.06	NS
<i>Septal</i>	0.48±0.05	0.47±0.05	NS
<i>Apical</i>	0.51±0.06	0.49±0.07	NS
<i>Lateral</i>	0.51±0.05	0.50±0.06	NS
<i>Peak filling rate (end-diastolic counts/s)</i>			
<i>Global</i>	2.66±0.65	2.39±0.56	NS
<i>Septal</i>	2.65±0.86	2.45±0.46	NS
<i>Apical</i>	3.62±0.97	3.25±0.90	NS
<i>Lateral</i>	3.47±0.75	3.34±0.79	NS
<i>Peak filling rate/peak ejection rate</i>			
<i>Global</i>	0.99±0.17	0.79±0.20	<0.001
<i>Septal</i>	0.95±0.25	0.81±0.18	<0.05
<i>Apical</i>	1.12±0.26	0.81±0.21	<0.001
<i>Lateral</i>	1.18±0.22	0.89±0.21	<0.001
<i>Time to peak filling rate (ms)</i>			
<i>Global</i>	171±46	189±40	<0.02
<i>Septal</i>	189±48	206±35	NS
<i>Apical</i>	168±51	185±50	NS
<i>Lateral</i>	150±40	158±28	NS
<i>Time to peak filling rate/diastolic time</i>			
<i>Global</i>	0.42±0.10	0.47±0.09	<0.02
<i>Septal</i>	0.45±0.11	0.51±0.10	NS
<i>Apical</i>	0.41±0.12	0.46±0.11	NS
<i>Lateral</i>	0.36±0.09	0.39±0.07	NS
<i>Total Δt (ms)</i>	52±23	77±33	<0.01
<i>Total Δt/diastolic time</i>	0.13±0.07	0.20±0.10	<0.01

Values represent mean ± SD.

Fig.3. The value of total Δt /diastolic time, quantification of asynchronous diastolic filling, increased significantly following dialysis.

R-R interval was due to changes in diastasis. There was no statistically significant decrease in the diastolic interval after dialysis, and neither systolic nor diastolic blood pressure was altered.

Echocardiographic parameters (Table II)

Following dialysis, the LV end-diastolic dimension, LV end-diastolic volume and left atrial dimension all decreased significantly by 6% ($p < 0.001$), 13% ($p < 0.01$) and 13% ($p < 0.01$), respectively, from the initial values of 51 ± 6 mm, 127 ± 36 ml and 31 ± 5 mm, respectively, implying preload reduction. Stroke volume decreased significantly by 15% from 86 ± 28 to 73 ± 24 ml ($p < 0.01$). The LV end-systolic dimension, LV end-systolic volume and cardiac output all tended to decrease, but no statistically significant differences were observed, and the ejection fraction also did not change significantly.

Radionuclide-derived parameters (Table III)

The ejection fraction showed no change following dialysis. The peak ejection rate, which is a sensitive indicator of subtle improvements in systolic function,^{16,17} increased or tended to increase globally and regionally. The time to end-systole decreased, but the time to end-systole corrected for R-R interval showed no change. Since arterial blood pressure did not alter after dialysis, these findings probably resulted from an improvement in LV systolic function and a decrease in stroke volume. Thus, there was an improvement in LV peak ejection rate and an increase in heart rate following dialysis, two

Fig.4. There was a negative correlation between the change in the ratio of the peak filling rate to the peak ejection rate (Delta (peak filling rate/peak ejection rate)) and the change in the total Δt /diastolic time (Delta (Total Δt /diastolic time)), with a greater increase in asynchrony being seen with the greater reduction in the relative global peak filling rate after dialysis.

events which would be expected to increase the peak filling rate and shorten the time to peak filling rate^{10,15-17}. However, the peak filling rate showed no improvement and a delay or tendency to delay in the time to peak filling rate occurred globally and regionally despite a slight shortening of diastolic time. The ratio of peak filling rate to peak ejection rate was reduced for the global left ventricle and for each of the three regions following dialysis, indicating a failure of LV filling to improve in comparison with the increase in peak ejection rate.

Following dialysis, total Δt and total Δt /diastolic time showed significant increase in 13 of the 15 patients (Fig. 3), indicating an increase in asynchronous diastolic filling. There was a negative correlation between the change in the ratio of global peak filling rate to global peak ejection rate and the change in the total Δt ($r = -0.62$, $p < 0.01$) or the total Δt /diastolic time ($r = -0.62$, $p < 0.01$). Thus, asynchronous LV filling increased as the relative global peak filling rate decreased in comparison with the global peak ejection rate after dialysis (Fig. 4).

Simple correlations between changes in radionuclide-derived parameters and those in metabolic parameters following dialysis (Table IV)

TABLE IV SIMPLE CORRELATION COEFFICIENTS BETWEEN CHANGES IN RADIONUCLIDE-DERIVED PARAMETERS AND THOSE IN METABOLIC PARAMETERS AFTER DIALYSIS (n=15)

	PER	TES	PFR	TPFR	TPFR/DT	PFR/PER	Total Δt	Total $\Delta t/DT$
BUN	0.42	0.03	0.75**	-0.23	0.11	0.51	-0.45	-0.45
Cr	0.32	-0.15	0.63*	0.17	0.09	0.49	-0.50	-0.46
K	-0.19	0.13	0.17	-0.26	-0.37	0.45	-0.69**	-0.51
Ca	0.23	-0.09	-0.19	0.06	0.25	-0.43	0.36	0.36
P	-0.13	0.27	0.06	-0.24	0.03	-0.14	0.06	0.18
UA	-0.19	-0.20	0.28	0.18	-0.05	0.38	-0.37	-0.32
BW	-0.12	-0.002	0.40	0.13	-0.03	0.57*	-0.49	-0.42

Abbreviations: BUN=blood urea nitrogen, Cr=creatinine, K=potassium, Ca=Calcium, P=phosphorus, UA=uric acid, PER=peak ejection rate, BW=loss of body weight, TES=time to end-systole, PFR=peak filling rate, TPFR=time to peak filling rate, DT=diastolic time.

**= $p < 0.01$, *= $p < 0.05$

The biochemical influences on the diastolic filling were evaluated using simple correlation coefficients (Table IV). There were significant correlations between the changes in global peak filling rate and in blood urea nitrogen ($r=0.75$, $p<0.01$) or creatinine ($r=0.63$, $p<0.05$). Thus, the greater the decrease in blood urea nitrogen or creatinine after dialysis, the greater was the decrease in global peak filling rate, although there was no statistically significant decrease in the global peak filling rate after dialysis but the tendency to decrease existed. There was a significant negative correlation between changes in total Δt and changes in the potassium level ($r=-0.69$, $p<0.01$), so that the greater was the decrease in potassium the greater was the increase in total Δt or asynchronous LV filling. There was a significant positive correlation between the loss of body weight and the changes in the ratio of global peak filling rate to global peak ejection rate ($r=0.57$, $p<0.05$), indicating that the global peak filling rate may decrease in comparison with the global peak ejection rate as the water removal increases.

DISCUSSION

Changes in LV filling following dialysis

Dialysis did not improve LV filling either globally or regionally in comparison with LV systolic function. There is general agreement that dialysis produces beneficial effects on LV systolic function in azotemic patients!¹⁻⁹ The pattern of LV filling may be

altered by numerous factors other than LV diastolic function and hemodynamic changes, including metabolic changes due to dialysis. The changes in these factors that occur following dialysis make the interpretation of LV filling changes more complicated. Since overall LV filling during dialysis may be determined by a combination of these factors, each one would need to be analyzed separately to determine its relative contribution. Simple correlation analysis of the changes in radionuclide-derived and metabolic parameters following dialysis showed that some of the metabolic changes correlated with changes in LV filling (Table IV). The levels of blood urea nitrogen, creatinine and potassium, which change in association with hemodynamic alterations, were significantly related to the LV filling. It is unknown whether the metabolic consequences of dialysis had a direct or indirect (probably through simply a preload factor) effect on LV filling, since many other factors are also altered by dialysis. It would be necessary to evaluate fully the direct effects of metabolic changes due to dialysis on LV filling. Few patients were included in this study. If more patients are studied, partial correlation coefficients or multiple linear regression analysis will be helpful in this regard.

LV filling in early diastole is complex and depends on multiple factors in addition to the metabolic changes, such as the LV relaxation rate,^{12,18,19} LV systolic function,¹⁰ the afterload,²⁷ the preload,^{16-18,21,28} the atrioventricular pressure gradient,^{18,20} the

heart rate,¹⁰ mitral valve function,¹⁸ asynchronous wall motion¹⁴⁻¹⁷ and the pericardium.²² The interaction of these factors must be considered to study the origin of the failure of LV filling to improve following dialysis.

The LV systolic function as assessed by the peak ejection rate and the heart rate increased significantly following dialysis, and these changes would be expected to improve LV filling.^{10,15-17} Afterload as assessed by arterial blood pressure did not alter significantly after dialysis. Mitral valve function and the pericardium were assessed by echocardiography as normal in all patients, and there is little possibility that mitral valve function and the pericardium changed following dialysis. Since the relevant hemodynamic parameters were not obtained in this study, it was not possible to judge the effects of other factors on LV filling.

Among the most likely causes for the failure of an improvement in LV filling to occur following dialysis may be a reduction in venous return due to water removal, the preload reduction that normally occurs during dialysis. In this study, the more the body weight declined due to water removal after dialysis the more the global peak filling rate decreased in comparison with the global peak ejection rate (Table IV). This supports the above-mentioned possibility. The decrease in venous return induced by dialysis should result in a lower mitral valve opening pressure, which would account for the decrease in peak filling rate and the delay of the time to peak filling rate.

Yellin et al¹⁸ have reported that preload reduction due to hypovolemia caused both impairment of LV relaxation and impairment of early mitral inflow. Other investigators have reported that asynchronous wall motion was accompanied by the impairment of LV relaxation.²³ These findings strongly suggest that the preload reduction induced by dialysis may cause impairment of early diastolic filling in association with asynchronous LV wall motion. Regarding LV filling, it has been reported that after the mitral valve opens, the incoming jet of blood strikes the apex and spreads out to flow up the septal walls to the base of the left ventricle in both normal and diseased hearts.²⁴ This incoming blood flow pattern may produce asynchrony in early diastole, which

could be exaggerated when preload or venous return decrease following dialysis, since the amount of blood returning to the left ventricle lessens and the inflow blood velocity probably decreases. Similar patterns of global and regional LV filling have been described after isosorbide dinitrate administration in normal subjects and in patients with coronary artery disease, and the changes observed in LV filling are best explained by the effects of preload reduction.^{16,17}

This study indicates that early diastolic asynchronous filling after dialysis may be associated with a failure of LV diastolic filling to improve. This occurs despite the concomitant improvement in LV peak ejection rate and increase in heart rate, which would normally be expected to improve LV diastolic filling. Thus, in patients on dialysis, assessment of LV filling requires careful attention, since the pattern and timing of LV filling are altered by dialysis, and such changes may have clinical significance because excessive water removal by dialysis may affect the diastolic LV filling.

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