Original Article

Relationships between Echocardiographic Findings, Pulse Wave Velocity, and Carotid Atherosclerosis in Type 2 Diabetic Patients

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The purpose of the present study was to analyze the relationships between echocardiographic findings, brachial-ankle pulse wave velocity, and carotid atherosclerosis in type 2 diabetic patients. In 70 type 2 diabetic patients without cardiovascular disease, pulse wave velocity was measured using an automatic waveform analyzer, and the carotid plaque score was obtained by carotid ultrasonography. The left ventricular wall thickness and the indexes of left ventricular diastolic function (the peak velocity of early rapid filling [E velocity], the peak velocity of atrial filling [A velocity], and the E/A ratio) were obtained by echocardiography. Brachial-ankle pulse wave velocity correlated significantly with the carotid plaque score, but the correlation was weak (r=0.37, p=0.001). The brachial-ankle pulse wave velocity demonstrated a strong correlation with the A velocity (r=0.73, p<0.001), the ratio of E to A (E/A) (r=−0.63, p<0.001), and the deceleration time of the E velocity (r=0.48, p<0.001). Stepwise regression analysis showed that the A velocity (β coefficient=0.42, p<0.001) and ventricular septal thickness at the left ventricular outflow tract (β coefficient=0.27, p=0.001) were independently associated with brachial-ankle pulse wave velocity. Stepwise regression analysis indicated that ventricular septal thickness at the left ventricular outflow tract (β coefficient=0.38, p=0.001) was independently associated with the plaque score. These results indicate that left ventricular diastolic dysfunction as revealed by increased peak velocity of atrial filling reflects arterial stiffening in type 2 diabetic patients. In addition, myocardial wall thickening at the left ventricular outflow tract reflects not only arterial stiffening but also carotid atherosclerosis. Therefore, these abnormal echocardiographic findings of left ventricular diastolic dysfunction and myocardial wall thickening may be useful markers of the presence of progressive arteriosclerosis in type 2 diabetic patients. (*Hypertens Res* 2005; 28: 965–971)

***Key Words*: arteriosclerosis, pulse wave velocity, carotid ultrasonography, echocardiography, diastolic dysfunction**

Introduction

Patients with type 2 diabetes mellitus have latent impaired cardiac function because of microvascular myocardial perfusion abnormalities or asymptomatic coronary artery disease (*1*, *2*). Screening for cardiac dysfunction may be important for type 2 diabetic patients, even if the patients are at the early

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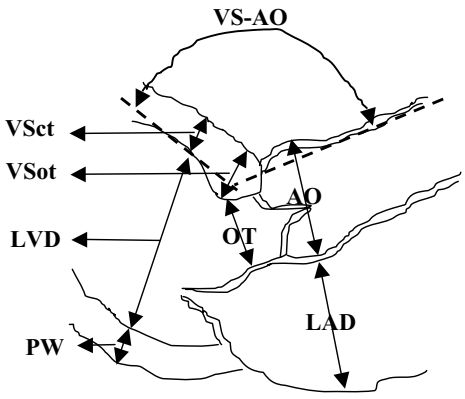

Fig. 1. *Measurements of left ventricular (LV) structural parameters: the ventricular septal thickness at the LV outflow tract (VS_{ot}), the dimensions of the LV outflow tract (OT), the angle between the ventricular septum and ascending aorta (VS-AO), the ventricular septal thickness at the chordae tendineae level (VS_{ct}), the LV end-diastolic dimension at the chordae tendineae level (LVD), the LV posterior wall thickness at the chordae tendineae level (PW), the dimensions of the ascending aorta (AO), and the end-systolic dimension of the left atrium (LAD). The VS_{ot}, OT, and VS-AO were measured at the end-diastolic phase by two-dimensional echocardiography. The VS_{ct}, LVD, PW, AO, and LAD were measured by M-mode echocardiography.*

stage of type 2 diabetes mellitus without cardiovascular events (*3*). Doppler echocardiography can detect left ventricular diastolic dysfunction even in patients with normal left ventricular systolic function (*4*). It has recently been reported that at least 30% of patients with congestive heart failure have preserved systolic function and that these patients have diastolic dysfunction (*5*). Thus, echocardiographic examination may be needed for clinical-course observation of cardiac function and prevention of heart failure in type 2 diabetic patients.

Both carotid ultrasonography and pulse wave velocity are established markers of arteriosclerosis (*6–9*). Although several studies (*10*, *11*) have demonstrated that the two markers are correlated, the correlation is not close. Arteriosclerosis involves two important changes: thickening and stiffening of the arterial wall (*12*). Therefore, the arterial stiffening as assessed by pulse wave velocity may be different from the arterial thickening as assessed by carotid ultrasonography. Although a recent study has reported that brachial-ankle pulse wave velocity reflects cardiac function as assessed by echocardiography in patients with hypertension (*13*), the correlation between echocardiographic findings and brachial-ankle pulse wave velocity has not been fully evaluated. The purpose of the present study was to clarify the relationships between echocardiographic findings, pulse wave velocity, and carotid atherosclerosis in type 2 diabetic patients.

Table 1. Clinical and Ultrasonographic Characteristics of the Subjects

Number (male/female)	70 (34/36)
Age (years)	62±5
BMI (kg/m^2)	23.5±12.1
Systolic BP (mmHg)	130±16
Diastolic BP (mmHg)	80±10
HbA1c (%)	10.1±3.2
Total cholesterol (mg/dl)	201±9
Triglyceride (mg/dl)	198±124
baPWV (cm/s)	1,520±131
Plaque score	1.1±1.6
Echocardiographic parameters	
EF (%)	71±4
E (m/s)	0.61±0.09
A (m/s)	0.77±0.05
E/*A*	0.83±0.24
DcT (ms)	237±46

BMI, body mass index; BP, blood pressure; baPWV, brachial-ankle pulse wave velocity; EF, left ventricular ejection fraction; *E*, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; *E*/*A*, the ratio of *E* to *A*; DcT, deceleration time of early diastolic transmitral flow.

Methods

Subjects and Protocol

Seventy consecutive patients who were diagnosed as having type 2 diabetes at Sakaide Municipal Hospital were entered in the present study from April 2004 to the end of February 2005. Informed consent was obtained from all of the participants. None of the subjects had a history of any atherosclerotic cardiovascular diseases or stroke. Blood pressure was determined in the outpatient clinic using the conventional cuff method. Brachial-ankle pulse wave velocity, echocardiography, ultrasongraphy of the carotid artery, and blood sampling were performed in the morning after a 12-h overnight fast. Plasma total cholesterol, triglyceride, and HbA1c were measured by standard laboratory techniques. This protocol was approved by the Ethical Committee of Sakaide Municipal Hospital.

Assessment of Pulse Wave Velocity

Brachial-ankle pulse wave velocity was measured using an automatic waveform analyzer (VaSera VS-1000; Fukuda, Tokyo, Japan). Details of the methodology have been described elsewhere (*14*). Measurements were taken with subjects lying in a supine position after resting for at least 5 min. Electrocardiographic electrodes were placed on both wrists, and cuffs were wrapped on the bilateral brachia and ankles. Pulse volume waveforms at the brachium and ankle

Table 2. Correlation Coefficients of Linear Regression Analysis between Brachial-Ankle Pulse Wave Velocity and Other Parameters

	r	*p* value
Age	0.67	<0.001
Systolic BP	0.51	<0.001
Plaque score	0.37	0.001
LV structure		
VS_{ot}	0.63	<0.001
VS_{ct}	0.34	0.004
PW	—	N.S.
LV mass index	0.33	0.006
VS-AO	−0.34	0.004
LAD	0.37	0.002
LV diastolic function		
E	—	N.S.
A	0.73	<0.001
E/*A*	−0.63	<0.001
DcT	0.48	<0.001

BP, blood pressure; LV, left ventricular; VS_{ot}, ventricular septal thickness at left ventricular outflow tract; VS_{ct}, ventricular septal thickness at chordae tendineae level; PW, left ventricular posterior wall thickness at chordae tendineae level; VS-AO, angle between the ventricular septum and the ascending aorta; LAD, left atrial dimension; *E*, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; *E*/*A*, the ratio of *E* to *A*; DcT, deceleration time of early diastolic transmitral flow.

were recorded using a semiconductor pressure sensor.

Ultrasonographic Measurement of Carotid Plaque Score

Details of the carotid ultrasonic examination methods were published previously (*15*). We used a high-resolution B-mode ultrasonic machine (PowerVision 6000; Toshiba, Tokyo, Japan) with a 10.0-MHz transducer yielding an axial resolution of 0.1 mm. The regions from 30 mm proximal to the beginning of the dilation of the bifurcation bulb to 15 mm distal to the flow divider of both common carotid arteries were scanned. All measurements were made at the time of scanning with an electronic caliper and were recorded on photocopies. Intima-media thickness was measured on a longitudinal scan of the carotid arteries. We defined a plaque as an area with focal intima-media thickness ≥1.1 mm, and the plaque score was calculated as the sum of the maximum thicknesses of all plaques measured in mm on the near and far walls of the vessels (*15*).

Echocardiographic Examination

Two-dimensional and M-mode echocardiography was performed using an echocardiographic instrument (PowerVision 6000; Toshiba) with a 2.5-MHz transducer. We first measured the following left ventricular structural parameters: the ventricular septal thickness at the left ventricular outflow tract (VS_{ot}), the dimensions of the left ventricular outflow tract (OT), the angle between the ventricular septum and the ascending aorta (VS-AO), the ventricular septal thickness at the chordae tendineae level (VS_{ct}), the left ventricular end-diastolic dimension at the chordae tendineae level (LVD), the left ventricular posterior wall thickness at the chordae tendineae level (PW), the dimensions of the ascending aorta (AO), and the end-systolic dimension of the left atrium (LAD). VS_{ot}, OT, and VS-AO were measured at the end-diastolic phase by two-dimensional echocardiography (Fig. 1). VS_{ct}, LVD, PW, AO, and LAD were measured by M-mode echocardiography.

The left ventricular mass was calculated according to the Penn convention (*16*) using the formula: left ventricular mass $=0.80 \times 1.04 \times [(PW + VS_{ct} + LVD)^3 - (LVD)^3] + 0.6$. The left ventricular mass index was calculated as the left ventricular mass divided by the body surface area. We next measured the parameters of left ventricular diastolic function by recording the left ventricular diastolic inflow using pulsed Doppler echocardiography (*17*). The left ventricular diastolic filling pattern was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and the peak velocity of atrial filling (A velocity) were recorded, and the ratio of E to A (*E*/*A* ratio) was calculated. The deceleration time of E velocity (DcT) was measured as the time interval from the E-wave peak to the decline of the velocity to baseline values. Because all subjects in the present study had a normal left ventricular systolic function (left ventricular ejection fraction ≥55%), no subject had a pseudonormal left ventricular diastolic filling pattern (*18*).

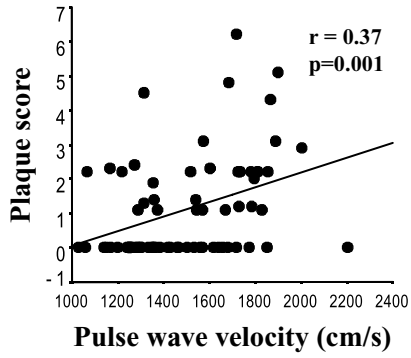

Fig. 2. *Correlation between plaque score and pulse wave velocity.*

Statistical Analysis

Data are expressed as the mean±SD. Statistical analysis was performed using an SPSS software package (SPSS, Chicago,

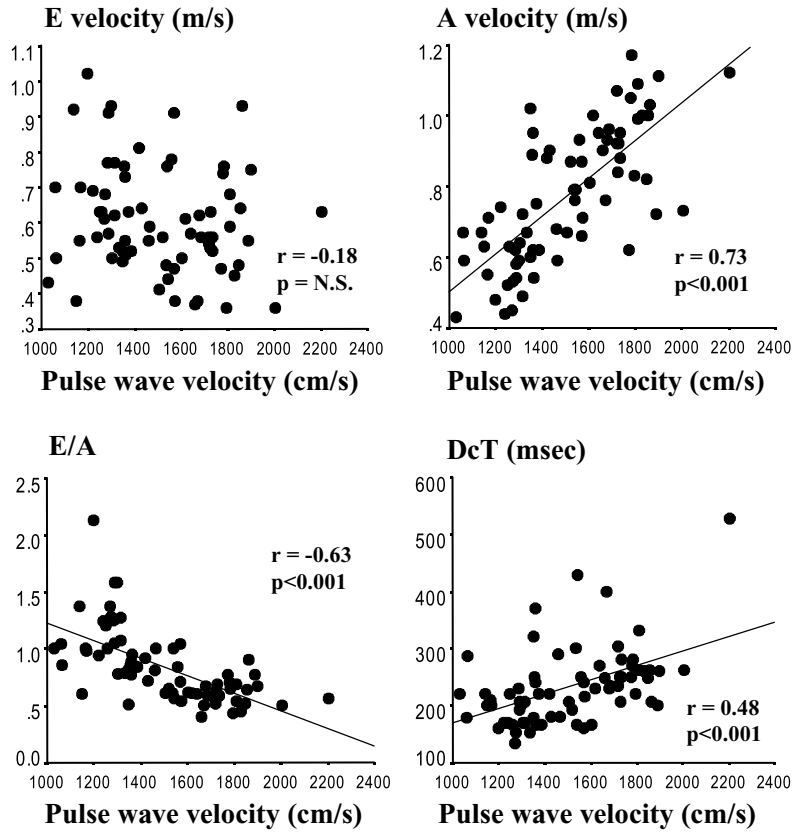

Fig. 3. *Correlation between pulse wave velocity and peak early diastolic transmitral flow (E velocity), peak late diastolic transmitral flow (A velocity), the ratio of E to A (*E/A*), and the deceleration time of E velocity (DcT).*

USA). Linear regression analysis was performed to evaluate the association between brachial-ankle pulse wave velocity and other variables. Stepwise multiple regression analysis was performed to determine the correlation and independent variables for the brachial-ankle pulse wave velocity and plaque score. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Clinical and Ultrasonographic Characteristics in Patients with Type 2 Diabetes

Clinical and carotid ultrasonographic parameters and the echocardiographic results of the patients with type 2 diabetes in the present study are summarized in Table 1. Their mean left ventricular ejection fraction was 71±4%; all patients had normal systolic function (left ventricular ejection fraction ≥55%). Their mean *E*/*A* was 0.83±0.24, and the mean DcT was 237±46 ms.

Association between Brachial-Ankle Pulse Wave Velocity and Other Variables

Linear regression analysis was performed to examine the relationship between brachial-ankle pulse wave velocity and other variables. The significantly associated parameters are shown in Table 2. The value for brachial-ankle pulse wave velocity correlated positively with age ($r=0.67$, $p<0.001$) and systolic blood pressure ($r=0.51$, $p<0.001$). Brachial-ankle pulse wave velocity correlated significantly with the plaque score, but the correlation was weak ($r=0.37$, $p=0.001$) (Fig. 2).

The value for brachial-ankle pulse wave velocity value was significantly associated with the following left ventricular structural parameters: VS_{ot}, VS_{ct}, the left ventricular mass index, VS-AO, and LAD. The correlation with VS_{ot} was the closest ($r=0.63$, $p<0.001$). In addition, the brachial-ankle pulse wave velocity was significantly associated with the parameters of left ventricular diastolic function. The brachial-ankle pulse wave velocity demonstrated a strong correlation with A velocity ($r=0.73$, $p<0.001$), *E*/*A* ($r=-0.63$, $p<0.001$), and DcT ($r=0.48$, $p<0.001$) (Fig. 3).

Table 3. Multiple Regression Analysis of Brachial-Ankle Pulse Wave Velocity and Significantly Associated Variables

Independent variables	β coefficient	*t* value	*p* value
A velocity	0.42	5.19	<0.001
Age	0.34	4.26	<0.001
VS_{ot}	0.27	3.42	0.001
	F ratio=52.83, r^2=0.71 (p<0.001)		

A velocity, peak late diastolic transmitral flow; VS_{ot}, ventricular septal thickness at the left ventricular outflow tract.

Table 4. Multiple Regression Analysis of Plaque Score and Significantly Associated Variables

Independent variables	β coefficient	*t* value	*p* value
VS_{ot}	0.38	3.42	0.001
Systolic BP	0.31	2.84	0.006
	F ratio=16.96, r^2=0.34 (p<0.001)		

VS_{ot}, ventricular septal thickness at left ventricular outflow tract; BP, blood pressure.

Assessment of the Factors Related to Brachial-Ankle Pulse Wave Velocity and Plaque Score

A stepwise multiple regression analysis was performed to adjust for the influences of different pathogenic factors on brachial-ankle pulse wave velocity and plaque score in all patients. Stepwise regression analysis indicated that A velocity (β coefficient=0.42, p<0.001), age (β coefficient=0.34, p<0.001), and VS_{ot} (β coefficient=0.27, p=0.001) were independently associated with brachial-ankle pulse wave velocity (Table 3). Stepwise regression analysis indicated that VS_{ot} (β coefficient=0.38, p=0.001) and systolic blood pressure (β coefficient=0.31, p=0.006) were independently associated with the plaque score (Table 4). Thus, the parameter of left ventricular diastolic function was independently associated with the brachial-ankle pulse wave velocity but not with the plaque score.

Discussion

This study presents data regarding relationships between echocardiographic findings, brachial ankle pulse wave velocity, and carotid ultrasonography. These data lead us to the following conclusions: 1) the correlation between brachial-ankle pulse wave velocity and carotid ultrasonography is not close; 2) myocardial wall thickening at the left ventricular outflow tract is the only independent predictor of both indexes of brachial-ankle pulse wave velocity and carotid ultrasonography; and 3) the parameters of left ventricular diastolic function correlate closely with brachial-ankle pulse wave velocity but not with the findings of carotid ultrasonography.

Although several studies have demonstrated that arterial stiffness as assessed by pulse wave velocity correlates with atherosclerotic changes as revealed by carotid ultrasonography, the correlation is not close (*10*, *11*, *13*). Yambe *et al*. have reported that the correlation coefficient of the relationship between brachial-ankle pulse wave velocity and plaque score is 0.24 (p<0.01) in patients with hypertension (*13*). Our results agree with the concept that arterial stiffness as assessed by brachial-ankle pulse wave velocity differs from arterial thickening as assessed by carotid ultrasonography, and we have demonstrated that this concept is applicable to patients with type 2 diabetes. However, we did not measure the intima-media thickness to evaluate carotid atherosclerosis. Because several studies have demonstrated a significant relationship between pulse wave velocity and intima-media thickness (*10*, *13*), we concluded that atherosclerotic changes as assessed by intima-media thickness might produce a close correlation between arterial stiffness and thickness. We did not analyze the relationship in nondiabetic patients. In order to clarify this issue, further studies will be needed in normal subjects and patients with atherosclerosis-related diseases other than diabetes mellitus.

The UK Prospective Diabetes Study (UKPDS) has shown that strict blood pressure control decreases the risk of macrovascular complications such as stroke in patients with type 2 diabetes (*19*). These results have recently increased awareness that strict control of blood pressure is necessary to prevent the progression of macroangiopathy in diabetic patients. Our study has shown that systolic blood pressure correlates well with the brachial-ankle pulse wave velocity (r=0.51, p<0.001) (Table 2) and is a major determinant of the plaque score obtained from carotid ultrasonography (Table 4). This finding is in agreement with the results of the UKPDS. However, our results provide new information indicating that VS_{ot} obtained from echocardiography is a major determinant of both brachial-ankle pulse wave velocity and plaque score (Tables 3, 4) and may be a marker of arteriosclerosis.

It has been found in several studies that pulse wave velocity correlates with the degree of left ventricular hypertrophy (*20*, *21*). Although left ventricular hypertrophy is assessed by measuring the left ventricular mass index by echocardiography, it is time-consuming to calculate the value. In contrast, measurement of VS_{ot} is simple and may be useful for evaluating arteriosclerosis. In fact, the correlations between VS_{ot} to the plaque score and brachial-ankle pulse wave velocity were closer than those of the left ventricular mass index to the plaque score and brachial-ankle pulse wave velocity in the current study (Table 2).

Elderly patients with hypertension show a thickened ventricular septum at the left ventricular outflow tract in echocardiograms (*22*, *23*). Our study has demonstrated for the first time that VS_{ot} correlates with indexes of arteriosclerosis independent of age and blood pressure in type 2 diabetic patients. We cannot determine the precise mechanism by which ventri-

cular septal thickness correlates with brachial-ankle pulse wave velocity. Tenenbaum *et al*. reported that diabetic women presented a high prevalence of increased ventricular septal thickness (*24*). The accumulation of myocardial collagen and interstitial fibrosis in diabetic patients may be dominant at the ventricular septal wall compared to other regions of the wall, and this distribution of histological changes may contribute to the close correlation between the ventricular septal thickness and brachial-ankle pulse wave velocity.

A recent study has demonstrated that brachial-ankle pulse wave velocity correlates with the parameter (*E*/*A*) of cardiac diastolic function assessed by Doppler echocardiography and may be a risk factor for diastolic heart failure in patients with hypertension (*13*). However, echocardiographic parameters such as *E*/*A* are influenced by age (*25*, *26*). Brachial-ankle pulse wave velocity is also influenced by age and blood pressure (*27*, *28*). We therefore examined the independence of the relationship between brachial-ankle pulse wave velocity and parameters of cardiac diastolic function and found that the A velocity is independently associated with brachial-ankle pulse wave velocity. Left ventricular diastolic dysfunction is characterized by decreases in the E velocity, prolongation of the deceleration time of the E velocity, and increases in the A velocity, and these characteristics reflect an impairment of left ventricular relaxation, which is one of the diastolic functions (*5*, *17*).

Several limitations exist in assessing cardiac diastolic function by left ventricular diastolic inflow patterns obtained from pulsed Doppler echocardiography. For example, patients with severe left ventricular systolic dysfunction show a pseudonormalization of left ventricular diastolic inflow patterns, and they demonstrate normal values for *E*/*A* even if their left ventricular diastolic function is impaired (*17*, *18*). However, all the subjects in the current study showed normal left ventricular systolic function (left ventricular ejection fraction $\geq$55%) and did not appear to show a pseudonormalization of left ventricular diastolic inflow. Thus, the increase in A velocity is indicative of augmented atrial contraction, which is compensation for impaired left ventricular relaxation in the early phase of left ventricular diastole. Therefore, the increase in A velocity is indicative of left ventricular diastolic dysfunction, and was an independent predictor of arterial stiffening in the current study.

We cannot determine the precise mechanisms by which brachial-ankle pulse wave velocity correlates with left ventricular diastolic function. Left ventricular hypertrophy is one of the major determinants of left ventricular diastolic function (*29*). In fact, the A velocity and *E*/*A* correlated with VS_{ot} ($r=0.49$, $p<0.001$ and $r=-0.47$, $p<0.001$) and VS_{ct} ($r=0.32$, $p=0.006$ and $r=-0.37$, $p=0.001$) in the current study. Therefore, in the present study the left ventricular wall thickening may have contributed, at least in part, to the left ventricular diastolic dysfunction. Another explanation is that histological changes in the left ventricular and aortic wall in diabetic patients may contribute to the correlation between left ventricular diastolic function and aortic stiffness. Several studies of diabetic cardiomyopathy have demonstrated an accumulation of myocardial collagen leading to interstitial and perivascular fibrosis, which correlate with left ventricular early diastolic and systolic dysfunction (*3*, *30*). In addition, there have been some reports that collagen accumulation may contribute to aortic wall stiffness in the type 2 diabetic rat model, which would accelerate the aging process in the aortic wall (*31*, *32*). Therefore, the similarity in the histological changes in the myocardium and arterial wall may contribute to the good correlation between arterial stiffness as assessed by brachial-ankle pulse wave velocity and left ventricular stiffness as expressed by left ventricular inflow patterns by Doppler echocardiography.

In conclusion, left ventricular diastolic dysfunction as revealed by increased A velocity reflects arterial stiffening in type 2 diabetic patients. In addition, myocardial wall thickening at the left ventricular outflow tract reflects not only arterial stiffening but also carotid atherosclerosis. Therefore, abnormal echocardiographic findings of left ventricular diastolic dysfunction and myocardial wall thickening may be useful markers of progressive arteriosclerosis in type 2 diabetic patients.

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