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Thallium-201 scintigraphy after dipyridamole infusion with low-level exercise. III. Clinical significance and additional diagnostic value of ST segment depression and angina pectoris during the test

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Intravenous dipyridamole thallium testing is a useful alternative procedure for assessing coronary artery disease (CAD) in patients who are unable to perform maximal exercise tests. Ischaemic ST segment depression and angina pectoris are frequently observed during the test, in particular when exercise is added to dipyridamole infusion. To establish the clinical significance and additional diagnostic value of these markers of ischaemia during dipyridamole low-level exercise testing (DXT) 57 patients with CAD (group A), 21 patients with normal or near-normal coronary arteries at coronary arteriography (group B), and 20 healthy subjects with low likelihood of CAD (group C) were studied.

During DXT ischaemic ST segment depression was observed in 28 patients (47%) of group A and in two patients (10%) of group B. Angina pectoris was experienced by 35 patients (61%) of group A and by five patients (24%) of group B. The positive predictive value of both ST depression and angina pectoris was high (88 and 93%, respectively), but the negative predictive values were low (42 and 40%, respectively). Combining ST segment analysis with the findings of thallium imaging significantly increased the diagnostic accuracy of the test.

ST segment depression, angina pectoris, and thallium abnormalities were highly specific findings if the study population consisted of asymptomatic subjects with a low likelihood of CAD (group C).

Sensitivity for the detection of the presence of CAD increased with the extent of CAD for all parameters studied. Thus, ST depression and angina pectoris, alone or in combination, during DXT have little diagnostic significance, although sensitivity is increased in patients with triple-vessel CAD. Analysis of the ST segment provides additional information and should therefore be included in the overall interpretation of the test results. A marked difference in the false positive rates for all parameters was observed between asymptomatic subjects and angiographically normal patients with chest pain syndromes, which can be explained by selection bias.

Introduction

Ischaemic ST segment changes and angina pectoris during maximal treadmill or bicycle exercise provide important diagnostic information in patients suspected of having coronary artery disease (CAD)[1,2]. Many patients, however, are unable to perform maximal exercise due to limitations of non-cardiac origin. An alternative to exercise tests consists of increasing myocardial blood flow by pharmacologic vasodilatation of the coronary circulation by intravenous dipyridamole in combination with thallium-201 myocardial perfusion imaging[3–5]. Mild exercise should be added to dipyridamole infusion because it improves the 'heart-background ratio', it may further increase coronary flow with an increase in myocardial oxygen demand which leads to an enhanced spatial

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*Table 1 Extent of coronary artery disease in patients from group A**

Extent of coronary artery disease (CAD)	Number of patients (%)
Single-vessel disease CAD	26 (46)
Two-vessel disease CAD	18 (32)
Three-vessel disease CAD	13 (23)
Total CAD patients	57 (100)

*Group A are patients with significant CAD on coronary arteriography.

contrast[6,7], and it significantly decreases the occurrence of non-cardiac side-effects after dipyridamole infusion[8].

As ischaemic ST segment depression and angina pectoris are frequently reported during dipyridamole low-level exercise testing (DXT) and, because their meaning is uncertain, the purpose of this study was to establish the clinical significance and additional diagnostic value of these markers of ischaemia during DXT in patients with chest pain syndromes and in healthy asymptomatic subjects.

Methods

STUDY POPULATION

Excluded were patients with a recent myocardial infarction, unstable angina pectoris, overt congestive heart failure, patients who did not discontinue cardiac medication (except for shortacting nitrates), patients with other cardiac abnormalities, such as rheumatic or congenital heart disease, patients after aorto-coronary bypass surgery, and patients in whom interpretation of the ST segment was not possible. A total of 98 subjects were studied and divided into three groups: Group A: 57 patients with significant CAD on coronary arteriography (Table 1), Group B: 21 patients referred for coronary arteriography because of chest pain but with angiographically normal or near-normal coronary arteries, and Group C: 20 healthy asymptomatic subjects not referred for coronary arteriography but with a likelihood of CAD less than 1%[5]. The design of the study was prospective. Patients from Group A and B were studied because of suspected CAD. The decision to perform perfusion imaging and cardiac catheterization was taken at the same time and was therefore independent of the test results. The clinical characteristics of all subjects are shown in Table 2.

DXT PROTOCOL

Antianginal medication and aminophylline derivates were discontinued at least 24 h before the test. Antianginal medication was substituted by shortacting nitrates. The patients were requested to inform our department in the event of progressive angina pectoris and prior to dipyridamole infusion careful history was taken to exclude patients with recent progression of anginal symptoms. Patients were administered dipyridamole (Persantin®, Boehringer Ingelheim) intravenously 0·14 mg kg^{-1} bw min^{-1} for 4 min in an upright position[4]. This was followed by low-level exercise (60 RPM/30 W) for 3 min on a bicycle, still in an upright position[8]. Two min after termination of dipyridamole infusion, a bolus of 74 MBq thallium-201 (Mallinckrodt Diagnostica) was injected and exercise was continued for 1 min. Two min after thallium-201 injection the patients were brought into a supine position. Eight min later scintigraphic imaging was started. During the first 30 min electrocardiogram, blood pressure and heart rate were recorded every minute. In cases of serious angina pectoris and/or symptomatic haemodynamic changes, 125–250 mg aminophylline (a dipyridamole antagonist) was administered intravenously[9–11]. If necessary, nitroglycerin was administered sublingually.

THALLIUM-201 IMAGING

Ten min after thallium-201 injection, planar scintigraphic imaging of the initial uptake was started. After 4 h the redistribution scintigrams were obtained. Imaging was performed in the anterior, 30° and 70° left anterior oblique (LAO) views. The duration per view was 10 min. Visual analysis of the images was performed by two experienced observers by 'semiquantitative' analysis, as previously described[5,12].

CORONARY ARTERIOGRAPHY

Patients underwent coronary arteriography according to the Sones or Judkins technique in multiple left anterior and right anterior oblique positions and in views with cranial and caudal angulation. Coronary obstructions were considered significant if they caused at least 50% reduction of the lumen diameter of a major branch.

ELECTROCARDIOGRAPHIC CHANGES

ECG leads CM5 and CC5 were registered simultaneously by means of a commercially available cardiograph (Philips Cardiopan CR 330) with a paper speed of 25 mm s^{-1} and an amplitude

Table 2 Clinical characteristics of all subjects

Characteristics	Group A	Group B	Group C
Number of subjects	57	21	20
Male (%)	41 (72%)	14 (67%)	20 (100%)
Age (years) (mean ± SD)	61 ± 10	52 ± 10	35 ± 5
Range	35–80	33–72	28–47
Previous infarction			
Anterior	4 (7%)	—	—
Inferior	8 (14%)	—	—
Dipyridamole/low-level exercise testing			
Systolic blood pressure (mmHg)			
At rest (mean ± SD)	160 ± 24	148 ± 18	131 ± 22
Change (mean ± SD)	14 ± 28	33 ± 18	26 ± 10
Diastolic blood pressure (mmHg)			
At rest (mean ± SD)	92 ± 13	91 ± 13	81 ± 14
Change (mean ± SD)	3 ± 13	−5 ± 13	−7 ± 8
Heart rate (beats min^{-1})			
At rest (mean ± SD)	78 ± 15	79 ± 16	75 ± 12
Change (mean ± SD)	32 ± 12	38 ± 13	34 ± 9
Angina pectoris	35 (61%)	5 (24%)	0 (0%)
Ischaemic ST segment changes	28 (47%)	2 (10%)	0 (0%)
Side-effects‡	9 (16%)	3 (14%)	1 (5%)
Perfusion defects on thallium images	44 (77%)	3 (14%)	0 (0%)
Aminophylline	1 (2%)	0 (0%)	0 (0%)
Nitroglycerin	6 (11%)	0 (0%)	0 (0%)

A = patients with significant CAD on coronary arteriography; B = patients without significant CAD on coronary arteriography; C = subjects with low likelihood of CAD; SD = standard deviation; ‡ = minor complaints (headache, nausea, and vertigo); number of subjects are submitted with percentages in parentheses.

calibration of 0·1 mV mm^{-1}. Ischaemic ST segment depression after dipyridamole infusion was defined according to criteria used for exercise electrocardiography. A test was considered positive if the following ST segment changes occurred: (1) a junctional depression ≥ 1 mm followed by a horizontal or downsloping ST segment during at least 80 ms after the J-point in three consecutive ECG complexes with a normal ST segment at rest[13]; (2) a junctional depression with upsloping ST segment in which the ST segment still shows a depression of ≥ 2 mm during at least 80 ms after the J-point in three consecutive ECG complexes with a normal ST segment at rest[14]; (3) an additional junctional depression ≥ 2 mm followed by a horizontal or downsloping ST segment during at least 80 ms after the J-point in three consecutive ECG complexes with an ST segment depression at rest.

CHEST PAIN

Chest pain after dipyridamole infusion was considered present if the patient experienced unequivocal angina pectoris, defined by its character (sensation of pressure or heavy weight on the chest) and by its localization (over the sternum or near to it). Slight chest discomfort was considered a normal reaction.

STATISTICAL ANALYSIS

The positive and negative predictive values of ST segment depression, chest pain and thallium-201 defects alone and in combination were calculated as the true positive/all positive and true negative/all negative test response rates. The diagnostic accuracy was calculated as the ratio of true test responses and all test responses. Sensitivity was defined as the frequency of positive tests in patients with CAD[15]. The significance of differences between the characteristics of the methods used was assessed by McNemar's test[15]. A P value of less than 0·05 was considered significant. Values are given as mean ± standard deviation.

Results

During DXT ischaemic ST-segment depression was observed in 28 patients (47%) of group A (significant CAD) and in two patients (10%) of group B

Table 3 Results of various markers of ischaemia for the detection of CAD derived from groups A and B

	Angina pectoris	ST depression	AP ± ST
Prevalence of CAD	57/78 (73%)	57/78 (73%)	57/78 (73%)
Positive predictive value	35/40 (88%)	28/30 (93%)	42/47 (89%)
Negative predictive value	16/38 (42%)	19/48 (40%)	16/31 (52%)
Diagnostic accuracy	51/78 (65%)	47/78 (59%)	58/78 (74%)*

AP ± ST = Angina pectoris and/or ischaemic ST segment depression; CAD = coronary artery disease; * = $P < 0{\cdot}05$ compared with other parameters.

Table 4 Thallium-201 imaging: additional value of angina pectoris and ischaemic ST segment depression for the detection of CAD derived from group A and B

	Tl-201	Tl-201 ± AP	Tl-201 ± ST
Prevalence of CAD	57/78 (73%)	57/78 (73%)	57/78 (73%)
Positive predictive value	44/47 (94%)	47/55 (85%)	50/56 (89%)
Negative predictive value	18/31 (58%)	13/23 (57%)	15/22 (68%)
Diagnostic accuracy	62/78 (79%)	60/78 (77%)	65/78 (83%)♯

AP = angina pectoris; ST = ischaemic ST segment depression; CAD = coronary artery disease; Tl-201 = thallium-201 imaging; ± denotes and/or; ♯ = $P < 0{\cdot}05$ compared with other parameters.

(no significant CAD). Silent ischaemia (ST segment depression without angina pectoris) was observed in eight patients, all with CAD, but only four of these patients (50%) showed thallium abnormalities. Angina pectoris was experienced by 35 patients (61%) of group A and by five patients (24%) of group B. Definite ischaemia, defined as ST depression and angina pectoris was found in 23 patients. Of these, two had a normal coronary arteriogram and three had a normal thallium scintigram. In none of the patients had exercise to be discontinued because of early appearance of angina pectoris or ST depression. If the study population consisted of asymptomatic subjects with a low likelihood of CAD (group C), no ST segment depression, angina pectoris or perfusion defects were observed. One patient of group A received intravenous aminophylline and sublingual nitroglycerin because of severe angina pectoris, while five other patients of group A received only nitroglycerin for the same reason. No cardiac events, such as sustained ventricular arrhythmias or myocardial infarction occurred during DXT.

The results of the markers of ischaemia (ST depression and angina pectoris, alone and in combination), derived from patients in groups A and B are presented in Table 3. There was no significant difference between the presence of ST depression and angina pectoris in predicting CAD, whereas the combination (ST depression and/or angina pectoris) had a significantly better diagnostic value than each of the separate markers. Table 4 presents the additional value of ST depression and angina pectoris in combination with results of thallium imaging in group A and B patients. It was observed that the diagnostic accuracy of thallium imaging increases when ST segment analysis is included in the evaluation. The positive predictive value was high (85–94%), irrespective of the parameter used. The negative predictive value was lowest for ST depression alone and highest for the combination of ST depression and thallium-201 abnormalities (Tables 3 and 4).

In addition, the sensitivity for the detection of the presence of CAD in patients with one-, two-, and three-vessel CAD from group A was evaluated. The sensitivity showed an increasing trend with the extent of CAD for all parameters studied, starting at an average of 45% for ST depression in patients with one- and two-vessel CAD and ending at 100% for ST depression and/or thallium perfusion defects in patients with three-vessel CAD (Fig. 1). Looking

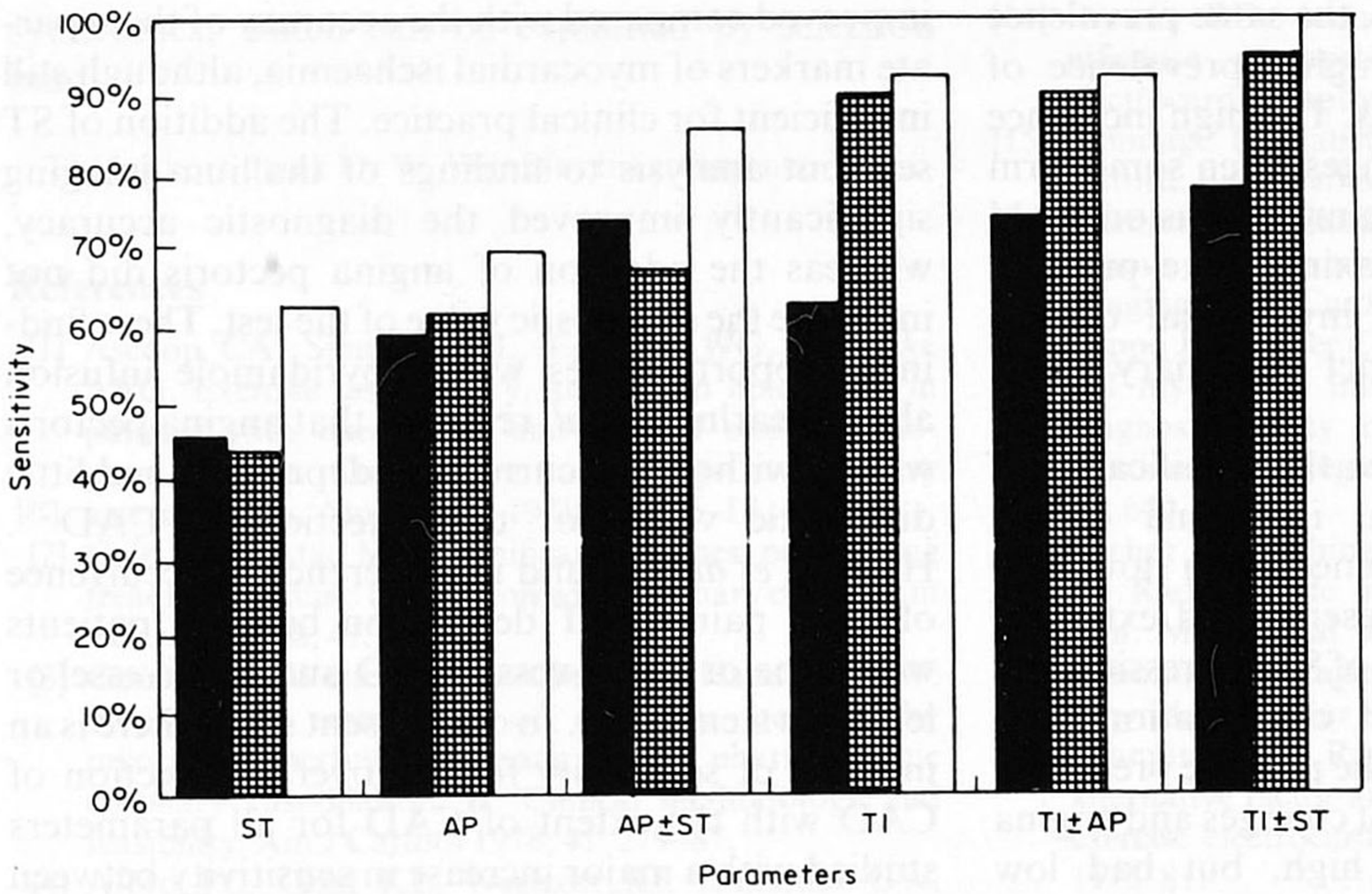

Figure 1 Sensitivity of the various parameters according to the extent of coronary artery disease. AP = angina pectoris; ST = ischaemic ST segment depression; Tl = thallium-201 imaging; CAD = coronary artery disease; ± denotes and/or. ■ = single-vessel CAD; ▦ = two-vessel CAD; □ = three-vessel CAD.

at ST depression, angina pectoris, and the combination (ST depression and/or angina pectoris) the most distinct jump in sensitivity was observed between the one- and two-vessel vs the three-vessel groups, whereas for thallium defects alone, or in combination (thallium defects and/or ST depression and thallium defects and/or angina pectoris) the most significant increase in sensitivity was between the one-vessel vs the two- and three-vessel groups (Fig. 1).

Discussion

Intravenous dipyridamole thallium imaging is a safe and efficacious stress procedure for the detection of presence, location, and extent of CAD and is especially useful in patients who are unable to perform maximal exercise tests[5,8,16]. Dipyridamole is administered to increase coronary blood flow in order to detect flow disparities by thallium-201 perfusion imaging in patients with significant CAD. Reversible perfusion defects represent regions with transient hypoperfusion relative to the adjacent regions. During maximal exercise thallium-201 testing the coronary blood supply is directed by the myocardial oxygen consumption in a very tight manner, so that hypoperfusion in this situation must represent a region with oxygen deprivation and it is appropriate to use the terms hypoperfusion and ischaemia as synonyms. As Gould *et al.* pointed out[3], during pharmacologic vasodilatation the coronary blood supply is in excess of the demand and in regions with hypoperfusion the blood flow is not always reduced in an absolute sense. Therefore, in contrast to exercise scintigraphy, regions with dipyridamole-induced hypoperfusion should not be considered as necessarily ischaemic.

In spite of these considerations ST segment depression and angina pectoris are frequently reported cardiac effects of intravenous dipyridamole[5,8,16,17]. Angina pectoris and/or ST depression in combination with reversible perfusion defects makes it likely that myocardial ischaemia is present, in particular when this is accompanied by regional wall motion abnormalities[18]. ST depression with concurrent hypoperfusion in the absence of chest pain may reflect silent ischaemia. Myocardial ischaemia during coronary vasodilatation by dipyridamole is caused by coronary steal phenomena, which cause endocardial hypoperfusion and ischaemia because blood is shunted away from the subendocardium to the subepicardium. A second type of coronary steal may be related to collateral vessels between two vascular beds with impaired blood flow in patients with multivessel disease[3].

In a previous study in which we added low-level exercise to dipyridamole infusion compared with dipyridamole infusion alone, we found significantly

fewer non-cardiac side-effects, the same prevalence of angina pectoris, and a higher prevalence of ischaemic ST segment changes. The high incidence of ischaemic ST segment changes when some form of exercise is added to dipyridamole infusion could be explained by a higher maximal rate–pressure product, implicating higher myocardial oxygen demands and more distinct coronary steal phenomena[8].

The present study describes the significance of clinical signs of myocardial ischaemia during dipyridamole infusion combined with low-level exercise in relation to the presence and extent of CAD and the additional value of ST depression and angina pectoris occurring in combination with thallium-201 abnormalities. The positive predictive values of ischaemic ST segment changes and angina pectoris during DXT were high, but had low negative predictive values, which makes these parameters of little practical value. Chest pain during DXT was not a very specific finding in patients of group B compared with group C subjects. This difference may be due to referral bias as group B patients were selected for coronary arteriography because of chest pain syndromes[19]. Some of these angiographically 'normal' patients with the traditional hallmarks of myocardial ischaemia, ST segment depression and/or angina pectoris, may have had significant coronary artery disease, underestimated by coronary arteriography. Especially in patients with multivessel CAD there is usually diffuse disease rather than just circumscribed segmental lesions[20]. Because the reference vessel diameter itself is decreased in these cases, the functional significance of stenoses is easily underestimated. Other patients may have had subcritical stenoses with functional effects on coronary perfusion during maximal hyperaemia induced by pharmacologic vasodilatation[21,22]. Two of 23 patients with definite ischaemia, represented by angina and ST depression, had a normal coronary arteriogram and one of these patients showed thallium redistribution. Therefore, ST segment changes and angina pectoris may be related to abnormalities of coronary perfusion causing myocardial ischaemia by other conditions than atherosclerotic lesions of the epicardial arteries[23–27]. Silent ischaemia, represented by ischaemic ST depression without chest pain, was found in eight patients, all in group A, but this was supported by thallium redistribution in only half of the cases.

The diagnostic accuracy of the combination of ST segment changes and/or angina pectoris was improved compared with the accuracy of the separate markers of myocardial ischaemia, although still insufficient for clinical practice. The addition of ST segment analysis to findings of thallium imaging significantly improved the diagnostic accuracy, whereas the addition of angina pectoris did not influence the diagnostic value of the test. These findings support studies with dipyridamole infusion alone. Pearlman *et al.* reported that angina pectoris with or without concurrent ST depression had little diagnostic value for the detection of CAD[28]. Homma *et al.*[16] found no difference in occurrence of chest pain or ST depression between patients with none or single-vessel CAD and multivessel or left main stem CAD. In our present study there is an increase of sensitivity for the overall detection of CAD with the extent of CAD for all parameters studied with a major increase in sensitivity between the two- and three-vessel CAD groups for the ST depression and/or angina pectoris, whereas the increase in sensitivity for thallium was most prominent between the single- and two-vessel CAD groups, leading to very high sensitivity values in the subgroups with multivessel CAD, which is a finding with practical importance.

One may wonder if the addition of mild exercise to dipyridamole infusion causes additional risks to the patient. In our experience more than 500 dipyridamole tests have been performed (of which 400 with low-level exercise) and no patient developed sustained ventricular arrhythmias, myocardial infarction, or death. Lewen *et al.*[29] described a case of prolonged myocardial ischaemia after dipyridamole infusion with handgrip exercise requiring emergency coronary angioplasty. In almost all instances severe cardiac and non-cardiac side-effects can be reversed with the dipyridamole-antagonist aminophylline[5,8–11].

In conclusion, ST depression and angina pectoris, alone or in combination, occurring during DXT have little diagnostic significance, although sensitivity is increased in patients with triple-vessel CAD. Combining ST segment analysis with the finding of thallium imaging significantly increases the diagnostic accuracy of the test, especially in patients with single vessel CAD, and leads to a very high sensitivity in patients with multivessel CAD (97%). Therefore, ST segment analysis should be included in the overall interpretation of the dipyridamole thallium test results. An important difference in false positive rates for all parameters was observed between asymptomatic subjects and angiographically normal patients with chest pain

syndromes, which can be explained by selection bias.

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