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ORIGINAL ARTICLE

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Coronary pressure measurement to determine treatment strategy for equivocal left main coronary artery lesions

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Abstract It is often hard to select a treatment strategy for equivocal left main coronary artery (LMCA) disease. We investigated the usefulness of coronary pressure (CP) measurement for determining the treatment strategy in intermediate LMCA disease. We measured CP in 15 consecutive patients with equivocal LMCA disease (age 67.6 ± 7.5 years, 14 males). Myocardial fractional flow reserve (FFRmyo) was obtained as the ratio of CP distal to the lesion/aortic pressure under maximal coronary dilation. Patients with FFRmyo ≥0.75 and <0.75 received medical therapy and coronary artery bypass grafting (CABG), respectively, and were followed up for 32.5 ± 9.7 (20–47) months. Eight patients received medical therapy and 7 patients underwent CABG in accordance with the FFRmyo criteria noted above. FFRmyo of the LMCA was 0.91 ± 0.01 and 0.61 ± 0.03 in patients who received medical and surgical therapy, respectively. Neither reference vessel diameter, minimal lumen diameter, nor percent diameter stenosis was significantly different between patients who received medical and surgical therapy. During the follow-up period, no patients with medical therapy showed symptoms due to the LMCA lesion. Similarly, 5 of 7 patients with CABG showed improvement of symptoms and the remaining 2 patients were hospitalized with congestive heart failure. No cardiac death was recorded in the patients with medical or surgical therapy. In conclusion, the present results clearly demonstrated that CP is clinically useful for determining the treatment strategy for equivocal LMCA lesions but coronary angiography is not.

Key words Coronary artery disease · Follow-up · Catheterization · Angiography · Revascularization

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Introduction

A large part of the myocardium of the left ventricle is perfused by the left main coronary artery (LMCA). Although acute obstruction of the LMCA is not frequently encountered,[1] acute LMCA obstruction causes severe hemodynamic deterioration, frequently resulting in rapid fatality.[2–4] Evaluation of the severity of LMCA stenosis is thus important in order to avoid severe ischemia and/or prevent acute LMCA obstruction.

Although new methods for assessment of coronary artery have been developed,[5,6] coronary arteriograms are now still widely used as a standard method for evaluation of coronary stenosis. However, coronary arteriograms, even when quantitative, apparently have some limitations.[7] Assessment of LMCA disease by coronary angiography is often suboptimal.[8–10] Although LMCA lesions have been reported to be revascularized by percutaneous coronary intervention,[11,12] coronary bypass grafting (CABG) is the standard treatment strategy for significant LMCA disease. Although methods for CABG have been developed,[13] CABG clearly has its own risks. It is thus essential to determine whether equivocal LMCA lesions require CABG.

Myocardial fractional flow reserve (FFRmyo), calculated from coronary pressure (CP) measurement, theoretically represents physiological coronary reserve and was reported to be a useful index for determining the functional severity of coronary artery disease.[14] Several subsequent studies[15,16] demonstrated that a cutoff FFRmyo value of 0.75 can distinguish lesions with inducible reversible ischemia at exercise from those without. We thus hypothesized that CP measurement can be used to determine whether LMCA

lesions require revascularization. To test this hypothesis, it would be worthwhile to evaluate prospectively the outcome of deferred CABG in patients with intermediate LMCA lesions based on FFRmyo. There are only a few reports[17–19] that followed up LMCA disease treatment based on FFRmyo results. Each of those studies had a relatively small number of patients, and additional studies are thus essential to evaluate the usefulness of CP measurements for determining the treatment strategy in equivocal LMCA disease. Accordingly, we studied the usefulness of FFRmyo for decision making regarding coronary revascularization by means of CABG in patients with intermediate LMCA lesions.

Patients and methods

We measured CP in 15 consecutive patients with angiographically intermediate stenosis, defined below, in the LMCA. They consisted of 14 men and 1 woman aged 37–87 years (mean ± SD 67.6 ± 7.5 years). The characteristics of the patients studied are summarized in Table 1.

Cardiac catheterization

The patients' medication was continued until cardiac catheterization. All patients were given 100 IU/kg of heparin intravenously at the beginning of cardiac catheterization and additional heparin was administered if the procedure lasted >90 min. Coronary angiography was performed using multiple views by the standard percutaneous transluminal method using a femoral approach.

Quantitative coronary angiography

The angiographic severity of the LMCA lesion was measured by quantitative coronary angiography with an automated edge detection algorithm (Super DF Series, Digital Fluorography System; Toshiba, Tokyo, Japan). The reference vessel diameter was obtained from the diameter of the guiding catheter. Two orthogonal projections of the coronary arterial lesion during the end-diastolic phase were used to perform biplane analysis of the minimal lumen diameter and the percent stenosis of the coronary artery diameter.

Definition of equivocal LMCA disease

Coronary arteriograms were evaluated visually by two cardiologists who were not aware of any clinical characteristics of the patients. Intermediate LMCA disease was defined as LMCA stenosis of more than 25% but less than 75%, determined by visual assessment. Patients for whom the two cardiologists disagreed about the judgment of the coronary stenosis status were excluded from the present study.

Table 1. Clinical, angiographic, and coronary pressure characteristics and coronary risk factors of patients with LMCA disease associated or not associated with reduced FFRmyo

	Total	FFRmyo ≥0.75	FFRmyo <0.75	Probability
No. of patients	15	8	7	
Age (years)	67.6 ± 7.5	65.5 ± 8.1	70.0 ± 6.4	NS
Sex (male:female)	14:1	7:1	7:0	NS
AP:OMI	8:7	4:4	4:3	NS
Angiographic findings				
Reference diameter (mm)	3.47 ± 0.78	3.63 ± 0.71	3.29 ± 0.87	NS
MLD (mm)	1.75 ± 0.36	1.66 ± 0.87	1.84 ± 0.26	NS
% diameter stenosis	48.6 ± 8.1	48.4 ± 7.8	48.9 ± 9.0	NS
FFRmyo				
for LMCA	0.77 ± 0.15	0.91 ± 0.07	0.62 ± 0.03	<0.0001
for LAD -LMCA	0.74 ± 0.15	0.86 ± 0.10	0.61 ± 0.03	<0.0001
for LCx -LMCA	0.77 ± 0.17	0.90 ± 0.07	0.61 ± 0.08	<0.0001
Stenosis in other coronary trees				
LAD	2	1	1	
LCx	0	0	0	
RCA	3	0	3	
Coronary risk factor				
Hypertension	8	4	4	NS
Hyperlipidemia	8	4	4	NS
Diabetes mellitus	12	7	5	NS
Obesity	5	2	3	NS
Smoking	2	1	1	NS

FFRmyo for LMCA represents FFRmyo obtained from coronary pressure difference just across the LMCA lesion. FFRmyo for LAD and LCx represents FFRmyo obtained from coronary pressure differences between the distal coronary pressure of LAD and LCx, respectively, and aortic pressure. Probability indicates significance of differences of values of patients with FFRmyo ≥0.75 versus those with FFRmyo <0.75

MLD, minimum lumen diameter; FFRmyo, myocardial fractional flow reserve; NS, not significant; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery

Measurement of intracoronary pressure

Isosorbide dinitrate (2.5 mg) was administered into the coronary artery every 30 min throughout the procedure. A pressure monitoring guide wire (Wave Wire; JOMED, Rancho Cordova, CA, USA) was zeroed, calibrated, and advanced through the catheter into the coronary artery and positioned as distally as possible. Maximal myocardial hyperemia was then induced by intravenous continuous infusion of adenosine triphosphate (150 μg/kg per minute). FFRmyo was then calculated at the maximal hyperemia as the ratio of the simultaneously recorded aortic pressure (Pa) and distal coronary pressure (Pd), i.e., Pd/Pa. We positioned the tip of the catheter slightly separated from the ostium of the LMCA, not engaged deeply into the LMCA lesion. Thereafter, the pullback pressure via the left anterior descending coronary artery (LAD) was obtained from a point as distal as possible to the proximal part of the LMCA under steady-state maximal hyperemia. Similarly, the pullback pressure tracing via the left circumflex coronary artery (LCx) was also obtained. In cases in which the lesion was localized in the LMCA, FFRmyo across the LMCA lesion <0.75 was considered to indicate significant stenosis with respect to physiological criteria, based on previously reported studies (Fig. 1).[15] In cases in which the LMCA lesion extended to just proximal to the LAD and/or to the LCx, when both the pullback pressure tracings from a position proximal to the LAD and LCx to the coronary orifice showed FFRmyo <0.75, the LMCA stenosis was considered to be significant and the higher value of the two FFRmyos was taken as LMCA FFRmyo. Conversely, if either or both of the pullback pressure tracings from just proximal to the LAD and/or from the LCx to the coronary orifice showed FFRmyo ≥0.75, the LMCA stenosis was considered not to be significant, and significant stenosis was judged to be located in either the LAD or LCx if they showed FFRmyo <0.75.

Treatment and follow-up

In patients with insignificant LMCA lesions, CABG was deferred and the patients were followed up with medication. Conversely, patients with significant LMCA stenosis as defined above were assigned for treatment by coronary revascularization by means of CABG. The follow-up period was 32.5 ± 9.7 (range 20–47) months. The occurrence of one of three cardiac events, namely cardiac death,

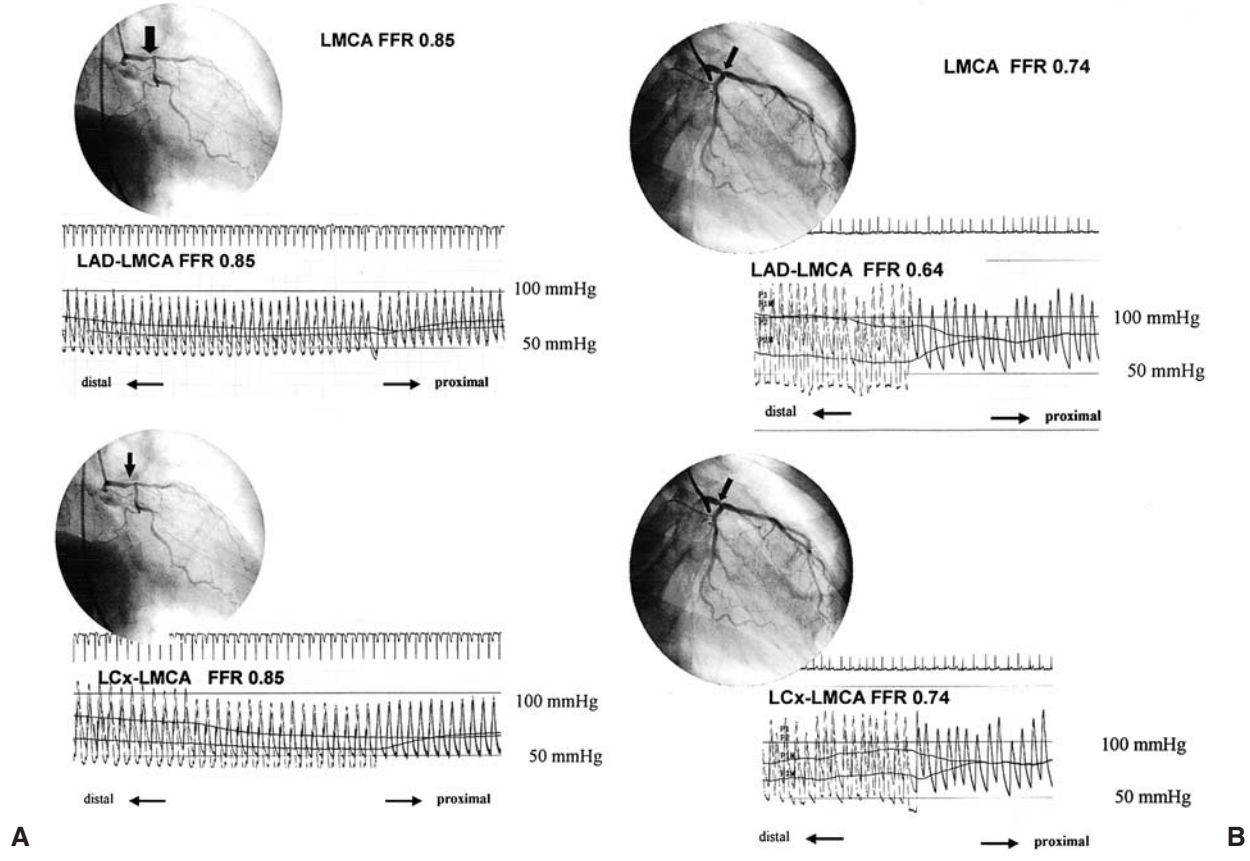

Fig. 1A,B. Representative coronary pressure measurements. **A** A patient with myocardial fractional flow reserve (FFRmyo) for LMCA ≥0.75 who received medical treatment. **B** A patient with FFRmyo for LMCA <0.75 who underwent coronary artery bypass surgery. *LMCA*, left main coronary artery; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex coronary artery; *FFR*, fractional flow reserve

nonfatal myocardial infarction (MI), or anginal attack, was monitored.

Statistical analysis

To study the differences in angiographic and pressure measurements between patients with and without reduced FFRmyo, we used Student's unpaired *t*-test. The chi-square test or Fisher's exact probability test was used to compare proportional data between the two groups when appropriate. All values were expressed as mean ± SD, and *P* values of less than 0.05 were considered significant.

Results

Among 15 patients enrolled in the present study, 8 (53.3%) showed LMCA FFRmyo ≥0.75 (0.91 ± 0.07), and were followed up with medication without CABG. The remaining 7 (46.7%) patients had LMCA FFRmyo <0.75 (0.61 ± 0.03) through the LMCA lesion, and underwent CABG. Because the exercise test was not performed in all patients examined, it could not be determined whether there were characteristic differences in exercise tests before the CP study between patients with decreased FFRmyo and those with FFRmyo within the normal range. No notable differences in symptoms were present between the two groups.

Coronary angiographic findings and coronary pressure measurements of the two groups

There were no significant differences in reference vessel diameter, minimal lumen diameter, or percent diameter stenosis between patients with decreased FFRmyo and patients with FFRmyo within the normal range (Table 1). One patient with FFRmyo <0.75 across the LAD lesion and with FFRmyo ≥0.75 through the LMCA lesion underwent coronary angioplasty in the proximal lesion of the LAD, and the FFRmyo across the LMCA lesion (0.90) was not reduced thereby (case 5 in Table 2).

Treatment and clinical outcome

In the eight patients with FFRmyo within the normal range, we administered full medical therapy, including statin therapy and lifestyle modification (Table 1). During the follow-up, none of the eight patients treated with medication (FFRmyo ≥0.75) showed any symptoms (Table 2). Follow-up coronary angiography revealed no significant differences in minimal lumen diameter or percent diameter stenosis between the initial measurements and those at follow-up (Table 3). Moreover, FFRmyo for the LMCA did not change significantly during the follow-up period.

Of the seven patients with FFRmyo <0.75 for the LMCA lesion who received CABG, five presented no symptoms during follow-up (Table 4). Congestive heart failure occurred in the remaining two patients, in whom reduced left ventricular ejection fraction was already observed at the initial study.

Discussion

The present study indicated that CP measurement for equivocal LMCA disease was useful for decision making about the optimal treatment strategy but QCA was not.

We carefully measured CP across the LMCA lesions. The position of the coronary guiding catheter is critical for determination of FFRmyo across LMCA lesions. When the tip of the catheter was engaged in the LMCA, precise measurements of FFRmyo across the LMCA stenosis could not be obtained in some cases. We positioned the tip of the catheter slightly distant from the ostium of the LMCA in order to precisely measure the pressure proximal to the LMCA stenosis. The pressure wire was gradually pulled back under fluoroscopy. We were careful not to allow deep engagement of the tip of the catheter into the LMCA during the gradual pulling-back of the pressure wire. These careful CP measurements provided a precise measurement of FFRmyo across the LMCA lesion, and the data were further analyzed.

Table 2. Clinical, angiographic, and pressure measurement characteristics and follow-up clinical events of patients in the medical group

No.	Age (years)	Sex	Diagnosis	MI location	EF	RVD	MLD	%DS	Location	LMCA FFRmyo	Follow-up period	Event
1	70	M	OMI	Inf	49	4.4	1.8	59	Orifice	0.82	14	None
2	73	M	OMI	Inf	50	2.9	1.5	48	Distal	0.85	32	None
3	58	M	AP	–	57	2.8	1.8	36	Orifice	0.85	39	None
4	66	M	OMI	Inf	50	2.8	1.6	43	Distal	0.90	31	None
5	52	M	OMI	Inf	48	4.5	2	56	Distal	0.90	35	None
6	60	M	AP	–	55	3.8	1.7	55	Orifice	0.99	37	None
7	75	M	AP	–	52	3.7	2	46	Distal	0.99	22	None
8	70	F	AP	–	60	4.1	2.3	44	Orifice	1.00	16	None
Mean	65.5				52.625	3.625	1.837	48.375		0.913	28.25	
SD	8.071				4.274	0.709	0.256	7.763		0.072	9.647	

OMI, old myocardial infarction; AP, angina pectoris; RVD, reference vessel diameter; MLD, minimal lumen diameter; %DS, percent diameter stenosis; LMCA, left main coronary artery; FFRmyo, myocardial fractional flow reserve

Table 3. Angiographic follow-up results in medically treated patients

No.	RVD		MLD		%DS		FFRmyo		Location
	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	
1	4.4	4.3	1.8	1.6	59	63	0.82	0.8	Orifice
2	2.9	2.8	1.5	1.5	48	46	0.85	0.85	Distal
3	2.8	2.9	1.8	1.8	36	38	0.85	0.86	Orifice
4	2.8	2.7	1.6	1.5	43	44	0.9	0.92	Distal
5	4.5	4.7	2	2	56	57	0.9	0.9	Distal
6	3.8	3.6	1.7	1.6	55	56	0.93	0.91	Orifice
7	3.7	3.8	2	2.1	46	45	0.99	0.99	Distal
8	4.1	4	2.3	2.3	44	43	1	1	Orifice
Mean	3.625	3.6	1.837	1.8	48.375	49	0.905	0.904	–
SD	0.709	0.741	0.256	0.302	7.763	8.586	0.066	0.068	–

RVD, reference vessel diameter; MLD, minimal lumen diameter; %DS, percent diameter stenosis; FFRmyo, myocardial fractional flow reserve

Table 4. Clinical, angiographic, and pressure measurement characteristics and follow-up clinical events of patients in the surgical group

No.	Age (years)	Sex	diagnosis	MI Location	EF	RVD	MLD	%DS	Location	LMT FFRmyo	Follow-up period	Event
1	66	M	OMI	inf	32	2.1	1.3	38	Body	0.56	41	CHF 5 times
2	66	M	AP	–	54	4	1.8	55	Distal	0.58	17	None
3	73	M	OMI	inf	50	2.9	1.4	52	Distal	0.59	19	None
4	75	M	OMI	inf	46	2.5	1.5	40	Body	0.62	37	None
5	75	M	AP	–	56	3.6	1.9	47	Body	0.62	18	None
6	76	M	AP	–	40	4.6	2.5	46	Distal	0.64	23	CHF 5 months later
7	59	M	AP	–	52	3.3	1.2	64	Orifice	0.65	18	None
Mean	70.0	–	–	–	47.14	3.29	1.66	48.86	–	0.61	24.71	–
SD	6.4	–	–	–	8.55	0.87	0.45	8.99	–	0.03	10.01	–

OMI, old myocardial infarction; AP, angina pectoris; RVD, reference vessel diameter; MLD, minimal lumen diameter; %DS, percent diameter stenosis; LMCA, left main coronary artery; FFRmyo, myocardial fractional flow reserve; CHF, congestive heart failure

No relationship between the value of CP across the LMCA stenosis and the angiographical severity of the lesion was obtained by the present edge detection methods. The video densitometry method for QCA was not used in this study. That method, however, also has some limitations such as errors caused by vessel orientation and dense background from the surrounding tissue.[20,21] Even when the severity of LMCA lesions was measured by the video densitometric method, the relationship between CP and the angiographic severity was thought to be insignificant. Because we did not have any data obtained from the densitometric method, further discussion about the video densitometric method for measurement of LMCA lesions would be inappropriate. Furthermore, suboptimal assessment of LMCA disease by coronary angiography has been reported in many cases because of the complicated anatomical location of the LMCA.[8–10] Gerber et al.[22] reported a higher detection rate of significant LMCA lesions by intravascular ultrasound (IVUS) than by coronary angiography. When the LMCA lesion was immeasurably short, diffusely diseased, or obscured by overlapping vessels, the severity of the LMCA stenosis was especially difficult to determine by angiography. Angiographic assessment is therefore not sufficient for the accurate evaluation of LMCA stenosis.

Regarding treatment strategy, occlusion of the graft occurs occasionally when LMCA stenosis is not functionally significant,[23] and unnecessary bypass surgery is therefore performed in equivocal LMCA disease when the severity of LMCA stenosis is evaluated solely by coronary angiography. We did not find any patients in the medically treated group who showed any symptoms due to the LMCA lesion. Similar results have been reported by Abizaid et al.,[24] who followed 122 patients with moderate LMCA stenosis for 1 year. In their study, the correlation of minimum lumen diameter determined by quantitative coronary angiography and that determined by intravascular ultrasound was weak, and the 1-year event rate was low. That study together with our results indicates that most patients with moderate LMCA stenosis do not benefit from CABG, and such patients may not have functionally significant LMCA stenosis. Our results demonstrated that CP measurement can reasonably identify patients who will benefit from CABG, but coronary angiography cannot.

Left main coronary artery stenosis is known to be frequently associated with coronary stenosis in other parts of the coronary artery.[25] When stenotic lesions are located in other parts of coronary arteries with functionally insignificant LMCA stenosis, there are cases in which percutaneous coronary intervention for this lesion is the appropriate strategy instead of CABG. This situation actually occurred in one of our patients in the medical group. Evaluation of the LMCA lesion by a physiological approach is thus useful

for selection of the treatment strategy for LMCA disease.

The present study included patients with inferior wall old myocardial infarction. There are patients with LMCA stenosis associated with previous myocardial infarction at a location perfused by the LAD or LCx. De Bruyne et al.[26] reported that CP can distinguish those with positive from those with negative single-photon emission computed tomography imaging of the old myocardial infarction, and the value of FFRmyo depends on the mass of viable myocardium. The pullback pressure via the LAD and LCx obtained from a point as distal as possible to the proximal part of the LMCA can thus provide information regarding the indication of revascularization when LAD and/or LCx lesions are responsible for an old myocardial infarction.

There are few reports in which the treatment strategy was selected based on CP results in patients with equivocal LMCA disease.[17–19] Bech et al.[17] found progression of LMCA stenosis accompanied by anginal pain in 2 (8.3%) of 24 medically treated patients with FFRmyo ≥0.75. In contrast, none of our medically treated patients showed anginal pain. No information regarding changes in angiographic stenosis and/or CP during the follow-up period was provided in the previous study. In the present study, follow-up coronary angiography showed no progression of LMCA stenosis in any of the eight medically treated patients. Angina events due to progression of LMCA stenosis seemed to be more frequent in the previous study than in the present study, though the significance of the difference could not be determined definitively because the present study included a relatively small number of patients. The minimum lumen diameter and reference diameter were shorter and longer, respectively, in our medically treated patients than in their medical patients. Percent diameter stenosis was also larger in our medically treated patients than in their medical patients. These angiographic differences between our and their medical group cannot be explained at present, and were apparently opposite with respect to the presumably different follow-up results regarding LMCA progression. Rupture of coronary plaque in the LMCA followed by thrombus formation is likely to result in catastrophic events. We treated patients in the medical group carefully with intensive medical therapy, including statin and angiotensin-converting enzyme inhibitors. The present full medication therapy may have limited the progression of LMCA stenosis. Because the present study included a relatively small number of patients, detailed discussion of this issue would be inappropriate.

There were several limitations in the present study, one of them being that it included a relatively small number of patients because LMCA stenosis is not frequently encountered.[1] The careful follow-up, especially follow-up coronary angiography and CP measurement performed in all medical treatment group patients, may have partly compensated for this limitation. In conclusion, CP measurement for equivocal LMCA disease was very useful for making decisions about the need for CABG, but coronary angiography was not.

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