

Coronary Artery Dilatation Exceeding 4.0 mm During Acute Kawasaki Disease Predicts a High Probability of Subsequent Late Intima–Medial Thickening

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Abstract. We used intravascular ultrasound (IVUS) to compare the degree of coronary artery dilatation during the acute phase of Kawasaki disease with the extent of intima–medial thickening more than 10 years later. We wanted to determine if there was a threshold degree of dilatation that was highly predictive of later thickening. Twenty-eight patients with a mean age of 17.3 ± 1.7 years were studied; the mean interval from the initial selective coronary angiography to the IVUS study was 15.0 ± 1.6 years. We measured the maximum intima–medial thickness of selected coronary arterial segments in IVUS images and measured the largest diameters of the corresponding coronary arterial segments in the initial coronary angiograms. A significant correlation was found between the initial diameters of the coronary arteries and the intima–medial thickness more than 10 years later in the right coronary, the left anterior descending coronary, and the left circumflex arteries. The coefficient of correlation was 0.77 ($n = 120$, $p < 0.0001$), and for the bifurcation of the left coronary artery it was 0.50 ($n = 26$, $p < 0.01$). For this study, abnormal intima–medial thickness was defined as more than 0.40 mm. When the initial coronary arterial dilatation exceeded 4.0 mm, the sensitivity was 28/31 (90%) and the specificity was 87/89 (98%) in the right coronary, the left anterior descending coronary, and the left circumflex arteries. For the bifurcation of the left coronary artery, the sensitivity was 14/21 (67%) and the specificity was 5/5 (100%).

Key words: Kawasaki disease — Coronary aneurysm — Localized stenosis — Intravascular ultrasound — Intimal thickening

Kawasaki disease (KD) is an acute febrile disease complicated by coronary arterial lesions in 10% to 15% of the patients [14, 16]. In the acute phase of KD, coronary arterial dilatations may develop that, in some patients, may persist for years. In others, they either regress or evolve into stenotic lesions. Stenotic lesions can lead to myocardial ischemia and even myocardial infarction [10, 11]. These events influence the prognosis of the patient.

Regression and stenotic lesions are mainly caused by thickening of the vessel walls. It is unknown whether thickening of the vascular wall can develop more than 10 years after the acute illness, but such information is essential to determine patient prognosis. Recently, assessment and quantitative measurements of the vascular wall by intravascular ultrasound (IVUS) in coronary atherosclerosis have become useful in its diagnosis and elucidation of morbidity [2, 4, 5, 9, 12].

We examined the coronary arteries of a group of patients more than 10 years after an episode of acute KD using IVUS with special attention to the relationship between dilatation of coronary arteries in the acute phase and late thickening of the vessel walls.

With respect to aneurysms at the bifurcation of the left coronary artery (LCA), we analyzed the impact of their peripheral extension as well as their diameter on late thickening of the vascular walls. We compared the intima–medial thickness of extended aneurysms which were dilated to segment 7 and/or segment 13 with that of localized aneurysms.

Patient Population

Twenty-eight patients were studied—20 males and 8 females. All participants gave informed consent for the IVUS study. The mean age at IVUS study was 17.3 ± 1.7 years (\pm SD) (range 14.5–21.1 years) and the mean age at the onset of KD was 2.4 ± 1.8 years

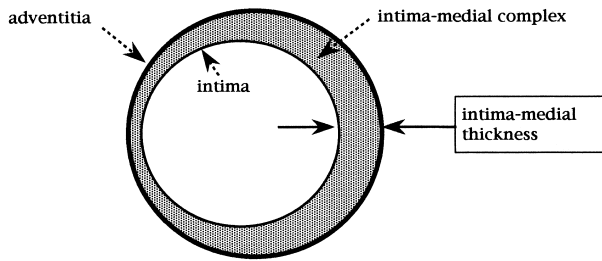


Fig. 1. Measurement of intima–medial thickness. Frames showing the greatest thickness of the vascular wall in respective segments were chosen. Intima–medial thickness is the greatest length from inside the vessel to the medial–adventitial border in the chosen frame.

(range 4 months to 6.4 years). All 28 patients underwent an initial coronary angiogram (CAG) less than 100 days after the onset of KD. The mean interval from the onset of KD to the initial CAG was 61 ± 19 days (range 30–98 days). All 28 had coronary arterial lesions due to KD. The mean interval from the initial coronary angiographic study to the IVUS study was 15.0 ± 1.6 years (range 10.8–18.3 years). The treatments of the acute phase of KD were as follows: aspirin (13), aspirin and steroid (7), steroid (1), or none (7). All patients had been treated with antiplatelet agents since the initial CAG. The mean total cholesterol was 162 ± 30 (range 119–225).

Methods

Intravascular Ultrasound Imaging and the Initial Selective Coronary Angiograms

The IVUS study was performed as follows. After anticoagulation with heparin and a dose of nitroglycerin, diagnostic coronary angiography was performed. After a 0.014-mm guidewire was advanced through a 6F guiding catheter, a 3.5-F and 30-MHz intravascular ultrasound catheter (Boston Scientific, Inc., USA) was inserted. The intravascular ultrasound equipment used was SONOS (Model 2400A, Hewlett–Packard, Inc., Palo Alto, CA, USA) and we recorded the ultrasonic images continuously on s-VHS videotape.

Coronary arterial lesions after KD by IVUS were characterized by intima–medial thickening. Because IVUS cannot identify the borderline of intima and media, we measured intima–medial thickness as a marker of intimal thickening of the coronary artery (Figs. 1 and 2). In all 28 cases at IVUS study, there was no thrombus. The maximum intima–medial thickness of respective coronary arterial segments in the ultrasonic images was measured by two independent observers. Frames showing the thickest vascular wall in respective segments were chosen by both observers. Each observer then made two measurements of the maximum intima–medial thickness at the frame using a software program (Hewlett–Packard). Measurements by each observer and between observers were reproducible with high correlation coefficients ($r = 0.99$). The diameters of coronary arteries at the corresponding coronary arterial segments in the initial selective CAGs were also measured by two observers. In the branches, the greatest diameter

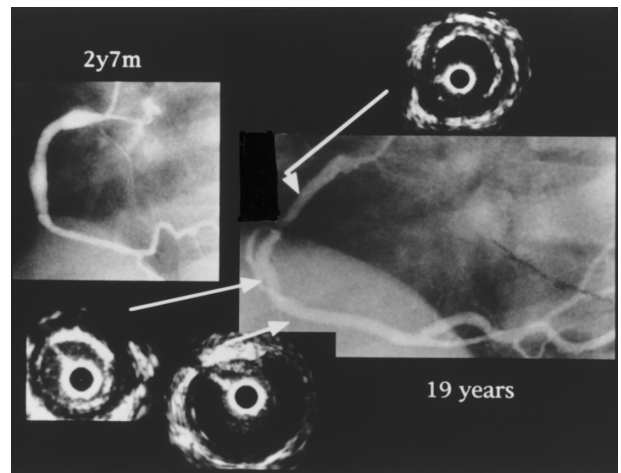


Fig. 2. Coronary angiograms and intravascular ultrasound images. This 19-year-old patient had Kawasaki disease at the age of 2 year 7 months. In the first angiogram, the maximum diameters of the coronary arteries were as follows: Segments 1, 2, and 3 were 5.2, 6.5, and 2.5 mm, respectively. By IVUS, the maximum intima–medial thicknesses of the vascular wall were as follows: Segments 1, 2, and 3 were 1.34, 1.93, and 0.21 mm, respectively.

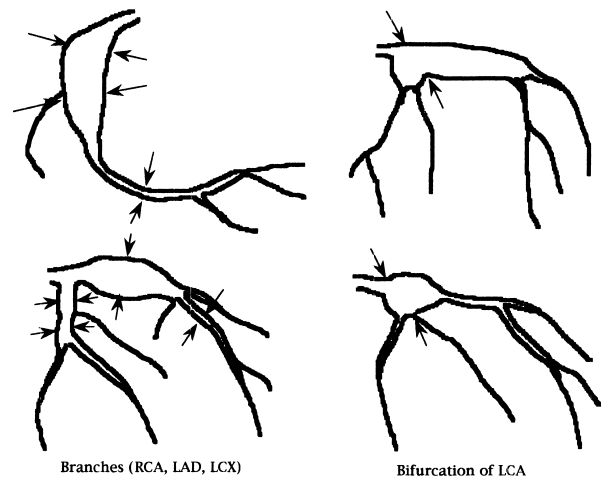


Fig. 3. The diameters of the coronary arteries in the initial selective angiograms at the segments corresponding to those measured at IVUS. In the branches the greatest diameter is taken as the point of maximal dilatation. At the left coronary artery (LCA) bifurcation the length as shown in the figures was measured. LAD, left anterior descending artery; LCX, left circumflex; RCA, right coronary artery.

of the segment is taken as the point of maximal dilatation. At the bifurcation of LCA, the diameter shown in Fig. 3 was measured. Measurements between observers were reproducible with a high correlation coefficient ($r = 0.98$).

The number of branches examined by IVUS were as follows: right coronary artery (RCA), 24; left anterior descending coronary artery (LAD), 23; and the left circumflex artery (LCX), 22. The number of segments evaluated in respective branches were as follows: RCA, 52; LAD, 36; and LCX, 32. The bifurcation of the LCA was examined in 26 patients.

Table 1. Coronary artery lesions at intravascular ultrasound study

	Localized stenosis	Regression	Dilated lesion	“Normal”	Total
RCA	4	19	5	24	52
LAD	3	8	4	21	36
LCX	3	3	1	25	32
Bifurcation of LCA		9	15	2	26

RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; LCA, left coronary artery.

The number of coronary artery lesions in respective segments at IVUS study are summarized in Table 1. In this study, localized stenosis was classified as 25%, 50%, or 75% stenosis. Regression indicates segments that were normal in selective CAGs in the IVUS study, although they were dilated in the initial CAGs.

We investigated the relationship between the coronary artery diameter at the initial selective CAGs and the degree of the intima-medial thickening observed more than 10 years later in the branches and at the bifurcation of the LCA.

We compared the threshold value of coronary arterial dilatation in the acute phase of KD with the degree of vascular wall thickening more than 10 years later in the branches and at the bifurcation of the LCA. For this study, intima-medial thickness exceeding 0.40 mm was defined as abnormal.

For aneurysms at the bifurcation of the LCA, we compared the intima-medial thickness of an extended aneurysm group (7 patients) with a localized aneurysm group (17 patients). For this study, extended aneurysm indicates an aneurysm at the bifurcation of the LCA extending to segment 7 and/or segment 13 in the initial selective CAGs (Fig. 4). Localized aneurysm implies an aneurysm at the bifurcation of the LCA which did not involve either segment 7 or segment 13 in the initial selective CAGs (Fig. 5). For the intima-medial thickness at the bifurcation, we compared extended aneurysms with localized aneurysms.

Linear regression analysis was used to correlate variables. The unpaired *t*-test was used to compare the difference between groups.

Results

A significant correlation was found between the diameters of the coronary arteries in the initial CAGs and the intima-medial thickness of the vascular wall in the RCA, the LAD, and the LCX ($r = 0.77$, $n = 120$, $p < 0.0001$) (Fig. 6). For the bifurcation of the LCA, it was 0.50 ($n = 26$, $p < 0.01$) (Fig. 7). Except for the bifurcation of the LCA, we found that the greater the arterial diameter in the acute phase, the thicker the intima-medial more than 10 years later.

When the initial coronary arterial dilatation exceeded 4.0 mm in the branches, the sensitivity was 28/31 (90%) and the specificity was 87/89 (98%) (Table 2). For the bifurcation of the LCA, when coronary arterial dilatation exceeded 4.0 mm the sensitivity was 14/21 (67%) and the specificity was 5/5 (100%) (Table 3).

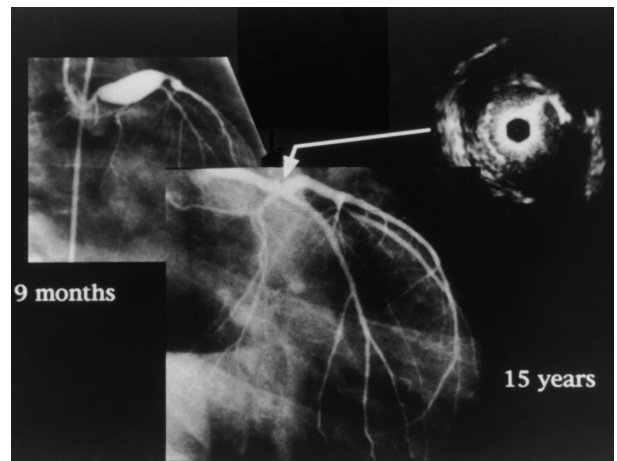


Fig. 4. Extended aneurysm at the bifurcation of the left coronary artery. This 15-year-old patient had Kawasaki disease at the age of 9 months. In the first angiogram, the maximum diameter at the bifurcation of the left coronary artery was 8.0 mm. This was an extended aneurysm. By IVUS, the maximum intima-medial thickness at the bifurcation of left coronary artery was 2.2 mm.

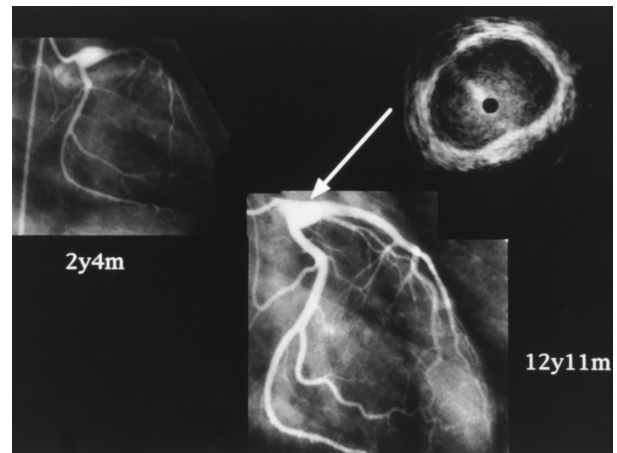


Fig. 5. Localized aneurysm at the bifurcation of the left coronary artery. This 12-year-old patient had Kawasaki disease at the age of 2 years 4 months. In the initial angiogram, the maximum diameter at the bifurcation of the left coronary artery was 6.5 mm. This was a localized aneurysm. By IVUS, the maximum intima-medial thickness at the bifurcation of left coronary artery was 0.24 mm.

We show respective coronary arterial lesion groups (“normal,” dilated lesion, regression, and localized stenosis) in CAGs in the IVUS study between the diameters of the coronary arteries in the first CAGs and the intima-medial thickness of vascular wall in the RCA, the LAD, and the LCX (Fig. 8). The normal group is clustered in the lower left portion of Fig. 8. On the other hand, the localized stenosis group is scattered in the right upper portion. The dilated lesion group tends to cluster in the middle. The regression group can be classified into two

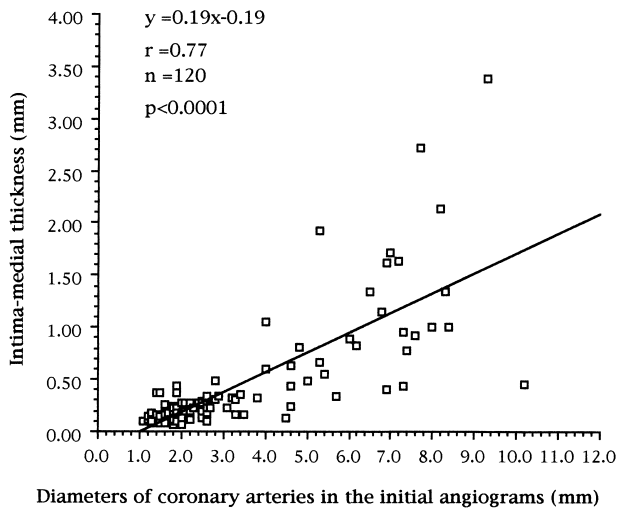


Fig. 6. Relation between diameters of coronary arteries in the initial coronary angiograms and intima-medial thickness in branches. A significant correlation was found between the diameter of the coronary arteries in the initial CAGs and the intima-medial thickness of the vascular wall in the RCA, the LAD, and the LCX.

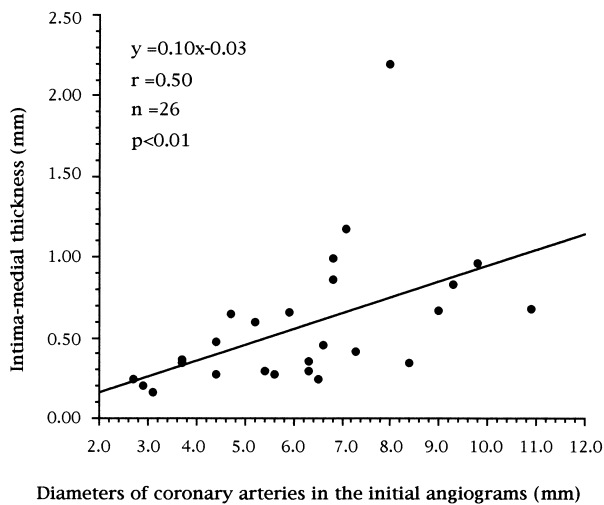


Fig. 7. Relation between diameters of coronary arteries in the initial coronary angiograms and intima-medial thickness at the bifurcation of the left coronary artery. A significant correlation was found between the diameter of the coronary arteries in the initial CAGs and the intima-medial thickness of the vascular wall at bifurcation of the left coronary artery.

apparent subgroups. One group is clustered in the right portion of the normal group, and the other group is similar to the localized stenosis group. The intima-medial thickening of all segments in the localized stenosis group was more than 0.80 mm, and the diameter at the initial CAGs exceeded 6.0 mm.

For the bifurcation of the LCA, the coefficient of correlation was low. We compared the intima-medial thickness of an extended aneurysm group with that of

Table 2. Sensitivity and specificity (RCA, LAD, LCX)^a

	Diameter of coronary artery in the acute phase	
	≤4.0 mm	>4.0 mm
Intimal thickening –	87 (98%)	3 (10%)
Intimal thickening +	2 (2%)	28 (90%)

RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.

^a Intimal thickening is defined as intima-medial thickness of more than 0.40 mm.

Table 3. Sensitivity and specificity (bifurcation of LCA)^a

	Diameter of coronary artery in the acute phase	
	≤4.0 mm	>4.0 mm
Intimal thickening –	5 (100%)	7 (33%)
Intimal thickening +	0	14 (67%)

LCA, left coronary artery.

^a Intimal thickening is defined as intima-medial thickness of more than 0.40 mm.

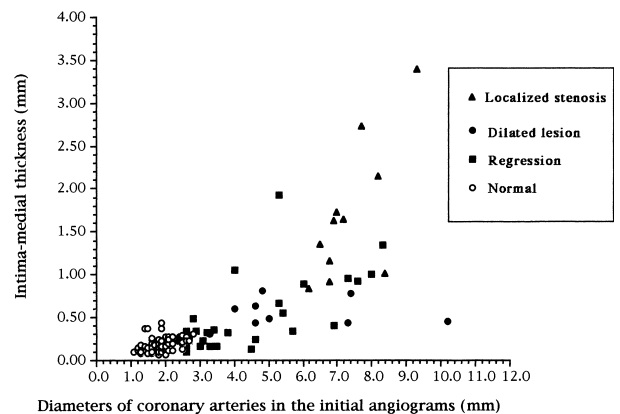


Fig. 8. Relation between diameters of coronary arteries in the initial coronary angiograms and intima-medial thickness in branches. The respective coronary arterial lesion groups were shown in CAGs in the IVUS study between the diameters of coronary arteries in the initial coronary angiograms and the intima-medial thickness in branches.

a localized aneurysm group. The mean intima-medial thickness of the extended aneurysm group was 1.00 ± 0.58 mm, whereas that for the localized aneurysm group was 0.42 ± 0.18 mm. The difference is highly significant ($p = 0.001$) (Fig. 9).

Discussion

Coronary arterial lesions in KD result from an acute phase vasculitis. Appearances vary from an angiographically normal artery to severe localized stenosis with calcification. One change after inflammation due to KD is thickening of the vascular wall, which in pathologic studies is described as intimal thickening with destruction of the media [8, 15]. Using IVUS, it has been reported that stenotic lesions result from thickening of the vascular wall [7, 17]. We determined the relationship between diameters of the coronary arteries in the acute phase and intima-medial thickness in the main branches and the LCA bifurcation more than 10 years later.

The normal value of intima-medial thickness at equivalent locations in individuals of a similar age is less than 0.30 mm [1, 3, 13]. In this study, we defined abnormal thickening of the intima-medial as more than 0.40 mm. In IVUS studies of adult, intima-medial thickening of more than 0.50 mm is usually defined as abnormal. If this value is used, the sensitivity is 23/31 (74%) and the specificity is 89/89 (100%). When the risk zone of the coronary artery is dilated above 4.0 mm, there is a high probability of subsequent thickening. This measurement has good sensitivity and good specificity.

Based on these data, it is prognostically useful in following patients with coronary arterial lesions due to KD to perform selective coronary angiography in those patients with coronary arterial lesions within 2 or 3 months after the acute onset. Coronary arterial dilatation during acute KD can now be detected by two-dimensional echocardiography [6, 18], and diameter measurement of the coronary arteries by two-dimensional echocardiography correlates well with that at selective CAGs. The threshold value in our study may be useful in determining the extent of follow-up of patients with coronary arterial lesions due to KD. However, the precise detection of coronary arterial lesion by two-dimensional echocardiography may be limited to the proximal portion of bilateral coronary arteries.

Thickening at the bifurcation of the left main coronary artery did not correlate strongly with the diameters of the coronary arteries in the first CAGs. This may be explained by the difference of arterial types. Coronary arteries are muscular, whereas the ascending aorta is an elastic vessel. The most proximal portion of the left main artery is of transitional structure. Furthermore, the characteristics at the bifurcation may also explain the difference.

The intima-medial thickness at the bifurcation of the left coronary arteries more than 10 years after KD was related to the involvement of the more peripheral artery as well as to the diameter of the

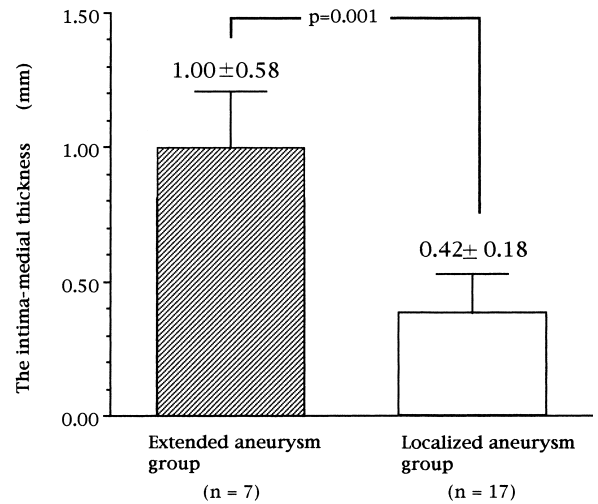


Fig. 9. Intima-medial thickness in extended aneurysm group and localized aneurysm group. The intima-medial thickness of the extended aneurysm group was significantly higher than that of the localized aneurysm group.

coronary aneurysms. Large and cylindrical-shaped aneurysms which extend to segment 7 and/or segment 13 are especially related to later intima-medial thickening leading to localized stenosis.

The threshold value, highly predictive of later intimal thickening, is coronary arterial dilatation of more than 4.0 mm. The data show that the extent of the initial vessel dilatation can be used to predict those patients at high risk of subsequent problems and is therefore clinically useful in the follow-up of patients after KD. It is uncertain whether mild intimal thickening after KD may be a risk factor for atherosclerosis in the future. Careful follow-up is essential in patients who have coronary arterial dilatation greater than 4.0 mm in the acute phase of KD.

On the other hand, if coronary arterial dilatations are <4.0 mm in the acute phase of KD, the possibility of late vascular wall thickening is low. It may be considerable to stop follow-up in the patients without coronary arterial dilatation >4.0 mm in the acute phase of KD.

The normal coronary artery diameter for patients less than 6 years old is within 2.0 mm, except for the left main coronary artery. The risk value for late thickening is 4.0 mm.

Conclusions

There is a significant correlation between the diameters of coronary arteries in acute phase of KD measured at coronary angiography and subsequent intima-medial thickness observed more than 10 years

later. This relationship holds for the RCA, the LAD, and the LCX. Extended aneurysms at the left main bifurcation also carry a high risk of future stenosis. The threshold value for acute phase dilatation which suggests a high risk of vascular wall thickening 10 years later is >4.0 mm.

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