Assessment of left ventricular longitudinal function in cats with subclinical hypertrophic cardiomyopathy using tissue Doppler imaging and speckle tracking echocardiography

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ABSTRACT. Hypertrophic cardiomyopathy (HCM) in cats is characterized by concentric left ventricular (LV) hypertrophy and both diastolic and systolic dysfunction. Although impaired cardiac function detected by tissue Doppler imaging (TDI) in cats with HCM was previously reported, reference ranges of TDI in normal cats and cats with HCM have been reported as widely variable. Two-dimensional speckle tracking echocardiography (STE) was useful for assessment of cardiac function in human patients with HCM, but clinical utility was not known in cats. The aim of this study was to assess global and segmental LV myocardial function using STE in cats with HCM whose TDI variables were within the reference range. A total of 35 cats of different breeds were enrolled in this study. The HCM group (n=22) was cats diagnosed as HCM without left atrial enlargement and with normal TDI measurements. HCM cats were further divided into a segmental hypertrophy (S-HCM) group and a diffuse hypertrophy (D-HCM) group. The control group consisted of 13 clinically healthy cats. No cats in any group showed any clinical symptoms. Conventional echocardiography, TDI, and global and segmental STE indices were evaluated and compared between groups. Only the longitudinal strain rate during early diastole was significantly decreased in both HCM groups, even in all segments including those without hypertrophy in S-HCM group. This study suggests that STE parameters are the more sensitive variables compared with conventional TDI parameters to detect early myocardial diastolic dysfunction in cats with HCM.

KEY WORDS: cardiomyopathy, feline, speckle tracking echocardiography, strain, tissue Doppler imaging

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Hypertrophic cardiomyopathy (HCM) is the most common heart disease in cats [21, 37] and is characterized by concentric left ventricular (LV) hypertrophy and both diastolic and systolic dysfunction. Diastolic dysfunction leads to left atrial (LA) enlargement and subsequent congestive heart failure. Systolic dysfunction occurs with the progressive disease process [47]. Cats in the early stage of HCM are asymptomatic [45], although myocardial dysfunction can occur with disease progression [1, 29].

Diastolic dysfunction is considered to be a primary abnormality of the disease [23, 29], and evidence for this has been provided by both invasive and noninvasive studies [4, 25]. Systolic dysfunction also occurs probably due to pathological fibrosis and increased matrix connective tissue [22, 47]. Although both short- and long-axis strains were reported to be depressed in human patients with HCM [5, 28], several studies indicated that longitudinal strain parameters were significantly affected, and a similar finding was reported in cats with HCM [31].

Tissue Doppler imaging (TDI) allows non-invasive assessment of myocardial function and has demonstrated segmental and global myocardial dysfunction in cats with

HCM [7, 9, 12, 16, 17, 27, 31, 42]. The longitudinal velocity profiles include peak systolic myocardial velocities (s') and peak early diastolic myocardial velocities at the mitral annulus (e') [16, 27, 44]. Previous studies have reported that s' or e' in LV free wall and interventricular septum (IVS) are reduced in cats with HCM. However, TDI is angle dependent [46], and the reported reference ranges for TDI in normal cats (s'; 1.9–8.7 m/sec, e'; 2.2–10.2 m/sec) [4, 7, 9, 12, 16, 17, 27, 31, 42] and cats with HCM (s'; 0.5–6.0 m/sec, e'; 0.6–5.4 m/sec) [7, 9, 27, 31, 42] are highly variable.

Two-dimensional speckle tracking echocardiography (STE) is a relatively new approach designed to assess ventricular function. STE has no angle-dependence and allows the assessment of any segment of the heart [3]. Some longitudinal STE parameters have been shown to correlate with MRI and pathological findings [30, 38]. The usefulness of STE analysis for assessment of cardiac function in human patients with HCM [5, 6, 24, 40], dogs with cardiomyopathies [10, 11, 48] and healthy cats [41] has been reported.

We hypothesized that STE analysis is a more sensitive technique to evaluate early myocardial impairment compared with TDI and can detect myocardial dysfunction in the subclinical HCM when TDI variables were still within the normal reference range. The aim of this study was to assess global and segmental LV longitudinal function using STE in cats with HCM whose TDI variables were within the reference range.

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MATERIALS AND METHODS

Animals: Study groups consisted of 22 cats with HCM and 13 clinically healthy cats (control group). Cats with HCM were prospectively recruited from patients presented to Azabu University Veterinary Teaching Hospital, because of suspected cardiac disease from April 2012 to January 2014.

The HCM group included cats diagnosed as HCM without left atrial enlargement (the left atrium-to-aortic root (LA/Ao <1.5) [26] and with normal TDI variables. Cats in the control group were either client-owned (n=3) or experimental cats (n=10) determined to be clinically healthy on the basis of clinical history, physical examination, blood pressure measurement, conventional echocardiographic examination, thoracic radiographs, CBC and serum chemistry panels. No cats in either group showed any clinical signs. None of the cats in either group were receiving treatment or medication at the time of enrollment into the study.

Echocardiographic examination: All echocardiographic images were acquired using an ultrasound unit equipped with a 7 MHz and 10 MHz transducer (Vivid 7 dimension, GE Medical System, Tokyo, Japan). Echocardiographic examination was performed by three sonographers (KS, YF and TA). All echocardiographic measurements were directly performed on the screen freeze-frame images, and then, 3 consecutive measurements were averaged for each value. Cats were gently restrained in lateral recumbency. The aortic and left atrial diameters at the end-systole and LA/Ao were measured from the right-sided parasternal short-axis view at the level of the aortic valve using a 2-dimensional method as previously described and validated [14, 43]. Left ventricular internal diameters (LVIDd), IVS and LV free wall thickness at the end-diastole (IVSd and LVFWd, respectively) were measured from the right parasternal short-axis view at the level of the chordae tendineae, and the LV shortening fraction (FS) was then calculated. The sub-aortic IVS thickness was measured at the end-diastole from the right parasternal 5-chamber view. Heart rate (HR) was calculated from M-mode images.

HCM was determined when the IVSd and/or LVFWd was 6 mm or more on the M-mode echocardiographic examination and the right parasternal long-axis view in the absence of pressure overload and systemic diseases known to cause LV hypertrophy [23]. LV thickness was measured at least in 4 left ventricular sites from the short axis view [37], and the mean value of 3 consecutive beats of the thickest segment among measured ventricular sites (LVTs) was calculated. HCM cats were divided into 2 groups; HCM with segmental hypertrophy (S-HCM group) and diffuse hypertrophy (D-HCM group). S-HCM was defined as when hypertrophy was seen in 50% or more of the LV region, but the whole region was not thickened. D-HCM was defined as when the whole LV regional was hypertrophied [37]. Continuous-wave Doppler was used to measure maximal systolic left ventricular out flow tract velocity to confirm an LV outflow obstruction characterized by turbulent aortic flow of high velocity (>2 m/s) [13].

Tissue Doppler imaging: All color TDI examinations were performed as previously described [27]. The septal and lateral aspects of the mitral annulus were sampled using

the left 4-chamber apical view. A 2×2 mm sample without angle correction was used. The mean value in 3 consecutive cardiac cycles in a single cine loop was used for statistical analysis. The normal reference range of s' was defined as greater than 6 cm/sec, and that of e' was defined as greater than 5.4 cm/sec based on previous reports [4, 7, 9, 12, 16, 17, 27, 31, 42].

Speckle tracking echocardiography: Longitudinal strain and strain rate were determined from the left apical four-chamber view. The frame rate used for this study to analyze STE indices ranged from 100 to 155 frames per second. Images were acquired from cine loops triggered by the QRS complex, and off-line image analysis was performed using commercial software (EchoPAC PC, GE Medical System, Tokyo, Japan). The principle of speckle tracking analysis was described in previous studies [19, 41, 47, 49]. Endocardial borders in the end-systolic frame of the 2-D images were manually traced to measure the left ventricular internal diameter at end systole. In S-HCM group, regions of interest were adjusted to LVFW that were not hypertrophied. The computer software automatically tracked myocardial motion and created 6 regions of interest in each image (baseseptum, middleseptum, apicalseptum, apicallateral, middlelateral and baselateral). The tracking quality of myocardial motion was automatically evaluated by the computer software to determine whether it was reliable, and the quality was expressed as valid or failed. When the computer software indicated the tracking had failed, the observer re-traced the endomyocardium until the quality was expressed as valid. The cardiac cycles used for analyses were determined by a simultaneous ECG (from R to R wave).

Peak longitudinal systolic strain (SL) and peak longitudinal strain rate during systole and early diastole (SrLs and SrLe) were measured in 6 segments from the basal, middle and apical regions of the septal and lateral walls (Fig. 1). Global values represent the average measurements from these 6 ventricular segments. The global peak longitudinal strain rate during late diastole (SrLa) was also measured, and SrLe/SrLa was calculated. STE parameters were calculated from three consecutive cardiac cycles on the same frame, and the mean value was used for analysis.

Statistical analyses: All measurements were expressed as mean $\pm$ SD. All analyses were performed by one observer (KS). Statistical analyses were performed using computer software (SPSS Statistics version 21.0, Chicago, IL, U.S.A.). All echocardiographic data were visually inspected and tested for normality by the Kolmogorov-Smirnov test. Comparisons for age, body weight and echocardiographic data among the 3 groups were performed using one-way analysis of variance. When normality was rejected, the Kruskal-Wallis test was used. Gender among groups was assessed by χ^2 test. When a significant difference was detected, multiple comparisons were evaluated by use of Bonferroni correction. In the S-HCM and D-HCM groups, correlations between following parameters were examined by use of Spearman's rank correlation coefficient; global values of STE parameters vs. IVSd or LVFWd, mean values of STE parameters in 3 segments of IVS or LVFW vs.

Fig. 1. Longitudinal strain rate tracking for one cardiac cycle obtained from the left 4-chamber apical view. Six curves with different colors depict respective myocardial segments of left ventricle (basal, middle and apical regions of the septal and lateral). Systolic and early diastolic values of longitudinal strain rate (SrLs, SrLe and SrLa) were calculated.

Table 1. Characteristics of S-HCM, D-HCM and control groups

Index	Unit	Control Group	S-HCM Group	D-HCM Group	P value
Number		13	17	5	
Gender	F/M	5/8	6/11	2/3	NS
Age	months				
	Mean±SD	39.2 ± 36.4	38.9 ± 31.4	45.6 ± 17.2	NS
	Range	7–110	6–108	24–73	
Body Weight	kg	3.92 ± 0.83	3.97 ± 1.91	4.08 ± 1.10	NS
Breeds		Norwegian Forest Cat 2 Domestic Shorthair 11	Scottish Fold 4 American Shorthair 3 Maine Coon 1 Exotic Shorthair 1 Ragamuffin 1 Norwegian Forest Cat 1 American Curl 1 Domestic Shorthair 5	Scottish Fold 1 American Shorthair 1 Maine Coon 1 Domestic Shorthair 2	

NS: Not significant.

IVSd or LVFWd. Intraobserver variability for each global STE parameter was assessed by calculation of coefficients of variation (CV) using the formula: $CV = (SD/\text{arithmetic mean of measurements}) \times 100$ [15]. Coefficients of variations were considered clinically acceptable if $<10\%$ [27].

RESULTS

Animals: The characteristics of all groups are shown in Table 1. S-HCM group and D-HCM group included 17 and 5 cats, respectively. IVS hypertrophy without LV free wall hypertrophy was seen in all cats included in S-HCM group. In S-HCM and D-HCM groups, 17 and 4 cats showed dynamic LV outflow obstruction due to SAM, respectively.

Echocardiography examination: The results of conventional echocardiography are shown in Table 2. Those IVSd, LVFWd, LVTSd, FS and aortic flow of high velocity were significantly higher, and LVIdD was significantly lower in both HCM groups than in the control group (both $P < 0.05$). There was no significant difference in HR and LA/Ao. In S-HCM and D-HCM groups, the maximum wall thicknesses at end-diastole ranged from 6.0 to 8.2 mm.

TDI: TDI could be assessed in all cats without summation of the e' and late diastolic myocardial velocities. The results of TDI are shown in Table 2. There were no significant differences in s' and e' among 3 groups.

STE: STE was assessed in all cats without summation of e wave and a wave. Table 3 shows the results of global

Table 2. Results of conventional echocardiography and TDI parameters

	Unit	Control group	S-HCM Group	D-HCM Group	P value
LVIDd	cm	1.60 ± 0.10	1.43 ± 0.20*	1.40 ± 0.20*	0.007
IVSd	cm	0.40 ± 0.03	0.62 ± 0.05**	0.73 ± 0.06**†	<0.001
LVFWd	cm	0.40 ± 0.04	0.44 ± 0.05*	0.65 ± 0.08**†	<0.001
FS	%	40.7 ± 7.5	60.3 ± 10.2**	60.1 ± 10.9**	0.002
LA/Ao		1.21 ± 0.14	1.22 ± 0.10	1.23 ± 0.11	NS
aortic flow of high velocity	m/sec	0.98 ± 0.20	3.22 ± 1.05**	2.90 ± 1.26**	<0.001
LVTSD	cm	0.42 ± 0.05	0.63 ± 0.25**	0.67 ± 0.46**	<0.001
HR	bpm	165 ± 39	178 ± 29	168 ± 10	NS
s' (Lateral)	cm/sec	7.30 ± 0.70	7.38 ± 0.89	7.42 ± 0.98	NS
s' (Septal)	cm/sec	7.12 ± 0.66	7.33 ± 0.54	7.00 ± 1.18	NS
e' (Lateral)	cm/sec	8.70 ± 1.88	8.78 ± 2.02	8.73 ± 1.17	NS
e' (Septal)	cm/sec	6.95 ± 1.05	6.90 ± 0.99	7.00 ± 0.71	NS

LVIDd: Left ventricular internal diameters at end-diastole; IVSd: Interventricular septum wall diameters at end-diastole; LVFWd: Left ventricular free wall diameters at end-diastole; FS: Left ventricular shortening fraction; LA/Ao: Left atrium-to-aorta ratio; LVTSD: Left ventricular thickest segment diameters at end-diastole; HR: Heart Rate; s' (Lateral): Peak systolic myocardial velocities at mitral annulus of lateral aspect; s' (Septal): Peak systolic myocardial velocities at mitral annulus of septal aspect; e' (Lateral): Peak early diastolic myocardial velocities at mitral annulus of lateral aspect; e' (Septal): Peak early diastolic myocardial velocities at mitral annulus of septal aspect; NS: Not significant. *: Significant difference compared with control group by multiple comparison ($P < 0.05$). **: Significant difference compared with control group by multiple comparison ($P < 0.01$). †: Significant difference compared with S-HCM group by multiple comparison ($P < 0.01$).

Table 3. Results of global values in the STE parameters

	Unit	Control group	S-HCM group	D-HCM group	P value
SL	%	-24.6 ± 2.6	-23.2 ± 2.9	-23.5 ± 3.1	NS
SrLs	/sec	-3.50 ± 0.46	-3.36 ± 0.56	-3.49 ± 0.57	NS
SrLe	/sec	5.07 ± 0.96	3.34 ± 0.49**	3.30 ± 0.39**	<0.001
SrLa	/sec	3.08 ± 0.25	2.12 ± 0.55**	2.10 ± 0.49**	<0.001
SrLe/SrLa		1.65 ± 0.31	1.66 ± 0.40	1.65 ± 0.37	NS

SL: Peak systolic longitudinal strain; SrLs: Peak longitudinal strain rate during systole; SrLe: Peak longitudinal strain rate during early diastole; SrLa: Peak longitudinal strain rate during late diastole; NS: Not significant. **: Significant difference compared with control group by multiple comparison ($P < 0.01$).

values in the STE indices of all groups. SrLe and SrLa showed significant differences between control and S-HCM groups ($P < 0.001$), and between control and D-HCM groups ($P < 0.001$). There was no significant difference in SrLe/SrLa among 3 groups. Table 4 showed the results of segmental values in the STE indices of all groups. SrLe in all segments was significantly decreased in both HCM groups in comparison with the control group ($P < 0.01$). SrLe in all segments including those without hypertrophy was also decreased in S-HCM group. Median and interquartile ranges of global and segmental values of SrLe in all groups are shown in Figs. 2 and 3.

Intraobserver variability of STE indices was 4.98% in SL, 3.55% in SrLs, 4.40% in SrLe and 3.89% in SrLa. CVs in all parameters were considered low.

There were no significant correlations between STE parameters (global values of STE parameters, mean values in 3 segments of IVS and mean values in 3 segments of LVFW) and end-diastolic wall thickness (IVSd and LVFWd) ($P > 0.05$).

DISCUSSION

The present study revealed that global and segmental SrLe

were significantly decreased in HCM cats with normal TDI parameters, and SrLe decreased even in the segments that were not hypertrophied in S-HCM group. Since CVs were considered low in the present study as well as a previous study [41], STE analysis can be applicable for the assessment of cardiac function in cats.

A previous study assessed strain parameters measured by color TDI, which was different from our method, in cats with HCM [47]. TDI has major disadvantages, including angle dependence, limited spatial resolution and deformation analysis (only allowed in one dimension). TDI is the method that assesses cardiac function in a focal area. STE is a novel technique that evaluates left ventricular function more objectively and quantitatively and does not have the limitations seen in TDI [33]. STE also allows the segmental assessment of the heart. STE parameters would be considered a more sensitive technique compared with conventional TDI parameters to detect early myocardial diastolic dysfunction in this population.

In the present study, diastolic myocardial dysfunction was observed in LV free wall segments that were not hypertrophied. Previous studies also indicated that myocardial relaxation was reduced in the segments that were not yet hypertrophied in human, rabbits and cats [8, 9, 32, 35, 36].

Table 4. Results of segmental values in STE parameters

	Unit	Control group	S-HCM group	D-HCM group	<i>P</i> value	
SL	%	basSept	-24.3 ± 4.1	-23.3 ± 5.1	-23.5 ± 6.9	NS
		midSept	-26.6 ± 3.5	-24.9 ± 4.1	-25.4 ± 4.3	NS
		apSept	-26.3 ± 3.5	-26.2 ± 3.7	-27.2 ± 2.0	NS
		apLat	-28.0 ± 3.9	-25.6 ± 4.5	-25.1 ± 2.9	NS
		midLat	-22.6 ± 3.2	-21.5 ± 3.4	-21.1 ± 3.6	NS
		basLat	-19.8 ± 4.0	-17.9 ± 3.4	-18.6 ± 3.9	NS
SrLs	/sec	basSept	-3.20 ± 0.92	-3.10 ± 0.68	-3.00 ± 1.64	NS
		midSept	-3.65 ± 0.70	-3.42 ± 0.55	-3.32 ± 0.72	NS
		apSept	-4.10 ± 0.36	-3.78 ± 0.67	-4.12 ± 0.54	NS
		apLat	-4.00 ± 0.36	-3.80 ± 0.78	-4.15 ± 0.56	NS
		midLat	-3.27 ± 0.59	-3.18 ± 0.72	-3.24 ± 0.58	NS
		basLat	-2.78 ± 0.71	-2.89 ± 0.69	-3.12 ± 0.39	NS
SrLe	/sec	basSept	4.02 ± 1.15	2.63 ± 0.76**	2.65 ± 0.67*	0.001
		midSept	4.66 ± 0.96	3.05 ± 0.70**	3.39 ± 0.56*	<0.001
		apSept	6.22 ± 1.07	4.04 ± 0.83**	3.77 ± 0.38**	<0.001
		apLat	6.28 ± 1.13	4.16 ± 1.04**	3.90 ± 0.27**	<0.001
		midLat	4.94 ± 1.46	3.37 ± 0.76**	3.53 ± 0.52*	0.002
		basLat	4.49 ± 1.47	2.78 ± 0.64**	3.05 ± 0.63*	<0.001
SrLa	/sec	basSept	2.93 ± 0.21	2.04 ± 0.54**	2.00 ± 0.32**	<0.001
		midSept	3.05 ± 0.21	2.15 ± 0.61**	2.20 ± 0.69*	<0.001
		apSept	2.88 ± 0.22	2.10 ± 0.61**	2.10 ± 0.28*	<0.001
		apLat	3.13 ± 0.22	2.11 ± 0.56**	2.10 ± 0.74**	<0.001
		midLat	2.97 ± 0.21	2.15 ± 0.62**	2.02 ± 0.37*	<0.001
		basLat	3.00 ± 0.21	2.10 ± 0.63**	2.18 ± 0.67**	<0.001

SL: Peak systolic longitudinal strain; SrLs: Peak longitudinal strain rate during systole; SrLe: Peak longitudinal strain rate during diastole; midSept: Middleseptum; apSept: Apicalseptum; apLat: Apicallateral; midLat: Middlelateral; basLat: Basalateral; NS: Not significant. *: Significant difference compared with control group by multiple comparison ($P<0.05$) **: Significant difference compared with control group by multiple comparison ($P<0.01$)

Fig. 2. Boxplot comparing global SrLe. The boxes represent the interquartile ranges. Horizontal bar represents the median value for all groups. SrLe significantly decreased in S-HCM and D-HCM groups in comparison with the control group. ** $P<0.01$.

Nagueh *et al.* speculated that myocardial dysfunction prior to LV hypertrophy might provide the stimulus for the devel-

opment of LV hypertrophy. Chetboul *et al.* and MacDonald *et al.* reported that reduced diastolic function was observed in Maine Coon cats before development of LV hypertrophy. However, their case/case series were all single breeds, and no hypertrophy has occurred in LV yet, which was different from our case series. Our results suggested that LV with normal thickness in HCM cats did not always relate to normal segmental myocardial function.

Although SL has been reported to decrease with progressive LV concentric hypertrophy [47], it was not significantly changed in the present study. This discrepancy in the results could be partly due to the difference in the stages of disease and the ages of the populations. A previous report indicated that systolic dysfunction deteriorated as disease progressed [47]. Since all cats in the HCM group in the present study showed no left atrial enlargement, which was considered in the early stage of HCM, systolic function was presumably preserved. An association between aging and systolic function was previously reported in cats [7, 31]. A relationship between aging and myocardial pathologic progression was also previously described [1]. Since our cases consisted of relatively young cats and the disease was in the early stage, systolic function was considered still preserved.

There was no significant difference in SrLe/SrLa among groups in the present study. Baktir *et al.* described early

Fig. 3. Segmental SrLe values in normal and HCM groups. The boxes represent the interquartile ranges. Horizontal bar represents the median value for each group. SrLe significantly decreased in all segments in S-HCM and D-HCM groups, compared with the control group. basSept: Baseseptum; midSept: Middleseptum; apSept: Apicalseptum; apLat: Apicallateral; midLat: Middlelateral; basLat: Baselateral. ** $P < 0.01$.

diastolic dysfunction in human patients with non-alcoholic steatohepatitis using STE and found the decreased SrLe and SrLa with normal SrLe/SrLa in longitudinal images [2]. Although underlying heart disease was different from our study, their results were similar to ours.

Several previous reports indicated that e' in the LV free wall and IVS decreased in cats with HCM in comparison with normal cats [7, 27, 31]. The previous literature included HCM with congestive heart failure, and the cats were on some medications. Cats in HCM group in the present study were considered to be at a much earlier disease stage than previously reported cats with HCM, since there were no significant differences in TDI parameters.

Saito *et al.* and Popovic *et al.* reported that the LV wall thickness may not reflect the severity of myocardial fibrosis, but that strain reflects the severity of fibrosis in human patients with HCM [38, 39]. Correia *et al.* and Kobayashi *et al.* reported that myocardial strain was influenced by a methodology to determine LV regional function as well as myocyte disarray and myocardial fibrosis [18, 30]. The present study demonstrated that STE parameters were decreased in non-hypertrophied LVFW and there were no significant correlations between STE and LV wall thickness. Abnormal STE parameters may imply some degree of myocardial fibrosis, although a further study is warranted.

There are over 4 limitations in the present study. First, the number of cats available for both groups was limited. Second, both groups consisted of several feline breeds, and the breed might interact with echocardiographic parameters [20, 34]. Different breeds may carry different HCM-associated genes, which could demonstrate different functional manifestations although not known. Third, no blinding process was used for data analyses. Fourth, pathological examination was not available. Finally, we did not compare STE and TDI in the radial and circumferential direction, and did not assess twist nor torsion. A further study is warranted to assess the relevance.

The present study suggests that STE parameters were sensitive variables to detect early myocardial diastolic dysfunction in cats with HCM. In addition to genetic screening, echocardiographic preclinical diagnosis using STE would afford the opportunity to prevent development of LV hypertrophy with early drug therapy in the future and to avoid unfavorable breeding programs.

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