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Measurement of Cardiac Output by Pulse Dye Densitometry Using Indocyanine Green

A Comparison with the Thermodilution Method

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Background: **A new method for determining cardiac output (CO, l/min) using dye dilution combined with pulse dye densitometry (PDD), based on the principle of pulse oximetry, has been developed. The aim of the study was to determine the accuracy and precision of PDD by comparing it with the thermodilution method.**

Methods: **A prospective study was performed in 22 patients having surgery who were monitored using a pulmonary arterial catheter. In addition to the catheter, a specially designed photodetector was placed on the nasal wing. Ten milliliters of ice-cold indocyanine green dissolved in a 5% glucose solution (0.5 mg/ml) was injected. The dye and thermal dilution curves were simultaneously measured to calculate CO. Three to six injections were performed before and after surgery. Paired data were assessed in absolute terms, and the percentage errors were calculated by the degree of agreement and compared at three levels of CO (low $\leq$ 3.5 $<$ medium $\leq$ 6 $<$ high) by analysis of variance.**

Results: **The mean and SDs of the differences between dye and thermodilution CO were 0.16 $\pm$ 0.80 l/min or 4.5 $\pm$ 19.6% for 191 paired data. Measurement after surgery failed in one patient. The percentage error with low CO (9.3 $\pm$ 19.3%) was greater ($P < 0.05$) than those obtained with other CO.**

Conclusions: **Pulse dye densitometry could measure CO repeatedly in patients having major surgery with the same degree of accuracy as the thermodilution method; however, a considerable degree of error was observed in some patients. (Key words: Measurement: cardiac output; indicator dilution technique; thermodilution technique; dye dilution technique. Indocyanine green. Evaluation studies.)**

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ALTHOUGH relatively noninvasive techniques for measuring cardiac output have been described, techniques such as impedance, echocardiography, and Fick's method have not gained widespread clinical acceptance because of their unreliability or the cumbersome procedures involved. Thus, the thermodilution method for measuring cardiac output remains a clinical standard.

Pulse oximetry, which can detect arterial oxygen saturation noninvasively, continuously, and without calibration, has widened the scope of clinical monitoring. The principle of pulse oximetry is based on the theory that the pulsatile components of the absorbances of red and infrared light transmitted through tissue are related to arterial hemoglobin oxygen saturation.[1] As the calculation is based on the ratio of the pulse absorbance signals obtained at two wave lengths, the signal can be amplified and arterial hemoglobin oxygen saturation can be estimated even during a small pulse amplitude. If the same principle was applied to some substance in the blood other than hemoglobin and its alteration due to arterial blood pulsation was determined, its concentration in the arterial blood could be estimated regardless of the strength of the incident light, composition of the tissues, or the site of detection. Based on these qualifications, Aoyagi *et al.*[2-5] developed a new method to measure cardiac output by analyzing the pulsatile change in indocyanine green concentration in the peripheral arterial blood without direct blood sampling.

The aim of this study was to compare this new technique with the standard thermodilution technique.

Methods

Patients

Twenty-two patients having major surgery under general anesthesia and requiring monitoring of pulmonary artery pressure during surgery in Gunma University Hos-

pital from February 1, 1996 until May 31, 1996, and from November 15 until December 20, 1996 were selected for inclusion in this study whenever the equipment and investigators were available. Institutional approval and written informed consent from each patient were obtained.

Investigational Procedure

After induction of anesthesia, a pulmonary artery catheter (744H-7.5 French; Baxter Healthcare Corp., Irvine, CA) was floated into the pulmonary artery *via* the right internal jugular vein. After the pulmonary arterial catheter had been inserted, cardiac output was measured before skin incisions were made. A 10-ml solution of ice-cold indocyanine green dissolved in a 5% dextrose solution (0.5 mg/ml) was injected into the right atrium through a CO-SET (closed injectate delivery system for cold injectate model 93-600, Baxter Healthcare) in which the temperature of the injectate was measured at the injectate port. The thermal dilution curve was recorded at the pulmonary artery (Vigilance; Baxter Healthcare) and the dye dilution curve of indocyanine green was simultaneously recorded at the nasal wing (alae nasi) by a specially designed optical sensor that sandwiched the nasal wing between the light-emitting diodes and a photodiode measuring the intensity of the light transmitted through the nasal wing. The optical sensor was connected to the pulse dye densitometer (R470; Nihon-Kohden, Tokyo, Japan). The injections were repeated three to six times at an interval of 2 min for each injection for each patient during the preoperative period. Injections of indicator were done regardless of the respiratory cycle. In 12 patients, the procedure was repeated on the surgical table at the completion of the surgery before they were transferred to the intensive care unit.

Indocyanine Green

Injections of 5 mg indocyanine green (tricarbocyanine dye) were repeated three to six times for a measurement lasting about 10 min. Indocyanine green injected into the central vein mixed with blood in the right atrium and right ventricle and most of the dye associated with the α_1-lipoproteins and remained in the intravascular space.[6] After passage through the pulmonary circulation, the time-concentration curve of the first pass through the nasal wing was detected by pulse dye densitometry and used to calculate cardiac output. The dye is nontoxic, except for rare cases of anaphylaxis. It is cleared from the blood exclusively by the liver without undergoing either intrahepatic conjugation or enterohepatic recirculation,[7] and its transport into hepatocytes is considered to be irreversible due to extensive binding within the cell.[8] Thus, after complete mixing with the circulating blood, the blood concentration of the dye is in exponential decay. The algorithm of pulse dye densitometry was constructed to work through 30 pulses after the peak height of the dye curve to complete calculation of cardiac output, and thus a period of about 90 s after the dye injection was required for the device to be readied for the next dye injection. The blood dye concentration 90 s after the injection of 5 mg dye was sufficiently low to measure cardiac output with a new injection of 5 mg dye, although some trace concentration of the dye remained in the circulating blood. The peak gain in the blood dye concentration after the dye injection of 5 mg was 5 - 10 mg/l. In successive injections, the device determines the basal level of blood dye concentration when the injection of the dye starts, and the dye concentration-time area above this basal level is calculated when the next injection is performed. Repeated injections of 5 mg dye did not affect cardiac output measurements to any degree, although the maximum amount tolerable in a 24-h period has not been established.

Principle of Pulse Dye Densitometry and Calculation of Cardiac Output

Because a detailed description of pulse dye densitometry has been reported previously,[2-4] only an outline is given here. The principle of pulse oximetry can be used to measure the relative concentration of substances in the blood stream that absorb a certain wave length. Pulse oximetry is used to calculate the ratio of oxyhemoglobin concentration to reduced hemoglobin concentration by measuring the difference in absorbance between wave lengths of 660 nm and 890 nm. In pulse dye densitometry, two wave lengths (805 and 890 nm) are used to measure the ratio of indocyanine green concentration to hemoglobin concentration. This is because the extinction coefficient of indocyanine green in blood is at its maximum at 805 nm and is nearly zero at 890 nm; therefore, we can obtain a large change in optical density that correlates with the change in indocyanine green concentration. In addition to this, the difference in the oxyhemoglobin and reduced hemoglobin extinction coefficients at these wave lengths is small enough to be negligible. Accordingly, the indocyanine green concentration can be photometrically calculated from the ratio of its concentration to the

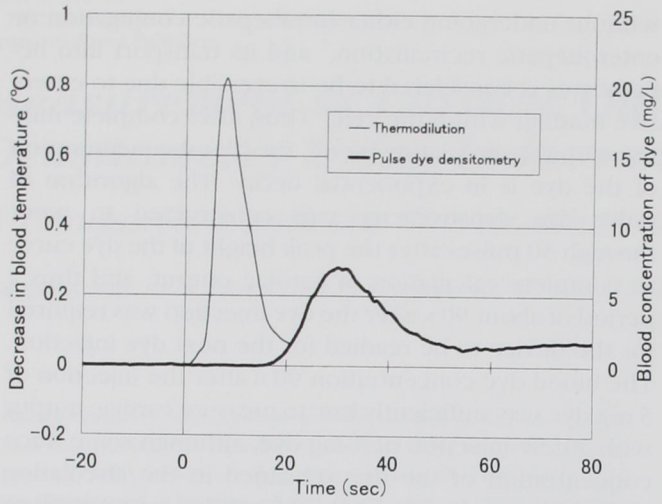

Fig. 1. Thermo- and dye-dilution curves were measured simultaneously in a patient by injecting 10 ml ice-cold 5% dextrose solution containing 5 mg indocyanine green into the right atrium at time 0. Abscissa, time (s); left ordinate, decrease in blood temperature (°C); and right ordinate, blood concentration of indocyanine green (mg/l).

hemoglobin concentration for each pulse, using the hemoglobin value measured by other means. Then blood concentrations of indocyanine green and the cardiac output were assessed using a custom-made device (R740, Nihon-Kohden, Tokyo, Japan). For thermodilution, calculation of the cardiac output was performed using a standard cardiac output computer (Vigilance). Both methods were based on the same principle originally described by Stewart-Hamilton,[9] and the specific calculation of dye dilution cardiac output (R740, Nihon-Kohden, Tokyo, Japan) used the algorithm described by Lilienfied and Kovach.[10] In the thermal dilution calculation formula, the computation constant of the catheter that we used was 0.574, and thus the numerator of the computation formula for cardiac output was calculated to be 57.4% of its theoretical value (a typical dye dilution curve by pulse dye densitometry and a thermodilution curve obtained simultaneously are shown in figure 1).

Statistics

The analysis of agreement is based on the method proposed by Bland and Altman[11] for comparing two methods of evaluation of the same parameter. The differences between the dye and thermodilution methods were plotted against the average of the two methods. Bias and precision were evaluated using the mean and standard deviation of the differences between the dye and thermodilution methods. Bias measures systematic error between the methods, and precision quantifies the random error or variability. The limits of agreement were defined as the mean difference ± 2 SD. To determine whether the differences between the methods depend on cardiac output in absolute terms, the percentage difference [100 × (difference in cardiac output between the methods)/(mean of cardiac output by the two methods)] was calculated and plotted against the average of the two methods. Percentage and absolute differences were compared for three levels of mean cardiac output of dye and thermodilution; that is, low ($\leq$ 3.5 l/min), medium ($\geq$ 3.5 l/min and $<$ 6 l/min), and high ($>$ 6 l/min) by one-way analysis of variance. When a significant difference ($P < 0.05$) was obtained, *post hoc* tests were performed using Fisher's protected least-significant difference.

Results

The demographic data of the patients are summarized in table 1. One hundred ninety-one paired data were obtained from 22 patients. In 10 patients, measurement of cardiac output was performed only before surgery, one patient was also included in this group when measurement after surgery failed to detect a pulsatile signal, whereas in the other patients measurements were performed before and after surgery. In the latter patients, the circulatory conditions were different before and after surgery, and thus it is unlikely that they unequally weighted the results (table 1). Each measurement had a small variation around each mean value, as indicated by the 0.32 ± 0.16 variation of the mean SD of the SD of the mean difference in each measurement, although the mean differences between the two methods ranged from 1.85 to -1.11 l/min (table 1). The errors and percentage errors of the paired dye and thermal dilution cardiac outputs were plotted against their mean values (the mean of the difference and its SD were 0.157 ± 0.798 l/min and 4.5 ± 19.6% in the absolute and percentage errors, respectively; figs. 2 and 3). The percentage differences were significantly great for determining low cardiac output, although the absolute values of the differences were identical for the three levels of cardiac output (table 2).

Discussion

More than three decades ago, the accuracy of the thermodilution method for measuring cardiac output

Table 1. Demographic Data of the Patients and Cardiac Outputs Determined by the Thermal and Dye Dilution Methods, and Their Differences (Dye-thermal)

Patient No.	Disease or Surgery	Age (yr)	Gender	BSA (kg/m^2)	N	Cardiac Output (L/min; mean ± SD)		
						Dye	Thermal	Difference
1	Lung cancer	77	M	1.51	5	3.72 ± 0.35	4.83 ± 0.26	−1.11 ± 0.17
					5	5.10 ± 0.47	5.22 ± 0.23	−0.13 ± 0.45
2	CABG	65	M	1.79	6	3.17 ± 0.14	4.07 ± 0.25	−0.90 ± 0.15
3	Adrenal tumor	49	M	1.60	5	7.15 ± 0.55	6.78 ± 0.24	0.37 ± 0.60
					3	9.01 ± 0.52	7.70 ± 0.36	1.31 ± 0.69
4	MVR, AVR	64	M	1.6	6	2.43 ± 0.31	2.48 ± 0.13	−0.05 ± 0.32
					6	5.34 ± 0.26	4.98 ± 0.37	0.35 ± 0.40
5	CABG	69	M	1.41	6	3.25 ± 0.32	2.51 ± 0.26	0.73 ± 0.42
6	AVR	46	M	1.81	5	3.37 ± 0.24	4.34 ± 0.23	−0.90 ± 0.31
7	AVR	74	M	1.38	5	2.66 ± 0.13	3.24 ± 0.15	−0.58 ± 0.05
					6	6.12 ± 0.72	5.93 ± 0.46	0.19 ± 0.56
8	AVR	61	M	1.47	5	2.71 ± 0.13	3.26 ± 0.09	−0.55 ± 0.14
					6	7.84 ± 0.24	8.75 ± 0.39	−0.91 ± 0.33
9	AVR, CABG	75	M	1.39	6	3.48 ± 0.53	2.45 ± 0.16	1.03 ± 0.42
10	AVR	75	F	1.22	4	5.21 ± 0.23	3.78 + 0.26	1.44 ± 0.19
					6	3.13 ± 0.32	2.85 ± 0.10	0.28 ± 0.30
11	CABG	67	M	1.49	6	3.92 ± 0.23	3.27 ± 0.18	0.66 ± 0.30
12	CABG	69	F	1.43	6	4.12 ± 0.38	3.50 ± 0.21	0.62 ± 0.35
					6	5.48 ± 0.36	5.90 ± 0.50	−0.42 ± 0.73
13	Lung cancer	68	M	1.60	6	3.32 ± 0.19	2.85 ± 0.32	0.49 ± 0.16
14	CABG	77	M	1.56	6	3.63 ± 0.50	2.82 ± 0.34	0.89 ± 0.46
					6	4.51 ± 0.32	3.90 ± 0.14	0.61 ± 0.25
15	TAA	70	M	1.54	6	3.71 ± 0.44	3.27 ± 0.59	0.44 ± 0.22
					6	5.97 ± 0.25	5.15 ± 0.14	0.82 ± 0.37
16	TAA	62	M	1.55	6	3.51 ± 0.35	3.22 ± 0.26	0.30 ± 0.26
17	CABG	48	M	1.88	5	3.82 ± 0.17	4.52 ± 0.29	−0.70 ± 0.38
18	CABG	63	F	1.39	6	3.05 ± 0.48	2.93 ± 0.27	0.12 ± 0.30
					6	3.94 ± 0.24	5.03 ± 0.29	−1.09 ± 0.35
19	CABG	55	M	1.63	6	4.53 ± 0.26	4.47 ± 0.27	0.06 ± 0.27
20	TAA	39	M	1.98	6	5.97 ± 0.28	6.47 ± 0.35	−0.50 ± 0.33
21	CABG	69	F	1.38	5	3.65 ± 0.38	2.54 ± 0.17	1.11 ± 0.27
					6	5.42 ± 0.20	3.57 ± 0.10	1.85 ± 0.21
22	AVR	74	F	1.30	6	2.40 ± 0.21	2.52 ± 0.22	−0.12 ± 0.05
					6	4.50 ± 0.22	4.32 ± 0.16	0.18 ± 0.12
	SD of difference							0.32 ± 0.16

The first line shown for each patient is a measurement performed before the start of skin incision and the second line for the same patient is a measurement obtained at the end of surgery. In patients 2, 5, 6, 9, 11, 13, 16, 17, 19, and 20 only a measurement before the start of skin incision was performed.

BSA = body surface area; N = number of injections; M = male; F = female; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; AVR = aortic valve replacement; TAA = thoracic aortic aneurysm.

was compared with the dye dilution method. At that time, some researchers found an excellent correlation over a wide range of cardiac output values, whereas others observed that the thermodilution method systematically overestimated the dye dilution cardiac output values.[1,2] Engineering and technical improvements have made the thermodilution method a standard in the clinical measurement of cardiac output because it can be performed repeatedly with a nontoxic, nonaccumulating, nonrecirculating thermal indicator, although it requires a delicate procedure to insert the pulmonary arterial catheter. Recently, a new method for measuring cardiac output by determining the pulse dye concentration in the peripheral arterial blood has been developed,[2-4] and it is time for this new system to be compared with the thermodilution method. Neither the thermodilution method nor the pulse dye densitometry method provides an unequivocally correct measurement, so we assessed the precision and accuracy of pulse dye densitometry using the degree of agree-

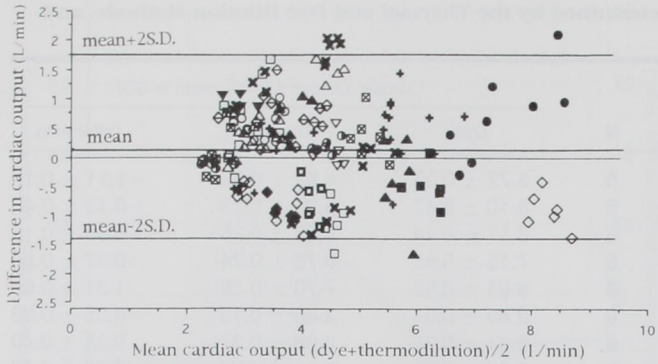

Fig. 2. Difference in cardiac output measured by pulse dye densitometry and the thermodilution method (dye-thermodilution) plotted against their respective means. Each patient is represented by a different symbol. The *horizontal lines* indicate the mean and the mean ± 2 SD. Bias = 0.16 ± 0.80 l/min (mean ± SD).

ment.[11] Pulse dye densitometry overestimated 0.16 l/min of thermodilution or 4.5% of the estimated cardiac output (figs. 2 and 3), which proved that it had no clinically significant systematic bias. In the bias graph, points were randomly dispersed above and below the mean of the error line over a wide range of cardiac outputs (fig. 2). Thus we could see no obvious relation between the difference and mean. The values (mean difference ± 2 SD) are known to be the limits of agreement (upper and lower lines in figures 2 and 3), which indicated that 95% of the dye or thermal dilution cardiac output might be 1.6 l/min or 39.2% above or below the estimated cardiac output. Although the errors were not influenced by the level of cardiac output in absolute terms, the percentage errors depended on the level of cardiac output (significantly great for low cardiac output of ≤ 3.5 l/min; fig. 3 and table 2). This might be due to the nature of the indicator dilution method, the error of which has been reported for patients with low cardiac outputs.[13] Each method measured cardiac output accurately according to its own parameters because the mean of the SD of the mean difference of cardiac output in each measurement was small (0.32 ± 0.16; table 1). However, a considerable difference in the two methods was observed in some patients. Because each patient is indicated by a different symbol (figs. 2 and 3), the small scattering for three to six indicator injections obtained for any one patient and the considerable deviation in values obtained by the different methods in some patients are clearly shown. This might be due to an intrinsic error in either method or both.

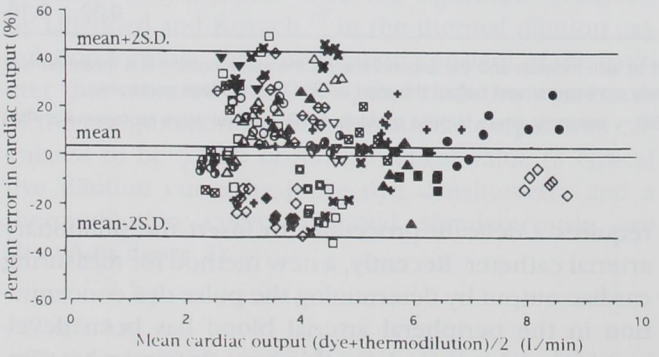

Fig. 3. Percentage difference in cardiac output measured by pulse dye densitometry and the thermodilution method against their respective means. Percentage difference = (dye-thermodilution) · 100/(dye + thermodilution) · 0.5. Each patient is represented by a different symbol, which is identical to that used in figure 1. The horizontal lines express the mean and the mean ± 2 SD. Bias = 4.5 ± 19.6% (mean ± SD).

The validity of pulse dye densitometry depends on whether this method could measure blood dye concentration as accurately as is theoretically possible.[3] Although Aoyagi *et al.*[2] have presumed that tissue factors affect the validity of pulse oximetry and pulse dye densitometry contained a constant compensating for tissue factors in its formula,[3] the blood dye concentration measured by pulse dye densitometry had a correlation with blood dye concentration measured *ex vivo* as follows: (blood dye concentration measured by pulse dye densitometry) = 1.011 · (blood dye concentration measured *ex vivo*) − 0.029, and correlation coefficient of 0.993.[3,14] These preliminary investigations have proved that this instrument can measure the dye concentration in blood accurately; however, in some patients a considerable difference in cardiac outputs determined by the two methods was apparent. As for factors that may effect the validity of the thermodilution method, it contains a constant in its calculation formula that given in Methods. We believe that the problems inherent to each method are the cause of the present results.

The thermodilution method has a within-technique variability, even in stable conditions, and Stetz *et al.*[15] estimated that a minimal difference of 22% for a single thermodilution cardiac output measurement is required before we can conclude that a real change in cardiac output exists. Accordingly, three or more thermodilution measurements were averaged to reduce random and systematic errors. However, we simultaneously compared each measurement of dye and thermodilution cardiac output, because the purpose of this investigation was to determine the relation between the simul-

Table 2. Comparison of the Difference in Cardiac Output (Dye-thermodilution Method) for Three Levels (Low, Medium, and High) of Mean Cardiac Output of Dye and Thermodilution

Level of Mean Cardiac Output (L/min)	Low (≥3.5)	Medium (3.5–6)	High (>6)
No. of measurements	70	99	22
% difference in cardiac output (dye-thermodilution) × 100/ (dye + thermodilution) × 0.5	9.3 ± 19.3*	2.2 ± 20.7	−0.5 ± 11.3
Absolute difference in cardiac output (L/min)	0.291 ± 0.586	0.104 ± 0.896	−0.032 ± 0.882

* $P = 0.04$ *versus* high group and $P = 0.02$ *versus* medium group by one factor ANOVA. Differences in cardiac output are expressed as the mean ± SD.

taneous measurement of dye and thermodilution cardiac output, and not to obtain the averaged cardiac output representing a certain circulatory condition. Similarly, injections were not synchronized to the ventilatory cycle, although the variability of the intermittent measurement may have been reduced by injecting the indicator at the same respiratory phase.[16]

Because pulse dye densitometry is based on the theory of pulse oximetry, it cannot work when a pulse absorbance signal is not detected. Although technical developments have improved the ability of pulse oximetry to detect and amplify small pulse signals,[1] in one of the 22 patients (1 of 13 measurements after surgery) included in this investigation, pulse dye densitometry did not detect the pulsatile flow after a cardiopulmonary bypass. A diminished pulse wave amplitude leading to failure of signal detection was caused by vasoconstriction but not by hypotension.[1] It was suggested that the microcirculation, which could not be detected by conventional hemodynamic assessment, was disturbed due to vasoconstriction, although the cardiac output and arterial blood pressure were well maintained with the support of catecholamines and vasodilators. At the low level of cardiac output observed in this investigation (the lowest cardiac output: 2.16 l/min (1.66 $l \cdot min^{-1} \cdot m^{-2}$) in dye dilution and 2.1 l/min (1.49 $l \cdot min^{-1} \cdot m^{-2}$) in thermodilution under general anesthesia, this system was able to work. However, the extremely low cardiac output accompanying vasoconstriction may be an important obstacle for pulse detection. One of the characteristics of pulse dye densitometry is the ability to detect the blood dye concentration regardless of the detection site as long as a suitable probe is available. If any site that is relatively unaffected by peripheral vasoconstriction were found for pulse detection, it might widen the clinical utility of this system. We used a nasal probe to measure the dye concentration because the nasal wing provided a more rapid and clearer pulsatile change in dye concentration than that obtained from a finger.

The bias between pulse dye densitometry and the thermodilution methods is clinically negligible; however, the error during low cardiac output was significantly great. This method for measuring cardiac output has great promise in the clinical field and the error noted previously may be considered acceptable depending on the clinical situation. Pulse dye densitometry can measure cardiac output repeatedly in patients having major surgery with the same degree of accuracy as the thermodilution method. However, a difference in values obtained with this method and the thermodilution method was observed in some patients, the cause of which has yet to be determined.

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