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Original article

Impact of stroke volume on prognostic outcome in patients with atrial fibrillation and concomitant heart failure with preserved ejection fraction

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ABSTRACT

Background: Atrial fibrillation (AF) can lead to a decrease in stroke volume (SV) despite a preserved left ventricular ejection fraction (LVEF). However, no previous studies have evaluated the prognostic importance of the decreased SV in patients with AF and concomitant heart failure with preserved ejection fraction (HFpEF).

Methods: We retrospectively studied the cases of 1520 consecutive patients who had undergone right heart catheterization. HFpEF (New York Heart Association functional class ≥II and LVEF ≥50%) was observed in 574 patients. We selected 47 patients with persistent AF with a heart rate of 40–110 bpm and HFpEF without other underlying heart diseases.

Results: Among a total of 47 patients, 16 (34%) had normal SV [SV index (SVI) >35 ml/m^2 and 31 (66%) patients had low SV (SVI ≤ 35 ml/m^2)]. During the follow-up period of 1115 ± 305 days, 14 patients (30%) met the composite endpoint defined as cardiac death and admission due to worsening heart failure. Cox proportional hazard ratio analysis showed that SVI was a predictor of the endpoint, independently of the cardiac index and other parameters. Kaplan–Meyer analysis showed that low SVI was significantly associated with a poor prognosis, with an event-free rate of 58% at the mean follow-up period of 991 days (log-rank $p = 0.02$). In the multiple regression analysis, a high systemic vascular resistance index and a high heart rate were independent determinants of low SVI.

Conclusions: Our findings suggest that low SV had a significant impact on prognosis in patients with AF despite the preserved LVEF. The SVI depended on the heart rate and SVRI.

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in patients with heart failure with preserved ejection fraction (HFpEF) [1–3] and each condition predisposes the patient to the other [4]. Patients with AF and concomitant HFpEF suffer from a worse prognosis, including increased mortality [2,3,5,6].

Many patients with AF develop a modest decline in left ventricular (LV) performance, which has an important effect on cardiac hemodynamics [7,8]. AF causes the loss of "atrial kick" and a reduction in LV diastolic filling, resulting in a decline in LV stroke volume (SV) [9,10] despite preservation of the left ventricular ejection fraction (LVEF). However, no previous studies have evaluated the prognostic importance of the decreased SV in patients with AF and concomitant HFpEF. Therefore, the aim of the present retrospective analysis was to investigate the prognostic

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importance of the decreased SV in patients with AF and concomitant HFpEF.

Methods

Patients and data collection

We retrospectively analyzed all consecutive patients who had undergone right heart catheterizations (RHCs) at Kitano Hospital, Osaka, Japan over a period of 6 years (January 2010 to August 2016). If patients had undergone multiple RHCs during the study period, only the hemodynamic and clinical data from the earliest qualifying study were analyzed.

We selected patients with persistent AF (PeAF) and symptomatic HFpEF [New York Heart Association (NYHA) functional class ≥II and LVEF ≥50%] who underwent transthoracic echocardiography (TTE) within a week of the RHC. The clinical AF syndrome was determined based on the predominant arrhythmia presentation at the time of admission, when RHC was performed, and defined as persistent if typical AF episodes lasted >7 days [11,12]. We excluded patients with a history of cardiac surgery, implanted pacemaker or cardiac defibrillator, moderate or severe valvular heart disease, acute decompensated heart failure, or significant congenital heart disease. Patients with tachycardia (>110 beats/min) [13,14] or bradycardia (<40 beats/min) and treated with hemodialysis were also excluded. Patients were then further subdivided into two groups depending on whether they had normal SV, defined as SVI >35 ml/m^2, or low SV, defined as SVI ≤35 ml/m^2, despite a preserved LVEF [15]. Furthermore, we added a control group comprising patients with sinus rhythm and HFpEF who did not meet the exclusion criteria.

The primary endpoint was defined as a composite of cardiac death and hospitalization due to worsening heart failure. The clinical, electrocardiographic, laboratory, echocardiographic, and RHC data were collected from the medical records at the time of RHC. Clinical data included demographics, presenting symptoms, coronary artery disease, estimated glomerular filtration rate, and medication at RHC. A high-dose loop diuretic was defined as ≥40 mg/day of oral furosemide. The diuretic dose was converted to the furosemide equivalent dose as follows: furosemide 40 mg = azosemide 60 mg = torasemide 20 mg [16,17].

This retrospective study was approved by our institutional review board, with a waiver for individual consent.

Echocardiography

All TTE examinations were performed by an expert sonographer (level 3 according to the definitions of the American Society of Echocardiography) and the results were interpreted by experienced attending physicians at our echocardiography laboratory. Any disagreements were resolved by consensus [18]. The LV end-diastolic dimension, LV end-systolic dimension, LVEF, left atrial (LA) dimension, and LA volume index were measured in accordance with previously published guidelines [19]. LV mass index and relative wall thickness were calculated according to the guidelines of the American Society of Echocardiography and indexed for body surface area [20]. The degree of native valvular regurgitation was classified according to the guidelines of the American Society of Echocardiography [21]. The transmitral flow velocity curves in diastole and the mitral annular tissue Doppler imaging signals were obtained as previously described [22]. The peak velocity of early-diastolic filling velocity across the mitral valve (E) and the deceleration time (DT) were measured. The peak early diastolic tissue Doppler velocity of the mitral annulus (e') on the apical 4-chamber view was measured and the E/e' ratio was calculated. All TTE measurements were determined using the average of at least three cardiac cycles.

RHC

All RHCs were performed at rest, using a Nihon Kohden RMC 4000 system (Tokyo, Japan). A 7F balloon-tipped fluid-filled Swan-Ganz catheter (Edwards Lifescience, Irvine, CA, USA) was inserted into the internal jugular or femoral vein for venous access. Heart rate and aortic blood pressure (BP) were measured immediately before the study. The electrocardiogram was simultaneously recorded. Pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and right atrium pressure (RAP) waveforms were recorded under fluoroscopy after calibration with the zero level set at the mid-thoracic line. Cardiac output (CO) was determined using the thermodilution method [23]. Routinely, at least five cardiac measurements were obtained. We averaged them after the maximum and minimum values were excluded. The cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance index (SVRI) were calculated using the following formulas: CI (l/min/m^2) = CO (l/min)/body surface (m^2); SVI (ml/m^2) = CI (l/min/m^2)/HR (beats/min); SVRI (dyne/s/cm^{-5}/m^2) = (Mean BP[mmHg] − Mean RAP[mmHg])/CI (l/min/m^2) × 79.92. All hemodynamic measurements were performed before contrast injection. All pressure measurements with AF rhythm were averaged across a minimum of 10 heart cycles at end-expiration.

Statistical analysis

All continuous variables are presented as mean ± standard deviation and categorical variables are presented as n (%). They were compared using the t-test or Mann–Whitney test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. The univariate and multivariate hazard ratios with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression analysis. We performed univariate Cox proportional hazards regression analysis using age, gender, the echocardiographic parameters, and the RHC parameters as variables. We then performed a multivariate Cox proportional hazards regression based on stepwise selection with a model using predictors with $p < 0.10$ on the univariate analysis to determine the independent predictors of the endpoint. The multiple linear regression analysis was performed to examine the determinants of SV with stepwise selection ($p < 0.10$ for retention). The Kaplan–Meier method was used to evaluate the event-free rate. The statistical analysis was conducted using MedCalc (version 15.8; MedCalc Software, Ostend, Belgium) and R software (version 3.5.1; The R Foundation, Vienna, Austria). The results were considered significant at a threshold of $p < 0.05$.

Results

The patients were selected for the present study as shown in Fig. 1. We retrospectively studied 1520 consecutive patients who had undergone RHC. Among these, 574 (38%) patients had HFpEF (LVEF ≥50% and NYHA functional class ≥II). We excluded 454 patients; therefore, the cohort comprised 47 (3%). Normal SV was observed in 16 patients (34%) and low SV in 31 (66%) despite a preserved LVEF [15]. The purpose of RHC was the assessment of chronic heart failure in all patients of the final cohort.

The patients' characteristics according to their SV are shown in Table 1. The echocardiographic findings are shown in Table 2. There was no significant difference in LV size or systolic function between patients with normal SV and low SV. The RHC findings are shown in Table 3. SVI was remarkably low across our

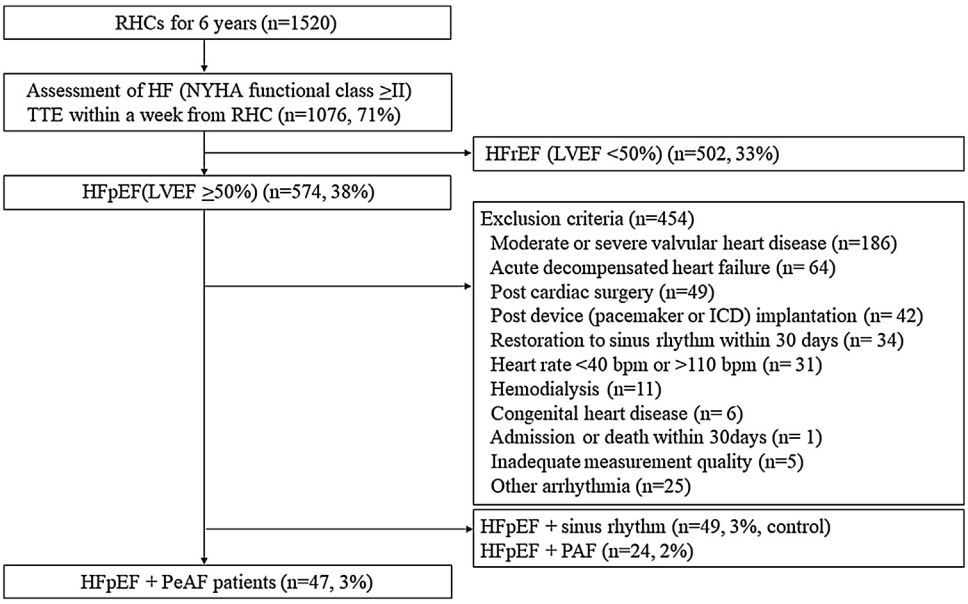

Fig. 1. Flow diagram of patient selection. RHC, right heart catheterization; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association functional class; TTE, transthoracic echocardiography; ICD, implantable cardioverter defibrillator.

entire cohort despite a preserved LVEF (33 ± 11 ml/m^2). The patients with low SV had higher heart rates (82 ± 18 vs. 67 ± 12; $p = 0.008$), higher mean aortic blood pressure (91 ± 12 vs. 80 ± 8; $p = 0.003$), and higher SVRI (3203 ± 782 vs. 2007 ± 342; $p < 0.001$) than patients with normal SV. During the follow-up period of 1115 ± 305 days (median, 964 days; range, 51–2637 days), 14 patients (30%) met the composite primary endpoint without missing data. The primary endpoints consisted of 1 cardiac death and 13 hospitalizations due to worsening heart failure. In the Cox proportional hazard ratio analysis, the SVI and SVRI (SVI, $p = 0.04$; SVRI, $p = 0.09$) were the predictive factors of the primary endpoint with a p-value <0.10 on univariate analysis. The SVI was the only significant predictor of the endpoint on the multivariate Cox proportional hazard ratio analysis (hazard ratio, 0.94; 95% CI, 0.880–0.997; $p < 0.04$). Decreased SVI was significantly associated with poor prognosis, with an event-free rate of 58% at the mean follow-up period of 991 days on the Kaplan–Meier analysis ($p = 0.02$; Fig. 2).

In the multiple regression analysis, high SVRI and high heart rate were independent determinants of low SVI (Table 4).

Table 1
Patient characteristics.

	Sinus rhythm ($n = 49$)	PeAF rhythm ($n = 47$)	p-Value	PeAF rhythm		
				Normal SV ($n = 16$)	Low SV ($n = 31$)	p-Value
Age (years)	69 ± 14	73 ± 10	0.15	71 ± 13	74 ± 8	0.47
Female sex (%)	16 (33%)	20 (43%)	0.32	9(56%)	11(35%)	0.19
BSA (m^2)	1.6 ± 0.2	1.6 ± 0.3	0.7	1.6 ± 0.2	1.7 ± 0.3	0.69
NYHA functional class	2.1 ± 0.3	2.2 ± 0.4	0.15	2.1 ± 0.3	2.3 ± 0.3	0.13
HT (%)	42 (86%)	38 (81%)	0.52	13(81%)	25(81%)	0.96
eGFR <60 ml/min/1.73 m^2 (%)	25 (51%)	25 (53%)	0.83	10(63%)	15(48%)	0.36
CAD (%)	16 (33%)	10 (21%)	0.21	3(19%)	7(23%)	0.76
Diabetes mellitus (%)	21 (43%)	14 (30%)	0.19	4(25%)	10(32%)	0.61
Dyslipidemia (%)	17 (35%)	12 (55%)	0.33	4(25%)	8(26%)	0.95
Prior HF admission (%)	7 (14%)	9 (19%)	0.46	2(13%)	7(23%)	0.41
ACEI or ARB (%)	39 (80%)	36(77%)	0.72	9 (56%)	27 (87%)	0.02
β-blocker (%)	37 (76%)	37(79%)	0.71	13 (81%)	24 (77%)	0.76
Aldosterone antagonist (%)	12 (24%)	25 (53%)	0.004	7 (44%)	18 (58%)	0.36
Other diuretics (%)	23 (47%)	35 (74%)	0.006	10 (63%)	25 (81%)	0.18
Loop diuretics	21 (43%)	34 (72%)	0.004	10 (63%)	24 (77%)	0.28
High-dose loop diuretics	9 (18%)	11 (23%)	0.55	2 (13%)	9 (29%)	0.21
Tolvaptan	0 (0%)	5 (11%)	0.03	2 (13%)	3 (10%)	0.77
Thiazide	6 (12%)	2 (4%)	0.16	1 (6%)	1 (3%)	0.63
Digitalis (%)	0 (0%)	7 (15%)	0.005	2 (13%)	5 (16%)	0.74
Ca antagonist (%)	32 (65%)	21 (45%)	0.04	10 (63%)	11 (35%)	0.08
Statins (%)	13 (27%)	5 (11%)	0.05	0 (0%)	5 (16%)	0.15
Anticoagulant agents (%)	3 (6%)	46 (98%)	< 0.001	15 (94%)	31 (100%)	0.34

Normal SV is defined as an SVI >35 ml/m^2 and low SV was defined as SVI ≤35 ml/m^2 despite preserved LVEF. Values are mean ± standard deviation. PeAF, persistent atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; CAD, coronary artery disease (defined as ≥1 coronary artery with ≥50% stenosis); eGFR, estimated glomerular filtration rate; HF, heart failure; HT, hypertension; NYHA, New York Heart Association; SV, stroke volume; SVI, stroke volume index.

Table 2
Transthoracic echocardiography findings.

	Sinus rhythm ($n=49$)	PeAF rhythm ($n=47$)	p-Value	PeAF rhythm		
				Normal SV ($n=16$)	Low SV ($n=31$)	p-Value
LVEF (%)	59 ± 6	58 ± 6	0.45	59 ± 6	57 ± 5	0.11
LVDd (mm)	49 ± 7	48 ± 6	0.55	48 ± 7	48 ± 5	0.69
LVDs (mm)	33 ± 6	35 ± 6	0.13	34 ± 6	35 ± 5	0.33
E/e'	14 ± 5	14 ± 5	0.78	14 ± 5	14 ± 5	0.51
E wave velocity (cm/s)	78 ± 29	96 ± 25	<0.001	107 ± 24	90 ± 24	0.01
e' (cm/s)	6.4 ± 3.9	7.3 ± 2.4	<0.001	8.6 ± 3.1	6.6 ± 1.5	0.02
DT (ms)	230 ± 61	173 ± 42	<0.001	176 ± 32	171 ± 46	0.43
LA dimension (mm)	38 ± 6	45 ± 6	<0.001	45 ± 8	45 ± 6	0.63
LA volume index (ml/m^2)	27 ± 11	44 ± 14	<0.001	44 ± 18	44 ± 12	0.84
LV mass index (g/m^2)	103 ± 34	92 ± 24	0.13	89 ± 24	93 ± 24	0.59
Relative wall thickness	0.37 ± 0.1	0.37 ± 0.06	0.68	0.37 ± 0.05	0.37 ± 0.06	0.83

Values are mean ± standard deviation. PeAF, persistent atrial fibrillation; SV, stroke volume; DT, deceleration time; LA, left atrium; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction.

Table 3
Right heart catheterization findings.

	Sinus rhythm ($n=49$)	PeAF rhythm ($n=47$)	p-Value	PeAF rhythm		
				Normal SV ($n=16$)	Low SV ($n=31$)	p-Value
Systolic BP (mmHg)	126 ± 17	120 ± 15	0.14	116 ± 12	122 ± 15	0.1
Mean BP (mmHg)	84 ± 12	87 ± 12	0.24	80 ± 8	91 ± 12	0.003
Heart rate (beats/min)	68 ± 10	77 ± 17	0.03	67 ± 12	82 ± 18	0.008
Cardiac index (L/(min m^2))	3.2 ± 0.7	2.4 ± 0.6	<0.001	2.9 ± 0.4	2.1 ± 0.5	<0.001
SVI (ml/m^2)	47 ± 9	33 ± 11	<0.001	44 ± 9	27 ± 6	<0.001
Mean PAP (mmHg)	19 ± 7	24 ± 7	<0.001	23 ± 9	25 ± 6	0.28
Mean PCWP (mmHg)	11 ± 6	16 ± 6	<0.001	15 ± 7	16 ± 6	0.27
RAP (mmHg)	6.3 ± 3.8	8.5 ± 3.6	0.005	8.3 ± 4.1	8.6 ± 3.4	0.51
SVRI (dyne/s/cm^{-5}/m^2)	2029 ± 562	2796 ± 875	<0.001	2007 ± 342	3203 ± 782	<0.001

Values are mean ± standard deviation. PeAF, persistent atrial fibrillation; BP, aortic blood pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrium pressure; SV, stroke volume; SVI, stroke volume index; SVRI, systemic vascular resistance index.

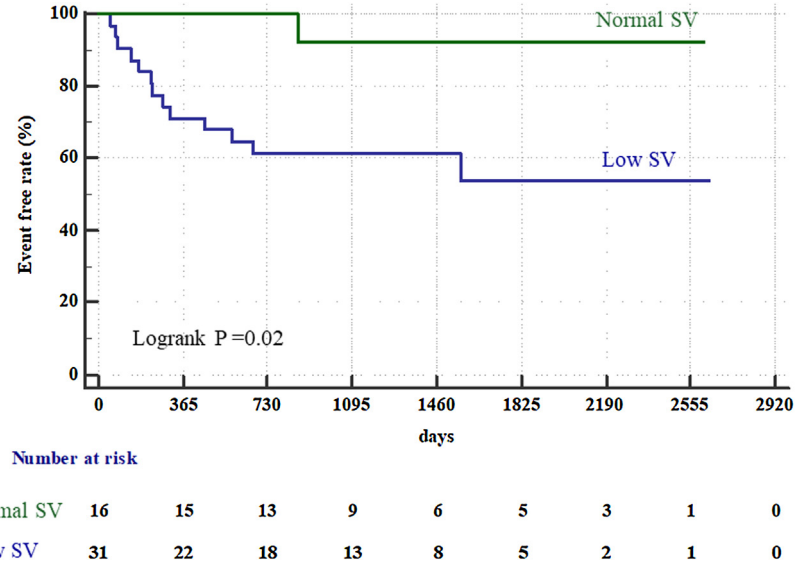

Fig. 2. Kaplan–Meier event-free rates of cardiac death and hospitalization due to worsening heart failure. Normal SV defined as a SVI >35 ml/m^2 and low SV defined as SVI ≤35 ml/m^2. SV, stroke volume; SVI, stroke volume index.

Discussion

In the present study, we assessed the impact of SV on the prognosis of patients with PeAF and concomitant HFpEF. Overall, we found that: (1) SVI was an independent predictor of the primary endpoint defined as cardiac death and admission due to worsening heart failure; (2) high SVRI was one of the independent determinants of low SVI; and (3) heart rate was also an independent determinant of low SVI, although patients with tachycardia (>110 beats/min) were excluded from the present study.

AF can lead to HFpEF, and their coexistence confers a poor prognosis [3,24]. In fact, cardiac death from heart failure is more frequent than stroke-related death in patients with AF, although AF

Table 4
Determinants of the SVI.

	PeAF rhythm patients ($n = 47$)	Univariate		Multivariate
		r^2	p-Value	p-Value
Age (years)	73 ± 10	0.0005	0.88	–
Female sex (%)	20 (43%)	0.0005	0.88	–
Systolic BP (mmHg)	120 ± 15	0.01	0.46	–
Heart rate (beats/min)	77 ± 17	0.45	<0.0001	<0.0001
Mean PAP (mmHg)	24 ± 7	0.001	0.8	–
PCWP (mmHg)	16 ± 6	0.009	0.54	–
RAP (mmHg)	8.5 ± 3.6	0.003	0.7	–
SVRI (dyne/s/cm^{-5}/m^2)	2796 ± 875	0.45	<0.0001	<0.0001
LVDd (mm)	48 ± 6	0.00003	0.97	–
LVDs (mm)	35 ± 6	0.03	0.28	–
LV mass index (g/m^2)	92 ± 24	0.001	0.78	–
Relative wall thickness	0.37 ± 0.06	0.0005	0.88	–

Values are mean ± standard deviation. PeAF, persistent atrial fibrillation; BP, aortic blood pressure; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrium pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index.

plays a critical role in the pathogenesis of cardioembolic stroke [24–26]. Many patients with AF develop a decline in SV compared to patients with sinus rhythm because of the loss of effective atrial contraction [10]. The SV can further decrease in AF patients if the heart rate increases with a rapid ventricular response. The results of our present study revealed that low SV in AF patients with HFpEF is associated with cardiac death and admission due to worsening heart failure.

SVRI was an independent determinant of low SVI. This suggested that excessive LV afterload, due to arteriosclerosis, was associated with the low SV in patients with AF and HFpEF. This was consistent with the result in a previous study indicating the poor prognosis in patients with paradoxical low-flow, low-gradient severe aortic stenosis [15]. Therefore, the reduction of blood pressure using vasodilators may be an important factor in the management of patients with PeAF and HFpEF. In addition, heart rate was also an independent determinant of low SVI; however, we had excluded patients with tachycardia (heart rate > 110 beats/min). It can be posited that appropriate heart rate control is one of the important facets of management of AF patients, even those without excessive tachycardia. However, the Race II trial suggested that lenient and strict heart rate control strategies make no difference in the cardiovascular outcomes of AF patients [13]. Further clinical studies to assess the optimal heart rate and blood pressure in patients with AF are required.

Limitations

The present study has several limitations. First, it was designed as a retrospective and single-center study and had a relatively small sample size. Second, we could not identify an echocardiographic parameter to definitively explain the different RHC results, i.e. normal and low SV. This might be due to errors resulting from the time interval between echocardiography and RHC (2.2 ± 2.2 days). Future prospective studies that can overcome the drawbacks of the present study will be needed.

Conclusions

Low SV in patients with AF and concomitant HFpEF is associated with a poor prognostic outcome. The SVI in those patients depended on the heart rate and SVRI.

Conflicts of interest

The authors declare that there is no conflict of interest.

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