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Original Article

Levosimendan improves cardiac function, hemodynamics, and body inflammation in patients with acute myocardial infarction and heart failure

Xiaoxia Sun[1], Congying Wei[2], Lei Li[1], Chao Qu[3]

[1]Cardiovascular Division, Xianyang First People's Hospital, No. 10, Biyuan Road, Qindu District, Xianyang 712000, Shaanxi, China; [2]Cardiovascular Division, Xianyang Central Hospital, No. 78, Renmin East Road, Weicheng District, Xianyang 712000, Shaanxi, China; [3]Cardiovascular Ward I, Xi'an Fifth Hospital, No. 112, Xiguanzheng Street, Lianhu District, Xi'an 710000, Shaanxi, China

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Abstract: Objective: To examine the effects of levosimendan on cardiac function, hemodynamics, and body inflammation of patients with acute myocardial infarction and heart failure. Methods: A retrospective analysis was conducted on 113 acute myocardial infarction patients with heart failure (admitted to Xianyang First People's Hospital from September 2018 to January 2022). According to the treatment plan, patients were categorized into a control group (n = 53) (treated with conventional diuresis and vasodilation) and observation group (n = 60) (treated with levosimendan in addition to the treatment of the control group). Indexes were compared between the two groups before and after treatment, including effectiveness rate, mean pulmonary arterial pressure (PAMP) and pulmonary capillary wedge pressure (PCWP). Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction (LVEF) were monitored before and after treatment by color Doppler ultrasonography. Serum high-sensitivity C-reactive protein (hs-CRP) levels were measured before and after treatment. Logistic analysis was applied to screen independent factors affecting treatment efficacy. Adverse reactions and life quality after 6 months of treatment were compared between the two groups. Results: The overall response rate of the observation group was higher than that of the control group ($P<0.05$). Changes in PAMP and PCWP in the two groups before and after treatment were significantly different. Patients in the observation group had improved indicators compared with the control group (all $P<0.05$). After treatment, the cardiac function indexes and inflammation-related factors of the observation group were improved more than those of the control group ($P<0.05$). Patients in the observation group had a lower incidence of adverse reactions and a higher life quality 6 months after treatment compared to the control group ($P<0.05$). Diabetes and treatment regimen were independent risk factors affecting treatment efficacy by logistic regression analysis. Conclusion: The administration of levosimendan helps improve cardiac function, hemodynamics, and body inflammation in patients with acute myocardial infarction and heart failure, with fewer adverse reactions and higher safety.

Keywords: Acute myocardial infarction, heart failure, levosimendan, cardiac function, hemodynamics, body inflammation level

Introduction

Acute myocardial infarction (AMI) is a cardiac emergency that seriously endangers human health. It is an acute ischemic necrosis of myocardium caused by coronary artery occlusion, with the main clinical manifestations of persistent severe retrosternal pain, increased serum myocardial necrosis markers, and progressive changes in ECG, which are often complicated by shock, heart failure, arrhythmia, and other symptoms [1, 2]. Heart failure is a common complication of AMI, mainly manifesting as decreased cardiac output, metabolic disorders of tissues and organs, systemic circulation and/or pulmonary circulation congestion, which seriously affect patients' life quality and even cause death. Therefore, it is necessary to actively take effective treatment measures to improve patients' cardiac function [3, 4].

At present, the drug treatment for acute heart failure is mostly based on inotropes, vasodilators, and diuretics [5]. Traditional non-digitalis inotropes can up-regulate the consumption of myocardial oxygen, and their short-term use is beneficial to patients with acute heart failure. However, long-term application of non-digitalis inotropes can lead to arrhythmia and myocardial stunning, which increases the hospitalization and mortality rates [6, 7]. Levosimendan, a novel calcium sensitizer that effectively enhances myocardial contractility, is significantly effective in the treatment of chronic cardiac insufficiency [8]. Studies have revealed [9] that levosimendan can effectively reduce the hospitalization rate of heart failure patients. Nonetheless, few studies have analyzed its effect on hemodynamics and body inflammation levels in patients with AMI and heart failure.

In our study, the effects of levosimendan were observed on cardiac function, hemodynamics, and body inflammation levels in AMI patients with heart failure, so as to suggest ideas for the refinement of medication regimens.

Materials and methods

Study design and patients

113 AMI patients complicated by heart failure, admitted to Xianyang First People's Hospital from September 2018 to January 2022 were retrospectively categorized into a control group (CG) (n = 53, treated with conventional diuresis and vasodilation) and an observation group (OG) (n = 60, treated with levosimendan on the basis of the control group). Inclusion criteria: (1) Meets the diagnostic criteria for AMI with heart failure; (2) Aged ≥18 years; (3) With complete clinical data. Exclusion criteria: (1) With other heart diseases; (2) With liver, kidney and other important organ dysfunction; (3) With severe infectious diseases and immune dysfunction; (4) With malignant tumors. This study had been approved by Xianyang First People's Hospital ethics committee and conformed to the Declaration of Helsinki.

Data collection

Patients in the CG were given conventional treatment, including regulation of blood lipids, anticoagulation, use of diuretics, vasodilators, cardiotonic agents, and control of blood pressure and blood glucose. OG patients were treated with levosimendan (Qilu Pharmaceutical Co., Ltd., batch number: 150626) based on CG, and levosimendan 12.5 mg was added to 5% glucose injection 500 ml by intravenous pumping (micropump infusion method) at an initial dose of 12 μg/kg, gradually escalated to 0.2 μg/(kg min) and maintained for 24 h. Patients in both groups were treated for 1 week, followed by evaluation of relevant indicators. We obtained patient treatment data from medical records, including cardiac function, and hemodynamics, and compared the electronic data capture results of these patients to ensure that the data were correct and complete.

Outcome measures

Primary indicators: (1) The therapeutic efficacy of the two groups was evaluated, compared, and categorized into significantly effective: symptoms significantly improved, with LVEF >50%; effective: symptoms improved, with LVEF <50%; ineffective: failed to meet the above criteria. Overall response rate (%) = (markedly effective cases + effective cases)/ total cases × 100%. (2) Color Doppler ultrasonography was used to detect and compare the improvement of cardiac function before and after treatment, including left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction (LVEF). (3) Serum high-sensitivity C-reactive protein (hs-CRP) levels were measured by CX7 biochemical analyzer (Beckman Coulter, USA) before and after treatment. (4) Hemodynamic values, including pulmonary capillary wedge pressure (PCWP) and mean pulmonary arterial pressure (PAMP), were assessed and compared before and after treatment between the two groups.

Secondary indicators: (1) The incidence of adverse reactions was observed and compared between two groups, including arrhythmia, hypokalemia, aggravated heart failure, and hypotension. (2) Minnesota Living with Heart Failure Scale (MLHFQ) [10] was used to evaluate patients' life quality in the two groups after treatment, including three domains: physical domain, emotional domain, and other domains. Higher scores indicate worse life quality.

Statistical methods

The collected data were processed and analyzed as well as visualized using SPSS 20.0

Table 1. Comparison of general data

Variable	Observation Group n = 60	Control Group n = 53	t/X^2	P
Gender			0.029	0.864
Male	33 (55.00)	30 (56.60)		
Female	27 (45.00)	23 (43.40)		
Age (years)			0.002	0.963
≥62	41 (68.33)	36 (67.92)		
<62	19 (31.67)	17 (32.08)		
BMI (kg/m^2)			0.015	0.902
≥23	31 (51.67)	28 (52.83)		
<23	29 (48.33)	25 (47.17)		
Smoking history			0.211	0.646
Yes	37 (54.00)	31 (58.49)		
No	23 (46.00)	22 (41.51)		
Alcohol history			0.020	0.887
Yes	40 (66.67)	36 (67.92)		
No	20 (33.33)	17 (32.08)		
Combined hyperlipidemia (years)			0.529	0.467
Yes	38 (63.33)	37 (69.81)		
No	22 (36.67)	16 (30.19)		
Combined diabetes			0.001	0.976
Yes	27 (45.00)	24 (45.28)		
No	33 (55.00)	29 (54.72)		
Concomitant medications			0.010	0.951
β.951mita	19 (31.67)	16 (30.19)		
ACEI/ARB	31 (51.67)	27 (50.94)		
Digoxin	10 (16.66)	10 (18.87)		
Revascularization			0.003	0.954
PCI	45 (75.00)	40 (75.47)		
CABG	15 (25.00)	13 (24.53)		

BMI, Body Mass Index.

software and GraphPad Prism 8 software. Among these, Student t-test and Paired t-test was applied for inter-group and intra-group comparisons respectively, expressed as t. Chi-square test was used for enumerated data. Statistical differences were indicated when $P<0.05$.

Results

General information

Subject groups were comparable due to insignificant differences identified in gender, age, and BMI ($P>0.05$, **Table 1**).

Comparison of treatment efficacy

The ORR of the OG was 96.67%, which was significantly higher than 73.58% of the CG ($P<0.05$, **Table 2**).

Comparison of cardiac function before and after treatment between the two groups

Before treatment, no significant difference was identified in LVEDD, LVESD, or LVEF levels between the two groups ($P>0.05$). After treatment, LVEDD and LVESD levels went lower while LVEF level was elevated in both groups ($P<0.05$), and those indexes in the OG were superior to those of the CG ($P<0.05$, **Figure 1**).

Comparison of serum inflammatory factors before and after treatment between the two groups

Before treatment, no significant difference was observed in serum hs-CRP levels between the groups (all $P>0.05$); while after treatment, the above indicators were lower in the OG than the CG ($P<0.05$, **Figure 2**).

Table 2. Comparison of efficacy between the two groups [n (%)]

Efficacy	Observation Group n = 60	Control Group n = 53	X^2	P
Markedly effective	35 (58.33)	22 (41.51)	3.186	0.074
Effective	23 (38.33)	17 (32.08)	-	-
Invalid	2 (3.33)	14 (26.42)	-	-
Overall response rate	58 (96.67)	39 (73.58)	12.34	<0.001

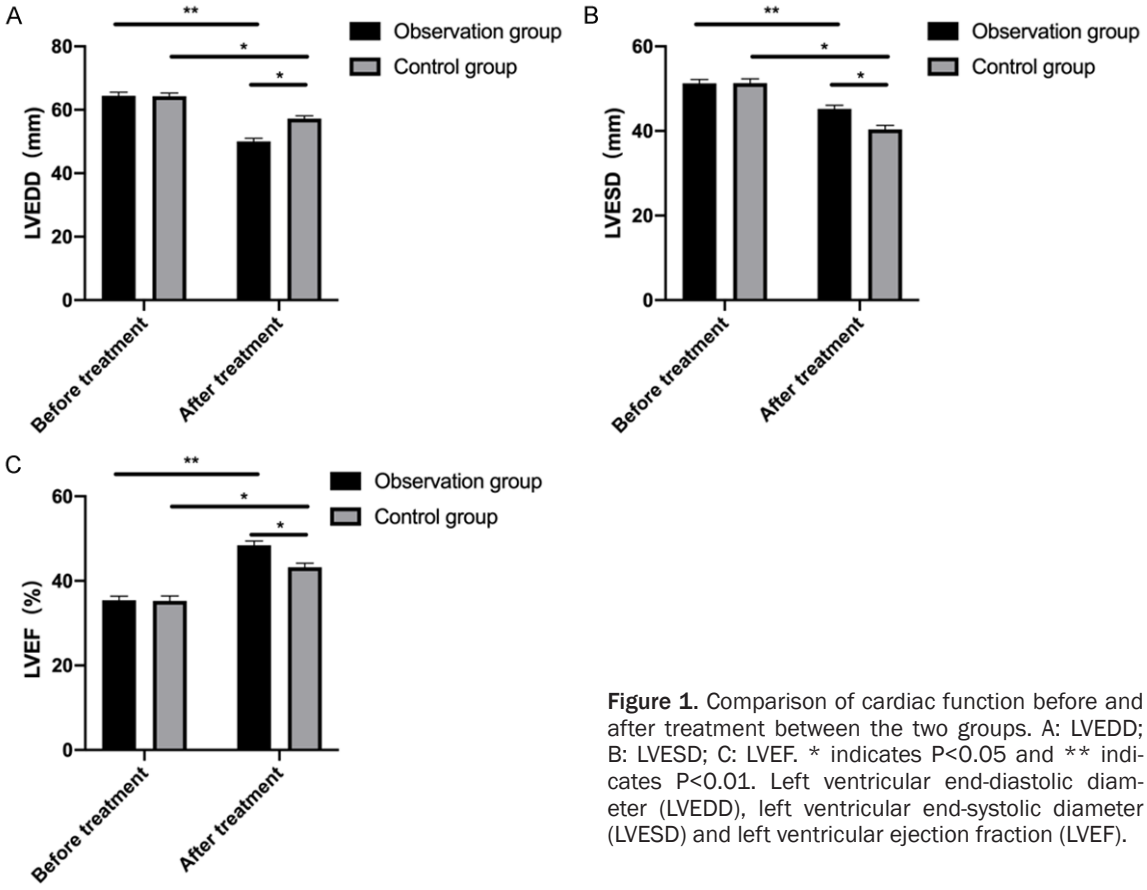

Figure 1. Comparison of cardiac function before and after treatment between the two groups. A: LVEDD; B: LVESD; C: LVEF. * indicates P<0.05 and ** indicates P<0.01. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction (LVEF).

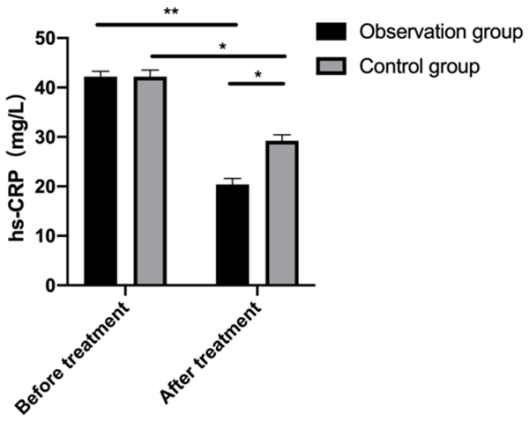

Figure 2. Comparison of serum hs-CRP before and after treatment between the two groups. * indicates P<0.05 and ** indicates P<0.01. Serum high-sensitivity C-reactive protein (hs-CRP).

Comparison of hemodynamic values

Before treatment, no evident difference was identified in PCWP and PAMP between the two groups (all P>0.05). After treatment, PCWP and PAMP went lower in both groups than those before treatment, but indexes in the OG were markedly lower than those in the CG (all P<0.05, **Figure 3**).

Analysis of risk factors affecting patients' curative effect

According to the treatment conditions, patients were divided into an effective group (n = 97) and ineffective group (n = 16). Univariate analysis showed that both diabetes and treatment regimens were factors affecting their

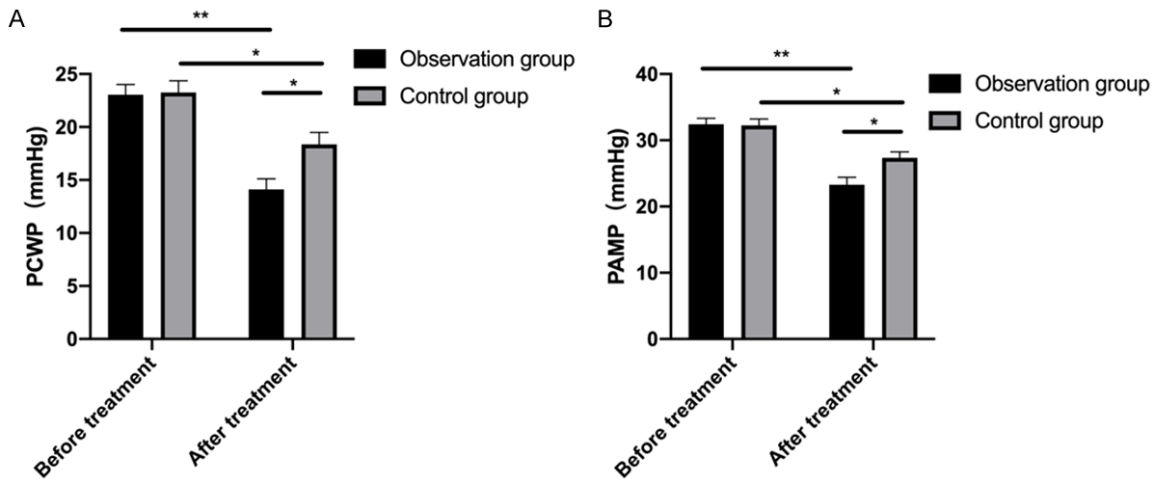

Figure 3. Comparison of hemodynamic values between the two groups. A: PCWP; B: PAMP. * indicates P<0.05 and ** indicates P<0.01. Pulmonary arterial pressure (PAMP) and pulmonary capillary wedge pressure (PCWP).

Table 3. Univariate analysis

Variable	Effective group (n = 97)	Ineffective group (n = 16)	X^2 value	*P* value
Gender			0.344	0.558
Male (n = 63)	53 (54.64)	10 (62.50)		
Female (n = 50)	44 (45.36)	6 (37.50)		
Age	62.35±1.22	62.31±1.25	0.020	0.887
BMI			0.036	0.848
≤23 kg/m^2 (n = 59)	51 (52.58)	8 (50.00)		
>23 kg/m^2 (n = 54)	46 (47.42)	8 (50.00)		
Smoking history			0.120	0.729
yes (n = 68)	59 (60.82)	9 (56.25)		
no (n = 45)	38 (39.18)	7 (43.75)		
Combined with diabetes			5.579	0.018
yes (n = 61)	48 (49.48)	13 (81.25)		
no (n = 52)	49 (50.52)	3 (18.75)		
Revascularization			0.004	0.982
PCI (n = 85)	73 (75.26)	12 (75.00)		
CABG (n = 28)	24 (24.74)	4 (25.00)		
Therapeutic regime			5.909	0.015
Levosimendan used (n = 60)	56 (57.73)	4 (25.00)		
Levosimendan not used (n = 53)	41 (42.27)	12 (75.00)		

BMI, Body Mass Index.

Table 4. Value assignment

Variable	Assignment
Combined with diabetes	yes = 1, no = 0
Therapeutic regime	Levosimendan not used = 1, Levosimendan used = 0

prognosis (**Table 3**). We then assigned values (**Table 4**), and diabetes and treatment regimens were found to be independent risk factors affecting the treatment efficacy by logistic regression analysis (**Table 5**, P<0.05).

Table 5. Multivariate analysis

Variable	B	S.E.	Wals	P	Exp (B)	95% C.I. of EXP (B)	
						Lower limit	Upper limit
Combined with diabetes	1.615	0.665	5.612	0.019	4.995	1.321	18.455
Therapeutic regime	3.229	0.811	16.1832	0.003	27.975	5.144	123.174

Table 6. Adverse reactions comparison

Efficacy	Observation Group n = 60	Control Group n = 53	X^2	P
Arrhythmia	2 (3.33)	5 (9.43)	1.802	0.179
Hypokalemia	1 (1.67)	1 (1.89)	0.008	0.929
Heart failure aggravated	1 (1.67)	3 (5.66)	1.315	0.252
Hypotension	1 (1.67)	4 (7.55)	2.301	0.129
Overall Incidence Comparison	5 (8.33)	13 (24.53)	5.511	0.019

Table 7. Comparison of incidence of MLHFQ score after treatment between the two groups

Items	Observation Group n = 60	Control Group n = 53	t	P
Somatic domain	12.96±1.03	16.15±1.01	16.58	<0.001
Emotional domain	8.17±0.39	9.94±0.9	13.84	<0.001
Other domains	16.22±0.39	18.12±0.67	18.48	<0.001

Minnesota Living with Heart Failure Scale (MLHFQ).

Comparison of incidence of adverse reactions

The OG had a lower incidence of adverse reactions than the CG (8.33% vs. 24.53%, P<0.05, **Table 6**).

Comparison of MLHFQ scores after treatment between the two groups

After treatment, all dimensions of life quality scores in OG were lower than in the CG. This indicated a better quality of life for OG patients (P<0.05, **Table 7**).

Discussion

The clinical manifestations of myocardial infarction are common sudden onset of persistent severe retrosternal crushing pain, arrhythmia, shock, heart failure, etc. Heart failure, a common complication of AMI, has a serious impact on patient's life and health [11]. Therefore, exploring effective treatment options is of vital clinical significance for AMI patients with heart failure.

We analyzed the efficacy of levosimendan in AMI patients with heart failure, and levosimendan was found to effectively improve the therapeutic effect, as well as the cardiac function and hemodynamics of patients. Conventional treatment for heart failure is mainly through the administration of diuretics, vasodilators, angiotensin converting enzyme inhibitors, β-receptor antagonists and inotropic drugs. Inotropic drugs can increase the concentration of intracellular Ca^{2+} in patients and the content of cyclic adenosine monophosphate, so as to up-regulate myocardial adduction and maintain hemodynamic stability. However, they will also increase myocardial oxygen consumption and predispose to arrhythmia, leading to a rise in mortality if administered for a long period of time [12, 13]. Levosimendan, a new inotropic agent, is a calcium sensitizer that binds to troponin C in cardiomyocytes, with both calcium sensitizing activity and potassium channel opening function and without increasing myocardial oxygen consumption. It can enhance myocardial contractility, with both inotropic and vasodilator effects, thereby improving the blood flow supply to the coronary arteries and clinical symptoms of patients and maintaining hemodynamic stability [14, 15]. Levosimendan has previously been proven to be effective in improving hemodynamics and activity endurance of patients with heart failure [16], which is similar to our observations.

In addition to cardiac function and hemodynamic parameters, we also compared serum inflammatory factors before and after treatment between the two groups. Myocardial infarction can cause irreversible damage to the myocardium, causing complex pathologic changes that lead to persistent dysfunction of the myocardium. Inflammatory factors play a pivotal role in this process, since they are positively correlated with disease severity and are critical to take into consideration [17]. Myocardial infarction can activate inflammatory cells such as macrophages and increase the secretion of cytokines such as TNF-α and IL-6. The former can stimulate the liver to produce hs-CRP, and the above factors are involved in the acute inflammatory response process of AMI with heart failure [18]. Moreover, increased levels of inflammatory factors such as TNF-α and IL-6 are not conducive to myocardial perfusion, and will accelerate myocardial hypertrophy and fibrosis, promote myocardial cell necrosis and apoptosis, and accelerate ventricular remodeling and deterioration of cardiac function. IL-6 and TNF-α can be used as independent factors for the severity of heart failure and prognosis [19, 20].

We observed that serum hs-CRP was markedly decreased in both groups after treatment, but the decrease was more evident in the OG than in the CG, suggesting that levosimendan can more significantly reduce the inflammatory status and improve the prognosis of AMI patients with heart failure than milrinone. In past research, levosimendan has been found to reduce serum lipid peroxide, IL-6, TNF-α, and apoptotic signaling factor levels in patients with heart failure, with anti-inflammatory, antioxidant, and anti-apoptotic effects [21, 22]. This is consistent with our observations. We conducted multivariate regression analysis to further analyze the independent factors affecting the cure rate. Both diabetes and levosimendan were found to be independent factors affecting the curative effect. Previous studies [23, 24] found that diabetes was an important risk factor for AMI and a common complication of AMI hospitalized patients. In addition, our research results also showed that for patients with AMI and heart failure, levosimendan has a relatively independent and significant effect. Finally, we also compared the adverse reactions and quality of life between the two groups. The results revealed that the OG held a markedly lower incidence of adverse reactions and a evidently better quality of life than the CG. The safety of levosimendan in the treatment of heart failure has also been demonstrated in previous studies [25, 26].

In summary, levosimendan can effectively improve cardiac function, hemodynamics, and serum inflammatory factors in AMI patients with heart failure with good efficacy and safety. However, this study also has some limitations. First, due to the small sample size, the conclusions of this study remain to be further analyzed, and we will carry out multicenter large-sample studies to demonstrate our results. Second, we did not follow up and analyze the long-term prognosis of patients, so that their recurrence rate remains unknown. We will subsequently strengthen the follow-up of patients and further improve the data.

Disclosure of conflict of interest

None.

Address correspondence to: Chao Qu, Cardiovascular Ward I, Xi'an Fifth Hospital, No. 112, Xiguanzheng Street, Lianhu District, Xi'an 710000, Shaanxi, China. E-mail: 619754723@qq.com

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