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ORIGINAL ARTICLE

Melatonin for nondippers with coronary artery disease: assessment of blood pressure profile and heart rate variability

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The aim of this study was to assess the effects of 5 mg melatonin before sleep in patients with coronary artery disease (CAD) and with an abnormal circadian pattern of blood pressure (BP) on changes in circadian BP profile and heart rate variability (HRV). Sixty patients with CAD, nondippers aged 48–80 years (male 75%), were included. In addition to previous treatment, they were randomly allocated to melatonin or placebo. After 90 days, a second 24-h BP monitoring was carried out. Each patient had two sessions (before randomization and at the end of study) of 24-h ECG monitoring to assess the changes in HRV. Inclusion of melatonin led to BP pattern normalization in 35% of patients in the melatonin group and in 15% of controls (P=0.609). This effect was reached not only by a decrease in nighttime BP, but also by an increase in daytime BP (significant in the melatonin group). A nonoptimal effect for BP profile was observed in 12.5% of patients: extreme- or reverse dippers. In patients with conversion from nondippers to dippers (responders), an increase in standard deviation of normal-to-normal intervals between initial and final HRV analyses was observed. Nonresponders represented an increase in the mean circadian heart rate. To avoid nonoptimal effects, the inclusion of melatonin in pharmacotherapy of patients with CAD should be based on monitoring of circadian BP profile, before and during treatment. As melatonin caused not only a nocturnal decrease in BP but also a daytime increase, it should not be recommended in patients with 'high normal' values of BP because of the danger of induction of arterial hypertension.
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Keywords: blood pressure; coronary artery disease; melatonin; nondipping

INTRODUCTION

Melatonin is now widely popularized in media as a remedy that helps people fall asleep, and its preparations can be bought over the counter. This hormone, synthesized in the pineal gland, is produced from tryptophan converted to serotonin, and its secretion is inhibited by light, both natural and artificial. Melatonin is believed to be involved in regulating 'the biological clock'; its secretion was shown, among other things, to be connected to the circadian physiological fluctuations of body temperature.[1] Studies so far have proven that melatonin biosynthesis decreases after the age of 40 years. It has also been pointed out that patients with ischemic heart disease, regardless of their age, have deficits of this hormone.[2–4] In the observation of patients with arterial hypertension, it was shown that the group with impaired circadian rhythms of arterial blood pressure (BP), nondippers, had reduced melatonin synthesis.[5,6] A proper circadian BP rhythm is connected with a lower risk of left ventricular hypertrophy or of episodes of myocardial ischemia, both silent and symptomatic, in comparison with nondippers.[7] Therefore, a pharmacological intervention aimed at normalizing the circadian rhythm could theoretically help in reducing the risk of the above-mentioned complications. In view of the wide availability of melatonin preparations, the question arises whether they can be taken without a doctor's control by patients with coronary artery disease (CAD), both those treated hypotensively and those without arterial hypertension. The aim of this study was to assess the tolerance of using melatonin by patients with CAD who were nondippers, with special attention paid to changes in the circadian BP profile and heart rate variability (HRV).

METHODS

This study included 62 ambulatory patients with CAD confirmed by coronary angiography, in whom a 24-h ambulatory blood pressure monitoring (ABPM) showed a change in mean systolic pressure during sleep in comparison with mean systolic pressure in the daytime of less than 10%. The study included both normotensive patients and those with diagnosed essential arterial hypertension. The group included 45 men (75%) and patients were aged between 48 and 80 years (mean age 60.9 ± 5.6). They were informed about the purpose of the study and agreed to take melatonin regardless of the quality of sleep. They were randomly assigned to melatonin or placebo treatment in a 2:1 ratio. The study complies with the Declaration of Helsinki Principles and Declaration of

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Tokyo, its protocol was approved by the local commission for bioethics of the Medical University of Lodz (resolution no. RNN/50/04/KE) and informed consent was obtained from the subjects. Two patients withdrew consent before the 30th day of study and were not included in the analysis.

Automatic BP measurements were taken noninvasively by means of the Tracker NIBP (DelMar Reynolds, Hartford, UK) over a period of 24 h of normal activity in ambulatory conditions. Between 0600 and 2300 hours, BP measurements were taken at 15-min intervals and, between 2300 and 0600 hours, every 30 min. The patients were required to maintain a record of sleeping and waking times during monitoring, and these were included in the analysis of results. The following variables were calculated: the individual mean systolic (SBP) and diastolic BP (DBP) during sleep, the so-called mean pressure at night (SBPnight, DBPnight), and during waking hours, the so-called mean pressure at daytime (SBPday, DBPday), as well as the mean circadian SBP and DBP (SBP24 and DBP24). Two ABPM examinations were conducted for each patient: the first one at baseline, before the melatonin/placebo treatment, and the second one on the last day of the 90-day-long treatment. Short-acting melatonin (5 mg) or placebo was taken between 2100 and 2300 hours. The norms for the optimal values of ABPM were based on the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[8] Moreover, each patient had two sessions of 24-h ECG monitoring (Pathfinder 700; DelMar Reynolds). The following parameters of HRV were analyzed during the two Holter sessions: standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (rMSSD), as well as mean circadian heart rate (meanHR24) and minimal heart rate at night (minHRnight).

Pulse wave velocity (PWV) was measured by means of an automatic device for measuring carotid–femoral transit or propagation of the pulse pressure wave (the COMPLIOR system). This method for assessing PWV was described for the first time by Asmar *et al*.[9]

As responders, we considered those patients treated with melatonin in whom the final ABPM showed the expected dipper-type profile of BP, and as nonresponders, those who still remained in the group of nondippers. By the term 'nonoptimal effect' was understood the nocturnal decrease in averaged systolic pressure in comparison with daytime values $>20\%$ or a nocturnal increase in SBP.

Statistical analysis

All results were expressed as mean ± s.d. Two-tailed unpaired *t*-tests were carried out to compare the changes in results, as the differences between values before and after treatment in all patients had a normal distribution.

To compare patients treated with melatonin with those on placebo, as well as responders and nonresponders, according to the results before and after treatment, two-tailed unpaired *t*-tests were used, provided that the distribution of result values was normal. When this assumption was not fulfilled, a two-tailed unpaired Mann–Whitney test was carried out. The Kolmogorov–Smirnov test was used to distinguish normal from nonnormal distribution of results. *P*-value <0.05 was considered to be statistically significant.

The predictor of responsiveness was this initial parameter, which had significantly different values in the group of responders before melatonin supplementation in comparison with the group of nonresponders.

RESULTS

The clinical characteristics of the patients and their pharmacological treatment are shown in Tables 1 and 2. As a beneficial effect of melatonin treatment was regarded a change in the circadian profile of arterial BP, which enabled the patient to be transferred from the group of nondippers to the group of dippers, who run a smaller risk of cardiac complications. Such a beneficial effect was observed in 35% of patients treated with melatonin and in 15% taking placebo. The influence of the 90-day-long melatonin treatment, a daily dose of 5 mg or placebo taken in the evening, on the circadian BP and HR profile in the study group and in controls is shown in Table 3.

The difference between the mean decrease in systolic pressure in the study group before and at the end of the treatment was 6.4%.

Table 1 The occurrence of risk factors in the study group and controls

Risk factor of atherosclerosis	*Melatonin group* (n=*40*), n *(%)*	*Placebo group* (n=*20*), n *(%)*	*Significance,* P
Age[a]	61.15 ± 6.75	53.61 ± 13.6	0.004
Male sex	31 (77)	13 (65)	0.302
Dyslipidemia	25 (62)	14 (70)	0.565
Arterial hypertension	23 (57)	17 (85)	0.033
Diabetes mellitus	13 (32)	4 (20)	0.311
Smoking	8 (20)	6 (30)	0.387
Obesity	7 (17)	10 (50)	0.008

[a]Value ± s.d. for age.

Table 2 The pharmacological treatment in the study group and controls

Pharmacological group	*Melatonin group* (n=*40*), n *(%)*	*Placebo group* (n=*20*), n *(%)*	*Significance,* P
β-Blockers	40 (100)	20 (100)	1.0
Antiplatelet compounds (aspirin and/or clopidogrel)	40 (100)	20 (100)	1.0
Statins	29 (72)	13 (65)	0.319
Calcium channel antagonists	20 (50)	5 (25)	0.064
Angiotensin-converting enzyme inhibitors	18 (45)	14 (70)	0.067
Mononitrates	11 (27)	3 (15)	0.218
Diuretics	10 (25)	8 (40)	0.187
Angiotensin receptor antagonists	6 (15)	5 (25)	0.345
Fibrates	4 (10)	4 (20)	0.282
Trimetazidine	2 (5)	4 (20)	0.067
Oral anticoagulants	2 (5)	0 (0)	0.309
α-Adrenolytics	1 (2)	1 (5)	0.611
Sibutramine	0 (0)	1 (5)	0.153
Oral antidiabetics	10 (25)	3 (15)	0.375
Insulin	3 (7.5)	1 (5)	0.128

We decided that it was possible to alter the circadian decrease in BP roughly by that value by including a dose of 5 mg of melatonin in the therapy. The two larger groups that emerged at the end of melatonin treatment were patients who still remained in the group of nondippers—classified as nonresponders (night/day SBP ratio: 0–10%), consisting of 21 people (52.5%)—and patients in which an optimal effect was obtained, the so-called dippers—classified as responders (night/day SBP ratio: 10–20%), consisting of 14 people (35%). The remaining two smaller groups were extreme dippers, consisting of 3 people (7.5%), and reverse dippers, consisting of 2 people (5%). When dippers and extreme dippers after treatment were regarded as individuals with a night/day SBP ratio greater than 10%, and nondippers and reverse dippers were considered as those with a night/day SBP ratio smaller than 10%, a trend was observed ($P=0.084$) toward a significant difference in the effect of melatonin between the active treatment and placebo groups (Table 4).

A comparison of the age structure of the two groups showed that nonresponders were more diversified with respect to their age than

were responders, Table 5. The former group included both the oldest participant (aged 80 years) and the youngest participant (aged 48 years) of our study (mean age 62.1 ± 6.6), whereas in the responders group, the age range was 53–72 years (mean age 61.4 ± 4.2). Both groups were predominantly male; men constituted 81 and 79% of patients in the two groups, respectively.

In the responders group, the mean value of PWV was 10.6 ± 1.8 m s^{-1} and in nonresponders, it was 10.6 ± 1.9 m s^{-1} (P=0.981).

Table 3 Assessment of changes of parameters before and after treatment in the study group and controls

Parameter	*Before treatment (B)*	*After treatment (A)*	*Significance: B* vs. *A* (P)
SBP24 (mm Hg), M	120 ± 13	122.9 ± 13.3	0.081
P	124 ± 15.2	125.3 ± 16.5	0.615
Significance: M *vs.* P	*P*=0.322	*P*=0.583	
DBP24 (mm Hg), M	69.1 ± 8.9	70.7 ± 8.7	0.206
P	72.5 ± 9.8	74.1 ± 16.1	0.363
Significance: M *vs.* P	*P*=0.268	*P*=0.218	
SBPday (mm Hg), M	121.2 ± 12.9	126.1 ± 13.1	**0.005**
P	125.8 ± 16	128.1 ± 16.7	0.385
Significance: M *vs.* P	*P*=0.268	*P*=0.628	
DBPday (mm Hg), M	70.3 ± 9.4	73.1 ± 8.7	**0.012**
P	73.9 ± 10.5	76.4 ± 10.5	0.212
Significance: M *vs.* P	*P*=0.223	*P*=0.231	
SBPnight (mm Hg), M	117.4 ± 14	113.2 ± 14.2	**0.049**
P	117.6 ± 13.6	117.3 ± 16.3	0.884
Significance: M *vs.* P	*P*=0.959	*P*=0.357	
DBPnight (mm Hg), M	64.6 ± 9.6	62.4 ± 8.6	0.112
P	66.2 ± 9.2	65.5 ± 10.6	0.636
Significance: M *vs.* P	*P*=0.562	*P*=0.256	
SDNN (ms), M	126.7 ± 34.7	132 ± 34.1	0.147
P	108.4 ± 34.3	114.7 ± 30.2	0.362
Significance: M *vs.* P	*P*=0.081	*P*=0.75	
rMSSD (ms), M	29.6 ± 19.7	29.8 ± 18	0.919
P	27.1 ± 16.2	26.7 ± 16.2	0.901
Significance: M *vs.* P	*P*=0.713[a]	*P*=0.557	
Night/day SBP ratio (%), M	3.6 ± 7	10 ± 7.3	**<0.001**
P	6.1 ± 2.5	8.4 ± 5.2	0.101
Significance: M *vs.* P	*P*=0.523	*P*=0.455	
minHRnight (1 min^{-1}), M	52.5 ± 7.5	53.2 ± 8	0.289
P	56.6 ± 9.5	56.3 ± 10.8	0.774
Significance: M *vs.* P	*P*=0.09	*P*=0.25	
MeanHR24 (1 min^{-1}), M	67.6 ± 9.6	69.8 ± 10.9	**0.018**
P	71.7 ± 12.6	73.6 ± 13.5	0.242
Significance: M *vs.* P	*P*=0.201	*P*=0.283	

Abbreviations: A, after treatment; B, before treatment; M, melatonin treatment; P, placebo; minHRnight, minimal heart rate during sleep; meanHR24, mean heart rate during 24 h; SBP/DBPday/night, mean systolic/diastolic pressure during active/passive hours monitoring; rMSSD, root mean square of successive difference; SDNN, standard deviation of normal-to-normal intervals; SBP24/DBP24, mean systolic/diastolic pressure during 24 h monitoring. Values are bold when $P<0.05$.
[a]Two-tailed unpaired Mann–Whitney test.

Noteworthy is the case of three patients (7.5%) in whom the difference between diurnal and nocturnal BP values during melatonin treatment was excessive; in extreme cases it was 26.8% for systolic pressure and 32.9% for diastolic pressure. It is a significant observation, because a difference higher than 20% is connected to an increased risk of ischemic episodes of the heart and brain, and people with this type of circadian profile are referred to as extreme dippers. This subgroup consisted of two men and a woman, whose age was below the mean age of the population studied. Among controls, one extreme dipper was found. As can be seen from Table 3, after 90 days, melatonin taken in the evening caused a significant acceleration of the meanHR24 in the entire study group (P=0.018), as well as an increase in SBPday, P=0.005; DBPday, P=0.012; day/night SBP ratio, $P<0.001$ and a decrease in SBPnight, P=0.049. No significant difference was observed between responders and nonresponders before treatment. For responders and nonresponders, one difference was noted at the end of the observation: after 90 days of treatment, responders had a significantly higher SDNN, hence the HRV in these patients increased, owing to melatonin supplementation, P=0.041. In nonresponders, the meanHR24 increased significantly after melatonin treatment (P=0.006), Table 5. To summarize, in the study group, two modes of reaction to melatonin supplementation were observed. In some patients, melatonin had a stronger influence on the change in day/night SBP ratio ($P<0.001$) and in others, on the acceleration of pulse frequency.

DISCUSSION

In view of the large number of reports on the influence of melatonin on the functioning of the circulatory system, it seemed interesting to check whether it would be possible to modify an abnormal circadian BP rhythm in cardiac patients. In the study group of 40 patients with CAD and an abnormal circadian BP profile, after a 90-day-long therapy that involved adding melatonin to the previous standard treatment, a variety of effects were observed with about circadian BP profile.

An important point is the possibility of interactions of melatonin with other medicines taken by the patients. Cowen *et al.*[10] have shown that patients treated for arterial hypertension with β-adrenolytics had lower concentrations of melatonin than did patients who were receiving diuretics. All our patients were receiving medicines from this group, hence they can be regarded as comparable in this respect. An interesting interaction was observed by Lusardi *et al.* After melatonin was added to an antihypertensive treatment with nifedipine, the nocturnal BP values rose by about 6.5 mm Hg and the HR by about 3.9 per min.[11] On the basis of the results obtained, these authors warn against regarding melatonin as 'a simple diet supplement'. Admittedly, from among the patients analyzed in this study, 20 people were taking calcium channel antagonists, but toward the end of melatonin therapy, the mean circadian values of SBP were higher for the whole group by about 2.9% (P=0.081), and of DBP

Table 4 Comparison of effects after melatonin treatment or placebo

Effect of treatment	*Melatonin*, n *(%)*	*Placebo*, n *(%)*	*Significance*, P
Number (%) of individuals with night/day SBP ratio >10%	17 (42.5)	4 (20)	0.084
Number (%) of individuals with night/day SBP ratio <10%	23 (57.5)	16 (80)	
Change in night/day SBP ratio (%)	6.4 ± 6.45	2.3 ± 3.95	0.01

Abbreviation: SBP, systolic blood pressure.

Table 5 Comparison between responders and nonresponders: demographic data, assessment of changes of ABPM and ECG Holter monitoring parameters before and after treatment

Parameter (unit)		*Nonresponders*	*Responders*	*Significance: responders* vs. *nonresponders* (P)
Age (year)		62.1 ± 6.6	61.4 ± 4.2	0.54
Male gender (%)		81	79	0.999
Body mass index		27.32 ± 4.1	27.64 ± 1.73	0.96
	B	121.5 ± 12.7	115.9 ± 12	0.204
SBP24 (mm Hg)	A	124.6 ± 13.9	119.3 ± 10.5	0.234
Significance: B *vs.* A		*P*=0.234	*P*=0.252	
	B	71.7 ± 9	66.3 ± 8.8	0.09
DBP24 (mm Hg)	A	73.0 ± 9.5	68.7 ± 6.5	0.152
Significance: B *vs.* A		*P*=0.462	*P*=0.498	
	B	122.1 ± 12.1	117.6 ± 12.8	0.293
SBPday (mm Hg)	A	126.7 ± 14.5	123.1 ± 10.1	0.435
Significance: B *vs.* A		*P*=0.093	*P*=0.066	
	B	72.7 ± 9.7	67.6 ± 9.7	0.138
DBPday (mm Hg)	A	74.7 ± 9.8	71.7 ± 6.5	0.323
Significance: B *vs.* A		*P*=0.165	*P*=0.072	
	B	119.0 ± 15.8	114.4 ± 10.2	0.344
SBPnight (mm Hg)	A	118.3 ± 13.7	106.6 ± 11.3	**0.012**
Significance: B *vs.* A		*P*=0.81	***P*=0.043**	
	B	67.3 ± 9.2	62.1 ± 10	0.127
DBPnight (mm Hg)	A	66.7 ± 8.5	58.4 ± 6.1	**0.003**
Significance: B *vs.* A		*P*=0.74	*P*=0.171	
	B	120.9 ± 28.4	133.4 ± 41.8	0.296
SDNN (ms)	A	121.0 ± 27.2	143.6 ± 35.6	**0.041**
Significance: B *vs.* A		*P*=0.964	*P*=0.275	
	B	28.5 ± 23.2	31.6 ± 16.9	0.096[a]
rMSSD (ms)	A	25.6 ± 17.3	33.6 ± 20	0.219
Significance: B *vs.* A		*P*=0.17	*P*=0.433	
	B	3.4 ± 6.3	2.9 ± 8.8	0.84
Night/day SBP ratio (%)	A	6.0 ± 3.7	14,9 ± 2.2	<**0.001**
Significance: B *vs.* A		***P*=0.038**	***P*<0.001**	
	B	53.6 ± 7.2	50.9 ± 7.8	0.31
minHRnight (min^{-1})	A	55.3 ± 7.9	51.8 ± 8.2	0.215
Significance: B *vs.* A		*P*=0.068	*P*=0.294	
	B	68.9 ± 9.1	66.2 ± 11.6	0.449
meanHR24 (min^{-1})	A	72.5 ± 10.5	68.2 ± 11.6	0.267
Significance: B *vs.* A		***P*=0.006**	*P*=0.197	

Abbreviations: A, after treatment; B, before treatment; minHRnight, minimal heart rate during sleep; meanHR24, mean heart rate during 24 h; rMSSD, root mean square of successive difference; SDNN, standard deviation of normal-to-normal intervals; SBP24/DBP24, mean systolic/diastolic pressure during 24 h monitoring.
Values are bold when $P<0.05$.
[a]Two-tailed unpaired Mann–Whitney test.

by about 1.6% ($P=0.206$). This observation is especially significant in the case of patients with BP values described as 'high normal'; it can be argued whether administering melatonin to this group of patients will not change BP values into those defined as 'arterial hypertension I'.

The literature with regard to the problem of an abnormal BP pattern contains studies that examine a possible connection of this phenomenon with diabetes mellitus, with impaired autonomic regulation of BP by the nervous system and increased stiffness of coronary vessels as a consequence of their remodeling.[12,13] Impaired autonomic regulation of the circulatory system and its connection with the lack of circadian BP variability were also studied in patients with arterial hypertension. Guasti *et al.*[14] have proven on the basis of a 24-h ABPM, a time domain analysis of sinus rhythm variability, and an examination of baroreflexes that the factors that contribute to an impairment of the sympathetic and parasympathetic regulation of the cardiovascular system modify both HR and BP variability to the same extent. The hypothesis that an impairment of the BP profile may be dependent on the patient's sex was not confirmed.[15] Lekakis *et al.*[16] have proven that increased stiffness of the large arteries assessed by means of PWV measurements is connected to the phenomenon of nondipping; however, in our study, there was no significant difference in the mean PWV between responders and nonresponders ($P=0.981$).

The most disturbing observation in our study, however, is the fact that in three patients, the mean arterial BP at nighttime decreased excessively (by more than 20%) during melatonin treatment (a dose of 5 mg). This type of reaction carries the potential danger of increasing

the risk of episodes of ischemia of the myocardium or of the central nervous system, as well as the risk of hemorrhagic stroke or damage to the retina in ophthalmological patients.[17–20] In the case of extreme dippers who require hypotensive treatment, we must be extremely careful while selecting the kind of medicines and their doses, especially if the patients are elderly or have concurrent diseases of the cardiovascular system.

Study limitations

An important limitation of our study is the small size of the population examined. Certainly, examining a larger population would produce a better statistical credibility of the results and could affect the percentage of patients in the particular categories on the basis of the circadian variability of arterial BP, but it probably would not change the qualitative result of the analysis.

There are still controversies in the literature regarding the method of assessing the circadian BP rhythm that was used in our study. There are opinions questioning the validity of ABPM for diagnosing nondipping because of the low reproducibility of results. In spite of this, considering that Zakopoulos *et al.*[21] proved a high reproducibility of the results obtained by means of this method on the basis of four ABPM measurements performed on the same patients at intervals of 30 days, we decided to perform one 24-h BP measurement before melatonin treatment and on the last day of therapy.

It must be emphasized that we did not know the patients' status with regard to the secretion of endogenous melatonin. Admittedly, it is possible to determine its serous concentration at nighttime by means of immunofluorescence; however, before blood samples are collected, the patient must be kept in darkness for many hours with only filtered light (similar to a darkroom in which photographic film is processed). Another method, testing for the presence of melatonin metabolites in urine, requires a careful collection of urine samples during nighttime. As the study was planned for ambulatory conditions and for patients who were active professionally or at least family wise, we decided not to determine the possible deficit of endogenous melatonin by means of the above-mentioned methods.

Researchers investigating the problem of influence of melatonin supplementation on the improvement of BP values in an animal model of arterial hypertension suggest that the effect of treatment depends on the etiology of hypertension. Spontaneously hypertensive rats (the animal model of arterial hypertension with the increased activity of the sympathetic system) are more sensitive to melatonin than are transgenic rats, TGR(mRen-2)27, with an upregulated renin–angiotensin–aldosterone system.[22] In our study, the etiology of arterial hypertension, which was present in the case of some patients, was also not known, but the differences in reaction to melatonin supplementation suggest that the group was not homogenous in this respect. Similar to our previous publication, no relationship was found between the effect of melatonin supplementation and the presence or accumulation of classical risk factors of ischemic heart disease nor between the kind of pharmacological treatment used.[23]

CONCLUSIONS

To avoid nonoptimal effects, the application of melatonin in the pharmacotherapy of patients with CAD should be based on the monitoring of the circadian BP profile, performed before and during treatment. As melatonin caused not only a nocturnal decrease in BP but also a daytime increase, it should not be recommended in patients with values of BP described as 'high normal' because of the danger of induction of arterial hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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