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ORIGINAL ARTICLE

Urinary albumin excretion is associated with true resistant hypertension

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Resistant (or refractory) hypertension (RH) is a clinical diagnosis based on blood pressure (BP) office measurements. About one third of subjects with suspected RH have indeed pseudo-resistant hypertension and 24-h ambulatory-blood pressure-monitoring aids to precisely identify them. Our aim was to determine those clinical, laboratory or echocardiographic variables that may be associated with subjects with sustained hypertension (namely true RH). We carried out a cross-sectional analysis of 143 patients consecutively enrolled with the clinical diagnosis of RH. All patients underwent clinical-demographic, laboratory evaluation, 2D-echocardiography and 24-h ambulatory-blood pressure-monitoring. Pseudo-resistant hypertension or white-coat RH was defined if office BP was $\geqslant$140 and/or 90 mm Hg and 24-h BP $<$130/80 mm Hg. One-hundred and three (72%) patients had true RH and 40 (28%) patients had white-coat RH. True RH patients had significantly higher diabetes prevalence and higher office-systolic blood pressure (SBP) levels. Regarding target organ damage, left ventricular mass index (LVMI) and 24-h urinary albumin excretion (UAE) were also higher in true RH after adjustment for possible confounders ($P=0.031$ and $P=0.012$, respectively). In a logistic regression analysis, only office-SBP (multivariate OR (95%CI): 1.030 (1.003–1.057), $P=0.030$) and UAE (multivariate OR (95% CI): 2.376 (1.225–4.608), $P=0.010$) were independently associated with true RH. We conclude that true resistant hypertension is associated with silent target organ damage, especially UAE. In patients with suspected RH, assessment of 24 h ambulatory BP is the most accurate way to detect a population with high risk for target-organ damage.

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Introduction

Resistant (or refractory) hypertension (RH) is defined as a condition where blood pressure (BP) remains above goal in spite of the use of an optimal triple-drug regimen in full dosages, including a diuretic.[1,2] This is always a clinical diagnosis established on the basis of office-BP measurements. However, the use of 24-h ambulatory blood-pressure monitoring (ABPM) has allowed the identification of a proportion of subjects with normal 24-h BP values, that is, white-coat RH (WCRH). It is estimated that about one third of patients with suspected RH have indeed WCRH,[3–5] showing office BP $\geqslant$140 and/or 90 mm Hg and 24-h ABPM $<$130/80 mm Hg. Therefore, ABPM is required to confirm the refractoriness of hypertension.

On the other hand, the importance of adequately diagnosing and treating patients with RH is outlined by its recognized higher prevalence of target-organ damage[3,6–8] and cardiovascular diseases[9–11] in comparison with subjects with controlled hypertension. In this way, left ventricular hypertrophy (LVH) has been diagnosed in near 50–75% of patients with RH.[7,9,12] As for data referred to microalbuminuria (MA) in RH, there are scarce data reported in the literature, although Nogueira *et al.*[13] reported a 29.4% prevalence of MA in RH patients. Considering the cardiovascular risk of these patients, the event-free survival is near three-fold reduced in patients with true RH (T-RH) in comparison with

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responder hypertensives[9] and is reduced more than six times in RH patients in the higher tertile versus the lower tertile of diastolic BP.[10]

Taking these data into account, we aimed in this study to determine some clinical, laboratory or echocardiographic variables that may be tightly associated with subjects with T-RH and may therefore help the clinician to identify these patients.

Patients and methods

Study population

We carried out a cross-sectional analysis of a cohort of 143 consecutively enrolled patients with RH, aged 35–75, from four hypertension units at corresponding university hospitals in Barcelona, Spain. The local Institutional Ethic Committees approved the study protocol. Written informed consent was obtained from all participants. The investigation conforms to the principles outlined in the declaration of Helsinki. Office RH diagnosis was made according to the current guidelines,[1,2] that is, sustained office BP $\geqslant$140 and/or 90 mm Hg despite a therapeutic plan with at least three drugs in adequate doses, including a diuretic, for a minimum of 3 months. All patients were submitted to a standard protocol where demographic and anthropometric characteristics, cardiovascular risk factors and clinical associated conditions were recorded and all these subjects underwent complete laboratory evaluation including 24-h UAE assessment, 2D-echocardiography and 24-h ABPM.

Diabetes mellitus was diagnosed by means of medical history or by undergoing antidiabetic treatment or by two fasting glucose measurements of 126 mg dl^{-1} or greater. All diabetic patients had type 2 diabetes mellitus. Dyslipidemia was defined as serum cholesterol level >200 mg dl^{-1} (5.2 mmol l^{-1}) and/or serum triglyceride level above 150 mg dl^{-1} (1.7 mmol l^{-1}) or if treatment with lipid-lowering drugs had been implemented. Smokers were considered as those with an active smoking habit over the last year. Secondary hypertension was screened by clinical history and physical and routine laboratory examination. Specific diagnostic procedures were carried out after the guidelines recommendations if any secondary cause of hypertension, such as renal parenchymal disease, renovascular hypertension or primary aldosteronism, was suspected. Thus, patients with secondary hypertension were excluded, and those with estimated glomerular filtration rate (according to the MDRD study equation) lower than 30 ml per min 1.73 m^{-2} of any aetiology. Patients on long-term corticosteroid or non-steroidal anti-inflammatory therapies were also excluded from study participation. Poor adherence was also ruled out through a standard validated questionnaire by a trained nurse. Moreover, patients with any acute disease or who had suffered a cardiovascular event in the earlier six months were not included. Earlier history of cardiovascular disease was considered in case of confirmed stroke (other than transient ischaemic attack), acute myocardial infarction or unstable angina, hospitalization because of heart failure or ischaemic peripheral vascular disease.

Office BP measurement

Office BP was measured in the outpatient clinic by a trained nurse. After 5 minutes of rest in the sitting position, BP was measured using the appropriate size cuffs and considered as the average of three measurements spaced by 2 min with a validated oscillometric semiautomatic device (Omron 705IT, Kyoto, Japan). The average of these BP measurements obtained in at least two separated visits was assumed as the definitive office BP value considered in this study. Additional measurements were taken if the first two were quite different.

Ambulatory BP monitoring

Twenty-four-hour-ABPM was carried out in all patients with a validated Spacelabs-90207 device (Issaquah, WA, USA) and suitable sized cuffs. The monitoring was carried out on a working day, starting at around 8–10. Ambulatory BP readings were obtained at 20-min intervals throughout both the awake and asleep periods. Awake and asleep periods were considered from 10 to 20 h and from 0 to 6 h, respectively. All patients included in the study had recordings of good technical quality (at least 80% of valid readings). T-RH was confirmed if hypertensive individuals had 24-h systolic BP $>=$ 130 mm Hg and/or 24-h diastolic BP $>=$ 80 mm Hg. Otherwise, white-coat (or isolated office) RH (WCRH) was defined if office BP was $\geqslant$140 and/or 90 mm Hg and 24-h BP $<$130 and 80 mm Hg.

Echocardiography

Echocardiographic examinations were carried out with the patients in the partial left decubitus position. End-diastolic ventricular internal diameter, end-diastolic interventricular septum thickness and posterior wall thickness were measured. Left ventricular (LV) mass calculation was performed according to the American Society of Echocardiography recommendations.[14] This validated with necropsy ASE-recommended formula to estimate LV mass from LV linear dimensions was used.[15] LV mass was indexed to body surface area to give LVMI. The diagnosis of LVH was considered if LVMI >125 g m^{-2} in men and >110 g m^{-2} in women.[1]

Urinary albumin excretion

Urinary albumin excretion (UAE) rate (measured by turbidimetry; lower detection limit: 0.3 mg dl^{-1}; intra-assay and interassay variation coefficients: 1.3 and 4.3%, respectively) was evaluated twice in

a month in corresponding sterile 24-h urine collections. Final shown values for UAE are the average of both determinations.

Statistical analysis

Continuous data were described as mean ± s.d. for those with normal distribution and as median and interquartile range for asymmetrically distributed data. Qualitative data were expressed as percentage. Bivariate comparisons between patients with T-RH or with WCRH were carried out by unpaired *t*-tests or ANOVA in continuous normally distributed data, by nonparametric Mann–Whitney test in asymmetrically distributed data, or by χ^2-test in categorical data. The association of UAE (log-transformed) and LVMI with T-RH was tested by ANOVA after adjustment for all of the potential confounders which were used as covariates (age, gender, office-SBP and diabetes for both of them plus estimated glomerular filtration rate and body mass index for UAE). Logistic regression analyses were used to identify the independent factors associated with T-RH, with T-RH used as the dependant variable. The criterion to select variables to enter the multivariate analysis was a *P*-value $\leqslant 0.20$ and to remain in the final model was a *P*-value <0.05. The method for introduction of variables was stepwise forward. Multivariate odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated for each independent associated variable. The procedure stopped at this level because of the lack of significance of the remaining variables. The search for the best cut-off value of UAE associated with T-RH was assessed by the receiver-operating characteristic (ROC) curve analysis. Hence, sensitivity was plotted against 1-specificity to examine the point of best trade-off between both of them. All of the statistics were performed using statistical package SPSS version 14.0 (Chicago, IL, USA) and statistical significance was assumed if a null hypothesis could be rejected at $P<0.05$.

Results

A total of 143 patients were included in the study. The mean age was 61.1 ± 9.4years and women accounted for 41.5% of the patients. According to ABPM, 103 (72%) patients had T-RH and 40 (28%) had WCRH. As per the protocol, all patients were taking a diuretic and 136 out of 143 (95%) patients were treated with an ACE inhibitor and/or an angiotensin II receptor-antagonist. The percentage of patients treated with a calcium-channel blocker, a β-blocker, an α-blocker or a central vasodilator was 77, 60, 38 and 6%, respectively. We did not find significant differences between both groups regarding to the antihypertensive medication regimens (data not shown). Baseline characteristics of T-RH and WCRH patients are shown in Table 1. In comparison with patients with WCRH, patients with T-RH had significantly higher prevalence of diabetes, higher office-SBP (O-SBP) values, fasting blood glucose, glycated haemoglobin and UAE, and higher echocardiographic LVMI. Furthermore, we evaluated the relationship of LVMI and UAE with T-RH and WCRH after adjusting for the possible confounders. LVMI remained significantly higher in T-RH after adjustment for age, gender, O-SBP and diabetes ($P=0.031$) and UAE was also significantly higher in T-RH after adjusting for the same confounders plus estimated glomerular filtration rate and body mass index ($P=0.012$).

We carried out a logistic regression analysis (stepwise forward) with the presence or absence of true resistant hypertension as dependent variable and those known to be tightly related to the severity of hypertension or those which had shown to be related to T-RH in the bivariate analysis, that is, age, gender, body mass index, diabetes, O-SBP, estimated glomerular filtration rate, UAE and LVMI, as independent variables. The results showed that only O-SBP (OR (95%CI): 1.030 (1.003–1.057), $P=0.030$) and log-transformed UAE (OR (95%CI): 2.376 (1.225–4.608), $P=0.010$) remained independently associated with T-RH (Hosmer & Lemeshow goodness of fit: $P=0.019$).

Owing to the increasing evidence that the threshold for MA, currently established at a level of UAE higher than 30 mg/24 h, could underestimate patients with incipient target-organ damage,[12,16–19] we aimed to seek if a lower cut-off value of UAE was also associated with T-RH. Consequently, a receiver-operating characteristic (ROC) curve analysis was performed for this purpose. After plotting sensitivity against 1-specificity to examine the point of best trade-off between both of them, we found 15 mg/24 h as the most reliable cut-off. The area under the ROC curve was 0.69 (95% CI: 0.60–0.78; $P<0.001$) for UAE (Figure 1). Moreover, in a reciprocal analysis we categorized MA at UAE level $\geqslant$15 mg/24 h. Microalbuminuria defined at this different threshold remained significantly associated to T-RH with respect to WCRH (63.1 vs 27.5%; $P<0.001$).

Discussion

The results of this study show that more than one quarter of patients with RH had normal ABPM values. Further on, UAE is, among several clinical variables, the one which better associates with T-RH in patients with suspected RH, only comparable to BP '*per se*'.

The real prevalence of RH is unknown, although both cross-sectional and outcome studies suggest that it is not uncommon and estimated to range from around 5% in general practise to 25–30% in referral clinics.[20] Data obtained from studies such as the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE)[21] or the

Table 1 Baseline characteristics of true RH (T-RH) and white-coat RH (WCRH) patients

	T-RH (n = *103*)	*WCRH* (n = *40*)	P
Clinical data			
Age (year)	60.7 ± 9.8	62.7 ± 7.8	0.26
Gender, male	59%	55%	0.66
Body mass index (kg m^{-2})	30.9 ± 5.3	31.3 ± 4.5	0.68
Diabetes	34%	15%	0.022
Dyslipidemia	55%	48%	0.40
Smoking habit	15%	13%	0.68
Duration of hypertension (year)	6.2 (3.3; 15.1)	5.7 (3.5; 12.8)	0.73
Earlier history of CVD	23%	18%	0.48
Blood pressure			
Office-SBP (mm Hg)	159.2 ± 17.4	149.5 ± 15.1	0.002
Office-DBP (mm Hg)	89.6 ± 13.1	85.9 ± 10.5	0.08
Laboratory parameters			
Cholesterol (mg dl^{-1})	201.8 ± 33.7	200.8 ± 37.0	0.88
LDL-cholesterol (mg dl^{-1})	127.1 ± 28.1	124.8 ± 31.4	0.67
HDL-cholesterol (mg dl^{-1})	52.4 ± 13.0	53.9 ± 12.5	0.54
Triglycerides (mg dl^{-1})	114.5 (80.3; 146.0)	109.5 (78.4; 144.5)	0.44
Fasting blood glucose (mg dl^{-1})	120.6 ± 39.5	107.4 ± 21.5	0.012
Glycated haemoglobin HbA_1c (%)	5.7 ± 1.4	5.0 ± 0.7	0.001
High-sensitivity CRP (mg dl^{-1})	0.55 (0.30; 1.19)	1.0 (0.30; 1.90)	0.16
Serum creatinine (mg dl^{-1})	1.09 ± 0.29	1.06 ± 0.23	0.56
eGFR (ml min 1.73 m^{-2})	70.5 ± 20.5	69.7 ± 17.2	0.83
UAE (mg 24 h^{-1})	28 (7.6; 123)	9 (4.83; 18.6)	$<$0.001
MA	50%	18%	0.012
Echocardiographic parameters			
LVMI (g m^{-2})	142.6 ± 47.3	121.4 ± 35.8	0.006
LVH	67%	51%	0.08

Abbreviations: CVD, cardiovascular disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, glomerular filtration rate estimated by MDRD equation (Modification of Diet in Renal Disease study); LDL and HDL, low- and high- density lipoproteins, respectively; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MA, microalbuminuria (24 h-urinary albumin excretion $\geqslant$30 mg/24 h and $<$300 mg/24 h); SBP, systolic blood pressure; UAE, urinary albumin excretion.
Data given as mean ± s.d., median (quartile 1; quartile 3) or percentage (%).

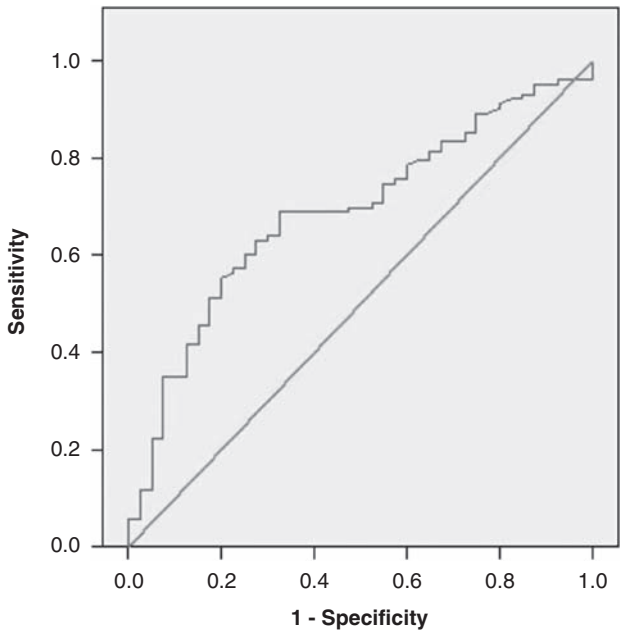

Figure 1 Receiver operating characteristic (ROC) curve analysis for the whole predictive performance of urinary albumin excretion with respect to the occurrence of true resistant hypertension.

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT)[22] reported a prevalence about 40–50% in hypertensive patients over 55 years of age with at least one additional risk factor. Moreover, it is likely that this condition will become increasingly common, because of an aging population with comorbidities and a progressively increase in obesity prevalence. Regardless of the true prevalence, resistance to therapy leaves the patient exposed to the consequences of often very high levels of BP. Indeed, patients with RH have higher target end-organ damage than treated patients with controlled hypertension, in particular arterial wall thickening, carotid plaques, retinal vascular changes, LVH and nephrosclerosis,[3,6,7] which translates into a higher overall cardiovascular risk.[9–11] However, uncontrolled hypertension is not synonymous with RH. Some patients exhibit normal 24-h BP values, so they must be considered to have pseudo-resistance. The prevalence of pseudo-resistant hypertension related to a isolated office high-BP effect is reported to range from 27 to 37%[3–5] and these patients manifest less severe target-organ damage and less cardiovascular risk in comparison to patients with T-RH.[8–11,23] In our study, we have

found that 28% of patients with suspected RH had normal 24-h ABPM values. This data is quite similar to that reported in the literature, mostly as for referral hypertension units. It is important that, our study shows that MA has a significant higher prevalence in patients with true RH in comparison to patients with pseudo-resistant hypertension.

There is no doubt that ABPM is a key tool in the diagnosis of T-RH. Ambulatory BP monitoring permits to identify those hypertensive patients who are not truly resistant to treatment.[3] There is some recent evidence suggesting that home BP monitoring could also be reliable enough. Thus, in patients with chronic kidney disease, Agarwal *et al*. reported that the strength of the relationship between proteinuria and systolic BP as assessed through home BP measurement was weaker than for ABPM but stronger than with clinic or office BP measurement.[24] Furthermore, as for the prognostic value of ABPM, several authors have reported that ambulatory BP control is superior to office BP control in predicting cardiovascular risk and outcomes in patients with RH.[9,10,11,25] However, it could be sometimes useful to own some accurate, non-invasive, cost-effective and readily available parameter to help clinicians raise suspicion of true refractoriness, just until ABPM is available to confirm the diagnosis.

An increasing amount of evidence points out to the tight relationship between UAE and BP levels. Recent data from large population-based studies show that the prevalence of MA is 11–17% in hypertension.[26] More than that, several authors reported that BP is the only determinant of MA in essential hypertension at different stages, from never-treated mild hypertensive patients[27–29] to high-risk hypertensives such as those included in the LIFE study.[30] As shown in all these studies, 24-h SBP but not office-SBP predicted MA. This is also in accordance with the data reported by Agarwal *et al*. in a cohort of patients, mostly men, with chronic kidney disease. They found a tight relationship between proteinuria and systolic BP, and this correlation was highest for ambulatory BP and lowest for routine clinic BP.[24,31] Our study confirms this earlier shown relationship in a slightly younger cohort of patients of both sexes without *a priori* chronic kidney disease. Furthermore, in our study, estimated GFR was not an independent predictor of systolic BP and this is consistent with the findings of Agarwal and Anderson. These data strengthen the growing knowledge of the main role of albuminuria as a marker of vascular inflammation beyond glomerular filtration rate '*per se*'. In our study, we also report information about LVH and we found that LVMI remained significantly higher in T-RH after adjustment for potential confounders. This finding reinforces the relationship between sustained hypertension and higher prevalence of target-organ damage. However, after performing logistic regression, MA but not LVMI remained in the model, suggesting that albuminuria is a stronger marker of sustained hypertension. These findings also give support to the hypothesis suggested by Salles *et al*.[12] as for different mechanisms for target-organ damage in this population. They reported a link with systemic inflammation and LVH in those patients with resistant hypertension but normal albuminuria.

There is scarce reported information regarding to patients with RH, but MA seems to occur in them with a prevalence ranging from around 17–29%.[7,12,13] Our study shows that, the only two variables that independently predict the occurrence of T-RH versus WCRH are UAE and O-SBP. Trying to find a useful tool to recognize true-RH in the office, Muxfeldt *et al*.[3] proposed a scoring system including six clinical, laboratory and electrocardiographic variables. Easier than that, we have shown that MA shows the best association with true refractoriness in patients with suspected RH.

On the other hand, recent data from several large population-based studies have issued the need to establish a lower threshold for MA because it has been shown that values well below the currently accepted 30 mg/24 h predict subclinical cardiovascular disease,[32] cardiovascular outcomes and all-cause mortality, whether in settings of diabetes, hypertension, nondiabetes, nondiabetes/nonhypertension or the general population.[16–18,33–35] This relationship has scarcely been studied in RH patients, a not uncommon subgroup of subjects with high cardiovascular morbidity and mortality. To our best knowledge, the possibility of a lower threshold to consider MA in patients with RH and its relationship with refractoriness in suspected patients has not been reported earlier. Although our results deserve further confirmation in a larger population, the findings of this study reinforce the elsewhere suggested belief that a lower UAE cut-off to define MA, such as 15 mg/24 h, correlates well with higher BP values and, therefore, with higher risk patients.

There are some limitations that should be pointed out. First of all, this study has a cross-sectional design, so the future occurrence of target-organ damage and cardiovascular or renal outcomes and death according to UAE rate is not explored. However, our primary aim was to characterize the clinical variables that are more closely associated with true RH in the clinical setting, therefore making the cross-sectional design the most favourable for this analysis. Moreover, this objective has been, as far as we honestly believe, widely accomplished by the finding of the tight relationship between UAE and RH. Secondly, we have not explored the pathophysiological mechanisms for the presence of MA in these patients, although the main known causes of MA such as diabetes, smoking habit or a decreased glomerular filtration rate have been discarded. Indeed, as it has been specified, the relationship between MA and T-RH was adjusted by diabetes presence, an evident confounder. The more

plausible cause of MA seems to be the bad control of BP by itself, according to the data we have obtained in this study. Finally, ABPM was measured in the non-dominant arm, whereas office BP was recorded in the arm in which BP was higher. Direct comparison of both BP measurements is, thus, not carried out systematically in the same arm, which would be better as suggested by Agarwal *et al.*[36] However, our study was conducted attending the recommendations of current guidelines[1] and we do not expect substantial differences in the results obtained.

In conclusion, this study shows that, in addition to O-SBP, UAE is independently associated with T-RH. Moreover, our results suggest that the use of a lower threshold of MA, as the UAE cut-off of 15 mg/24 h, could be a reliable marker of true resistance. It remains to be shown if this new threshold is also a better predictor of fatal and nonfatal cardiovascular outcomes in these patients and if lowering MA below this point in them would result in improving long-term morbidity and mortality survival. Anyway, given the known fact that MA indicates a high cardiovascular risk, this finding in patients with RH should lead to confirm refractoriness by carrying out 24-h ABPM and to search for a strict control of blood pressure.

What is known about this topic

- Resistant hypertension prevalence ranges from around 5–30% of treated hypertensive patients[20] and is associated with higher- target end-organ damage and overall cardiovascular risk than patients with controlled hypertension.[3,6,7,9–11]
- About one third of patients with suspected resistant hypertension have indeed white-coat resistant hypertension.[3–5] Ambulatory blood pressure monitoring is a useful tool to confirm the refractoriness of hypertension.
- The prevalence of microalbuminuria as defined by urinary albumin excretion $\geqslant 30$ mg/24 h and < 300 mg/24 h in patients with resistant hypertension ranges from around 17–29%.[7,12,13]

What this study adds

- This study shows that urinary albumin excretion is the clinical variable that better associates with true resistant hypertension in comparison with patients who have white-coat resistant hypertension.
- We have also found that 15 mg/24 h, a lower than usual cut-off of urinary albumin excretion, seems to be a reliable threshold of microalbuminuria to identify them.

Conflict of interest

The authors declare no conflict of interest.

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