Urotensin II and Cardiomyopathy in End-Stage Renal Disease

Carmine Zoccali, Francesca Mallamaci, Frank Antonio Benedetto, Giovanni Tripepi, Patrizia Pizzini, Sebastiano Cutrupi, Lorenzo Malatino

Abstract—Circulating urotensin (UTN) is increased in patients with heart failure and in patients with renal diseases, and UTN antagonism is currently considered as a potential treatment for these conditions. Contrary to this contention, studies in end-stage renal disease suggest that, perhaps because of interference with sympathetic and NO systems, UTN may be cardioprotective. Therefore, we investigated the relationship between circulating UTN and echocardiographic parameters of left ventricular function (midwall fractional shortening), left atrial volume, and myocardial geometry (mean wall thickness and relative wall thickness) in 191 patients with end-stage renal disease. UTN was associated directly \((r=0.39; P<0.001)\) with left ventricular systolic function and inversely with left atrial volume \((r=-0.40; P<0.001)\) and the muscular component of the left ventricular (UTN versus mean wall thickness: \(r=-0.30, P<0.001\); UTN versus relative wall thickness: \(r=-0.32, P<0.001\)). Adjustment for a series of 11 risk factors produced a relatively small change in the strength of these relationships. However, further adjustment for plasma norepinephrine or, particularly so, for the endogenous inhibitor of NO synthase asymmetrical dimethyl arginine produced a 33% to 50% decrease in the strength of such associations. Of note, there was a strong UTN-asymmetrical dimethyl arginine interaction in determining midwall fractional shortening \((P=0.001)\) and mean wall thickness \((P=0.006)\). These data support the hypothesis that high UTN is cardioprotective in end-stage renal disease and that interference by UTN with sympathetic activity and NO synthesis represents an intermediate mechanism mediating the favorable echocardiographic profile of patients with high UTN. Additional mechanistic insights may be needed before launching long-term clinical trials with UTN antagonists in patients with end-stage renal disease. (Hypertension. 2008;51:326-333.)

Key Words: asymmetrical dimethyl arginine ■ cardiomyopathy ■ cardiovascular risk ■ end stage renal disease ■ sympathetic activity ■ urotensin II
serve to mitigate the high risk associated with sympathetic overactivity and NO inhibition in ESRD. This hypothesis was corroborated by cognate observations showing that high plasma UTN predicts better clinical outcomes, ie, reduced CV complications in ESRD and longer survival in patients with stage 3 to 4 chronic kidney disease. Of note, in ESRD, UTN is strongly related in an inverse fashion with relatively low UTN levels than in those with relatively higher levels and vice versa.

To have an insight into this problem, we have now studied the relationship among UTN, LV systolic function, and parameters of LV mass in a large population of patients with ESRD. Analyses described in this study coherently demonstrate that high UTN is associated with better-preserved LV systolic function and with lower LV myocardial wall hypertrophy in this population.

Methods

Protocol

The protocol was in conformity with the ethical guidelines of our institution, and informed consent was obtained from each participant. To minimize the effect of cyclic variations of body fluid volume status on echocardiographic parameters, all of the measurements were performed during a midweek nondialysis day, always between 8 AM and 1 PM.

Patients

A total of 191 hemodialysis patients (106 mol/L; 85 women) who had been on regular dialysis treatment for ≥6 months (median duration of regular dialysis treatment: 43 months; interquartile range: 20 to 105 months) without intercurrent cardiac ischemia or other intercurrent illnesses or history of congestive heart failure were considered eligible for the study. Patients were being treated three weekly with standard bicarbonate dialysis (Na: 138 mmol/L; HCO3: 35 mmol/L; K: 1.5 mmol/L; Ca: 1.25 mmol/L; Mg: 0.75 mmol/L) by cuprophane or semisynthetic membranes (dialysis filters surface area: 1.1 to 1.7 m²). Dry weight was established for each patient on a trial-and-error basis and was defined as the weight below which the patient suffered frequent hypotensive episodes during the latter part of the dialysis session and experienced malaise, cramps, and dizziness postdialysis. The average fractional urea clearance in these patients was 1.21±0.27.

Laboratory Measurements

Blood sampling was performed after an overnight fast between 8 AM and 10 AM always during a nondialysis day, before the echocardiographic study (see below). After 20 to 30 minutes of quiet resting in a semirecumbent position, samples were taken into chilled EDTA Vacutainers, placed immediately on ice, centrifuged within 30 minutes at −4°C, and the plasma stored at −80°C before assay. Serum cholesterol, albumin, calcium, and phosphate measurements were made using standard methods in the routine clinical laboratory. The methods of measurement of plasma norepinephrine, C-reactive protein (CRP), and plasma ADMA were reported elsewhere.

Plasma UTN was determined by a high-sensitivity enzyme immunoassay using an antibody (Phoenix Pharmaceuticals) that does not cross-react with endothelin-1, angiotensin II, adrenomedullin, calcitonin gene–related peptide, and brain natriuretic peptide. Furthermore, investigations specifically related to the present study were performed at Phoenix Laboratories to test the cross-reactivity of this antibody with human pre-pro UTN (10-125), UTN-related peptide, and UTN 4or11 and 5-11 fragments. These additional studies showed no cross-reactivity (0%) with pre-pro UTN, 19.8% cross-reactivity with UTN-related peptide, and 15% and 22% cross-reactivity with UTN 4-11 and 5-11 fragments. The intra-assay coefficient of variation was 12%, and all of the samples were processed in a single assay. Plasma UTN was also measured in a group of 167 normotensive healthy subjects with normal serum creatinine (estimated glomerular filtration rate: >80 mL/min) well matched to ESRD patients as for age (average age: 58 years; 131 males and 36 females).

Echocardiography

These studies were performed within 2 hours after blood sampling. All of the echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography by an observer unaware of biochemical results. LV mass was calculated according to the Devereux formula and indexed to height1/2 (LVM/H). LV hypertrophy (LHV) was defined by an LVM of ≥47 g/m² in women or ≥50 g/m² in men. The height-based indexing of LV mass was specifically chosen to minimize any potential distortion attributable to extracelluar volume expansion (surface area indexing being weight sensitive). Mean wall thickness (MWT) was calculated by the standard formula [MWT= (posterior wall thickness+interventricular septum thickness)/2]. The relative wall thickness (RWT: 2*posterior wall thickness/LV end diastolic diameter) was also calculated as an index of the LV geometric pattern. Systolic function was measured by mean wall fractional shortening (mwsF) according to the method of Shimizu et al as described in full detail by De Simone et al. We elected to use this parameter because of its high reliability and because in patients with ESRD it is an indicator of LV systolic dysfunction more sensitive than the standard ejection fraction. Left atrial volume (LAV) was calculated by the biplane area-length method from the apical 4-chamber and 2-chamber views, and measurements were obtained at the end of left ventricle systole.

Statistical Analysis

Data are reported as mean±SD, median, and interquartile range, or as the percentage of frequency, as appropriate. Data that did not show a Gaussian distribution were log transformed before the correlation study.

The independent relationship between plasma UTN and echocardiographic parameters was tested in statistical models of increasing complexity. In a first model we adjusted for classical (Framingham) risk factors (age, sex, smoking, diabetes, cholesterol, and systolic pressure), previous CV events, risk factors peculiar to ESRD (hemoglobin, calcium×phosphate product, duration of regular dialysis treatment, and CRP). To explore the etiologic hypothesis that UTN, endothelial dysfunction, and sympathetic activity are in the same causal pathway leading to cardiomyopathy, we also modeled parameters of LV function and LV geometry by separately testing the effect of ADMA and norepinephrine on the multivariate regression coefficient (first model) of plasma UTN. Furthermore, we performed a formal analysis of the biological interaction between UTN and plasma ADMA according to the method described by Greenland and Rothman. The association of UTN with concentric LVH was tested by univariate and multivariate logistic regression analysis.

Multivariate models were all of adequate statistical power (≥17 patients for each variable in the final model). Data are expressed as the standardized regression coefficient (β) and P value. All of the calculations were done using a standard statistical package (SPSS 9.0.1).

Results

The prevalence of diabetes mellitus in the study population was 15% (ie, 28 patients of 191). Ninety-four patients had had ≥1 backward CV complication. In particular, 46 patients had had 1 CV event (myocardial infarction in 5 cases, anginal episodes in 25 cases, peripheral artery diseases in 9 cases,
Plasma UTN was twice higher (P < 0.01) than that in healthy subjects (median: 3.3 ng/mL; interquartile range: 2.4 to 4.6 ng/mL). UTN was above the upper limit of the reference range (cutoff: 3.7 pg/mL) in the majority of patients (129 of 191 [67%]) and was similar (P = 0.37) in diabetic (6.2; interquartile range: 2.8 to 11.2 ng/mL) and nondiabetic patients (7.2; interquartile range: 3.8 to 12.1 ng/mL).

In Table 1 the study population is categorized on the basis of the median value on plasma UTN. Patients with plasma UTN higher than the median value were older, were more frequently treated with antihypertensive drugs, and had lower heart rates. Furthermore, they showed lower plasma levels of ADMA and norepinephrine but did not differ as for sex, smoking habits, diabetes mellitus, background CV complications, serum calcium and phosphate, and their product or CRP. Of note, mwFS was 16% higher in patients with UTN, more than the median value in the other group. MWT, RWT, and LAV, as well as LVMI and the prevalence of LVH, were all lower in patients with UTN above the median value compared with those below the median. Univariate regression analyses substantially confirmed these associations (Table 1, last column). The association between UTN and mwFS, MWT, RWT, and LAV is presented in detail in Figure 1. Again, UTN was strongly related in a direct fashion with LV systolic function (mwFS). In addition, it was also correlated inversely with the muscular component of the left ventricle (MWT and RWT) and with LAV but was independent of the cavitary component (LV end diastolic diameter). Such an anatomic association pattern indicated that UTN is specifically associated with concentric LVH. Indeed, UTN was substantially lower in patients with concentric LVH (median: 3.2 pg/mL; interquartile range: 1.9 to 14.9 pg/mL) than in
those with eccentric LVH (median: 7.3 pg/mL; interquartile range: 3.4 to 11.5) or normal LVMI (median: 9.8 pg/mL; interquartile range: 6.3 to 14.9 pg/mL; \( P < 0.001 \)). Accordingly, in a logistic regression analysis, a 1-pg/mL increase in plasma UTN predicted an 8% lower risk for concentric LVH (odds ratio: 0.92; 95% CI: 0.87 to 0.97; \( P = 0.004 \)).

**Multivariate Analyses**

On multivariate analysis adjusting for a large series (\( n = 11 \); see Table 2 and Figure 2, model 1) of risk factors, including Framingham risk factors, background CV complications, hemoglobin, calcium-phosphate product, CRP, and duration of dialysis treatment (Figure 2, model 1), produced a relatively modest change in the correlation coefficient (\( \beta \)) of the UTN-LV systolic function (mwFS) relationship. Addition into this model of either norepinephrine (Figure 2, model 2) or, even more, of ADMA (Figure 2, model 3), produced a relatively much-pronounced reduction in the strength of this link, which nonetheless remained highly significant. Likewise, the UTN-MWT, UTN-RWT, and UTN-LAV links underwent only a relatively mild change in the correlation coefficients of these relationships in analyses adjusting for model 1 covariates (Table 2), but again these associations, although significant, became relatively much weaker in models adjusting either for norepinephrine or ADMA (Figure 2). In multivariate logistic regression analysis adjusting for the 11 variables listed in Table 2, a 1-pg/mL higher plasma UTN predicted a 6% lower risk for concentric LVH (\( P = 0.05 \)). Of note, UTN interacted with ADMA in determining mwFS (\( P = 0.001 \)) and MWT (\( P = 0.006 \)). Indeed, in patients with ADMA below the median value, both mwFS and MWT were unaffected by UTN being similar in patients with low and high UTN, whereas in patients with ADMA above the median value, those with high UTN exhibited relatively higher mwFS and lower MWT (Figure 3).

**UTN and Echocardiographic Parameters in Patients Without Background CV Complications**

Because patients with background CV events constitute a very high risk category in the ESRD population, we performed separate analyses restricted to the 97 CV event-free patients. In these analyses, the strength of the associations between UTN and mwFS (\( \beta = 0.36; P = 0.001 \)), MWT (\( \beta = -0.27; P = 0.008 \)), RWT (\( \beta = -0.33; P = 0.001 \)), and LAV (\( \beta = -0.22; P = 0.04 \)) did not differ from that found in the whole study population. Furthermore, multivariate analyses confirmed that these links, although still significant, were to an important extent reduced after the adjustment for norepinephrine (\( \beta \) decrease: 12% to 26%) and for ADMA (\( \beta \) decrease: 21% to 37%).

**Discussion**

High-plasma urotensin is a marker of relatively well-preserved LV systolic function and LV geometry in patients with ESRD. These cross-sectional data are in keeping with prospective cohort studies indicating that high UTN predicts a lower incidence of CV events in patients with ESRD and generates the hypothesis that a favorable effect of UTN on
cardiomyopathy may contribute to the cardiovascular-protective effect of this peptide in these patients.

**Urotensin in Renal Diseases and in ESRD**

The kidney is an important organ for UTN synthesis. The parent compound pre-pro-UTN is highly expressed in endothelial and smooth muscle cells of renal vessels, as well as in tubular cells, and it is excreted in the urine at concentrations substantially higher than the plasma UTN concentration. The kidney synthesizes relevant amounts of UTN, and together with the lung and the liver actively secretes UTN into the systemic circulation. Thus, similar to other autacoids, UTN may also act as a circulating hormone. Plasma UTN is much increased in patients with renal diseases, including minimal change glomerulopathy, diabetic nephropathy, chronic kidney disease in general, and ESRD in particular.

**UTN and Cardiomyopathy in ESRD**

LHV is an adaptive process aimed at minimizing ventricular wall stress. Several factors, including hypertension, anemia, hyperparathyroidism, high sympathetic activity, and accumulation of ADMA, all contribute to increase LV mass in ESRD. Contrarily to in vitro studies showing that UTN promotes myocardial cell growth, we found that UTN is associated directly with LV systolic function and inversely with the muscular component of LV mass (mWFS) and with LAV, ie, a parameter that, in dialysis patients, in large part reflects diastolic dysfunction. Overall, these coherent relationships imply that high UTN may have a cardioprotective effect in uremic humans. Of note, these relationships were largely independent of arterial pressure, Framingham risk factors, and risk factors peculiar to ESRD. ESRD is a situation that imposes a combined volume and pressure overload to the left ventricle and that entails a very high risk for CV death, ie, a risk 100 times higher than that in the coeval general population. The favorable LV function profile in patients with high UTN that emerged in this survey is in keeping with previous studies indicating that high UTN heralds a lower mortality risk in patients with myocardial infarction, a reduced risk for incident CV events in patients with ESRD, and a lower mortality in stage 3 to 5 chronic kidney disease patients.

### Table 2. Multiple Regression Analysis of Multiple Models of mWFS, MWT, RWT, and LAV

<table>
<thead>
<tr>
<th>Covariates</th>
<th>β (P)</th>
<th>95% CI of β</th>
<th>Covariates</th>
<th>β (P)</th>
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<th>Covariates</th>
<th>β (P)</th>
<th>95% CI of β</th>
<th>Covariates</th>
<th>β (P)</th>
<th>95% CI of β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urotensin</td>
<td>0.34 (&lt;0.001)</td>
<td>0.19 to 0.47</td>
<td>Age</td>
<td>-0.13 (0.08)</td>
<td>-0.27 to 0.03</td>
<td>Urotensin</td>
<td>-0.24 (&lt;0.001)</td>
<td>-0.38 to -0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.08 (0.28)</td>
<td>-0.23 to 0.08</td>
<td>Sex</td>
<td>0.03 (0.69)</td>
<td>-0.13 to 0.18</td>
<td>Sex</td>
<td>0.03 (0.69)</td>
<td>-0.13 to 0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>-0.08 (0.31)</td>
<td>-0.23 to 0.07</td>
<td>Smoking</td>
<td>0.11 (0.16)</td>
<td>-0.04 to 0.26</td>
<td>Smoking</td>
<td>0.11 (0.16)</td>
<td>-0.04 to 0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.22 (0.002)</td>
<td>-0.35 to -0.08</td>
<td>Diabetes</td>
<td>0.10 (0.14)</td>
<td>-0.04 to 0.23</td>
<td>Diabetes</td>
<td>0.10 (0.14)</td>
<td>-0.04 to 0.23</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.05 (0.51)</td>
<td>-0.18 to 0.09</td>
<td>Cholesterol</td>
<td>0.003 (68)</td>
<td>-0.11 to 0.16</td>
<td>Cholesterol</td>
<td>0.003 (68)</td>
<td>-0.11 to 0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous CV events</td>
<td>-0.05 (0.51)</td>
<td>-0.19 to 0.11</td>
<td>Previous CV events</td>
<td>0.007 (0.38)</td>
<td>-0.09 to 0.21</td>
<td>Previous CV events</td>
<td>0.007 (0.38)</td>
<td>-0.09 to 0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>0.01 (0.87)</td>
<td>-0.13 to 0.14</td>
<td>Hb</td>
<td>0.007 (32)</td>
<td>-0.21 to 0.08</td>
<td>Hb</td>
<td>0.007 (32)</td>
<td>-0.21 to 0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>-0.06 (0.34)</td>
<td>-0.20 to 0.07</td>
<td>CRP</td>
<td>0.05 (0.46)</td>
<td>-0.08 to 0.19</td>
<td>CRP</td>
<td>0.05 (0.46)</td>
<td>-0.08 to 0.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca×P</td>
<td>-0.08 (0.25)</td>
<td>-0.21 to 0.06</td>
<td>Ca×P</td>
<td>0.006 (0.34)</td>
<td>-0.07 to 0.20</td>
<td>Ca×P</td>
<td>0.006 (0.34)</td>
<td>-0.07 to 0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDT duration</td>
<td>0.15 (0.04)</td>
<td>-0.30 to -0.003</td>
<td>RDT duration</td>
<td>0.16 (0.003)</td>
<td>0.01 to 0.31</td>
<td>RDT duration</td>
<td>0.16 (0.003)</td>
<td>0.01 to 0.31</td>
<td></td>
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</tr>
</tbody>
</table>

Data are expressed as standardized regression coefficient (β) and P value. RDT indicates regular dialysis treatment; BP, blood pressure; Hb, hemoglobin.
Importantly, in this study we found that the association of UTN with LV systolic function and LV wall thickness holds true in ESRD patients without background CV events, implying that these links are not confined to patients with very advanced CV disease but apply also to the ESRD population with milder forms of cardiomyopathy.

Although in vitro studies and the hemodynamic response to acute injections of UTN are of importance for unraveling mechanisms whereby this compound interferes with the CV system, experiments based on chronic infusion of UTN seem of paramount importance, because these experiments better reproduce the steady-state situation in diseases characterized by high UTN levels. To date, only 2 studies of chronic infusion of UTN have been performed in experimental models. In the first study, UTN administered intravenously for 2 weeks to Sprague-Dawley rats did not change BP but reduced myocardial contractility. More recently, Harris et al investigated the effect of UTN in chronically volume-overloaded rats (aortocaval fistula). Intriguingly, UTN in this model caused a marked improvement in LV contractility, as well as a clearcut decrease in LV end diastolic pressure as compared with UTN-treated control rats. Of note, these changes were associated with normalization in the expression of all of the Ca regulatory proteins in myocardial cells (SERCA-2, Na/Ca exchanger, and phospholamban), which were overtly deranged in the corresponding control model. Altogether, these findings suggest that UTN during chronic

**Figure 2.** Multivariate modeling of mwFS, MWT, RWT, and LAV. Model 1 covariates are presented in full detail in Table 2. \( \beta \) is the correlation coefficient of these models. In models 2 and 3, the correlation coefficient of model 1 is sequentially adjusted for norepinephrine and ADMA.

**Figure 3.** Interaction between ADMA and UTN in determining mwFS. Data were appropriately adjusted according to statistical models described in Table 2.
volume overload positively affects cardiac performance by favorably modulating the expression of Ca-regulatory proteins in myocardial cells. Chronic volume overload increases in width and in length the muscular component of the LV without modifying chamber volume in the compensated phase of cardiomyopathy. Thus, our data showing that high UTN in ESRD patients is associated with better LV systolic function but relatively lower LV myocardial thickness and LAV are in keeping with these experimental findings in the volume-overloaded rat.

**Are UTN, Norepinephrine, and ADMA in a Causal Pathway Leading to LVH and LV Dysfunction in ESRD?**

In multivariate analyses adjusting for traditional and nontraditional risk factors for LV dysfunction and LVH including emerging risk factors like norepinephrine and ADMA, high UTN was coherently confirmed as an independent correlate of relatively better-preserved LV systolic function and lower LV myocardial thickness and LAV. However, we also noted that whereas adjustment for a series of 11 risk factors, including Framingham risk factors, produced a relatively small change in the strength of these relationships, adjustment for norepinephrine or, particularly so, for ADMA produced a 33% to 50% decrease in the strength of such associations. We believe that this observation may underlie a pathophysiological pathway impinging on LV function and geometry, which encompasses UTN and the sympathetic and NO systems. Norepinephrine and ADMA are considerably raised in patients with LV dysfunction, and both high norepinephrine and high ADMA are implicated in the risk for CV events and in LV disorders in ESRD patients. It was observed that these 2 factors are not only strongly interrelated but are also in the same pathway, with ADMA perhaps acting downstream to norepinephrine, leading to CV complications in this population. This hypothesis was also supported by interaction analysis showing that, selectively in patients with high ADMA (Figure 3), concomitantly high UTN levels denote a favorable echocardiographic profile, i.e., relatively higher mwFS and relatively lower MWT and LAV. Altogether, our data in ESRD patients are in keeping with the favorable action of UTN administration in the chronic volume overload model in the rat and suggest that mitigation of the deleterious effects of sympathetic overactivity and, particularly so, of endogenous NO inhibition by ADMA may be a mechanism underlying the protective effect of UTN in this condition.

**Study Limitations**

The first limitation of this study is that it is based on the measurement of peripheral venous UTN, which may not reflect local expression of this peptide in the heart. A second limitation of our study derives from its cross-sectional design. As discussed previously, high UTN may be causally involved in the modulation of LV systolic dysfunction in dialysis patients. However, the opposite viewpoint is possible in theory. In other words, it can also be hypothesized that cardiac disease lowers plasma UTN, as seems to be the case in acute coronary syndromes. The issue of causality cannot be resolved on the basis of the present cross-sectional data. Finally, it is important to note that because of the relative imprecision of the method of measurement of circulating UTN, because of regression dilution bias, our study may substantially underestimate the true association between UTN and echocardiographic parameters of the left ventricle in dialysis patients.

**Perspectives**

High-circulating UTN is associated with better LV systolic function, less pronounced myocardial wall thickness, and lower LAV in patients with ESRD. Increased UTN is a strong predictor of a lower risk for CV events in these patients. Our data lend support to the hypothesis that a UTN-dependent protective effect on uremic cardiopathy may represent an intermediate mechanism mediating the favorable effect of this peptide on CV outcomes in these patients. Urotensin antagonists are being tested in patients with renal diseases. Although preliminary results indicate that UTN antagonism is well tolerated, we believe that, at this stage of knowledge, mechanistic insights are still needed before launching long-term clinical trials based on solid outcome measures like death and CV events in patients with ESRD.

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**Disclosures**

None.

**References**

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