GFR, proteinuria and circadian blood pressure

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Abstract

Background. Hypertension is common, and arterial pressure rhythms are impaired in patients with chronic kidney disease (CKD). Emerging evidence suggests that consideration of excretory function together with proteinuria may provide a more holistic assessment of the extent of derangement in renal function.

Methods. To evaluate the independent relationships of estimated GFR and proteinuria with the mean level of and the circadian variation in blood pressure, we evaluated 336 patients, 184 (55%) patients with CKD (eGFR <60 or urine protein/creatinine >0.22) and 152 (45%) without CKD.

Results. The mean level of systolic and diastolic BP increased with increasing severity of proteinuria as well as with increasing impairment in GFR. When proteinuria and eGFR were considered together in the same regression model, proteinuria—not eGFR—was related to the severity of hypertension. Non-dipping was present in 52% of those with eGFR >60 and 55% in those with no proteinuria. Non-dipping was seen early in the course of impaired GFR or proteinuria. Adjusted for proteinuria, the odds ratio for non-dipping in those with CKD was 1.71 (95% CI 1.03–2.84, \(P = 0.036\)). The odds ratio for non-dipping in those with proteinuria was 1.75 (95% CI 1.00–3.08, \(P = 0.049\)) when adjusted for CKD. A cosinor model that evaluates the midline estimating statistic of rhythm (MESOR) and circadian variation revealed that proteinuria was a stronger determinant of MESOR compared to the CKD stage; the CKD stage in addition to proteinuria did not further add to the determination of MESOR. The amplitude of variation was markedly blunted in patients with the earliest stages of derangement in kidney function whether it was assessed by proteinuria or eGFR.

Conclusions. These results demonstrate a graded relationship of proteinuria and eGFR with the mean level of BP and a non-graded relationship with circadian variation. Consideration of these two simple tests of renal function may better assist in gauging the severity of hypertension in patients with CKD.

Keywords: ambulatory BP monitoring; diagnostic test; haemodialysis; home BP; hypertension

Introduction

The assessment of renal excretory function commonly made by the measurement of serum creatinine and estimating the glomerular filtration rate (GFR) is of critical importance in the management of patients with CKD. Proteinuria, although not a marker of excretory function, nonetheless represents, in a qualitative and ill-defined way, the sum of kidney podocyte, vascular and tubular functions. It is hardly surprising that proteinuria has emerged as a strong marker of the future deterioration in GFR and the occurrence of cardiovascular events [1]. It stands to reason that the joint assessment of GFR and proteinuria in patients with CKD may provide a more complete assessment of the extent of derangement in renal function that ultimately may provide insights into why hypertension in patients with CKD is so hard to treat [2].

Not only is hypertension very common among patients with CKD, arterial pressure rhythms are often impaired such that the nocturnal decline in BP is abrogated, abolished or reversed in these patients [3]. The degree of impairment of GFR or extent of proteinuria may determine the severity of hypertension or the level of derangement in circadian blood pressures. Although the relationships of GFR, hypertension and dipping are well established [3–7], that proteinuria may be associated with severity of hypertension is less well recognized [8–11]. More importantly, the independent relationship of proteinuria with non-dipping that leads to a higher nocturnal BP is poorly understood.

The measurement of nocturnal BP is more than a physiological curiosity. In children and adolescents with type 1 diabetes and no clinical kidney disease including the absence of microalbuminuria, nocturnal BP elevation was related to the presence of glomerulopathy [12]; thus nocturnal hypertension was able to reveal the presence of subclinical renal disease. More importantly, night time BP elevation could predict the morphological changes of diabetic nephropathy in these patients [13]. In patients with type 1 diabetes mellitus, the lack of nocturnal dipping predicted the future occurrence of albuminuria [14]. Measurement of ambulatory BP could predict the occurrence of proteinuric pre-eclampsia [15]. In patients with CKD, non-dipping was related to...
faster progression of kidney disease [16]. However, in the latter study, proteinuria was not measured. If proteinuria affects dipping, then it is possible that the faster progression reported earlier may be confounded by the occurrence of proteinuria. Thus, it is important to understand the unique contribution of estimated GFR (eGFR) and proteinuria on the circadian pattern and overall BP.

The purpose of this analysis was to understand the independent contribution of eGFR and proteinuria with the mean level of BP as well as dipping in patients with and without CKD. Although the above models are simpler to analyse and describe, the joint relationships of eGFR and proteinuria on overall BP and circadian changes were analysed using a more robust rhythmometric cosinor model.

Methods

Study cohort

This prospective study recruited consecutive patients (n = 336) from the renal clinic and a general medicine clinic of the Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis. The patients were excluded for a body mass index (BMI) > 40 kg/m², acute renal failure, receiving renal replacement therapy, atrial fibrillation or change in their antihypertensive drugs within 2 weeks of study enrolment. Chronic kidney disease (CKD) was defined as the presence of proteinuria on a spot urine specimen when the protein/creatinine ratio was 0.22 g/g or more, or eGFR was < 60 mL/min/1.73 m² by the four-component MDRD formula: 186 × creatinine − 1.154 × age − 0.203 × 0.744 if female and × 1.21 if black [17]. Serum creatinine was not calibrated to Cleveland Clinic. A urine protein/creatinine ratio of > 0.22 g/g correlates with a urine protein excretion of > 300 mg/day, the standard definition of clinical proteinuria [18]. Accordingly, we selected this threshold of a urine protein/creatinine ratio to reflect CKD. The urine protein/creatinine ratio was measured on a single spot urine specimen collected either before or after ambulatory BP monitoring.

The Institutional Review Board of Indiana University and the Research and Development Committee of the VA Medical Center approved this study, and all patients gave their written, informed consent.

Ambulatory blood pressures

The patients underwent 24-h ambulatory BP monitoring with the Space-labs 90207 monitor (Space-labs, Inc., Redmond, WA, USA), a monitor that has been validated by the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. The monitor recorded BPs every 20 min during the day (06:00–22:00) and every 30 min at night (22:00–06:00). The patients recorded their sleep and wake times during the ambulatory BP monitoring. These times were used to calculate sleep and wake averages. Ambulatory BP monitoring was considered adequate if 14 systolic and diastolic measurements were obtained during the day and 7 during the night based on the guidelines of the European Society of Hypertension [19]. Dipping was defined as a sleep/wake mean arterial pressure ratio of 0.9 or less [20].

Statistical analysis

A linear mixed model with maximal likelihood estimation was used to analyse the data [21]. These analyses take into account the correlated nature of the observations and missing data [22].

We divided patients into four clinically relevant groups: eGFR > 60, 45–60, 30–45 and < 30 mL/min/1.73 m². We also divided patients into four clinically relevant severities of proteinuria: protein/creatinine ratios < 0.22 g/g; 0.22–1; 1–3 and > 3 that correlate with no, mild, moderate and severe proteinuria, respectively. The average ambulatory BP was calculated for each patient, and a mixed model with maximal likelihood estimation was used to estimate the effect of categories of proteinuria and categories of eGFR on systolic and diastolic BP, respectively. To calculate the effect of GFR and proteinuria on non-dipping, we calculated the Mantel–Henzel odds ratios for non-dipping in GFR categories adjusted for proteinuria and then we calculated the odds ratios for non-dipping in proteinuria categories adjusted for GFR categories. Dipping was also modelled as a continuous variable (higher fractions mean less dipping) with proteinuria and GFR categories as predictors. Proteinuria was defined as a spot protein/creatinine ratio of < 0.22 and CKD as a GFR of < 60 mL/min/1.73 m². An interaction effect between CKD and proteinuria was also tested.

The mean level and circadian pattern in arterial pressure during the 24-h period were analyzed with the cosinor change model [23]. This method entails fitting an oscillating curve to temporal haemodynamic variables with a 24-h periodicity. The cosinor model describes the rhythmic cycle as y = b0 + b1 × Cos[2πt/24] + b2 × Sin[2πt/24], where y represents the observed systolic BP, diastolic BP or pulse pressure; b0, b1 and b2 are regression coefficients; and t represents time elapsed after midnight in hours. The constant 2π/24 represents the 24-h periodicity of BP. The coefficient b0 represents the 24-h rhythm-adjusted average intercept value of arterial pressure. The regression coefficients b1 and b2 are the coefficients for the cosine and sine components, respectively, and collectively describe the amplitude of the cosine curve, which is defined as amplitude = √(b1² + b2²). The amplitude represents half the extent of rhythmic change in a cycle approximated by the fitted curve, which implies that it can be interpreted as the mean deviation across the time span. Thus, the model considers the intercept and an oscillatory change in a unified manner. Using the above cosinor model, we examined the effects of proteinuria and eGFR on the intercept and the amplitude of the variation in arterial pressure.

All analyses were performed using Stata 10.0 (Stata Corp. College Station, TX). P-values are two sided and significance set at 0.05. R.A. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Results

Of the 336 patients, 184 (55%) patients had CKD (estimated GFR < 60 mL/min/1.73 m² or urine protein/creatinine > 0.22) and 152 (45%) had no CKD. The baseline characteristics of these groups are shown in Table 1. As would be expected, patients with CKD had lower GFR, more proteinuria, higher BUN and lower haemoglobin. Patients with CKD were also older and tended to use less tobacco and alcohol. There were no differences in sex and race distribution between groups. Patients with CKD had more gout, diabetes mellitus, coronary artery disease and peripheral vascular disease and also used nearly twice as many antihypertensive drugs.

At any level of GFR, worse proteinuria was a determinant of higher systolic and diastolic BP (P < 0.0001 for both systolic and diastolic BP). Patients with worse GFR had greater proteinuria (chi square 104.6, P < 0.0001). Therefore, when proteinuria was not considered in the model, the CKD stage had a pronounced effect on systolic and diastolic BP. However, when proteinuria was accounted for, the CKD stage did not independently add to the prediction of either systolic or diastolic BP (P > 0.2). Thus, proteinuria but not eGFR was related to systolic and diastolic BP (Figure 1).

We defined reduction in the mean arterial pressure from wake to sleep of > 10% as dipping. Figure 2 shows that the proportion of non-dippers was 52% in people with normal eGFR, 69% in those with stage 3A CKD, 68% in those with stage 3B CKD and 74% in those with more advanced CKD (chi square 13.0, P = 0.005). The proportion of non-dippers was 55% in people with no proteinuria, 78% in those with mild proteinuria, 67% in those with moderate proteinuria and 77% in those with severe proteinuria (chi square 13.6, P = 0.004). The prevalence of non-dipping increased in a quantum fashion at the earliest stage of CKD or proteinuria.
Table 1. Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>All patients</th>
<th>No CKD</th>
<th>CKD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>336 (100%)</td>
<td>152 (45%)</td>
<td>184 (55%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.5 (12.6)</td>
<td>59.4 (13.1)</td>
<td>68.6 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>321 (96%)</td>
<td>145 (95%)</td>
<td>176 (96%)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>White</td>
<td>259 (77%)</td>
<td>115 (76%)</td>
<td>144 (78%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>74 (22%)</td>
<td>36 (24%)</td>
<td>38 (21%)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.3 (22.1)</td>
<td>93.8 (23.7)</td>
<td>92.8 (20.8)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.1 (6.3)</td>
<td>29.7 (6.6)</td>
<td>30.3 (6.6)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Alcohol user</td>
<td>78 (23%)</td>
<td>50 (33%)</td>
<td>28 (15%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Current</td>
<td>81 (24%)</td>
<td>47 (31%)</td>
<td>34 (19%)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>187 (56%)</td>
<td>68 (45%)</td>
<td>119 (65%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>67 (20%)</td>
<td>37 (24%)</td>
<td>30 (16%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>114 (34%)</td>
<td>27 (18%)</td>
<td>87 (47%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of gout</td>
<td>52 (15%)</td>
<td>9 (6%)</td>
<td>43 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>118 (35%)</td>
<td>40 (26%)</td>
<td>78 (42%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>43 (13%)</td>
<td>15 (10%)</td>
<td>28 (15%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>47 (14%)</td>
<td>5 (3%)</td>
<td>42 (23%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The Mantel–Henzel odds ratio for non-dipping in those with CKD was 1.71 (95% CI 1.03–2.84, P = 0.036) when stratified for proteinuria. The Mantel–Henzel odds ratio for non-dipping in those with proteinuria was 1.75 (95% CI 1.00–3.08, P = 0.049) when stratified for CKD.

Figure 3 shows that both CKD (beta 0.039, P = 0.001) and proteinuria (beta 0.025, P = 0.047) were associated with dipping defined as the ratio of sleep to awake mean arterial pressure. Compared to the reference group of patients with no CKD and no proteinuria (eGFR >60 and protein/creatinine <0.22), patients with CKD and no proteinuria had less dipping. In the group with proteinuria, the presence of CKD reduced the mean dipping ratio by a degree that was similar to the group without proteinuria. In other words, no interaction effect between proteinuria and CKD was seen. Similar results were obtained for dipping defined as the ratio of sleep to awake systolic BP.

The effect of eGFR and proteinuria on the mean level of systolic BP and circadian variation is shown in Figure 4. Increasing impairment in renal function was associated with an increasing level of systolic BP. The occurrence of proteinuria had a more profound association with a higher systolic BP. Any impairment of GFR or occurrence of proteinuria was associated with the blunted circadian variation in systolic BP.

The interaction effects of impairment of GFR and the occurrence of proteinuria are explored in Figure 5. The mean systolic ambulatory BP was 127.4 mmHg (95% CI 125.2–129.7) in those without proteinuria or impairment in GFR. In those with CKD alone, the mean systolic BP was 129.2 mmHg (95% CI 126.2–132.2) and in those with proteinuria alone the systolic BP was 139.8 mmHg (95% CI 135.7–143.9). In those with both CKD and proteinuria, the systolic BP averaged 141.6 mmHg (95% CI 138.9–144.3). No interaction effect between CKD and proteinuria was seen. The amplitude of variation in systolic BP in those without CKD or proteinuria was 14.4 mmHg (8.0–20.9 mmHg) which was highly statistically significant (P < 0.0001). In
Proteinuria, GFR, and BP profiles

Fig. 1. Box-plot showing the combined effect of eGFR and proteinuria on the mean 24-h ambulatory systolic and diastolic BP. Compared to the reference group of patients with no CKD (no proteinuria, eGFR > 60, left most box plot), patients with lower GFR but with similar proteinuria had no increment in systolic BP. Similar comparisons can be made for those with mild (0.22–1 g/g creatinine), moderate (1–3 g/g creatinine) or severe (> 3 g/g creatinine) proteinuria that across the GFR categories also do not show an increasing level of BP.

Fig. 2. Prevalence of non-dipping in relation to proteinuria and CKD. The proportion of patients is shown for categories of CKD (left panel) and proteinuria (right panel). Proteinuria was defined as none, protein/creatinine ratio < 0.22 g/g, mild (0.22–1 g/g), moderate (1–3 g/g) and severe (> 3 g/g). CKD was defined as estimated GFR of 45–60 mL/min/1.73 m² (stage 3A), 30–45 mL/min/1.73 m² (stage 3B) and < 30 mL/min/1.73 m² (stages 4 and 5). The presence of CKD was associated with an increased prevalence of non-dipping but increasing severity was not. Likewise, the presence of proteinuria was associated with non-dipping, but increasing severity was not.

those with proteinuria, the amplitude was 3.4 mmHg (−1.9 to 8.6) and in those with CKD it was 4.7 mmHg (−1.0 to 10.5). Neither of these amplitudes was different from zero. Thus, circadian variation in systolic BP was only seen in the absence of CKD and proteinuria.

Discussion

It is generally believed that salt and water overload with advancing renal failure is responsible for the vast majority of hypertension in patients with CKD. A recent study from China supports the notion that patients with advancing CKD have an increasing level of renal failure [24]. The prevalence of isolated systolic hypertension based on office-recorded BP was 28.1% in stage III CKD, 39.4% in stage IV CKD and 45.7% in stage V CKD. Age and the CKD stage were both independent determinants of systolic hypertension. We confirmed these observations using ambulatory BP recordings by finding an increase in the mean systolic and diastolic BP with advancing renal failure. However, lower GFR was also strongly associated with proteinuria. When proteinuria was considered in the model that included GFR, there was no independent effect of impaired kidney function on BP.
In fact, patients with moderate to advanced CKD had levels of BP similar to those with normal kidney function provided they had no proteinuria (Figure 1). However, at any stage of CKD, an increasing level of proteinuria was associated with increasing BP (Figure 1). These data challenge the strongly held belief that impairment of renal function is independently associated with hypertension. Proteinuria is more strongly associated with arterial stiffness [25] and endothelial dysfunction [26]; therefore, it is plausible that proteinuria reflects an arterial-stiffness-associated increase in BP more strongly in older people with CKD. Our data support epidemiological observations in community-based surveys that albuminuria is associated with worse BP control [10].

It is also well established that impairment in GFR can impair the usual decline in BP seen during sleep. Our study confirms these observations and extends them by noting that dipping is not further impaired with advancing stages of renal failure (Figure 2). This provides support for the observations of Rosansky et al. who reported that in 53 older veterans with hypertension, increasing severity of renal dysfunction was not related to the extent of dipping [6]. However, our data are in contrast to that of Farmer et al. who found a direct relationship between plasma creatinine and non-dipping [4]. These differences may be due to differences in populations studied or due to methods used for statistical analyses. More importantly, proteinuria even of mild severity was associated with blunted circadian rhythm and the absence of dipping. The effect of impaired GFR and proteinuria on dipping was additive, not multiplicative (Figure 3). Since non-dipping is associated with proteinuria and also with progression of kidney disease, our study suggests that proteinuria—rather than non-dipping—may be related to progression of kidney disease. As a specific example, Davidson et al. reported that non-dipping was associated with progression of kidney disease, but they did not measure proteinuria [16]. Similarly Farmer et al. associated non-dipping with CKD progression, but did not report proteinuria [7]. Had proteinuria been considered as a reason for progression, the association of non-dipping with progression may have weakened or vanished.

Non-dipping is thought to be a compensatory phenomenon to produce natriuresis in volume-overloaded
patients. If so, then early kidney disease would be associated with volume overload and result in non-dipping. This would explain the high prevalence of non-dipping in patients with mild proteinuria or early impairment of GFR. However, ongoing impairment would not increase the prevalence of non-dipping and simply elevate the overall BP. Thus, the change in pattern of BP would be an earlier sign of kidney disease and/or the occurrence of endothelial dysfunction, which is consistent with the results of other investigators [12,13].

If non-dipping is causally associated with impaired GFR or proteinuria then restoration of dipping may have the potential to heal kidney disease. In an 8-week prospective, uncontrolled study, Minutolo et al. studied 32 non-dippers with GFR <90 mL/min/1.73 m² and with good BP control (daytime BP <135/85 mmHg) [27]. By changing the time of dosing of one of the antihypertensive agents that the patients were receiving from the morning to the evening, the authors reported a decrease in the night/day ratio in 94% of subjects, such that 88% of the patients became dippers. These changes resulted in a modest reduction in 24-h protein excretion. Dietary sodium restriction has also been reported to restore dipping [28,29] and also reduction in albuminuria [30]. These results provide a conceptual framework of modulating proteinuria by restoring the dipping status that may reduce the rate of progression of kidney disease.

There are some limitations to our study. Given that the participants were veterans, we had few women in our study. Thus, the results of the study may not be applicable to women. Also, our sample was composed predominantly of older people and our results may not apply to younger people. Finally, observational studies, such as this, cannot prove causation. Thus, a cause and effect relationship between circadian BP, GFR and proteinuria cannot be established. However, we believe that this is the first prospective study of ambulatory BP monitoring in patients with and without CKD that evaluates the independent effects of proteinuria and renal function on the overall BP, circadian rhythm and the dipping phenomenon. Instead of treating dipping as a dichotomous variable, we used all available data to make statistical inferences.

Our study has clinical and research implications. For the clinicians, our study demonstrates that both the degree of proteinuria and extent of impairment of GFR are associated with elevated ambulatory BP. Thus, masked hypertension should be suspected in patients with well-preserved GFR but proteinuria. For researchers, our study has implications when assessing the prognostic importance of non-dipping. Non-dipping is associated with left-ventricular hypertrophy, strokes and poor long-term outcomes [31]. However, GFR and/or proteinuria are frequently not reported in these studies such that the confounding relationship of these conditions with long-term outcomes cannot be accounted for. Early kidney failure or mild proteinuria can increase the prevalence of dipping. Since renal failure and proteinuria are both linked to poor long-term outcomes, it is quite possible that non-dipping is a marker of kidney disease. Future studies should measure GFR and proteinuria when evaluating the unique contribution of non-dipping to long-term outcomes. Without these measurements, it would be difficult to attribute poor renal and cardiovascular outcomes to non-dipping.

Conflict of interest statement. None declared.

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Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience

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Abstract

Background. The prevalence of glomerular diseases differs according to geographic area, race, age and indications for a renal biopsy. This study was conducted to evaluate the distribution and changing patterns of renal diseases during the past 20 years in a large patient population in Korea.

Methods. Patients aged 16 years or older who underwent a renal biopsy at Severance Hospital in the Yonsei University Health System from 1987 to 2006 were enrolled. All medical records were reviewed retrospectively.

Results. In total, 1818 patients (M:F = 1.02:1) were reviewed. Glomerulonephritis (GN) comprised 85.9% of the total biopsied cases. The most common primary GN was IgA nephropathy (IgAN) (28.3%), which was followed by minimal change disease (MCD) (15.5%), membranous nephropathy (MN) (12.3%), focal segmental glomerulosclerosis (FSGS) (5.6%) and membranoproliferative GN (MPGN) (4.0%). The most common secondary GN was lupus nephritis (8.7%). The most common idiopathic nephrotic syndrome was MCD (38.5%), which was followed by MN and IgAN. Among 128 (7.4%) patients who were HBsAg-positive, MN (30.5%) and MPGN (21.1%) were the most common GN. When the incidence rates between 1987–91 and 2002–06 were compared, IgAN increased from 25.6 to 34.5%, while MCD (from 23.2 to 7.0%) and MPGN (from 6.7 to 1.7%) decreased significantly (P < 0.01).

Conclusions. IgAN was the most common primary GN, and MCD was the most common cause of nephrotic syndrome. In the 5-year quartile comparison, the relative frequency of IgAN increased, while the relative frequency of MCD and MPGN decreased significantly during the past 20 years.

Keywords: adult; glomerulonephritis; nephrotic syndrome; prevalence; renal biopsy

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