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Expanding Insights Into the Role of Nocturnal Blood Pressure Variation in Children

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Ambulatory blood pressure (BP) monitoring, when available, is now the standard of care in diagnosing and treating childhood hypertension. With this, increasing focus is being placed upon the importance of circadian variation in BP and previously difficult to observe phenomena, including nocturnal hypertension and dipping. What are we to make of ambulatory BP monitoring reports relating to these components, such as "isolated nocturnal hypertension" or "inadequate nocturnal dipping"?

Nocturnal hypertension is common among children at increased risk of adverse long-term cardiorenal outcomes, including those with obesity, a history of prematurity, congenital cardiac disease, and solid organ transplant recipients.[1] Compared to daytime measurements, nocturnal BP better predicts cardiac and kidney events in large cohorts of adults.[2] Nocturnal hypertension predicts early cardiovascular damage and progression to kidney failure in children with kidney disease, and future albuminuria in children with type 1 diabetes.[3–5] Large studies among children without similar risk factors are awaited, but there is no reason to suspect these observed relationships would not hold true.

Dipping, or the proportional reduction in BP overnight, is an independent predictor of cardiovascular events among adults after adjustment for nocturnal or 24-hour BP. Nevertheless, the incremental clinical benefit of incorporating dipping into the definition of hypertension beyond daytime, nocturnal, and 24-hour BP is unclear.[6] Similarly, though nondipping is common among children with chronic disease, particularly kidney disease, the clinical value of this measurement in itself is uncertain and isolated nondipping is not considered to meet the definition of hypertension by current ambulatory BP monitoring criteria.[1]

The study by Bakhoum *et al.*,[7] published in this issue of *Kidney International Reports*, expands our understanding of nocturnal dipping, focusing on children with kidney disease who are participating in the Chronic Kidney Disease in Children study. Chronic Kidney Disease in Children is a longstanding, well conducted prospective cohort study capturing the trajectory of children with chronic kidney disease, where data are relatively scarce compared to children with kidney failure. This study included 620 children, among whom a relatively high proportion had progressive chronic kidney disease during the observed period, with 169 children reaching kidney failure across a median follow-up of nearly 3 years. The investigators report both time-to-event analyses (Cox proportional regression) for the outcome of kidney failure and correlated data analysis (linear mixed effect) for the repeated measures of iohexol glomerular filtration rate (iGFR) and urine protein-to-creatinine ratio (uPCR), the explanatory variable of interest being dipping status at baseline and during the study, adjusted for relevant covariates. Consistent with prior research, a threshold of ≥10% reduction in nocturnal BP was used to define a normal dipping status. The results did not demonstrate a statistically significant relationship between dipping status and kidney failure. The hazard ratio for nondipping was 1.08 (95% confidence interval [CI] 0.77–1.51) overall; 1.21 (95% CI 0.53–2.77) and 1.05 (95% CI 0.71–1.55) in those with and without glomerular disease, respectively. Sensitivity analyses, including retaining dipping as a continuous variable, failed to disprove the null hypothesis (hazard ratio 1.01 per 1% systolic dipping, 95% CI 0.98–1.04). Neither dipping status at

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baseline nor dipping status with time predicted either repeated measure (iGFR or uPCR). Baseline 24-hour mean systolic BP, baseline uPCR, and baseline iGFR were all negatively corelated with change in iGFR (i.e., a higher value was associated with a greater decrease in iGFR over time). An older age at entry was associated with an increasing uPCR, whereas a higher baseline iGFR or baseline uPCR was associated with a relative reduction in uPCR over time (noting that the average trend was an increase in uPCR over time).

The Chronic Kidney Disease in Children study is one of the richest sources of data for children with chronic kidney disease internationally. The original study methods were rigorous, and the statistical approach adopted in this analysis was well chosen to answer the authors' question. Nevertheless, the precision about some estimates does not rule out a clinically significant difference, particularly where data were categorized (e.g., for dipping status and kidney failure, where the 95% CI spans a 23% reduction in the hazard ratio to a 51% increase). In addition to participant number, power was limited by the length of follow-up. The latter is made more important by an apparent divergence of the survival curves after approximately 7 years (though the Supremum test was not significant, hypothesis tests to detect a deviation in proportional hazards have limited power for binary events in a dataset of this size).[8] It might be that a longer period of observation is required to observe the effect of dipping status on progression of chronic kidney disease. Measuring changes in intermediate or surrogate markers, such as uPCR and iGFR, can be useful to minimize the chance of missing a distal divergence in effect. To this end, the lack of association between dipping status and either covariate is reassuring.

These data support the exclusion of dipping status from the definition of hypertension in current guidelines. They are also of interest, given the controversy regarding the timing of antihypertensive medication administration. Previous data had supported a role for chronotherapy, the hypothesis being that evening dosing would best maintain or restore nocturnal dipping and thus result in better outcomes compared to morning dosing. However, the large Treatment in Morning versus Evening trial, recently presented at the European Society of Cardiology Congress 2022 failed to demonstrate any benefit to evening dosing (peer-reviewed publication awaited; ISRCTN18157641).

There may be some clinical scenarios or different groups in whom dipping status provides useful information. In children presenting with untreated hypertension, nondipping is associated with secondary causes of hypertension, and reverse dipping (an increase in BP overnight) is often observed among children with renovascular disease.[9] Therefore, though the findings of Bakhoum *et al.*[7] add to the body of evidence against incorporating dipping status into routine follow-up and more specifically for children with kidney disease, we should avoid abandoning the measure altogether. As ambulatory BP monitoring becomes more accessible, we look forward to seeing more studies examining the importance of nocturnal dipping that should further define its role in clinical care.

DISCLOSURE

All the author declared no competing interests.

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