Role of Twenty-Four-Hour Ambulatory Blood Pressure Monitoring in Children on Dialysis

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Summary

Background and objectives Pre- or postdialysis BP recordings are imprecise, can be biased, and have poor test-retest reliability in children on dialysis. We aimed to examine the possible differences between pre- and postdialysis BP levels and 24-hour ambulatory BP monitoring (ABPM) in diagnosis of hypertension (HTN).

Design, setting, participants, & measurements Twenty-four children on dialysis had 24-hour ABPM in the interdialytic period, and values were compared with average pre- and postdialysis systolic BP (SBP) and diastolic BP (DBP) recordings that week. Each patient had an echocardiogram to determine presence of left ventricular hypertrophy (LVH).

Results By ABPM, 8% of patients had white coat HTN and 12% had masked HTN. There was no significant difference in diagnosis of systolic HTN based on ABPM daytime SBP mean or load and postdialysis SBP. However, only 15% of patients had diastolic HTN based on postdialysis measures, whereas 46% of patients had significantly elevated daytime DBP loads and 71% had high nighttime DBP loads on ABPM. Forty-eight percent of patients were SBP nondippers. Children with LVH had higher daytime and nighttime SBP loads, significantly higher daytime and nighttime DBP loads, and lesser degree of nocturnal dipping of SBP compared with those who did not.

Conclusion ABPM is more informative than pre- and postdialysis BPs and improves the predictability of BP as a risk factor for target organ damage. Diagnosis and treatment monitoring of HTN among pediatric dialysis patients is enhanced with addition of ABPM.

Introduction

Hypertension is common in children with ESRD receiving dialysis and is a significant risk factor for cardiovascular disease (1). Diagnosis of hypertension in children receiving dialysis is challenging because of treatment-related hemodynamic fluctuations and the altered day-night BP rhythm seen in the setting of chronic renal failure (2). Although repeated daily casual measurements are used to monitor BP in this population, ambulatory BP monitoring (ABPM) may be a superior technique.

ABPM uses a wearable, oscillometric BP device to automatically measure and record BPs at prescribed intervals (every 20 minutes when awake and every 30 minutes to 1 hour during sleep) over an entire 24-hour period. ABPM allows the evaluation of mean BPs in the patient’s own environment throughout the day, minimizing the effect of outlying measurements and anxiety-induced BP elevations. Furthermore, ABPM allows assessment of a child’s overall exposure to elevated BP throughout the day (BP load) and changes to normal circadian BP pattern, information unavailable from casual-BP measurements. In addition, ABPM is able to uncover masked hypertension, a condition in which BP is normal in the clinic setting but high at other times during the 24-hour day.

ABPM has been shown to be more representative of hypertension risk than casual-BP measurements and has become a well-accepted method of assessing BP in adult patients on dialysis (3). Additionally, ABPM correlates better with end-organ damage (4,5). ABPM has been used in children and adolescents and has proven to be both reliable and feasible (6). In children with normal renal function, ABPM has been found to be superior to casual-BP monitoring in the diagnosis of hypertension (6). Although some studies have evaluated the role of ABPM in children on dialysis, limited data exist for this subset of the pediatric patient population.

This study was undertaken to better define the role of ABPM in pediatric patients on dialysis. We compared ABPM data in 24 children receiving dialysis with casual-BP measurements and correlated our findings with echocardiographic data to study the relationship between ABPM hypertensive parameters and end-organ cardiovascular injury.
Materials and Methods

Patients

All hemodialysis (HD) and peritoneal dialysis (PD) patients followed in the pediatric chronic dialysis center at Lucile Packard Children's Hospital were reviewed. Patients under 5 years of age were excluded because of limited ABPM normative data. Patients with primary cardiac disease were also excluded to allow accurate assessment of cardiac injury. Patients on HD received dialysis three times weekly for 3 to 4 hours. PD patients received continuous cycling peritoneal dialysis with five to eight exchanges overnight for 9 to 12 hours plus a single daytime dwell. All dialysis patients had been receiving dialysis for at least 1 month before enrollment and were stable clinically. Before enrollment, patients received anti-hypertensive therapy according to the local standard of care based on casual measurements obtained pre- and postdialysis and at monthly clinic visits. The study was approved by Stanford Institutional Review Board.

Casual-BP

Casual-BP was obtained by an oscillometric device immediately before and after dialysis treatment in all patients. Pre- and postdialysis BP measurements obtained from 2 days before and 2 days after the day of ABPM were used for analysis. Casual-BP hypertension was diagnosed when the average of the four postdialysis BP measurements was greater than the 95th percentile for age-, gender-, and height-based norms (7) or if systolic BP (SBP) was >140 mmHg and diastolic BP (DBP) was >90 mmHg (8), whichever value was lower. Predialysis casual-BPs are more likely to be affected by maximal fluid overload and have been shown to be less reliable than postdialysis casual-BPs (9,10); thus, postdialysis casual-BP values were used for all comparative purposes.

ABPM

ABPM was performed using Spacelabs 90207 noninvasive oscillometric monitor (Spacelabs, Redmond, WA), which has been validated in adults and children according to the British Hypertension Society Protocol. The monitor records BP and heart rate on the nondominant arm every 20 minutes while awake and hourly while asleep for a total of 24 hours. Monitoring was initiated at the end of the hemodialysis treatment for HD patients and during daytime hours for PD patients. Patients were asked to keep a personal record documenting activities and sleeping times. Daytime (wake-time) and nighttime (sleep-time) for each child was defined according to her or his activity log for that day. To be included in analysis, a minimum of at least 40 successful daytime readings and 8 successful nighttime readings were required. ABPM recordings were edited for outlying values (SBP >240 or <70 mmHg and DBP >150 or <40 mmHg).

Mean ambulatory SBP and DBP during the entire 24-hour period, daytime and nighttime, were calculated by Spacelabs analysis software. Mean BP levels were compared with normative ABPM values (11); mean BP levels greater than the ambulatory 95th percentile, based on gender and height, were considered elevated. BP load was defined as the percentage of readings greater than the ambulatory 95th percentile, based on gender and height (11,12), for daytime and nighttime SBP and DBP or daytime SBP >130 mmHg or DBP >80 mmHg and nighttime SBP >120 mmHg or DBP >70 mmHg (13), whichever value was lower. A load >25% was considered elevated (14). Although controversy exists regarding optimal definition of hypertension by ABPM, we used the definition proposed by most experts, which requires both presence of elevated mean SBP or DBP and a SBP or DBP load >25% (11,15). Nocturnal dipping was defined as the percentage decline in ABPM mean SBP and DBP levels from day to night ([mean daytime ABPM – mean night-time ABPM]/ mean day ABPM × 100) (11). The presence of adequate dipping was defined by a nocturnal BP decrement of ≥10% below daytime BPs.

White coat hypertension is defined as casual-BPs >95th percentile with ambulatory normotension. Masked hypertension is defined as ambulatory hypertension with casual-BP <95th percentile. These definitions applied to our patients were of limited utility because the majority of our patients already carried a clinical diagnosis of hypertension and were receiving anti-hypertensive therapy.

Left Ventricular Mass Index

Left ventricular mass (LVM) was calculated from 2D-guided M-mode echocardiographic measurements of the left ventricle. LVM index (LVI) was calculated by dividing LVM (g) by height (m) exponentiated to the power of 2.7 (gm/m².7) to correct for effects of age, gender, and overweight status (16,17). Left ventricular hypertrophy (LVH) was defined as LVI >95th percentile (18).

Statistical Analysis

Descriptive statistics are presented as percentages, means, and SD. t test or χ² test and Fisher exact test were used for analysis of continuous or categorical variables. Casual-BP and ABPM standard deviation scores were obtained based on age-, gender-, and height-based norms in children (7,12). Multivariate analysis and Pearson/Spearman correlation were used for examining relationships for all parametric or nonparametric variables. P ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.1.2 (SAS Institute, Cary, NC).

Results

Patient Demographics

A total of 24 patients were included in this study, 22 receiving HD and 2 receiving PD, representing 89% of our dialysis population. Demographic and clinical characteristics of the patients are shown in Table 1. Patients had a mean age of 14.8 ± 4.2 years (range, 5 to 20 years), and 46% of them were boys. Predominant causes of ESRD were vasculitis (17%), unknown etiology (17%), autoimmune disease (12%), and reflux nephropathy (12%). The mean duration of dialysis at enrollment was 514 ± 560 days (range, 32 to 2329 days). Eighteen of 24 (72%) patients were receiving anti-hypertensives at the time of ABPM.

Assessment of Hypertension

Data from each ABPM obtained were adequate for interpretation; mean number of successful readings was 51 ±
19 (range, 41 to 75), with mean percentage of successful readings being $82 \pm 15.7\%$ (range, 53 to 100%). The profiles for mean casual and ABPM SBP and DBP are shown in Table 2. As expected, mean predialysis casual-SBP was significantly greater than both mean postdialysis casual-SBP ($127 \pm 11.5 \text{ mmHg}; P = 0.04$) and mean 24-hour ABPM-SBP ($127 \pm 11.5 \text{ mmHg}; P = 0.04$). However, pre- and postdialysis casual-DBP and mean 24-hour ABPM DBP values were almost identical ($74 \pm 11.3 \text{ mmHg}; 72 \pm 11.6 \text{ mmHg}$).

Table 3 details the classification of BP findings according to casual or ABPM readings. Twenty-one percent (5/24) of the children had hypertension based on postdialysis casual-SBP, and 25% (6/24) had hypertension based on the ABPM criteria of elevated daytime systolic mean and daytime systolic load. However, only three of these children had hypertension diagnosed by both casual-BPs and ABPM. There was a moderate positive correlation between casual-BP and daytime ABPM standard deviation scores (SBP: $r = 0.59, P = 0.0023$; DBP: $r = 0.53, P = 0.0076$).

Of the five children who had hypertension based on postdialysis BP measurements, two had normal ABPM. Whereas ABPM would reclassify these patients (8%) as having white coat hypertension (Table 3), this definition does not strictly apply because both patients already carried a diagnosis of hypertension and were receiving anti-hypertensive medications. Three patients (12%) had abnormal ABPM but normal postdialysis BPs and would be recategorized by ABPM results as having masked or not optimally controlled hypertension; however, these patients also carried a diagnosis of hypertension and were receiving anti-hypertensive medication.

Overall, ABPM showed that a striking number of patients had abnormal BP parameters. As shown in Figure 1, 42% of the children had elevated daytime systolic loads, and 46% had elevated daytime diastolic loads; 58% had elevated night-time systolic loads and 71% had elevated night-time diastolic loads. ABPM also showed that 48% of the children were nocturnal SBP nondippers, and 25% were DBP nondippers.

**Correlation of BP Parameters and LVH**

As shown in Figure 2, 59% of the children had LVH and another 12% had LVMI at the 95th percentile. Children on more intensive anti-hypertensive therapy (three agents)
had a higher LVMI compared with those who were on two or less anti-hypertensive agents \((P = 0.03)\). There was no association between postdialysis casual-SBP\((P = 0.13)\) or postdialysis casual-DBP\((P = 0.14)\) and the presence of LVH. Children with LVH had significantly higher ABPM daytime diastolic loads (mean, 58 \(versus\) 21\%; \(P = 0.002\)) and night-time diastolic loads (mean, 71\% \(versus\) 46\%; \(P = 0.005\)) compared with those without LVH. There was a trend toward greater daytime systolic load (42\% \(versus\) 22\%; \(P = 0.06\)) and night-time systolic load (58\% \(versus\) 42\%; \(P = 0.06\)) in children with LVH \(versus\) those without; however, this failed to reach statistical significance (Figure 3). Children with LVH also had significantly lower percentage of nocturnal dipping compared with children who did not have LVH (6.2 \(versus\) 11.0\%; \(P = 0.04\); Figure 4).

**Discussion**

Hypertension is highly prevalent in both adults and children receiving dialysis therapy and is one of the major contributors to morbidity associated with ESRD (1,3). Children on dialysis are vulnerable to adverse cardiovascular effects of hypertension. Because 40\% of mortality in children on maintenance dialysis in the United States is caused by cardiovascular causes (19), accurate diagnosis and treatment of hypertension is likely to improve long-term outcomes. In both children and adults with normal renal function, ABPM has been found to be superior to casual-BPs when diagnosing hypertension (20–22). Similar findings have been seen in children with chronic kidney disease (23,24). The diagnosis and treatment of hypertension in children on dialysis is often based on casual-BP measurements obtained immediately before and after a dialysis treatment. Unfortunately, these measures may be imprecise and biased, with poor test–retest reliability; ABPM may be a more sensitive and specific method of substantiating diagnosis of hypertension. Additionally, ABPM provides a much more comprehensive BP profile than casual-BP measurement. For example, casual-BP monitoring does not identify diurnal BP abnormalities, which may lead to inaccurate diagnosis and inadequate management of hypertension. Furthermore, ABPM provides load data, which quantifies true cardiovascular hypertensive burden. Although the use of ABPM in children receiving dialysis has been previously described (25–30), overall number of patients in this subset studied to date is limited. In this study, we examined the potential benefit of addition of ABPM to casual-BP measurements in 24 stable pediatric dialysis patients.

Hypertension is common in children and adolescents with chronic kidney disease, with many receiving anti-hypertensive therapy at the time of dialysis initiation (19); North American Pediatric Renal Transplant Cooperative study reports 77\% of children on dialysis have uncontrolled or controlled hypertension at baseline (31). In this analysis, our cohort was representative of children on dialysis, because 72\% of the children were receiving anti-hypertensives.

We compared casual postdialysis BP measurements with ABPM in 24 children on maintenance dialysis. ABPM re-
LVH were more likely to have elevated BP loads, both systolic and diastolic (42% and 46%, respectively), suggesting suboptimal BP control. In a similar study of 12 children on chronic hemodialysis, Sorof (26) found similarly elevated 24-hour SBP (35%) and DBP (36%) loads. Interestingly, our study also showed a markedly higher prevalence of elevated loads at night time (SBP: 24%; DBP: 21%).

Analysis by Covic and Goldsmith (36) reported that 58% of patients with renal insufficiency showed the nondipper profile. ABPM has been used to characterize altered circadian BP patterns in children on chronic HD as well, and a high prevalence of nondipping has been reported. Sorof (26) found that 92% of children on chronic HD who had SBP nondipping and 42% had DBP nondipping. In our study, 48% of the children were nocturnal SBP nondippers and 25% were DBP nondippers. Our echocardiographic data support the concept that nocturnal BP is an independent predictor of LVMI in HD patients, because children with LVH were found to have significantly decreased nocturnal dipping of their systolic BPs (P = 0.04). This suggests that the degree of nocturnal change in BP may be an important tool for cardiovascular risk stratification.

Our study has several important limitations. Our population was small, and the study is observational in nature. It is also important to note that our data represent a single classification five of eight patients with a diagnosis of hypertension. This alone highlights the importance of performing ABPM in children receiving dialysis. After ABPM, two patients were reclassified from “hypertensive” to “well-controlled BPs,” and three were reclassified from “well-controlled BPs” to “hypertensive”; these patients had their anti-hypertensive regimens adjusted.

Furthermore, ABPM provided important information regarding BP loads in our patients. Although 25% of patients were diagnosed with hypertension by casual-BPs and mean ABPM BPs, a larger proportion of children had elevated systolic and diastolic loads (42% and 46%, respectively), suggesting suboptimal BP control. In a similar study of 12 children on chronic hemodialysis, Sorof (26) found similarly elevated 24-hour SBP (35%) and DBP (36%) loads. Interestingly, our study also showed a markedly higher prevalence of elevated loads at night time (SBP: 24%; DBP: 21%).

Our results are also concordant with studies in children that have associated elevated BP loads with an increased risk for LVH (5,32), an independent predictor of mortality in hemodialysis patients and a reasonable surrogate for adverse cardiovascular consequences of hypertension in this population (33). Sorof et al. (5) described a significant correlation between 24-hour SBP load and LVMI in hypertensive children. Similarly, we found that children with LVH were more likely to have elevated BP loads, both during the day and night. Although this trend existed for both SBP and DBP, it only reached statistical significance for DBP; this association between LVH and elevated DBP load, to our knowledge, has not been previously described in this subset of patients. These findings suggest that an isolated elevated BP load, systolic or diastolic, even in the setting of a normal ABPM mean BP, may lead to target end-organ damage and left ventricular remodeling. It is possible that more aggressive anti-hypertensive therapy, aimed at reducing BP loads, may reduce long-term cardiovascular morbidity and mortality. Additionally, it may be necessary to modify the diagnostic criteria for ABPM; patients with an elevated BP load and normal mean BP may be best classified as hypertensive and deserving of anti-hypertensive therapy. If we reclassified our patients and included those with an isolated elevated BP load as being hypertensive, a greater proportion of the children in this analysis would carry a diagnosis of systolic hypertension (42 versus 21%) and diastolic hypertension (46 versus 15%).

Finally, ABPM also provides data regarding BP circadian rhythms and allows one to classify patients as “dippers” or “nondippers” based on the nightly percent decrement in BP. Nondipping in chronic HD patients may be an independent predictor of poor clinical cardiovascular outcomes and is associated with a worsened cardiovascular survival rate compared with dipping (34,35). Such disturbances of circadian rhythm of BP are well documented in patients with renal insufficiency. For example, the meta-analysis by Covic and Goldsmith (36) reported that 58% of adults with ESRD and advanced chronic kidney disease showed the nondipper profile. ABPM has been used to characterize altered circadian BP patterns in children on HD as well, and a high prevalence of nondipping has been reported. Sorof (26) found that 92% of children on chronic HD who had SBP nondipping and 42% had DBP nondipping. In our study, 48% of the children were nocturnal SBP nondippers and 25% were DBP nondippers. Our echocardiographic data support the concept that nocturnal BP is an independent predictor of LVMI in HD patients, because children with LVH were found to have significantly decreased nocturnal dipping of their systolic BPs (P = 0.04). This suggests that the degree of nocturnal change in BP may be an important tool for cardiovascular risk stratification.

Our study has several important limitations. Our population was small, and the study is observational in nature. It is also important to note that our data represent a single
center report. However, despite its size, our study does represent one of the larger cohorts of ABPM evaluation in children receiving chronic dialysis. Our data add to the growing body of literature that highlights the need for a multicenter collaborative study to better address this issue. It is also important to note that ABPM profiles in PD patients might be different from those in HD patients; the nocturnal dialysis period is included in the ABPM profile and the interdialytic weight gain/intradialytic weight loss pattern in PD patients may affect BP level and rhythmicity. Also, the nocturnal dialysis procedure might influence patient’s sleep and nocturnal BP dipping pattern. However, our results showed a similar trend when we excluded the two PD patients.

In summary, our study confirmed the high prevalence of ABPM BP abnormalities in pediatric dialysis patients. Data generated by ABPM seem to provide a superior estimate of ABPM BP abnormalities in pediatric dialysis patients. Data in two PD patients. Our results showed a similar trend when we excluded the pattern in PD patients may affect BP level and rhythmicity. Additionally, patients with LVH had a higher prevalence of nondipping. These additional parameters described by ABPM not only assist in the diagnosis and categorization of hypertension but may also provide prognostic cardiovascular data. We believe that ABPM may improve evaluation of hypertension and cardiovascular risk stratification in this high-risk population. We suggest that ABPM should become the standard for hypertension diagnosis and evaluation of anti-hypertensive therapy in children receiving chronic dialysis.

Disclosures
None.

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