Superior consistency of ambulatory blood pressure monitoring in children: implications for clinical trials

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Background **Casual office blood pressure (CBP) measurements are still standard in antihypertensive drug trials. In pediatric hypertensive trials, ethical considerations, very low disease prevalence and the marked impact of white-coat hypertension create the need for very sensitive and reproducible techniques of BP assessment. We hypothesized that ambulatory BP monitoring (ABPM) may identify treatment effects more sensitively than CBP and thereby reduce sample sizes required in pediatric antihypertensive trials.**

Methods **Standard deviations (SDs) were used to assess population variability of CBP and ABPM at baseline and after 6 months standardized antihypertensive treatment from a trial investigating the BP-lowering effect of ramipril in children with chronic kidney disease.**

Results **In 157 hypertensive children, ramipril had a similar mean BP-lowering effect on clinic and ambulatory 24-h BP for systolic (−10 vs. −11 mmHg, P = NS) and diastolic values (−9 vs. −11 mmHg, P = NS). However, the SDs of the CBP responses were up to 39% larger than those of ABPM (SBP 15.5 vs. 9.4; DBP 13.8 vs. 8.8; both $P<0.0001$). Using power analysis, we demonstrate that, depending on the magnitude of the expected antihypertensive effect and trial design, the utilization of ABPM in antihypertensive drug efficacy studies allows reduction of sample sizes by 57–75%. This reduction of cohort size with ABPM is substantially greater than previously observed for adults.**

Conclusion **The primary use of ABPM can substantially reduce the number of children put at potential risk in blinded antihypertensive drug trials by up to three quarters.**
J Hypertens **27:1568–1574 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2009, **27**:1568–1574

Keywords: adolescents, ambulatory blood pressure measurement, antihypertensive drugs, children, clinical trial, hypertension

Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; CBP, casual office/clinic blood pressure measurement; CKD, chronic kidney disease (KDOQI classification)

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Received 2 December 2008 **Revised** 27 March 2009
Accepted 5 April 2009

Background

Twenty-four-hour ambulatory blood pressure (BP) monitoring (ABPM) is gradually gaining acceptance in the diagnostic and therapeutic management of both adult and pediatric hypertensive patients. In children, ABPM is usually feasible from 4 to 5 years of age. The marked dependence of BP on age and body size, as well as the more marked circadian BP variation in children resulting from their greater physical activity mandate the use of specific pediatric reference ranges, and such data have been established [1]. Although office mercury or aneroid sphygmomanometry has been considered gold standard until recently [2], its use is increasingly questioned given the frequent clinic visits required to diagnose hypertension correctly and in the light of increasing evidence suggesting a superior correlation of ABPM with end-organ damage in children as in adults [3].

The interest in antihypertensive drug trials in children has markedly increased in recent years due to the mandatory provision of pediatric data introduced by regulatory authorities both in the United States and Europe. However, antihypertensive trials in children are challenging, due to the very low incidence of pediatric hypertension, the limited cooperation of younger children with BP measurements and venepunctures and the interference of frequent long distance travel to specialized

This work was presented in part as 'Superior consistency of ambulatory vs. office blood pressure monitoring in children', by C. Hadtstein, E. Wühl, F. Schaefer and the ESCAPE trial group, Poster presented at the 14th Conference of the International Pediatric Nephrology Association (IPNA), 31 August to 4 September 2007, Budapest, Hungary.
* See Acknowledgement section.

0263-6352 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32832cb2a8

clinics with schooling and social life. Moreover, a high prevalence of white-coat, as well as masked, hypertension compromises the detection of dose-related treatment responses in pediatric trials [4]. Finally, the multimorbidity of children with chronic kidney disease, the largest group of pediatric patients with diagnosed hypertension, complicates their inclusion in clinical trials. As a result, randomized clinical trials in pediatric hypertension usually require recruitment efforts on a global scale to meet cohort size requirements. Hence, the quest for sensitive and consistent technologies to monitor treatment responses in pediatric antihypertensive drug trials is a task of eminent ethical as well as economic relevance.

In order to address the usefulness of ABPM in detecting antihypertensive treatment responses in children, we analyzed data collected in the ESCAPE trial, the largest pediatric antihypertensive drug study performed to date, in which concomitant office BP and ABPM monitoring was used to detect treatment responses in children with high-normal or elevated BP.

Methods

Patients

BP measurements were obtained from children taking part in the multicenter ESCAPE trial (Effect of Strict blood pressure Control and ACE inhibition on Progression of chronic renal failure in pEdiatric patients). This randomized controlled clinical trial involved children aged 3–20 years with stages 2–4 chronic kidney disease with elevated or high-normal BP (>50th percentile for age and height) at baseline [5]. Baseline casual BP (CBP) and ABPM measurements were obtained at the end of a 6-month run-in phase following an ACE inhibitor wash-out period of at least 2 months (see Wühl *et al.* [5] for details). Following the baseline measurements, a fixed single daily dose of ramipril (6 mg/m^2 body surface area) was administered either alone or in addition to the background antihypertensive medication. BP control was evaluated by CBP every 2 months and by ABPM every 6 months. After 6 months, patients were randomly assigned to either continued conventional (aiming at 24-h mean arterial BP below 95th percentile) or intensified BP control (target 24-h mean arterial pressure (MAP) <50th percentile) and followed for a total of 60 months. Here we provide a comparative analysis of the BP response to the initial therapeutic intervention (standardized administration of ramipril to all patients) according to CBP and ABPM, respectively. Although the ESCAPE trial, exploring the renoprotective effect of intensified BP control, included children with any BP more than the 50th percentile, the analysis presented here was restricted to the 157 patients with baseline BP more than the 90th percentile (i.e. the level considered to warrant antihypertensive treatment in children with chronic kidney disease (CKD) according to current international guidelines [2]) in order to appropriately simulate the setting of a pediatric antihypertensive trial.

The study protocol was designed in adherence to the declaration of Helsinki and approved by the ethical committees at each of the participating centers. Written informed consent was given by all parents, and informed consent or assent was obtained from the patients as appropriate.

Blood pressure measurements

ABPM was performed with a standard oscillometric monitor (Spacelabs 90207; Spacelabs, Redmond, Washington, USA). The most appropriate of three cuff sizes was fitted to the nondominant arm. Recordings were taken every 15–20 min during the day and every 30–60 min at night. Although 83% of ABPMs were of very good quality (i.e. length at least 22 h, gaps no longer than 2 h), all ABPM profiles were included in the analysis to reflect a 'real-life' situation. The shortest ABPM was 16 h long and the longest gap was 7.8 h.

CBP measurements were taken using standard auscultatory devices with valid calibration certificates compliant with local quality assurance policies. The same set of devices was used for the repetitive measurements in each participating unit. CBPs were taken at the clinic visits by skilled healthcare professionals in sitting position after 5–10 min rest on the nondominant arm using a cuff of appropriate size for the age of the child, according to international recommendations [2].

Statistics

Data were stored and analyzed with SAS (SAS Institute, Cary, North Carolina, USA). Statistics are given as mean ± SD. P values of less than 0.05 were considered significant. Comparisons of group means were made with the unpaired Student's t-test, whereas the F-test was used to compare standard deviations.

For power calculations, we assumed a confidence level (α) of 0.05 and a power level of 0.95. Power analyses were performed using the PROC POWER procedure of SAS for both crossover and parallel group study designs. For crossover study designs, the correlations between first and second measurements assumed in the model were taken to be the same as the correlation in the original cohort. For correlations, Pearson's correlation coefficients are provided.

Standard deviation scores (SDSs) for daytime, night-time and 24-h BP were calculated using the LMS tables of Wühl *et al.* [1]. Normal values for the calculation of SDSs of height and BMI were taken from Prader *et al.* [6] and Schaefer *et al.* [7], respectively. Creatinine clearance was estimated with the Schwartz formula [8].

Results

Patient characteristics

Baseline and 6-month BP measurements were available in 157 pediatric patients (45% male children). The most common group of underlying renal diagnoses was renal hypo/dysplasia (63%), followed by glomerulopathies (18.5%) and hereditary and other renal diseases (18.5%). Mean patient age at baseline was 11.3 ± 3.7 (range 3.6–20) years. There were 17 (11%) preschool children under 6 years of age, 75 children between 6 and 12 years (48%) and 65 children over 12 years old (42%). Mean BP was elevated at 2.1 ± 1.1 SDS 24-h SBP and 2.6 ± 1.6 SDS 24-h DBP. Mean creatinine clearance was 49 ± 22 ml/min*1.73 m^2 with most children suffering from CKD stage 3 (48%).

Blood pressure

The results of clinic and ambulatory BP measurements are shown in Table 1. Clinic BP showed a consistently wider scatter across the population, with standard deviations (SDs) of ABPM measurements being between 24 and 30% smaller. An even larger difference in distribution homogeneity was observed for the longitudinal change in BP during antihypertensive treatment. The SD of the observed BP response was 39% (SBP) and 36% (DBP) lower with ABPM than with clinic BP. The marked difference in consistency of the BP response is illustrated in Fig. 1. The superior consistency of ABPM was also reflected by closer correlations of initial with repeat ABPM ($r = 0.58$ SBP, $r = 0.48$ DBP) than CBP measurements ($r = 0.38$ SBP, $r = 0.32$ DBP, all $P < 0.0001$).

Model calculations

Based on the observed SDs of the change in BP (Table 1), required minimal trial sample sizes to detect a treatment-induced BP reduction as significant were calculated relative to the expected magnitude of the BP effect and the choice of study design. In a crossover design, children would be randomized to receive placebo and drug sequentially (or in reverse order), whereas in a parallel group design, a cohort of children would be split randomly to receive either drug or placebo. Table 2 shows the anticipated numbers of patients needed to detect a significant BP difference of 3, 5 or 10 mmHg. With a crossover design, 64–75% less children would be required in an ABPM study compared with a study using CBP as a primary endpoint. In a study with parallel group design, the use of ABPM would require 57–63% less children.

Factors affecting blood pressure distribution

A number of potential factors affecting the distribution of baseline BP and of the response to treatment with the two methods were examined by subgroup analyses. There was no difference in the SD of the BP change between children above and below 6 years of age or between prepubertal and pubertal children. Similarly, no difference was found between the sexes or between children with more or less advanced CKD (Table 3). In all subgroups, the pattern of lower SDs for ABPM compared with clinic BP readings was consistent.

The baseline BP level impacted on the variability of ambulatory, but not office BP. This was mainly due to the larger BP-lowering effect picked up by ABPM compared with clinic readings (see Table 3).

Discussion

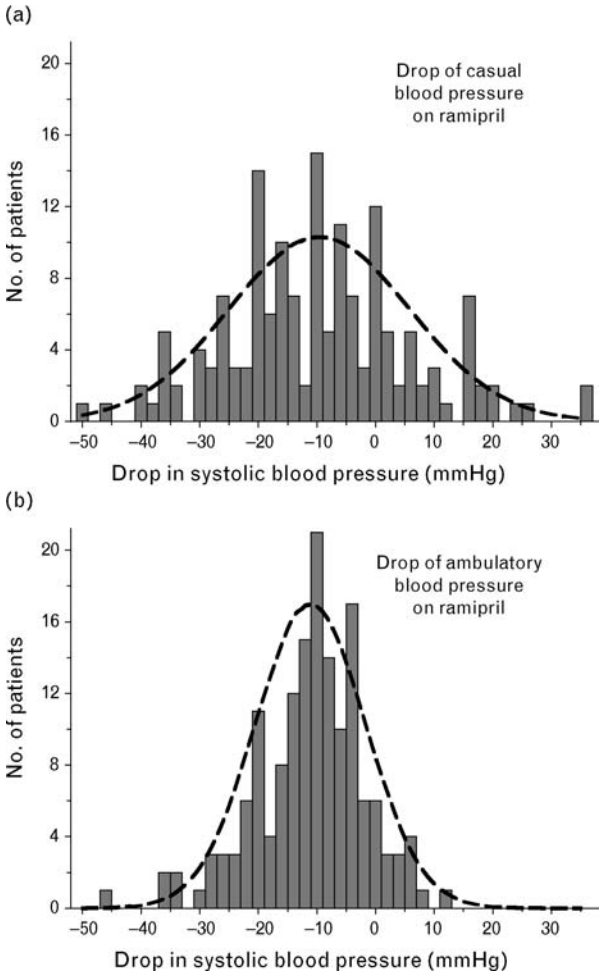
The incidence of hypertension in the pediatric age group is steadily increasing owing to the growing global epidemic of childhood obesity [9]. Although a broad consensus has emerged regarding the urgent necessity for randomized clinical trials in pediatric hypertension and is reinforced by legal requirements, the realization of such trials is a challenging task. Apart from general ethical issues regarding the enrollment of children in clinical trials, pediatric antihypertensive drug trials are hampered by multiple practical issues. As a result, sample size is a

Table 1 Clinic and 24-h ambulatory blood pressures at baseline and after 6 months ramipril treatment in 157 hypertensive children with chronic kidney disease

	Mean ± SD	Difference in SDs (%)	*P* value for difference in means	*P* value for difference in SDs
Baseline				
Clinic SBP	122.1 ± 13.0	26	<0.0001	<0.001
ABPM SBP	127.0 ± 9.6			
Clinic DBP	76.4 ± 11.0	24	<0.0001	<0.001
ABPM DBP	80.6 ± 8.4			
After 6 months treatment				
Clinic SBP	112.5 ± 14.6	27	<0.001	<0.001
ABPM SBP	115.9 ± 10.7			
Clinic DBP	67.7 ± 12.7	30	0.03	<0.0001
ABPM DBP	69.7 ± 8.9			
Change from baseline to 6 months				
Clinic SBP	−9.6 ± 15.5	39	NS	<0.0001
ABPM SBP	−11.1 ± 9.4			
Clinic DBP	−8.7 ± 13.8	36	NS	<0.0001
ABPM DBP	−11.0 ± 8.8			

ABPM, ambulatory blood pressure monitoring.

Fig. 1



Change in casual blood pressure (a) and 24-h systolic blood pressure (b) after 6 months of antihypertensive treatment with ramipril. Dashed line: Gaussian distribution to illustrate difference in SD (width of curve).

very critical issue in pediatric hypertension trials. Although adult trials typically include several thousand participants, the largest pediatric placebo-controlled antihypertensive trial published to date enrolled 268 children [10].

The use of ABPM is now well established in adult medicine, and a growing body of evidence supports a superior correlation of ABPM abnormalities with both end-organ damage and mortality when compared with CBP readings [11–13]. However, these findings cannot be transferred uncritically to children, who are much more physically active, resulting in higher ABPM than CBP values (also found here) and a lower rate of successful readings on ABPM. Also, mortality is an unsuitable endpoint in children. Despite the sometimes limited device acceptance of children, ABPM is generally feasible from 6 years of age onward [14], and in many children above the age of 3 years [15]. A success rate of over 85% has even been described in infants and toddlers [16]. Abnormal ABPM profiles predict end-organ damage even in the presence of a normal clinic BP in children [3].

Despite the growing evidence for the superior quality of the information provided by ABPM, clinicians, healthcare providers and regulatory authorities have been slow in implementing the preferential use of this methodology in the diagnostic and therapeutic management of hypertensive children. As of today, the great majority of pediatric antihypertensive trials have used office BP readings to define primary study endpoints, guided by consensus clinical practice recommendations and derived obligations imposed by regulatory authorities. The aim of this paper was to examine how much the use of ABPM in pediatric antihypertensive drug trials can help to minimize the number of patients required to enroll in order to demonstrate statistically significant therapeutic effects.

Table 2 Power analysis of sample size requirements to detect BP effects in a pediatric antihypertensive drug trial using either clinic blood pressure measurements or 24-h ambulatory blood pressure monitoring, based on SDs of BP changes observed in ESCAPE trial (α error: 5%, power: 95%)

	Blood pressure	CBP (*n*)	24-h ABPM (*n*)	Sample size reduction by use of ABPM (%)
3 mmHg difference				
Parallel group design	SBP	695	257	63
	DBP	551	225	59
Crossover design	SBP	436	111	75
	DBP	374	118	68
5 mmHg difference				
Parallel group design	SBP	251	93	63
	DBP	199	82	59
Crossover design	SBP	159	41	74
	DBP	136	44	68
10 mmHg difference				
Parallel group design	SBP	64	24	63
	DBP	51	22	57
Crossover design	SBP	41	12	71
	DBP	36	13	64

ABPM, ambulatory blood pressure monitoring; CBP, clinic blood pressure.

Table 3 Subgroup analysis of mean (±SD) blood pressure change after 6 months of ramipril in different subgroups (comparison of ambulatory and clinic measurements)

	Clinic SBP	ABPM SBP	Clinic DBP	ABPM DBP
Sex				
Male	$-9.4 \pm 15.4^{*}$	-12.5 ± 9.9	$-8.5 \pm 12.4^{*}$	-11.8 ± 8.4
Female	$-9.7 \pm 15.6^{*}$	-10.0 ± 8.8	$-8.9 \pm 15.0^{*}$	-10.2 ± 9.1
Difference in SD	NS	NS	NS	NS
Age				
<6 years	-17.0 ± 14.3	-15.6 ± 11.8	-13.0 ± 16.0	$-13.6 \pm -9.5^{*}$
≥6 years	$-8.7 \pm 15.4^{*}$	-10.6 ± 9.0	$-8.2 \pm 13.6^{*}$	-10.7 ± 8.7
Difference in SD	NS	NS	NS	NS
CKD stage				
2–3	$-10.1 \pm 14.6^{*}$	-10.7 ± 8.8	$-8.3 \pm 13.4^{*}$	-10.2 ± 8.5
4–5	$-7.6 \pm 18.4^{\dagger}$	-13.0 ± 11.1	$-10.1 \pm 15.3^{\dagger}$	-13.7 ± 9.4
Difference in SD	NS	NS	NS	NS
Blood pressure				
<99th percentile	$-9.2 \pm 14.8^{*}$	-9.0 ± 7.2	$-9.2 \pm 13.9^{*}$	-8.9 ± 6.7
>99th percentile	$-10.2 \pm 16.7^{\dagger}$	-15.0 ± 11.5	-7.9 ± 13.9	-14.6 ± 10.8
Difference in SD	NS	$P < 0.0001$	NS	$P < 0.0001$

ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease. *P* values for difference in SD between clinic and ABPM. $^{*}P \leq 0.001$. $^{\dagger}P < 0.01$.

The recently completed ESCAPE trial provided an opportunity to compare the sensitivity of conventional CBP and 24-h ABPM values in detecting the antihypertensive effect of a standardized antihypertensive intervention. The SDs of 24-h BP values obtained by ABPM were found to be approximately 25% smaller than those noted with CBP readings. This finding is in agreement with most pediatric reports comparing CBP with ABPM [3,17–20]. Only a single study showed an equal spread of CBP and ABPM measurements [21], and none reported consistently better reproducibility of CBP. However, several studies were equivocal: Matsuoka and Awazu [22] found the ABPM scatter to be smaller in 77 girls but not in 59 boys; Kavey *et al.* [23] found superior ABPM distribution in 62 white-coat hypertensive children, but not in 57 truly hypertensive children; Stergiou *et al.* [24] found a lower scatter of ABPM in 23 normotensive children, but not in 34 hypertensive children; finally, Mitsnefes *et al.* [25] found smaller variability of ABPM results in 16 untreated children with CKD but not in 13 children on antihypertensive medication. While the results of these smaller single-center studies are compatible with a more marked consistency advantage of ABPM at lower BP levels, our findings clearly demonstrate the superior reproducibility of ABPM in children with prehypertension and overt hypertension.

Furthermore, our study provides evidence that the full benefit of ABPM becomes apparent when the response to a BP-lowering intervention is considered. The SDs of the BP response to our standardized therapeutic intervention were 36–39% narrower than those observed with CBP readings. This difference translates into a remarkable reduction of cohort size requirements by 57–73%, depending on the trial design and the magnitude of the expected BP reduction.

ABPM was superior to CBP independent of patient age, the prevailing BP level and the degree of chronic renal insufficiency. Notably, the reduction of cohort size was substantially greater than that calculated for adults by Stergiou *et al.* [26], who found that a parallel group design using ABPM to detect a 10 mmHg SBP difference needed 43% less patients than CBP (63% less in our study) and 27% less for a 5 mmHg DBP difference (59% less in our study).

A small potential source of bias in our calculations is given by our assumption that ABPM variability is similar with active and placebo treatment. In the past, the ethicality of placebo use in pediatric antihypertensive efficacy trials has been questioned. As a consequence, only a single placebo-controlled antihypertensive drug trial using ABPM in children has been published to date. Comparing allopurinol and placebo in 30 children aged 11–17 years with essential hypertension, Feig *et al.* [27] found identical SD of SBP in the two groups and a slightly larger SD of DBP in the placebo group. The only other pediatric ABPM study using a placebo control group explored the efficacy of stimulant medications for attention deficit hyperactivity disorder (ADHD) [28]. BP was raised in 13 children with active drug treatment, but the SD of 24-h SBP and DBP did not differ between the placebo and active drug groups. A recent study comparing angiotensin receptor blockers and placebo in 105 young adults at high risk of hypertension found no difference of SDs between the two groups, despite a significant absolute BP reduction in the treatment group [29].

A second potential limitation of our study is that CBP measurements were not taken under quite the strictly standardized conditions that have become the norm for clinical trials in children after the start of the ESCAPE trial. For example, the aneroid devices used for office BP measurement were not formally validated using an established protocol but were calibrated locally in different hospitals. Also, the variable number of measurements allowed if the first reading was unsuccessful may have

contributed to the larger SDs of the CBP measurements. On the other hand, we feel that including a range of devices provided a better reflection of the 'real-life' situation. In parallel, the inclusion of a few lower quality ABPMs may have increased the SDs with this method to some degree, but this again reflects common practice.

In view of the numerous ethical and practical challenges associated with the enrollment of children in randomized, controlled antihypertensive drug trials, the superior sensitivity of ABPM in detecting treatment-induced BP changes provides a strong argument in favor of using this methodology to define primary endpoints in future trials. It also lends support to the serial use of ABPM in clinical practice to monitor the effect of therapy modifications in hypertensive children.

It should be noted that the superior consistency of ABPM in picking up responses to antihypertensive treatment adds to the wealth of additional qualitative and quantitative information provided by ABPM, such as nocturnal BP dipping, circadian and ultradian BP rhythmicity [30–32] and the daytime and night-time levels and variation in heart rate [33].

In conclusion, our work provides a strong rationale for expert bodies and regulatory authorities to consider recommending the primary use of ABPM in pediatric randomized clinical trials submitted for approval purposes. With its wide availability, proven technical feasibility across the pediatric age range, availability of high-quality pediatric reference data [1] and superior sensitivity in detecting pharmacological treatment effects demonstrated in this study, the time has come for ABPM to become the method of choice in randomized pharmaceutical trials. The investment in ABPM technology and logistics should be readily returned by the benefits of improved data quality, which will permit substantial reductions in the number of children exposed to potentially hazardous study conditions.

Acknowledgements

Support for this study was obtained from the European Commission (5th Framework Programme (QLG1-CT-2002-00908), the Boehringer Ingelheim Stiftung, the Baxter Extramural Grant Program and Aventis Pharma.

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F.S. has worked as advisor for Novartis, AstraZeneca, Bristol Myers Squibb and Boehringer Ingelheim, and has received research grants from Novartis.

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