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Review

Hypertension in chronic kidney disease: Role of ambulatory blood pressure monitoring

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ABSTRACT

Children with chronic kidney disease have a markedly increased risk of cardiovascular morbidity and children with end stage renal disease have an estimated 30 times greater risk of cardiovascular mortality than the general pediatric population. In adults, the link between hypertension and cardiovascular disease is well-documented but that association has not been so readily apparent in children with chronic kidney disease. This may be in part because the early changes in blood pressure that occur in these patients do not necessarily manifest with changes in casual blood pressure measurements. Ambulatory blood pressure monitoring, with its ability to gather multiple readings both during the normal activities of the day and the night, is felt to be a more veritable measure of blood pressure. Its use in children has been hampered by limited data on normative values and difficulties in blood pressure classification, while its use in adults is ever expanding. However, with an increasing number of studies in children with chronic kidney disease, ambulatory blood pressure has revealed a greater prevalence of abnormal findings in this population and has been shown to better predict cardiovascular risk than current standards. Two large multi-center studies in Europe and North America have revealed even greater utility of ambulatory blood pressure measures in this population. It is hoped that continued use of ambulatory monitoring in children will help overcome some of its perceived limitations while also validating its use in those at high risk of cardiovascular morbidity.

1. Introduction

Ambulatory blood pressure monitoring has been in use for nearly four decades in the adult population [1], however its application has become more commonplace in clinical and research use in that population over the last 15 years. Like other medical technologies, ambulatory blood pressure monitoring use in the pediatric population has lagged behind that of their adult counterparts with reasons for its limited use having varied from technical restrictions of the devices and a dearth of expertise to a lack of standardized measures and subjective definitions of hypertension. However, as this technology is being studied to a greater degree in pediatrics, its utility in certain populations is being fully recognized.

One of the populations of great interest is children with chronic kidney disease, as they not only have a greater risk of cardiovascular morbidity but they also have a higher incidence of abnormal ambulatory blood pressure findings. Children with chronic kidney disease have increased rates of left ventricular hypertrophy [2–4], abnormal flow mediated vasodilation [5], and carotid intimal medial thickening [6] while the mortality rates of children who progress to needing maintenance dialysis are 30 times greater than the general pediatric population with cardiovascular disease being the leading cause [7]. Rates of abnormal ambulatory monitoring findings, mainly masked hypertension, are around 7% in the general pediatric population [8], but are several-fold higher in children with chronic kidney disease. Thus, this population may be ideally suited to be the "torchbearer" for studies using ambulatory monitoring and the development of standards of care and utilization. This review addresses the advantages and limitations of ambulatory blood pressure monitoring use in children with chronic kidney disease, provides data gathered to date from its use in that population, and discusses its potential for future use.

2. Advantages and Limitations of ABPM in Pediatric CKD

Blood pressure has traditionally been performed as a single measurement obtained in the physician's office under certain idealized conditions (at rest for five minutes with arm held level to the heart). Though these measurements may be performed repeatedly, with at least three elevated readings recommended to make the diagnosis of hypertension [9], this casual blood pressure reading, a single snapshot in the course of the entire day, has been the "gold standard" determinant of hypertension [10]. This is mainly based off its practicality to

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perform, as it is a simple process that can easily be taught and replicated, so it has utility as a screening measure for the general population.

Technological advancements, such as oscillometric techniques and micro-chip technology, led to the advent of ambulatory blood pressure monitoring, allowing for multiple accurate automated blood pressure readings throughout a continuous period and now using a variety of cuff sizes. Proponents of ambulatory blood pressure monitoring argue that this method gives a "truer" measure of blood pressure [11]. Firstly, it assesses blood pressure during normal daily activities, not the artificial scenario which takes place in the physician's office. Therefore, much like a Holter monitor or a stress test compares to an in-office electrocardiogram, ambulatory blood pressure monitoring reflects blood pressure during the normal vicissitudes of daily activities rather than a single instant. Secondly, ambulatory monitoring provides multiple measures over time, and therefore may be more reliable and reproducible, while also being less susceptible to observer bias. Lastly, the diurnal measures over 24 h of monitoring may account for circadian rhythms and other contributors to blood pressure variability that cannot be captured by other standard measurement methods [12].

Because 24 h ambulatory monitoring gives multiple blood pressure readings over time, monitoring results may be analyzed in different ways, each with its own strengths and weaknesses. Blood pressure may be analyzed as an averaged measure, like 24-h mean, daytime mean, or nighttime mean blood pressure. Averaged values are not robust parameters, are possibly skewed by extreme values, and do not yield information on frequency of blood pressure elevation. However they offer much more consistent information than a single measurement. Ambulatory monitoring also allows for assessment of blood pressure load, or the frequency in which readings exceed a certain parameter, typically the 95th percentile. Although blood pressure load does reflect how often blood pressure is excessive, it cannot tell you how much it is excessive. Therefore, interpretation of both mean values and overall blood pressure load may help in determining overall risk [13].

2.1. Normative Data in Children

For a long period of time, ambulatory blood pressure studies in children were limited by a lack of normative data for this population. In 1997, the largest cross-sectional cohort of nearly 1150 children receiving ambulatory blood pressure monitoring [14] reported their findings as a basis for normative data. Five years later, a separate, slightly smaller study of almost 950 children was able to report data such that standardized scores were able to be derived [15]. The data from these two studies comprise the current normative data standards for pediatric ambulatory blood pressure monitoring, with cut point values slightly higher than those reported for casual blood pressure readings by the Fourth Report on High Blood Pressure in Children and Adolescents [9]. The discrepancies between the ambulatory and casual blood pressure standards may be explained by differences in measurement method, as ambulatory standards are based off oscillometric measurements, which are known to be higher, while casual standards are derived from auscultative measures. Others attribute the slight elevation in ambulatory measures to the expected rise in blood pressure during normal daily activities. The ambulatory normative data has other limitations, not just in total numbers of patients, but also in the age and heterogeneity of patients, as both study populations were comprised mainly of taller, healthy German schoolchildren. Additionally, the data reported from these studies showed very little variability in diastolic blood pressure values across age groups and heights, unlike the auscultative norms in children, calling into question the validity of these measures.

2.2. Ambulatory Blood Pressure Classification

Using these ambulatory blood pressure standards and comparing to casual measures, an overall classification system was established, first in adults [16], but also in children [17]. Familiar classifications include normotension, when the casual and ambulatory results (mean AND load) are both normal, and white coat hypertension, when the casual blood pressure is elevated but ambulatory results (mean AND load) are normal. Ambulatory hypertension, which may be thought of as confirmed hypertension, is when both the casual and ambulatory measures are elevated. Masked hypertension, once termed reverse white coat hypertension, is when there is a normal casual blood pressure reading but elevated ambulatory (mean OR load) findings. The currently recommended schema of classification for children was updated in 2014 [18] and is summarized in Table 1.

The addition of blood pressure load parameters along with mean ambulatory measures expanded the number of abnormal ambulatory monitoring results and, thus, capturing more individuals at potential risk. However, it also added more strata in the classification system. Having more than half of all ambulatory blood pressure readings above the 95th percentile, i.e. a blood pressure load >50%, is classified as severe ambulatory hypertension and is appropriately considered higher risk for end organ injury. Also, an elevated blood pressure load with normal ambulatory means (load NOT mean) but slightly elevated casual blood pressure measures would be classified as pre-hypertension. The most recent updates to this classification system [18] had modification of casual blood pressure cut-offs for normotension and pre-hypertension being changed from the 95th to 90th percentile. However, despite the addition of further strata, there are still ambulatory monitoring results that may not fit into any of the current categories. Also, the currently recommended classifications do not account for other factors (systolic vs. diastolic, day vs. night) which may have greater prognostic significance.

2.3. Diurnal Variation

Through the observation of patterns over a full 24 h, it was discovered that blood pressure has diurnal variation, with decreased measures during sleep. [19] This physiologic "dipping" is normally a 10% decrease from the mean daytime blood pressure while sleeping. Lack of this relative decrease, or "non-dipping", can only be detected by 24 h ambulatory monitoring. In Fig. 1, two different abnormal ambulatory blood pressure patterns are displayed. Isolated daytime hypertension (Fig. 1B) differs from diurnal hypertension (Fig. 1A) by the presence of appropriate dipping shown in the middle third of all of the ambulatory

Table 1
Suggested revised schema for staging of ambulatory BP levels in children [18].

Classification	Office BP[1]	Mean ambulatory SBP or DBP[2,3]	SBP or DBP Load, %[3,4]
Normal BP	<90th %tile	<95th %tile	<25%
White coat HTN	≥95th %tile	<95th %tile	<25%
Pre-HTN	≥90th %tile or >120/80 mm Hg	<95th %tile	≥25%
Masked HTN	<95th %tile	>95th %tile	≥25%
Ambulatory HTN[5]	>95th %tile	>95th %tile	25–50%
Severe ambulatory HTN (at risk for end-organ damage)	>95th %tile	>95th %tile	>50%

%tile indicates percentile; BP, blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
[1] Based on the National High Blood Pressure Education Program Task Force normative data.[9]
[2] Based on normative pediatric ABPM values.[15]
[3] For either the wake or sleep period of the study, or both.
[4] For patients with elevated load but normal mean ABPM and office BP that is either normal (<90th percentile) or hypertensive (≥95th percentile), no specific ABPM classification can be assigned based on current evidence and expert consensus. These 'unclassified' patients should be evaluate on a case-by-case basis, taking into account the presence of secondary HTN or multiple CV risk factors.
[5] Some clinicians may prefer the term "sustained" HTN rather than ambulatory HTN.