Novel Nephrology

Merriam-Webster’s online dictionary defines the adjective “novel” as

1. new and not resembling something formerly known or used, or
2. original or striking, especially in conception or style.

Both definitions apply to the topics covered in this special section, which include noninvasive or minimally invasive diagnostic techniques as well as new interventions to treat disease, all of which can be performed by nephrologists.

Ambulatory blood pressure monitoring is sufficiently new that many insurers authorize payment only for the “exclusion of white coat hypertension.” Jones eloquently discusses the role of ambulatory blood pressure monitoring in white coat hypertension and its opposite, masked hypertension, and the significance of the nocturnal “dip” in blood pressure with regard to long-term prognosis and end organ damage. This noninvasive technique can help predict which type I diabetic patients are at risk for kidney disease and which patients need to be monitored for left ventricular hypertrophy.

Gosmanova and O’Neill discuss the benefits of renal ultrasonography performed by nephrologists to both the patient and the practice of nephrology. Nephrologist-performed ultrasonography is convenient and provides that “clinical correlation recommended” routinely by interpreting radiologists, thus improving patient care. Equipment costs are relatively low, training and certification are available, and it’s fun!

Vats explains how molecular diagnostics can elucidate the pathophysiology of genetic kidney diseases, specifically nphrotic syndrome and cystic kidney disease. Rapid and specific diagnosis of viral transplant infections using quantitative PCR assays is already improving patient care, and genetic advances may lead to personalized care and point-of-contact diagnosis in the future.

Sherbotie delivers a brief but comprehensive review of continuous renal replacement therapies, including which systems can be used for pediatric patients or therapeutic plasma exchange.

Since 2000, the American Society of Diagnostic and Interventional Nephrology (ASDIN) has worked to establish best coding practices and a comprehensive coding manual for dialysis and vascular access procedures. Pfeifer outlines how the ASDIN has worked to improve the quality of care that patients receive related to vascular access, peritoneal dialysis access, and ultrasonography. He also discusses ASDIN’s Procedure Outcomes Registry, an Internet database that is also available to nonmembers. Procedural certification is available through the ASDIN.

While not yet standard of care, each of these novel techniques is likely to rapidly become “best practice.” A common theme is the issue of cost and reimbursement by third party payers. Costs will need to be weighed against long-term benefits as our nation’s health care programs evolve. We’ve made considerable progress since Koff constructed the prototypical dialysis machine from sausage casings and an automobile water pump during World War II. The techniques discussed in this section suggest that the best is yet to come. It’s an exciting time to be a nephrologist.

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Hypertension and Ambulatory Blood Pressure Monitoring

By Deborah P Jones

Ambulatory blood pressure monitoring (ABPM) is a noninvasive, automated method for measurement of brachial artery blood pressure (BP) in a nonclinical setting. The two major benefits of ABPM are that the measurements reflect the diurnal pattern of BP of the individual and that data are obtained outside the clinic or hospital setting. There are excellent reviews on use of ABPM in children and adults (1–3). This article will cover the basics of ABPM—methodology, applications, and indications.

Monitors and software for ABPM are available from numerous manufacturers. Some of these have been validated. See www.dableducation.org for a list of available monitors that have been tested and the outcome of their validation. Most devices use an oscillometric method for detection of BP; however, auscultatory monitors are also available. The former are preferred by most clinicians because of the reduced likelihood for artifact. Auscultatory devices have the advantage of measuring systolic BP (SBP) and diastolic BP (DBP), whereas oscillometric monitors estimate SBP and DBP by detection of mean BP using the manufacturer’s algorithm.

As with casual BP measurement, with ABPM the cuff must be adjusted to properly fit the upper arm to avoid erroneous readings. The cuff is placed on the non-dominant arm and is connected to the recording device. Calibration using a mercury sphygmomanometer and y-connector at the beginning of the study should be performed by trained persons. Patients are instructed to hold their arm still when they feel the cuff inflating to allow successful detection of the BP. After 24 hours, the recording device is docked to a computer with manufacturer’s software to allow computation of mean 24-hour SBP, DBP, mean BP, and heart rate.

Monitors are programmed to measure BP in intervals of 15–30 minutes in most cases. The typical monitoring period lasts 24 hours. Patients are asked to record the times of various activities including bedtime and awakening. Alternatively, a standard sleep period is set from midnight to 6 a.m. Awake and sleep periods are analyzed separately and allow calculation of the nocturnal decline (dipping) in BP. Ten percent or greater is generally accepted as a normal nocturnal decline. In addition, the BP load or percent of readings greater than a designated threshold are calculated separately for awake and sleep periods and combined to yield the BP load for the 24-hour period. One may also evaluate heart rate and BP variability or other patterns in BP, one of which is the ultradian rhythm, which is shorter than the circadian rhythm within a 24-hour period. Ultradian rhythms are analyzed in periods of six to 12 hours in which variations may be the result of changes in sympathetic activity.

Normal values for ABP were initially assigned by correlating the ABP to the corresponding clinic BP threshold of 140/90, which was the definition of clinic hypertension, or from normal reference populations. More recently, normal values for ABP have been obtained using cardiovascular endpoints (4). The suggested values for normal and abnormal ABP in adults are found in Table 1. The definition of normal and abnormal ABP in children has been challenged by the paucity of hard endpoints and available reference values. The largest reference values were obtained by the German working group. Their generalizability is limited due to the homogenous ethnicity of the population sampled, which was uniformly Caucasian. However, a position paper on ABPM in children has concluded that these reference standards are currently

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the best available for interpretation of ABPM in children (3). ABPM is superior to clinic BP measurement in assigning cardiovascular risk. Numerous studies in adults with hypertension (HTN), both untreated and treated, have found that abnormal ABPM is independently associated with a morbid and fatal cardiovascular events.

A landmark study looking at cardiovascular (CV) morbidity (defined as both fatal and nonfatal CV events per 100 patient years) evaluated baseline ABPM in untreated persons with HTN. Investigators found that the rate of events was similar among normotensive controls and in individuals diagnosed with white coat HTN (0.47 and 0.49, respectively). White coat HTN (WCH) is defined as having an elevated office BP and normal ABPM. The rate of hypertensive “dippers” and “nondippers” was much higher at 1.79 and 4.99, respectively (5). Nondippers refers to individuals who display absence of normal nocturnal dipping.

These dramatic differences in risk persisted after controlling for age, gender, diabetes, and left ventricular mass. In a separate study of adults with treated HTN with median follow-up of five years, the adjusted risk of a CV event was significantly associated with both baseline systolic and diastolic HTN as measured by ABPM after adjusting for known risk factors including smoking status, diabetes, body mass index (BMI), lipid levels, and office BP (6).

With ABPM, the clinic-effect or “white-coat” effect on BP measurement is minimized. Although the significance of WCH is still debated, studies indicate that the cardiovascular risk of individuals with WCH is similar to those with normal BP or is significantly less compared to those with abnormal ABPM. The only indication for ABPM currently reimbursed by the Centers for Medicare and Medicaid Services is to rule out WCH. The prevalence of WCH may vary depending on the thresholds selected. When WCH is defined as a mean daytime ABP >130/80 in untreated adults, the risk for CV disease is similar to normotensive individuals (7). Others argue that WCH conveys an intermediate risk for cardiovascular disease and microalbuminuria.

Masked HTN is defined as abnormal ABPM in the setting of normal clinic BP. Masked HTN has been found to increase the risk for left ventricular hypertrophy in both adults and children. Ascertainment of masked HTN is possible only when patients undergo ABPM. At-risk groups such as patients with CKD, diabetes, and post-transplantation may benefit from characterization of BP using ABPM to allow optimization of their antihypertensive treatment regimen. One pediatric study of individuals with type 1 diabetes without end-stage renal disease observed baseline found elevated nighttime BP to predict the onset of microalbuminuria (8).

Generally, a decline of 10 percent from day to nighttime mean BP is considered normal. Approximately one-fourth of hypertensive patients are classified as nondippers. Occasionally BP at night is higher than during the day, a state referred to as “reverse-dipping.” Hypertensive nondippers have higher rates of cardiovascular complications compared to hypertensive dippers. Nighttime BP appears to be a fairly robust indicator of prognosis. Sleep quality and quantity may impact nocturnal BP levels. When sleep is judged to be affected by the ABPM, night time values are of particular importance (9).

Clinic BP levels may lead to misclassification of an individual as hypertensive. Among individuals being treated for essential HTN by primary care physicians, the agreement between the assessment of BP control by office measurement and by ABPM was poor; the indication for ABPM appears to be the greatest in those who are judged to have controlled BP using clinic measurements (10). Failure to ascertain the presence of HTN may be particularly important in the setting of CKD, in which hypertension is known to impact the rate of progression. Forty percent of adults with CKD were believed to have normal BP based upon clinic measurements yet were hypertensive based upon ABPM (11). Analysis of the baseline data from the African American Kidney Disease Cohort revealed that more than half of participants had abnormal nocturnal decline with nighttime HTN. Of those who were believed to have controlled HTN, ABPM demonstrated masked HTN in 70 percent. Even those with HTN only at night had significantly greater target organ damage (12). Among children with CKD stages 2-4, masked HTN was found in 38 percent of the participants. HTN based upon ABPM was the strongest independent predictor of left ventricular hypertrophy, not GFR (13). Reliance on clinic BP levels alone to ascertain the degree of HTN may miss an opportunity to modify a major risk factor for progression of cardiovascular and renal target organ damage, thus the utility of ABPM cannot be understated.

Individuals who fail to demonstrate the expected decline in BP during sleep (nondippers) may have even higher risk for cardiovascular events or cardiac remodeling compared to those with HTN who do “dip” during sleep. Children with type 1 diabetes mellitus, loss of the normal diurnal variability in BP preceded the development of overt microalbuminuria. None of the children who developed microalbuminuria would have been considered hypertensive based on office measurements (8). ABPM is an invaluable tool to improve CV risk and to determine the success of therapeutic interventions in type 1 or 2 diabetics.

It is proposed that use of ABPM to measure the treatment effect of antihypertensive medication reveal significant differences in the pharmacodynamic profile of different classes of medications that can be ascertained by analyzing the circadian BP patterns before and after initiation of treatment. Furthermore, use of ABPM significantly lowers the sample size required to establish treatment effect—ABPM is consistently superior to casual measurement of BP, which is typically used as the monitoring measure treatment effect (14).

The cost effectiveness of ABPM has been analyzed by estimating the incidence of new onset HTN and prevalence of WCH (15). Comparing annual treatment costs with and without use of ABPM, the estimated annual cost for each patient was as low as $130. In other words, use of ABPM to distinguish which individuals are likely to benefit from initiation of antihypertensive therapy is likely to reduce the cost of management of hypertension because it is cost effective compared with treatments costing more than $130/year. This is much lower than the annual cost for treatment of HTN averaged over five years, which was estimated to be $580. ABPM can significantly lower the sample size required for cardiovascular events or cardiac remodeling compared to those with HTN who do “dip” during sleep. Children with type 1 diabetes mellitus, loss of the normal diurnal variability in BP preceded the development of overt microalbuminuria. None of the children who developed microalbuminuria would have been considered hypertensive based on office measurements (8).

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References
15. Krakoff LR. Cost-effectiveness of ambulatory blood pressure monitoring for cardiovascular events or cardiac remodeling compared to those with HTN who do “dip” during sleep. Children with type 1 diabetes mellitus, loss of the normal diurnal variability in BP preceded the development of overt microalbuminuria. None of the children who developed microalbuminuria would have been considered hypertensive based on office measurements (8).

Table 1. Reference values for ABPM in adults (4).

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<th>24-hour</th>
<th>Daytime</th>
<th>Nighttime</th>
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<tbody>
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<td>&lt;100/65</td>
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<tr>
<td>Normal BP</td>
<td>&lt;125/75</td>
<td>&lt;130/85</td>
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<tr>
<td>Ambulatory HTN</td>
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