WHITE PAPER

THE USE OF AMBULATORY BLOOD PRESSURE MONITORING IN DRUG DEVELOPMENT

Robert Kleiman, MD
TABLE OF CONTENTS

LIMITATIONS OF CLINIC BLOOD PRESSURE MEASUREMENTS .................................................4
WHAT IS BLOOD PRESSURE, AND WHY MEASURE IT? .......................................................5
AMBULATORY BLOOD PRESSURE MONITORING ..................................................................6
THE USE OF ABPM IN CLINICAL DRUG DEVELOPMENT ....................................................8
  Some Classes of Drugs with Off-Target Hypertensive Effects ..............................................8
  Advantages and Disadvantages of Different BP Measurement Methods for Clinical Trials ..................................................................................................................9
SUMMARY AND CONCLUSIONS ............................................................................................9
Almost everyone has had the experience of having their blood pressure (BP) measured in a doctor’s office. While you sit on an exam table, someone places a BP cuff on your arm, places a stethoscope head (usually cold) against your arm, manually squeezes a little bulb to inflate the BP cuff until it hurts, and then slowly lets the cuff deflate. This type of clinic BP measurement may be performed by a nurse, a technician or a physician, using a mercury sphygmomanometer (developed in the late 19th century) or perhaps with an aneroid sphygmomanometer (developed during the 20th century). During the past 10-15 years, many physician offices have even switched to using a digital sphygmomanometer, which performs oscillatory measurements rather than auscultation, and which measures the BP automatically as a cuff inflates and deflates. Digital BP devices are easy to use, allowing their use by staff who are not medically trained. These are essentially the same as the home BP devices, or the BP device that you may encounter in a drugstore or supermarket.
LIMITATIONS OF CLINIC BLOOD PRESSURE MEASUREMENTS

Although the use of mercury and aneroid sphygmomanometers has been a standard part of medical care for nearly 100 years, typical clinic BP measurements suffer from several significant failings. First, all of the auscultatory methods which involve the use of a stethoscope are limited by the experience and diligence of the person performing the measurement. Releasing the pressure in the cuff too rapidly or too slowly, or mistaking extraneous noises for the Korotkoff sounds, can result in spurious measurements. There is also a natural tendency to round off the measurements of the systolic and diastolic BP. When the person performing the measurements doesn’t have great confidence in the precision of their measurements, the natural reaction is to round off the values. How often do we really believe that anyone has a BP that is exactly 120/80? Numerous studies have demonstrated that the precision of clinic BP measurements is quite poor, with large inter- and intraobserver variability.¹,²

Digital BP instruments have the advantage here, in that they remove the human component and thus reduce some of this variability. There are some concerns, however, about the calibration of these devices.

A further issue concerns the significance of a BP measurement performed in a doctor’s office. We are really interested in a patient’s BP during their normal daily activities (which fortunately does not involve a visit to a doctor’s office on a daily basis for most of us), not under the artificial condition of being in a medical clinic. In drug development, we are interested in understanding the blood pressure effects of a new drug over the course of the entire day, not just for the short time that the subject is at the clinic. Indeed, research has clearly demonstrated the “white coat hypertension” effect – a significant rise in BP when someone visits a doctor’s office – in at least 15% of normotensive patients.³ After all, how many of us are nervous or downright terrified when we visit a doctor? Another 10% of patients have “masked” hypertension, with normal BP in the doctor’s office, but at least sporadic hypertension during their normal activities.⁴

These issues regarding the precision of the measurement of BP in the office, as well as the concerns about white coat hypertension and masked hypertension, have led to questions about the utility of clinic BP measurements both in clinical medicine as well as during drug development. Should we really make decisions about the treatment of hypertension or the cardiovascular safety of a new drug based on a spot measurement of BP performed under artificial circumstances and with questionable precision?
WHAT IS BLOOD PRESSURE, AND WHY MEASURE IT?

In order to understand the concerns about clinic BP measurements that have led to the development of newer methods of characterizing BP, it is helpful to consider the physiology of blood pressure, as well as the epidemiology of hypertension. First, when we measure “blood pressure”, we are attempting to measure the pressure that the blood exerts against the walls of the arterial system. (When we discuss “blood pressure”, we generally mean arterial blood pressure. One can evaluate venous blood pressure as well, which may become important in certain medical conditions). One can measure arterial blood pressure directly by placing a pressure sensing catheter directly in a peripheral artery or in the aorta, but such invasive methods are hardly practical for general clinical use. Instead, we rely on noninvasive measurements of the BP in peripheral arteries (most commonly the brachial artery in the upper arm).

There are many different components which contribute to the arterial blood pressure, most notably the force generated by contraction of the left ventricle, the volume of circulating blood, and the resistance of the peripheral arterial system. Numerous other factors alter the BP – drugs, the autonomic nervous system, renal function, circulating hormones, etc. However, arterial BP is an important determinant of how we feel and of our general health. Hypotension, whether due to blood loss, an overdose of antihypertensive medications, or left ventricular dysfunction, will produce hypoperfusion of critical organs and can lead to lightheadedness, syncope or death. Hypertension, no matter the specific etiology, has effects on our health. Epidemiologic studies have very clearly demonstrated that on a population basis, every mm increase in BP corresponds to a higher risk of stroke and myocardial infarction, and higher mortality.5-7 Furthermore, numerous studies have demonstrated that treatment of hypertension reduces cardiovascular events and reduces mortality.8-10 The pathophysiology is easy to understand – increased blood pressure puts more strain on the heart, which must generate the force to pump blood against the peripheral resistance in order to generate the arterial BP. Similarly, elevated blood pressure means that arteries are exposed to greater wall stress, increasing the rate at which atherosclerosis develops.

We are therefore interested in measuring blood pressure for a variety of reasons – sometimes to evaluate and treat current symptoms, but far more commonly because we wish to reduce the rate of subsequent cardiovascular events. However, what we really would like to know is an individual’s blood pressure pattern over the course of the full day, not just at a single point in time (especially if that point in time may not be representative of the blood pressure at other times during the day). Having an elevated BP for a few moments while in a medical office, but
otherwise having normal BP, may not really put any stress on the heart or vasculature. In contrast, having persistently elevated BP is of far greater concern.

It therefore stands to reason that a spot determination of BP in a medical office, given that it may not be truly representative of one’s BP throughout the day, may not really be what we want to measure. Instead, it seems that a measurement of BP throughout the day may be more helpful in understanding a patient’s cardiovascular risk or the effects of a new drug on BP and therefore risk of cardiovascular AEs.

**AMBULATORY BLOOD PRESSURE MONITORING**

Ambulatory blood pressure monitoring, or ABPM, was developed as a method to overcome some of the limitations of in clinic measurements of BP. An ambulatory BP monitor is comprised of a BP cuff which is connected by a rubber tube to a portable unit which contains a pump to inflate the cuff, batteries and the electronic circuits to measure the BP and heart rate (HR) and store the data, as shown in Figures 1 and 2. Typical ABPM units are usually about the size of a large smartphone (though somewhat thicker) and can be programmed to measure the BP at flexible intervals over 24 hours. A typical inflation schedule might involve inflations every 15-30 minutes during the day, and every 30-60 minutes at night. Some devices include an activity monitoring system, which allows for correlation between patient activity and BP/HR measurements (this can be very useful for differentiating between waking and sleeping hours, and in detection of spurious measurements during activity). The devices are meant to be used on an outpatient basis as the patient goes about their daily activities, though strenuous activities (and showering!) are discouraged. Since the cuff will inflate periodically, it is very important that the patient be well prepared for the experience.

**Figure 1. Mortara Ambulo 2400 ABPM Device and Cuff**

![Mortara Ambulo 2400 ABPM Device and Cuff](image)
ABPM allows collection of BP and HR measurements over the course of a full day. This is very helpful in eliminating false positive results due to white coat hypertension, as well as avoiding false negative results due to masked hypertension. The BP response during the daytime and hours of sleep are usually evaluated independently, and there are certain BP patterns during sleep which have independent prognostic value (at night, most people have a slight decrease in BP and HR, but some patients have a “reverse dip” and have BP increase during sleep). Figure 3 shows a typical 24-hour BP recording. Note the dip in BP during the sleep hours, when the activity level also falls off.
THE USE OF ABPM IN CLINICAL DRUG DEVELOPMENT

ABPM has become useful in drug development in several settings. First, ABPM is the gold standard for use during the development of new antihypertensive drugs. When the precise BP lowering effects of a medicine must be characterized, ABPM is indispensable.\textsuperscript{11,12} ABPM allows a careful characterization not just of a new drug’s mean BP lowering effect, but also permits a careful examination of the time course of the antihypertensive effects. This can allow a far better understanding of the real duration of antihypertensive effects of a medicine than any other method. ABPM allow us to know for sure whether a new drug controls hypertension for a full dosing interval, or if the effects wear off too soon, potentially leaving the patient unprotected during part of the day.

Similarly, ABPM has become very useful for collecting BP data about new drugs which are not designed to treat hypertension, but which may have unintended, off target effects which increase or decrease BP. Many common non cardiac medications have clear effects on BP, but typical clinic BP measurements are really only able to detect a very large effect. Table 1 lists some of the drugs which are known to produce increases in BP. We know, however, that even small BP increases over a long period of time are harmful, especially in patients with preexisting risk factors for cardiovascular disease, such as diabetes, hyperlipidemia, or cigarette smoking. It is likely that drugs which produce a small, prolonged increase in BP may also increase the rate of stroke, MI and other cardiovascular complications. A new non cardiac medication which produces a BP effect may upset the BP control of a patient who is already hypertensive, and may even precipitate a hypertensive crisis. It is thus important to characterize the BP effects of any new drug, and ABPM is a very useful tool in quantifying such an effect.\textsuperscript{13,14} ABPM is not used in the evaluation of every new drug, but is extremely useful for a new drug where there is a known class BP effect, or where preclinical or early phase trials suggest an effect on BP.\textsuperscript{15-17} Table 2 lists some of the advantages of using ABPM in clinical trials.

Some Classes of Drugs with Off-Target Hypertensive Effects

- Corticosteroids
- Androgens, Estrogens, Progestins
- Recombinant human erythropoietin (EPO)
- NSAIDs, Acetaminophen
- Sympathomimetic amines (ephedrine, pseudoephedrine)
- MAO Inhibitors
- Cyclosporine
- Sibutramine, Serotonin-Norepinephrine Reuptake Inhibitors
- Tyrosine Kinase Inhibitors
- VEGF inhibitors
**Migraine meds**

**Advantages and Disadvantages of Different BP Measurement Methods for Clinical Trials**

<table>
<thead>
<tr>
<th>BP Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Office BP Measurement (Auscultation)</td>
<td>Widely available</td>
<td>Observer bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observer “rounding”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>White coat hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Masked hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manual Data entry into CRF</td>
</tr>
<tr>
<td>Office Electronic BP Measurement</td>
<td>Ease of use, readily available</td>
<td>White coat hypertension</td>
</tr>
<tr>
<td></td>
<td>Eliminates observer bias</td>
<td>Masked hypertension</td>
</tr>
<tr>
<td></td>
<td>Improved reproducibility</td>
<td>Manual data entry into CRF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concerns about calibration</td>
</tr>
<tr>
<td>ABPM</td>
<td>Eliminates Observer Bias</td>
<td>Requires careful counseling of patients to be successful</td>
</tr>
<tr>
<td></td>
<td>Eliminates concerns about white coat and masked hypertension</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Data collected over full 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allows assessment of BP during sleep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Centralized collection of data without need for manual data entry</td>
<td></td>
</tr>
</tbody>
</table>

**SUMMARY AND CONCLUSIONS**

The limitations of clinic blood pressure measurements are well documented, and extend both to clinical practice and to clinical trials during drug development. The availability of ABPM for use in clinical trials overcomes many of the shortcomings of clinic BP measurements, and allows for the precise assessment of the BP effects of new drugs over a full 24 hours, and not just at one or two points following dosing. The expanded use of ABPM during clinical trials will allow us to much better characterize the small but often persistent BP side effects which may be produced by noncardiac medications. Ultimately, such data will finally allow us to better understand the cardiovascular risks of new medications.
REFERENCES


7. pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61


ABOUT ERT

ERT is a global data and technology company that minimizes uncertainty and risk in clinical trials so that customers can move ahead with confidence. With nearly 50 years of clinical and therapeutic experience, ERT balances knowledge of what works with a vision for what’s next, so we can adapt without compromising standards.

Powered by the company’s EXPERT® technology platform, ERT’s solutions enhance trial oversight, enable site optimization, increase patient engagement and measure the efficacy of new clinical treatments while ensuring patient safety. Since 2014, more than half of all FDA drug approvals came from ERT-supported studies. Pharma companies, biotechs and CROs have relied on ERT solutions in 10,000+ studies spanning more than three million patients to date. By identifying trial risks before they become problems, ERT enables customers to bring clinical treatments to patients quickly — and with confidence.