



## Noninvasive Tools Used Nowadays in both, Clinical Practice and Trials in Order to Assess Blood Pressure

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### Abstract

Hypertension affects currently around 1 billion people worldwide and cardiovascular disease remains the most frequent cause of mortality worldwide. Hypertension societies publish cyclically recommendations how to diagnose and manage this illness. Some of them describes tools used to diagnose this disease, others do not. However nowadays many new methods are introduced to assess blood pressure (BP) values. Some of them allow only to obtain central or systolic BP, others are used currently only in animal studies. Some studies proved that they may be a useful tool to assess BP values noninvasive in the future. Here we present a short review regarding methods described in literature to assess BP.

### Keywords

Hypertension, Noninvasive assessment, Blood pressure, Clinical research, Animal studies

### Abbreviations

ABPM: Ambulatory blood pressure monitoring; ACC: American college of cardiology; AHA: American heart association; AP: Arterial pressure; BP: Blood pressure; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; ESC: European society of cardiology; HBPM: Home blood pressure monitoring; JNC 8: Eight joint national committee; PPG: Photoplethysmography; PTNT: Polish society of hypertension; PTT: Pulse transit time; PWV: Pulse wave velocity; SBP: Systolic blood pressure

### Introduction

Cardiovascular diseases (CVD) remain the most frequent cause of mortality worldwide. One of the key risk factors for CVD is hypertension [1]. Although good blood pressure (BP) control may decrease incidence of related deaths and effective treatment is available, first correct hypertension diagnosis has to be made as well as assessment of treatment effectiveness is needed [2]. Both of the above-mentioned goals may be achieved with the aid of different non-invasive tools to assess BP.

### Devices Used for Everyday Blood Pressure Measurement

Nowadays the most frequently used method to assess BP is office BP measurement with auscultatory or oscillometric semiautomatic sphygmomanometers [3]. Due to ban on mercury now sphygmomanometers base on aneroid devices, which proved to be accurate [4]. Although this method has certain limitations, i.e. white coat hypertension, auscultatory gap and influence of cuff inflation and deflation time on BP values [5].

For home use oscillometric devices are recommended, due to its ease to use and satisfactory accuracy [6]. Though, patients should be advised to use devices validated according to standard international protocols [5]. Wrist devices may be very useful in severely obese patients, but their measurements are influenced by wrist position [7].

Ambulatory BP monitoring (ABPM) is obtained with the use of portable BP measuring devices on non-dominant arm for the period of 24 hours. The patient wears a standard cuff and a computer, which weights around 500 g and is worn on a belt or over the shoulder, during the whole time of the study. It provides BP values during patients' normal, daily activity and reduces risk of white coat hypertension [8]. Although, in ABPM measurements arm position may influence obtained BP values [9].

### Everyday BP Measurement and Hypertension Definition according to International Guidelines

American College of Cardiology (ACC)/American Heart Association (AHA) and Eight Joint National Committee (JNC 8) guidelines do not discuss methods of BP assessment [10,11]. European Society of Cardiology (ESC), Polish Society of Hypertension (PTNT) as well as ACC/AHA and JNC 8 guidelines define hypertension as BP values above 140 or 90 mmHg for systolic (SBP) and diastolic (DBP), respectively, if office BP measurements are used [3,10,11]. Some conditions must be fulfilled in order to make proper BP measurement, for example patient must be seated, at least 2 measurements must

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**Table 1:** Indications, advantages, limitations and instructions for correct use of ambulatory blood pressure monitoring.

| Ambulatory blood pressure monitoring                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Indications                                                                                                                                                                                                                                                                                                                                                                                                                                 | Advantages                                                                                                                                                                                                                                                                                                                                                              | Limitations                                                                                                                                                                                                                                                                       | Instructions for correct use                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>- confirmation of HTN diagnosis in patients with grade I HTN and low/medium cardiovascular risk;</li> <li>- suspicion of "white coat HTN";</li> <li>- suspicion of masked HTN;</li> <li>- suspicion of hypotension or autonomic nervous system dysfunction;</li> <li>- diagnosis of truly drug-resistant HTN;</li> <li>- HTN in pregnant women;</li> <li>- HTN in patients with glaucoma;</li> </ul> | <ul style="list-style-type: none"> <li>- measurements are taken in patient's normal environment;</li> <li>- more reliable than office BP values;</li> <li>- more measurements, than in the office;</li> <li>- may have better predictive value for cardiovascular morbidity and mortality than office measurements;</li> <li>- gives information about CBPP;</li> </ul> | <ul style="list-style-type: none"> <li>- high study costs;</li> <li>- low availability;</li> <li>- low reproducibility, though higher than standard office measurements;</li> <li>- limitations in patients' compliance;</li> <li>- patient may not return the device;</li> </ul> | <p><i>Physicians should:</i></p> <ul style="list-style-type: none"> <li>- take measurements on both arms and if the difference is &lt;10 mmHg choose the non-dominant arm, if difference &gt;10 mmHg – arm with higher values;</li> <li>- choose size of the cuff;</li> <li>- give instructions to the patient;</li> </ul> <p><i>Patients should:</i></p> <ul style="list-style-type: none"> <li>- undertake standard daily activity;</li> <li>- limit cardiovascular exercise;</li> <li>- stay still and avoid talking during measurements;</li> <li>- keep the arm supported during measurement;</li> <li>- record relevant daily events;</li> </ul> |

BP: Blood pressure; CBPP: Circadian blood pressure profile; HTN: Hypertension

**Table 2:** Limitations, advantages and instructions for correct use of home blood pressure monitoring.

| Home blood pressure monitoring                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Advantages                                                                                                                                                                                                                                                                                                                                                                                 | Limitations                                                                                                                                                                                                                                                           | Instructions for correct use                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <ul style="list-style-type: none"> <li>- includes patient in the treatment process;</li> <li>- may be used if ABPM is unavailable, not tolerated or refused;</li> <li>- more reliable than office BP values;</li> <li>- more measurements, than in the office;</li> <li>- may have better predictive value for cardiovascular morbidity and mortality than office measurements;</li> </ul> | <ul style="list-style-type: none"> <li>- patient may take the measurements incorrectly;</li> <li>- patient may not follow instructions for correct use;</li> <li>- patient may forget about measurements;</li> <li>- patients may use invalidated devices;</li> </ul> | <ul style="list-style-type: none"> <li>- at least 5 minutes rest before measurement;</li> <li>- at least 2 measurements each time;</li> <li>- preferably 2 measurements daily before drug administration;</li> <li>- at least 4 days, preferably for a week;</li> <li>- discard measurements taken on the 1<sup>st</sup> day;</li> <li>- calculate the average from the readings left;</li> <li>- physicians may ask the patient to bring the device to the office and control correct use of the device;</li> </ul> |

ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure

be taken, cuff and bladder dimensions must be adapted to the arm circumference. Additionally during the first visit BP should be measured on both arms [3]. Those conditions are given in both, ESC and PTNT guidelines [3,12].

Lower BP values are defined as hypertension when ABPM or home BP monitoring (HBPM) are used. They provide numerous BP measurements taken outside of the clinical environment, which are expected to be more reliable than office BP values [3,10-12]. American guidelines do not relate to ABPM value in hypertension diagnosis [10]. Regarding ESC guidelines patient should be instructed to stop talking or moving during cuff infiltration and to remain engaged in normal daily activities, though he should provide dairy with symptoms or actions which may potentially influence BP values. Normal BP values are defined as: SBP under 135 mmHg and DBP under 85 mmHg during awake hours, SBP under 120 mmHg and DBP under 70 mmHg during nighttime. Mean BP values calculated from all available values assessed during measurement should be under 130 and 80 mmHg for SBP and DBP respectively [3]. In PTNT guidelines there are no instructions for patients, but other data are in agreement with ESC guidelines [12]. This method provides additionally data such as circadian blood pressure profile, BP load or morning surge. Though, those additional data is still considered as experimental, since their predictive value has not been fully cleared yet [3]. Although, studies proved that ABPM outcomes are more sensitive as clinical risk predictor for cardiovascular outcomes, morbidity and mortality [3,13,14].

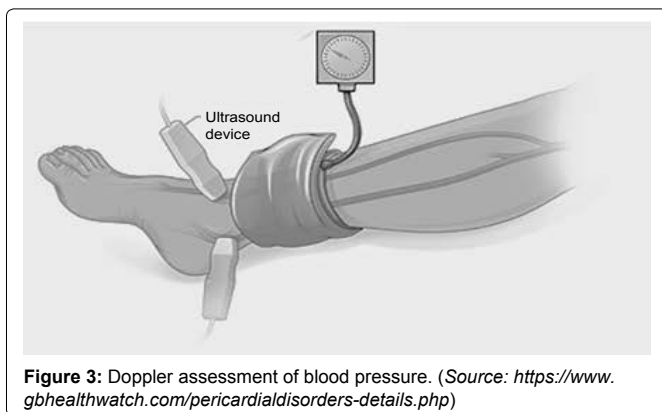
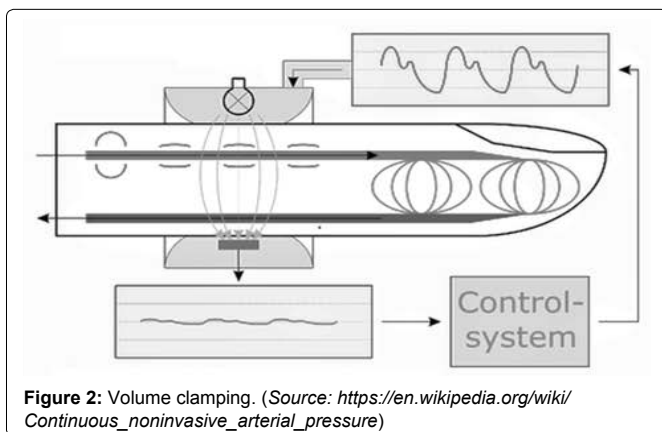
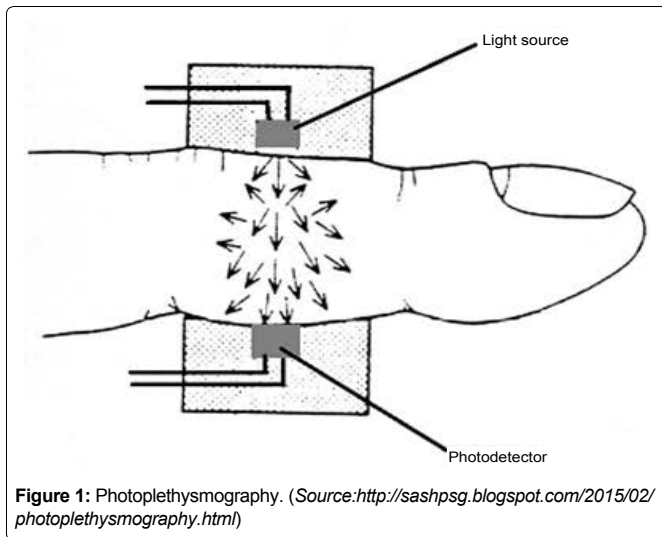
Table 1 summarizes indications, advantages, limitations and instructions for correct use of ABPM.

Home BP monitoring involves patients' self-measurement of BP, sometimes with support of family member or trained health provider. Again JNC 8 guidelines do not state conditions to diagnose hypertension with HBPM [10]. Regarding ESC guidelines measurement should be obtained for 7 days, at least 3 to 4 days, both in the mornings and in the evenings. We should bear in mind that special conditions should be kept, such as 5 minutes rest before measurement and 2 measurements taken each time. Some authors reported that HBPM outcomes have better predictive value of cardiovascular morbidity and mortality than office measurements [3,14]. Polish Hypertension Society gives the same conditions to obtain proper home BP value [12]. Table 2 summarizes advantages, limitations and indications for correct use of HBPM.

## Devices for BP Measurement Used in Clinical Trials and Studies Conducted on Animals

### Central SBP measurement

One of the non-invasive methods to assess central BP is carotid artery pressure measurement. Due to proximity of carotid artery we assume that the pressure values measured on the carotid artery can surrogate values in the aorta. To obtain carotid pressure values we use applanation tonometry and then analysis of the carotid waveforms. We scale them to DBP and mean BP values measured on brachial artery, since they do not vary markedly in the arterial tree [15]. However, this method is highly observer-dependent and is not often used in routine clinical practice [16]. We could also register brachial waveforms, what may be easier and less operator-dependent, but then we need generalized transfer function, identification of



the late systolic shoulder of the peripheral pressure waveform, or a proprietary algorithm to obtain central BP due to factors moulding pulse wave shape remote to aorta [16]. It may be easier to obtain radial waveform, but due to brachial-to-radial amplification it should not be calibrated to the brachial mean and diastolic BP [16,17].

It is worth mentioning that central SBP is usually measured on carotid site and should not be confused with peripheral SBP, measured on brachial artery, since it may be overestimated in young subjects. It may be due to higher peripheral artery stiffness, which increase with age and other conditions diagnosis, such as hypercholesterolemia or hypertension [18]. Central BP values are becoming more interesting for physicians firstly due to their higher than brachial BP values' predictive value for cardiovascular events [19-22]. Secondly, in latest research differential effects of antihypertensive drugs on central BP are starting to be described [23,24].

### Photoplethysmography

The photoplethysmogram, which allows to estimate skin blood flow, and measures not only BP, but also cardiac output and oxygen

saturation, consists of light source and sensor system (Figure 1) [25]. This method includes waveform measurement and from those parameters we can obtain blood volume pulse and then BP. Photoplethysmography (PPG) allows to measure BP on such issues as finger, toe or even ear lobe [26]. However, those outcomes may be influenced by temperature and sympathetic activity [27,28]. On the other hand, it is worth emphasizing that this method is inexpensive and convenient, even if imprecise in some cases [29].

### Volume clamping

Above-mentioned limitations of PPG may be omitted since in 1973 Penaz introduced his novel method to assess BP [30]. It includes additionally to PPG fingertip cuff occlusion (Figure 2). In this method the blood flow oscillations are detected and the finger cuff keeps the volume in the finger arteries constant. From the values of pressure needed to keep the volume in the finger arteries constant obtained by cuff arterial pressure can be calculated indirectly [31,32]. In 1998, after reviewing 43 papers regarding this method's accuracy Imholz *et al.* stated, that this method is an accurate tool to assess mean and diastolic BP, and despite the fact that differences in SBP reached statistical significance, they remained clinically irrelevant [33]. Recently Wagner *et al.* proved those outcomes in their study [32]. Additionally beat-to-beat BP changes and BP variability measured with volume clamping method proved to be accurate and reliable comparing to invasive methods [33]. It is worth mentioning that this method has no risk of infection or bleeding in contrast to invasive tools [32].

### Pulse transit time

Another method now being considered for use in "real-life" is pulse transit time (PTT). It is defined as time between R-wave on the electrocardiogram and peripheral pulse-wave (obtained mainly with the use of PPG). Further from the PTT we calculate pulse wave velocity (PWV) and after that on the base of PWV and BP relation software can calculate BP [34]. Authors also reported that PTT may be used in order to obtain absolute SBP, when an individual correction for the offset of the relation between PWV and BP is performed [35].

### Doppler assessment of BP

Using Doppler machine we as well may obtain BP values, though due to sensitivity of the method it is more likely used in case of low pressures' measurement (Figure 3) [36]. After inflating the cuff to values above SBP we begin to deflate it. The first sound heard by the Doppler machine over the brachial artery is considered SBP [37]. Some authors reported that SBP measured by the Doppler technique agree more closely with directly obtained BP than values assessed by other techniques, such as palpation and auscultation [37]. Some newer devices may measure also DBP, though those measurements correlated less satisfactory with direct measurements than SBP, authors described, that they correlated well [38].

A modification of Doppler method is laser Doppler assessment of BP. This method is more accurate than PPG in case of low BP values, i.e. in case of critical leg ischemia. In laser Doppler moving blood cells cause changes in frequency shift of the reflected light, what is obtained by this method. In order to assess SBP with this method we have to inflate the cuff and then deflate it slowly. The SBP is defined as the moment when signal reappears or rises from the baseline. Additionally minute microcirculatory blood perfusion in the skin is detectable in laser Doppler [39].

### Electrical impedance tomography

This modern technology is a non-invasive tool to analyze bioimpedance signals. It measures intra-thoracic impedance changes in relationship to cardiovascular activity [40]. This method relies on the fact that pulse pressure propagates along arteries, what causes increase of blood volume what is associated with decrease in local impedance. Based on mathematical models others proved that this method is useful in obtaining arterial pulsatility in descending aorta, what may lead to continuous central BP assessment [41]. To the best

**Table 3:** Methods used in clinical trials and animal studies.

| Method                                                               | Advantages                                                                                                                                                                         | Limitations                                                                                                                                                                                                                                        | Clinical use/ future possibilities                                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Carotid pressure measurement</b>                                  | - better prediction of cardiovascular events than peripheral BP values;                                                                                                            | - highly observer dependent;<br>- peripheral interferences;<br>- imprecise;                                                                                                                                                                        | - noninvasive central BP measurement;                                                                              |
| <b>Brachial waveform</b>                                             | - better prediction of cardiovascular events than peripheral BP values;                                                                                                            | - generalized transfer function is needed;<br><br>-identification of the late systolic shoulder of the peripheral pressure waveform;<br><br>- proprietary algorithm to obtain central BP due to factors moulding pulse wave shape remote to aorta; | - noninvasive central BP measurement;                                                                              |
| <b>Radial waveform</b>                                               | - easier to obtain than brachial waveform;<br><br>- better prediction of cardiovascular events than peripheral BP values;                                                          | - brachial to radial amplification;<br><br>- should not be calibrated to brachial BP;                                                                                                                                                              | - noninvasive central BP measurement;                                                                              |
| <b>Photoplethysmography</b>                                          | - allows to measure BP on ear lobe, finger or toe;<br><br>- additional information regarding oxygen saturation and cardiac output;                                                 | - may be imprecise;<br><br>- outcomes may be influenced by temperature and sympathetic activity;                                                                                                                                                   | - noninvasive, continuous BP measurements;<br><br>- especially in neonates and children;                           |
| <b>Volume clamping</b>                                               | - noninvasive method;<br><br>- good reproducibility;<br><br>- information regarding beat-to-beat BP changes;                                                                       | - differences in SBP may reach statistical significance;<br><br>- arterial pressure is calculated indirectly;                                                                                                                                      | - noninvasive, continuous BP measurement;                                                                          |
| <b>Pulse Transit Time</b>                                            | - short-term changes in BP may be detected;<br><br>-continuous measurement is possible;                                                                                            | - affected by arterial stiffness, autoregulation and wave reflection in peripheral arteries;                                                                                                                                                       | - continuous noninvasive BP measurements;                                                                          |
| <b>Doppler assessment of SBP (including laser Doppler)</b>           | - very sensitive method;<br><br>- useful in low BP values;<br><br>- good reproducibility;                                                                                          | - high costs;<br><br>- a lot of equipment is needed;                                                                                                                                                                                               | - critical ischemia, when BP is not detectable by other methods;                                                   |
| <b>Electrical Impedance Tomography</b>                               | - analyzes pulse in the aorta;<br><br>- free of peripheral interferences;                                                                                                          | - complicated reconstruction algorithms;<br><br>- lack of sufficient data regarding usage;                                                                                                                                                         | - new method;<br><br>- introduced to animal studies;                                                               |
| <b>High Definition Oscillometry</b>                                  | - allows measurements of AP in heart frequencies up to 500 bpm;<br><br>- allows to accomplish direct SBP and DBP;<br><br>- linearity during deflation;<br><br>- real time control; | - long term recordings are unavailable;<br><br>- we found no human studies;                                                                                                                                                                        | - studies regarding pharmacology in animals;                                                                       |
| <b>Radiofrequency Ultrasound Wall Tracking of the carotid artery</b> | - well correlated with directly measured SBP;<br><br>- gives information about central BP;<br><br>- noninvasive;<br><br>- more adequate in children;                               | - needs to be calibrated to mean and DBP measured i.e. with sphygmomanometer on brachial artery;<br><br>- amplification between brachial and carotid artery;                                                                                       | - noninvasive control of central BP, i.e. in ICU stations;<br><br>- noninvasive control of central BP in children; |
| <b>Telemonitoring system</b>                                         | - improves treatment goal's achievement;<br><br>- allows better patient monitoring;                                                                                                | - low availability;<br><br>- high costs;                                                                                                                                                                                                           | - monitoring of patients, especially older, with multiple comorbidities;                                           |

AP: Arterial pressure; BP: Blood pressure; DBP: Diastolic blood pressure; ICU: Intensive care unit; SBP: Systolic blood pressure

of our knowledge, currently it is used in order to assess BP only in clinical trials and animal studies. An MRI-based 3D hemodynamic thorax model was built, on which Braun et al. investigated the possibility to measure mean aortic BP using this method, though studies in humans are needed for detailed evaluation [40].

### High definition oscillometry

Conventional oscillometry measures mean arterial pressure (AP) and from this parameter systolic AP and diastolic AP are calculated. In high definition oscillometry pulse amplitudes are based on real-time analysis of artery oscillations. Additionally this method allows to measure AP by heart frequencies up to 500 beats per minute and to maintain linearity during deflation [42]. This method is used mainly in animal studies regarding pharmacology. The newest approach in oscillometry is based not on the mathematical algorithm to calculate systolic and diastolic BP from mean BP. It allows to accomplish direct, both DBP and SBP measurements [43].

### Radiofrequency ultrasound wall tracking of the carotid artery

This method measures carotid pressure changes from calibrated

distension waveforms [44]. Carotid wall tracking measurements should be calibrated to the mean and diastolic BP (obtained by for example sphygmomanometry on brachial artery). It allows measuring only central SBP. Outcomes of this method proved to be well correlated with directly measured BP [45].

### Self BP measurements and telemonitoring system

Currently it is emphasized that despite hypertension diagnosis many patients fail to achieve their treatment goals [46]. Some authors reported that telemonitoring systems of HBPM may be helpful to improve hypertension treatment's management [47,48]. Telemonitoring is a technology used to monitor patients' status from a distance [49]. Notifications are sent to physicians when i.e. BP values are outside of normal range, so they can consult this patient immediately if needed [50]. This can reduce patients' both, travel and off-work time and allow better patients' compliance [50].

### Conclusions

Although multiple noninvasive methods to assess BP values are described and proposed in multiple studies, they are nowadays



mainly used in research and animal studies. They are not evaluated by international societies and their diagnostic value remains unclear. Multiple new devices to obtain noninvasive continuous BP values are proposed. They may be very useful in case for example of cardiac surgery and postoperative monitoring of BP. They may limit the number of infections associated with invasive BP monitoring. [Table 3](#) gives a brief summarization of novel methods' advantages as well as disadvantages.

Additionally the availability of ABPM may become better during next years. Its predictive value is better than predictive value of standard office BP measurements. It also allows to monitor drug effectiveness during the whole day and that may improve timing of drugs' administration.

Home BP monitoring is highly patient dependent. It may be influenced by patients' device and, sometimes, their inability to obtain proper BP values. Although this method in long-term may help to include patient's into the treatment process and may allow better compliance.

Due to limited availability and also lack of data regarding evaluation by international societies authors of this paper consider new methods interesting and perhaps useful in the future. A limitation in their introduction to standard medical use may be high costs and need to invest in new equipment.

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