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Blood pressure measurement and assessment of arterial structure and function: an expert group position paper

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Measuring blood pressure (BP) and investigating arterial hemodynamics are essential in understanding cardiovascular disease and assessing cardiovascular risk. Several methods are used to measure BP in the doctor's office, at home, or over 24 h under ambulatory conditions. Similarly, several noninvasive methods have been introduced for assessing arterial structure and function; these methods differ for the large arteries, the small ones, and the capillaries. Consequently, when studying arterial hemodynamics, the clinician is faced with a multitude of assessment methods whose technical details, advantages, and limitations are sometimes unclear. Moreover, the conditions and procedures for their optimal implementation, and/or the reference normality values for the parameters they yield are not always taken into sufficient consideration. Therefore, a practice guideline summarizing the main methods and their use in clinical practice is needed.

This expert group position paper was developed by an international group of scientists after a two-day meeting during which each of the most used methods and techniques for blood pressure measurement and arterial function and structure evaluation were presented and discussed, focusing on their advantages, limitations, indications, normal values, and their pragmatic clinical application.

Keywords: ankle-brachial index, arterial stiffness, blood pressure, blood pressure variability, capillaroscopy, cardio-ankle vascular index, central blood pressure, intima-media thickness, pulse analysis, pulse wave velocity, retinal microcirculation

Abbreviations: ABI, ankle brachial index; AI, artificial intelligence; BP, blood pressure; BPV, blood pressure variability; CAVI, cardio-ankle vascular index; cDBP, central diastolic blood pressure; Cf PWV, carotid-femoral pulse wave velocity; cSBP, Central systolic blood pressure; CV, cardiovascular; CVD, cardio-vascular disease; DBP, diastolic blood pressure; HVM, handheld vital microscopy; IMT, intima-media thickness; LEAD, lower extremity artery disease; MBP, mean blood pressure; MH, masked hypertension; OBP, office blood pressure; pDBP, peripheral diastolic blood pressure; pSBP, peripheral systolic blood pressure; PWA, Pulse Wave Analysis; PWV, Pulse wave velocity; SBP, systolic blood pressure; WCH, White coat hypertension

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INTRODUCTION

Understanding and accurately assessing arterial blood pressure (BP), arterial function and structure stand as pillars in cardiovascular evaluation. The intricate interplay between these components considerably influences overall cardiovascular function and pathophysiology, making their comprehensive evaluation crucial in research and in clinical practice. This expert-group position paper aims at presenting most of the diverse noninvasive methods and technologies used for evaluating arterial BP, arterial function, and structure, supporting their importance in predicting, diagnosing, and managing cardiovascular dysfunctions and diseases.

BP is a vital and complex hemodynamic physiological parameter reflecting the heart's efficiency, the elasticity of the arteries, and the systemic vascular resistance. Standardization of the methodologies for BP evaluation is crucial to achieve reliable and comparable results among different techniques and studies. Recently, several international recommendations have stressed the importance of using only BP devices that have passed established validation procedures [1–3]. They also describe in detail the methodology for each of the BP measurement techniques, both in and out of the medical setting. In this position paper, we focus on the important methodological and technological aspects and the relevance of their implementation in clinical practice.

In parallel to measuring BP, assessing arterial function and structure holds large significance in understanding cardiovascular function and health status. Arterial function characterizes the dynamic properties of the arteries, encompassing their ability to dilate, contract, and respond to hemodynamic changes. Several techniques are used to assess various manifestations of the arterial functions, such as, ankle/brachial index (ABI), pulse wave analysis (PWA), pulse wave velocity (PWV), cardio-ankle vascular index (CAVI) and others. Some of these techniques have been shown to be useful for early detection and intervention in cardiovascular disease, and others as independent markers predicting cardiovascular events and mortality. In this paper, the essential technical aspects of the most used techniques are described, as well as the scientific interest for their application in research and in clinical practice.

Complementing assessments of arterial function and structure of the large and small arteries provides a comprehensive understanding of vascular health. Ultrasound imaging allows evaluating arterial structure and geometry, e.g. intima-media thickness (IMT) which has been reported as surrogate marker for atherosclerosis. Other techniques can be used to study small arteries directly, such as capillaroscopy for subcutaneous vessels and capillaries, or retinoscopy, a more recent technique which directly evaluates retinal microcirculation. In this position paper, benefits, limitations, and indications of some of these techniques are discussed.

The multifaceted evaluation of BP alongside assessments of the function and structure of large and small arteries constitutes a cornerstone in cardiovascular health assessment. The integration of various noninvasive techniques and imaging modalities empowers clinicians and researchers to comprehensively evaluate vascular health, enabling early detection, risk stratification, and tailored interventions, aiming at more efficient prevention of cardiovascular disease. This expert group position paper aims to clarify the use of some of these techniques, their clinical significance, and their collective impact on advancing cardiovascular care, for healthcare professionals in clinical practice and research.

To develop this position paper, an international group of expert researchers in BP and arterial structure/function participated in a two-day meeting in Paris, December 8–9 , 2023. During this meeting each of the most used methods and techniques for BP measurement and arterial function and structure evaluation was separately presented and discussed focusing on their advantages, limitations, indications, normal values, and their pragmatic clinical application. Abstracts of all the presentations were submitted before the meeting, which were modified by considering key points of the discussions and formed the working draft for developing this position paper. A first draft of the manuscript was prepared and circulated to the authors for additional comments; the revised version was submitted to a review committee to produce a prefinal version, which was recirculated to all coauthors for final consensus.

OFFICE BLOOD PRESSURE MEASUREMENT

Office blood pressure (OBP) measurement is the most widely used method for screening, diagnosing, treating, and following individuals with hypertension, and in many settings worldwide it is the only method available for decision making in hypertension [1–5]. Also, it is the most well studied method with the strongest evidence on which the BP classification of hypertension, the recommended BP thresholds for treatment initiation, and treatment targets are based [1–5]. However, when used alone, OBP may often be misleading in diagnosing hypertension in several untreated and treated individuals, mainly due to the "white-coat" and the "masked" hypertension phenomena, and due to observer prejudice and bias, particularly when taken using manual auscultatory devices [1–6]. Therefore, OBP may lead to false estimation of the true every-day BP values leading to overtreatment or undertreatment of hypertension (Tables 1 and 2). Thus, whenever possible, diagnostic and treatment decisions should be made with confirmatory out-of-office BP measurement (home or ambulatory). If this is not possible, repeated OBP measurements should be taken at additional visits [1–5].

There are several methods and protocols for OBP measurement, including manual auscultatory, automated, and unattended OBP, which provide different BP levels often leading to different diagnoses [6]. For OBP measurement the use of automated electronic (oscillometric) upper arm cuff devices is preferred, which must have at least two independent and successful validation studies using the Universal Standard (AAMI-ESH-ISO) and should include arm circumference with minimum range 22–42 cm [1–3,7]. Additional validation data in arm circumference >42 cm and in children and pregnant women need to be available [1]. A device that takes triplicate readings automatically is preferred. If validated automated devices are

TABLE 1. Requirements for office (or clinic) BP monitors

Essential device features
- Automated electronic upper arm cuff devices
- Validation of device and cuffs in a general population using the AAMI/ESH/ISO Universal Standard (ISO 81060–2 : 2018) and its amendments
- Additional validation using the Universal Standard in special populations (arm circumference >42 cm, pregnant women, children)
- Same accuracy when using battery or AC
- Option for single measurement or for determining the measurement schedule (default triplicate automated measurement, or repeated measurements at various intervals)
- Display average and individual BP readings
- Automated memory storage
- Durability (calibration required every 2 years)
- Washable cuffs, or cuff covers, or disposable cuff covers
- Possibility to sanitize the device
- Reasonable cost of devices and cuffs

Optional device features
- Possibility for manual auscultatory method (digital countdown, or other) with cuff deflation according to the pulse rate or at 2–4 mmHg/sec
- Simultaneous both arms BP measurement (for initial assessment)
- Atrial fibrillation screening with specific algorithm or electrocardiogram technology (for selected populations, e.g., age ≥65 years)
- Possible use for ankle/brachial BP measurements (automated ankle-brachial index)
- Connectivity & interoperability, integration into the medical record
- Five-minute count down for sitting rest before measurement (should be able to cancel)

Other issues
- Battery capacity allowing
- 300 BP measurement before recharge
- Display other parameters: mean BP, pulse pressure, central BP, pulse wave velocity, etc.

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not available, then manual electronic auscultatory devices (hybrid) with LCD or LED mercury column-like display, digital countdown can be used [7–8]. Good quality shock resistant aneroid devices might also be used but require calibration at least once per year. Deflate at 2–3 mmHg/s rate and use Korotkoff sound 1 for systolic BP and sound 5 for diastolic in adults and children (Korotkoff sound 4 is used if sounds are present at < 40 mmHg point [1].

Despite the plethora of guidelines for proper OBP measurement in the last 30 years by many international and national hypertension societies and organizations, its implementation in clinical practice remains imperfect, resulting in considerable misdiagnosis and mismanagement (Table 2). The European Society of Hypertension and the International Society of Hypertension currently recommend taking triplicate automated OBP measurements after 5 min sitting rest and to calculate the average of the last two readings [1–3]. A recent International Consensus Statement supported by several hypertension societies and organizations aiming at standardizing OBP measurement recommended taking at least two measurements and using their average [5].

Unattended automated OBP measurement gives lower BP levels than the classic OBP measurement (close to those of daytime ambulatory BP), which however have uncertain thresholds for defining office hypertension [1–3]. Unattended automated OBP reduces but does not eliminate the white-coat, and the masked hypertension phenomenon which again are present as with classic OBP measurements. Thus, out-of-office BP evaluation with home or ambulatory monitoring is again needed in many cases for accurate diagnosis [1–3]. Moreover, unattended OBP measurement may not be feasible in several settings in clinical practice.

Further to sitting measurements, standing OBP should be measured in patients with hypertension, when there are symptoms suggesting postural hypotension, particularly in the elderly and in patients with neurodegenerative disease (e.g. Parkinson's, dementia) or diabetes. Standing BP should be measured after 1 min and again after 3 min standing [1].

The European Society of Hypertension Working Group on BP Monitoring and Cardiovascular Variability and STRIDE BP recently published a Consensus Statement with requirements for design and function of all BP measuring devices used for the management of hypertension, including office/clinic BP monitors (Table 1) [8].

HOME AND AMBULATORY BP MONITORING. CLINICAL IMPLICATIONS AND PRACTICE GUIDELINES

Office BP (OBP) measurement has important limitations, as it provides only a snapshot of BP in a specific setting, which is considerably different from real life. It causes an alert

TABLE 2. Advantages and limitations of office BP measurement

Office blood pressure measurement		
Advantages	**Limitations**	**Normal Values**
• Used in office / Clinic and research. • Most widely available method. • Most well studied method with strong prognostic value. • Easy to perform. • Low cost.	• Snapshot measurement. • Unusual conditions for patient. • White coat and masked hypertension phenomena. • Observer error and bias. • Questionable accuracy of many devices.	• Differ according to methodology. • Quality differs in guidelines and in clinical practice.

reaction in many individuals, and is affected by errors derived from the equipment, the observer, and the measurement technique. Moreover, OBP is unable to identify BP changes occurring out of the office, either during wake or sleep [1].

Therefore, out-of-office BP measurement presents a better capture of the real BP profile and behavior of the individual in his/her usual activities, using either 24 h ambulatory BP monitoring (ABPM) [9], or in a more familiar setting using home BP monitoring (HBPM) [10].

Advantages

Values obtained through HBPM or ABPM are better correlated with hypertension-mediated organ damage and better predict cardiovascular events and mortality [9,10]. In addition, their reproducibility is superior to that of OBP. HBPM, and ABPM are useful for the diagnosis of white-coat hypertension (WCH) and masked hypertension (MH); which have important prognostic implications. HBPM and ABPM are also useful in treated hypertensives for confirming controlled or uncontrolled BP, as well as to detect excessive BP lowering {1,2]. HBPM is widely available at relatively low cost, it appears to be the most feasible method for long-term monitoring in hypertensive patients and improves treatment adherence and control rates; it also offers information on mid- and long-term BP variability. ABPM is the method of choice for confirming true-resistant hypertension in patients uncontrolled on three or more drugs, offers information on short term, reading to reading and day-night BP variability allowing to assess the BP profile during daily activities and detects nocturnal hypertension and nondipping [1,9]. However, it is not widely available and is rather expensive, and not suitable for repeated use (Table 3).

Normal values

While waiting for outcome-based reference BP levels, normal values are defined according to the correspondent systolic/diastolic office BP of <140/90 mmHg. Hypertension is defined by average HBPM values $\geq$ 135/85 mm Hg (systolic/diastolic); 24-h BP $\geq$ 130/80 mm Hg; daytime BP $\geq$135/85 mm Hg; or nighttime BP $\geq$120/70 mm Hg. Daytime and nighttime mean values should correspond to awake and asleep periods adapted to each patient, avoiding fixed time windows for day and night definitions [1,9–10].

Clinical indications

In untreated individuals, HBPM is indicated to confirm the diagnosis of hypertension and to detect WCH and MH. In treated patients, HBPM is indicated to diagnose uncontrolled WCH and uncontrolled MH hypertension, as well as for titration of BP-lowering drugs, monitoring long-term BP control, ensure strict BP control where mandatory (high-risk patients, pregnancy), and to improve long-term adherence to treatment. HBPM is recommended for all treated hypertensive patients unless they are incapable to perform reliable HBPM or are anxious with self-monitoring [10].

TABLE 3. Advantages, limitations, and indications of ABPM and HBPM

Ambulatory blood pressure monitoring – ABPM	Home blood pressure monitoring – HBPM
Advantages	
Confirmation of Hypertension diagnosis	
Identification of WCH, MH, and uncontrolled/resistant hypertension	
Detection of excessive BP lowering	
Additional prognostic BP phenotypes	
Night-time readings	Measurement in a home setting,
Measurement in real-life settings	Patient engagement in BP measurement
Abundant information from a single 24h session, including short-term BP variability	Easily repeated and used over longer periods to assess day-to-day BP variability
	Can be used with telemonitoring and connection to electronic patient's files
Disadvantages	
Expensive and sometimes limited availability	Only static BP is available
Can be uncomfortable	No asleep measurements (some novel devices can take automatic measurements during sleep)
May induce arousals from sleep	Potential for measurement errors
	Monitoring may be too frequent, induce anxiety and lead to unsupervised treatment changes
Special indications	
Conditions in which WCH is more common, e.g.: grade I hypertension on OBP measurement, marked OBP elevation without organ damage, etc.	
Conditions in which MH is more common, e.g.: high-normal office BP, optimal / normal office BP in individuals with hypertension-mediated organ damage or at high total cardiovascular risk	
Suspected postural or postprandial hypotension	
Exaggerated BP response to exercise	
Considerable variability in office BP measurements	
Assessment of nocturnal BP and dipping status (e.g. nocturnal HT, sleep apnea, CKD, diabetes, endocrine hypertension, or autonomic dysfunction)	Long-term follow-up of treated individuals to improve adherence with treatment and hypertension control
Patient incapable or unwilling to perform reliable HBPM, or anxious with self-measurement	Patients unwilling to perform ABPM, or with considerable discomfort during the recording
Pregnancy	

Modified from [1,10], by permission (free access).
ABPM, Ambulatory Blood pressure Monitoring; BP, Blood Pressure; CKD, Chronic Kidney Disease; HBPM, Home Blood Pressure Monitoring; MH, masked hypertension; OBP, office blood pressure; RH, resistant hypertension; WCH, white-coat hypertension.

In untreated individuals, ABPM is indicated to diagnose hypertension, to detect WCH and MH, and to detect nocturnal hypertension and nondipping. It is the method of choice for assessing BP changes in patients with autonomic failure or with neurological disorders frequently associated to autonomic dysfunction (i.e. Parkinson's disease). In treated patients, ABPM is indicated for the diagnosis of uncontrolled WCH and MH, confirm the diagnosis of uncontrolled or resistant hypertension, ensure 24-h BP control in high-risk patients and pregnancy, confirm symptomatic hypotension due to excessive antihypertensive treatment, and to detect nocturnal hypertension and nondipping. In uncontrolled hypertension, ABPM should be repeated every 2–3 months. In controlled hypertension, once per year monitoring is reasonable [1,2,9] (Table 3).

Requirements and interpretation

For HBPM, properly validated upper-arm cuff oscillometric devices and cuff size which fits the individual's arm circumference are recommended [1,10]. Sets of 7-days measurement (minimum 3 days) with duplicates or triplicates readings both in the morning and in the evening (before meals and before drug intake in treated patients) as per initial diagnosis or before each office visit is the method of choice. Mean values of all measurements, discarding the first day is used for both diagnosis and follow-up [10].

For ABPM, upper-arm oscillometric validated devices with appropriate cuff size should be used. Preferred frequency of measurements is every 20 min both during daytime activity and sleep. Quality criteria include at least 20 valid awake and 7 valid asleep BP readings. 24-h average is the most consistent value for diagnosis and control. However, isolated daytime or nighttime hypertension should also be considered. In addition, the circadian pattern (dipping or nondipping) should be evaluated, yet the reproducibility of assessing parts of the 24 h profile is limited [1,9] (Table 3).

Future directions

HBPM and ABPM represent important advances in the accuracy of BP evaluation, with high impact on diagnosis and management. Cuffless BP measurement technologies have theoretical advantages for BP monitoring in terms of tolerability, identification of fast BP changes, and the possibility of a more detailed closer long-term monitoring. Unfortunately, at the present time these technologies lack well conducted validation studies assessing their accuracy using appropriate protocols. Thus, HBPM and ABPM remain the methods of choice for BP monitoring in hypertension and related disorders.

BLOOD PRESSURE VARIABILITY IN CLINICAL PRACTICE

A large body of evidence has consistently supported the relationship between BP levels and the risk of cardiovascular complications. In recent years, several independent studies have also indicated that this risk may not only depend on the magnitude of the BP elevation per se, but also, on the presence of other associated conditions such as increased blood pressure variability (BPV). This concept has been supported by a series of research reports, including experimental studies, population surveys, observational studies, and post hoc analyses of clinical trials in hypertension, showing that increasing values of BPV may predict development, progression, and severity of cardiac, vascular, and renal organ damage, as well as cardiovascular events and mortality [11,12]. This is the case for different components of BPV, including short- term changes over 24 h (assessed by 24 h ambulatory BP monitoring) [13], mid-term fluctuations measured at home day-by-day (self-home BP monitoring), or the long-term variations as in the case of office visit-to-visit BP changes (Fig. 1).

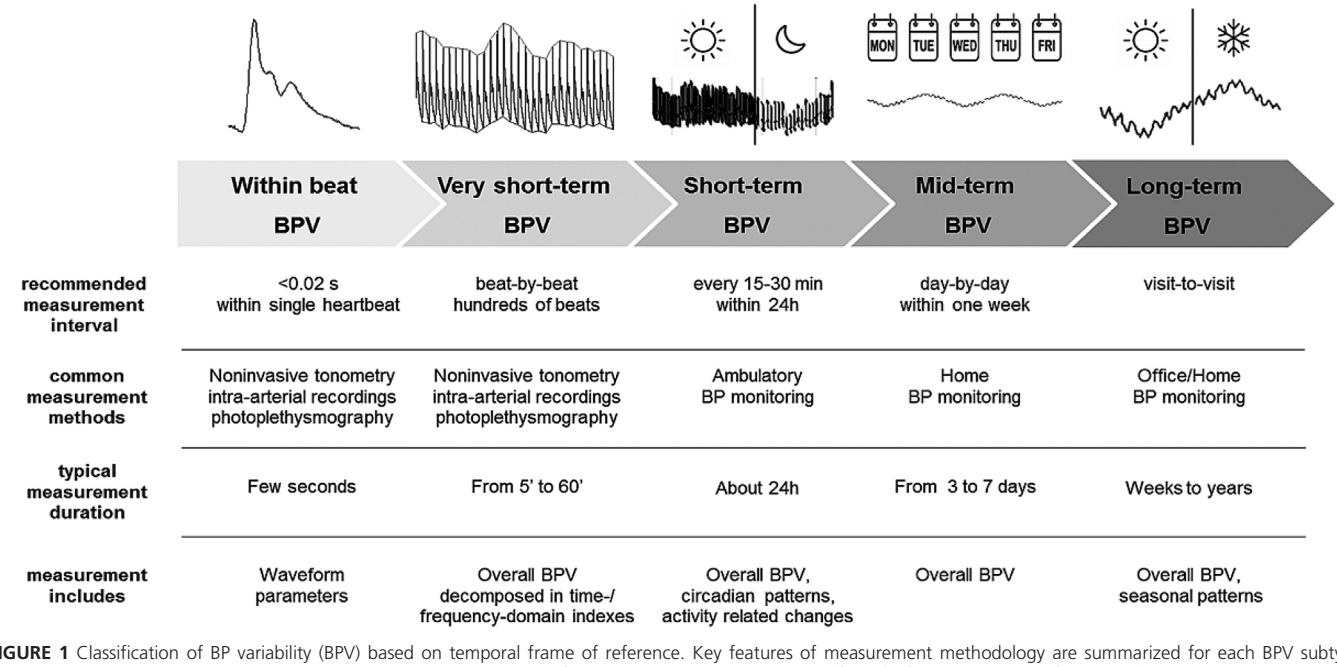

FIGURE 1 Classification of BP variability (BPV) based on temporal frame of reference. Key features of measurement methodology are summarized for each BPV subtype. ''Overall'' variability indicates total variance, including all components of BPV over a given time window. (from [16] by permission – free access).

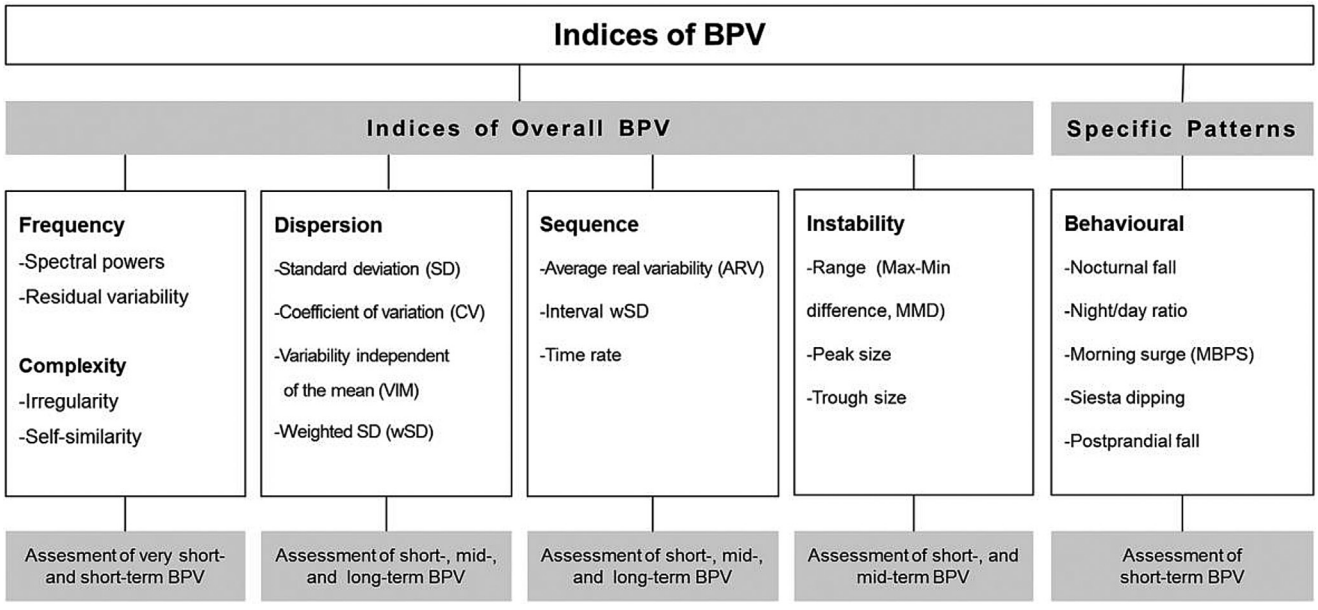

FIGURE 2 Main indices of blood pressure variability.

Remarkably, studies conducted in populations at high cardiovascular risk have shown increasing values of long term BPV in the individual subjects to be strong predictors of cardiovascular morbidity and mortality, even to a larger extent than average BP values. However, in subjects at low-to-moderate cardiovascular risk the contribution of long term BPV to cardiovascular risk prediction over and beyond average BP values has been shown to be only moderate. Evidence is also available that the BP changes between day and night, particularly the degree of BP dipping during sleep, are also related to prognosis, with absence of the nocturnal BP dipping being associated with increased rate of cardiovascular events and mortality.

It is a matter of ongoing debate which BP variability methods, parameters, and indices –established or emerging – are the most powerful in predicting risk and more reproducible, and thus more useful and relevant for clinical practice. Moreover, there is no agreement on whether and how out-of-office BP measurement should be best incorporated and used in daily practice to assess BP variability, to enhance the management of hypertension and to reduce the risk of cardiovascular events (Fig. 2).

Nevertheless, many studies have provided evidence on the prognostic importance of BPV independent of mean BP levels. In addition, the possibility to control BP variability with long-lasting antihypertensive drugs and drug combinations and by selecting specific drug classes has also been highlighted, although randomized controlled intervention trials on the possible impact on outcome of a reduction in BPV by treatment are not yet available [10,14–16]. Even in absence of these trials, however, BPV appears as interesting as the other emerging cardiovascular risk factors mentioned in recent international guidelines for cardiovascular prevention and hypertension management (Table 4). Moreover, at variance from BPV, most of these novel risk factors have no formal evidence supporting their ability to reclassify risk and are not easily or not at all modifiable in individual patients, while accumulating evidence suggests

TABLE 4. Advantages, limitations, and thresholds values of blood pressure variability (BPV)

Blood pressure variability		
Advantages	**Limitations**	**Available working thresholds**
- Increased BPV indicates impaired CV regulation - Increased BPV represents an independent CV risk factor - Increased BPV is associated with development and progression of organ damage and CV events - Elevated short-term BPV and deranged wake-sleep BP changes are associated with higher CV risk - ABPM report should include BPV indices (daytime SD, night-time SD, and 24h weighted SD of SBP and DBP)	- Gaps in evidence on its clinical relevance - Heterogeneous studies without standardization of BPV methods and indices - Lack of intervention trials showing that pharmacological reduction of BPV leads to better outcomes - No universally accepted BPV cut-off values	***Short-term BPV*** Daytime SD SBP >15.0-15.8 mmHg [19] Nocturnal SD SBP > 12.2-14.4 mmHg [20] 24h SD SBP > 12.8 mmHg 24h ARV SBP ≥16.2 mmHg 24h ARV DBP ≥ 12.4 mmHg [21–22] ***Mid-term BPV*** CV of average HBP values over 3–7 days >11% for SBP and >12.8% for DBP [23] 22.0 mmHg morning home SD SBP (99^{th} percentile) 12.0 mmHg morning home SD DBP (99^{th} percentile) [24] ***Long-term BPV*** In Hypertensives VVV SD of SBP > 15.6 mmHg (highest quartile) or >17.9 mmHg (highest quintile) [25]

CV, coefficient of variation; SD, standard deviation; VVV, visit-to-visit BPV.

that specific pharmacological interventions can modify BPV [17]. On such a background the time may thus have finally come to seriously consider use of BPV in clinical practice as an additional BP-related, potentially modifiable risk factor [18] (Table 4).

Because of the lack of some evidence, it is difficult to recommend BPV as a parameter to be used systematically in clinical practice, but BPV is of definite interest. Until specific studies to be carried out, BPV is currently limited to research and specialized centers; but this must not exclude its evaluation in patients with specific characteristics.

CENTRAL AORTIC BLOOD PRESSURE AND PULSE WAVE ANALYSIS

The pressure pulse generated in the proximal aorta due to left ventricular ejection generally increases in amplitude as it propagates towards the periphery due to characteristics of structure and function of the arterial vasculature. In large arteries, mean arterial pressure (MAP) is constant, so change in pulse amplitude is always associated with alterations in wave morphology, such that the area under the central and peripheral pulse wave is similar. In addition, central (cDBP) and peripheral (pDBP) arterial diastolic pressure are also almost similar, so changes in the shape of the pressure pulse wave are predominantly related to differences in central (cSBP) and peripheral (pSBP) systolic pressure. These fundamental physiological observations have been made from invasive measurements and are consistent with physiological considerations of pulse wave propagation [26,27]. The differences between cSBP and pSBP have been shown to spread over the range of 0–30 mmHg, with an average difference of 12 mmHg [26]. Because of the distribution of differences, it is not possible to estimate cSBP by subtracting 12 mmHg from measured pSBP. This would only capture 19% of the values that would be in the similarity range of MAP and DBP. These considerations generated interest in using the peripheral pulse wave to uncover the quantitative relative difference in cSBP and pSBP from noninvasive measurements [27].

The peripheral pressure pulse can be readily obtained noninvasively from the radial or carotid arteries using applanation tonometry or from the brachial artery using a partially inflated cuff. Analytical techniques of pulse wave analysis (PWA) are used to obtain a central aortic pressure waveform which is calibrated using the conventional measurement of blood pressure (BP) with a brachial cuff sphygmomanometer [28]. Methodology for this calibration varies and can potentially give different estimations of cSBP. The pulse waveform can be calibrated using MAP and pDBP or pSBP and pDBP and these differences have been assigned to the designation of specific device types [28]. Therefore, CBP can be calculated noninvasively from peripheral BP waveforms using tonometry or cuff-based devices and dedicated algorithms.

The use of PWA for computation of the central aortic pulse varies from a direct tonometric registration of the carotid pulse [29] to the use of mathematical models [27,30] to transform the time-sampled peripheral pulse to a central aortic pulse, from which pulse components and features can be obtained (e.g. augmentation index, subendocardial viability ratio).

The methodologies of estimating the central aortic pulse waveform using PWA [27,30] are generally robust. However, the calibration procedures can generate some potential confusion due to aspirations of obtaining the true cSBP [28]. Although there are necessary limitations with any noninvasive algorithm, the main factor causing differences in estimated cSBP and true cSBP is the inherent difference between invasive and noninvasive BP due to the operation of the cuff sphygmomanometer. However, it must be recognized that invasive pressure (therefor 'true') measurements are only essentially used in hospital (intensive care) settings, and all management and treatment of hypertension as well as calculations of cardiovascular risk is done using the brachial cuff sphygmomanometer. Hence, the relevant recommendations for central aortic pressure derived by PWA should be that quantitative values of cSBP and cDBP be obtained in relation to the conventional measurements of brachial systolic and diastolic pressures.

Reduction strategies of BP, as a modifiable cardiovascular risk, are currently based on office assessment of brachial artery BP. However, antihypertensive treatment based on brachial BP values reduces cardiovascular risk but does not completely reverse the hypertension-induced risk of morbidity events [2]. The potential effects beyond peripheral BP control may be due to specific protective properties of different antihypertensive drugs to affect central aortic pressure and arterial stiffness. Indeed, much work has focused on central pressure as a better predictor of hypertension-related end-organ damage, CV events, and CV mortality. Currently, with the simple assessment of brachial BP and without considering the effects that central pressure has on CV events, we may be treating or over-treating subjects who may not require treatment and not treating subjects who should be treated. Moreover, these findings highlight the need for the identification of specific populations that might benefit more from the central BP assessment and provide the basis for further investigations [2]. Clinical trials with hard endpoints and designed based on central and peripheral BP assessment are now required to confirm current data and to provide evidence that treatment guidance based on measurements of central BP result in better outcomes. Consequently, this might pave the way for the consideration to enter central BP assessment in the clinical management of hypertension. Nevertheless, such clinical trials are still lacking also because they are very difficult to set up. Furthermore, intercolinearity between the different BP parameters will make their interpretation weak and subject to caution (will the clinical benefit be related to the decrease of such or such BP parameter?). Therefore, more evidence is needed before stating that basing antihypertensive treatment guidance on central pressures rather than on peripheral BP could be one of the factors to be considered for future antihypertensive strategies (Table 5).

Because of the inconsistency of some diagnostic and prognostic data and the absence of clear cut-off values to differentiate normal from high CBP in the wider population, the widespread use of central BP measurement in the clinical management of hypertension cannot be recommended. An

TABLE 5. Advantages, limitations, and thresholds values of central blood pressure

Central (aortic) blood pressure		
Advantages	**Limitations**	**Thresholds values**
- Can be measured using several techniques. - CBP is associated to organ damage independently from peripheral BP. - Help to understand the physiology and Pathophysiology of several CV conditions.	- Different methods of calibration can be used, standardization is needed. - No consensus for validation of devices. - Conflicting results on the predictive value of CBP for CV events. -Similar risk prediction for peripheral and central BP. - Incremental prognostic value of CBP vs. brachial BP is unclear.	- Reference values are available but no conclusive normalcy thresholds.

CBP, central blood pressure.

interesting field of application in clinic may be isolated systolic hypertension in the young in which peripheral BP may be disproportionately elevated compared with normal central BP (Table 5) [2].

On the other hand, in research, the use of central pressure and other parameters such as augmentation index, and wave reflections indices, derived from pulse wave analysis helps to improve our understanding of the pathophysiology of many diseases, as well as some of their treatments. Therefore, for the present time, measurement of CBP is essentially reserved for clinical research and specialized centers.

ANKLE-BRACHIAL INDEX

Ankle-brachial index (ABI) is the ratio between the SBP measured at the ankle and the SBP measured at the brachial level. Measurement of ABI is simple, noninvasive, minimally time-consuming, and inexpensive; it is used for both the diagnosis and surveillance of lower extremity artery disease (LEAD), and the assessment of general atherosclerosis advancement and CV risk [31–33].

ABI measurement involves comparing SBP in the upper and lower limbs, considering the physiological increase in these values as the pulse wave travels through the arterial vessels, resulting from combined effect of pulse wave reflections and amplification, as well as changes in vessel wall thickness and properties. The presence of stenosis in the arteries of the aorta and /or lower limbs results in a decrease in the value of SBP measured in their distal section (and therefore also in a decrease in ABI), while pathological stiffening of the vessels results in an increase in this pressure (and an abnormal increase in ABI).

Indications

ABI should be measured for the clinical purposes in patients with clinical suspicion of LEAD and in patients without clinical suspicion but at risk of LEAD. Table 6 is summarizing the major indications of ABI [31–34]:

How to measure ankle brachial index

Despite the relative simplicity of the method, the data indicate significant heterogeneity in the protocols used, which makes interpretation difficult, especially in the case of serial studies in each patient [35]. Therefore, we suggest the following principles [31–33]:

Material

1. The examination should be performed using a Doppler method. The use of other methods (oscillometric, palpation, etc.) does not ensure sufficient accuracy and repeatability.
2. Assessment of SBP should be performed consistently on the upper and lower limbs using the same method — using a manually inflated cuff and a Doppler probe. The use of automatic oscillometric assessment on arm to simplify the protocol leads to an overestimation of the ABI.
3. It is recommended to use a 5–10 MHz Doppler probe and a cuff adjusted to the limb circumference (width of at least 40% of the limb circumference at the measurement site).
4. Automatic ABI assessment methods may be a promising time-saving alternative, especially in screening. Automated oscillometric and probably photoplethysmography methods seem to be more reliable than

TABLE 6. Indications of ankle/brachial index (ABI)

Indications of ABI	
Patients with clinical suspicion of LEAD	**Patient without suspicion but at risk of LEAD**
- Presence of LEAD symptoms (intermittent claudication) - Presence of other symptoms rest/exercise ischemia of the lower limbs - Presence of nonhealing lower extremity wound - presence of signs suggesting LEAD (pulse abolition, arterial bruit)	- CVD or atherosclerosis in other arterial bed - CVD associated diseases: - Age > 65 years - High total CV risk - Diabetes - CKD - Heart Failure - Aortic aneurysm

CKD, chronic kidney disease; LEAD, lower extremity arterial disease.

automated volume (dual-chamber) plethysmographic methods. Further evaluation studies are necessary [36].

Procedure

1. The measurement should be performed on each arm (with the cuff placed in the typical place and the Doppler probe on the brachial artery) and each ankle (with the cuff placed just above the malleoli and the Doppler probe on both the posterior tibial artery and the anterior tibial/dorsal pedis artery; in the absence of a signal of the above arteries, it is recommended to try the measurement on the peroneal artery).
2. All measurements should be performed in a lying position, in a situation that ensures the patient's comfort, considering the rest period to achieve stable BP values.
3. When using the cuff on lower limbs, it is recommended to avoid areas of ulceration. The cuff should not be applied over distal bypass.
4. It is recommended to use the routine order of measurements: clockwise or counterclockwise, starting from one of the upper limbs and repeated for that limb at the end if the difference in upper limb measurements suggests a white coat reaction.
5. For diagnosing/monitoring LEAD, it is recommended to estimate the ABI for each lower limb separately (by dividing higher of systolic BP measured on the given ankle by higher of the BP measured on both arms).
6. For CV risk assessment, lower of two measured ABIs should be used.

Interpretation

1. An ABI $\leq$0.90 should be considered the threshold for confirming the diagnosis of LEAD.
2. An ABI >1.40 suggests increased arterial stiffness. In the case of clinical suspicion of LEAD in such patients, toe-brachial index should be measured.
3. Both ($\leq$0.90 and >1.40) values of ABI should be considered as independent of others CV and mortality risk factors.

Measurement of ABI is relatively easy and requires only short training. It should be performed in all patients with symptoms or signs of LEAD as well as when arterial evaluation is needed such as in patients >65 years or at high CV risk (Table 7).

PULSE WAVE VELOCITY: TECHNIQUES AND ARTERIAL SEGMENTS FOR ROUTINE MEASUREMENTS

Since the arterial stiffness consensus [37], carotid-femoral pulse wave velocity (cfPWV) has been recognized, at least in Western European countries, as the gold standard for assessing arterial stiffness. In Asia, however, pulse wave velocity (PWV) over the brachial-ankle arterial segment (baPWV) would be preferred. In this section, we briefly review the pros and cons of the various techniques to assess PWV and the advantages and limitations of the various arterial segments.

PWV is the travelling speed of the wave (pressure) over an arterial segment. Today, several techniques and models allow the calculation of PWV from a single point of measurement using arterial pulse wave analysis [37]. As PWV is strongly correlated with age and BP, some prediction models estimate PWV from these and other parameters to estimate PWV (ePWV). While this method gives acceptable results in large cohorts, it does not provide accurate assessment of arterial stiffness at the individual level. As personalized medicine is crucial in routine clinical settings, this methodology will not be further discussed. However, in this review, we will concentrate only on PWV measured between two arterial points.

From the aortic roots to the smaller peripheral arteries, the properties of the arterial wall vary greatly. Numerous techniques have been developed to measure PWV on almost all the arterial segments. Imaging modalities such as Magnetic resonance Imaging (MRI) or ultrasounds allow the measurement of PWV on short arterial segments such as the carotid or the aortic arch. These are called local PWV as the obtained stiffness value is only valid over a short arterial segment (cross-section). Studying longer arterial segments (regional stiffness) involve using 2 probes. Peripheral arteries such as brachial-radial segment or femoral-tibial segment have been assessed in several studies. However, they have been found to be less affected by CV risk factors and age than central (aortic) PWV [38].

From a cardiovascular perspective, only PWV over an arterial segment including the aorta have been reported as strong predictor of CV risk; In particular, elevated cfPWV and baPWV are recognized as an independent CV risk factors thanks to numerous outcomes studies [39,40]. cfPWV studies have mainly been performed in Western countries with the Complior device or the SphygmoCor CVMS device. These two devices work by applying, either simultaneously for the Complior, or successively with the

TABLE 7. Advantages, limitations, and normal values of ankle/brachial index

Ankle brachial index		
Advantages	**Limitations**	**Normal Values**
- Easy to perform - Short training - Low cost - Association with CV prognosis	- Heterogeneity of techniques - Heterogeneity of measurement procedures - Need to validate the automated devices	- Due to the arterial hemodynamic, ABI must be physiologically greater than 1 (ankle SBP > brachial SBP) - Thresholds of ABI are < 0.90 >1.40

SphygmoCor CVMS, sensors at the carotid and the femoral site. However, these devices are not easy to use in routine settings because of the needed operator's expertise to record good quality pressure pulse. To simplify its use, Atcor have launched the SphgymoCor XCEL which measures the femoral pulse with a cuff positioned as high as possible on the thigh, but the carotid pulse is still manually recorded. Other less commercially available devices (Pulse Pen, Vicorder) also propose to measure cfPWV but for all of them, the difficulty to correctly measuring the pulse at the carotid level has greatly impaired their use in routine clinical settings.

While cfPWV is more used in Europe and the United States, Asian countries prefer to use brachial-ankle PWV (baPWV). baPWV has also be found to be related to premature aging and CV risk [40] provided that the patient does not suffer from peripheral artery disease (PAD) (defined as an ABI < 0.9) [41]. Measuring over the brachial-ankle arterial segment might dilute a little the contribution of the aorta on the PWV value, but it has the advantage to greatly simplify the measurement in routine clinical practice. No special expertise is required to record the pulse and measurements are obtained in only a few seconds. Moreover, these devices usually also assess PAD providing a 2-in-1 exam. This is the case for the Omron VP1000 and MESI mTABLET ABI systems. The latter also estimate cfPWV from baPWV for easier interpretation. Finally, we can mention 2 outsiders: Popmetre and Body cardio which also assess PWV over an arterial path which includes the aorta but do not measure the mainstream cfPWV or baPWV. We may also mention the Cardio-Ankle vacular Index (CAVI) measured using the VaSera device which also incorporate PWV (refer to the following section).

Table 8 summarizes the most common commercially available PWV devices and their functionalities in terms of sensor, studied arterial segment and medical usage.

Therefore, the expertise required to accurately measure cfPWV have limited its large routine clinical adoption. Simple, fast, and easy-to-use devices measuring baPWV and including ABI and/or BP measurements will help better manage patient with CV risk on a larger scale.

Normality and thresholds values: Numerous studies have attempted to define normal values and thresholds for PWV. Some have described absolute values, while others have reported values according to age and sex, or even BP. Furthermore, these values change depending on the geographical region, the population studied, and the arterial segment considered, as arterial stiffness increases from the center to the periphery, so the normality values differ depending on whether we are considering the aorta, the arm, or another arterial segment.

Given that the carotid-femoral is the gold standard, and the brachial-ankle is also widely used, only normality and thresholds values for these two arterial segments are considered. The recent meta-analysis of PWV from 167 studies with 509 743 healthy individuals from 34 countries yielded global age-standardized PWV means of 12.5 m/s for baPWV and 7.45 m/s cfPWV [42]. Global PWV levels were higher in men compared with women, with diminished baPWV sex differences with advancing age. Compared to Europe, baPWV was substantially higher in the Asian region, whereas cfPWV differed more by country [42]. This meta-analysis may aid increased clinical use of PWV as measure of vascular ageing. On the other hand, if we consider the threshold values taken into consideration by the European Society of Hypertension, which are based essentially on population and prognostic studies, the threshold values for defining the criteria of HMOD are slightly higher, namely 18 m/s for baPWV and 10 m/s for cfPWV [2]. For instance, these values are recommended for use in clinical practice [2].

Beside these technical aspects, a large body of evidence showed that arterial stiffness using cfPWV and baPWV can be clinically useful in different populations. Recent data suggest that increased arterial stiffness may be involved in the early stage of hypertension with stiffening preceding the development of hypertension. Moreover, studies showed that cfPWV or baPWV can more accurately classify CV risk compared with conventional risk-based scores; an advantage of relevance in young patients in whom the risk falls into the low or moderate level. According to the last 2023 ESH Hypertension guidelines, assessment of arterial stiffness (measurement of PWV) is part of the ''Basic

TABLE 8. Main features of widely used PWV devices

Device	type of sensor	Simult. meas.	PWV				BP	ABI	Operator independent	Usage
			CF	BA	CR	Other				
Complior	mechanical sensor	x	x	-	x	-	-	-	-	Research
Sphygmocor CVMS	tonometry	-	x	-	x	-	-	-	-	Research
Sphygmocor XCEL	tonometry +oscillometry	x	x	-	-	-	-	-	-	Research
Pulse Pen	tonometry	x	x	-	x	-	-	-	-	Research
Vicorder	oscillometry + Doppler	x	x		-	-	x	x	-	Research
Popmetre	PPG	x	-	-	-	Finger-toe	-	-	x	Clinical
Body Cardio Withings	Ballistography +impedance	x	-	-	-	Heart-foot	-	-	x	Patient use
Omron VP1000	oscillometry	x	-	x	-	-	x	x	x	Clinical
MESI mTABLET	oscillometry	x	Est.	x	-	-	x	x	x	Clinical

Simult.meas., Simultaneous measurement using 2 sensors. ABI, ankle brachial index; BA, brachial-ankle; BP, blood pressure; CF, carotid-femoral; CR, carotid-radial; PWV, Pulse Wave Velocity.

TABLE 9. Advantages, limitations, and thresholds values of Pulse wave velocity (PWV)

Pulse wave velocity		
Advantages	**Limitations**	**Reference Values**
- cfPWV is considered as the gold standard - Devices with automatic measurement are available - High prognostic value - Methods using direct measurements rather than calculation are preferred - Automatic validated methods with limited operator-dependency are preferred	- Difficult to apply in some patients (obese…) - Different algorithms used to measure or calculate PWV - Most techniques are operator-dependent - Training is needed - Accuracy of the distance measurement over the skin is questionable	- References values according to age and sex are available - References values of PWV are considered as the main element to calculate the vascular age - Abnormal thresholds: cfPWV > 10 m/s baPWV > 18 m/s

ba, brachial-ankle; cf, carotid-femoral.

screening tests" for Hypertension-mediated organ damages (Table 9) [2]. Despite these recommendations, there are several factors that can limit the extent to which these measurements can be carried out, such as lack of equipment, cost, socio-economic conditions in certain centers and countries, etc.

CARDIO-ANKLE VASCULAR INDEX

The cardio-ankle vascular index (CAVI) was recently developed in Japan for the assessment of structural and functional stiffness of the arterial tree from the origin of the aorta to the ankle [43]. CAVI is derived from the combination of the theory of stiffness parameter **β** and Bramwell-Hill's equation [44], using systolic and diastolic BP and pulse wave velocity (PWV). CAVI is measured by the automatic VaSera device (Fukuda Denshi, Japan). The CAVI is claiming its independency from BP levels at the time of measurement (Figure 3).

The VaSera device provides several parameters related to the arterial hemodynamic. In this system the method of Hasegawa PWV [45] is adopted using the ECG, the heart sound and the pulse waves recorded at brachial and ankle levels to provide the CAVI, PWV, ABI and other parameters (Fig. 3).

Conditions affecting the cardio-ankle vascular index measurement

Like the other techniques, measuring CAVI using the VaSera device may be affected by several parameters such as arteriosclerotic obliteration in lower limbs (ABI is < 0.9), arrhythmias, atrial fibrillation, etc. (Fig. 4).

Normal values

Several studies, mainly in Asia but also in Europe, have published normality values for CAVI. They have shown that:

1. Age and Sex: CAVI increases linearly with age. In men it is higher than in women in all age groups.
2. CAVI cut-off values of 8.0 and 9.0 (<8 for normal, ≥8 and ≤9 for borderline, ≥9 for abnormal) are proposed [46,47].

The prospective CAVI-J study in an Asian population showed increased risk of cardiovascular events and all-cause mortality in subjects with a CAVI of 9.5 and above [48]. Furthermore, the association of CAVI with increased cardiovascular morbimortality, and all-cause mortality was recently extended to European populations with lower cardiovascular risk and lower baseline CAVI in the multicentre prospective TRIPLE-A-study [49]. the latter study reported an optimal CAVI threshold of 9.25 in subjects ≥60 years to predict increased CV morbimortality [49].

Factors affecting cardio-ankle vascular index values

Numerous studies have revealed that CAVI is affected by several factors / diseases (Fig. 4) [46,50] such as:

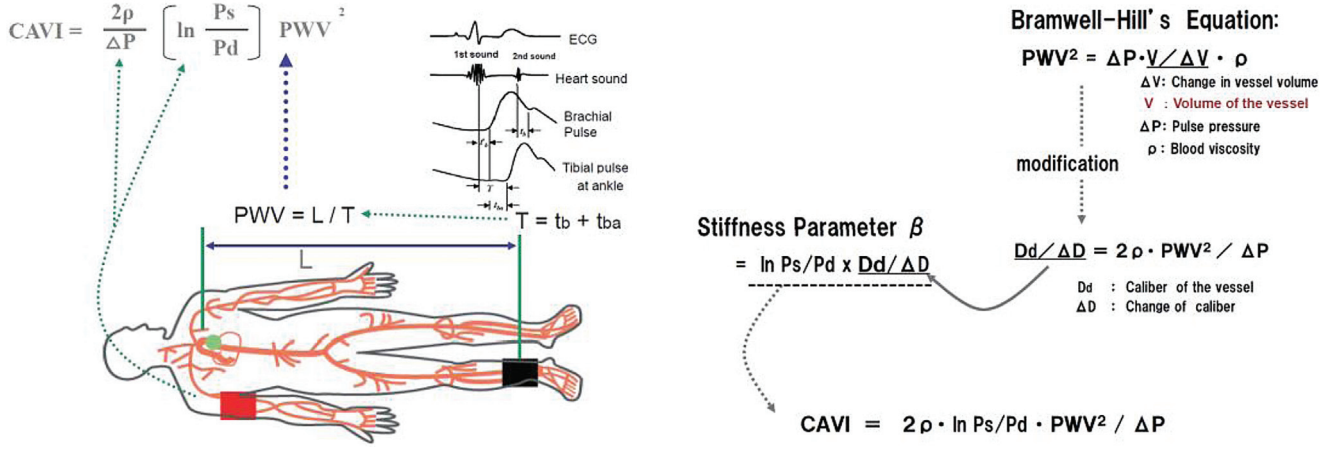

FIGURE 3 Measurement of CAVI and other parameters using the VaSera device.

1. diseases and risk factors [49,51]. Currently, CAVI is mainly

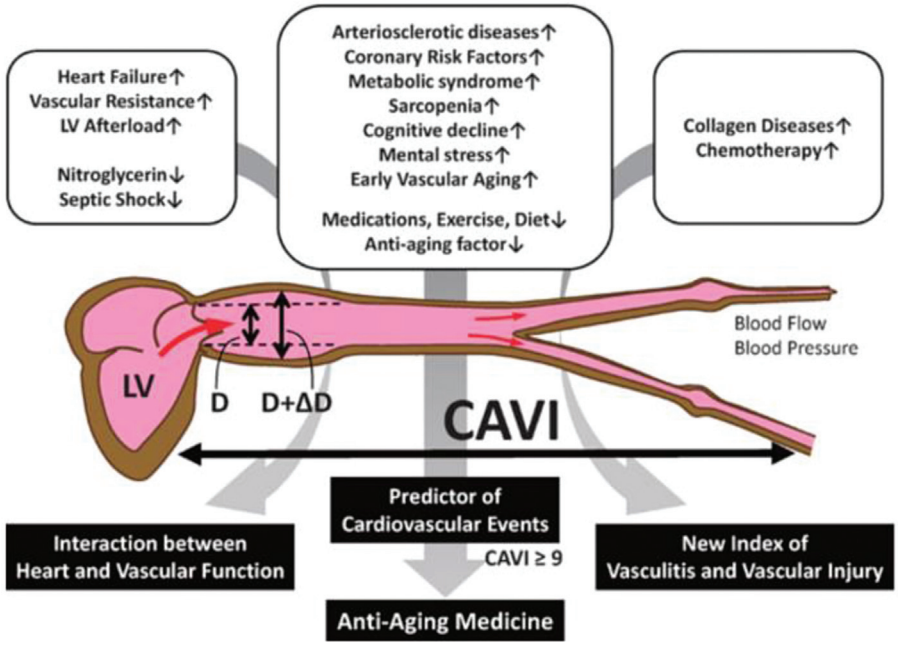

FIGURE 4 Factors affecting CAVI.

Arteriosclerotic diseases, high CAVI value is associated with coronary artery disease, chronic kidney disease, Intima-media thickness, cerebrovascular events, and dementia.
2. Cardiovascular risk factors: CAVI improvement was shown by the treatment of hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, obesity and weight reduction, sleep apnea, smoking, and inflammatory vascular disease.
3. Arterial Smooth Muscle constriction and dilatation, CAVI increases during cold stress, hypovolemia during hemodialysis, and decreases at sepsis, Nitroglycerin administration and Doxazosin Administration [50].
4. Other diseases: increased values of CAVI have been recently observed in sarcopenic elderly subjects [51].

As an index of overall arterial stiffness and independent from the BP level at the time of measurement, CAVI is easy to measure, almost not operator dependent and a reproducible method for the assessment of arterial structure and function. It could be used in everyday clinical practice as indicator for prediction and evaluation of cardiovascular used in Asia for CV prevention and diseases in clinic. In the western countries, more data is needed for its clinical use; in the meantime, it is mainly used by research and specialized centers (Table 10).

INTIMA-MEDIA THICKNESS – CURRENT STATUS

Carotid intima–media thickness, combines the thickness of the intimal and medial layer of the carotid artery, is quantified by carotid ultrasound. The possibility of precise measurement of carotid artery intima-media thickness (CIMT) in B-mode ultrasound imaging was firstly described in 1986 [52]. The association of carotid intima-media thickening, plaque, and stenosis with the risk of cardiovascular disease (CVD) was proven shortly thereafter [53]. More recently, a meta-analysis of 41 941 participants from 16 prospective studies, showed that near and far wall common carotid artery-IMT values were approximately linearly associated with CVD risk with an improvement in risk discrimination was highest when carotid IMT was measured at both walls [54].

TABLE 10. Advantages, limitations, and thresholds values of CAVI

CAVI		
Advantages	**Limitations**	**Thresholds Values**
- Automatic device - Operator-independent - Relatively easy to perform with minor training - Relatively BP independent - Includes several other arterial parameters	- New parameter: CAVI needs to be establish - Cost of the device: relatively expansive - Lack of comparison with the gold standard and other devices	- Higher values of CAVI in men than in women - CAVI increases linearly with age - Availability of normal values in men and women according to age - CAVI > 9 is abnormal

One of the main problems in interpreting IMT results is the differences in measurement methodology. These discrepancies can refer to either one or more of these parameters: the precise definition of the investigated carotid segment, the use of mean or maximal IMT, the measurement of near and far wall or only far wall IMT, use of a single or different angles, employing manual tracking or an automated software, including carotid plaques or not and uni- or bilateral measurements. To avoid this problem standards for IMT measurement have been developed.

Ultrasound examination of the carotid arteries is still quite widely used by clinicians, although the measurement of CIMT has recently lost its former importance for the practical purpose of CV risk stratification and reclassification. Similar situation occurred with the use of CIMT as the surrogate end point in clinical trials. Routine measurement of CIMT was no longer recommended in clinical practice for risk assessment of first atherosclerotic cardiovascular event by American College of Cardiology (ACC) and American Heart (AHA) guidelines in 2013 year (Class III/level of evidence B) [55]. This was mainly due to small potential of CIMT in the improvement of CVD prediction estimated by the Framingham Risk Score. In the next ACC/AHA guidelines in 2019, CIMT was not mentioned at any section. Increased CIMT is not synonymous with atherosclerosis, particularly in the absence of plaque. IMT represents rather subclinical vascular disease: ''arteriopathy'' especially in common carotid artery reflects hypertension-related hypertrophy. CIMT at the level of carotid bifurcations better reflects atherosclerosis and according to newest European Society of Hypertension (ESH) guidelines in 2023, IMT ''can be considered as a marker for the early stage of atherosclerosis'' [2].

The same guidelines stated that: CIMT predicts CV-risk and its value exceeding 0.9 mm is abnormal, moreover carotid plaque was defined by an IMT >1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of surrounding level [2]. These values are consistent with those given in the latest document: Mannheim Carotid Intima-Media Thickness and Plaque Consensus, which comprehensively discusses all methodological issues of ultrasound examination of the carotid arteries [56]. Practical guidelines on how to measure IMT can be found also in ESC E-Journal of Cardiology Practice Vol.13 [57].

In contrast to CIMT, the prognostic significance for cardiovascular events of atherosclerotic plaques found in the carotid arteries is very important. In 2021 European Society of Cardiology (ESC) guidelines on CV disease prevention in clinical practice stated that, systematic use of CIMT to improve risk assessment is not recommended (Class III/level of evidence B) due to lack of the methodological standardization, and absence of added value in predicting CVD. Carotid plaque assessment probably reclassifies CV- risk (Class IIb/level of evidence B). In both ESH guidelines from 2018 and 2023 carotid ultrasound imaging is recommended in patients with, previous TIA or stroke or carotid bruit, to detect significant carotid stenoses (>50% of the vessel lumen) (Class I/B) or may be considered to detect asymptomatic plaques/ stenoses in patients with documented vascular disease elsewhere (Class IIb/B) [2].

In recently published meta-analysis of 119 trials each 10 μm/year reduction in CIMT progression was associated with 9% relative CVD-risk reduction which support the usefulness of CIMT progression as a surrogate marker for CVD-risk in clinical trials [58].

Previous objections to CIMT like lack of measurement standardization and reference values as well as low reproducibility and operator dependence can no longer be maintained. Standardization of the method is provided by Mannheim Consensus [56]. Reference values were provided by Reference Values for Arterial Measurements Collaboration [59]. Used in new devices semi-automated or automated measurements, echo-tracking systems and very precise automatic radio-frequency intima/lumen edge definition guarantee high measurements quality and reproducibility (Table 11).

Novel methods used in carotid ultrasound examination such as plaque burden assessment, carotid arterial strain, shear wave elastography and AI- applications for carotid ultrasound are waiting for confirmation of their practical clinical utility.

Carotid imaging is recommended when presence of carotid bruit, previous TIA, cerebrovascular disease, or evidence of vascular disease.

RETINAL MICROCIRCULATION

The eye offers an ideal window to observe the (micro) vascular changes during the pathophysiology and treatment of cardiovascular and metabolic diseases. Ophthalmological inspection, with a focus on the retina, has been a standard procedure in the diagnostic work-up of hypertensive and diabetic patients for many decades [2]. The classical

TABLE 11. Advantages, limitations, and thresholds values of Intima media thickness (IMT) – Plaques

IMT - Plaques		
Advantages	**Limitations**	**Thresholds values**
-IMT considered as marker of atherosclerosis - Carotid IMT predicts CV risk - Progression of IMT can be reduced by interventions - Reduction of IMT progression is associated with reduction of CV outcomes - Presence of plaques has predictive value independent of conventional CV scores	- Addition of carotid IMT did not improve (or minimally improve) CV risk stratification - Need of ultrasound material - High cost - Training is needed - Times to observe changes is long - More data on the prognostic value of changes are needed	-The upper limit of normality varies with age - Carotid IMT > 0.9 mm is considered abnormal - Plaque is defined as IMT >1.5 mm or focal increase in thickness ≥ 0.5 mm or 50% of surrounding IMT

procedure was based on a semi-quantitative grading system.

For many years, assessment of retinal vessels was limited to fundoscopy performed mainly in patients with risk factors such as diabetes or hypertension, using a 4-grade classification. Fundoscopy allows detection of hemorrhages, microaneurysms, exudates and cotton wool spots (grade 3), papilledema, or macula edema (grade 4); these alterations are reproducible and predictive of mortality. Lesions grade 1 and 2 such as arteriolar narrowing or arteriovenous nicking are less reproducible and have less predictive value.

In the last decades new more precise quantitative and noninvasive technologies have become available to evaluate and follow-up changes in the retinal microcirculation. Some 20 years ago Wong, Hubbard and colleagues introduced a major new approach to retinal imaging which allows a quantitative analysis of the entire retinal microvascular network [60]. They used a nonmydriatic video camera with advanced software to analyze these networks off-line in terms of microvascular diameters, wall-to-lumen ratios, vessel densities, branching angles, and degree of vessel tortuosity. A major advantage of this approach is its potential to make repeated measurements in the same individuals for follow-up studies. Wong and colleagues recently reviewed the results in a range of patient or population-based studies [60–61]. Their work shows that this technology is suited for prognostic studies of the retinal microcirculation in the development or treatment of various cardiovascular and metabolic diseases.

Around the same time, Vilser *et al.* introduced the dynamic Retinal Vessel Analyzer (RVA, Imedos, Germany) to study retinal microvascular dynamics [62]. This noninvasive camera and image acquisition system allows not only the study of retinal microvascular morphology, but also the study of the dynamic changes in vessel diameter upon stimulation with flicker light. Although these latter changes have been interpreted as indicators of the regulation of vascular tone, the underlying physiological mechanisms still need further investigation. A recent review paper gives an excellent overview of the dynamic RVA applications [63]. Another potentially important new approach to noninvasive quantitative retinal microvascular imaging was the introduction of a scanning laser Doppler flowmetry (SLDF) by Harazny and colleagues from Heidelberg, Germany in 2007 [64]. This technique combines confocal and laser Doppler measurements of both structure and functional flow-related microvascular parameters. However, the clinical application of this approach has been limited due to a lack of commercial development of the necessary equipment.

Recently, a commercially available adaptive optics (AO) retinal imaging system for a wide range of clinical studies was developed in France (rtx-1 Adaptive Optics Camera; Imagine Eyes). This system was originally developed for astronomic applications, but it also allows acquisition of high-quality morphological images of retinal micro-vessels with a resolution of up to 1 micrometer. This system is now widely used throughout the world in ophthalmological centers collaborating with cardiovascular specialists. Rizzoni *et al.* [65] recently reviewed the initial results of this noninvasive method to evaluate retinal microvascular structure and function. Importantly, the measurement of wall to lumen ratio of retinal arterioles with this technique may have a clinical prognostic significance [66].

Finally, several imaging modalities have been applied to study retinal flow distribution patterns and microvascular network characteristics [66–70]. These modalities are based on advanced computer-based quantitative image analysis technology, allowing topological assessment of microvascular length, diameter, number, and branching patterns. Among these newer imaging modalities optical coherence tomography angiography (OCTA) is of particular interest since it allows a three-dimensional representation of retinal flow patterns [70].

This range of relatively new technologies has provided convincing evidence that the retinal microcirculation is an excellent marker and prognostic tool in hypertension and other cardiovascular and metabolic diseases. Retinal microvascular investigations are becoming more and more standard tools in the follow-up of patients with cardiometabolic disease, as well as in areas like oncology, in patients treated with drugs influencing microvascular growth, e.g. antiangiogenic drugs [71]. The degree of complexity may differ per technology discussed above. Some can be used standalone in a cardiovascular clinic, while others require a more intensive involvement of specialized ophthalmologists. A major advantage of such a multidisciplinary approach is the more precise long-term follow-up of patients at cardiovascular risk. Even in the absence of local eye disease, quantitative analysis of the retinal microcirculation enables quantification of systemic cardiovascular risk. In addition, retinal micro-vessel biomarkers can be used in large scale population-based follow-up studies or clinical trials aiming at assessing the effect of pharmacological or nutritional interventions in cardiometabolic diseases (Table 12).

CLINICAL MICROCIRCULATION MEASUREMENTS IN INTENSIVE CARE PATIENTS

Sepsis and septic shock are associated with a generalized circulatory failure leading to organ failure requiring intensive care. A further problem in the treatment of sepsis is the unavailability of suitable hemodynamic monitoring tools at the bedside, to identify the origin and nature of circulatory failure underlying sepsis, important to identify the type and adequacy of resuscitation procedures.

Shock, as defined by the recent European Society of Intensive Care Medicine consensus statement, is the inability of the circulation to maintain adequate tissue (read microcirculatory) perfusion. Guidelines advise the use of microcirculatory monitoring in addition to conventional hemodynamic monitoring if available.

Current evidence shows that the origin of circulatory failure leading to organ failure and requiring intensive care is principally related to the persistence of microcirculatory failure, a condition referred to as microcirculatory shock. Such microcirculatory abnormalities in sepsis are associated with a reduction in functional capillary density and the presence of plugged capillaries, together resulting in a decrease in the ability of tissues to extract oxygen from the circulation. Its persistence is predictive of adverse

TABLE 12. Advantages, limitations, and threshold values of retinal microcirculation

Retinal Microcirculation		
Advantages	**Limitations**	**Normal values**
- Direct evaluation of the vessel - Relatively easy to use - Evaluation of the function & structure of the retinal microcirculation	- Multiplicity of the techniques - Multiple parameters can be used - Choice of the most predictive value - Relatively high cost - Training is needed	-Absence of establish normal values

outcomes. Therefore, monitoring the microcirculation at the bedside is essential [72].

These insights have gained clinical acceptance through our introduction of hand-held vital microscopes (HVM) allowing direct bedside microcirculatory observations applied mainly sublingually. These devices consist of a light lens guide pipe attached to an image sensor at its end, and at its tip fitted with concentric green light-emitting diodes with a magnifying lens at its tip. Automatic analysis of these images can directly provide information regarding capillary red blood cell flow quantifying the convective capacity of the microcirculation and the density of RBC-filled capillaries (total vessel density and functional capillary density) as a measure of the diffusive capacity of the microcirculation [73,74]. Automated software for online analysis of the functional parameters of the microcirculation [74] allows point-of-care microcirculatory guided resuscitation of critically ill patients to be realized at the bedside. Besides microcirculatory hemodynamics leucocyte kinetics can also be quantified [75]. More than 500 articles have been published on the use of HVM specifically in intensive care and surgery. Analysis and classification of different classes of alterations allow a differential diagnosis to be made [73,74]. AI analysis has been applied to develop an AI-based algorithm to identify COVID-19 patients and to assess the compensatory mechanisms associated with respiratory distress [65–77]. Recently a new generation of low-cost HVM has been Introduced called the Oxycam which in addition to having embedded automatic AI-based Microtools software is fitted with blue and green light allowing ratio imaging of the different wavelengths which wavelengths which in addition to images of flowing blood cells provides images (pseudo-color: red highly saturated; blue low saturation) of the hemoglobin saturation of the red blood cell in the micro-vessels. It is expected that with the introduction of this new HVM technique, it will be possible to titrate therapy to target microcirculatory endpoints meeting the requirement that resuscitation should be able to normalize tissue red blood cell perfusion following shock (Table 13).

CONCLUSION

The present Expert Group Position paper developed by international experts and endorsed by six scientific societies summarizes the characteristics of 11 methods for assessing arterial hemodynamics. Among these methods are those for measuring blood pressure, as well as those for assessing the structure and function of large arteries, small arteries, arterioles, and capillaries. Each of these techniques studies a specific aspect of circulatory hemodynamics with its advantages, limitations, indications, and normal values. Many research studies are needed to clarify questions on the methodology and benefits of applying several of these techniques in the clinical setting. For now, it is up to the user to follow the optimal methodology and conditions for their implementation and to interpret the results based on established normal values or thresholds, integrating their results into a comprehensive approach to the individual.

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TABLE 13. Advantages, limitations, normal values, and use of Microcirculation in intensive care patients

Microcirculation in intensive care patient			
Advantages	**Limitations**	**Normal value**	**Indications**
- Sublingual microcirculatory imaging by HVM provides direct images of blood cells in the capillaries. - Various classes of alterations allow bedside differential diagnosis of microcirculatory dysfunction. - Quantification of Inflammatory activation by observation of leucocyte rolling and sticking to the vessel wall.	- Requires skill and training; (Pressure by the user on the HVM imposed on the tissue surface can cause an alteration in blood flow giving a pressure artifact) - Requires specialized software for analysis. - Difficult to make measurements in uncooperative patients, children, and babies.	- Values are dependent on the quality of optics - Current high-quality optics give a total vessel density between 18 and 20 mm/mm^2 - Covid shows a higher value, hypertension, and anemia lower values.	- Mainly used for research - Introduction of a new generation of HVM opens the way to point-care-use at the bedside. - High sensitivity and specificity in diagnosing different classes of shock, - Use in titrating vasoactive medication to control blood pressure at the bedside (e.g. catecholamines)

HVM, hand-held vital microscopes.

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Conflicts of interest

There are no conflicts of interest.

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