Methodology and Technology for Peripheral and Central Blood Pressure and Blood Pressure Variability Measurement: Current Status and Future Directions.
Position Statement of the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability

Short title: BP measurement methodology - technology

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CONFLICT OF INTEREST

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ABBREVIATIONS

ABPM, ambulatory blood pressure monitoring

ACEI, angiotensin-converting enzyme inhibitor

AOBP, automated office blood pressure measurement

ARB, angiotensin receptor blocker

ARV, average real variability

ASCOT, Anglo-Scandinavian Cardiac Outcome Trial

BP, blood pressure

BPV, blood pressure variability

CCB, calcium-channel blocker

ceBP, central blood pressure

CV, coefficient of variation

ESH, European Society of Hypertension

HBPM, home blood pressure monitoring

MRC, Medical Research Council

PP, pulse pressure

VIM, variance independent of mean

ABSTRACT

Office blood pressure measurement has been the basis for hypertension evaluation for almost a century. However, the evaluation of blood pressure out of the office using ambulatory or self-home monitoring is now strongly recommended for the accurate diagnosis in many if not all cases with suspected hypertension. Moreover, there is evidence that the variability of blood pressure might offer prognostic information which is independent of the average blood pressure level. Recently, advancement in technology has provided non-invasive evaluation of central (aortic) blood pressure, which might have attributes which are additive to the conventional brachial blood pressure measurement. This position statement developed by international experts deals with key research and practical issues in regard to (i) peripheral blood pressure measurement (office, home and ambulatory), (ii) blood pressure variability, and (iii) central blood pressure measurement. The objective is to (i) present current achievements, (ii) identify gaps in knowledge and issues concerning clinical application, (iii) present relevant research questions and directions to investigators and manufacturers for future research and development (primary goal).

KEYWORDS

Measurement, monitoring, peripheral blood pressure, brachial blood pressure, central blood pressure, aortic blood pressure, blood pressure variability, clinic blood pressure, self-measurement, ambulatory blood pressure.

INTRODUCTION

Non-invasive measurement of blood pressure (BP) remains the cornerstone for hypertension diagnosis and management [1]. Office BP measurement has been the basis for hypertension evaluation for almost a century. Yet, and although research is needed on several aspects, ambulatory (ABPM) or home (HBPM) monitoring is strongly recommended for the accurate diagnosis in many if not all cases with suspected hypertension [1-4]. More recently, advancement in technology provided non-invasive evaluation of central (aortic) BP, which might have attributes which are additive to the conventional brachial BP measurement [5].

A position statement on these issues was outlined by BP monitoring experts at the end of a Scientific Symposium organized by the European Society of Hypertension (ESH) Working Group on BP Monitoring and Cardiovascular Variability and the Hypertension Center STRIDE-7, Athens University, Greece, which took place in Athens during the 2014 ESH/International Society of Hypertension meeting. On the basis of that meeting, a writing group of four experts (G. Stergiou, G. Parati, V. Vlachopoulos, E. O'Brien) prepared a first draft which was circulated among all the authors of this document, and a final version of the statement was prepared and approved by all.

Three main topics are discussed in this paper: (i) peripheral BP measurement (office, home, ambulatory); (ii) BP variability (BPV); (iii) central aortic BP measurement. Objective of this statement is not to provide a systematic review of the above topics, but to (i) present current achievements, (ii) identify gaps in knowledge and issues concerning clinical application, (iii) present relevant research questions and directions to investigators and manufacturers for future research and development (*primary goal*).

I. PERIPHERAL BLOOD PRESSURE MEASUREMENT

I.I. Office BP Measurement Methodology and Technology

For almost a century the methodology of office BP measurement has remained virtually unchanged, and is still based on 2-3 seated readings taken by a doctor, nurse or medical assistant [1]. Recently there has been a major shift in BP monitoring technology, mainly due to the development of electronic devices, the progressive ban of mercury in several countries, and the increasing interest for out-of-office BP measurement.

Technology - Methodology

Currently the most widely used mercury-free devices are automated oscillometric BP monitors [6]. Some professional oscillometric devices allow repeated automated measurements and averaging; simultaneous both-arms measurements; arm and leg BP measurement and automated ankle-brachial index calculation; auscultatory BP measurement mode; detection of arrhythmia or specifically atrial fibrillation; automated memory, and PC link or bluetooth transfer of readings [7]. Professional mercury-free auscultatory devices (hybrid devices) have also been developed, with mercury like column and LCD or LED technology or aneroid device-like screen to display the cuff pressure [7]. Aneroid sphygmomanometers are also available for auscultatory BP measurement.

In terms of methodology, the automated office BP measurement (AOBP) concept has been introduced [8-10], which takes multiple automated readings using an electronic device with the patient resting alone in the office. AOBP decreases the white coat effect, correlates more closely with ambulatory BP and organ damage, and provides similar BP values as awake ambulatory BP [8-10]. A lower cut-point for high AOBP (135/85 mmHg) has been proposed compared to conventional office measurements [8,9].

Issues concerning clinical application

The main problem of office BP measurement is the setting per se, which may induce a white coat reaction. An additional major problem is the observer error and bias (prejudice and terminal digit preference) which

is present with all auscultatory devices (mercury, aneroid, or hybrid). It is recognized that manual auscultatory office BP measurement is often poorly performed in clinical practice. Automated devices prevent observer-related problems, yet they are still affected by the white coat phenomenon, which is lessened with AOBP. Devices developed for self-home monitoring are often used for office BP measurement in primary care.

The exclusive use of oscillometric devices for office BP measurement is still debatable, mainly due to their questionable accuracy in the presence of arrhythmia, and particularly atrial fibrillation [11]. There are also cases with disagreement between oscillometric and auscultatory measurements without clear reason. In atrial fibrillation auscultatory BP measurement is difficult and uncertain, and disagreement with oscillometric BP does not necessarily mean that the latter is less accurate [11]. On the other hand, undiagnosed atrial fibrillation might be missed if electronic BP measurement is only taken in the office and auscultation or pulse palpation is not used. Automated detection of atrial fibrillation during routine automated office BP measurement using an embedded algorithm would be useful for efficient screening [12,13].

Unmet needs - Future research and development

- The modern office BP measurement should provide an accurate and unbiased evaluation and fulfil the requirements for applying the method in clinical practice as currently recommended [11].
- The demise of mercury together with the longstanding failure to obtain standardized auscultatory measurement in clinical practice, strongly supports the widespread use of automated devices. Such devices should meet other requirements, such as taking and averaging multiple measurements, simultaneous both-arm BP measurement, PC link capacity to transfer measurements into medical records, and auscultatory BP measurement mode for selected cases according to the physician's discretion [11].
- Additional features should only be implemented if scientifically tested and endorsed by guidelines.
- AOBP seems to be a superior office BP measurement method, but deserves further investigation.

- Only validated devices should be used, and preferably those designed for professional use [11]. Annual service and recalibration is mandatory.

I.II. Ambulatory BP Monitoring Methodology and Technology

ABPM is currently regarded as the most reliable tool for BP assessment, because it provides an objective evaluation within 24 hours, takes multiple measurements in routine daily conditions, identifies the white coat and masked hypertension phenomena, and predicts cardiovascular events more accurately than office measurements [14]. Several organizations now recommend ABPM in many if not all cases with suspected hypertension [3,4,14-16], yet others still consider office BP as the reference measurement [17-18]. It should be recognized, however, that the superiority of ABPM over office BP-guided therapy, in terms of cardiovascular disease prevention, has never been tested in a randomized controlled trial [19].

Technology - Methodology

There are several small and light devices, and some have additional functions, including central BP and pulse wave velocity measurement, physical activity recording for awake and asleep BP evaluation, home BP monitoring function, elecrocardiography monitoring. New devices based on wrist tonometry or on pulse transit time measurement that are dependent on calibration by the brachial pressures offer a new level of wearability and patient acceptance that may overcome the inconvenience of traditional ambulatory devices, yet more validation data are needed before implementation. Pharmacy-based provision of ABPM service appears to be feasible, user friendly for doctors and patients and cost effective [20].

Issues concerning clinical application

Despite the widespread recommendation, ABPM is not being widely used in primary care in most countries. Main barriers are the high cost of devices, the time required for application and downloading, patients' discomfort, and the lack of reimbursement in most countries. ABPM reports are often misinterpreted by doctors.

Unmet needs - Future research and development

- Novel technological developments, including cloud based remote monitoring, integration into clinic patient management software and new patient friendly devices (in terms of size, cables, noise), are needed to remove major barriers to the routine use of ABPM in clinical practice.
- The monitor programming for routine use should be standardized according to current guidelines [14].
- The ABPM report should be standardized and uniform for all manufacturers and devices, presenting raw and summary data, 24h plots and automated interpretation of the findings (particularly for out-of-office services) according to current guidelines [14].
- The cost of the monitors can and should be considerably reduced. Focus should be directed towards all the barriers to using ABPM in primary care.
- Further to primary care practices, hypertension centers and specialist clinics, new models to develop standardized and simplified ABPM services might be more cost-effective and should be adequately tested, including healthcare providers in the private sector and pharmacy-based services.
- Only monitors validated using an established protocol, including evaluation in ambulatory conditions, should be used.
- Despite the enormous research evidence on ABPM [14], outcome data of office BP versus ABPM-guided therapy and on the optimal ABPM target are still awaited [19].

I.III. Home BP Monitoring Methodology and Technology

HBPM is being widely used in several countries and current guidelines recommend its use in most cases with treated or suspected hypertension [2,21,22]. This is because HBPM avoids the white coat and masked hypertension phenomena as well as the observer error and bias (with electronic devices), is popular among patients, might allow self-titration of treatment in selected patients [23], and has been shown to improve long-term compliance with treatment and hypertension control rates [2].

Technology - Methodology

A long list of validated oscillometric arm devices for HBPM is currently available on the market [7]. Additional features implemented in home monitors include automated memory, averaging of all, morning

and evening, or weekly readings, nighttime sleep BP monitoring function, implemented monitoring schedule, detection of arrhythmia or specifically atrial fibrillation, printer, or PC link.

Several wrist devices have passed established validation protocols, and some have implemented sensors to avoid incorrect positioning of the arm [7], yet they are still regarded as less accurate than arm devices and have problems in correct clinical application [2].

Issues concerning clinical application

Several monitors that have not been adequately validated are available on the market [7]. Wrist monitors require further technological improvement. The reporting bias (over- or under-reporting of self-measurements by patients) limits the reliability of the method and undermines its value in decision making in hypertension [24]. User education and medical supervision are necessary. The latter can be reduced with technological standardization of the method application.

Unmet needs - Future research and development

- For using HBPM in decision making, new technological solutions should be implemented to ensure an unbiased report of readings, which appears to be feasible and with relatively low cost.
- Ideally the HBPM report should be standardized and uniform for all manufacturers and devices, and include: number of measurements, average of all and of morning and evening readings, graphic presentation over time, and raw data.
- Technological solutions should be developed to ensure HBPM reporting according to the recommended monitoring schedule. The report should be based on selecting readings in accordance to the recommended schedule, with potential secondary average of all available readings.
- Technological solutions are needed to personalize HBPM reporting and avoid averaging of readings of different subjects.
- Only validated upper arm devices with automated memory and averaging (with little additional cost), PC link, or printing capacity should be used.
- Wrist home monitors require further technological improvement.
- More research is needed on the (i) hypertension threshold for HBPM [25], (ii) optimal schedule for

long-term HBPM in treated hypertensives, (iii) the optimal schedule for nocturnal HBPM and its clinical relevance and utility compared to ABPM [26-29].

I.IV. Home BP Telemonitoring

Technology - Methodology

Home BP tele-monitoring based on electronic monitors storing and transferring data to a remote computer is a promising, unbiased and potentially cost-effective tool, particularly for cases requiring tighter BP control (high-risk hypertension, diabetes, elderly, pregnancy, etc), and seems to be well accepted by patients and physicians [30,31]. Randomized and observational prospective studies have shown that home telemonitoring may improve BP control and cardiovascular risk compared to standard care [32,33].

Issues concerning clinical application

Complexity and cost are the main barriers to its wide clinical application.

Unmet needs - Future research and development

- User-friendly and low-cost applications should be developed aiming at wider implementation in more healthcare systems and patients.
- Prospective studies including hard endpoints and economic aspects, particularly in high-risk hypertensive patients are needed.
- Integrated multilevel patients' management programs involving different healthcare professionals (e.g. general practitioners, specialists, nurses, pharmacists, nutritionists, etc.) require thorough research, aiming at improving screening and management of hypertension and related comorbidities and thereby cardiovascular disease prevention.

I.V. Cuff Technology for BP Monitors

Technology - Methodology

For auscultatory BP measurement it is recommended that the size of the inflatable bladder of the cuff should match the individuals' arm circumference as too small or too large cuff might lead to over- or underestimation respectively [1,34].

Modern oscillometric devices can overcome the problem of miscuffing in obese individuals by using to a special software algorithm that provides accurate BP readings even when coupled to a single cuff of theoretically inappropriate size. Thus, oscillometric devices with a single cuff and the appropriate software algorithms have yielded accurate measurements over a wide range of arm circumferences, up to 40 cm and over [35,36].

The cuff shape affects the BP measurement accuracy in obese subjects with conically-shaped arm and forearm, with cylindrical arm and wrist cuffs shown to overestimate BP and tronco-conical cuffs to improve the measurement accuracy [37,38]. Tronco-conical cuffs should be used for arm circumference >32 cm [34].

Issues concerning clinical application

In clinical practice the availability of full range of cuffs to fit all arm sizes is rarely followed. There are additional issues in obese subjects regarding the wide availability of large cuffs, and cylindrical cuffs may overestimate BP.

Unmet needs - Future research and development

- Special attention should be given to the bladder size and shape and the cuff material.
- Separate validation studies in subjects with large arms are necessary.
- For devices with wide-range cuffs, clinical validations should ensure adequate testing across all the range of the recommended arm circumference distribution.

I.VI. Validation Protocols for Peripheral BP Monitors

Methodology

In the last thirty years strict validation protocols for BP monitors have been developed, which established accuracy standards and allowed the comparison between different studies and devices [39-41]. The ESH International Protocol simplified the validation procedure by reducing the sample size required, and greatly expanded this area of research with an impressive rise in the number of devices validated worldwide [41,42].

Issues concerning clinical application

The use of different validation protocols does not allow comparison between studies. The standard peer review process of validation studies by scientific journals often misses protocol violations. Some of the reported validation studies have unexpected results and questionable reliability. There is evidence that negative studies are often not published (publication bias).

Unmet needs - Future research and development

- Develop the ultimate validation protocol to be universally accepted by all bodies and countries.
- Statistical support of minimum sample requirement with adequate certainty for primary result.
- Define special populations with different BP measurement performance, validation requirements (e.g. children, adolescents, pregnancy, atrial fibrillation, diabetes, chronic kidney disease).
- Validation requirements to ensure even evaluation of all cuffs provided with each test device.
- Specific validation requirements for ambulatory BP monitors. Also for novel technologies of non-invasive beat-to-beat and wearable devices.
- Quality assurance of validation studies (centres accreditation, study registration, standardization of validation procedure and of reporting).
- Define standard procedures for peer review of validation studies.

Conclusions

- After several decades of applying peripheral BP measurements in the office, with ambulatory monitoring and at home, the current evidence suggests that ambulatory BP is the most accurate diagnostic method and home BP is the optimal method for long-term follow-up.
- Office BP has a role for screening, diagnosis and follow-up, but has the drawback of over-diagnosis in white coat hypertension and under-diagnosis in masked hypertension.
- Office BP may be better based on repeated automated BP measurement (AOBP), as does ambulatory and home BP.
- Although some organizations now recommend ABPM and HBPM as primary methods for decision making, further research is needed for universal acceptance.
- ABPM needs to become less costly and simpler, with more standardized procedures for initialization, reporting and interpretation, which should be similar with all devices and manufacturers.
- HBPM should become more observer independent and provide a standard automated report, which should be similar for all devices and according to guidelines.
- Home BP tele-monitoring is a modern solution for unbiased long-term follow-up of hypertension. More user friendly and cost-effective solutions need to be developed.
- The automated oscillometric BP measurement have dominated the ABPM and HBPM market, and is becoming popular for office BP measurement. There are still accuracy problems is some cases (e.g. atrial fibrillation) and further technological improvement is needed.
- Development of wide-range and tronco-conical cuffs for obese subjects is needed.
- Device validation is mandatory and a universal protocol should be agreed, which should cover all the aspects of BP monitoring with maximum accuracy and minimal resources.

II. BLOOD PRESSURE VARIABILITY

BP values vary markedly within the 24 hours: from beat-to-beat, minute-to-minute, hour-to-hour and day-to-night (short-term BPV). Substantial variation is also observed between measurements of different days (mid-term BPV) or between clinic visits performed over weeks, months, or years (long-term BPV) [43-47]. In physiological conditions these variations have been shown to represent an adaptive mechanism to

maintain homeostasis. However, sustained increases in BPV over time may also reflect alterations in cardiovascular regulatory mechanisms which may have prognostic relevance. Clinical and population studies showed that BPV may contribute to cardiovascular risk prediction, over and beyond average BP, although the degree of improvement in prediction is debated [48,49]. Increased BPV has been associated with higher risk of cardiovascular events, with this prediction depending on the basal risk. In low-to-moderate cardiovascular risk populations the contribution of BPV to risk stratification has been only marginal [50], whereas in high-risk subjects increased BPV appeared to have significant prognostic value, which might exceed that of average BP.

Classic distribution indices used for BPV estimation are the standard deviation and the coefficient of variation (CV) which includes the dependence on average BP [51]. Novel BPV indices have been introduced including: (i) Average real variability (ARV) reflects short-term reading-to-reading within-subject BPV [52]; (ii) Residual BPV assesses the spectral power of faster BP fluctuations remaining in the 24h tracing after exclusion of the slower circadian components of the 24h BP profile [53]; (iii) Weighted 24h BP SD selectively removes the contribution of nocturnal BP fall to 24h SD, by weighting daytime and night-time BP SD for the duration of these periods [54]; (iv) Variance independent of mean (VIM) applies non-linear regression analysis to exclude the effect of mean BP [44]. Several other indices have been applied [55].

Methodology for assessing different BPV types

Short-term BPV. Although an accurate assessment of fast BP fluctuations occurring within the 24 hours, ideally requires continuous beat-to-beat recording, its assessment is also possible through non-invasive, intermittent 24h ABPM at 15-20 min intervals [14,56]. The new BPV indices have been shown to better reflect the degree of short-term BP changes over 24 hours compared to SD and CV and the relation with cardiovascular outcome [44,46,52-54,57,58]. Alterations in the day-to-night profile (non-dipping, rising, extreme dipping, morning surge) have been suggested to have independent prognostic value [14,43].

Mid-term BPV. An extensive assessment of BPV in the mid-term can be obtained by ABPM over consecutive days. This is neither always well accepted by patients nor available in all clinical settings. Day-by-day BPV can also be calculated from several days HBPM. Indices of mid-term BPV are SD, CV and VIM [44]. Although HBPM cannot provide information on nighttime BP and 24h profiles as ABPM, it has the major advantage to provide information on the consistency of BP control over several days or weeks, i.e. over a time window better suitable for a clinical assessment than when considering long-term visit-to-visit BPV, thus allowing early adjustment of antihypertensive treatment. As HBPM is widely used and well accepted by patients, it might be ideal for day-by-day BPV evaluation [59].

Long-term BPV. Several studies have indicated that visit-to-visit BPV, quantified by several different indices (SD, CV, ARV, VIM), is highly reproducible [60] and has independent predictive value for organ damage and cardiovascular events [44], thus highlighting the importance of its assessment in clinical practice. Visit-to-visit BPV is commonly assessed by repeated office measurements, which have important limitations [14]. Although ABPM on repeated visits might theoretically represent an excellent approach for visit-to-visit BPV assessment, it is not always available, nor tolerated by patients for frequent repetitions. Repetition of HBPM over the week preceding each visit might represent an optimal approach to overcome the limitations of office BP and ABPM.

Issues concerning clinical application

Short-term BPV. There is still uncertainty on the optimal method and protocol for assessing short-term BPV from ABPM. This is mainly because not all studies in hypertension have systematically implemented ABPM for assessing short-term BPV, nor have quantified short-term BPV using standard approaches (i.e. avoiding different day-night periods, standardizing measurement intervals, BPV indices and individuals' behavior for preventing interference by daily activities).

Effects of antihypertensive treatment on short-term BPV. Clinical pharmacology trials implementing intra-arterial or noninvasive ABPM showed that antihypertensive drugs decrease SD, proportionally to the average BP decrease [56,61,62], suggesting that the effects of antihypertensive treatment on short-term

BPV may be attributed to BP lowering *per se*. However, among the few clinical trials exploring the effects of antihypertensive treatment on short-term BPV derived from intra-arterial beat-to-beat ABPM, there is evidence that beta-blockers may reduce BPV by improving baroreflex sensitivity [63]. Another study implementing non-invasive beat-to-beat ABPM showed that a calcium-channel blocker (CCB) reduced 24h SD and improved spontaneous baroreflex sensitivity [64]. The X-CELLENT study [65] showed greater reductions in different indices of non-invasive 24h BPV with CCB compared to diuretic, angiotensin receptor blocker (ARB) and placebo. In another study CCBs and diuretics induced larger 24h SD decline than angiotensin-converting enzyme inhibitors (ACEIs), ARBs or beta-blockers [66]. Moreover, in some studies the combinations of long-acting CCBs with diuretics or long-acting ARBs resulted in lower 24h BPV compared to monotherapies or combinations of shorter-acting drugs, suggesting a larger effect on short-term BPV [66] and better smoothing of the 24h BP profile (smoothness index) [67].

Mid-term BPV. Although HBPM represents the ideal method for assessing day-by-day BPV [59], it requires patient training and involvement which may not always be guaranteed. Moreover, there is large diversity among different studies regarding the HBPM protocols (1-5 readings per occasion, morning and/or evening, 2-26 days) and the different BPV indices applied [59]. Indeed, the optimal HBPM schedule for BPV evaluation remains unknown. Uncertainty also characterizes the choice of the index with the best prognostic value, the definition of thresholds for normality, intervention and treatment, the treatment effects on home BPV and the benefits from treatment induced home BPV reduction.

Effects of antihypertensive treatment on mid-term BPV. Few interventional studies in hypertension investigated whether reducing day-by-day home BPV with treatment, independent of average home BP reduction, improves cardiovascular outcome [59]. In the Ohasama study, baseline home BPV was higher in treated than untreated hypertensives [68]. Interventional studies assessing the effects of antihypertensive treatment on home BPV have been inconsistent. Some studies showed a beta-blocker to be related with lower home BPV [69], while others with higher home BPV [70]. A study in hypertensive patients showed reduction in average HBPM and BPV after 6 months of ARB treatment, yet only the change in average HBPM and not in home BPV or in maximum systolic HBPM were associated with albuminuria decline [71]. Another study reported increased systolic BPV in patients treated for <12 months with an ARB but not with

a CCB [28]. An *ad hoc* analysis of the J-CORE study comparing the effects of antihypertensive drugs on BPV found a CCB/ARB combination to be more effective in reducing systolic home BPV than the ARB/thiazide combination [28]. In the same study, significant reductions in pulse wave velocity induced by the ARB/CCB treatment (6 months) were independently correlated with systolic home BPV changes [72]. A non-randomized analysis found lower morning home BPV in diabetic subjects on CCBs than those on ACEIs or ARBs [73].

Long-term BPV. Identifying a standard method to obtain reproducible and valid estimates of visit-to-visit BPV and the optimal interval between visits is difficult, since the number of measurements and the measurement intervals between visits have not been consistent among studies evaluating the prognostic value of long-term BPV. Moreover, most of these studies evaluated SD and CV (which are dependent on mean BP), without considering VIM. Although office BP is the most common method to estimate visit-to-visit BPV in clinical practice, this approach may not reflect patients' actual BP burden nor BPV in the long-term, since office BP cannot be measured over a consistent number of visits, nor under usual life conditions and over a long period of time. Moreover, the white coat reaction in the office setting may induce acute BP rise which may interfere with a proper assessment of long-term BPV.

Effects of antihypertensive treatment on long-term BPV. Meta-analyses of trials using different antihypertensive drugs strongly support the prevailing role of average BP reduction for cardiovascular protection [74]. However, these data indicated that reductions in long-term BPV induced by some drug classes might confer additional benefits independent of average BP decline. *Post-hoc* analyses of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) and the Medical Research Council Trial of Treatment of Hypertension in Older Adults (MRC-elderly), showed that a CCB-based and a diuretic-based regimen was associated with lower intra-individual visit-to-visit BPV and lower stroke incidence, compared to beta-blocker-based regimens, independently of average BP reduction [45]. A meta-analysis comparing amlodipine versus other drugs also suggested a favorable effect on BPV assessed on a visit-to-visit basis [75]. Moreover, it has been hypothesized that certain drug combinations might be more effective in reducing intra-individual BPV. The above studies indicate that long-term BPV may be differentially affected by antihypertensive drug classes and their combinations, and that BPV effects might be related to

differential effects of drugs on cardiovascular protection, with larger BPV reduction with CCB-based treatment [75]. Contrasting observations were reported in a *post-hoc* analysis of the European Lacidipine Study on Atherosclerosis (ELSA) study, where no significant differences between a beta-blocker and a CCB on intra-individual visit-to-visit BPV were observed [76]. Indeed, while the outcomes considered in this study (carotid intima-media thickness and cardiovascular events) were significantly related to office or ambulatory systolic BP, with a tendency to be related also to 24h ambulatory SBP SD, no associations were found with on-treatment visit-to-visit office BPV [50].

Unmet needs - Future research and development

- Clinical and population studies have consistently supported the concept that BPV may contribute to cardiovascular risk prediction over and beyond average BP levels, emphasizing the importance of assessing BPV and consistency of BP control over time in treated hypertensives. However, no data are yet available on the BPV index that has the best performance as a risk factor.
- Studies are needed to clarify which component of BPV (short-, mid-, or long-term) should be used as the best parameter for risk stratification.
- There is no conclusive evidence as to whether BPV is just a risk marker accompanying BP elevation or an independent risk factor that should be modulated by treatment, and to what extent BP variability influences vascular damage or vascular damage augments BP variability.
- No interventional outcome study has been reported specifically addressing the BPV threshold indicating increased cardiovascular risk and BPV target to be achieved with treatment.
- Whether treatment-induced BPV reduction improves outcome is unknown. No *ad-hoc* randomized intervention study aiming at BPV lowering in hypertensive subjects has been reported, i.e. comparing patients on usual management vs. therapy targeted at controlling average BP and BPV.
- The evidence on the effects of different antihypertensive drug classes on BPV is limited and occasionally inconsistent. More data from randomized controlled intervention trials are needed.
- Future studies should determine whether treatment-induced reductions in specific short-term BPV components, or normalization of altered circadian BP patterns (e.g. restoration of the diurnal rhythm in

non-dippers or risers and attenuation of exaggerated morning surge) might improve cardiovascular prognosis independently of the average BP reduction.

- If the utility of BPV in clinical practice is established, then simple methods of measuring should be developed (e.g. algorithms into electronic BP monitors' memory).

III. CENTRAL BLOOD PRESSURE MEASUREMENT

Brachial BP predicts cardiovascular events, yet it is a poor surrogate for central BP (ceBP) (aortic or carotid), which is invariably lower. Although diastolic and mean arterial BP are relatively constant along the arterial tree, systolic BP increases towards the periphery (amplification), mainly due to arterial stiffness increase moving away from the heart and to the phenomenon of wave reflections [5,77-80]. The pulse pressure (PP) amplification, expressed as brachial/aortic PP ratio, varies from 1.7 at age <20 years to 1.2 at >80 years [81] and is dependent on sex. Amplification for systolic BP is most often expressed as peripheral-central systolic BP difference [82].

Conceptually, by representing the "true" pressure which when increased induces target organ damage, ceBP has the potential to predict cardiovascular outcomes better than brachial BP. Interestingly, in the very elderly and in heart failure the absolute BP level gives erroneous information about risk, and low BP in these cases may not be a sign of good arterial health but of left ventricular dysfunction, general ill health, nutrition, hydration, frailty and central nervous system degenerative disease; thus PP amplification or aortic wave reflection indices may impart more accurate information regarding risk [83,84]. Moreover, it is recognized that antihypertensive drugs may have differential effects on brachial compared with ceBP [85-89].

Because ceBP and brachial BP are largely interrelated and the latter alone is a powerful cardiovascular predictor, proving prognostic superiority of ceBP is difficult. Evidence of potential superiority of ceBP can be categorized according to the BP measurement method (invasive, office, or ambulatory) and the outcome (organ damage or cardiovascular events).

- Invasive studies have associated central PP with cardiovascular events better than peripheral PP [90].

- Office central PP is associated with target organ damage of the macrocirculation (heart and carotid arteries) [5,77-79], while organ damage regression is better associated with ceBP than peripheral PP reduction [91]. In meta-analyses ceBP was associated with subclinical target-organ damage more closely that brachial CeBP [92] and with adverse outcome, including mortality [93], while in individual trials ceBP or wave reflection indices have been associated with adverse outcome [83,89,94-98]. Moreover, low amplification (i.e. smaller peripheral-ceBP difference or higher than expected ceBP) has been associated with increased cardiovascular risk.
- Ambulatory ceBP monitoring enables demonstration of the circadian variation of systolic ceBP with lower PP amplification during sleep [99-102]. Aortic 24h PP is associated more closely than brachial 24h PP with left ventricular mass [101] and diastolic dysfunction [103].
- Data on ceBP measured at home are lacking.

These observations suggest that central PP may be associated with cardiovascular risk beyond peripheral BP and although such associations may be marginal [93], they might be more important in specific population subgroups, such as the young hypertensives or in individuals with high circadian variability of PP amplification [101]. A pertinent question is whether guiding management of hypertensive patients using ceBP in addition to brachial BP improves outcome. A single study showed that ceBP-guided management was associated with less medication use without adverse effects on left ventricular mass, aortic stiffness, or quality of life, compared to brachial BP-guided management [104]. Another study in heart failure patients showed medication titration guided by aortic ceBP to improve exercise capacity [105]. Studies with hard endpoints are required.

Technology - Methodology

Some studies obtained invasive ceBP, but this section is confined to non-invasive devices applicable to clinical practice. Non-invasive devices estimate the central equivalents of peripheral pressures, i.e. systolic, diastolic ceBP and PP. They also calculate indices expressing relations (regarding timing and/or

magnitude) between incident forward travelling and reflected waveforms, such as augmentation index and reflection magnitude.

The ceBP monitors record two types of waveforms, either carotid or peripheral (radial, brachial, femoral). In the first case, scaled waveforms are recorded at the carotid level with tonometry or ultrasound and no mathematical processing is required (only calibration) since this artery is considered itself a central artery. Although carotid PP is currently accepted as a substitute of aortic PP, the evidence suggesting that they are interchangeable is insufficient. In the second case, using several non-invasive methods, such as applanation tonometry, volume plethysmography, or cuff-based oscillometry, waves are acquired at the peripheral artery, and then the ceBP waveform is computed. There are various methodological and conceptual approaches based on transfer functions (either in time or frequency domain) [106-108], or proprietary algorithms/mathematical modelling [108]. These transfer functions or models transform the recorded peripheral waves to the corresponding aortic pressure waveforms. Another approach to calculate systolic aortic pressure is identification of the late systolic shoulder of the peripheral pressure waveform that has been found to have good correlation with the peak aortic pressure [109].

Most of the techniques currently available require operator-dependent acquisition of the initial waveform. Automated (operator-independent) approaches have also been developed.

Issues concerning clinical application

- The establishment of reference values is an important issue for clinical implementation. An international consortium recently published reference values of systolic ceBP and amplification in healthy subjects and in a population without traditional cardiovascular risk factors according to age, gender, and brachial BP [82]. These values were obtained using different devices with a wide geographical representation. Amplification is significantly influenced by cardiovascular risk factors, gender and height.
- All methods described require appropriate calibration of the recorded waveform, which by itself poses a significant problem [110,111]. When calibration is made with invasive recordings of the peripheral

artery (input values in the computational algorithms), high accuracy is achieved (minimal difference of output values from invasively measured aortic BP). Some methodological issues in the validation process pertain to the possible distortion of the waveforms by the catheters inserted in small diameter arteries. In contrast, when a non-invasive method (usually peripheral pressure measurement at the brachial artery by oscillometry or sphygmomanometry) is used for input values, there is a wide range of deviation (from invasively measured aortic BP). Furthermore, in the latter case the error in ceBP estimation may be different when peripheral systolic and diastolic BP, or systolic and mean BP are used for calibration. Another potential source of error is acquiring the pulse waveform at the radial artery and calibrating with pressure obtained at the brachial artery. The method assumes that there is negligible amplification from brachial to peripheral artery [79], but this is not accepted by all experts [112]. It is apparent however, that the magnitude of the error is dependent almost entirely on the accuracy of the non-invasive peripheral pressure measured by the brachial cuff.

- While methods employing the carotid measurement and subsequent scaling avoid the need for further processing (such as the use of transfer function) of the signal, high quality carotid pressure or distension waves may be difficult to obtain.
- Validation against invasive aortic (“true”) values has the inherent limitation that it applies only to specific patients’ populations because the validation can be performed in subjects undergoing catheterization for the diagnosis of cardiovascular disease.
- Regarding the generalized transfer functions, although they have been validated in a wide range of different pathophysiologic hemodynamic and cardiovascular conditions and also under various pharmacological interventions, they are subject to criticism that theoretically it is not possible to simulate all hemodynamic conditions and the consequences of pharmacological intervention.
- The identification of the second systolic peak approach has been less well tested and the second peak is not always easily detected in the waveform.
- Circadian fluctuation of systolic ceBP exists with lower PP amplification during sleep, which is not usually taken into account in results interpretation.
- There are no standardized protocols for device clinical validation in terms of wave recording, transfer functions or model use, and calibration.

- Whether validations should compare against devices with either invasive (“true”) aortic measurements, or leading non-invasive devices used in the vast majority of outcome studies, is a fundamental conceptual issue. The pioneering commercially available devices for non-invasive ceBP assessment (irrespective of the error in estimating the “true” ceBP) have shown potential predictive value. The analogy drawn is that with brachial BP measurement, which is routinely used in hypertension management and is accepted by regulatory authorities as being better validated than intra-arterial (brachial) pressure as surrogate of outcome: in this case, new oscillometric peripheral BP monitors are validated against mercury sphygmomanometers, rather than invasive brachial pressure.

Unmet needs - Future research and development

- Which parameter is superior in terms of risk prediction (i.e. ceBP systolic/diastolic, PP, PP amplification or indices of wave reflection (and which among each category?).
- Which is the optimal method for BP calibration? It is likely that optimal calibration settings and techniques are device dependent (different devices may perform better under different calibration).
- Which is the best method for estimating mean pressure?
- What threshold should be set for accuracy of ceBP measurements (deviation of calculated values from invasively obtained measurements?).
- Which is the most accurate method for ceBP estimation? Since a large number of different methods and techniques exists for non-invasive ceBP estimation (i.e. with and without transfer function, pressure wave recording technique, calibration etc), it remains unclear if the available apparatuses are equally accurate.
- What is the best reference standard method?
- Amplification should be universally reported in all studies since it negates the calibration problems.
- A consensus on which is the preferable way of reporting amplification (peripheral-central systolic BP difference or peripheral/central PP ratio) should be reached.
- Should devices be validated against invasive measurements or against “established” non-invasive devices?

- In validation studies with invasive aortic recordings all measurements should be obtained with minimal time intervals between the two methods of measurement.
- Which are the necessary steps for a validation protocol of new methods and devices (sample size, age range, signal quality, repeatability, different physiological conditions, pharmacological challenges, etc).
- Development of standardized protocol of measurement (conditions, posture, number of measurements, etc).
- Reference values and thresholds for clinical implementation have been proposed [113], yet their relation with risk needs verification in outcome trials.

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