Non-invasively obtained Central Blood Pressure: Barriers and Strategies to its Use in Practice

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Abstract

Recently, novel concepts and medical technologies have developed rapidly with enormous growth and unprecedented expansion in the range of interventions and knowledge offered for health professionals in their clinical decision making. This burgeoning innovation has not necessarily resulted in an incremental availability of knowledge to policymakers and clinicians. In this study critical translation gaps have been addressed strategically in the research-into-action cycle to improve outcomes and services.

Given widespread acceptance that waveform morphology and blood pressure (BP) differ considerably between the central aorta and peripheral arterial system, it is clear that BP measurements in the peripheral arteries cannot serve as direct substitutes for their central counterparts. Although non-invasive BP measured in the brachial artery (cuff BP) is the basis for the present management of hypertension, central blood pressure (CBP) has been shown to be the better predictor of cardiovascular outcomes than cuff BP. Consequently, there are substantial research efforts to develop non-invasive estimating methods for CBP, mainly based on the technique of applanation tonometry. However, CBP measured has not been widely adopted in clinical practice. One of the possible gaps is that tonometry-based measurement requires some skills and time to perform and it is a relatively expensive technique. Besides, the accuracy of the current tonometry-based techniques has been questioned. To identify and address the gaps of translating the evidence of the importance of CBP, a series of studies were conducted.

To identify existing gaps, I carried out a systematic review and meta-analysis of studies comparing tonometry-based CBP estimates with invasively measured central BP and found that present tonometry-based CBP estimating methods are acceptable

in theory, with small errors. However, there is substantial room for improvement in measurement accuracy of CBP.

To develop a more accurate, less expensive, and less technically dependent CBP measurement technique, the pulse wave analysis (PWA) technique for brachial pulse volume plethysmography (PVP) waveforms from an oscillometric blood pressure monitor was implemented. Evaluation demonstrated that large random and systematic errors are introduced into the central pulse pressure (PP) estimates when they are calculated as the difference between the estimated central systolic BP (SBP) and central or cuff diastolic BP (DBP), which can be improved substantially with the novel PWA approach. Subsequently, the novel technique was seamlessly incorporated into a standalone automatic BP monitor. In a rigorous validation study, it was demonstrated that CBP can be measured accurately by this stand-alone automatic blood pressure monitor.

To apply the CBP concept in clinical practice, the gap between innovation and clinical application should be closed. The diagnostic threshold for confirming a diagnosis of hypertension with CBP has never been proposed; I therefore derived and validated the diagnostic threshold of CBP based on two independent event-based cohorts with long-term follow-up.

With the proposed cut-off limits for the diagnosis of hypertension, the diagnostic accuracy of the stand-alone CBP monitor reference to invasively measured CBP was estimated. It was then suggested that traditional cuff BP may be reliable in confirming the diagnosis of hypertension and in justifying subsequent treatment with its high specificity. However, because of low sensitivity, the cuff BP could render possible management inaccessible to a considerable proportion of hypertensive subjects, who may be identifiable through the noninvasive CBP monitor.

Finally, in responding to the gap between clinical application and policy, a health economic evaluation was required to support the cost-effectiveness of the new emerging technique. A comprehensive Markov modelling was performed and this confirmed the cost-effectiveness of CBP monitoring, which resulted from a greater quality gain that outweighed its supplementary cost. Given more data supporting the diagnostic and prognostic role of CBP, it should be considered to be an effective strategy for the management of hypertension.

Declaration

NAME: Hao-min Cheng PROGRAM: Doctor of Philosophy

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CHAPTER 1: Introduction to the Study and the Concept of Translational Research

The intention of this thesis was to adapt current strategies for the management of high blood pressure by implementing the use of central blood pressure measurement. Using the concept of translational research (or knowledge translation), the possible gaps impeding the application of such a concept in clinical practice, which may bring about considerable benefit to a substantial amount of hypertensive subjects, were identified.

Researcher's Clinical experience In this Field of Study

I have been a cardiologist for 10 years (since 2003) in Taipei Veterans General hospital and the Faculty of Medicine of National Yang-Ming University, Taipei, Taiwan. As a visiting staff member in Taipei Veterans General Hospital, an internationally well-known medical centre with 2805 beds, I am experienced in the management of high blood pressure and other various cardiovascular disorders, and skilled in performing echocardiography and percutaneous coronary interventional procedures. My research interest is to assess cardiovascular hemodynamics by developing innovative diagnostic tools. I am also keen to adopt the principles of Evidence-based Health Care and Translational Research in clinical practice as well as in medical research and education.

The Concept of Central Blood Pressure

Although non-invasive BP measured in the brachial artery (cuff BP) is the basis for the present management of high blood pressure (HBP),[1, 2] there have been

numerous observations suggesting that waveform morphology[3-5] and blood pressure (BP)[4, 6-9] differ considerably between the central aorta and peripheral arteries. Therefore, BP measurements in the peripheral arteries cannot serve as direct substitutes for their central counterparts. Moreover, central blood pressure (CBP) has been shown to be the better predictor of cardiovascular outcomes than cuff BP.[10-14] Consequently, some non-invasive estimating methods for CBP have been developed, mainly based on the technique of applanation tonometry.[4, 15-17]

Non-invasive Tonometry-based CBP Estimating Methods

Acquired carotid arterial pressure waveform has been shown to be a robust surrogate for central aortic pressure waveform and can be used to obtain estimated central BP.[15, 18] The most common method to obtain central BP estimates is to acquire a peripheral arterial pulse waveform from the radial or brachial artery, which is subsequently transformed into a central aortic pressure waveform, using a generalized transfer function.[16, 19] Another approach has been proposed to bypass the transfer function approach based on the finding that the second radial pressure peak directly identified from a peripheral pressure waveform equates well with the peak (Systolic Blood Pressure = SBP) of central aortic pressure waveform.[20-22]

To obtain CBP by applanation tonometry, an experienced operator is required to record the pressure waveform. The waveform is then subjected to calibration, which scales the waveform according to cuff BP. The main challenge of the tonometry-based method resides in the technical threshold required for the waveform acquisition, which inevitably impedes the clinical application of such a concept and restricts its use within the research field.

Apparently, the concept of CBP has been used solely in the research field and there has been negligible clinical uptake of CBP estimating methods. This discrepancy

provided an opportunity to implement the concept of evidence-based health care and translational science to further improve the management of hypertension.

Evidence-based Health Care And Translational Science

To biomedical scientists, health care professionals, health service funders, and policy makers, of increasing central concern is the growing challenge to propel trustworthy scientific discovery through to widespread adoption, which subsequently benefits individuals and communities who seek health care. Faced with this challenge, the research and clinical communities conceived and initiated the movement of evidence-based practice and translational science, two seemingly different but clearly complimentary fields of endeavour.

Evidence-based Health Care

Professor David Sackett from the University of Oxford introduced the movement of Evidence-based practice in the early 1990s, and this subsequently became the hallmark of high quality medical care.[23] This concept emphasizes that a judicious clinical decision should be made by considering the best available evidence in the context where the health care is delivered, client preferences, and the professional expertise of the health professionals.[23] The term of evidence-based health care (EBHC) was coined by Professor Alan Pearson and colleagues through the establishment of The Joanna Briggs Institute (JBI) in the mid-1990s.[24] Along with other world leading international and independent organizations promoting EBHC, JBI involves itself in disseminating, implementing, and evaluating evidence-based guidelines in clinical settings and examining scientific and professional literature. By adopting a broader and holistic perspective of evidence as compared to Cochrane and Campbell Collaborations, the JBI model depicted four major components of the EBHC process,[24] which underscores the need for the generation, synthesis, transfer, and utilization of evidence derived from diverse research approaches in response to

variable and sophisticated clinical questions (Figure 1-1). In collaboration with international health care professionals across the globe, JBI generates evidence through various research approaches, synthesizes the evidence by conducting comprehensive systematic reviews; translates the best available evidence into clinical guidelines, and utilizes the evidence through best practice implementation projects with the intention of improving global health through a cyclical process

Figure 1-1.

shown in Figure 1-1.

Figure 1-1. The relationship between the translation science cycle and evidence-based healthcare.[25]

Framework of the JBI Model

Evidence Generation:

The JBI model suggests that healthcare evidence may derive from experience, expertise, inference, deduction, or the results of rigorous scientific studies.[24]

Whenever available, the best research evidence of feasibility, appropriateness, meaningfulness and effectiveness (FAME) should be used to inform health care delivery by clinicians who are attempting to respond to a specific clinical question.[24] The evidence is considered valid given the evidence-generating process is sound and derived from a paradigm corresponding to a correct methodology and method.

Evidence Synthesis:

As shown in Figure 1-1, there are three elements of synthesis: theory for a raised clinical question investigated with the synthesis, synthesis methodologies such as meta-analysis, and the systematic review of evidence.[24] Synthesis is the summary of the pooled results of primary research studies in which the research question might be answerable.

Evidence Transfer:

Transferring evidence involves more than dissemination or distribution of the generated and synthesized evidence. Careful development of strategies that identify suitable receivers of the transferred evidence should be included the transferring process. The target audience could be clinicians, managers, policymakers, consumers, or any other relevant stakeholders of the related clinical inquiry addressed by the evidence.[24] As a consequence, the JBI model depicts three elements in this stage, which consists of education and training, information delivery, and the transfer of evidence through organizational and team systems (Figure 1-1).

Evidence Utilisation:

To improve global health, the generated, synthesised, and transferred evidence should be utilised systematically on a larger scale involving groups, communities, organizations, systems, or countries. Individuals might be empowered to carry out the practice change through the evaluation of the impact of the rigorous evidence

on systems or outcomes. Strategies to achieve this goal include action research, clinical audit with best practice implementation projects, and practice-based learning and improvement. Subsequently, the evidence utilised individually may be embedded in health systems and organizations. Finally, through utilising the evidence systematically, global health improvement could be attained (Figure 1-1).

Translational Science

To facilitate the movement along the "evidence-to-practice" cycle in diverse practice settings, among diverse populations, and under diverse payment systems (figure 1-1), the Agency of Healthcare Research and Quality (AHRQ) in the United States recognised the need to improve the translation of basic and fundamental research findings into routine clinical practice. In 1999 and 2000, the first and second Translating Research into Practice (TRIP-I and TRIP-II) initiatives were launched by AHRQ to promote the utilization of rigorously derived evidence to improve patient care by funding 14 and 13 projects, respectively.[26, 27] Complimentary to EBHC, translational research aims to identify and close the gaps in the "research-into-action" process (Figure 1-1). Pearson et al. proposed, by modifying the dominant view of translation science, which overly emphasises the translation of the "basic/bench" results or discovery research into clinical application, that there are three critical translation gaps throughout the translational process (Figure 1-1).[25]

Gap 1–From Knowledge Need to Discovery:

The cycle begins with translating the need for knowledge in the "real world" into a scientific question that guides discovery research (Figure 1-1). The knowledge needs may be identified by patients, the community, clinicians, governments or other organizations and clarified through collaboration between researchers and the above end users of research with an integrated approach to topic selection.[25]

Gap 2–From Discovery to Clinical Application:

For a promising scientific discovery, the 2nd gap refers to the process of translating the findings of discovery research into clinical or policy application through experimental trials (not limited to drug trials) and other empirical studies. This process is the most widely addressed gap in which the majority of resource is invested internationally. However, the translational research commonly initiates and also stops here.

Gap 3–From Clinical Application to Action:

To further a clinical policy or action, the third gap addresses the translation of the findings of clinical research into practice. There are rare significant projects addressing this gap globally.

Figure 1-1 Integrates these three translation gaps into the JBI EBHC model to clarify and reconceptualise the complexities of improving global health outcomes.[25]

This thesis reports on a series of studies and analyses that applied the notion of translational science and EBHC to identify the possible gaps in the application process of the CBP concept. Beginning with a systematic review on the measurement accuracy of tonometry-based CBP estimating techniques, possible gaps were identified, in addition to the technical threshold required for executing applanation tonometry. Subsequently, possible solutions were examined and attempts to close these recognized gaps in the “evidence-to-practice” cycle were explored.

CHAPTER 2: Measurement Accuracy of Non-invasively Obtained Central Blood Pressure by Applanation Tonometry: A Systematic Review and Meta-analysis

Background to the Review

Blood pressure measurement has been used extensively in daily clinical practice to manage cardiovascular disease. However, BP determined at different sites can vary considerably and may be differently affected by antihypertensive drugs. [5, 6]

The gold standard of central BP measurements is aortic root BP, using a saline-filled catheter or an external pressure transducer with tip in situ,[28] which is not suitable for routine clinical practice. Recently, some noninvasive methods for estimating central BP are available.[4, 15, 16] Current common methods for the noninvasive estimation of central BP utilize applanation tonometry to acquire an arterial pressure waveform,[29] which is then subject to calibration and/or mathematical calculation (Figure 2-1, appendix II).

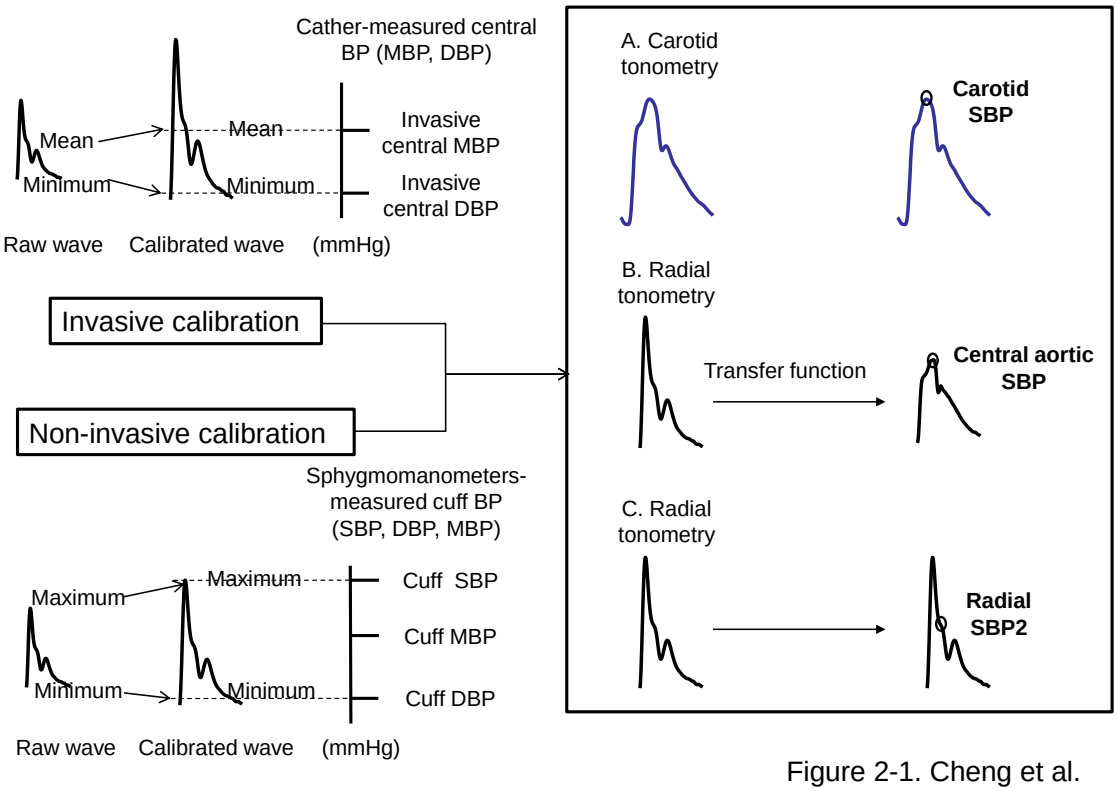

Figure 2-1. Cheng et al.

Figure 2-1. Illustrations of different methods used to estimate central blood pressure and the calibration procedures.

The discrepancy between the central and peripheral BP may magnify with the administration of vasoactive agents.[4, 7 30-33] Growing evidence from epidemiological studies [12, 13] and clinical observation[14] suggests that central BP may be more relevant than peripheral BP in predicting target organ damage and cardiovascular outcomes. Recent randomized controlled trials have also given impetus to the clinical application of central BP by demonstrating differential impacts of anti-hypertensive drugs on central and peripheral BP.[34, 35] As a consequence, the concept of central BP measurement was addressed in The 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension.[2] However, before recommending central BP measurement as a useful clinical tool, the accuracy of current central BP estimating methods should be systematically examined. Moreover, a recent meta-analysis of longitudinal studies suggested that elevated central BP was not significantly associated with a higher relative risk of clinical events as compared to elevated

brachial BP.[36] This may cast doubt on the accuracy of the noninvasively estimated central BP. Therefore, the aim of this systematic review and meta-analysis was to synthesize the available research evidence on the accuracy of current noninvasive measurement methods for central BP. Through our systematic review, professional societies can assess the accuracy of these central BP-estimating methods and identify potential barriers to this concept and possible areas for future research.

Methods

Inclusion Criteria

There was no restriction placed on language or year of publication. Studies were considered eligible if they satisfied the following criteria.

Type of study: The study had extractable data regarding measurementsbetween estimated and measured central BP.

Types of phenomena of interest: The study investigated the accuracy of noninvasive central BP-estimating methods using applanation tonometry in comparison with invasively obtained corresponding values. To provide reference of measurement accuracy, studies using invasive BP for pressure waveform calibration or obtaining peripheral pressure waveform by direct measurements of catheter were deemed eligible but meta-analysed separately.

Types of participant: Studies with adult subjects were considered, regardless of clinical diagnosis, co-morbidities, and treatments. The participants had to have been receiving paired measurements of estimates and invasively measured central BP.

Types of outcomes: This review included the following types of outcome measures: systematic bias and random error of estimates comparing with measured central BP.

Reference standard: The gold standard of central BP is aortic root BP measured with a saline-filled catheter or an external pressure transducer with tip in situ.

Search Strategy (appendix IIB)

The search strategy aimed to find both published and unpublished studies. Databases searched were: PubMed, CINAHL, Cochrane Library (including Cochrane DSR, DARE, and CCTR), Scopus, Web of Science, EMBASE, and Google Scholar, using all identified keywords and index terms. Reference lists of identified studies were also searched for further studies.

Assessment of Methodological Quality/Critical Appraisal

Research papers selected for retrieval were assessed by 2 reviewers for methodological validity prior to inclusion in the review using an original specific critical appraisal tool designed for the review. The methods and results of critical appraisal were summarized in appendix II.

Data Extraction

Data were extracted from papers using an original data extraction form for this review developed by consensus and based on the previous systematic reviews for measurement accuracy.[37] Differences in data extraction were resolved by consensus.

Data Synthesis

Study characteristics were extracted and summarized in table 2-1. For quantitative synthesis, the method developed by Dr Paula R Williamson for meta-analysis of method comparison studies,[38] which has been used to examine the accuracy of devices for measuring body temperature in children, was used.[37] In brief, the pooled estimates of systematic bias and random errors were obtained using an inverse variance weighted approach and the random effects model.[37] The former, also known as the Mantel-Haenszel weighted method, is a weighted sum of the

estimates from each of the primary studies. The weights are calculated by the inverse of the variance of the individual study estimates, which were the mean differences (MD) and standard deviation of differences (SDD) between the paired measurements in method comparison studies. Homogeneity was assessed using a standard large sample test.[39] Meta-analysis was based on DerSimonian-Laird weights for the random effects model,[39] which incorporates a between-study variance, was also used for statistical pooling for MD and SDD in the presence of significant heterogeneity across studies. To account for the source of heterogeneity, further subgroup analysis according to different central BP estimating methods was also performed. On forest plots, the individual and pooled 95% limits of agreements combining systematic and random errors between paired measurements of different central BP parameters were presented by subgroup analysis as well as in total.

Table 2-1. Population characteristics in individual studies about methods of estimation of central blood pressure

Study	Year		Setting	Attrition number	Sample size	Mean age (range)	Male (%)	CAD (%)	Central BP invasive reference method*	Sensor type and quality	Central BP index estimating method†	Calibration method‡	Type of BP monitor
Karamanoglu	1993	[16]	CAG	NS	14	53.7 (36~70)	92.9	85.7	HF	5F Millar	Custom-made GTF	D	NA
Karamanoglu	1996	[40]	CAG	NS	13	58.5	92.3	84.6	HF	6F Millar SPC 360	Carotid tonometry	CI	NA
Chen	1997	[19]	CAG	NS	20	59 (36~78)	80	60	HF	SPC-320	Custom-made GTF (ARX model)	CI	NA
Pauca	2001	[41]	Cardiac Surgery	NS	62	61	72.6	96.8	SF	Spectramed model T36AD-R with damping coefficient >0.3 and resonant frequency >20 Hz	GTF from SphygmoCor	D	NA
Van Bortel	2001	[18]	CAG	NS	19	57 (40~79)	89.5	NS	SF	NS	Carotid tonometry	CI	Dinamap
Soderstrom	2002	[42]	PTCA	NS	12	67.3 (62~76)	66.7	100	SF	Siemens Sircus 1281 with damping coefficient 0.35-0.5 and resonant frequency 25 Hz	GTF from SphygmoCor	D	NA
Davies	2003	[43]	CAG	NS	28	60	71.4	82	SF	Simens Rector	GTF from SphygmoCor	CC1	@HEM-705CP
Hope	2003	[44]	CAG	NS	78	63	78.2	NS	SF	NS	Custom-made GTF (saline-filled system)	CI	NA
Cloud	2003	[45]	CAG	NS	30	63.7 (27~84)	60	57	SF	NS	GTF from SphygmoCor	CC1	@HEM-70 CP
Smulyan	2003	[46]	CAG	NS	50	54 (33~82)	NS	NS	HF	6f Millar SPC 350	GTF from SphygmoCor	CC1	Colin?
Hope	2004	[47]	CAG	NS	42	64	66.7	NS	HF	Millar Microtip	Custom-made GTF	CI/CC2	DinamapTM XL 9301 Portable Monitor

Study	Year		Setting	Attrition number	Sample size	Mean age (range)	Male (%)	CAD (%)	Central BP invasive reference method*	Sensor type and quality	Central BP index estimating method†	Calibration method‡	Type of BP monitor
Pauca	2004	[20]	Cardiac Surgery	24	21	64 (41~87)	81	100	SF	Spectramed model T36AD-R with damping coefficient >0.2 and resonant frequency >20 Hz	SBP2	D	NA
[§#]Hope	2004	[48]	CAG	NS	19 DM/38 non-DM patients	66/65	NS	84/87	SF	NS	Custom-made GTF (saline-filled system)	CI	NA
Sharman	2006	[49]	CAG	13	30	56 (37~76)	70	70	HF	Millar model SSD-1008	GTF from SphygmoCor	CI	NA
Takazawa	2007	[21]	CAG	2	18	61 (47~78)	83.3	NS	HF	Pressure Wire RADI	SBP2	CC1	Colin TM 2740
Hope	2007	[50]	CAG	NS	93	61	63	NS	HF	Millar Microtip	Custom-made GTF	CI	NA
[§]Rajani	2008	[51]	Moderate aortic stenosis undergoing CAG	NS	14	74 (54~81)	71.4	NS	HF	SPC-464D	GTF from SphygmoCor	CI/CC1	[@]Omron 705CP
Hickson	2009	[52]	CAG	NS	38	60	NS	NS	HF	5f Millar SPC-454E	GTF from SphygmoCor/SBP2	CI	HEM-711A-E
Cheng	2010	[22]	CAG	NS	100	61.6	78	42	HF	2f Millar SPC 320	SBP2	D	Omron VP2000
Zuo	2010	[53]	CAG	2	45	62 (33~79)	73.3	71.1	SF	XDY-2003 with damping coefficient >0.3 and resonant frequency >30 Hz	GTF from SphygmoCor	CC1	[@]Omron 705 CPII
[&]Shih	2011	[54]	CAG	NS	40	64.1	80.4	52.2	HF	Dual sensor 2f Millar model SSD-1059	Custom-made GTF	D/CC1	[@]Microlife Watch BP Office
[§]Ding	2011	[55]	CAG	11	33	60.1 (45-83)	63.6	51.5	SF	GE Mac-Lab System with damping coefficient >0.3 and resonant frequency >20 Hz	GTF from SphygmoCor/ [§]SBP2	CC1	Omron HEM9000-AI

Results

Description of Search Process (Figure 2-2)

Figure 2-2 shows the details of search process. Twenty-one out of 30 eligible studies had extractable and sufficient outcome data from the papers [16, 18-22, 41-55] or from correspondence with the authors [40]. Twenty-two studies (857 subjects; mean age, 61.4 years; 69.2% male subjects) with a total of 1167 measurements were eligible for inclusion and subjected to meta-analysis in this review.

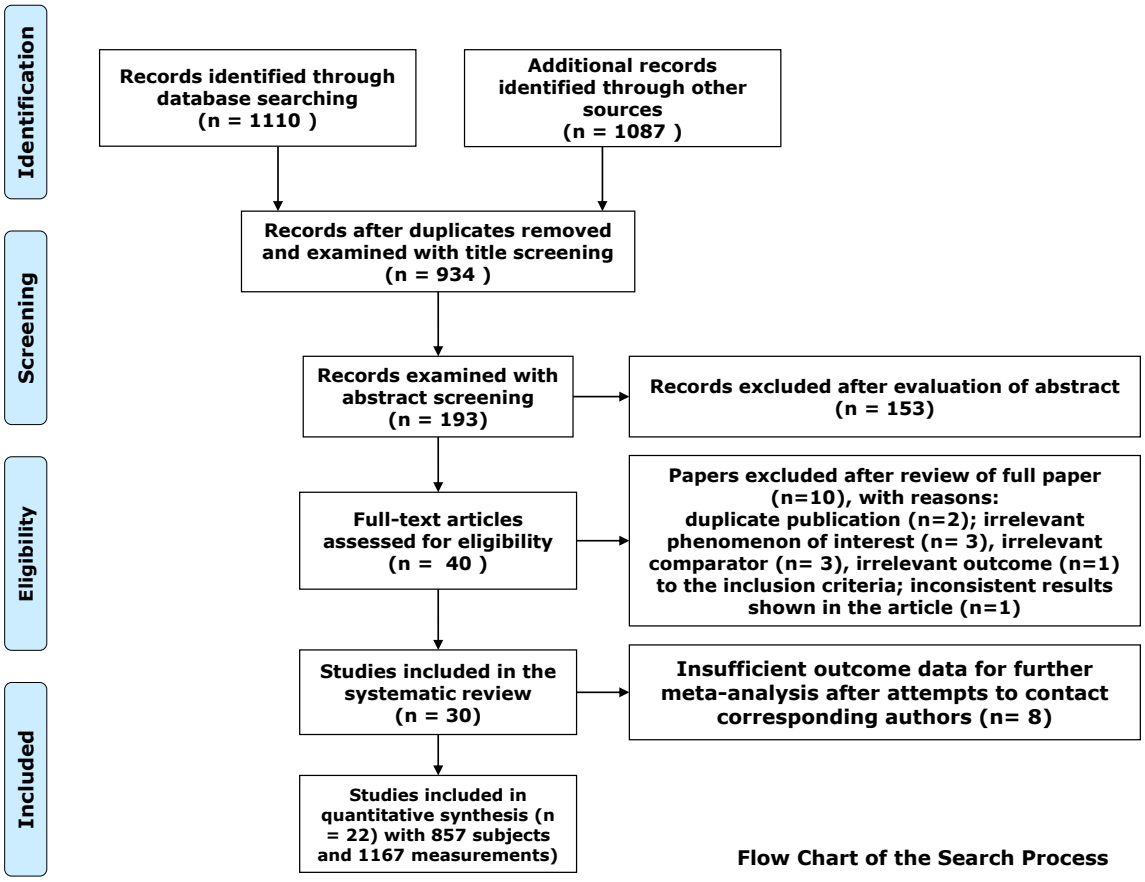

Figure 2-2. Flow chart of the search process

Summary of Included Studies

These studies were all conducted invasively in a catheterization laboratory or operating room and small in sample size (number range 12-100, mean 37.2). The

majority of studies applied generalized transfer function on peripheral pressure waveform (Figure 2-1, panel B) to obtain the estimated central BP (n = 17). Of the 17 studies using transfer function, 10 studies performed the analysis using the software program and transfer function from SphygmoCor (AtCor Medical, Sydney).

Calibration Methods

Current central BP estimation relies on the acquisition of peripheral pressure waveform, mostly by applanation tonometry. If the acquired peripheral waveforms were not directly measured, they were subject to calibration and then used for central BP estimation. The calibration methods in these studies were detailed in Table 2-1.

One common approach is to calibrate peripheral waveforms to match the aortic mean and diastolic BP (Figure 2-1, left upper panel) based on the widely accepted approach whereby mean and diastolic pressures from the central aorta to the peripheral artery have nearly the same values.[5]

The other calibrating method in these primary studies was to calibrate the peripheral waveform to match the arm BP measured by sphygmomanometers (Figure 2-1, left lower panel). Peripheral waveforms could be calibrated to cuff SBP and DBP[43] or cuff MBP and DBP[47]. The calibration process could become a source of measurement errors when cuff BP, which is not error-free, is used for calibration.

In real world clinical practice, the direct invasive measurement of peripheral BP or calibration by invasive aortic MBP/DBP (**invasive methods**) is impractical. It is essential to perform separate meta-analyses according to calibration methods (**invasive method**s vs. **non-invasive method**). Fifteen studies used invasive methods (6 by direct measurements and 10 by invasive calibration with one conducted both) and **9 studies** used non-invasive calibration. Two studies conducted both invasive

and non-invasive calibration for pulse waveforms.[47, 51] One study directly acquired peripheral waveforms and then recalibrated them using cuff BP.[54]

Meta-analysis of Systematic Bias and Random Error between Different BP Parameters and Corresponding Invasive Measured central BP

The 22 studies for quantitative synthesis included 857 individuals. Subjects in 4 studies[22, 41, 42, 49] underwent repetitive measurements after changes in hemodynamics after exercise or medication to provoke blood pressure changes with results presented separately. The results of meta-analysis for systematic and random errors of different BP parameters compared with corresponding invasively measured central BP values are summarized in Table 2-2. Most comparisons were characterized by significant heterogeneity in terms of MD and SDD. Residual heterogeneity was still evident in both MD and SDD between studies within the subgroup of different estimating methods.

Table 2-2. Meta-analysis* of mean difference and standard deviation of differences between different BP parameters and corresponding invasively measured central aortic BP with the heterogeneity test across studies

	MD (systematic bias)	SDD (random error)	95% Limits of agreement[&]	Chi-squared* (MD)	P value of heterogeneity* (MD)	Chi-squared (SDD)	P value of heterogeneity (SDD)	df
Estimated CSBP by invasive methods (16 studies, 21 comparison, 764 measurements)[#]	-1.1	4.1	-9.1 ~ 6.9	424.7	<0.0001	341.8	<0.0001	20
Estimated CDBP by invasive methods (9 studies, 13 comparison, 501 measurements)	-0.5	2.1	-4.6 ~ 3.6	1792	<0.0001	207.1	<0.0001	12
Estimated CPP by invasive methods (8 studies, 10 comparison, 395 measurements)	-0.8	5.1	-10.8 ~ 9.2	148.8	<0.0001	88.1	<0.0001	9
Invasive Peripheral SBP (6 studies, 9 comparison, 336 measurements)	9.1	6.9	-4.5 ~ 23	192.4	<0.0001	47.7	<0.0001	8
Invasive Peripheral DBP (5 studies, 8 comparison, 309 measurements)	0.1	2.3	-4.4 ~ 4.6	45.8	<0.0001	53.7	<0.0001	7
Invasive Peripheral PP (4 studies, 6 comparison, 285 measurements)	12.2	7.1	-3.6 ~ 24	106.1	<0.0001	8.2	0.14	5
Noninvasively Estimated CSBP (9 studies, 10 comparison, 384 measurements)	-8.2	10.3	-28.4 ~ 12	112.5	<0.0001	58.9	<0.0001	9

Noninvasively Estimated CDBP									
(8 studies, 8 comparison, 348 measurements)	7.6	8.7	-9.5	~ 25	215.5	<0.0001	52.57	<0.0001	7
Noninvasively Estimated CPP									
(5 studies, 5 comparison, 276 measurements)	-12.2	10.4	-32.5	~ 8.1	51.3	<0.0001	89.8	<0.0001	4
Cuff SBP									
(11 studies, 13 comparison, 415 measurements)	5.4	11.7	-17.6	~ 28	41	0.0001	54.9	<0.0001	12
Cuff DBP									
(8 studies, 9 comparison, 349 measurements)	7.5	8.7	-9.5	~ 25	57.1	<0.0001	51.8	<0.0001	8
Cuff PP									
(5 studies, 6 comparison, 277 measurements)	-0.7	13.2	-26.6	~ 25	25.2	0.0001	33.9	<0.0001	5

Not all studies provided comprehensive reporting on all central BP parameters. For meta-analysis, appropriate and extractable outcome data to examine agreement between invasively measured reference central BP parameters and corresponding estimated values were available from part of these studies as shown in Table 2-2 and respective Forest plots.

Of the invasive methods for estimation, the mean pressure differences of the estimated central BP were small with MD and SDD -1.1 ± 4.1 mmHg (95% limits of agreement **-9.1~6.9 mmHg**) for central SBP (Figure 2-3), -0.8 ± 5.1 mmHg (**-10.8~9.2 mmHg**) for central pulse pressure, and -0.5 ± 2.1 mmHg (**-4.6~3.6 mmHg**) for central DBP, as shown in Table 2-2 and Forest plots. Not only the systematic bias (MD) but also the random error (SDD) of the estimated central SBP and pulse pressure was reduced by applying invasive methods as compared to the differences between invasive brachial and central SBP and pulse pressure (Table 2-2). This suggests that the pressure amplification from the central aorta to peripheral arteries can be treated effectively with current theoretical frameworks of central BP estimation.

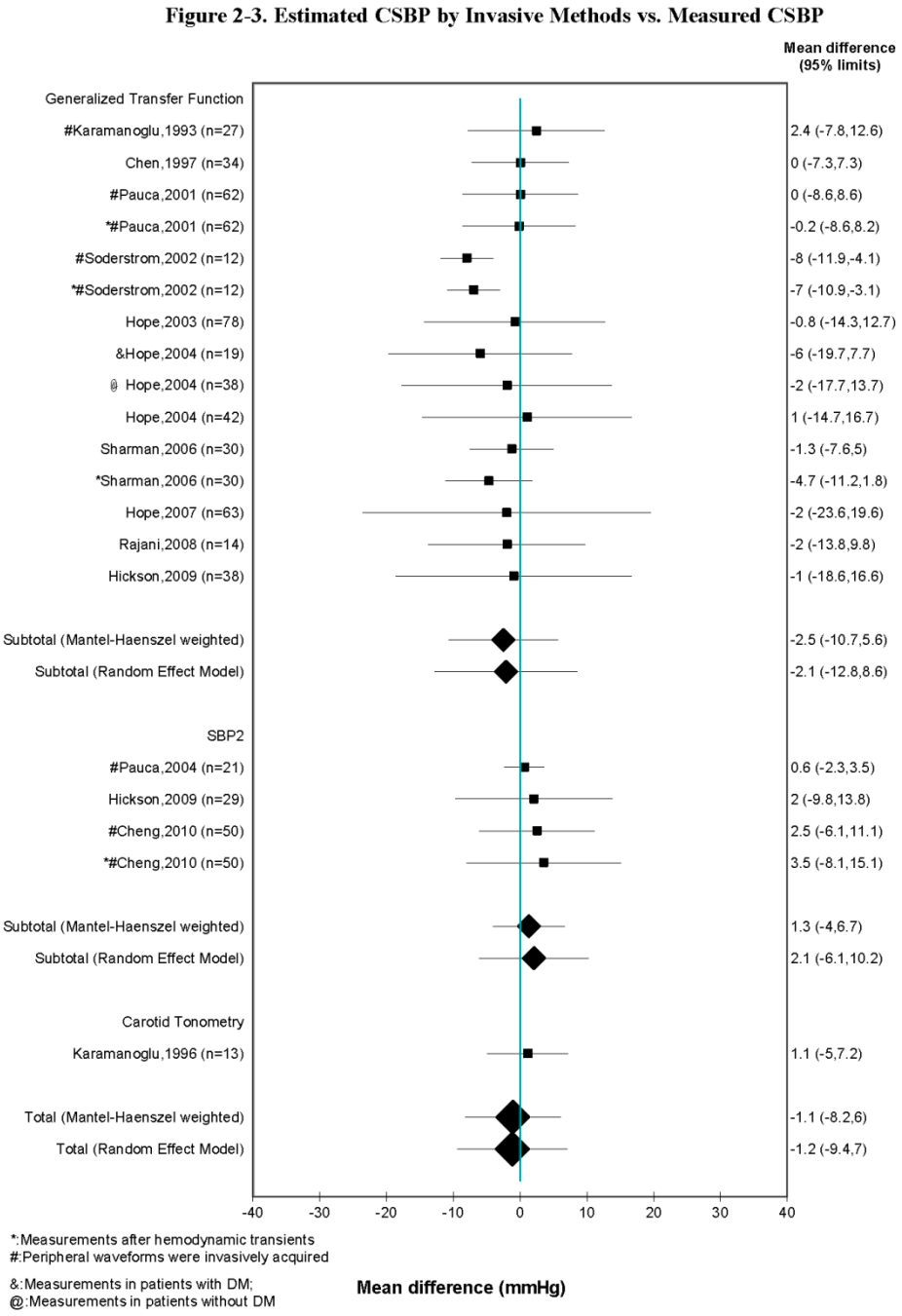

Figure 2-3. A Forest plot of the estimated central aortic SBP obtained with invasive methods vs. measured central SBP.

However, the errors inflated to -8.2 ± 10.3 mmHg (**-28.4~12.0 mmHg**) for estimating central SBP (Figure 2-4), -12.2 ± 10.4 mmHg (**-32.5~8.1 mmHg**) for central pulse pressure, and 7.6 ± 8.7 mmHg (**-9.5~24.6 mmHg**) for central DBP (Table 2-2), when the pressure waveform were calibrated by cuff BP. Similarly, large differences between cuff and invasive central BP have been demonstrated in our meta-analysis (Table 2-2). As compared to cuff SBP and pulse pressure, the random error of noninvasively estimated central SBP and pulse pressure was slightly reduced. The disagreement was still considerable in the subgroup analysis by different central BP methods as well as in studies using validated cuff BP monitors. When the studies reporting the use of **validated cuff BP monitors** for measurements were pooled, the errors were found to be similar: -6.7 ± 10.6 mmHg (**-27.4~14.1 mmHg**) for noninvasively estimated central SBP, -15.0 ± 11.1 mmHg (**-36.7~6.6 mmHg**) for central pulse pressure, and 10.8 ± 8.5 mmHg (**-5.9~27.6 mmHg**) for central DBP. Likewise, the cuff BP measured with validated sphygmomanometers had large MD and SDD with reference to corresponding invasively measured central BP: 2.8 ± 11.4 mmHg (-19.7~25.3 mmHg) for cuff SBP, -1.6 ± 12.0 mmHg (-25.1~21.9 mmHg) for cuff pulse pressure, and 9.7 ± 8.5 mmHg (-7.0~26.5 mmHg) for cuff DBP. In contrast to the considerably reduced systematic bias and random error of the invasive methods for estimating central SBP and pulse pressure, the measurement accuracy of noninvasively obtained central BP is suboptimal, even when the cuff BP monitors have passed the requirements according to international validation standards.

Figure 2-4. Non-invasively Estimated CSBP vs. Measured CSBP

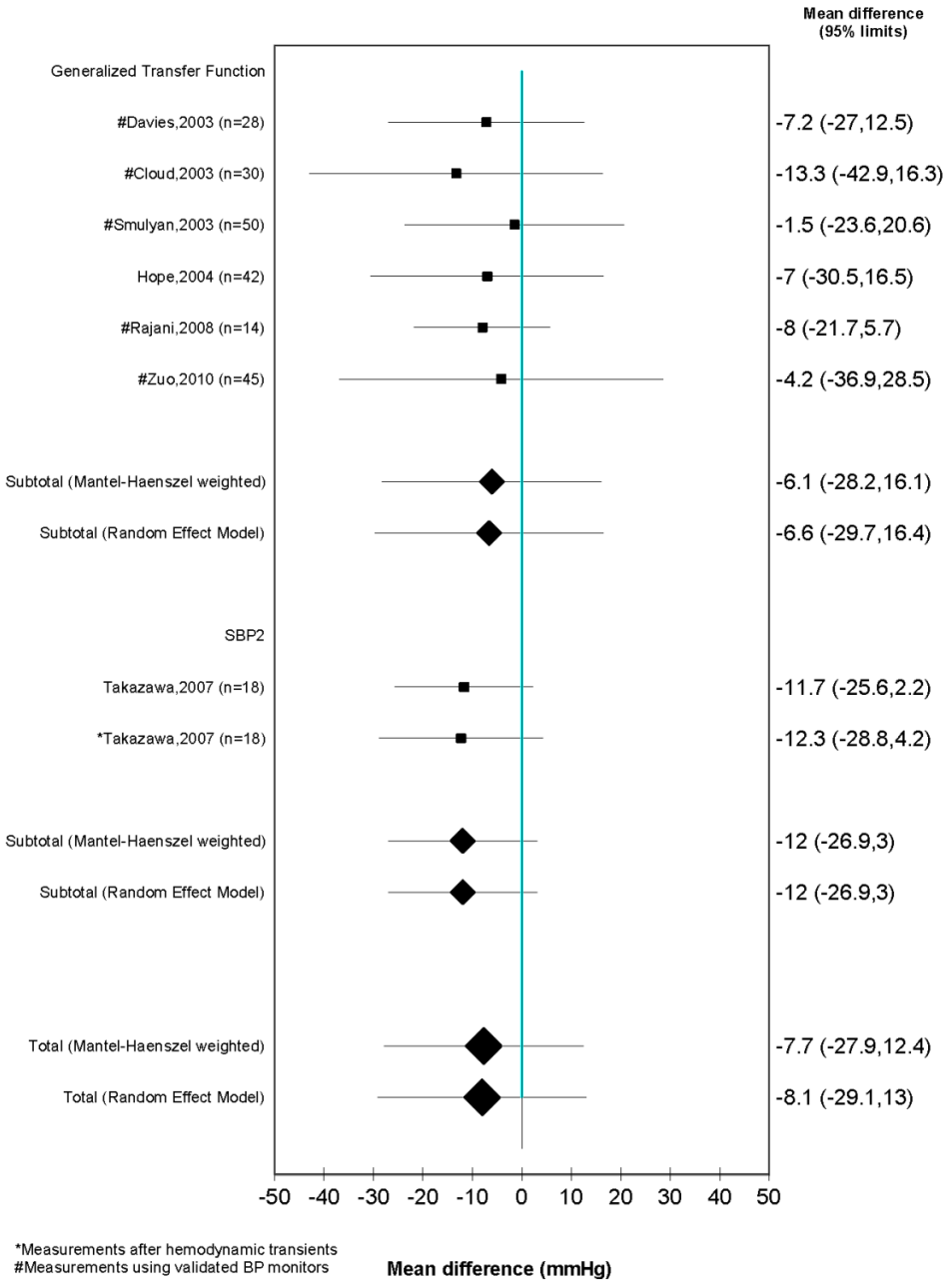

Figure 2-4. A Forest plot of the noninvasively estimated central aortic SBP vs. measured central SBP.

Device-specific Results

A comprehensive systematic search suggests that there have been only two devices which utilize applanation tonometry to estimate central BP that have undergone invasive validation (i.e. comparing central SBP estimates with invasively measured central BP). The two devices are SphygmoCor using a generalized transfer function approach, and HEM-9000 AI using a SBP2 method, respectively, which have been under patent protection for estimating central hemodynamics.

SphygmoCor (AtCor Medical, Sydney)

Of the 10 studies performing the analysis by the software program and GTF from SphygmoCor, 4 and 5 studies used invasive method and non-invasive calibration, respectively, and one study was conducted with both calibration methods. Of the studies with the invasive method, the errors were -2.4 ± 3.4 mmHg (-9.1~4.3 mmHg) for estimating central SBP, -2.6 ± 4.0 mmHg (-10.4~5.3 mmHg) for central pulse pressure, and 1.9 ± 1.5 mmHg (-1.2~4.9 mmHg) for central diastolic BP. Again, the errors of SphygmoCor system soared to -8.2 ± 11.6 mmHg (-30.9~14.5 mmHg) for estimating central SBP, -15.4 ± 10.2 mmHg (-35.3~4.6 mmHg) for central pulse pressure, and 9.3 ± 9.8 mmHg (-9.9~28.4 mmHg) for central DBP in studies conducted with non-invasive calibration.

HEM-9000AI (Omron Healthcare, Kyoto, Japan)

Only one invasive validation study of non-invasive central BP assessment was found for HEM-9000AI.[55] HEM-9000 AI only provides central SBP, which was estimated by the SBP2 method with a regression equation. The errors in this study for central SBP estimation were -2.0 ± 10.2 mmHg (-21.9~17.9 mmHg).

The tonometry-recorded waveforms (raw wave) are adjusted according to either the catheter-measured invasive central BP or sphygmomanometer-measured cuff BP.

The characteristics of the raw wave (maximum, mean, and minimum) are calculated first and then matched to the relevant BP values measured by invasive catheters or non-invasive BP monitors (i.e. mean and minimum correspond to MBP and DBP or maximum and minimum correspond to SBP and DBP, respectively). Panel A: Use of carotid artery applanation tonometry to obtain calibrated carotid pressure waveform; Panel B: Use of radial artery applanation tonometry and a **generalized transfer function** to reconstruct an aortic pressure waveform; Panel C: Identification of the late systolic shoulder of a tonometric radial pressure waveform (radial SBP2) to approximate central SBP. The calibration process may produce measurement errors when inaccurate cuff BP is used for non-invasive calibration.

The invasive method indicates that the peripheral pulse waveforms were either directly acquired or calibrated to invasive aortic MBP and DBP. Subtotal pooled point estimates are shown in the Forest plot within different subgroups categorized according to various methods for central SBP measurements (generalized transfer function, SBP2, and carotid tonometry). The square (or diamond for pooled point estimates) and horizontal line indicate the mean difference and 95% limits of agreement, respectively. The mean difference and 95% limits were extracted and calculated from primary studies (shown on right side), which were then pooled as subtotal or total point estimates of mean difference and its limits.

Discussion

Summary of Findings

The present review has shown that although current central BP estimating methods are acceptable by using invasive calibration, the error of these methods was large when cuff BP was used for non-invasive calibration. The invasive methods refers to applying these central BP estimating methods on the peripheral pulse waves which is directly measured or non-invasively acquired but calibrated using invasive aortic MBP and DBP. This calibrating practice is based on the widely accepted notion that MBP and DBP alter minimally along the arterial tree. [5]The findings from invasive methods suggest that the systematic bias and random error between peripheral BP and central BP could be reduced considerably (Table 2-2 and Figure 2-3) by applying these methods to estimate central BP. [4, 16, 40] Nevertheless, the effect of the above application diminished as for noninvasive calibration. As shown in studies conducted with noninvasive calibration by cuff BP, the errors of central BP estimation soared considerably (Table 2-2, Figure 2-4), even in studies using validated sphygmomanometers. In addition, there is substantial room for quality improvement in reporting and conducting primary studies according to critical appraisal results (appendix II).

The non-invasive method indicates that the peripheral pulse waveforms were calibrated to non-invasive cuff BP. Individual primary studies are sorted by subgroups of generalized transfer function and SBP2. Through our comprehensive search for invasive validation studies of central BP measurement, none study with cuff BP-calibrated carotid tonometry has ever been reported. Therefore, no subgroup of carotid tonometry is displayed in this Forest plot.

Strengths of this Study

This systematic review is in response to the long, ongoing debates on the validity of current central BP measures between the hypertensive society and a request for an independent systematic review.[56] Because many databases were comprehensively searched, it is unlikely that important pertinent studies have been overlooked. This systematic review also systematically and critically appraised the study quality based on previous consensus guidelines (Appendix II and table 2-S2).

Process of Central BP Estimation

The tonometry-based central BP estimating methods using generalized transfer function may suffer from serial errors that challenge their applicability,[54] including the robustness of the mathematical modelling between the peripheral and central aortic pressure waveform,[50] the quality of the acquired pressure waveform,[46] variable pulse pressure amplification between the brachial and radial arteries when brachial blood pressure values are used for calibrating radial pressure waveform,[57] and intrinsic discrepancy between the invasive brachial blood pressure values and those estimated with cuff-based sphygmomanometers. [43, 45] Therefore, carotid waveform [16]and radial waveform with the SBP2 method [6] were used as alternatives. However, according to subgroup analysis demonstrated in Figure 2-3 and 2-4, **the major source of estimation error is apparently not from pressure waveforms or estimating methods**.

Calibration Issues

It has been demonstrated in a previous study that a major source of error in estimating central BP by generalized transfer function may be from **inaccurate cuff BP** used for waveform calibration.[54] In this study, simultaneous high-fidelity brachial and central aortic pressure waveforms were both obtained invasively. It concluded that more than 96% of error in estimating central BP resulted from inaccurate cuff

BP for calibration. The study, however, hasn't examined other possible sources of errors, such as generalizability,[50] waveform quality,[46] and brachial-to-radial pulse pressure amplification[57] based on its study design.

Current sphygmomanometers appear to be a substantial barrier to the clinical application of the central BP concept as demonstrated in our meta-analysis results even when validated BP monitors are used for calibration. In real world clinical practice, all non-invasive central BP estimating methods can only calibrate peripheral waveforms by cuff BP. As shown in the left lower panel of Figure 2-1, one common calibrating practice is to adjust the peripheral waveform to make its peak and trough in correspondence with cuff SBP and DBP, respectively. However, the notion that mean and diastolic pressures from the central aorta to the peripheral artery have nearly the same values holds true only when both central and peripheral BP are measured invasively. It has been well recognized that there are large variations between indirect and direct blood pressure measurements.[58] Taking DBP as an example, large systematic bias and random error was noted between non-invasively estimated and measured central DBP (7.6 ± 8.7 mmHg) and between cuff DBP and measured central DBP (7.5 ± 8.7 mmHg) as shown in Table 2-2. It is apparent that cuff DBP considerably overestimates measured central DBP, which should correspond to invasive peripheral DBP, and introduces substantial errors into the estimated central DBP through the non-invasive calibrating process. The reason behind this is that the international standards for BP monitors request manufacturers to validate tested BP monitors against the mercury cuff method using Korotkoff sounds,[28, 59] which is actually not an accurate method to measure arm BP when it is compared with intra-arterial pressure.[58]

A variety of **calibrating methods** have been proposed to improve the non-invasive waveform calibration.[57, 60-62] The calibrating method used in two large-scale studies,

Framingham[63] and Asklepios[6] is adhered to the notion that mean BP and diastolic BP almost remain unaltered along the arterial tree. To calibrate carotid pressure waveforms, brachial mean BP is derived from integrated mean of a signal-averaged brachial pressure waveform obtained by tonometry. However, throughout our comprehensive search, there is no invasive validation study investigating the accuracy of this method against invasively measured central BP. Moreover, as shown in Figure 2-4, the random error of noninvasively estimated central SBP in one study using brachial mean and diastolic BP for peripheral waveform calibration was similar to other studies.[47]

Precision and Accuracy

As discussed in an editorial,[64] precision (random error) is important for a method to be applied in clinical research, and accuracy (systematic and random error) is mandatory for clinical application. Compared with the true gold standard of invasively measured central BP, the Achilles tendon of current central BP estimating methods is actually the random error, because systematic bias may be corrected by statistical normalization.[64]

Alternative Methods

This systematic review included studies conducted with applanation tonometry and excluded studies using different methods such as echo tracking,[18] finger pressure cuff,[65] and brachial cuff-based methods.[22, 66] However, these methods may suffer from similar sources of error as discussed above and have comparable ranges of errors shown in their primary invasive validation studies.

Limitations of this Review

Inadequate reporting is a common problem for systematic reviews, and this limitation also exists for method comparison studies. For several studies, even after

attempts were made to obtain results from corresponding authors, direct estimates of agreement between index and reference central BP measures remained unavailable.

Appendix Table 2-S1 shows that all included studies have different degrees of methodological weakness or lack of reporting clarity. For example, current popular techniques used to estimate central BP rely on good waveform acquisition by applanation tonometry, which is operator dependent and a less experienced operator may inevitably render the estimates less reliable or valid. All included studies were examined to establish whether the measurement is subject to "reliability checking" and performed by "trained professionals" (Appendix Table 2-S1). However, as demonstrated in the Forest plot (Figure 2-3 and 2-4) and a previous study,[54] the major influence on measurement accuracy may be still resulting from calibration methods.

The aim of this review was to systematically review all eligible studies and meta-analyze the results of agreement between paired central BP measurements presented in these studies. The conclusion might be confounded by the heterogeneity of study characteristics, estimation methods, and their conduction processes. However, we obtained the same trend across studies, as presented in Forest plots.

Moreover, the conclusion for invasive calibration is probably limited by the characteristics of participants enrolled in these validation studies, such as the high percentage of males and cardiovascular diseases. Most studies included in this review used radial-tonometry to estimate central BP in contrast to only two studies conducted with carotid-tonometry. More evidence from invasive validation studies supporting the use of carotid tonometry and the calibration method by brachial-tonometry is warranted.

Conclusion

The current tonometry-based central BP estimating methods are acceptable by using invasive calibration because they have small systematic and random errors. However, the errors were evident in the validation studies when cuff BP were used for noninvasive calibration. To implement central BP concept in clinical practice, evidence of improved measurement accuracy of these non-invasive methods by either more accurate cuff BP or better calibration methods should be demonstrated.

Perspectives

The BP amplification from central aorta to peripheral arteries, which varies substantially between subjects, causes conceivable discrepancy between central and peripheral BP. Noninvasive methods for estimating central BP are available and make it an attractive target for management of hypertension. Current available evidence on measurement accuracy of central BP estimating methods was comprehensively searched and synthesized in this systematic review and this revealed the existing gaps between practice and research evidence, which may guide future research in this area. Although the difference between central and peripheral BP can be reduced considerably by applying these tonometry-based estimating methods with invasive calibration, random error of these central BP estimates conducted with non-invasive calibration only slightly decreased as compared with those of cuff BP. The non-invasive calibration process using inaccurate cuff BP appears to be one of the gaps between practice and theory. Moreover, despite being adopted in large-scale studies, carotid tonometry and/or the calibration method by brachial-tonometry hasn't been supported by any invasive validation study, which is an apparent evidence gap. In this era of evidence-based medicine, efforts should be made to fill the above gaps in order to facilitate possible application of the attractive central BP concept in clinical practice.

Identified Translational Gaps And The Corresponding Strategies

Currently, the application of the CBP concept is mainly restricted in research fields even though its better prognostic value than that of cuff BP has been demonstrated.[12-14] One of the major barriers, or gaps, in propelling the advancement in the "evidence-to-practice" cycle is the technical threshold to perform applanation tonometry; a technique which usually requires an experienced operator to record the pressure waveform. Based on the concept of translational science, this gap relates to **Gap 3-From Clinical Application to Action.**

Through our systematic review and meta-analysis, it has been demonstrated that, in considering fulfilling the requirements of the international standards[28, 67, 68] for the accuracy of BP monitors, there is substantial room for improvement in terms of the measurement accuracy of current tonometry-based techniques for non-invasive CBP measurements. The above unmet need for knowledge relates to **Gap 1-From Knowledge Need to Discovery for the application of CBP concept.**

The solutions to the above two gaps can be solved separately. However, by investigating the oscillometric signals recorded during the BP measurement process of automatic BP monitors, the potential of the oscillometric signals for the purpose of measuring CBP are recognized (Chapter 3).[22, 69] This method can be equipped in the automatic BP monitors and, with the reduced skill requirement, successfully close the "**Clinical Application to Action " gap (Gap 3),**relating to the operational challenge associated with applanation tonometry. Furthermore, a process to solve the "**Knowledge Need to Discovery" gap (Gap 1),** by building a mathematic predicting model for non-invasive estimation of central pulse pressure, is detailed in Chapter 3.

CHAPTER 3: Measurement of Central Aortic Blood Pressure: Noninvasive Brachial Cuff-Based Estimation by a Transfer Function vs. a Novel Pulse Wave Analysis Method

Background

The hallmark of arterial hypertension is increased peripheral resistance, which results in an enhanced obstacle to blood flow at the arterioles and an elevated mean blood pressure (MBP).[5] In addition to this steady component of blood pressure, renewed interest in the pulsatile component, pulse pressure (PP) in particular, has been highlighted because of the accumulating evidence of its association with cardiovascular risk.[2, 70-73] PP - calculated as the difference of systolic (SBP) and diastolic (DBP) blood pressures - combines the effect of the intermittent ventricular ejection from the heart and exchange capacity of the aorta and large conduit arteries.[74, 75] Increased PP usually indicates increased arterial stiffness resulting from the alteration of the structure and function of large arteries at a given ventricular stroke volume.[74, 75] However, a substantial number of studies show that pulse pressure may not be better than SBP, DBP, or MBP in predicting cardiovascular events.[73, 76, 77]

On account of the pulse pressure amplification from central aorta to peripheral arteries and anatomical proximity to coronary arteries, heart, and carotid arteries, central aortic PP (PP-C) has been shown to carry better prognostic value than traditional brachial PP measured by cuff-based sphygmomanometers.[11-14, 78-80] However, inconsistent results also exist and fail to confirm the superiority of PP-C over cuff PP.[36, 63, 81]

Recent advances in the noninvasive estimation of central blood pressure using either tonometry-based[17, 20] or brachial cuff-based approaches[22, 66] have been focused on

central aortic SBP (SBP-C), with PP-C subsequently calculated from the estimated SBP-C and central or cuff DBP. However, the noninvasive SBP-C and PP-C bear substantial calibration errors equivalent to errors of the cuff SBP and PP in the measurement of intra-arterial brachial SBP and PP, respectively.[54] The measurement error for cuff PP is usually much greater than that for cuff SBP because the former bears measurement errors for both cuff SBP and DBP (Figure 3-1).[54] An inaccurate cuff PP invariably generates an inaccurate PP-C estimate.[58] The inherent large errors in cuff PP[58] and PP-C[46, 53] may have substantially reduced their prognostic values. It appears that no attempts have been made to improve the accuracy of cuff PP and PP-C estimates. Therefore, the aims of the present study were firstly to develop a novel brachial cuff-based pulse wave analysis (PWA) approach to directly estimate PP-C using a pulse waveform analysis, and secondly to investigate the accuracy of noninvasive brachial cuff-based estimation of PP-C by a generalized transfer function (GTF) or the PWA approach.

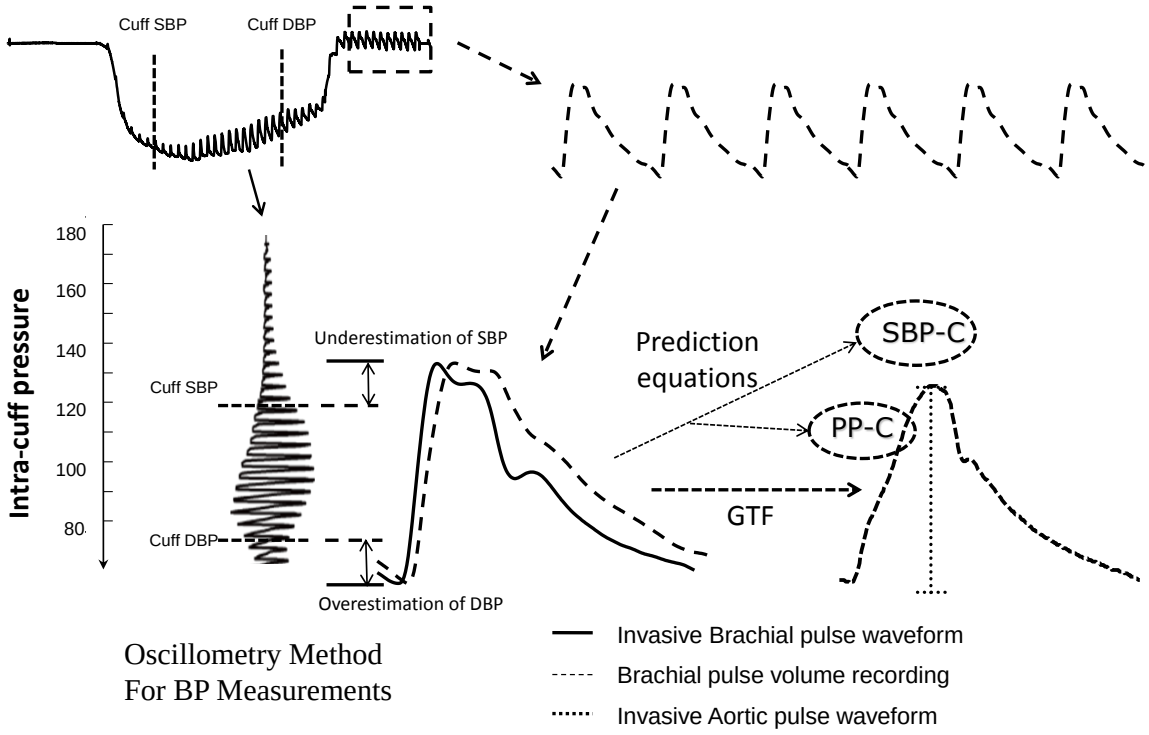

Figure 3-1. The Application of oscillometric signals

Figure 3-1. The application of oscillometric signals. The amplitude of intra-cuff oscillations is determined mainly by the relationship between intra-cuff pressure and intra-arterial pressure (left panel). The oscillometric method for blood pressure (BP) measurements (left lower panel) analyses this relationship and recognizes the cuff pressure at the arterial SBP and DBP by detecting some changes in the oscillations at these points. Oscillometric (cuff) BP usually underestimates intra-arterial brachial SBP and overestimates intra-arterial brachial DBP.[5, 58] The oscillations become stable with the steady intra-cuff pressure (right upper panel). As shown in the right lower panel, the signals, also known as pulse volume plethysmography, can be used as surrogates of intra-arterial pressure waveforms to estimate central systolic (SBP-C) and pulse pressure (PP-C) by either a generalized transfer function (GTF)[82, 83] or prediction equations.[22, 84]

Methods

Study population and Signal Acquisition Process

The study population combined subjects from two previous studies[22, 54] and consisted of a Generation Group (n = 40)[54] and a Validation Group (n = 100).[22] The population included subjects referred for diagnostic catheterization to examine coronary anatomy through a radial approach. Subjects were not included if they were in an unstable clinical condition, such as acute coronary syndrome and

peripheral arterial disease. Subjects with rhythms other than normal sinus rhythm and more than 3 mmHg pressure difference between left and right arms were also excluded. The study was approved by the Institutional Review Board at Taipei Veterans General Hospital and adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

The characteristics of the study subjects are summarized in Table 3-1.[22, 54, 83] Details of the signal acquisition process have been reported.[22, 54, 83] In brief, a custom-designed 2F dual-sensor high-fidelity micromanometer-tipped catheters (model SSD-1059, Millar Instruments Inc., U.S.A.) was delicately positioned with the first sensor at the ascending aorta and the second sensor at right brachial artery in subjects of the Generation Group to acquire simultaneous invasive brachial and aortic pressure waveforms. These waveforms were then used to construct the aorta-to-brachial GTF.[54, 83] Left arm pulse volume recording, also known as pulse volume plethysmography (PVP), was recorded by a validated oscillometric blood pressure monitor (WatchBP Office; Microlife AG, Widnau, Switzerland)[85] at mean cuff pressure of 60 mmHg for 30 seconds, which were then calibrated to cuff SBP and DBP. The rationale of cuff pressure selection has been provided in previous studies.[84] In the Validation Group, the 30 seconds' simultaneous central aortic pressure and left-arm PVP waveforms were recorded by a 2F micromanometer-tipped catheter (model SPC-320, Millar Instruments Inc., U.S.A.) and a commercially available oscillometric device (VP-2000, Colin Corporation, Komaki, Japan) at mean cuff pressure of 60 mmHg, respectively.[22] In both groups, all signals were recorded at baseline and 3 minutes after administration of a sublingual nitroglycerin (NTG), following the automatic measuring of the left brachial cuff blood pressures. The sampling rates of the signals for the Generation and Validation Group were 500Hz and 250Hz, respectively.

Table 3-1. Baseline characteristics of the study subjects.

	Generation Group[54] (n=40)	Validation Group[22] (n=100)
Characteristics		
Age, years	64.1 ± 14.0	61.9 ± 13.2
Men, %	80.4	74
Weight, kg	72.5 ± 13.4	69.8 ± 11.2
Waist circumference, cm	90.5 ± 11.3	90.9 ± 9.1
Height, cm	164.0 ± 7.9	163.1 ± 8.2
Body mass index, kg/m2	26.9 ± 4.1	26.2 ± 3.2
Smoking, %	28.3	24
Clinical diagnosis, %		
Hypertension	63	61
Type 2 diabetes mellitus	23.9	17
Dyslipidemia	37	33
Coronary artery disease	52.2	49
Chronic renal failure	2.2	3
Medications, %		
α-blockers	13	11
β-blockers	37	38
Calcium channel blockers	43.6	28
ACEI/ARB	52.2	35
Diuretics	17.4	14
Anti-platelet agents	80.4	66
Statins	41.3	32
Hemodynamic parameters		
Brachial SBP, mmHg	139 ±20	142 ± 21
Brachial DBP, mmHg	71 ± 10	72 ± 11
Brachial PP, mmHg	68 ± 19	70 ± 17
Aortic SBP, mmHg	135 ± 21	134 ± 21
Aortic DBP, mmHg	72 ± 9	71 ± 11
Aortic PP, mmHg	63 ± 19	63 ±17
Cuff SBP, mmHg	137 ±19	13 ± 20
Cuff DBP, mmHg	79 ± 10	78 ±12
Cuff PP, mmHg	58 ±17	58 ± 13
Baseline heart rate, beats/min	65 ± 10	68 ± 12
Left ventricular ejection fraction, %	57 ± 8	55 ± 9

ACEI/ARB = angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure

Data Analysis

Central and brachial SBP, DBP, and MBP were obtained from these ensemble-average aortic and brachial pressure waveforms. SBP and DBP were values at the peak and end-diastole of the averaged pressure waveform, respectively. MBP was determined from the total area under the averaged pressure waveform. Heart rate was calculated from the length of the pressure waveform.

Estimation of PP-C using a GTF approach

PP, the pressure change to create the pulse, is calculated as the pressure difference between SBP and DBP. Similarly, the non-invasive estimation of PP-C is obtained by subtracting central aortic DBP (DBP-C) from SBP-C. In other words, non-invasive PP-C is usually calculated by estimating SBP-C and DBP-C. There are numerous methods to obtain non-invasive SBP-C.[59] One common approach involves the reconstruction of central aortic pressure waveforms by transforming peripheral pressure waveforms with a GTF.[19] In addition, a previous study has demonstrated that GTF can be applied to pulse volume plethysmography (PVP) waves to obtain SBP-C with an accuracy comparable to a tonometer (Figure 3-1).[82]We therefore obtained SBP-C and DBP-C estimates by applying a previously validated GTF[54, 83] to PVP waves. Besides, it is a widely accepted notion that MBP and DBP alter minimally along the arterial tree.[5] Therefore, one arguable approach is to use cuff DBP as a DBP-C estimate by ignoring the measurement inaccuracy of sphygmomanometer. Therefore, two PP-C estimates were produced as below in the present study:

$PP\text{-}C_{TFSBP\text{-}TFDBP}$ = SBP-C – DBP-C;

$PP\text{-}C_{TFSBP\text{-}CUFFDBP}$ = SBP-C – cuff DBP

Both SBP-C and DBP-C were identified from the reconstructed aortic pressure waveform by exploiting the GTF on PVP waves.

Estimation of PP-C using a PWA approach

A Taiwanese research group has been successfully developing a novel method exploiting cuff-based PWA with a multivariate prediction model to estimate SBP-C.[22] The PWA method involves the identification of parameters relating to wave reflection and arterial compliance[86] on the brachial PVP waveform. The waveform parameters are input variables in the multivariate model, which include secondary peak systolic pressure (SBP2), pressure at onset of diastole (Pes), and areas under the pressure tracing in diastole (Ad) and systole (As).[22] Amplitudes of SBP2 are associated with the intensity of pressure wave reflection,[4, 87] and the latter three parameters are related to arterial compliance.[86] The validity and generalizability of this multivariate prediction model for the non-invasive estimation of SBP-C has been demonstrated in our previous studies.[22, 84]

Accordingly, by subtracting cuff DBP from the noninvasively estimated SBP-C, PP-C can therefore be calculated as below:

$$PP\text{-}C_{PWASBP\text{-}CUFFDBP} = \text{estimated SBP-C by the PWA method} - \text{cuff DBP}$$

In the present study, contrary to the above calculations which derive PP-C from SBP-C and DBP-C/cuff DBP, we directly estimated PP-C ($PP\text{-}C_{PWAPP}$) independently of SBP-C or DBP-C/cuff DBP by building up a novel noninvasive multivariate model adopting the same rationale as the above PWA approach.

The noninvasive multivariate prediction model to directly estimate PP-C was constructed by stepwise multiple linear regression analysis, which selected the best parameters from the calibrated PVP waveforms of Generation Group.[22] Potential waveform parameters were selected into or removed from the model according to stepping method criteria with F probability less than 0.05 for entry or above 0.10 for removal.

Statistical Analyses

All the baseline data were tested for normality using the Shapiro-Wilk test. Comparisons of paired blood pressure values and their differences were performed using the paired student *t* test or the paired-sample Wilcoxon signed rank test (non-parametric test). All baseline variables including waveform parameters in the multivariate model were normally distributed. Agreements between the measured and estimated PP-C values were examined using the Bland-Altman analysis and presented with mean and standard deviation (SD) of differences. Clinical parameters which significantly correlated with PP-C were examined for their effects on the performance of the prediction models by multivariate stepwise regression analysis. Statistical significance is declared at the two-tailed $P < 0.05$ level or attended by Bonferroni correction if multiple comparisons were performed.

Results

Performance of the GTF Approach in the Estimation of PP-C

Cuff PP underestimated the invasive PP-C at baseline and overestimated the invasive PP-C after NTG in both the Generation and Validation Groups (Table 3-2). As shown in the Bland-Altman analysis for the combined data in the Validation Group (Figure 3-2A), a systematic error, which was proportional to the magnitudes of PP-C, and a large scatter (SD of difference = 12.4 mmHg) were noted.

Table 3-2. Comparisons of cuff PP and various noninvasive estimates of PP-C with the invasively measured PP-C.

	Generation Group (n=80)						Validation Group (n=200)					
	Baseline (n=40)			After NTG (n=40)			Baseline (n=100)			After NTG (n=100)		
Blood pressure variable (mmHg)	Mean ± SD	p value of differences	R value	Mean ± SD	p value of differences	R value	Mean ± SD	p value of differences	R value	Mean ± SD	p value of differences	R value
Cuff PP	-4.9 ± 9.7*	0.0024	0.86**	5.8 ± 8.0**	<0.0001	0.82**	-4.5 ± 9.4**	<0.0001	0.84**	8.0 ± 12.0**	<0.0001	0.55**
PP-$C_{TFSBP-TFDBP}$	-9.6 ± 8.4**	<0.0001	0.90**	0.5 ± 8.1	0.7073	0.82**	-8.9 ± 8.6**	<0.0001	0.87**	2.0 ± 11.6	0.0829	0.58**
PP-$C_{TFSBP-CUFFDBP}$	-9.3 ± 8.3**	<0.0001	0.90**	0.9 ± 8.3	0.5202	0.81**	-7.6 ± 8.5**	<0.0001	0.87**	3.0 ± 11.6	0.0115	0.58**
PP-$C_{PWASBP-CUFFDBP}$	-8.5 ± 7.0**	<0.0001	0.93**	-3.7 ± 6.7*	0.0013	0.88**	-5.7 ± 7.2**	<0.0001	0.91**	-1.9 ± 7.4	0.0119	0.87**
PP-C_{PWAPP}	-0.9 ± 7.1	0.4325	0.93**	0.9 ± 5.7	0.331	0.91**	2.6 ± 6.8*	0.0021	0.92**	3.5 ± 7.4**	<0.0001	0.86**

*: Significance was set at p<0.01 with Bonferroni correction for multiple comparisons; **:p<0.001

PP-$C_{TFSBP-TFDBP}$: PP-C calculated from the estimated central systolic and diastolic blood pressure using a generalized transfer function approach

Estimated PP-$C_{TFSBP-CUFFDBP}$: PP-C calculated from the estimated central systolic blood pressure using a generalized transfer function approach and the cuff diastolic blood pressure

Estimated PP-$C_{PWASBP-CUFFDBP}$: PP-C calculated from the estimated central systolic blood pressure using a pulse wave analysis approach and the cuff diastolic blood pressure

PP-C_{PWAPP}: PP-C directly estimated from the novel pulse waveform analysis approach

NTG = nitroglycerin; PP = pulse pressure; PP-C = central pulse pressure

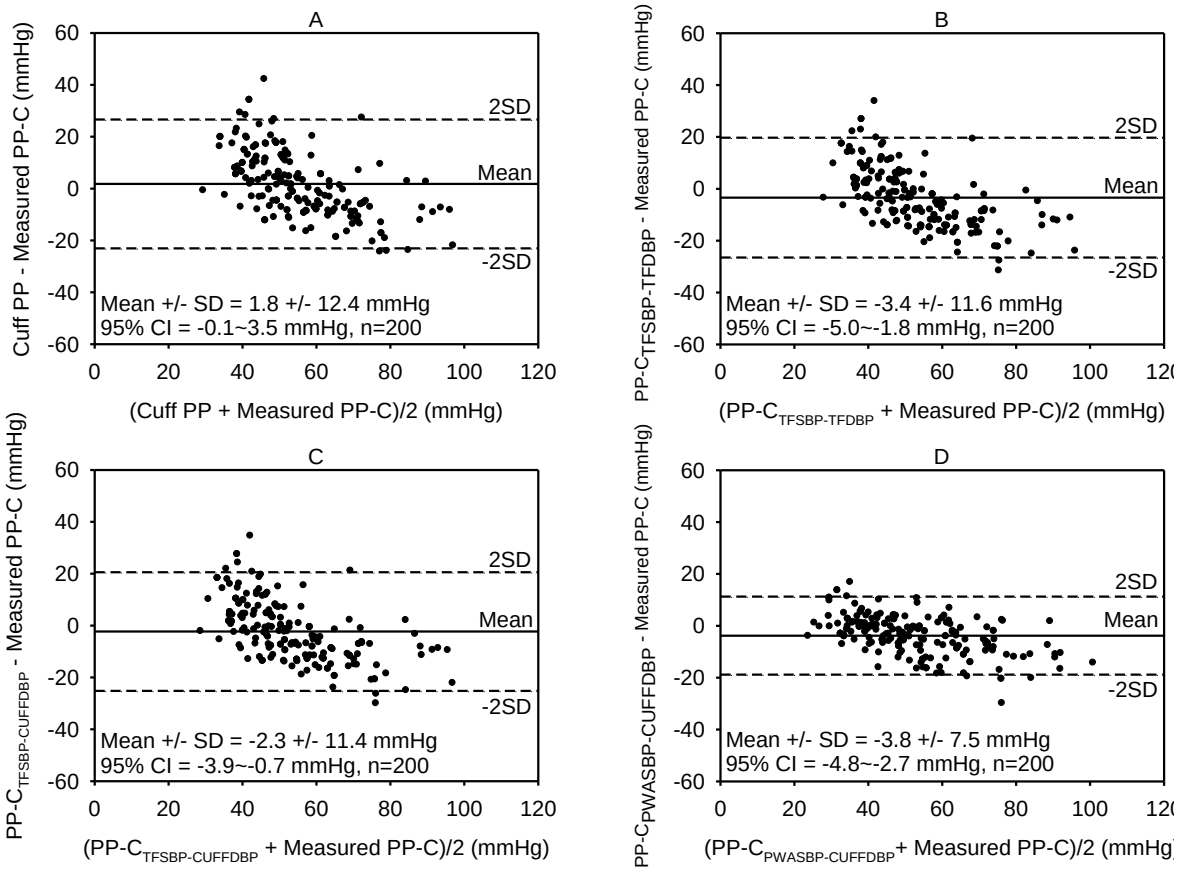

Figure 3-2.

Figure 3-2. Bland-Altman analyses combining measurements at baseline and after administration of nitroglycerin in the Validation Group (n=200).

Panel A: agreement between the invasively measured central aortic pulse pressure (PP-C) and the cuff pulse pressure (PP); Panel B: agreement between the measured PP-C and the calculated PP-C ($PP\text{-}C_{TFSBP\text{-}TFDBP}$) from the estimated central systolic blood pressure and diastolic blood pressure, using a generalized transfer function approach;[54] Panel C: agreement between the measured PP-C and the calculated PP-C ($PP\text{-}C_{TFSBP\text{-}CUFFDBP}$) from the estimated central systolic blood pressure and the cuff diastolic blood pressure, using a generalized transfer function approach; Panel D: agreement between the measured PP-C and the calculated PP-C ($PP\text{-}C_{PWASBP\text{-}CUFFDBP}$) from the estimated central systolic blood pressure and cuff diastolic blood pressure, using the PWA approach.[22]

As shown in Table 3-2, similar to cuff PP in the estimation of PP-C, PP-$C_{TFSBP-TFDBP}$ and PP-$C_{TFSBP-CUFFDBP}$ still considerably underestimated PP-C at baseline (all *P* values <0.01 of the paired comparisons). After NTG, although PP-$C_{TFSBP-TFDBP}$ and PP-$C_{TFSBP-CUFFDBP}$ only slightly overestimated PP-C, the scatters of differences (standard deviation of differences between paired measurements) were similar to those between PP-C and cuff PP. In particular, the observed proportional systematic error and large scatter in the Bland-Altman analysis for cuff PP persisted for PP-$C_{TFSBP-TFDBP}$ and PP-$C_{TFSBP-CUFFDBP}$ (Figure 3-2B and 3-2C, respectively).

Performance of the PWA Approach in the Estimation of PP-C

A multi-variate prediction model to estimate the invasively measured PP-C using parameters from the non-invasively calibrated PVP waveforms was constructed from the Generation Group as follows (see also Table 3-S1):

Estimated PP-C (PP-C_{PWAPP}) = -88.2 + 0.79 x Pes + 1.41 x As + 0.68 x Ad – 1.16 x DBP + 0.84 x heart rate

The full model R2 was 0.88 (*P*<0.001) and the partial R2 for Pes, As, Ad, DBP, and heart rate were 0.694, 0.123, 0.001, 0.055, and 0.012, respectively. The mean and SD of differences between the noninvasively obtained PP-C_{PWAPP} and the invasively measured PP-C at baseline and after NTG were -0.9 ± 7.1 and 0.9 ± 5.7 mmHg, respectively (Table 2-2). Clinical parameters including age, sex, height, weight, arm circumference, or left ventricular ejection fraction were input into the model but all of them failed to remain in the final model during the stepwise selection process.

The Bland-Altman analysis revealed no systematic bias in the estimation (Figure 3-3A).

The performance of the noninvasive multi-variate prediction model, which directly estimated PP-C, was further independently examined in the Validation Group. The mean and SD of differences between PP-C_{PWAPP} and the invasively measured PP-C at baseline and after NTG were 2.6 ± 6.8 and 3.5 ± 7.4 mmHg, respectively (Table 3-2). The Bland-Altman analysis revealed no proportional systematic bias in the estimation (Figure 3-3B).

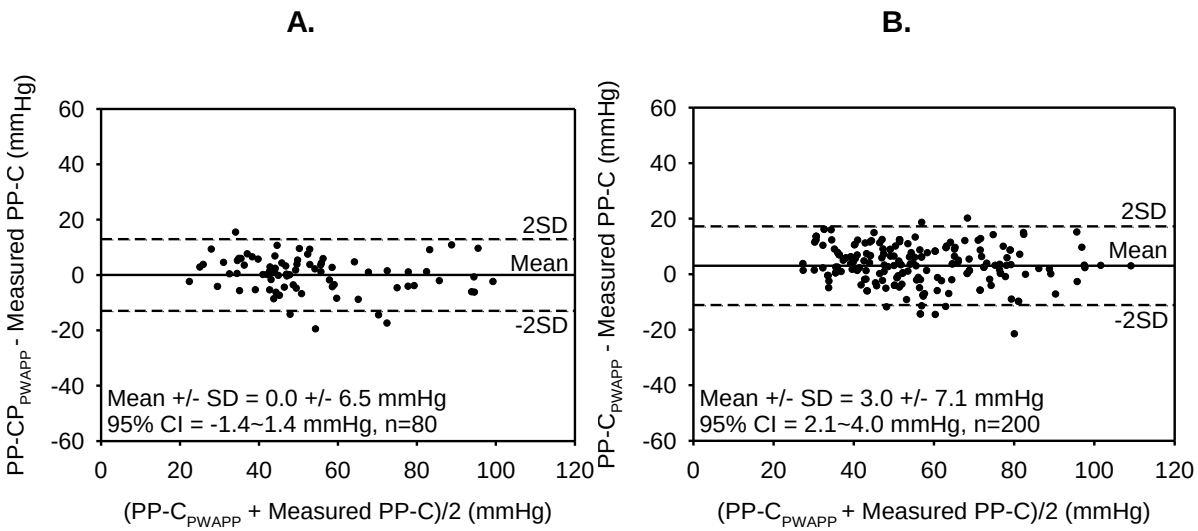

Figure 3-3.

Figure 3-3. Bland-Altman analyses combining measurements at baseline and after administration of nitroglycerin in the Generation and Validation Group. Agreement between invasively measured central aortic pulse pressure (PP-C) and the directly estimated PP-C (PP-C_{PWAPP}) by using the novel pulse wave analysis approach. Panel A: Generation Group (n=80); Panel B: Validation Group (n=200).

On the other hand, PP-$C_{PWASBP-CUFFDBP}$ underestimated the invasively measured PP-C both at baseline and after NTG in both the Generation and Validation Groups (Table 3-2). In the Bland-Altman analysis for the combined data in the Validation Group, an obvious but less pronounced proportional systematic error was also observed for PP-$C_{PWASBP-CUFFDBP}$ (Figure 3-2D).

Calibration errors and PVP Waveform Analysis

Table 3-3 shows the PVP waveform correlates of the errors of cuff blood pressures with reference to the invasive brachial blood pressures. Deviations of cuff SBP from invasive SBP measurements were weakly correlated with Pes and As identified from the PVP waveforms. On the other hand, deviations of cuff DBP and cuff PP from invasive measurements were moderately correlated with all parameters of PVP waveform, including SBP2, Pes, As, Ad, DBP.

Table 3-3. Correlation coefficients between errors of cuff blood pressures and brachial pulse volume plethysmography waveform parameters (n=280)

Cuff blood pressure error	SBP2	Pes	As	Ad	DBP	heart rate
Cuff SBP - Invasive brachial SBP	-0.056	-0.163*	-0.157*	-0.117	-0.006	0.124
Cuff DBP - Invasive brachial DBP	0.426**	0.496**	0.467**	0.359**	0.443**	-0.129
Cuff PP - Invasive brachial PP	-0.339**	-0.477**	-0.451**	-0.351**	-0.315**	0.201**

*: Significance was set at P<0.0083 with Bonferroni correction for multiple comparisons; **: p<0.001

Ad = area under the pressure tracing in diastole; As = area under the pressure tracing in systole; DBP = diastolic blood pressure; Pes = pressure at onset of diastole; SBP = systolic blood pressure; SBP2 = secondary peak systolic pressure.

Discussion

The upper arm cuff oscillometric method utilizing a GTF[66] or PWA[22, 88]can provide estimates of SBP-C comparable to radial tonometry[66, 88]or to invasive measurements.[22] However, the present study shows that a large random error and a proportional systematic error are expected when PP-C is calculated as the difference between an estimated SBP-C and an estimated DBP-C or a measured cuff DBP. In contrast, through the use of a novel PWA approach and a regression equation to directly estimate PP-C noninvasively, the accuracy can be improved substantially. This innovative method gives PP-C estimates corresponding to invasively measured PP-C and does not depend on the assumption that cuff SBP and DBP, which are used for waveform calibration, can faithfully reflect invasively measured brachial SBP and DBP.

It has been demonstrated clearly in a previous study that a noninvasive application of a GTF technique to a high quality brachial pressure waveform produces estimates of SBP-C and PP-C with errors equivalent to those of the oscillometric blood pressure

monitor in measuring the invasive brachial SBP and PP.[54] The transmission of the errors from cuff SBP and DBP to the estimate of SBP-C is also evident in a brachial cuff-based method with a transfer function-like algorithm.[66] In the Validation Group of the present study, cuff PP, PP-$C_{TFSBP-TFDBP}$, and PP-$C_{TFSBP-CUFFDBP}$ underestimated the invasively measured PP-C by 4.5 to 8.9 mmHg at baseline and overestimated by 2.0 to 8.0 mmHg after NTG with a SD of differences >8 mmHg (Table 3-2). The inaccuracy of the PP-C estimates was likely due to the fact that current sphygmomanometers usually underestimate intra-arterial brachial SBP and over-estimate intra-arterial DBP.[58] Indeed, we have also shown that the validated oscillometric blood pressure monitors used in the Generation Group (WatchBP Office; Microlife AG, Widnau, Switzerland)[54] and in the Validation Group (VP-2000, Colin Corporation, Komaki, Japan)[22] underestimated brachial SBP and overestimated brachial DBP (Figure 3-1). Because PP is the difference between SBP and DBP, the measurement error for PP is roughly the sum of measurement errors for SBP and DBP and thus is substantially greater than that for SBP.[54] Therefore, the GTF-derived PP-C (such as PP-$C_{TFSBP-TFDBP}$ and PP-$C_{TFSBP-CUFFDBP}$) may invariably be subject to large calibration errors.

It is proposed that a cuff-based noninvasive PWA prediction model can be used to estimate SBP-C with an error within the Association for the Advancement of Medical Instrumentation invasive validation criteria of 5 ± 8 mmHg.[22] However, the noninvasive SBP-C estimation model could not be directly used to estimate PP-C by simple subtraction of the cuff DBP from the estimated SBP-C (PP-$C_{PWASBP-CUFFDBP}$), probably because of the summation of the random errors and systematic biases from the cuff SBP and cuff DBP (Figure 3-4).[54] In the present study, a novel multi-variate prediction model to directly estimate PP-C. Our results indicate that the noninvasive prediction model can provide estimates of PP-C with an error within the

required criteria and without appreciable proportional systematic error was constructed. The successful correction of the systematic drift from the calibration errors was probably because the PVP waveform parameters, which are components for the estimation of arterial compliance,[86, 89] correlated well with both the invasive PP-C (data not shown) and errors of cuff blood pressure (Table 3-3). This is consistent with the observation that reduced arterial compliance may increase the cuff blood pressure measurement errors.[89] Therefore, the noninvasive multi-variate prediction model could consequently produce estimates for PP-C less susceptible to calibration errors from the inaccurate cuff SBP and DBP (Figure 3-4). Moreover, the utilization of a multi-variate linear regression modelling effectively integrates incremental contribution from each independent variable and therefore may provide better and more stable model prediction than that with only single variable.[21]

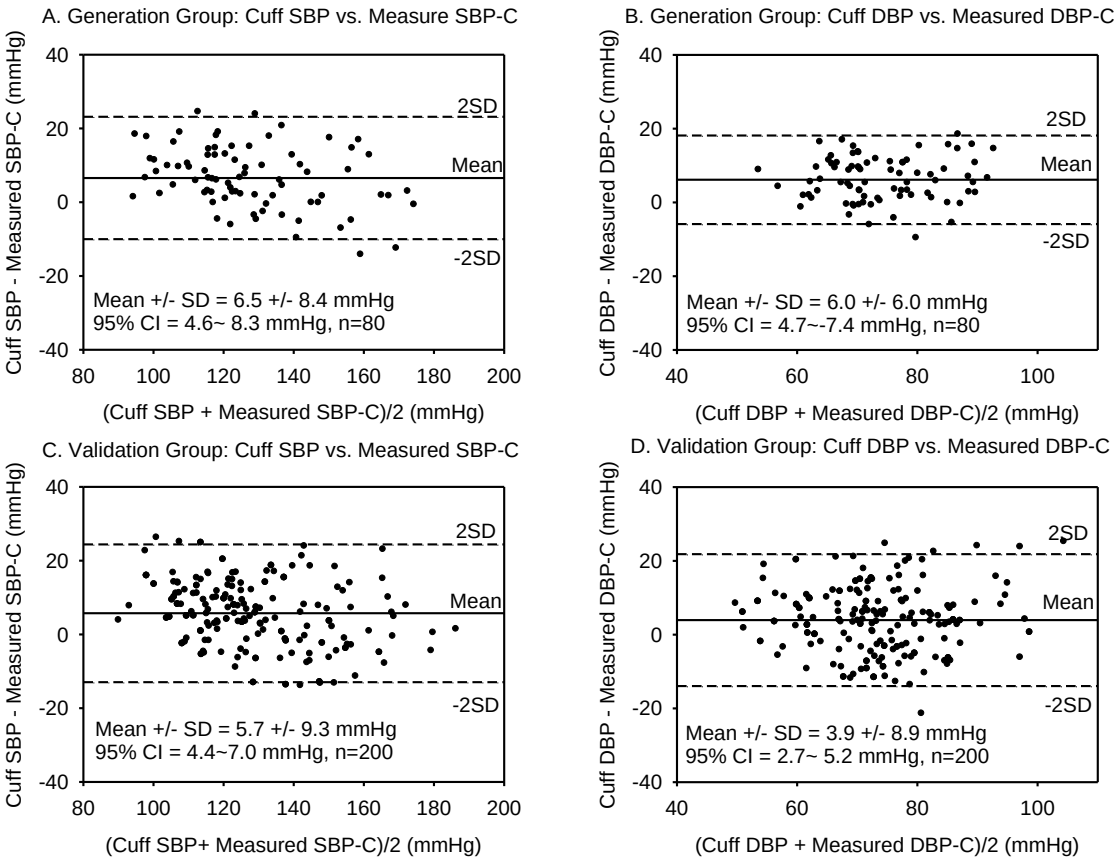

Figure 3-4.

Figure 3-4. Bland-Altman analyses combining measurements at baseline and after administration of nitroglycerin. Panel A: agreement between the invasively measured central aortic systolic blood pressure (SBP-C) and the cuff systolic blood pressure (SBP) in the Generation Group (n=80); Panel B: agreement between the invasively measured central aortic diastolic blood pressure (DBP-C) and the cuff diastolic blood pressure (DBP) in the Generation Group (n=80); Panel C: agreement between the measured SBP-C and the cuff SBP in the Validation Group (n=200); Panel D: agreement between the measured DBP-C and the cuff DBP in the Validation Group (n=200).

It is worth noting that cuff PP and estimates of PP-C calculated from the difference between the estimated SBP-C and DBP-C may carry a large random error and a systematic bias from measurement errors for cuff SBP and DBP (Table 3-2, Figure 3-2). The systematic bias may partly explain the negative results of the prognostic value for cuff PP[73, 76, 77] and PP-C.[36, 63, 81] It is anticipated that the prognostic value of PP-C may be further increased with improved accuracy of the estimated PP-C.

Study Limitations

The present proposed model was generated from and validated in subjects receiving diagnostic catheterization in the supine position. These patients were indicated mainly for cardiac catheterization with around 50% of the study population having coronary artery disease and being treated with a variety of vasoactive medications. Therefore, it remains to be determined whether the model can be applied to younger subjects and those in a sitting position. However, the accuracy of the validation results demonstrated in this study suggests that the PWA approach has the potential to ameliorate the calibration error for estimating PP-C.

In conclusion, the prognostic values of PP-C and cuff PP may be limited, because large random and systematic errors are introduced into cuff PP and the PP-C estimates. The inaccuracy of PP-C estimates may result from the fact that they are calculated as the difference between the estimated SBP-C and DBP-C or cuff DBP. This study therefore proposed and validated a novel cuff-based method to directly estimate PP-C, using a multi-variate prediction model incorporating parameters identified from a calibrated PVP waveform. The random error of the directly estimated PP-C was within the recommended criteria and no systematic drift was observed. The improved technique can seamlessly be incorporated into current oscillometric blood pressure monitors to provide accurate PP-C for routine clinical applications. Future studies are required to demonstrate the independent prognostic values of the directly estimated PP-C.

Strategies to Address Translational Gaps

With the novel “scientific discovery” of an accurate and user-friendly oscillometric CBP monitors, effort should be made to close the “**Discovery to Clinical Application”**

gap (Gap 2). For this most widely-addressed gap, a rigorous clinical trial should be designed to validate the measurement accuracy of the oscillometric CBP monitors with the built-in computational predicting models for central SBP and PP.

Faced with the challenges for a new technology, a validation study was conducted with the rationale and study design listed as following, and is reported in **Chapter 4**.

Challenges of the Validation studies for the Accuracy of Oscillometric Central BP Monitors

Although automatic BP monitors are subject to strict validation standards, it remains to be established how to test the measurement accuracy of emerging central BP monitors. **It would be prudent to validate the accuracy of the newly developed central BP monitors according to the standards previously defined for the automatic BP monitors.**

The following discussion summarizes the rationale of the study design of the validation study which attempts to respond to the new challenges for the relevant methods of this emerging technology, the “oscillometric central BP monitors”.

Reference standard (comparator):

The first challenge is the choice of a reference standard. For automatic BP monitors, the reference gold standard is the auscultatory method, Korotkoff sound, to measure arm BP. As for central BP measurement, it might be an acceptable practice to use the most widely used devise as a reference comparator given its accuracy is proved. However, since the real gold standard for central BP measurement ought to be invasive BP measurement at the ascending aorta, it is therefore appropriate to investigate the measurement accuracy of the “surrogate gold standard” by the “well-established” devise, SphygmoCor with reference to the invasively measured

central BP. According to a systematic review and meta-analysis,[90] the error of the non-invasive central BP measurement by SphygmoCor was −8.2±11.6 mm Hg (95% limits of agreement −30.9–14.5 mm Hg) for estimating central SBP, −15.4±10.2 mm Hg (−35.3–4.6 mm Hg) for central pulse pressure, and 9.3±9.8 mmHg (−9.9–28.4 mmHg) for central DBP. Apparently, the inaccuracy of SphygmoCor in central BP measurement is far beyond currently acceptable criteria, 5 ±8 mmHg. In this regard, we chose invasive BP as a "true reference standard" and adhered to AAMI's suggestions by considering to use either a saline-filled catheter or an external pressure transducer with tip in situ.[28] In the present validation study, a saline-filled catheter was used instead of a high-fidelity pressure catheter to invasively measure central BP. Another goal of the present study was to become a leading-edge validation study for similar devices. The pressure transducers in the contemporary catheterization laboratories are accurate in pressure measurements, but may not be good enough for waveform analysis, which does require high frequency components of signals. Considering the more invasive nature with one more catheter inside the subjects' vascular system, it might be less feasible to routinely use high-fidelity external-tip pressure catheters in validation studies for oscillometric central BP monitors, in which high-frequency waveform details, such as inflection points, are of less concern.

Validation process (how many patients and other requirements):

Except for ESH-IP, AAMI and BHS both require a total of 85 subjects with 255 measurements (3 for each) in the non-invasive validation studies. For invasive validation study, AAMI 2010 requires recruiting no fewer than 15 subjects with a minimum of 150 paired observations with a minimum of 5 and a maximum of 10 paired measurements per subject. The device should be tested over a range of

pressures—i.e., at least 10 % of subjects below 100 mmHg systolic, 10 % above 160 mmHg systolic, 10 % below 60 mmHg diastolic, and 10 % above 90 mmHg diastolic, with the remainder distributed between these outer limits. It was decided to adopt the most rigorous approach, recruiting subjects abiding by regulations for non-invasive validation, but also fulfilling all requirements set for studies using the invasive reference standard (see AAMI SP10: Validation with reference invasive blood pressure monitoring equipment).

The reported outcome and format:

This is an easily misunderstood part in terms of the value of standard deviation of band error; it should be clarified that the error-determination using intra-arterial BP as a reference standard is actually different from the traditional method (paired *t*-test) for calculating errors between paired measurements.

According to SP10, 2009[28], the measurement error should be determined as the following process:

"2.5 Determining the blood pressure error

The mean systolic blood pressure values ± 1 standard deviation of the invasive blood pressure curve obtained during the determination performed by the sphygmomanometer under-test should be used to determine the range of the variation of systolic blood pressure.

If the value obtained from the sphygmomanometer-under-test determination lies within the range of the variation of blood pressure (see 2.4), assign an error of 0 mmHg to this determination.

If the value obtained from the sphygmomanometer-under-test determination lies outside the range of the variation of blood pressure, subtract the value of the determination from the adjacent limit of the range of the variation of blood pressure. That difference represents the error for this determination.

EXAMPLE 1: The range of the variation of diastolic blood pressure is 73 mmHg to 82 mmHg. Diastolic blood pressure value determined by the sphygmomanometer-under-test is 76 mmHg. The error for this determination is 0 mmHg.

EXAMPLE 2: The range of the variation of diastolic blood pressure is 73 mmHg to 82 mmHg. Diastolic blood pressure value determined by the sphygmomanometer-under-test is 70 mmHg. The error for this determination is −3 mmHg.

From the errors of each determination of each patient, calculate the arithmetic mean of the error and its standard deviation.

The range of the variation of diastolic blood pressure shall be determined in the same way. ”

In this study, the data used for comparison with the criteria, 5 ±8 mmHg, is the “band error”. In addition, all tables are produced abiding by AAMI’s requests for reporting.

CHAPTER 4: Measurement Accuracy of A Standalone Oscillometric Central Blood Pressure Monitor: A Validation Report for Microlife WatchBP Office Central

Background

The blood pressure (BP) amplification from central aorta to peripheral arteries, which varies substantially between subjects, causes discrepancy between central blood pressure (CBP) and BP recorded at a person's upper arm.[4-9] Although mean BP (MBP) and diastolic BP (DBP) are relatively constant in the conduit arteries, systolic BP (SBP) and pulse pressure (PP) measured from peripheral arteries are usually higher than those measured at the origin of the arterial tree, namely, the aortic root.[3, 4] CBP can be estimated noninvasively, mainly based on the technique of applanation tonometry.[4, 15, 16] Thereafter, it has been shown that the noninvasively measured CBP and the conventional brachial BP respond to anti-hypertensive medications differently.[35, 91] Furthermore, the superior prognostic value of CBP over conventional brachial BP demonstrated in previous studies[12-14] has re-ignited the development of more convenient non-invasive methods for CBP measurements, including tonometry-based[17] and brachial cuff-based techniques.[22, 66]

Other studies have developed and validated a novel oscillometric method to estimate central SBP and PP.[22, 69, 84] Noninvasive central SBP and PP can be estimated according to separate multivariate regression equations with parameters derived from off-line analysis of the acquired brachial pulse volume plethysmography (PVP) waveforms calibrated to the noninvasive brachial SBP and DBP.[22, 69] This PVP waveform analysis method has the potential to be built into any stand-alone noninvasive blood pressure monitors to offer simultaneous readings of central and brachial BP for ambulatory and home applications. To date, there has

been no report for such a stand-alone CBP monitor validated against international standards.[28, 67, 68] In fact, there have been no international standards for the validation of the CBP monitors. Thus, the purpose of the present study was to validate the accuracy of a newly developed stand-alone CBP monitor incorporated with the PVP method, according to the invasive standard requirements for the noninvasive brachial blood pressure monitors from the Association for the Advancement of Medical Instrumentation (AAMI).[28]

Methods

Study Population

The study protocol was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taiwan, and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before the study.

All study subjects enrolled in this study were selected consecutively from those scheduled to undergo diagnostic cardiac catheterization and/or coronary angioplasty. Patients who had acute coronary syndrome, peripheral arterial disease, rhythms other than normal sinus rhythm, or more than 3 mmHg pressure differences between left and right arms, had been excluded from the studies. The study population was divided into two independent groups, namely the Generation Group (n = 56, age range 34-89 years) and the Validation Group (n = 85, age range 30-93 years) with characteristics given in Table 4-1.

Table 4-1. Characteristics of the study patients

Characteristics	Generation Group (n = 56)		Validation Group (n=85)	
	Mean ± SD	Range	Mean ± SD	Range
Men, %	66.1	-	69.4	-
Age, years	65.5 ± 13.7	34:89	64.8 ± 13.6	30:93
Age >80years, %	21.4	-	12.9	-
Height, cm	162.4 ± 10.5	141:183	163.8 ± 7.8	144:178
Weight, kg	68.8 ± 13.1	49:105	68.1 ± 11.7	46:103
Waist circumference, cm	87.7 ± 10.9	62:115	87.7 ± 10.7	64:105
Left arm circumference, cm	30.3 ± 2.8	26:39:00	29.9 ± 2.7	25:39:00
Body mass index, kg/m2	26.1 ± 4.2	17.5:38.1	25.4 ± 3.6	17.8:34.6
Left ventricular ejection fraction, %	52.5 ± 11.4	0.755556	53.1 ± 9.1	25:75
Smoking, %	17.9	-	11.8	-
Clinical diagnosis, %				
Hypertension	71.4	-	52.9	-
Type 2 diabetes mellitus	37.5	-	24.7	-
Dyslipidemia	53.6	-	37.7	-
Coronary artery disease	66.1	-	63.5	-
Chronic renal failure	8.9	-	3.5	-
Medications, %				
α-blockers	17.9	-	10.6	-
β-blockers	55.4	-	42.4	-
Calcium channel blockers	25	-	42.4	-
Angiotensin converting enzyme inhibitors	12.5	-	5.9	-
Angiotensin receptor blockers	37.5	-	27.1	-
Diuretics	35.7	-	28.2	-
Anti-platelet agents	71.4	-	68.2	-
Statins	51.8	-	45.9	-
Recruitment blood pressures, mmHg				
Aortic SBP	141 ± 27	83:200	135 ± 22	83:197
Aortic MBP	99 ± 14	68:132	97 ± 12	64:134
Aortic DBP	68 ± 12	44:107	70 ± 12	41:109
Aortic PP	73 ± 26	24:133	64 ± 23	0.925
Noninvasive aortic SBP	141 ± 25	81:194	134 ± 20	86:190
Noninvasive aortic DBP	69 ± 13	43:102	70 ± 10	43:102
Noninvasive aortic PP	73 ± 25	28:126	64 ± 21	28:126
Noninvasive brachial SBP	138 ± 23	91:196	132 ± 18	96:195
Noninvasive brachial DBP	76 ± 11	53:113	76 ± 10	48:113
Noninvasive brachial PP	62± 20	24:107	56 ± 16	0.988889
Baseline heart rate, beats/min	69 ± 10	45:95	69 ± 12	46:103

DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure; SBP = systolic blood pressure.

The techniques of estimating central SBP and PP separately using the PVP waveform analysis method have been built into a commonly used noninvasive BP monitor (WatchBP Office; Microlife AG, Widnau, Switzerland) as the prototype CBP monitor. The accuracy of the noninvasive brachial BP measured by the prototype CBP monitor met the requirements suggested by European Society of Hypertension International Protocol.[85] The algorithms for identification of the characteristic points on the PVP waveforms recorded within the prototype CBP monitor were refined and the predicting equations for central SBP and PP, were recalibrated using 191 measurements from 56 subjects in the Generation Group. Central DBP was simply the subtraction of central PP from central SBP. The final algorithms and prediction equations were then incorporated into the prototype CBP monitor. Thereafter, the accuracy of CBP obtained from this final version prototype CBP monitor was examined in the Validation Group.

The recruitment of subjects in the Validation Group strictly adhered to the published international standards.[28, 67, 68] Of the 95 subjects who entered the study, 10 were unable to successfully complete it (4 due to frequent atrial ectopic beats and 6 due to catheter damping). The remaining 85 subjects and 255 measurements formed the basis of this report.

The ranges and averages of the subjects' characteristics in the Validation Group are shown in Table 4-1 and Table 4-S1 in Appendix IV. They were at least 18 years old, 30.6% of participants were women, and 12.9% with age more than 80 years. Subjects with an invasive measurement of central SBP >160 mmHg, central SBP <100 mmHg, central DBP > 85 mmHg, and central DBP < 70 mmHg were 18.8, 10.6, 16.5, and 63.5%, respectively (see also Table 4-S1 in appendix IV).

Study Protocol

Upon arrival to the catheterization laboratory, the height, weight, and the circumference of the left upper arm were measured. All routine medications were continued at the time of the procedure. After local injection of 2–3 cc 1% lidocaine and successful placement of a 6F arterial sheath in the right radial artery, 2.5 mg verapamil was administered intra-arterially to prevent vasospasm during the catheterization. Then heparin (5,000 U) was administered intravenously after insertion of the arterial catheter. Intravenous atropine and/or sublingual nitroglycerin were given to selected patients before angiography. The appropriate size BP cuff was selected according to the manufacturer's direction, and was placed on the upper left arm with its lower edge 2.5 cm above the antecubital fossa. Before diagnostic catheterization, a large lumen 6F arterial catheter was advanced to the ascending aorta via right radial artery and placed 2 cm above the aortic valve under fluoroscopic guidance. The distal end of the catheter was positioned away from the walls of the aorta and perpendicular to the direction of blood flow to avoid the elevation of pressure readings resulting from kinetic energy transfer. All direct pressure measurements were obtained in the supine position during the process of automatic pressure measurement using the CBP monitor, with the left arm positioned at mid-chest level. The simultaneous direct pressure recording and the automatic pressure measurement were repeated after diagnostic coronary angiography and finally after left ventriculography with a total of three measurements for each participant in the Validation Group.

Automatic CBP Monitor and Automatic Pressure Measurement

The prototype automatic CBP monitor was built from a validated oscillometric arm blood pressure monitor (WatchBP Office; Microlife AG, Widnau, Switzerland) to perform PVP and instant PVP waveform analysis for the estimation of central SBP and PP. The CBP monitor incorporated a microcontroller MSP430F4617 (Texas Instruments, U.S.A), a pressure transducer, a 12-bits analog-to-digital converter (ADC), a flash memory, and a digital-to-analog converter to acquire and store the continuous PVP signals. The pressure transducer (MP3V5050, Freescale Semiconductor, Inc) had a linear range of 0-300 mmHg for acquiring oscillometric signals of cuff pressure. An instrumentational amplifier was seated behind the pressure transducer for reducing common mode signal and amplifying oscillometric signals. A band-pass filter was used to minimize the effect of baseline shift, with the cutoff frequency set at 0.5 to 30Hz. A 12-bit ADC which sampling rate of 256Hz was used to digitize the continuous pressure signals. To accurately maintain the cuff pressure at 60 mmHg, an air pump and an electrical controlled linear valve were used to adjust the inflating and deflating rate respectively. The PVP waveform analysis algorithm was implemented in C programming Language using Borland C++ Builder 6.0.

This prototype CBP monitor was customized to measure brachial SBP and DBP, followed by performing PVP at a cuff pressure of 60 mmHg. The PVP waveform was then calibrated to the brachial SBP and DBP and used for estimating central SBP and PP.[22, 69] The prediction equation of central PP measurements was produced by adopting the same theoretical framework for central SBP.[69](see on-line supplementary data for details.) The values of brachial SBP and DBP, and central SBP and PP displayed on the CBP monitor were the averages of two recordings separated

by one minute. Brachial PP was calculated as brachial SBP - brachial DBP. Central DBP was calculated as central SBP - central PP.

Direct Pressure Measurement

Invasive CBP was measured from the ascending aorta using a fluid-filled catheter system attached to Siemens-approved transducers with a resistance of 200 - 3000 Ohms and an equivalent pressure sensitivity of 5 µV/V/mmHg ± 10%.

To maximize the fidelity of the catheter-transducer systems, the catheters were thoroughly flushed outside the duration of pressure recording and avoided any unnecessary connections between the catheter and transducer.[92] The frequency range of the catheterization laboratory amplifier was 0–400Hz for pressure measurement (-50 to 400mmHg) with the accuracy of ± 1 mmHg or ± 3% exclusive of transducer.[22] The routinely checked natural frequency and damping coefficients of the system were 30 Hz (21-41Hz) and 0.2 (0.14-0.41), respectively, which surpassed the recommended guidelines.[28, 93] The pressure transducers had been warmed for a minimum of 30 minutes before calibration and use. Each transducer was calibrated against mercury immediately before pressure measurement with the zero reference level for pressure measurement set at mid-chest height, which was also used for balancing. Both calibration and balancing were checked before each measurement was performed. During all automated BP measurements using the CBP monitor, pressure tracings were recorded simultaneously and continuously with a recording of zero reference at the end of each pressure segment to check for and correct any measurable pressure drift.

Data Analysis

The recorded invasive central aortic pressure signals were analysed off-line using custom-designed software developed on a commercial software package (Matlab®, version 7.0, The MathWorks, Inc., U.S.A.). All processed individual signals were subjected to fully automatic batch analysis to avoid inter- and intra-observer variations. The invasively measured central SBP, DBP, and PP were determined from the highest readings, the lowest readings, and the amplitudes of all central aortic pressure waveforms recorded during the whole process of automatic pressure measurement using the prototype CBP monitor. Pressure measurements recorded during and after isolated premature beats were excluded from analysis; multiple premature beats during a single period resulted in removal of the patient from the protocol. The mean values of the invasive CBP ± 1 standard deviation represented the range of the variation of invasive reference CBP,[28] which served as the basis for comparison with indirect measurements.[28] All measurements were obtained from the tracings by one experienced observer blinded to the indirect readings and the clinical status of the patients.

Assessment of the Magnitude of Errors

Band error shown in Tables 4-2 and 4-3 was determined according to the suggestion of AAMI SP10 2009, which is the error used for comparison with the predefined criteria, 5 ± 8 mmHg.[28] In brief, band error was the extent that estimated BP fell outside the range of variation of invasively measured CBP as mentioned above. **Absolute error** presented in Table 4-2 represented the absolute value of difference between estimated CBP and measured range of variation of CBP. **Relative error** shown in Table 4-2 was similarly defined as absolute error, but was expressed as a percentage of the simultaneous direct measurement.

Overestimation/underestimation in Table 4-2 reflected the mean overestimation or underestimation of the difference between estimated CBP and measured mean value of CBP to display the tendency of the automatic CBP monitor to overestimate or underestimate direct readings. Table 4-2 also provides Pearson's correlation coefficients between indirect and direct BP recordings.

Table 4-2. Magnitude of error and correlation between estimated and measured CBP (estimated CBP – measured CBP, n = 255)

SBP	PP	DBP
Band error, mmHg		
(determined according to the suggestion of AAMI SP10 2009[28]; error is the extent that estimated CBP fell outside the range of mean ± S.D. of measured CBP		
Range (low : high)	– 8.6 : +14.9	–14.1 : +20.1	–19.2 : +15.3
Mean ± standard deviation	-0.4 ± 3.0	-0.4 ± 5.2	0.5 ± 4.2
Absolute error, mmHg		
(absolute value of difference between estimated and measured CBP)		
Range (low : high)	0.0 : +19.5	0.0 : +22.7	0.0 : +20.6
Mean ± standard deviation	4.3 ± 3.5	5.5 ± 4.3	5 ± 4.2
Relative error, %		
(absolute error*100%/measured CBP)		
Range (low : high)	0.0 : +19.2	0.0 : +70.3	0.0 : +33.7
Mean ± standard deviation	3.3 ± 2.9	10.2 ± 11.1	7.2 ± 6.4
Overestimation/underestimation, mmHg		
(difference between estimated and measured CBP)		
Range (low : high)	–12.9 : +19.5	–16.1 : +22.7	–20.6 : +20.0
Mean ± standard deviation	-0.6 ± 5.5	-0.4 ± 7.0	-0.2 ± 6.5
Correlation coefficients with measured CBP		
	0.97	0.95	0.83

CBP = central blood pressure; DBP = diastolic blood pressure;
SBP = systolic blood pressure; PP = pulse pressure.

Table 4-3. Validation results of band error between the calculated and measured CBP (n=255)

	<5 mmHg		<10 mmHg		<15 mmHg	
	number	Percentage,%	number	Percentage,%	number	Percentage,%
central SBP	225	88.2	252	98.8	255	100
central PP	177	69.4	235	92.2	252	98.8
central DBP	212	83.1	240	94.1	252	98.8

CBP = central blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; PP = pulse pressure

Statistical Analyses

The normality of all the blood pressure parameters was tested using the Shapiro-Wilk test. Because of the strict recruiting requirement of AAMI that aims at enrolling a representative group, all BP parameters were therefore normally distributed. Data are presented as mean ± standard deviation (SD). Agreements between the paired measurements were examined using the paired samples *t*-test and the Bland-Altman analysis. Statistical significance was declared at the two-tailed $P < 0.05$ level.

Results

Recruitment of Study Subjects

Overall, 56 and 85 subjects were included in the Generation and Validation Groups, respectively. As shown in Table 4-1, the age distribution and associated co-morbidity represented a study population with a wide variety of clinical characteristics. Table 4-S1 (on-line supplementary data) details the fulfilment of specific requirements of AAMI SP10[28] and the relative distribution of measured invasive CBP, which consisted of the wide scattered BP readings during measurements.

Validation Results with Reference to Invasive Measured CBP

Table 4-2 provides the magnitude of observed errors and correlation coefficients. The band errors for central SBP, PP, and DBP measurements were -0.4 ± 3.0, -0.4 ± 5.2, and 0.5 ± 4.2 mmHg, respectively. In contrast, the band errors for cuff SBP, PP, and DBP were -2.0 ± 6.0, -7.5 ± 9.7, and 3.3 ± 5.4 mmHg, respectively.

Table 4-3 shows the distributions of measurement errors within the range <5, <10, and <15 mmHg, which clearly surpassed all recommended standards including AAMI SP10,[28] British Hypertension Society protocol Grade A,[68] and European Society of hypertension international protocol 2010.[67]

Bland-Altman analyses for the noninvasive brachial and central SBP, PP, and DBP are shown in Figures 4-1 to 4-3. The mean differences and standard deviations between the noninvasive and invasive central SBP, PP, and DBP were -0.6 ± 5.5, -0.4 ± 7.0, and -0.2 ± 6.5 mmHg, respectively; well within the 5 ± 8 mmHg defined by AAMI SP10.[28] No remarkable systematic drift was observed. In contrast, the noninvasive brachial SBP slightly underestimated invasive central SBP but with large scattering and an obvious systematic bias proportional to magnitudes of measured values (Figure 4-1); the noninvasive brachial PP markedly underestimated invasive central PP with large scattering and an obvious proportional systematic bias (Figure 4-2); and the noninvasive brachial DBP substantially overestimated invasive central DBP but with acceptable scattering and a slight systematic drift (Figure 4-3).

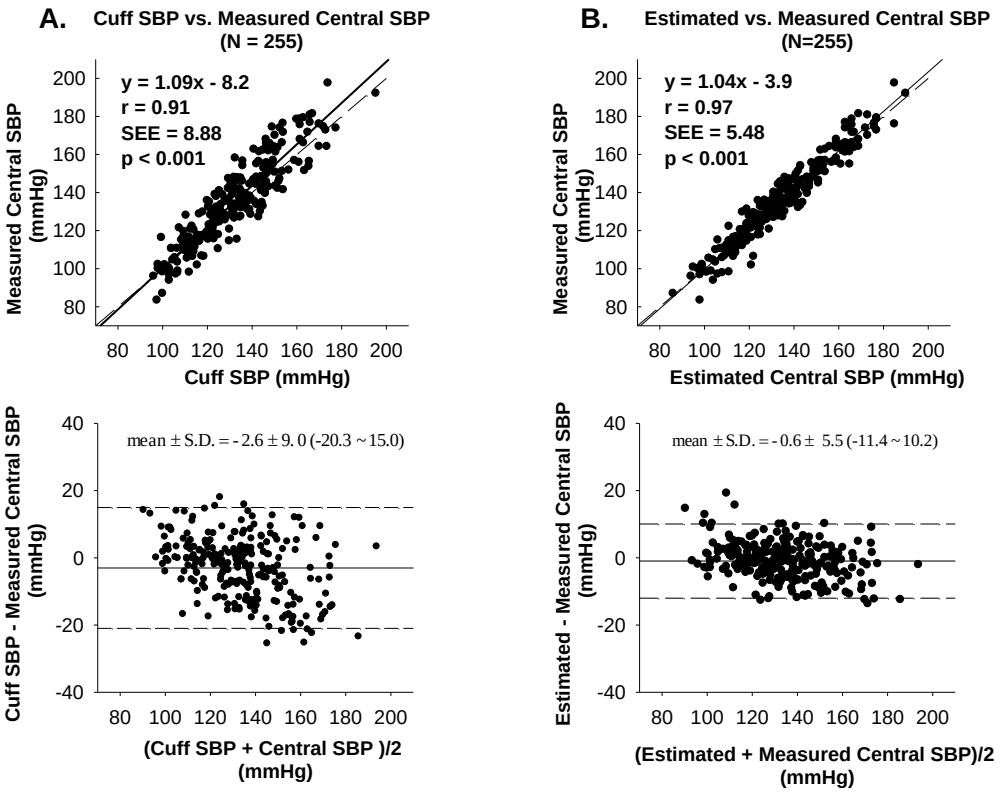

Figure 4-1.

Figure 4-1. Bland-Altman analyses. Panel A, agreement between the cuff SBP and measured central aortic SBP; Panel B, agreement between the estimated and measured central aortic SBP. Dashed lines indicate the boundaries of 2 standard deviations of the differences; dotted lines indicate lines of identity.

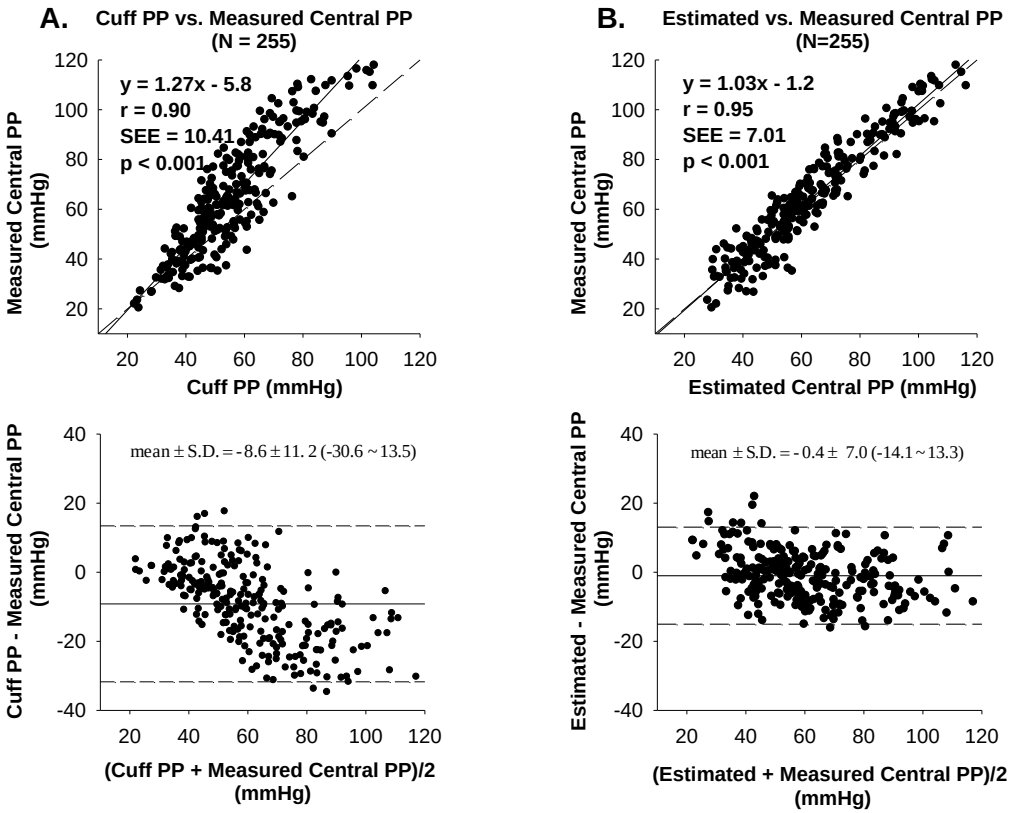

Figure 4-2.

Figure 4-2. Bland-Altman analyses. Panel A, agreement between the cuff pulse pressure (PP) and measured central aortic PP; Panel B, agreement between the estimated and measured central aortic PP. Dashed lines indicate the boundaries of 2 standard deviations of the differences; dotted lines indicate lines of identity.

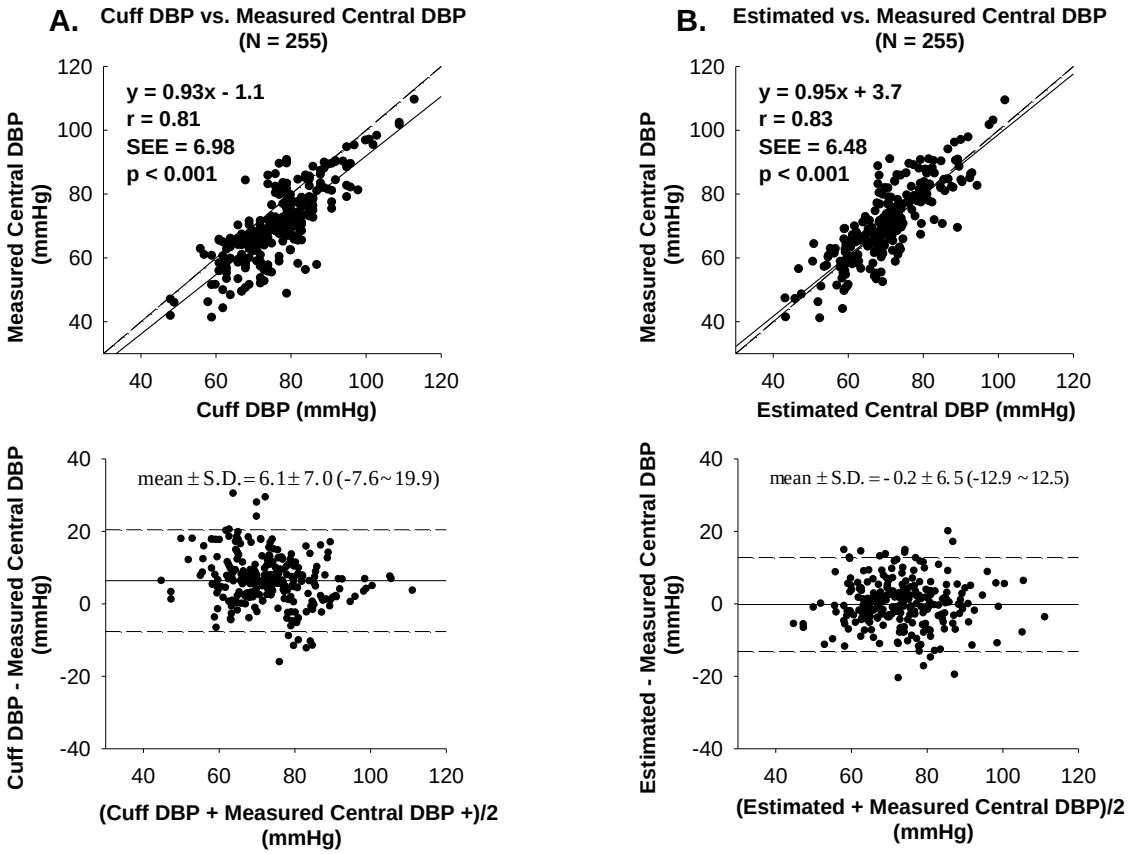

Figure 4-3.

Figure 4-3. Bland-Altman analyses. Panel A. Agreement between the cuff diastolic pressure (DBP) and measured central aortic DBP. Panel B, agreement between the estimated and measured central aortic DBP Dashed lines indicate the boundaries of 2 standard deviations of the differences; dotted lines indicate lines of identity.

The comparisons of measurement accuracy between cuff brachial BP and noninvasive CBP measured by the CBP monitor are presented in Figure 4-4. The band errors of noninvasive CBP with reference to the invasive CBP were close to zero and were significantly smaller than those of the corresponding cuff BP (all $p<0.001$ for SBP, PP, and DBP).

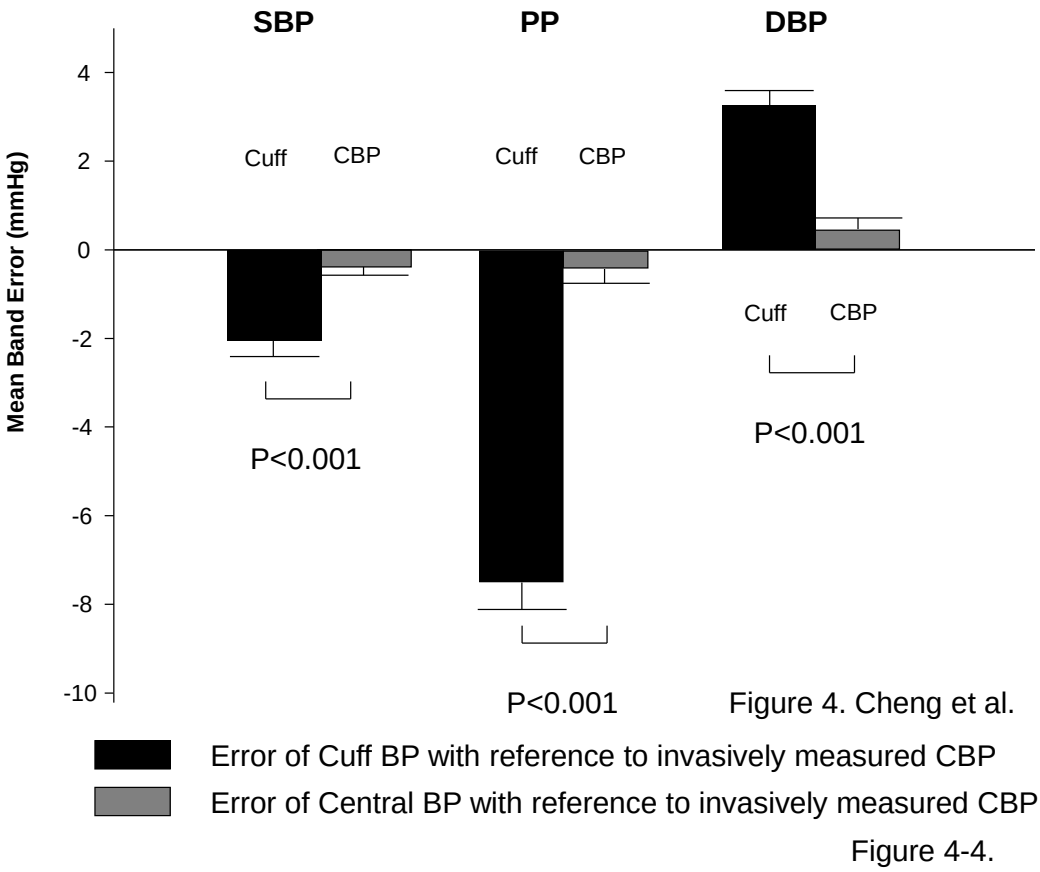

Figure 4-4. Mean band errors for determination of central aortic systolic blood pressure (SBP), pulse pressure (PP), and diastolic blood pressure (DBP) of the brachial BP (cuff BP) or CBP (CBP) measured by the stand alone CBP monitor. Error bars denote standard error of means.

Discussion

The present study is the first to report the validation results of a newly developed stand-alone CBP monitor against currently available international standards with reference to invasively measured CBP. The measurement accuracy of the CBP monitor has clearly surpassed all requirements of the international standards.[28, 67, 68]

With the advent of CBP monitors and their availability on the market, challenges to validate these devices are expected. The first challenge is the choice of reference standard. For automatic brachial BP monitors, the well-accepted reference standard

is the auscultatory method. As for the CBP monitors, the true reference standard for the CBP measurements should still be the invasive BP measured in the ascending aorta rather than other widely used devices, because of their large systematic and random errors as shown in a recent meta-analysis.[90] Therefore, the invasive BP was chosen as a "true reference standard" and adhered to AAMI's recommendations by using either a fluid-filled catheter or an external pressure transducer with tip in situ.[28] The results demonstrate that central aortic SBP and DBP are mainly determined from the low frequency components of the pressure waveforms recorded using either a high-fidelity catheter-tip or a fluid-filled catheter (on-line supplementary data, Figure 4-S1 in Appendix IV).[83] Therefore in the present validation study, a fluid-filled catheter was used instead of the high-fidelity pressure catheter to invasively measure CBP, because the high-frequency waveform details were of less concern.

AAMI requires a total of 85 subjects with 255 measurements (3 for each) in non-invasive validation studies.[94] For the invasive validation study, AAMI SP10 requires recruitment of no fewer than 15 subjects with a minimum of 150 paired observations with a maximum of 10 paired measurements per subject to be made.[28] The efforts of the present study represent the most rigorous approach, not only recruiting subjects according to the recommendations for non-invasive validation, but also fulfilling all requirements set for the invasive reference standard.[28]

According to AAMI-SP10[28] , error determination using the intra-arterial BP as the reference standard is different to the traditional method of calculating mean differences between paired measurements. The measurement error is determined by firstly calculating the range of variation of the invasive BP and, secondly, by

analysing the differences outside the above range. The calculations produce the "band error" with the predefined criteria of 5 ± 8 mmHg.[28]

Early validation data that compared the cuff BP measured by the indirect auscultatory method with the directly measured intra-arterial BP have revealed substantial discrepancies between the two measurements.[58, 95] The large systematic and random errors for the indirect auscultatory method reported in the official document of AAMI[28] have not precluded its use as a current standard for validating automatic BP monitors and clinical decision making. Therefore, when directly compared with the intra-arterial BP, current non-invasive BP monitors may also give BP values with similarly large systematic and random errors, even when they have passed the requirements of international validation protocols. The influence of such inaccuracy may have manifestly been ignored. The results of the present study confirm the variable magnitude of underestimation/overestimation of cuff BP at different ranges of the invasive CBP and dispute the use of cuff BP as surrogates for CBP.

Systolic Blood Pressure

Current CBP estimating techniques[15, 17, 21, 40, 41, 66] usually focus on central SBP. All methods require calibration of the noninvasively derived peripheral pressure waveforms using the cuff SBP and DBP, or cuff mean blood pressure and DBP. The errors of the cuff BP would invariably be transferred to the estimated central SBP.[54] To adjust the underestimation of cuff SBP, Takazawa et al. used a regression equation implemented in a radial tonometric device (HEM-9000AI) for the estimation of central SBP from a peripheral SBP2.[21]

Compared to the validation results of a recently proposed brachial cuff-based method for estimating central SBP using a transfer function like method (ARCSolver algorithm),[66] the current CBP monitor apparently has better agreement with the invasively measured CBP (mean difference: -0.6 ± 5.5 vs. 3.0 ± 9.5mmHg for central SBP; -0.2 ± 6.5 vs. -7.6 ± 7.1 mmHg for central DBP). A large difference between the cuff BP and the invasive CBP in the ARCSolver algorithm validation study (mean difference: 8.8 ± 10.4 mmHg for SBP, and -6.7 ± 7.3 mmHg for DBP, respectively) may have caused a large calibration error.[66] The accuracy of the ARCSolver algorithm remains to be validated when it is built into a stand-alone BP monitor. In contrast, the PVP waveform analysis method of the present study may partly account for the calibration error by using the noninvasively calibrated PVP waveforms to generate the mulit-variate prediction models.[22] In addition, the performance of the current CBP monitor in measuring cuff BP has been strictly validated (mean differences from the invasive CBP: -2.6 ± 9.0 mmHg for SBP and 6.1 ± 7.0 mmHg for DBP, respectively).

Diastolic Blood Pressure

DBP is critical for coronary perfusion and is important in the diagnosis of isolated systolic hypertension [96] and in understanding of the J-curve phenomenon.[97-100] Invasive brachial DBP usually equates with invasive central DBP.[5] However, current oscillometric BP monitors consistently overestimate DBP and may invalidate the use of DBP as an effective parameter in the classification of hypertension subtypes, the selection of adequate antihypertensive medications, and the assessment of myocardial ischemia.[97] The auscultatory method was introduced over 100 years ago. Until now, the PVP method may have the potential to improve the accuracy of non-invasive DBP measurement by obtaining more accurate central SBP and PP.

In conclusion, the present validation study suggests that central SBP, PP, and DBP can be measured accurately by a stand-alone automatic blood pressure monitor. The prognostic values of these CBP estimates should be further investigated.

Limitation of the Present Study:

The study population consisted of adult patients (age range 30 to 93 years) referred for evaluation of coronary anatomy and/or angioplasty, which may differ from the general population in the sex distribution and in the prevalence of underline medical history. However, our population may more appropriately represent persons in whom BP determinations are most often needed. Moreover, we used the fluid-filled systems for the invasive CBP measurements rather than micromanometer-tipped catheters. Given the documented frequency response of the system with carefully performed pressure recording procedures, the differences of the measured CBP between these two methods may be negligible.

Strategies for Addressing Translational Gaps

Following the attempt to address the "**Discovery to Clinical Application**" gap (Gap2), it is important to effectively deal with the "**Clinical Application to Action"** gap (Gap 3). The oscillometric CBP monitor, which meets international standards, is ready to be used for the management of hypertension. However, without knowledge of "diagnostic accuracy" in terms of sensitivity and specificity for confirming a diagnosis of hypertension with the CBP monitor, clinicians will not be able to make judicious judgements based on the non-invasive CBP values. For the clinical usefulness of the CBP monitor, it is imperative to provide clinicians with the diagnostic reference standard of CBP, which is reported in Chapter 5. Subsequently, the diagnostic

accuracy of CBP monitor for confirming a diagnosis of hypertension can be calculated (Chapter 6).

CHAPTER 5: Derivation and Validation of Diagnostic Thresholds for Central Blood Pressure Measurements Based on Long-term Cardiovascular Risks

Background

High blood pressure is one of the leading causes of global burden of diseases.[101] Although blood pressure (BP) is continuously distributed and its relation to cardiovascular risk has been suggested to be continuous,[102] clinicians relies on a diagnostic reference frame to classify patients into normotensives or hypertensives. Conventional BP is measured by auscultation of the Korotkoff sounds or automatic BP monitors (cuff BP), of which the cutoff 140/90mmHg has been used to diagnose high blood pressure.[1, 2, 103] With the subsequent advent of evidence-based evolution, ambulatory BP, by presenting the better prognostic value, has now been suggested as the reference standard for the management of hypertension.[104]

Nevertheless, both ambulatory BP and cuff BP are measured in the brachial arteries and it is well recognized that BP amplification from the central aorta to the peripheral arteries varies substantially between subjects and there is a discrepancy between central blood pressure (CBP) and cuff BP.[4-9] Currently, non-invasive CBP can be obtained by either tonometry-based[4, 15-17] or cuff-based techniques.[22, 66, 105] Similar to ambulatory BP, the superior prognostic value of CBP to cuff BP has also been demonstrated.[12-14, 36, 106] Furthermore, previous studies have suggested that CBP and ambulatory BP may have a similar ability to predict future outcomes.[107] Therefore, adopting CBP as a reference standard might further improve current hypertension management and is important for clinicians to interpret CBP values and to classify patients. However, it has never been investigated in longitudinal event-based studies.

This study aimed to derive the operational threshold for CBP based on an outcome driven approach,[108, 109] and to validate in another independent cohort its discriminatory ability for long-term cardiovascular outcomes.

Methods

Study Population

The present analysis was based on subjects from two independently recruited and longitudinally followed-up cohorts in Taiwan. The relationship of CBP to cardiovascular mortality has been reported on previously.[13] Therefore the participants of the previous study served as the Derivation Cohort, in which the diagnostic thresholds were generated. Subsequently, the discriminatory ability for cardiovascular mortality of these thresholds was tested in the other Validation Cohort. Details of the recruitment process and study protocols for Derivation and Validation Cohort were reported elsewhere,[13, 110-112] and were summarized as below with characteristics given in Table 5-1. All of the participants gave informed consent before enrolment.

Table 5-1. Baseline Characteristics of Individuals in the Derivation and Validation Cohorts

Parameter	Derivation Cohort (n = 1272)	Validation Cohort (n = 2501)	P-value
Age, years	52.3 ± 12.8	53.6 ± 12.0	0.0027
Body mass index, kg/m2	24.7 ± 3.6	24.2 ± 3.2	0.0000
Total cholesterol, mg/dl	198.1 ± 37.5	192.3 ± 39.1	<0.0001
LDL, mg/dl	123.1 ± 34.3	122.0 ± 37.3	0.3927
HDL, mg/dl	50.9 ± 13.1	47.7 ± 16.8	<0.0001
Heart rate, beats/min	73.6 ± 9.9	73.1 ± 10.2	0.1620
Cuff SBP, mmHg	139.2 ± 23.6	122.4 ± 17.0	<0.0001
Cuff DBP, mmHg	88 ± 14.6	68.2 ± 10.2	<0.0001
Cuff PP, mmHg	51.2 ± 16.6	54.2 ± 12.2	<0.0001
Central SBP, mmHg	127.6 ± 23.7	111.8 ± 16.1	<0.0001
Central DBP, mmHg	86.3 ± 14.2	70.2 ± 10.3	<0.0001
Central PP, mmHg	41.3 ± 15.7	41.5 ± 11.0	0.6560
Male gender, %	53	45	<0.0001
Dyslipidemia, %	57	69	<0.0001
Diabetes mellitus, %	5	0	<0.0001
Previous cardiovascular disease, %	0	0	1.00
Antihypertensive drug treatment, %	0	0	1.00
Smoking, %	24	24	0.517

MBP = mean blood pressure; PP = pulse pressure; SBP = systolic blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; DBP = diastolic blood pressure

Derivation Cohort

The Derivation cohort for generating diagnostic thresholds included 1272 normotensive and untreated hypertensive (SBP≥140 or DBP≥90 mmHg) Taiwanese participants (674 men, aged 30-79 years) drawn from a preceding community-based survey conducted in 1992 to 1993.[113]

Validation Cohort

The performance of the derived thresholds in Validation Cohort drawn from "The Cardiovascular Disease Risk Factors Two-Township study" (CVDFACTS), which was a community-based follow-up study focusing on risk factor evolution and

cardiovascular disease development in Taiwan, was examined.111, 112 Of the participants in CVDFACTS, a total of 3386 individuals had undergone CBP measurements during their cycle 4 examination (1997–1999). From that group, we excluded 617 participants who used anti-hypertensive drugs, 268 subjects with cardiovascular diseases or stroke history. Finally, 2501 individuals constituted the Validation Cohort.

Follow-up

By linking the database with the National Death Registry, the dates and causes of death among all participants in Derivation and Validation Cohort were retrieved. Subjects were considered to have survived if they did not appear on the National Death Registry on December 31, 2011. The median follow-up durations of the Derivation and Validation Groups were 17 and 13 years, respectively.

Blood Pressure Measurement

More than two sets of peripheral blood pressure measurements (cuff BP) were obtained from the right arm with at least five minutes apart after they were seated for at least 5 minutes. Cuff BP, taken manually using a mercury sphygmomanometer and standard-sized cuffs by experienced observers, was reported from the average of the last two consecutive measurements.

In the **Derivation Cohort**, right common carotid artery pressure waveforms were calibrated with brachial MBP and DBP to obtain Carotid BP.[15] The Carotid artery pressure waveforms were registered noninvasively with a tonometer,[12, 113] and has been demonstrated to closely resemble central aortic pressure waveforms. [15, 114, 115]
In the **Validation Cohort,** CBP was obtained with the SphygmoCor device (AtCor Medical, Sydney, Australia) in compliance with the manufacturer's instructions using radial arterial pressure waveforms and a validated generalized transfer function.[41]

The Radial arterial pressure waveforms, obtained by applanation tonometry using a solid state high-fidelity external Millar transducer and calibrated with cuff SBP and DBP, were then mathematically transformed by the validated transfer function[41] into corresponding central aortic pressure waveforms**.** Cuff and central pulse pressure (PP) was calculated as [SBP - DBP] and cuff mean blood pressure (MBP) was calculated as [DBP + (PP/3)].

Other Measurements

Overnight fasting serum and plasma samples were drawn for glucose, lipid, and other biochemical measurements. Dyslipidemia was defined according toThe Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[116] Diabetes mellitus was defined as a fasting glucose ≧126 mg/dL or using antidiabetic medication.[117] In both cohorts, individuals undergoing the BP measurements also completed a questionnaire-based interview containing items on demography, lifestyle, self-reported health conditions, medication history, and family history of disease.

Statistical Analysis

Data are presented as percents or mean ± standard deviation. The Student's t test and Chi-square test were used for between-group comparisons where appropriate. We calculated the sensitivity and specificity of each cutoff point of central and peripheral systolic BP (SBP) in 10-mmHg increments from 80 mmHg to 180 mmHg for cardiovascular mortality. Then we linked the points of central/peripheral BP and sensitivity/specificity to find the optimal cutoff point for central SBP that was equal in sensitivity and specificity (Figure 5-1).

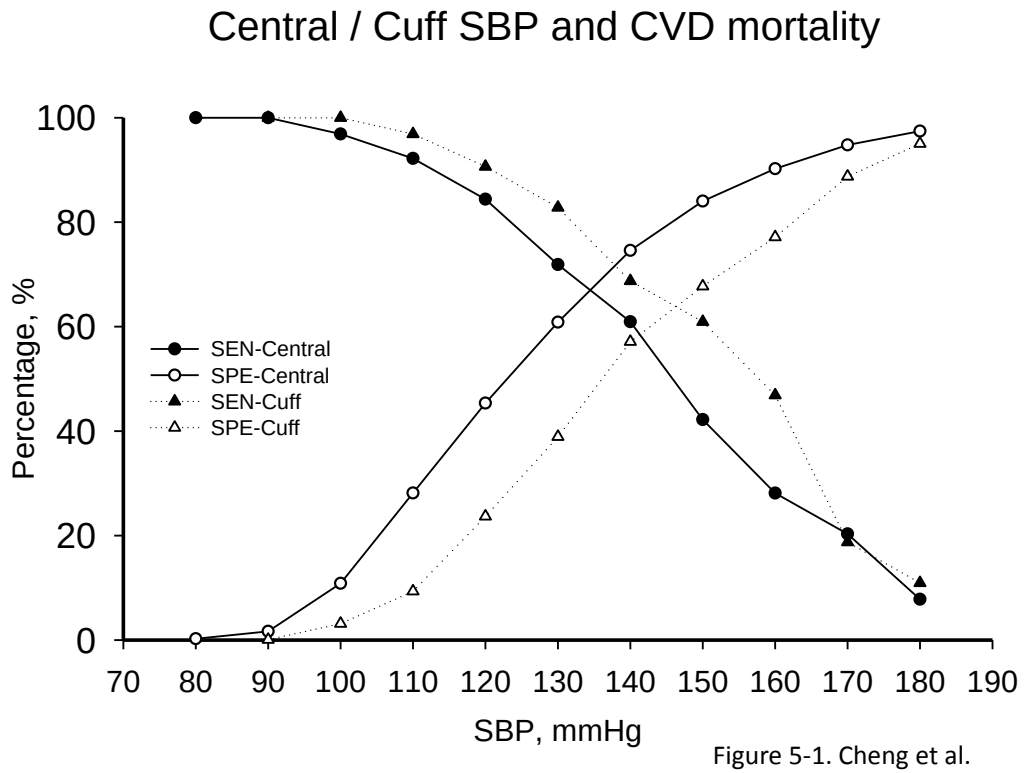

Figure 5-1. Cheng et al.

Figure 5-1. The Sensitivity and specificity by exploiting cuff SBP or central SBP for predicting cardiovascular mortality in Derivation Cohort. With the rise of SBP cutoffs, specificity improved at the expense of decreasing specificity. Reasonable cutoff limits for central SBP BP can then be determined by approximating to sensitivity or specificity of the guideline-endorsed cuff SBP cut points as demonstrated in Table 5-3.

Similar to a previous study deriving cutoffs for ambulatory BP,[108] diagnostic thresholds and their 95% confidence intervals for CBP were obtained by taking the following steps. First, the subjects in the Derivation Cohort with cuff BP coinciding with thresholds proposed by international guidelines were identified[1, 2, 103] and the corresponding cardiovascular mortalities were calculated (table 5-2). Secondly, the bootstrap method for each cutoff was used by randomly selecting 1000 times from CBP levels of the corresponding identified subjects. Thirdly, the mean and 2.5th and 97.5th percentiles from the re-sampling distribution were obtained to serve as the diagnostic thresholds of CBP with 95% confidence intervals. By identifying the central SBP levels with the sensitivity (or specificity; we chose the parameter with

the higher digit) most approximate to the above estimated values, the diagnostic thresholds for central SBP were determined (Table 5-3).

Table 5-2. Central BP Levels and Cardiovascular Mortalities with Different Cuff SBP and DBP Cutoffs Based on Conventional Criteria[1, 2, 103] in the Derivation Cohort

Hypertension Staging	Category	Diagnostic thresholds for Cuff BP, mmHg	Cardiovascular mortalities, %	Corresponding CBP Levels (95% CI), mmHg*
Optimal-Prehypertension	SBP	120	2.7	112.80 (111.15–113.61)
	DBP	80	4	80.92 (79.60–82.22)
Prehypertension-Hypertension	SBP	140	4.3	132.43 (130.89–133.88)
	DBP	90	5	90.98 (89.93–91.96)

* Point estimates and 95% CIs were obtained from the bootstrap distribution of 1000 random samples with replacement of CBP levels for participants in the Derivation Cohort.
CBP = central blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure

Table 5-3. Determining Central SBP Cutoff Values Based on the Sensitivity and Specificity Associated with Cuff SBP Cutoff Values for Predicting Cardiovascular Mortality*

	Cutoff	Sensitivity	Specificity
Cuff SBP	120	0.906	0.237
Central SBP	110.49	0.906	0.292
Central SBP	110	0.922	0.281
Cuff SBP	140	0.688	0.603
Central SBP	132.6	0.688	0.648
Central SBP	130	0.741	0.600

SBP = systolic blood pressure
*See also Figure 5-1 for the above approximation process

The Cox proportional hazard model was constructed to evaluate the performance of the proposed diagnostic thresholds of CBP for predicting cardiovascular outcomes. Survival time was calculated from the date of the CBP measurement to the date of death, or the end of follow-up (December, 31, 2011). The estimated hazard ratio of the Validation cohort was derived after accounting for gender, age, body mass index, smoking and alcohol consumption, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and serum total cholesterol. In line with large cohort studies,[102] BP was included firstly as a continuous term in the Cox regression model. Subsequently, based on different CBP thresholds for defining hypertension, BP was incorporated into the model as a dichotomous variable to evaluate the discriminative ability of the respective cutoff limits. All statistics were calculated using SAS 9.1 software.

Results

Baseline Characteristics of Participants

For the Derivation and Validation Cohorts, a total of 1272 (mean age 52.3 years, 30–79 years) and 2501 (53.6 years, 32–90 years) participants, respectively, were recruited to evaluate diagnostic thresholds of CBP (Table 5-1). The mean differences in the Derivation and Validation Cohorts were 11.6 ± 17.5 mmHg and 10.7 ± 4.8 mmHg between cuff and central SBP, and 9.9 ± 14.2 mmHg and 12.7 ± 5.0 between cuff and central PP, respectively (all $p < 0.001$). Compared with the Derivation Cohort, the participants in the Validation Cohort were older; had lower cuff BP and CBP values; and had a higher prevalence of dyslipidemia, diabetes mellitus, and previous history of cardiovascular diseases.

Derivation of Diagnostic Thresholds for CBP

Table 5-2 shows the risks of cardiovascular mortality of subjects with cuff SBP/DBP in agreement with the cutoff limits proposed by international guidelines. The risk was markedly elevated with increasing cuff SBP and DBP values. The central SBP and DBP corresponding to these cuff BP limits were calculated using a bootstrap procedure (Table 5-2).

As shown in Figure 5-1, sensitivity and specificity for predicting cardiovascular mortality with cuff and central SBP were calculated. With the rise of SBP cutoffs, the specificity improved but sensitivity dropped. The respective sensitivity and specificity at the cuff BP limits proposed by guidelines were then identified. By approximating to the identified estimated sensitivity or specificity, the central SBP levels corresponding to these limits were then derived (Table 5-3).

Based on the analysis in Tables 5-2 and 5-3, we proposed the outcome-driven diagnostic thresholds for CBP after rounding the point estimates to an integer value ending in 0 or 5 (Table 5-4). Based on these thresholds, categorization of BP distribution by CBP could be achieved.

Table 5-4. Proposal for Outcome-Driven Diagnostic Thresholds for Central BP Measurement*

	Central SBP , mmHg		Central DBP, mmHg
Optimal BP	<110	and	<80
Prehypertension	110–129	and/or	80–89
Hypertension	≥130	and/or	≥90

Threshold values were obtained by rounding the point estimates reported in Tables 5-2 and 5-3 to an integer value ending in 0 or 5.

Hazard Ratios for Cardiovascular mortality Stratified by Proposed Central Blood Pressure Thresholds in Validation Cohort

Cox proportional hazards modelling showed that central PP (per 10 mmHg) was significantly associated with cardiovascular mortality (1.102, 95% CI 1.027–1.082), total mortality (1.065, 1.027–1.104), and stroke (1.117, 1.003–1.243) in the Validation Cohort (all $p < 0.01$). In contrast, cuff BP was only significantly associated with total mortality (1.042, 95% CI 1.003–1.082). Table 5 shows the hazard ratio for cardiovascular outcomes in different BP categories based on the proposed CBP criteria in Table 4. In the entire Validation Cohort, the risk of developing cardiovascular outcomes was significantly higher in individuals with hypertension defined as a CBP value of ≥130/90 mmHg than those with optimal blood pressure. The performance of conventional international standards[1, 2, 103] and the CBP criteria in subgroup analysis in the Validation Cohort is presented in the online supplementary tables.

Table 5-5. Hazard Ratios† for Cardiovascular Mortality in Relation to Central Blood Pressure at Entry in the Validation Cohort (n = 2501)

	Total Death	**Cardiovascular Death**	**Stroke Death**
End points, n (%)	185 (7.4%)	34 (1.36%)	18 (0.72%)
‡Prehypertension vs. Optimal, hazard ratio (95% confidence interval)	1.31 (0.87–3.35)	1.59 (0.57–4.43)	1.93 (0.45–8.31)
‡Hypertension vs. Optimal, hazard ratio (95% confidence interval)	2.14 (1.36–3.35)	3.08 (1.05–9.05)	6.12 (1.43–26.21)
†Hazard ratios were adjusted for sex, age, body mass index, smoking and serum total cholesterol.			

‡Staging was according to the criteria for central blood pressure in Table 4.

Performance of Diagnostic Thresholds in Validation Cohort

As shown in Figure 5-2, through Cox proportional-hazards modeling, CBP 130/90mmHg was associated with the better discriminatory ability, characterized by higher Wald Chi-square and model R^2, than other diagnostic thresholds for defining hypertension.

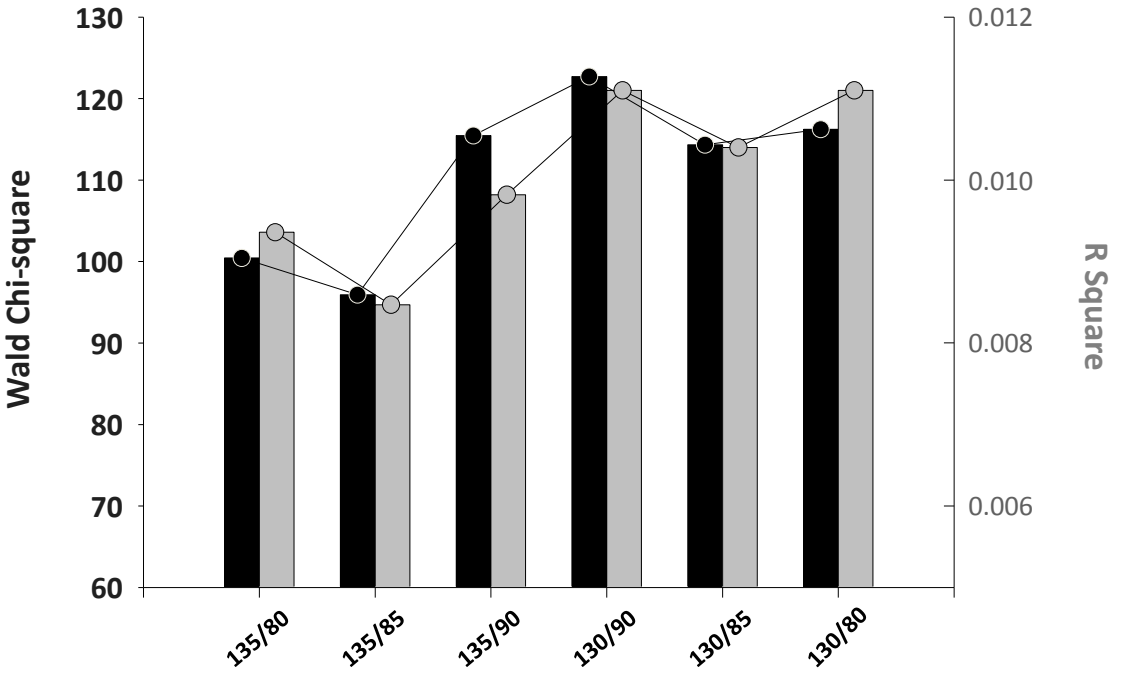

Figure 5-2. Cheng et al.

Figure 5-2. Incorporating the dichotomous variable of defined hypertension based on different CBP levels (x-axis) and the resultant contribution (Wald Chi-square and model R^2) to the predictive power of the Cox proportional-hazards model. CBP cutoff limit 130/90mmHg was associated with higher Wald Chi-square and model R^2 than other thresholds.

Discussion

The present study is the first to derive and validate outcome-driven diagnostic thresholds of CBP for the diagnosis of hypertension. Building on large consensus, current guidelines rely on cuff BP measurements at a clinic, home BP, or 24 hours ambulatory BP to categorize subjects with different levels of SBP and DBP, which is then exploited to predict their future cardiovascular risks.[2, 103, 118] However, all of these criteria are based on non-invasive BP measurements for brachial arterial pulses, which are generated from cardiac contractions and afterwards transmitted from the central aortic pulses: the origin of all arterial pulses. Physiologically, with its close proximity to vital organs and the better prognostic value, [12-14, 36, 106] CBP should be the truly effective BP relating to vascular events. Cuff BP is not so much as a surrogate but as a compromised measure imposed on practice because of technology limitations. With the accumulating evidence supporting the use of CBP for management of hypertension[2, 106] and the available techniques,[4, 15-17, 22, 66, 105] it is important to derive diagnostic thresholds of CBP that conform with previous guidelines and consensus on cuff BP. The other strength of this study is that, in addition to the threshold derivation through the rigorous statistical methods, it validates their discriminatory powers in another event-based cohort with long-term follow-up. In the Validation Cohort, the CBP was measured with a technique (radial tonometry and the generalized transfer function equipped on SphygmoCor) that was different from that used in the Derivation Cohort (carotid tonometry). Consistent results in the Derivation and Validation Cohorts suggest that the proposed thresholds (table 5-4) may be both reliable and valid.

Despite the rigorously derived and validated diagnostic thresholds of CBP measurements for the diagnosis of hypertension in agreement with current practice, caution should still be exercised in relation to the following observations. The relationship of BP to vascular mortality is continuous throughout middle and old age, i.e. a BP lower than the thresholds of current guidelines for hypertension management doesn't guarantee that that one is free from cardiovascular risk.[102] A recent systematic review has suggested that antihypertensive drugs used in the treatment for stage I hypertension have not been shown to reduce mortality or morbidity in RCTs, which may again challenge the legitimacy of these guideline-endorsed thresholds.[119] Although the above observations may not hold true for ambulatory BP or CBP, more studies should be conducted to clarify these issues. However, in the current Validation cohort, the best discriminatory power of our proposed CBP thresholds in predicting cardiovascular mortality was established (Figure 5-2).

Sharman et al. demonstrated that wide variation in the difference between cuff BP and CBP can occur among patients with similar cuff BP.[120] The reported magnitude of variation was similar between healthy and diseased subjects, which suggests that CBP measurements may further improve risk stratification. In this regard, although CBP and cuff BP correlated closely with each other, it would be inappropriate to assume directly from such a correlation that cuff BP is a surrogate of CBP. Rather, by incorporating the CBP criteria into clinical practice, whether there is incremental clinical benefit in the management of hypertension can be ascertained.

Age- and gender-specific reference values of CBP have been provided in the Anglo-Cardiff Collaborative Trial.[121] Both cuff BP and CBP increase with age and this could be a possible but not user-friendly clinical application by using reference values

stratified by age and gender. However, in current international guidelines, the classification of cuff BP disregards age, sex, and other cardiovascular risk factors for categorizing different BP levels. In the multivariate model, the results were consistent after accounting for these factors. In line with current clinical practice and considering the higher clinical events in aged population, the diagnostic thresholds of CBP without age and gender specification were proposed.

Spurious systolic hypertension, defined as high cuff BP and low CBP, is a not uncommon phenomenon in young age.[122] . Investigating a population of 750 subjects (352 men and 398 women) with age 26–31 years, Hulsen et al. report that subjects with this condition had comparable cardiovascular risk profiles to normotensives.[123] They used the 90th percentile of central systolic BP distribution to obtain the cutoffs of CBP (124/90 mmHg for men and 120/90 mmHg for women). The reference value was, however, unrepresentative of the general population and obtained solely for a different research purpose.

The distribution of central SBP was studied in a health check-up program in Japan with 10756 subjects.[124] Using Omron HEM-9000AI (HEM-9000AI; Omron Healthcare), they reported the reference value of central SBP, similar to this study's results, to be 112.6±19.2 and 129.2±14.9mmHg, which corresponded to optimal and normal BP categories, respectively. This study probably represented the very first effort to report the diagnostic threshold of CBP, but was limited in its study design – which was cross-sectional rather than an event-based cohort study. Therefore, the comparison of prognostic value between central and cuff BP couldn't be made to determine the incremental clinical benefit provided by their proposed diagnostic thresholds.

Limitation of the Present Study:

Because the present study population consisted of two Taiwanese populations, the generalizability of the conclusions in terms of ethnicity could be challenged. Nonetheless, thresholds have been supported by the similar reference values proposed in the aforementioned Japanese population.[124]

The techniques used in the Derivation and the Validation Cohort were carotid tonometry and SphygmoCor, respectively, which are the two most popular CBP measurement devices at present. Whether the same reference values should be used for different devices is arguable. Similar problems were encountered during the derivation process of diagnostic thresholds for ambulatory BP and home BP.[108, 125] However, with similar results obtained across various techniques, the adoption of the universal criteria of CBP for the diagnosis and management of CBP are reasonable.

Neither cuff BP nor non-invasive CBP estimates are error-free as compared with invasively measured counterparts. The relationship between BP and cardiovascular outcomes could be affected by measurement errors, which can be referred to as regression dilution bias or attenuation bias.[126, 127] Although the effect of the measurement error on the dilution of prognostic value has been clearly delineated, correction may be neither necessary nor appropriate in most applications.[128] Furthermore, the influence of measurement error on the discriminatory power of diagnostic power remains an unsettled issue for both conventional cuff BP and CBP and requires further research.

In conclusion, the present study derived and validated the diagnostic thresholds of CBP based on two independent event-based cohorts with long-term follow-up. In conformity with the staging criteria of current international guideline for the

diagnosis of hypertension, it is proposed that CBP 130/90mmHg to be used as cutoff limits for normality, which was characterized by a greater discriminatory power for cardiovascular mortality in our validation cohort. The present report represents an important step towards the application of the CBP concept in clinical practice.

Strategies for Addressing Translational Gaps

With the proposed CBP diagnostic thresholds, the diagnostic accuracy of CBP monitor for confirming a diagnosis of hypertension was calculated as reported in Chapter 6 to address the "**Clinical Application to Action Gap" (Gap 3)**.

CHAPTER 6: Diagnostic Accuracy of the Novel Strategy of Using Non-invasively Measured Central Blood Pressure for Confirming a Diagnosis of Hypertension

Background

Due to the established appreciation that waveform morphology[3, 4, 5] and blood pressure (BP)[4, 6-9] differ considerably between the central aorta and peripheral arterial system, BP measurements in the peripheral arteries cannot serve as direct substitutes for their central counterparts. Although noninvasive BP measured in the brachial artery (cuff BP) is the basis for the present management of high blood pressure (HBP) [1, 2] , central blood pressure (CBP) has been shown to be the better predictor of cardiovascular outcomes than cuff BP.[10-14] Consequently, there are substantial research efforts to develop non-invasive estimating methods for CBP, mainly based on the technique of applanation tonometry [4, 15-17] or alternatively by brachial cuff-based techniques [22, 66, 82, 84, 88, 129]. Recently developed novel methods, estimating central systolic blood pressure (SBP) [22] and central pulse pressure (PP)[69] from brachial pulse waves recorded with a regular brachial oscillometric BP cuff, have been seamlessly incorporated into a standalone oscillometric CBP monitor, which has an acceptable measurement accuracy against international standards (Chapter 4). For the purpose of clinical decision making, the diagnostic accuracy of cuff BP has been investigated in a systematic review with reference to ambulatory BP.[125] However, even with the superior prognostic value of CBP over cuff BP,[14] no studies investigating the diagnostic accuracy of cuff BP by exploiting CBP as the comparing reference standard have been reported in the literature. In Chapter 5, proposed reference values for CBP to detect HBP based on the prognostic analyses of two independent cohorts were proposed. Through the provision of reference

values for CBP, it is possible to regard CBP as the reference standard. Therefore, to make a diagnosis of HBP, this study attempted to evaluate the consequences of exploiting a new reference standard, the more prognostic CBP, to calculate the diagnostic accuracy of cuff BP and CBP estimates from a recently introduced and validated stand-alone CBP monitor.

Methods

Study Design and Rationale of the Reference Standard: Invasively Measured CBP

The first step of a diagnostic test study is to select a "proper" reference standard. As demonstrated in a previous systematic review of measurement accuracy of non-invasively obtained CBP [90], it may not be an acceptable practice to use other non-invasive CBP estimating methods as the reference standard. An appropriate reference standard ought to be the invasively measured CBP. To investigate the measurement and diagnostic accuracy of a novel, stand-alone CBP monitor, this study - in conjunction with a previous validation study as described in Chapter 4 - was conducted in the catheterization laboratory to simultaneously measure invasive and non-invasive CBP. The sponsor played no role in study design, data collection, data analysis, or manuscript preparation. The study protocol was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taiwan, and adhered to the principles of the Declaration of Helsinki. Written informed consents were obtained from all patients before the study.

Study Population

Subjects were enrolled consecutively from those scheduled to undergo diagnostic cardiac catheterization and/or coronary angioplasty. All data collection was planned before the simultaneous measurements of invasive and noninvasive BP.

Patients who had acute coronary syndrome, peripheral arterial disease, rhythms other than normal sinus rhythm, more than 3 mmHg pressure differences between left and right arms, or previous use of anti-hypertensive medication were excluded from the study and final analysis. Details of the recruitment process are shown in Figure 6-1

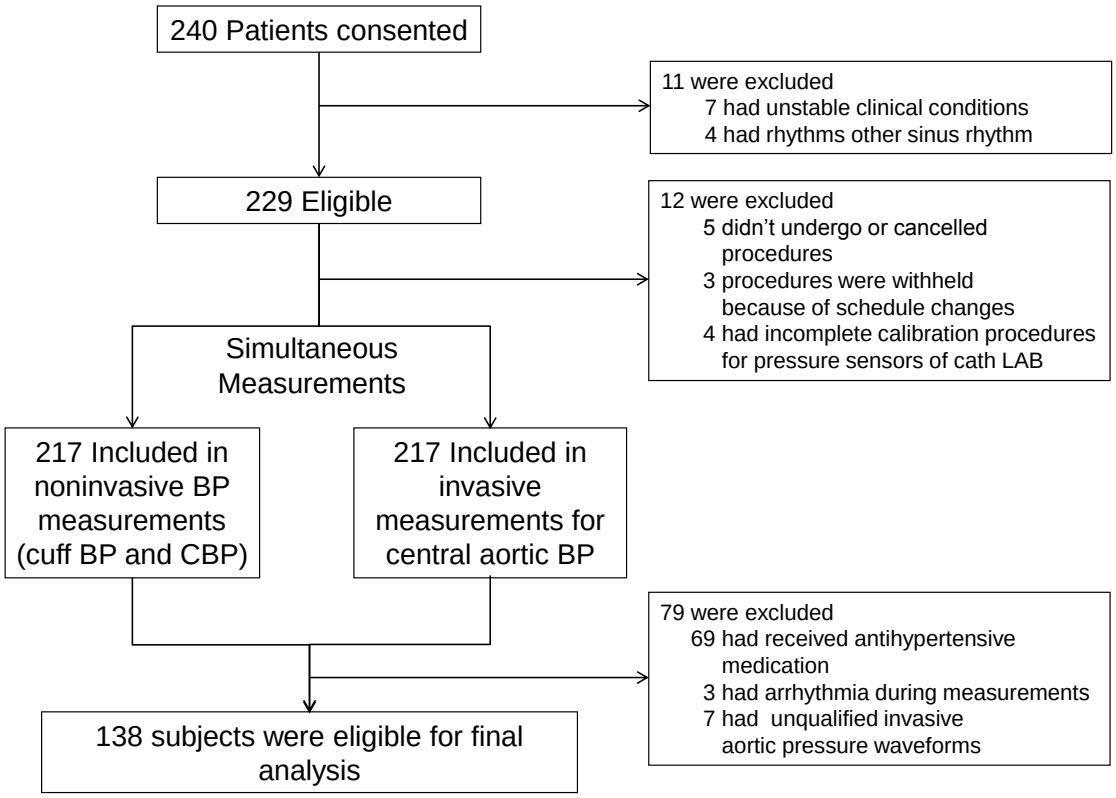

Figure 6-1. Flow Diagram of Patient Recruitment

Figure 6-1. Flow diagram of patient recruitment.

Study Protocol

The study protocol has been detailed in in Chapter 4. To summarize, after routine preparation for diagnostic coronary angiography with the appropriate size BP cuff being placed on the upper left arm with its lower edge 2.5 cm above the antecubital fossa, a large lumen 6F arterial catheter was advanced to the ascending aorta via the right radial artery and placed 2 cm above the aortic valve under fluoroscopic guidance. All direct pressure measurements were obtained in the supine position during the process of automatic pressure measurement using the CBP monitor, with the left arm positioned at mid-chest level. Only baseline measurements and subjects without previous use of hypertension medication were included in the present diagnostic accuracy analysis in order to avoid the possible confounding effects of hemodynamic perturbations. All participants received the invasive and non-invasive BP measurements simultaneously, which obtained cuff BP, non-invasive CBP estimates, and invasively measured CBP.

Automatic CBP Monitor and Automatic Non-invasive BP Measurement

The prototype automatic CBP monitor was built from a validated oscillometric arm blood pressure monitor (WatchBP Office; Microlife AG, Widnau, Switzerland) to perform PVP and instant PVP waveform analysis for the estimation of central SBP and PP [22, 69]. As described in Chapter 4, the CBP monitor provided readings of both cuff BP and CBP with the measurement accuracy of cuff BP [85]and CBP surpassing the requirements of the international standard. All the automatic BP readings were calculated from the two measurements and then stored digitally for comparison with the direct BP measurements.

Direct Pressure Measurement

A fluid-filled catheter system attached to Siemens-approved transducers with a resistance of 200 - 3000 Ohms and an equivalent pressure sensitivity of 5μV/V/mmHg ± 10% to invasively measure CBP at the ascending aorta was used. The catheters were thoroughly flushed outside the duration of pressure recording and avoided any unnecessary connections between the catheter and transducer to maximize the fidelity of the catheter-transducer systems [92]. The frequency range of the catheterization laboratory amplifier was 0–400Hz for pressure measurement (-50 to 400mmHg) with the accuracy of ± 1mmHg or ± 3% exclusive of transducer[22]. The routinely checked natural frequency and damping coefficients of the system were 30 Hz (21-41Hz) and 0.2 (0.14-0.41), respectively, which surpassed the recommended guidelines.[28, 93] The pressure transducers were warmed for a minimum of 30 minutes before calibration and use. Each transducer was calibrated against mercury immediately before pressure measurement with the zero reference level for pressure measurement set at mid-chest height, which was also used for balancing. Both calibration and balancing were checked before each measurement was performed. During all automated BP measurements using the CBP monitor, pressure tracings were recorded simultaneously and continuously with a recording of zero reference at the end of each pressure segment to check for and correct any measurable pressure drift. The direct pressure recordings were all performed by an experienced cardiologist familiar with angiographic procedures. The recorded invasive central aortic pressure signals were analysed off-line using custom-designed software developed on a commercial software package (Matlab®, version 7.0, The MathWorks, Inc., U.S.A.). All processed individual signals were then subjected to fully automatic batch analysis to avoid inter- and intra-observer variations. The invasively measured central SBP, diastolic BP (DBP), and PP were determined from

the highest readings, the lowest readings, and the amplitudes of all central aortic pressure waveforms recorded during the whole process of automatic pressure measurement using the prototype CBP monitor. Pressure measurements recorded during and after isolated premature beats were excluded from the analysis; multiple premature beats during a single period resulted in the removal of the patient from the protocol. All measurements were obtained from the tracings by one experienced observer who was blinded to the indirect readings and the clinical status of the patients. The sampling rate of the signals was 500Hz

Data Analysis

For detecting HBP by exploiting cuff BP, the recommendation of the international guidelines for the management of HBP[1, 130] with the diagnostic criteria defining HBP as SBP≧140mmHg or DBP≧90mmHg were adhered to. However, reference values have not been proposed for CBP previously. The study process attempted to analyse the optimal cutoffs for the diagnosis of HBP with CBP measurements in two independent cohorts and the findings suggested that subjects with central SBP≧130mmHg or central DBP ≧90mmHg could be categorized as having HBP as reported in Chapter 5. The diagnostic criteria with such CBP cutoffs have been shown to be more discriminative than cuff BP in predicting cardiovascular mortality. However, since there are no well-established international standards for the diagnosis of HBP with CBP, sensitivity analysis were performed by using different cutoffs for both the reference standard and non-invasive CBP estimates to investigate the diagnostic performance of cuff BP and non-invasive CBP. Subgroup analyses were also performed by gender, in subjects with age >65year, diabetes mellitus, and coronary arterial disease.

Statistical Analyses

The normality of all parameters were tested using the Shapiro–Wilk test. Categorical data are shown as proportions. Continuous data was presented as means and standard deviations (SD) or as medium and interquartile ranges when appropriate. With a study power of 80% and a 10% dropout rate, a sample size of 135 patients was needed to show a significant difference of accuracy in detecting HBP between cuff BP and noninvasive CBP with an estimated accuracy of 0.7 and 0.9, respectively [131, 132]. The diagnostic performance of cuff BP and non-invasive CBP, both from the CBP monitor, were determined with reference to invasively measured CBP by measuring sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, accuracy, and diagnostic likelihood ratio [131]. Uncertainties as represented by a 95% confidence interval were calculated using a bootstrap approach by sampling with replacement by performing 1,000 replications for all of the analyses [131]. The McNemar test was used for comparing measures of diagnostic accuracy. Statistical significance was determined at the two-tailed $P < 0.05$ level.

Results

The study population in the final analysis was enrolled from Sep 2010 through Oct 2011 and comprised 138 subjects with a mean age of 62.9 ± 13.5 (30-93) years, of which 98 (71%) were male, 22 had (16%) diabetes mellitus, and 78 (57%) had coronary arterial disease. Subjects' other characteristics and medications are presented in Table 6-1. No participants had reported ever experiencing adverse events related to the procedures.

Table 6-1. Characteristics of the study patients

	Patient Demographics (N= 138)
Characteristics	**Included Subjects**
Men, %	71
Age, years	62.9 ± 13.5
Height, cm	164.3 ± 8.3
Weight, kg	69.2 ± 12.4
Waist circumference, cm	87.5 ± 10.9
Left arm circumference, cm	28.1 ± 2.6
Body mass index, kg/m2	25.6 ± 3.8
Left ventricular ejection fraction, %	53.2 ± 9.6
Smoking, %	18
Clinical diagnosis, %	
Type 2 diabetes mellitus	16
Dyslipidemia	38
Coronary artery disease	57
Medications, %	
Anti-platelet agents	62
Statins	43
Recruitment blood pressures, mmHg	
Central SBP	130 ± 20
Central MBP	95 ± 12
Central DBP	70 ± 12
Central PP	60 ± 19
Cuff SBP	130 ± 18
Cuff MBP	93 ± 12
Cuff DBP	76 ± 11
Cuff PP	54 ± 15
Baseline heart rate, beats/min	69.0 ± 11.6

DBP = diastolic blood pressure; MBP = mean blood pressure;
PP = pulse pressure; SBP = systolic blood pressure.

Diagnostic Performance of the Entire Sample

Defined as invasively measured CBP≧130/90mmHg, the prevalence of HBP of the total population was 52%. With invasively measured CBP as the reference standard, the diagnostic performance of the traditional criteria using cuff BP ≧140/90mmHg

was sensitivity 49% (95% confidence interval [CI]: 44-53%), specificity 94% (92-96%), PPV 90% (86-93%), NPV 63% (59-66%), positive likelihood ratio 8.3 (5.8-11.7), negative likelihood ratio 0.55 (0.50-0.59), accuracy 70% (67-73%) , and diagnostic likelihood ratio 15.3 (10.1-22.5), (Table 6-2). In contrast, by exploiting the noninvasive CBP from the CBP monitor to make a diagnosis of HBP, the sensitivity was 93% (95% CI: 91-95%), specificity was 95% (94-97%), PPV was 96% (94-97%), NPV was 93% (90-95%), positive likelihood ratio was 21.5 (14.6-32.6), negative likelihood ratio was 0.07 (0.05-0.10), accuracy was 94% (93-96%), and diagnostic likelihood ratio was 305.5 (0.9-517.1).

Table 6-2. Diagnostic Performance of Oscillometric Central Blood Pressure Monitors for Confirming A Diagnosis of High Blood Pressure with reference to invasive central aortic BP 130/90mmHg

	Sensitivity,%	Specificity,%	Positive predictive value,%	Negative predictive value,%	Positive likelihood ratio	Negative likelihood ratio	Accuracy,%	Diagnostic Odds Ratio	P value*
Total population (n=138), prevalence of HBP 52%									
Cuff BP	49 (44-53)	94 (92-96)	90 (86-93)	63 (59-66)	8.3 (5.8-11.7)	0.55 (0.50-0.59)	70 (67-73)	15.3 (10.1-22.5)	<0.001
Central BP	93 (91-95)	95 (94-97)	96 (94-97)	93 (90-95)	21.5 (14.6-32.6)	0.07 (0.05-0.10)	94 (93-96)	305.5 (0.9-517.1)	
Men (n=98), prevalence of HBP 55%									
Cuff BP	54 (49-58)	93 (91-95)	91 (87-94)	62 (59-66)	8.2 (5.7-12.0)	0.50 (0.45-0.54)	71 (69-74)	16.5 (11.0-25.2)	<0.001
Central BP	94 (92-96)	95 (93-97)	96 (94-98)	93 (91-96)	21.9 (14.3-36.1)	0.06 (0.04-0.08)	95 (93-96)	390.8 (0.9-718.5)	
Women (n= 40), prevalence of HBP 45%									
Cuff BP	33 (29-37)	95 (94-97)	86 (81-90)	64 (60-67)	7.6 (5.2-11.2)	0.70 (0.65-0.75)	67 (65-70)	10.9 (7.1-16.8)	0.002
Central BP	89 (86-92)	95 (94-97)	94 (92-96)	91 (89-94)	20.3 (14.3-30.5)	0.12 (0.09-0.15)	92 (91-94)	176.7 (0.9-290.0)	
Age >65yrs (n= 58), prevalence of HBP 66%									
Cuff BP	47 (44-51)	95 (93-97)	95 (92-97)	50 (46-54)	10.6 (6.6-17.7)	0.55 (0.51-0.60)	64 (61-67)	19.3 (11.3-33.0)	<0.001
Central BP	97 (96-98)	95 (93-97)	95 (93-96)	95 (93-97)	21.7 (13.6-36.1)	0.03 (0.02-0.04)	97 (95-98)	838.2 (0.9-1618.2)	
Coronary Arterial Disease (n= 78), prevalence of HBP 50%									
Cuff BP	44 (39-48)	90 (88-93)	81 (76-86)	63 (59-66)	4.6 (3.4-6.3)	0.62 (0.57-0.68)	68 (65-71)	7.4 (5.2-10.6)	<0.001
Central BP	92 (90-94)	93 (90-95)	92 (90-94)	93 (90-95)	13.0 (9.7-17.9)	0.08 (0.06-0.11)	93 (91-94)	161.3 (0.9-254.5)	
Diabetes Mellitus (n= 23), prevalence of HBP 43%									
Cuff BP	50 (45-55)	92 (90-94)	83 (78-88)	71 (67-74)	6.7 (4.9-9.1)	0.54 (0.49-0.60)	74 (71-77)	12.4 (8.5-17.6)	0.031
Central BP	90 (87-93)	92 (90-94)	90 (87-93)	92 (90-95)	12.0 (9.0-15.9)	0.11 (0.08-0.14)	91 (90-93)	114.2 (0.9-179.6)	

Cuff BP = non-invasive brachial BP by automatic Sphygmomanometers

Central BP = noninvasive central BP measured central blood pressure monitors

*P value of McNemar test comparing the diagnostic accuracy between two tools

As shown in Figure 6-2, the difference between effects of the negative result on post-test probability (cuff BP vs. noninvasive CBP) is more pronounced than that of the positive result, which indicates that given a negative test result (no HBP) of cuff BP, the clinician can be less confident that the subject is actually free from HBP, in which case the non-invasive CBP may be more helpful.

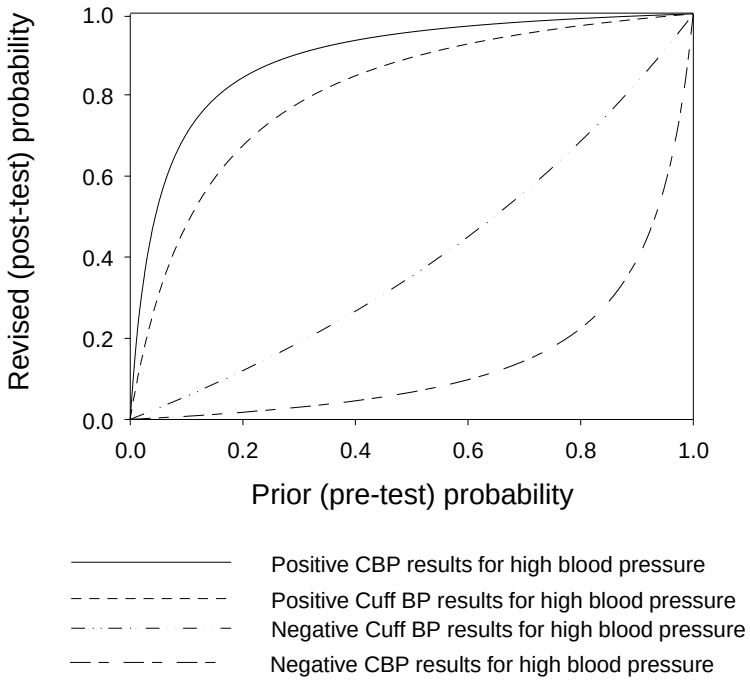

Figure 6-2. Revised probability after BP measurements

Figure 6-2. Bayes Theorem: illustration of the conditional probability of HBP given different pretest probabilities subsequent to positive or negative test results of cuff BP or non-invasive CBP estimates. For example, if pretest probability is 0.5, which is the same as the probability of a coin toss coming up heads, the post-test probability of HBP after a positive result of cuff BP is lower than that after non-invasive CBP (0.89 vs. 0.96). On the contrary, given the pretest probability of 0.5 and negative test results, the post-test probabilities for cuff BP and noninvasive CBP were 0.35 and 0.07, respectively.

Subgroup Analysis and Results with Different Cutoffs

Table 6-2 also shows the diagnostic performances of cuff BP and non-invasive CBP for detecting HBP in different subgroups. In general, the performances of cuff BP in different subgroups were all characterized by high sensitivity, high PPV, high positive likelihood ratio (the higher the better), but low sensitivity, low NPV, and high negative likelihood ratio (the lower is the better). These findings suggested that although a positive result of cuff BP may render a correct HBP diagnosis highly probable, a negative result of cuff BP may not be sufficient to exclude a definite diagnosis of HBP across different subgroups of subjects. In contrast, the accuracy of noninvasive CBP was significantly higher than that of cuff BP and the former may be capable of identifying subjects with false negative results of cuff BP in all subgroups of patients.

Table 6-3 shows the effects of different reference values (different CBP cutoffs) on the diagnostic performances of cuff BP and noninvasive CBP. Despite the lower cutoffs resulting in higher HBP prevalence, similar findings were observed amid results with different cutoffs.

Table 6-3. Analysis of the Influence of Different Reference Values of invasive aortic BP for High Blood Pressure on the Diagnostic Performance of Oscillometric Central Blood Pressure Monitors for Confirming A Diagnosis of High Blood Pressure (N = 138)

	Sensitivity,%	Specificity,%	Positive predictive value,%	Negative predictive value,%	Positive likelihood ratio	Negative likelihood ratio	Accuracy, %	Diagnostic Odds Ratio	P value*
130/90 mmHg, prevalence of HBP 52%									
Cuff BP	49 (44-53)	94 (92-96)	90 (86-93)	63 (59-66)	8.3 (5.8-11.7)	0.55 (0.50-0.59)	70 (67-73)	15.3 (10.1-22.5)	<0.001
Central BP	93 (91-95)	95 (94-947)	96 (94-97)	93 (90-95)	21.5 (14.6-32.6)	0.07 (0.05-0.10)	94 (93-96)	305.5 (0.9-517.1)	
135/90 mmHg, prevalence of HBP 38%									
Cuff BP	60 (56-65)	92 (90-94)	82 (78-86)	79 (76-82)	7.4 (5.7-9.7)	0.43 (0.38-0.48)	80 (77-82)	17.3 (12.3-24.4)	<0.001
Central BP	89 (85-92)	91 (88-93)	85 (82-89)	93 (91-95)	9.5 (7.6-12.2)	0.12 (0.09-0.16)	90 (88-92)	78.2 (0.9-120.0)	
130/85 mmHg, prevalence of HBP 54%									
Cuff BP	47 (43-51)	94 (91-96)	90 (86-93)	60 (56-63)	7.6 (5.3-11.4)	0.57 (0.52-0.62)	68 (65-71)	13.4 (8.7-20.8)	<0.001
Central BP	89 (87-92)	95 (93-97)	96 (94-97)	88 (85-91)	19.7 (13.3-31.2)	0.11 (0.09-0.14)	92 (90-94)	179.2 (0.9-317.4)	
135/85 mmHg, prevalence of HBP 42%									
Cuff BP	57 (52-61)	93 (90-95)	85 (80-89)	75 (72-78)	7.8 (5.8-10.6)	0.47 (0.41-0.52)	78 (75-80)	16.8 (11.6-24.5)	<0.001
Central BP	83 (79-86)	91 (89-94)	87 (84-91)	88 (85-90)	9.7 (7.4-12.9)	0.19 (0.15-0.23)	88 (86-90)	51.7 (0.9-75.0)	
130/80 mmHg, prevalence of HBP 58%									
Cuff BP	45 (41-49)	95 (93-97)	92 (89-95)	56 (52-59)	9.0 (6.0-13.9)	0.58 (0.53-0.63)	66 (63-69)	15.6 (9.8-24.6)	<0.001
Central BP	87 (85-90)	91 (93-95)	95 (93-96)	84 (81-88)	13.1 (9.3-18.7)	0.13 (0.11-0.17)	90 (88-92)	98.8 (0.9-153.2)	

Cuff BP = BP measured by automatic sphygmomanometers

Central BP = BP measured by central Blood Pressure Monitors

HBP = high blood pressure

*P value of McNemar test comparing the diagnostic accuracy between two tools

Discussion

The present study represents the first attempt to evaluate the diagnostic performance of cuff BP and noninvasive CBP with reference to a newly proposed standard for detecting HBP. Similarly, it is among the pioneer efforts to exploit CBP as a clinically useful diagnostic tool to facilitate clinical decisions for the management of HBP. With the superior prognostic ability of CBP over cuff BP[10-14], this study substituted the former for the later to be the diagnostic reference for HBP. As a consequence of the change of reference standard to invasively measured CBP, the study demonstrates that traditional cuff BP is characterized by low sensitivity, low NPV, and high negative likelihood ratio, although specificity, PPV, and positive likelihood ratio were not low. These findings of high false negative rates suggest that the conventional strategy may overlook a considerable proportion of patients who might benefit from the corresponding management for HBP subsequent to a diagnosis being made. On the contrary, it may justify the use of cuff BP through the high true positive rate for HBP management, because a positive test result of cuff BP may render a correct diagnosis not unlikely (high specificity, high PPV, and high positive likelihood ratio). The global burden of HBP estimated in 2005 showed that approximately 1 billion people worldwide had HBP, with the number expected to increase to 1.56 billion people by the year 2025, which is about 1 out of every 4 adults being afflicted with hypertension [133]. The tremendous burden of HBP, especially in economic developed countries, suggests us considering circumspectly on the appropriateness of current diagnostic strategy for HBP management, particularly for those who might have been overlooked, creating lost opportunities for receiving suitable management.

The oscillometric CBP monitor has emerged as a new technology for BP measurement,[22, 66, 82, 88, 129, 134, 135] following a first report in 2009.[136] With the

incorporation of the novel estimating methods for CBP[22, 69] into standard oscillometric BP monitors, the new device will be readily available for the daily practice of HBP management. This study demonstrates that the non-invasive CBP from the validated oscillometric CBP monitor, as detailed in Chapter 4, is characterized by significantly increased accuracy for detecting HBP (Table 6-2 and 6-3, all $p<0.05$ in different subgroups and by different cutoffs), and is therefore capable of identifying population overlooked by traditional strategies by lowering the false negative rate.

As shown in a previous systematic review and meta-analysis [90], cuff SBP and DBP overestimate invasively measured central SBP and DBP by 5.4mmHg and 8.7mmHg, respectively. It is probably reasonable to have the central BP cutoffs between 130-135/80-85mmHg by considering the BP amplification phenomenon [121] and that original cuff BP cutoff for HBP is 140/90mmHg. The previous analyses in Chapter 5 on two independent cohorts also support this viewpoint. More importantly, similar trends were observed in the analysis by different cutoffs.

The reason behind the high false negative rate (low sensitivity, low NPV, high negative likelihood ratio) of cuff BP could be partly explained by the observation that the cuff BP measurement errors are increased in patients with reduced arterial compliance [58, 137], which has been associated with aging and HBP [138]. In our study, this speculation was supported by the finding that cuff BP had the lowest accuracy in the subgroup aged more than 65years. Cuff BP, even surpassing the requirements of international standards, could still underestimate BP considerably,[58] and may neglect a substantial amount of HBP patients.

Although the application of Bayes' theorem assumes that sensitivity, specificity, and likelihood ratio are constant over patient population [139], variations of these parameters with prevalence or population heterogeneity have been suggested in

previous studies [140, 141]. However, a diagnostic test has no bearing on management but provides the probability of a status for clinicians to make the relevant change of management. As shown in Table 6-2 and 6-3, the similar patterns of the diagnostic performance of cuff BP and CBP across different subgroups and different cutoffs indicate that such variations may not affect the conclusion of the present study.

Limitations of the Present Study:

The study sample consisted of adult patients referred for evaluation of coronary anatomy and/or angioplasty, which may differ from the general population in the sex distribution and in the prevalence of underline medical history. Although this study population may more appropriately represent persons in whom BP determinations are warranted, further large-scale studies with improved representativeness might be needed to confirm our findings. In addition, the study attempted to adhere strictly to the diagnostic procedures recommended by the guideline[1, 2]; however, some of the procedures, such as BP measured in the sitting position, were impeded by the invasive nature of our measuring process.

Conclusion

With the high specificity and PPV, traditional cuff BP may be reliable in confirming a diagnosis of HBP and justify subsequent treatment. However, as a consequence of the low sensitivity and NPV, cuff BP could render possible management inaccessible to a considerable proportion of HBP patients, who may be identifiable through the noninvasive CBP from the CBP monitor

Strategies for Addressing Translational Gaps

The study has demonstrated the measurement accuracy (Chapter 3 and 4) and diagnostic accuracy (chapter 6) of the CBP monitor. To facilitate evidence utilisation by addressing the "**Clinical Application to Action"** gap, it is useful to begin with the

investigation of the impact of rigorously evidence on systems or outcomes. A mathematic model is capable of estimating costs and consequences over an extended time horizon and subject to change over time.[142] If a novel technology is considered to have favourable cost-effectiveness, policy makers, clinician, organizations, and communities could be more likely to carry out appropriate movements to improve patients' global health. I therefore conducted a comprehensive and complex decision modelling for health economic evaluation for the CBP monitor.

CHAPTER 7: Health Economic Evaluation of the Novel Strategy of Using Non-invasively Measured Central Blood Pressure for Confirming a Diagnosis of Hypertension:

Background

High blood pressure (HBP) is among the leading causes of global burden of disease.[101] By 2025, it is estimated that around 1.56 billion people, which is about 1 out of every 4 adults, will be afflicted with HBP[133]. To manage HBP, a diagnosis has traditionally been made through blood pressure (BP) measurements at brachial arteries by sphygmomanometers (cuff BP) after a raised initial reading.[1, 104, 130] However, discrepancy has long been recognized between central aortic BP (CBP) and peripheral BP,[5, 6] which may magnify with administration of vasoactive agents [4, 7, 30-33]. The interest of the clinical application of CBP has been driven largely by the recent randomized controlled trials which demonstrated the differential impacts of anti-hypertensive drugs on CBP and cuff BP. [34, 35] Moreover, it has been shown that CBP may have the superior prognostic value over cuff BP,[12-14] which suggests that it could serve as a more relevant target for HBP management. As a consequence, The 2007 ESH-ESC Practice Guidelines has addressed the concept of CBP for the Management of Arterial Hypertension measurement.[2]

With the availability of noninvasive methods for CBP measurements,[4, 15-17, 22, 66] this longstanding concept could now have the potential to be implemented in daily practice of HBP management. However, as for any new emerging technology, the cost-effectiveness should be evaluated in a relevant clinical setting. Lovibond et al. had performed a comprehensive probabilistic cost-effectiveness analysis of options for the diagnosis of HBP by constructing a sophisticated Markov model.[143] CBP, however, has not been included as a comparing strategy.

Besides, as a central role to integrate all the relevant evidence about a disease and health interventions, mathematic model is capable of estimating costs and consequences over an extended time horizon and subject to change over time. [142] Recently, Karnon et al proposed methods to probabilistically calibrating models in economic evaluation to account for uncertainty by exploring the consistency of model predictions with observational data.[142, 144] Therefore, the aims of the present study were to reconstruct and probabilistically calibrate the Markov model by Lovibond et al to compare CBP with cuff BP for confirming a diagnosis of HBP.

Methods

Model Strategies

The model was modified from an established Markov model in 2011143, 145 to evaluate a hypothetical primary care population aged 35 years or older with initial raised BP higher than 140/90mmHg and the equivalent prevalence of risk factors to those of a general population. In this cost-effective analysis, the strategies in comparison were conventional clinical BP (cuff BP) and CBP monitoring with a 3 month diagnostic cycle.104

With the perspective corresponding to the original Markov model, this reconstructed Markov model estimated lifetime quality-adjusted life year (QALY), cost, and incremental cost-effectiveness ratio (ICER) with an annual discount rate 3.5%.143 The model was constructed with a cycle length of 3 months in EXCEL 2010. I conducted the analysis in ten age- and gender-stratified groups (men and women with age 35-44, 45-54, 55-64, 65-74, and above 75 years) to calculate the time spent in each state, total cost and QALY by different strategies for 60 years.

Model Structure

The structure of the model has been detailed elsewhere.[143] In summary, all individuals in the model began from a starting state of suspected to have HBP (but actually they are either normotensive or hypertensive), subsequently moved to the diagnosed states (normotensives with true negative or false positive and hypertension with true positive or false negative), and then resided in these healthy states or changed to event states (myocardial infarction, unstable angina, stable angina, stroke, and transient ischemic attack and status post these events). Transitions were determined from probabilities calculated based on previous studies with age and gender stratifications. A total of 1260 time-varying and gender dependent transient probabilities (126 for each subgroup with 10 subgroups = 1260) were used to construct this Markov model.

Model Parameters and Assumption

Table 7-1 summarizes the input data which were updated from the original Markov cohort.[143, 145]

The model needed the following categories of parameter estimates related to state transition: prevalence, diagnostic inputs, cardiovascular risks, quality of life multiplier, and cost (table 7-1). Updated information after the original model published in 2011was included when available, such as non-cardiovascular mortality.[146] The major modifications on the model were the new comparing diagnostic option (CBP) and the calibration procedure (see below).

Table 7-1. Base-case model inputs adapted and updated from the established Markov model by Lovibond, et al. [145]

Description	Data	Distribution	Source
Cohort setting			
Prevalence	16-68%(age and gender dependent)	fixed	HSE 2006[147];Hodgkinson et al[125, 145]
Diagnosis inputs*			
Sensitivity	cuff BP 48.6%; CBP 93.1%	beta[148]	Chapter 6
Specificity	cuff BP 93.9%; CBP 95.5%	beta[148]	Chapter 6
Time until diagnosis complete	3 months	fixed	NICE guideline[104, 145]
Cardiovascular risks			
Non-cardiovascular death, 2010	0.08-13.3% (age and gender dependent)	fixed	ONS Mortality statistics: Deaths registered in 2010[146] with circulatory death excluded[145]
CHD by true normotensive or hypertensive (10years)	0.9-23.6% (age and gender dependent)	Framingham CHD and stroke risk equations: fixed Blood pressure: normal Total cholesterol: normal HDL cholesterol: normal % diabetes: beta % smoker: beta	Framingham risk equations with risk factor profiles based on HSE 2006[145, 146, 149]
Stroke by true normotensive or hypertensive (10years)	0.3-11.3% (age and gender dependent)	as above	as above
Distribution of CHD (myocardial infarction, unstable angina, stable angina , CHD death)	age and gender dependent	fixed	Ward et al 2007[150]
Distribution of stroke events (stroke, transient ischemic attack, stroke death)	age and gender dependent	fixed	Ward et al 2007[145, 150]
RR for CHD on treatment	0.633-0.717 (age and gender dependent)	Relative risks: lognormal % on 1, 2, 3 drugs: Dirichlet	Law et al 2009[151]; HSE distribution of people on 1-3 drugs[147 145]
RR for stroke on treatment	0.526-0.717 (age and gender dependent)	as above	as above

Description	Data	Distribution	Source
SMR after myocardial infarction	2.68 (95% CI: 2.48, 2.91)	Lognormal	Danish MONICA stud[145, 152]
SMR after unstable angina	2.19 (95% CI: 2.05, 2.33)	Lognormal	NICE guideline[145, 153]
SMR after stable angina	1.95 (95% CI: 1.65, 2.31)	Lognormal	Rosengren et al[145, 154]
SMR after stroke	2.72 (95% CI: 2.59, 2.85)	Lognormal	Bronnum-Hansen et al[145, 155]
SMR after transient ischemic attack	2.72 (95% CI: 2.59, 2.85)	Lognormal	Oxfordshire Community Stroke Project[145, 156]
Probability of normotensives turn to hypertensive	15%-38% (age and gender dependent)	beta	HSE 2006[147]
Check-up frequency for true negative and false negative	Every 5 years	n/a	based on current practice[145]
Quality of life multiplier			
Subjects without any events	0.704-0.909 (age and gender dependent)	beta	EQ-5D from HSE 2006[145, 149]
Death	0	n/a	by definition
Myocardial infarction	0.76	beta	Ward et al[150]
Unstable angina	0.77	beta	as above
Stable angina	0.808	beta	as above
Stroke	0.629	beta	as above
Transient ischemic attack	1	fixed	as above
Cost			
Cuff BP device	£42.00	Gamma	Median from NHS supply chain[145]
CBP device	£4,000	Gamma	Median from product catalogue[145, 157]
Nurse Practice	£10.00	fixed	PSSRU 2010 unit costs[145, 158]
Family doctor Practice	£28.00	fixed	PSSRU 2010 unit costs[145, 158]
Maintenance cost per year	Cuff BP £58.1; CBP £426.6	Gamma	NICE guideline[145] and Median from product catalogue[145, 157]
Initial diagnostic cost with cuff BP (3-months cycle)	**£38.46**	Estimated as a function of other parameters	NICE guideline[104] and PSSRU 2010 unit costs[158 145]
Initial diagnostic cost of diagnosis	**£41.41**	Estimated as a function of other parameters	as above

Description	Data	Distribution	Source
with CBP (3-months cycle)			
Initial myocardial infarction cost (3months)	£4,792.00	fixed	Palmer et al[145, 158, 159]
Hypertension treatment cost (3months)	£7.8-8.2 (drug only; age and gender dependent)	% on 1, 2, 3 drugs: Dirichlet	NICE guideline[104], unit cost[158], and British National Formulary 60[145, 160, 161]
Cost after myocardial infarction (3months)	£141.00	fixed	NICE guideline[104, 145, 158]
Initial unstable angina cost (3months)	£2,875.00	Gamma	Assumed to be 60% of initial myocardial infaction costs[145]
Cost after unstable angina (3months)	£85.00	Gamma	Assumed to be 60% of costs after myocardial infarction[145]
Initial stable angina cost (3months)	£400.00	fixed	NICE guideline[162 143, 161]
Cost after stable angina (3months)	£6.00	fixed	NICE guideline[162] and British National Formulary[160]
Initial stroke cost (3months)	£9,630.00	fixed	Youman et al[145, 158, 163]
Cost after stroke (3months)	£559.00	fixed	Youman et al[145, 163]
Initial transient ischemic attack cost (3months)	£992.00	fixed	Ward et al[150] and NICE guideline[158, 164, 165] and British National Formulary 60[160]
Cost after transient ischemic attack (3months)	£26.00	fixed	NICE guideline and British National Formulary 60[160]
Check-up	£28.00	fixed	PSSRU 2010 unit costs[158]

HSE = health survey for England; CHD = coronary heart disease; cuff BP = conventional clinical blood pressure monitor; CBP = central BP monitor; NICE = National Institute for Health and Clinical Excellence; Office for National Statistics = ONS; RR = relative risks; SMR = standardised mortality ratio

*:To account for the inverse relationship between sensitivity and specificity, we modeled the sensitivity as a function of specificity and the diagnostic odds ratio[148]

#: RR of false positives for CHD and stroke on treatment was assumed to be 1[145]

The reconstructed model challenged the current practice by considering the invasively measured CBP to be the reference standard because of its superior prognostic value to cuff BP.[14] The probabilities of true positive, false negative, false positive, and true negative after cuff BP or CBP were estimated from respective sensitivity and specificity. The joint and inverse relationship between sensitivity and specificity was accounted by modeling the sensitivity as a function of specificity and the diagnostic odds ratio.[166] These parameters were obtained on the basis of a study comprised of 138 subject receiving cuff BP and non-invasive CBP simultaneously, as detailed in Chapter 6.

The device cost of a CBP monitor was estimated from the information provided on catalogues or homepages from manufacturers (Table 7-1) with uncertainty dealt with deterministic or probabilistic sensitivity analysis (see below). Because the clinical settings and the diagnostic process are similar between two arms, the cost estimates relating to diagnosis were kept the same except for the device investment and maintenance expenditure.

Model Calibration

The calibration process for the reconstructed model adhered to the 7-step methodology proposed by Karnon et al.[142, 144] I used the 10 years-averaged annual cardiovascular mortality rates (35-44, 45-54, 55-64, 65-74) of the general population in UK as the calibration target.[146] The observed mortality rates and their distribution boundaries were then compared with the 10 years-averaged annual cardiovascular death rates of subjects without a diagnosis of hypertension (true negative and false negative) estimated with Framingham risk equations[167] in the model. As for the convergence criteria and stopping rule, 1000 input parameter sets, with all their output estimates within the boundaries of the observed data, were included into the probabilistic calibration process. Of the whole included parameter sets, Chi-square

test was used to calculate the goodness-of-fit, which was subsequently transformed into cumulative probabilities for random sampling.[142] Probabilistically selecting from these qualified input parameter sets, the Monte Carlo simulation with 1000 repeated random sampling[168] was performed using Excel Visual Basic Application (VBA) Macros.

Uncertainty and Sensitivity Analysis

I used both probabilistic and deterministic sensitivity analysis to account for the uncertainty of the model. For each input parameter, a probability distribution was determined by its point estimate and standard error (table 7-1). During the simulation of randomly selecting process, the joint uncertainty of individual input parameters was propagated. Because some potential determinants for cost-effectiveness are probably highly correlated, we also specified alternative scenarios for deterministic sensitivity analysis.

Regression dilution bias (or attenuation bias) has been proposed to delineate the effect of measurement error or random noise of the predictor on the estimating outcome.[126, 127] It was suggested that the greater the variance in the measurements of predictor (such as cuff BP in our study), the closer the estimated slope must approach 0 instead of the true gradient (such as cardiovascular risk in our study. However, despite of such observation, correction could be neither necessary nor appropriate in most applications.[128] The risk equations used in the study, the Framingham risk equations, are based on cuff BP, which is not an accurate measure for BP measurements and could introduce regression dilution bias into the risk estimation. I therefore proposed (Appendix VI) the use of risk adjusting equations to account for the above effect and perform a sensitivity analysis with the adjusted risk.

Results

Base case Cost-effectiveness

To obtain 1,000 convergent parameter sets in all 10 subgroups, I ran an average of 1615.4 ± 25.1 (1582~1663) iterations for a subgroup of the probabilistic calibration. For men and women of all ages, the CBP strategy was more cost-effective than cuff BP as shown in Table 7-2. In both genders, the QALY gain increased and incremental cost declined with age, which jointly resulted in decreasing incremental cost-effectiveness ratio (ICER) in older age groups, except for that of men aged more than 75 years. The incremental cost of the CBP strategy was at deemed cost-effective at a willingness-to-pay threshold 20,000 £ /QALY.

Table 7-2. Probabilistic sensitivity analysis for incremental cost, QALY and ICER of CBP compared with Cuff BP using the calibrated Markov model

	Incremental Cost (95% CI)	**Incremental QALYs** (95% CI)	**ICER** (95% CI)	**More cost-effective strategy**	**Probabilities of cost-effectiveness***
Men, 40 years	£190 (168 to 217)	0.12 (0.08 to 0.17)	£1640 (1229 to 2187)	CBP	100.00%
Men, 50 years	£152 (132 to 174)	0.16 (0.13 to 0.2)	£958 (839 to 1114)	CBP	100.00%
Men, 60 years	£143 (126 to 162)	0.26 (0.23 to 0.3)	£546 (509 to 602)	CBP	100.00%
Men, 70 years	£116 (102 to 130)	0.50 (0.48 to 0.53)	£229 (209 to 251)	CBP	100.00%
Men, 75+ years	£371 (368 to 374)	0.70 (0.69 to 0.70)	£534 (530 to 538)	CBP	100.00%
Women, 40 years	£232 (203 to 258)	0.09 (0.04 to 0.15)	£2750 (1729 to 4934)	CBP	99.80%
Women, 50 years	£242 (218 to 270)	0.11 (0.07 to 0.16)	£2286 (1607 to 3272)	CBP	100.00%
Women, 60 years	£207 (186 to 233)	0.15 (0.12 to 0.2)	£1357 (1157 to 1612)	CBP	100.00%
Women, 70 years	£300 (270 to 324)	0.34 (0.3 to 0.37)	£893 (850 to 945)	CBP	100.00%
Women, 75+ years	£200 (195 to 205)	0.88 (0.88 to 0.89)	£226 (222 to 231)	CBP	100.00%

CBP = central blood pressure; Cuff BP = conventional clinical blood pressure monitoring; ICER = incremental cost effectiveness ratio (£)

* at willingness-to-pay threshold 20,000 £/QALY

From the probabilistic sensitivity analysis (Table 7-2 and Figure 7-1), the propagation of joint uncertainty didn't affect the decision of cost-effectiveness favouring CBP in all subgroups. The probability for CBP to be the more cost-effectiveness strategy was all 100%, except in women aged 40years with the probability of 99.8%. It was clearly cost-effective to adopt the CBP strategy as opposed to cuff BP.

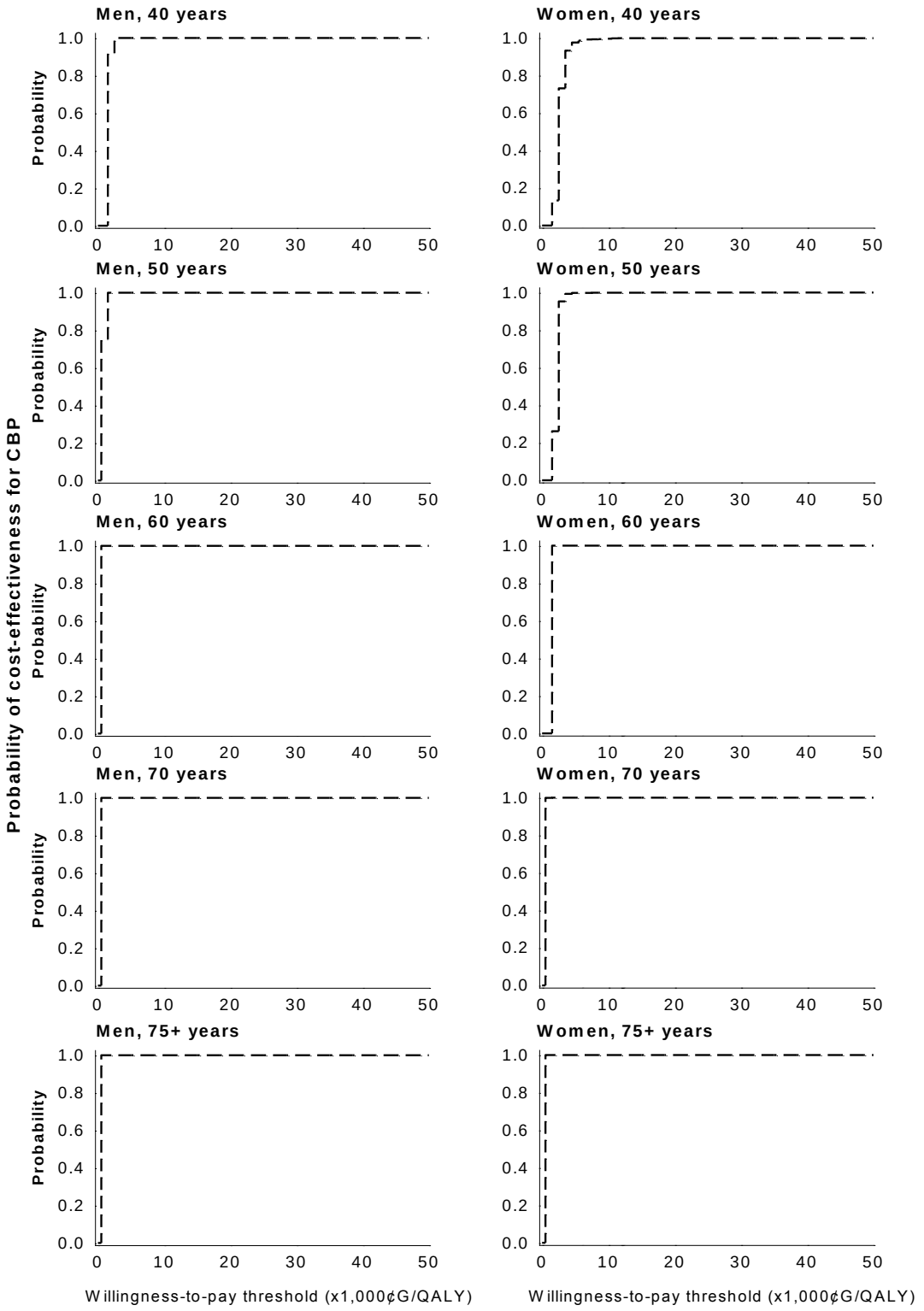

Figure 7-1. Cost-effectiveness acceptability curves for central blood pressure monitoring strategy (CBP) vs. conventional clinical blood pressure strategy stratified by different ages and genders. The analysis was performed by 1000 Monte Carlo probabilistic simulations that represent uncertainty on a probabilistically-calibrated Markov model (see text for details).

Alternative Scenarios

Table 7-3 shows the results of the deterministic sensitivity analysis varying the base-case assumptions and inputs. These scenarios consisted of the variable assumptions such as declined QALY associated with treatment, decreased diagnostic performance of CBP monitoring, different CBP costs, different prevalence of HBP, whether risk reduction was applied to normotensive but treated subjects, and follow-up percentage of subjects diagnosed as not hypertensive. CBP remained the more cost-effective strategy suggested by results of these alternative scenarios (Table 7-3).

Table 7-3. Deterministic sensitivity analysis for incremental cost, QALY and ICER of CBP compared with Cuff BP using the calibrated Markov model for men aged 60 years

	Incremental Cost	Incremental QALYs	ICER	More cost-effective strategy*
2% QALY decrement on treatment	£135	0.15	£888	CBP
5% QALY decrement on treatment	£135	0.01	£10,975	CBP
CBP sensitivity set to 80%	£91	0.17	£540	CBP
CBP specificity set to 80%	£147	0.24	£601	CBP
CBP device cost doubled	£151	0.25	£618	CBP
CBP device cost halved	£127	0.25	£518	CBP
Prevalence set to 80%	£134	0.24	£549	CBP
Prevalence set to 120%	£135	0.25	£552	CBP
Risk reduction applied to all treated people	£132	0.2	£674	CBP
Risk reduction based on half doses	£162	0.2	£830	CBP
diagnosed as not hypertensive receiving following check-up set to 60%	£168	0.27	£612	CBP
Adjusted cardiovascular risk by equations proposed in the appendix	£130	0.28	£470	CBP

CBP = central blood pressure; Cuff BP = conventional clinical blood pressure monitoring; ICER = incremental cost effectiveness ratio (£); QALY = quality-adjusted life years

* at willingness-to-pay threshold 20,000 £/QALY

By Monte Carlo simulation, cost-effectiveness acceptability curves across different age and gender groups are plotted in Figure 7-1. Of all subgroups, the probabilities of CBP strategy to be cost-effective reached 100% immediately with increasing thresholds of willingness-to-pay from zero, except for the group of women aged 40years, in which the probability was 99.8%.

In addition, with the adjusted risk derived from equations accounting for the regression dilution bias, the results were consistent with those from un-adjusted risk estimates (Table 7-3).

Discussion

Principal Findings

The study evaluated the effectiveness, costs, and cost-effectiveness of CBP compared with cuff BP monitoring as a diagnostic tool for confirming a diagnosis of HBP in a population with suspected BP greater than 140/90mmHg. Through comprehensive probabilistic and deterministic sensitivity analysis on a probabilistically calibrated Markov model, it was consistently suggested that CBP monitoring is a cost-effective strategy across all age- and gender- stratified subgroups when compared to conventional cuff BP. The key driver of the superior cost-effectiveness of CBP monitoring is its QALY gain from better sensitivity than cuff BP (Table 7-2), which indicates that CBP monitoring resulted in fewer false negative results (i.e. hypertension without a correct diagnosis), in which condition subsequent treatment is not provided. Therefore, a better sensitivity may be associated with the QALY gain. In contrast, with improved specificity, the waste of anti-hypertensive treatment on normotensives with a wrong diagnosis (false positive) can be avoided.[143] In this regard, improved specificity may be associated with cost decline. As a result of the similar specificity between CBP and cuff BP monitoring in this model, the cost-saving effect of CBP monitoring was thus not obvious.

Strengths and Limitations

The present model extended the work by Lovibond et al,[143, 145] which compared the cost-effectiveness of cuff BP, home BP, and ambulatory BP for the diagnosis of HBP

by constructing a comprehensive Markov model. This comparison was made between CBP and cuff BP, which represents pioneer work rather than routine clinical practice, to investigate the cost-effectiveness of this new emerging technology. The strength of the study is that it further performed probabilistic calibration on the modified and updated Markov model by comparing the model outputs with observed epidemiologic data, which is beneficial to the reduction of model uncertainty. However, to my knowledge, the diagnostic performance of CBP monitoring has not been reported except for the report in Chapter 6. The model based the calculation on this individual study, which inevitably restricts its generalizability. However, in the analysis of alternative scenarios, the study demonstrates that CBP strategy is still more cost-effective even when its sensitivity and specificity were reduced to 80%.

Comparison with Other Studies

This study is the first economic evaluation to compare the cost-effectiveness between conventional cuff BP and central BP strategy. Although this model was reconstructed from that by Lovibond et al,[143, 145] the results of these two studies could not be compared with each other. The main reason behind this is that these two studies used a different reference standard, which heavily influences the diagnostic performance of the respective tested diagnostic tool. In the model by Lovibond et al., ambulatory BP monitoring was considered as the reference standard[125] because of its better relationship to cardiovascular outcomes and end organ damage.[169-173] As a result, the sensitivity and specificity of ambulatory BP were assumed to be 100%,[125] which was consequently associated with cost reduction and QALY gain when comparing to a diagnostic test with a lower sensitivity and specificity as discussed above. It is recognized that the reference BP standard should have a better prognostic value. It has been previously demonstrated that office CBP may be comparable to ambulatory BP in predicting future outcomes,[107] which

justifies the rationale of adopting invasively measured CBP as the reference standard in the model. Although the current guideline suggests ambulatory BP as the better diagnostic tool for hypertension than office BP,[104] CBP might be playing an increasingly prominent role with the growing evidence supporting its prognostic value.[36]

I and Lovibond et al. assumed that normotensives falsely classified as having hypertension could not benefit from the inadvertent antihypertensive treatment. In their deterministic analysis, the reversal of this assumption did change the conclusion of the most cost-effective strategy to cuff BP monitoring.[143, 145] The cost-saving effect of a better specificity (fewer false-positive) of home BP or ambulatory BP was counteracted by the QALY gain of a lower specificity of cuff BP (more false-positive) through the above altered assumption by applying risk reduction on false-positive subjects. The finding along with the concept that BP is continuously associated with an increasing risk of stroke and heart attacks[102] prompted some criticism of the study conclusions.[174] In the model developed in this study, the specificity of CBP monitoring was close to cuff BP and therefore this alternative scenario had a comparable influence on both arms and failed to change the decision of cost-effectiveness.

Future Research and Policy Implications

Although the output of the modified Markov model has been compared with updated epidemiological data, its accuracy could still be improved by future research. More studies investigating the diagnostic performance of CBP with the provision of sensitivity and specificity across different population may render the model more generalizable. Despite the fact that prevalence seemed not to be a key driver in cost-effectiveness as demonstrated in the sensitivity analysis, these data, by using CBP as reference test, might further improve the model specification and

validity. Finally, as discussed above, whether antihypertensive treatment is effective in reducing the cardiovascular risks of normotensives should be further demonstrated, especially for subjects with BP lower than but close to the cutoffs of the reference diagnostic standard.

Conclusion

In the calibrated Markov model, CBP monitoring, which challenges the traditional concept of HBP diagnosis, was found to be more cost-effective than conventional cuff BP for confirming a diagnosis of hypertension across different age- and gender-stratified subgroups. The key driver of this cost-effectiveness is the QALY gain, which indicates improved health, at the expense of acceptable incremental cost. The conclusion is consistent with probabilistic and deterministic sensitivity analysis and suggests that CBP monitoring should be considered in the management of HBP.

CHAPTER 8: Discussion and Conclusion

Restatement of the Clinical Problem and the Research Outcome

Although the CBP concept has been recognised for decades, the widespread application of CBP in clinical practice has never been achieved, even with the demonstration of its superior prognostic value.[12-14, 106] Basing on the framework of EBHC and translational science (Figure 1-1), I identified the barriers to the application of the CBP concept for the management of hypertension in the "evidence-to-practice" cycle. Subsequently, I succeeded in developing corresponding strategies for these identified gaps. Through a series of studies and analyses and attempt to fill in the gaps from "unmet need" to "clinical action", I have demonstrated the usefulness of utilising the JBI EBHC framework[24] and translational science cycle in propelling scientific discovery through to the improvement of global health.[25]

Summary of Identified Gaps and Strategies

Usefulness of a Systematic Review: Action or Unmet Need?

As demonstrated in Figure 1-1, the systematic review plays an important role in the cycle of EBHC and translational science. A rigorously conducted systematic review for evidence synthesis can sometimes guide the movement of a novel scientific discovery toward clinical policy and/or individual or systematic clinical action. However, it may also reveal an "unmet need for knowledge" and suggest that "more research is required". It is demonstrated in the systematic review and meta-analysis[90] (Chapter 2) that in addition to the skill threshold for the tonometry-based CBP estimating techniques, there is room for improvement in the measurement accuracy of these techniques. These gaps in clinical application identified through

the conduct of the systematic review provided opportunities for basic and clinical research relating to the CBP concept. Based on the categorization suggested by Pearson et al.,[25] we summarized the following identified gaps and corresponding strategies:

Gaps and Strategies for Conventional Techniques: [4, 15, 16]

Gap 3-From Clinical Application to Action

There are some non-invasive CBP measuring techniques based mainly on applanation tonometry.[4, 15, 16] To obtain CBP by applanation tonometry, an experienced operator is required to identify the peripheral pressure waveform. The waveform is then subjected to calibration, which is to scale the waveform with cuff BP. The first barrier of these techniques to clinical application is the technical threshold for the waveform acquisition.

This represents the first attempt to propose the use of oscillometric signals (Figure 3-1) for the purpose of measuring CBP.[136] This innovation can be applied using automatic BP monitors, which largely renders the skill for CBP measurements inconsequential. CBP can now be measured just as easily as cuff BP.

Gap 1-From Knowledge Need to Discovery for the application of CBP concept

The 2nd gap in tonometry-based CBP techniques,[4, 15, 16] as demonstrated in our systematic review and meta-analysis, is the measurement inaccuracy of non-invasive CBP estimates. Errors were evident in the validation studies when cuff BP was used for non-invasive calibration, which represents an apparent “unmet need for knowledge”.

To fill in this gap, as clarified in Chapter 3 and previous journal publications,[22, 69, 84] I presented the process of building up prediction models by identifying key parameters retained in the oscillometric signals. The predicting targets for the

models were the invasively measured central SBP and PP, the gold standards. The generated equations were then validated in another independent study group. It was demonstrated that the technique not only reduces the complexity of the operating process, but also improves the overall accuracy of CBP measurements mainly through the improved calibration process.

Gaps and Strategies for Novel Oscillometric CBP Monitors Utilizing the Approach of Pulse wave analysis:[22, 69, 84]

Gap 1-From Knowledge Need to Discovery:

As discussed above, the unmet need for applying the CBP notion has now been addressed by the development of oscillometric CBP monitors utilizing the pulse-wave-analysis technique. On the basis of the theory of "the diffusion campaign",[175] these new developments, even with reduced complexity and improved accuracy, still have been facing the challenges for use in clinical practice, the translational gaps.[27]

Gap 2-From Discovery to Clinical Application:

Following the establishment of a scientific discovery, rigorous clinical experiments are required to comply with current regulations for the approval for use in clinical practice. This widely addressed "from-bench-to-bedside" gap requires carefully designed and scrupulously conducted clinical studies. I therefore conducted an invasive validation study, abiding by current international standards, [28] for the standalone CBP monitor equipped with the novel method. The results of the validation study are presented in Chapter 4. The validation study suggested that CBP can be measured accurately by a stand-alone automatic BP monitor.

Gap 3-From Clinical Application to Action:

After being available for clinical use, a new scientific discovery is then faced with a complex gap (Gap 3) demanding considerable efforts to move along the cycle of EBHC and translational science (Figure 1-1). The relevant strategies for this gap may include evidence-synthesis, transfer, and utilization.[25] Stepping over this gap represents a continuing effort until the improvement of global health is achieved through embedding the innovation through organizational and system change. Therefore, it is unlikely that strategies for this gap could cover all aspects constituting the challenges or difficulties for this "clinical application to action" gap. However, I started with the evaluation of the clinical impact of applying CBP concept in clinical practice, the first step of Evidence-transfer.

Considering that the concepts of home BP and ambulatory BP monitors have been successfully diffused across physicians and clinicians, these "successful stories" can be helpful in the effective application of the CBP concept. International guidelines for the management of hypertension[1, 103, 130] all provide reference values of conventional clinical office BP with sphygmomanometers, Home BP, and ambulatory BP for confirming a diagnosis of hypertension and monitoring the effects of treatment. In the process of clinical decision making for hypertensive patients, the challenges facing clinicians with CBP are as much as those with home BP or ambulatory BP.

For clinicians to make a diagnosis, clinical decisions are usually based on diagnostic criteria or thresholds. Therefore, it is essential to provide diagnostic thresholds of CBP, as has been done in Chapter 5, where these reference values are derived and validated with two independent longitudinal event-based cohorts. Moreover, a clinical decision is usually made by considering and interpreting the sensitivity and specificity of a diagnostic test. With the diagnostic accuracy study reported in

Chapter 6, clinicians can now make judicious decisions based on non-invasive CBP values provided by CBP monitors for confirming a diagnosis of hypertension.

For policy makers, it is imperative to take "cost-effectiveness" into consideration to decide whether or not a novel diagnostic tool or treatment is financially viable. I therefore performed a comprehensive and complicated health economic analysis using a modification of Markov mathematical modelling and reported the results in Chapter 7. The favourable cost-effectiveness of CBP monitors may empower clinicians or policy makers to adopt this innovation.

Implications for Clinical Practice

The global burden of hypertension is estimated to increase from 1 billion in 2005 to 1.56 billion people worldwide by the year 2025, which is about 1 out of every 4 adults being afflicted with hypertension.[133] The tremendous burden of hypertension suggests that better diagnostic strategies with CBP, which carries better prognostic value than conventional cuff BP, might benefit a considerable proportion of the population, particularly those who might have been overlooked, creating lost opportunities for receiving suitable management.

The present work represents a pioneering effort to exploit CBP as a clinically useful diagnostic tool to facilitate clinical decisions in the management of hypertension. With the superior prognostic ability of CBP over cuff BP[10-14], this study substituted the former for the later to be the diagnostic reference for hypertension. I demonstrate in Chapter 6 that, with high specificity, traditional cuff BP is reliable in confirming a diagnosis of hypertension and in justifying subsequent treatment. However, as a consequence of the low sensitivity and NPV, cuff BP could render possible management inaccessible to a considerable proportion of HBP patients, who may be identifiable through noninvasive CBP from the CBP monitor. Further

decision modelling for health economic analysis in Chapter 7 also challenges the traditional concept of hypertension diagnosis and suggests that CBP monitoring has superior cost-effectiveness than conventional cuff BP in the management of hypertension.

To step over the of "clinical application-to-action" gap (Gap 3), more research effort should be taken to support the better clinical outcomes that arise out of the use of the novel oscillometric BP monitoring for the management of hypertension. As illustrated in Figure 1-1, with more evidence being generated for CBP monitoring, clinicians and researchers can adopt the process of Evidence-synthesis, Evidence-transfer, and Evidence-utilization to attain the final goal of clinicians, the improvement of "Global health".

Conclusion

The difference between CBP and brachial BP has been a recognized for decades. Despite this well established understanding, no wide-scale clinical application has been developed to date. I conducted a systematic review and meta-analysis to uncover the possible unmet need for this concept. Subsequently, strategies were set up to close the translational gaps between "discovery" and "clinical application" and between "clinical application" and "action". The series of studies presented in this thesis suggest that the cycle of JBI EBHC and translational science is valuable and beneficial to researchers and clinicians for translating research into practice. More evidence supporting this innovation is required to facilitate relevant diffusion campaigns.

Appendices

Appendix I: Published Papers by HM Cheng Relating to this Thesis

Full texts of the following articles are presented at the end of the thesis.

*: HM Cheng as a first author

**: HM Cheng as a corresponding author

1. Cheng HM**, Lang D, Pearson A, Worthley SG. Measurement Accuracy of Non-invasively Obtained Central Blood Pressure: A Systematic Review and Meta-analysis. The Joanna Briggs Institute Library of Systematic reviews. 2011;9(44):1900

2. Hao-Min Cheng**, M.D., Catalin Tufanaru, M.D., Dora Lang, R.N., Alan Pearson, AM, PhD. Measurement Accuracy of Non-invasively Obtained Central Blood Pressure by Applanation Tonometry: A Systematic Review and Meta-analysis. Int J Cardiol. 2012; May 21. [Epub ahead of print].

3. Hao-Min Cheng*, Shih-Hsien Sung, Yuan-Ta Shih, Shao-Yuan Chuang, Wen-Chung Yu, Chen-Huan Chen. Measurement of Central Aortic Pulse Pressure: Noninvasive Brachial Cuff-based Estimation by A Transfer Function vs. A Novel Pulse Wave Analysis Method. Am J Hypertens. Aug 10. [Epub ahead of print].

4. Shih YT, Cheng HM*, Sung SH, Hu WC, Chen CH. Quantification of the calibration error in the transfer function-derived central aortic blood pressures. Am J Hypertens 2011; 24(12): 1312-7.

5. Shih YT, Cheng HM*, Sung SH, Hu WC, Chen CH. Comparison of two generalized transfer functions for measuring central systolic blood pressure by an oscillometric blood pressure monitor. J Hum Hypertens 2012.

6. Sung SH, Cheng HM*, Chuang SY, et al. Measurement of central systolic blood pressure by pulse volume plethysmography with a noninvasive blood pressure monitor. Am J Hypertens 2012; 25(5): 542-8.

7. Mei-Mei Lin, M.D, Hao-Min Cheng**, M.D., Shih-Hsien Sung, M.D., Chao-Feng Liao, M.D., Ying-Hwa Chen, M.D., Po-Hsun Huang, M.D., PhD., Chen-Huan Chen, M.D. Estimation of central aortic systolic pressure from the second systolic peak of the peripheral upper limb pulse depends on central aortic pressure waveform morphology. J Hypertens. 2012 Mar;30(3):581-6

8. Hao-Min Cheng*, Shih-Hsien Sung, Yuan-Ta Shih, Shao-Yuan Chuang, Wen-Chung Yu, Chen-Huan Chen. Measurement Accuracy of a Standalone Oscillometric Central Blood Pressure Monitor: A Validation Report for Microlife WatchBP Office Central. Am J Hypertens. 2012; in press

9. Cheng HM**, Tufanaru C, Pearson A, Chen CH. Automated blood pressure measurement in atrial fibrillation: a systematic review and meta-analysis. J Hypertens 2013; 31(1): 214-5

Appendix II. The Protocol, Search strategy, Critical Appraisal Instrument, and Data Extraction Instrument of the Systematic Review

Appendix IIA. Systematic Review Registration

The protocol of this systematic review was registered and could be retrieved from the following web address:

http://www.jbiconnectplus.org/ViewSourceFile.aspx?0=5138

Appendix IIB. Search strategy

Medline search strategy:

central blood pressure*[tw] OR aortic blood pressure*[tw] OR carotid blood pressure*[tw]

hypertens*[tw]

blood Pressure/

exp blood pressure determination/ all subheadings

blood pressure measur*[tw]

(applanation tonometry*[tw] OR arterial tonometry*[tw])

1 or 2 or 3 or 4 or 5 or 6

transfer function*[tw] OR SphygmoCor*[tw] OR AtCor*[tw]

7 and 8

secondary peak radial systolic[tw] OR late systolic shoulder[tw] OR late systolic peak*[tw])

Omron HEM*[tw]

10 or 11

7 and 12

pressure waveform*[tw]

(carotid arteries[mh] OR carotid arter*[tw])

14 and 15

7 and 16

diagnos*[tw]

diagnostic Techniques and Procedures

exp Diagnostic Errors/ all subheadings

exp diagnostic tests, routine/ all subheadings

18 or 19 or 20 or 21

Bland-Altman analys*[tw] OR agreement[tw]

accuracy[tw] or precision[tw] or reliability[tw] or validity[tw]

23 or 24

Validation Studies [Publication Type]

Validation Studies as Topic

26 or 27

22 or 25 or 28

9 or 13 or 17

29 and 30

Final 887 (5th Aug 2011)

Appendix IIC. Methods and Results of Critical Appraisal

Assessment of Methodological Quality/Critical Appraisal

Research papers selected for retrieval were assessed by 2 reviewers for methodological validity prior to inclusion in the review using an original specific critical appraisal tool designed for the review. The critical appraisal tool (Appendix) was developed by consensus based on the critical appraisal criteria used by Craig et al in 2000[175]and 2002[37] as well as appraisal instruments STARD[176] and QUADAS [177]for diagnostic test accuracy. The 2 Craig et al systematic reviews investigated the measurement accuracy of different body temperature measuring methods. Body temperature was the tested continuous variable and the agreement between new and reference standard methods were examined. The appraisal tool for measurement accuracy studies used in these 2 systematic reviews was based on the recommendations for the critical appraisal of diagnostic studies.[178]

Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

Appraisal instruments

Reviewer	Date			
Authors	Year			
Record Number				
Criteria and Rationale for Assessing Methodological Quality of the Method Comparison Study*	Yes	No	No Stated	NA
· Was there clear selection criteria to enroll participants into studies?				
· Were cuff BP measurements performed using validated BP monitors over arms? BP monitors are very popular and un-validated BP monitors produce unreliable and invalid results				
· Were all measurements carried out concurrently or immediately sequentially? Where there is a delay between the two readings, any difference in results could potentially be attributed to a change in actual blood pressure.				
· Was acquisition of waveforms performed by trained professionals? Where there is a statement that the waveform acquisition was performed by professionals who have received training and were experienced in these procedures.				
· Were acquired waveforms examined for its reliability?# Where there is statement reporting the reproducibility of measurements				
· Were the test and reference standard measured independently (blind) of each other? · Were the index test and reference standard interpreted independently?				
· Did patients receive the same reference standard regardless of the index test result? (differential verification)				
· Was the second reading taken before any interventions were given? Avoid treatment paradox				
· Were statistical method appropriately performed?				
· Was the spectrum of patients representative of the patients who will receive the test in practice? External Generalization				
· Was the execution of the index test described in sufficient detail to permit replication of the test?				
· Was the execution of the reference standard described in sufficient detail to permit replication of the test?				
· Were uninterpretable test results reported?				
· Were withdrawals from the study explained?				

*Criteria was graded as yes, no, not stated, or not applicable

Criteria modified specifically for blood pressure

□ Included □ Excluded; Reason _____

Methodological quality

Results of critical appraisal were summarized in the following table

Different degrees of methodological weakness or lack of clear reporting were identified through the critical appraisal of all studies. Only 17 out of 20 studies used clear selection criteria to enroll participants. Only 5 of 9 studies with noninvasive calibration reported measuring cuff BP with validated sphygmomanometers. Most of the studies (21 of 22) performed index and reference measurements concurrently or sequentially without delay. Except for 6 studies in which peripheral waveforms were acquired by direct measurement, only 4 out of 16 studies provided evidence that peripheral pressure waveforms were obtained by trained professionals. Reliability of the acquired waveforms was checked in only 11 studies. None of the studies provided a description of the blinding process or clarified if the index tests and reference standards were measured independently (blinded) of each other. Seventeen out of 22 studies were free from partial and differential verification bias, which indicated that all patients in the studies received the same comparison measurement tests, regardless of initial results. Appropriate statistics to examine agreement between different methods were noted in all but one study after studies with insufficient outcome data were excluded. Because all studies were performed on subjects receiving cardiac catheterization or cardiac surgery, the legitimacy of their external generalization was questioned by both reviewers. Most studies provided enough details for replicating both index tests and methods to conduct reference measurements (20 of 22 and 19 of 22, respectively). Only 3 studies described related treatment for uninterpretable results. Reasons for a subject's withdrawal from measurements were stated in 5 studies.

Table 2-S1. Critical Appraisal of Included Studies

Study		Selection	#Equipment validation	Measurement times	#Trained professionals	#Reliability checking	Blinding	Avoid differential verification	Appropriately statistics	External generalization	Index replication	Reference replication	Reporting	Attrition
Karamanoglu	1993 [16]	N	NA	Y	NA	NA	N	NS	Y	N	Y	Y	NS	NA
Karamanoglu	1996 [40]	N	NA	NS	NS	NS	NS	NS	Y	N	Y	Y	NS	NA
Chen	1997 [19]	N	NA	Y	NS	NS	NS	N	Y	N	Y	Y	Y	NA
Pauca	2001 [41]	Y	NA	Y	NA	Y	NS	Y	Y	N	Y	Y	NS	NA
Van Bortel	2001 [18]	N	NA	Y	Y	NS	NS	Y	Y	N	Y	Y	NS	NA
Soderstrom	2002 [42]	Y	NA	Y	NA	Y	NS	Y	Y	N	Y	Y	NS	NA
Davies	2003 [43]	Y	Y	Y	Y	NS	NS	Y	Y	N	Y	Y	NS	NA
Hope	2003 [44]	Y	NA	Y	NS	NS	NS	Y	Y	N	Y	Y	NS	NA
Cloud	2003 [45]	Y	Y	Y	Y	NS	NS	Y	Y	N	Y	N	NS	NA
Smulyan	2003 [46]	Y	NS	Y	NS	Y	NS	Y	Y	N	Y	Y	NS	NA
Hope	2004 [47]	Y	N	Y	NS	NS	NS	Y	Y	N	Y	Y	NS	NA
Pauca	2004 [20]	Y	NA	Y	NA	Y	NS	Y	Y	N	Y	Y	Y	Y
Hope	2004 [48]	N	NA	Y	NS	NS	NS	Y	Y	N	N	N	NS	NA
Sharman	2006 [49]	Y	NA	Y	NS	Y	NS	Y	Y	N	Y	Y	NS	Y
Takazawa	2007 [21]	Y	NS	Y	NS	Y	NS	NS	Y	N	Y	Y	NS	Y
Hope	2007 [50]	Y	NA	Y	NS	NS	NS	Y	Y	N	Y	Y	NS	NA
Rajani	2008 [51]	Y	Y	Y	NS	Y	NS	Y	Y	N	Y	Y	NS	NA
Hickson	2009 [52]	Y	NA	Y	NS	NS	NS	NS	Y	N	N	N	Y	NA
Cheng	2010 [22]	Y	NA	Y	NA	Y	NS	Y	Y	N	Y	Y	NS	NA
Zuo	2010 [53]	Y	Y	Y	Y	Y	NS	Y	Y	N	Y	Y	NS	Y
Shih	2011 [54]	Y	Y	Y	NA	Y	NS	Y	Y	N	Y	Y	NS	NA
Ding	2011 [55]	Y	NS	Y	NS	Y	NS	Y	N	N	Y	Y	NS	Y

NS = not stated; NA = not applicable; #: Criteria modified specifically for central blood pressure measurement

Selection = clear selection criteria;

Equipment validation = were cuff BP measurements performed using validated BP monitors over arms? (BP monitors are very popular and un-validated BP monitors produce unreliable and invalid results)

Measurement times = were all measurements carried out concurrently or immediately sequentially? (Where there is a delay between the two readings, any difference in results could potentially be attributed to a change in actual blood pressure)

Trained professionals = was acquisition of waveforms performed by trained professionals? (Where there is a statement that the waveform acquisition was performed by professionals who have received training and were experienced in these procedures)

Reliability checking = were acquired waveforms examined for its reliability? (where there is statement reporting the reproducibility of measurements);

Blinding = were the test and reference standard measured independently (blind) of each other? (were the index test and reference standard interpreted independently?)

Avoid differential verification = did patients receive the same reference standard regardless of the index test result?

Appropriate statistics = were statistical method appropriately performed?

External generalization = was the spectrum of patients representative of the patients who will receive the test in practice?

Index replication = was the execution of the index test described in sufficient detail to permit replication of the test?

Reference replication = was the execution of the reference standard described in sufficient detail to permit replication of the test?

Reporting = were reasons or details of uninterpretable test results reported? (N = if data missing but not reported, NS = no report on this issue)

Attrition = were withdrawals from the study explained? (sampling process described and reasons of withdrawals explained, NA = no withdrawal is stated in this study)

Appendix IID. Studies Selected for Retrieval

Adji A, Hirata K, Hoegler S, O'Rourke MF. Noninvasive pulse waveform analysis in clinical trials: similarity of two methods for calculating aortic systolic pressure. *Am J Hypertens* 2007; 20(8):917-922.

Chen CH, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan WL et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure: validation of generalized transfer function. *Circulation* 1997; 95:1827-1836.

Chen CH, Ting CT, Nussbacher A, Nevo E, Kass DA, Pak P et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension* 1996; 27:168-175.

Cheng HM, Wang KL, Chen YH, Lin SJ, Chen LC, Sung SH et al. Estimation of central systolic blood pressure using an oscillometric blood pressure monitor. *Hypertens Res* 2010; 33(6):592-599.

Cloud GC, Rajkumar C, Kooner J, Cooke J, Bulpitt CJ. Estimation of central aortic pressure by SphygmoCor requires intra-arterial peripheral pressures. *Clin Sci (Lond)* 2003; 105(2):219-225.

Davies JI, Band MM, Pringle S, Ogston S, Struthers AD. Peripheral blood pressure measurement is as good as applanation tonometry at predicting ascending aortic blood pressure. *J Hypertens* 2003; 21(3):571-576.

Ding FH, Fan WX, Zhang RY, Zhang Q, Li Y, Wang JG. Validation of the Noninvasive Assessment of Central Blood Pressure by the SphygmoCor and Omron Devices Against the Invasive Catheter Measurement. *Am J Hypertens.* 2011;24:1306-11.

Fetics B, Nevo E, Chen CH, Kass DA. Parametric model derivation of transfer function for noninvasive estimation of aortic pressure by radial tonometry. *IEEE Trans Biomed Eng* 1999; 46(6):698-706.

Guilcher A, Brett S, Munir S, Clapp B, Chowienczyk PJ. Estimating central SBP from the peripheral pulse: influence of waveform analysis and calibration error. *J Hypertens* 2011; 29(7):1357-1366.

Hickson SS, Butlin M, Mir FA, Graggaber J, Cheriyan J, Khan F et al. The accuracy of central SBP determined from the second systolic peak of the peripheral pressure waveform. *J Hypertens* 2009; 27(9):1784-1788.

Hope SA, Antonis P, Adam D, Cameron JD, Meredith IT. Arterial pulse wave velocity but not augmentation index is associated with coronary artery disease extent and severity: implications for arterial transfer function applicability. *J Hypertens* 2007; 25(10):2105-2109.

Hope SA, Meredith IT, Cameron JD. Effect of non-invasive calibration of radial waveforms on error in transfer-function-derived central aortic waveform characteristics*. Clin Sci (Lond)* 2004; 107(2):205-211.

Hope SA, Meredith IT, Tay D, Cameron JD. 'Generalizability' of a radial-aortic transfer function for the derivation of central aortic waveform parameters. *J Hypertens* 2007; 25(9):1812-1820.

Hope SA, Tay DB, Meredith IT, Cameron JD. Comparison of generalized and gender-specific transfer functions for the derivation of aortic waveforms. *Am J Physiol Heart Circ Physiol* 2002; 283(3):H1150-H1156.

Hope SA, Tay DB, Meredith IT, Cameron JD. Use of arterial transfer functions for the derivation of aortic waveform characteristics. *J Hypertens* 2003; 21(7):1299-1305.

Hope SA, Tay DB, Meredith IT, Cameron JD. Use of arterial transfer functions for the derivation of central aortic waveform characteristics in subjects with type 2 diabetes and cardiovascular disease. *Diabetes Care* 2004; 27(3):746-751.

Karamanoglu M, Feneley MP. Derivation of the ascending aortic-carotid pressure transfer function with an arterial model. *Am J Physiol Heart Circ Physiol* 1996; 271(6 Pt 2):H2399-H2404.

Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993; 14:160-167.

Kohara K, Tabara Y, Tomita H, Nagai T, Igase M, Miki T. Clinical usefulness of the second peak of radial systolic blood pressure for estimation of aortic systolic blood pressure. *J Hum Hypertens* 2009; 23(8):538-545.

Munir S, Guilcher A, Kamalesh T, Clapp B, Redwood S, Marber M et al. Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. *Hypertension* 2008; 51(1):112-118.

Pauca AL, Kon ND, O'Rourke MF. The second peak of the radial artery pressure wave represents aortic systolic pressure in hypertensive and elderly patients. *Br J Anaesth* 2004; 92(5):651-657.

Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001; 38(4):932-937.

Rajani R, Chowienczyk P, Redwood S, Guilcher A, Chambers JB. The noninvasive estimation of central aortic blood pressure in patients with aortic stenosis 204. *J Hypertens* 2008; 26(12):2381-2388.

Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J et al. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. *Hypertension* 2006; 47(6):1203-1208.

Shih YT, Cheng HM, Sung SH, Hu WC, Chen CH. Quantification of the Calibration Error in the Transfer Function-Derived Central Aortic Blood Pressures. *Am J Hypertens.* 2011.

Simkus GJ, Fitchett DH. Radial arterial pressure measurements may be a poor guide to the beneficial effects of nitroprusside on left ventricular systolic pressure in congestive heart failure. *Am J Cardiol* 1990; 66(3):323-326.

Smulyan H, Mukherjee R, Sheehe PR, Safar ME. Cuff and aortic pressure differences during dobutamine infusion: a study of the effects of systolic blood pressure amplification. *Am Heart J* 2010; 159(3):399-405.

Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME. Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. *Hypertension* 2003; 42(2):150-155.

Soderstrom S, Nyberg G, O'Rourke MF, Sellgren J, Ponten J. Can a clinically useful aortic pressure wave be derived from a radial pressure wave? *Br J Anaesth* 2002; 88(4):481-488.

Studinger P, Ungi I, Lenard Z, Mersich B, Rudas L, Kollai M. Use of generalized transfer function-derived central blood pressure for the calculation of baroreflex gain. *J Hypertens* 2008; 26(6):1156-1162.

Takazawa K, Kobayashi H, Shindo N, Tanaka N, Yamashina A. Relationship between radial and central arterial pulse wave and evaluation of central aortic pressure using the radial arterial pulse wave. *Hypertens Res* 2007; 30(3):219-228.

Takazawa K, O'Rourke MF, Fujita M, Tanaka N, Takeda K, Kurosu F et al. Estimation of ascending aortic pressure from radial arterial pressure using a generalised transfer function. *Z Kardiol* 1996; 85 Suppl 3:137-139.

Takazawa K, Tanaka N, Takeda K, Kurosu F, Ibukiyama C. Underestimation of vasodilator effects of nitroglycerin by upper limb blood pressure. *Hypertension* 1995; 26(3):520-523.

Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, Vanmolkot FH, Staessen JA, Kragten JA, Vredeveld JW, Safar ME, Struijker Boudier HA, Hoeks AP. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens.* 2001;19:1037-44.

Wei R, Im JJ, Park SH, Jung NS. Estimation of central blood pressure using radial pulse waveform. 2007 *International Symposium on Information Technology Convergence, Proceedings* 2007;250-253.

Westerhof BE, Guelen I, Stok WJ, Lasance HA, Ascoop CA, Wesseling KH et al. Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest. *J Appl Physiol* 2008; 105(6):1858-1863.

Williams B, Lacy PS, Yan P, Hwee CN, Liang C, Ting CM. Development and validation of a novel method to derive central aortic systolic pressure from the radial pressure waveform using an N-point moving average method. *J Am Coll Cardiol* 2011; 57(8):951-961.

Zhang Y, Agnoletti D, Protogerou AD, Wang JG, Topouchian J, Salvi P et al. Radial late-SBP as a surrogate for central SBP. *J Hypertens* 2011; 29(4):676-681.

Zuo JL, Li Y, Yan ZJ, Zhang RY, Shen WF, Zhu DL et al. Validation of the central blood pressure estimation by the SphygmoCor system in Chinese. *Blood Press Monit* 2010.

Appendix IIE. Data Extraction Instruments

Reviewer			Date		
Authors			Year		
Record Number					
Study Method (Design)					
Setting					
Center					
Participants					
	Inclusion Criteria				
	exclusion Criteria				
Recruitment	□	Based on presenting symptoms or other test results			
	□	Others			
Sampling	□	Consecutive enrolled based on defined criteria			
	□	Others methods for further selection:			
Flow Chart	□	No._____ of participants satisfying the criteria for inclusion but not undergoing the study and stated the reason_____			
Country of Study					
Measurement Method					
Data collection	□	Prospective	□	Retrospective	
	□	Trained Professionals executing the noninvasive measurements	□	Trained Professionals executing the invasive measurements	

Number of trained professionals					
	□	Methods for calculating reproducibility			
Study Duration	Year	to	Month	to	
	□	Central BP Measured by Transfer function			
		□	SphygmoCor		
		□	Other methods using TF		
	□	Central BP Measured by Carotid tonometry			
	□	Central BP Measured by SBP2			
	□	Central BP Measured by NPMA method			
□ Cuff BP measured over arms					
	□	Cuff BP measured over wrists			
Type of cuff BP monitor					
Site of cuff BP measured	□	Arm		□	Wrist
Calibration method	□	SBP/DBP □	MBP/DBP □	Other	Other
Number of participants					
Any interval and treatment between	□	Yes	□	No	

invasive and non-invasive tests						
□ External Pressure Catheter	name					
	□	Fluid filled pressure transducer system	damping coefficient			
			resonant frequency			
	□	Radial artery approach				
	□	femoral artery approach				
Population description						
Number of total participants						
age range of participants						
mean age of participants		SD				
BMI		SD				
Arm circumferences		SD				
Proportions (%) of male among participants						
Proportions (%) HTN						
Proportions (%) CAD						

Proportions (%) Type 2 Diabetes Mellitus					
Proportions (%) Dyslipidemia					
Proportions (%) Chronic renal failure					
Proportions (%) Smoking					
Proportions (%) Calcium channel blocker					
Proportions (%) Angiotensin converting enzyme blockade					
Proportions (%) Diuretics					
Proportions (%) Beta-blocker					
Proportions (%) alpha blockade					
Proportions (%) Angiotensin-II receptor blockade					
Proportions (%) Statin					
Proportions (%) antiplatelet agents					
Means of differences					
95% CI					

SD of differences					
Pearson r of correlations					
Means of differences					
95% CI					
SD of differences					
Pearson r of correlations					
Means of differences					
95% CI					
SD of differences					
Pearson r of correlations					
Means of differences					
95% CI					
SD of differences					
Pearson r of correlations					
Means of measurement					
SD of measurement					

95% CI of measurement					
Means of measurement					
SD of measurement					
95% CI of measurement					
Tested Device					
Means of measurement					
SD of measurement					
95% CI of measurement					
Reference Standard					
Means of measurement					
SD of measurement					
95% CI of measurement					
Adverse events					
Subgroup analysis performed for variability	□	yes	□	no	
Author Conclusion(discussion for clinical applicability)					
Comments					

Appendix IIF. Excluded Studies

Fetics B, Nevo E, Chen CH, Kass DA. Parametric model derivation of transfer function for noninvasive estimation of aortic pressure by radial tonometry. *IEEE Trans Biomed Eng* 1999; 46(6):698-706.

Reason for exclusion: Duplicated paper

Hope SA, Tay DB, Meredith IT, Cameron JD. Comparison of generalized and gender-specific transfer functions for the derivation of aortic waveforms. *Am J Physiol Heart Circ Physiol* 2002; 283(3):H1150-H1156.

Reason for exclusion: Duplicated paper

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Reason for exclusion: Incongruent with review inclusion criteria for comparative reference method **(Types of Comparator)**

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Reason for exclusion: Incongruent with review inclusion criteria for measurement methods using applanation tonometry **(Types of Phenomena of Interest)**

Simkus GJ, Fitchett DH. Radial arterial pressure measurements may be a poor guide to the beneficial effects of nitroprusside on left ventricular systolic pressure in congestive heart failure. *Am J Cardiol* 1990; 66(3):323-326.

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Reason for exclusion: Incongruent with review inclusion criteria for outcome of interest. **(Types of outcomes)**

Williams B, Lacy PS, Yan P, Hwee CN, Liang C, Ting CM. Development and validation of a novel method to derive central aortic systolic pressure from the radial pressure waveform using an N-point moving average method. *J Am Coll Cardiol* 2011; 57(8):951-961.

Reason for exclusion: Inconsistent results between their Table 6 and Figure 5 of this article. This study is not included to avoid hampering scientific validity of the review.

Details as below

Potentially serious errors were noted in the small invasive validation study (n = 20). In their Table 6, the mean difference between the oscillometric noninvasive SBP and the invasive central SBP was -7.5 ± 6.2 mmHg (standard error of difference per patient, n = 20), which would equal -7.5 ± 27.7 mmHg [standard deviation; standard error is standard deviation divided by the square root of case number, (n=20)]. In addition, the mean difference between the NPMA-derived noninvasive central SBP and the invasive central SBP was 0.4 ± 6.2 mmHg (standard error), which would equal 0.4 ± 27.2 mmHg (standard deviation). Such a large standard deviation does not match the extremely impressive linear regression and Bland-Altman analysis results in their Figure 5.

Even if 0.4 ± 6.2 mmHg were, in fact, mean ± standard deviation that had been mislabeled as mean ± standard error, a standard deviation of 6.2 mmHg could not

produce the Bland-Altman plot in their Figure 5. The data points of the invasive validation study for the noninvasive application of NPMA scatter around -5 ~ +5 mmHg, well within only 1, not 2 standard deviation boundaries of the limits of agreement.

The data in their Figure 5 shows the average central SBP for each 10-s block (i.e., 10 data points per patient, 200 points in total) for both invasive and noninvasive measurements and give a mean difference of 0.41 ± 2.5 mm Hg (standard error), which would equal 0.41 ± 35.5 mmHg (standard deviation). A mean difference of 0.41 ± 35.5 mmHg would never produce a Bland-Altman plot like that in Figure 5.

Appendix III. Statistical and Technical Details of the Pulse Wave Analysis Approach for the Measurement of Central Aortic Blood Pressure

Table 3-S1. Multiple lineal regression analysis of the non-invasive pulse wave analysis model for direct estimation of PP-C (independent variable)

Parameters included in the final model	Unstandardized regression coefficients	95% CI		p-values	R^2
Pes	0.79	0.42	~ 1.16	<0.001	0.694
As	1.41	0.84	~ 1.97	<0.001	0.123
Ad	0.68	0.12	~ 1.23	0.017	0.001
DBP	-1.16	-1.52	~ -0.81	<0.001	0.055
heart rate	0.84	0.25	~ 1.43	0.006	0.012
All tested covariate in the model	Unstandardized regression coefficients	95%CI		p-values	R^2
SBP	0.22	-0.22	~ 0.66	0.326	0.002
MBP	-0.56	-1.81	~ 0.69	0.377	0
DBP	-0.87	-1.6	~ -0.14	0.02	0.059
SBP2	-0.16	-0.62	~ 0.3	0.478	0.005
Pes	1	0.35	~ 1.66	0.003	0.511
As	1.47	0.77	~ 2.17	<0.001	0.202
Ad	0.64	0.05	~ 1.24	0.035	0.03
heart rate	0.9	0.19	~ 1.62	0.014	0.077

PP-C = central aortic pulse pressure

SBP2 = secondary peak systolic pressure (SBP2) on peripheral pressure waveform

Pes = pressure at onset of diastole, sometimes is referred to as incisura pressure

Ad = areas under the pressure tracing in diastole

As = areas under the pressure tracing in diastole systole

SBP = systolic blood pressure

MBP = mean blood pressure

DBP = diastolic blood pressure

Appendix IV. Subject Recruitment Process of the Validation Report for Microlife WatchBP Office Central

Methodology for central blood pressure measurements built in this standalone central blood pressure monitors[22, 84]

We've successfully developed a novel method exploiting cuff-based pulse wave analysis (PWA) with a multivariate prediction model to estimate central systolic blood pressure (SBP-C).[22] The PWA method involves the identification of parameters relating to wave reflection and arterial compliance[86] on an ensemble-averaged brachial pulse volume plethysmography (PVP) waveform calibrated to cuff systolic (SBP) and diastolic (DBP) blood pressures. The waveform parameters are input variables in the multivariate model, which include secondary peak systolic pressure (SBP2), pressure at onset of diastole (Pes), and areas under the pressure tracing in diastole (Ad) and systole (As).[22] Amplitudes of SBP2 are associated with the magnitude of the reflected pressure wave,[4, 87] and the latter three parameters have been related to arterial compliance.[86] The validity and generalizability of this multivariate prediction model for the non-invasive estimation of SBP-C has been demonstrated in our previous studies.[22, 84]

Conceptually, central pulse pressure (PP-C) can be calculated as below:

$$PP\text{-}C_{PWASBP\text{-}CUFFDBP} = \text{Estimated SBP-C by the PWA method} - \text{cuff DBP}$$

In contrast, in the prototype standalone oscillometric central blood pressure monitor, we directly estimated PP-C (PP-C_{PWAPP}) independently of central SBP or DBP

using a novel PWA noninvasive multivariate prediction model. The noninvasive multivariate prediction model was constructed by stepwise multiple linear regression analysis, which selected the best parameters from the calibrated PVP waveforms of Generation Group.[22] Potential waveform parameters were selected into or removed from the model according to stepping method criteria with F probability less than 0.05 for entry and above 0.10 for removal.

Supplementary Tables:

Numbers of the study subjects recruited into the required categories with different central blood pressure ranges for the Validation Group are shown in Table 4-S1.

Table 4-S1. Screening and recruitment details and measured central blood pressure in each recruitment range in the Validation Group

Total screened number		95	
Total excluded number		10	
Total recruited number		85	
		Number (N = 85)	Percentage, %
At least 10 % of the subjects shall have a systolic blood pressure > 160		16	18.8
At least 10 % of the subjects shall have a systolic blood pressure < 100		9	10.6
At least 10 % of the subjects shall have a diastolic blood pressure > 85		14	16.5
At least 10 % of the subjects shall have a diastolic blood pressure < 70		54	63.5
Central SBP measurements, n = 255	mmHg	Number	Percentage, %
Very low	<90	2	0.8
Low	90–129	108	42.4
Medium	130–160	107	42
High	161–180	34	13.3
Very high	>180	4	1.6
Overall range (low : high), mmHg	83 : 197		
Central DBP measurements, n = 255	mmHg	Number	Percentage, %
Very low	<40	0	0
Low	40-79	202	79.2
Medium	80-100	50	19.6
High	101-130	3	1.2
Very high	>130	0	0
Overall range (low : high), mmHg	41 : 109		

DBP = diastolic blood pressure; SBP = systolic blood pressure.

The magnitude of errors for central and brachial blood pressures measured by the prototype automatic central blood pressure monitor with reference to the tertiles of the invasively measured central blood pressures in the low-, mid-, and high-pressure ranges is shown in Table 4-S2. In contrast to the tendency of overestimation at low central blood pressure and underestimation at high central blood pressure by the noninvasive brachial blood pressures, the non-invasive central blood pressures differed little from the reference invasive central blood pressures in the different central blood pressure categories.

Table 4-S2. Magnitude of band error, subgrouped by the level of measured CBP

CBP	SBP		PP		DBP	
(Estimated - measured CBP)	mean	standard deviation	mean	standard deviation	mean	standard deviation
1st tertile	0.8	3.1	2.2	5.8	2.4	4
2nd tertile	-0.5	2.4	-1	3.9	0.4	3.1
3rd tertile	-1.4	3	-2.5	4.8	-1.4	4.4
Cuff BP	SBP		PP		DBP	
(cuff BP - measured CBP)	mean	standard deviation	mean	standard deviation	mean	standard deviation
1st tertile	0.8	4	0.5	4.9	6.4	6.5
2nd tertile	-1.2	5	-6.2	6.7	2.9	3.4
3rd tertile	-5.7	6.8	-16.8	7.8	0.5	4.1

CBP = central blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; PP = pulse pressure;

Central SBP cutpoints = 1st tertile: <125.8 mmHg; 2nd tertile: 125.8-143.3 mmHg; 3rd tertile: > 143.3 mmHg.

Central PP cutpoints = 1st tertile: <52.2 mmHg; 2nd tertile: 52.2-73.9 mmHg; 3rd tertile: > 73.9 mmHg.

Central DBP cutpoints = 1st tertile: <125.8 mmHg; 2nd tertile: 125.8-143.3 mmHg; 3rd tertile: > 143.3 mmHg.

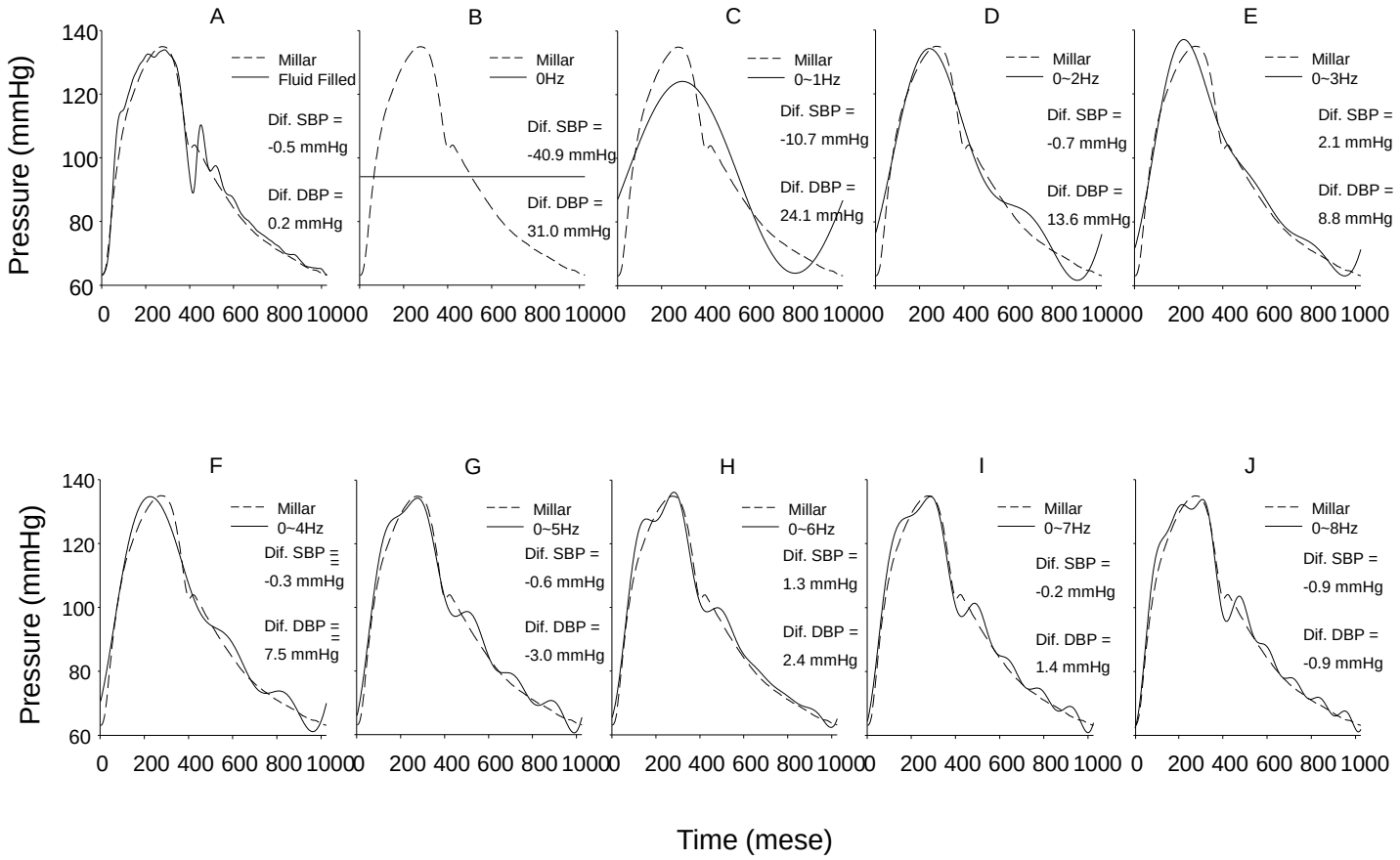

Figure 4-S1: An example of fluid-filled central aortic pressure waveforms in comparison with the simultaneously recorded high fidelity central aortic pressure waveform is shown in Figure S1. This example demonstrates that there are only small differences between the direct blood pressures measured using a fluid-filled and a high fidelity pressure catheters. Only low frequency components (0~4 Hz) of the fluid-filled central aortic pressure waveform are required for the determination of central SBP. More low frequency components (0~8 Hz) of the fluid-filled central aortic pressure waveform are required for the determination of central DBP. **Panel A:** Comparison between the ensemble-averaged central aortic pressure waveforms by a high fidelity catheter-tip Millar catheter and a fluid-filled catheter. Dif SBP = SBP

by fluid-filled catheter – SBP by Millar catheter; Dif DBP = DBP by fluid-filled catheter – DBP by Millar catheter. **Panels B to J**, Fluid-filled central aortic pressure waveforms reconstructed from the low-frequency components are compared with the high-fidelity pressure waveform

Appendix V Hazard Ratios for Cardiovascular Mortality in Relation to Cuff Blood Pressure at Entry in the Validation Cohort

Table 5-S1. Hazard Ratios† for Cardiovascular Mortality in Relation to Cuff Blood Pressure at Entry in the Validation Cohort (n = 2501)

	Total Death	**Cardiovascular Death**	**Stroke Death**
End points, n (%)	185 (7.4%)	34 (1.36%)	18 (0.72%)
Cuff blood pressure			
‡Prehypertension vs. Optimal, hazard ratio (95% confidence interval)	1.26 (0.83–1.92)	0.94 (0.34–2.59)	3.93 (1.07–14.37)
‡Hypertension vs. Optimal, hazard ratio (95% confidence interval)	2.13 (1.35–3.36)	2.22 (0.80–6.18)	0.80 (0.19–3.40)

† Hazard ratios were adjusted for sex, age, body mass index, smoking, and serum lipid levels.

‡Staging was according to the criteria of international standards. [1, 2, 103]

Appendix VI. Risk Adjustment Method for Health Economic Evaluation of the Novel Strategy of Using Non-invasively Measured Central Blood Pressure for Confirming a Diagnosis of Hypertension

Equations for adjusting cardiovascular risk, obtaining from an inaccurate BP measure:

Let

Risk for TP = α

Risk for TN = β

Observed positive 10 year risk = Rh

Observed negative 10year risk = Rn

The following is the basics of diagnostic measures:

P(TP) = sensitivity; where TP = true positive

P(FN) = 1- sensitivity; where FN = false negative

P(FP) = 1- specificity; where FP = false positive

P(TN) = specificity; where TN = true negative

The risk estimated from inaccurate BP measure (cuff BP) can hold the following relations:

$Rh = \alpha \times P(TP) + \beta \times P(FP)$; where Rh = risk of hypertensives

$Rn = \alpha \times P(FN) + \beta \times P(TN)$; where Rn = risk of normotensives

By solving the above equations, we can obtain α and β

Corrected risk for TP: $\alpha = ((Rh+Rn)*\text{specificity}-Rn)/(\text{sensitivity}+\text{specificity}-1)$

Corrected risk for TN: $\beta = (Rh+Rn)*\text{sensitivity}- Rh)/(\text{sensitivity}+\text{specificity}-1)$

Table 7-S1. Cardiovascular risk estimates based on original calculation results with Framingham risk equations and the adjusted risk by equations proposed in the appendix

	Original Risk	Adjusted Risk	
CHD of true normotensive (10years)	0.9-17.5% (age and gender dependent)	0.7-15.1% (age and gender dependent)	Framingham risk equations with risk factor profiles based on HSE 2006[145, 146, 152]
CHD of true hypertensive (10years)	1.7-23.6% (age and gender dependent)	1.9-26.0% (age and gender dependent)	as above
Stroke of true normotensive (10years)	0.3-4.7% (age and gender dependent)	0.2-3.6% (age and gender dependent)	as above
Stroke of true hypertensive (10years)	0.7-11.3% (age and gender dependent)	0.8-12.5% (age and gender dependent)	as above

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