35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

The Barriers to Clinical Application of Non-invasively Obtained Central Blood Pressure*

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Abstract— **With the demonstration of superior prognostic value of central blood pressure (CBP) beyond traditionally used brachial BP, there have been increasing interest in the development of novel devices reporting parameters of CBP. The emerging devices for non-invasive estimation of CBP, based on either tonometry-based or cuff-based techniques, were evaluated with various validation studies. Therefore, the research community and clinicians have been faced with challenges regarding the conduction and interpretation of the validation studies for the non-invasively obtained CBP. We summarize here the barriers to the clinical application of the CBP concept, which provide research opportunities to further the subsequent translation.**

I. Introduction

Given widespread acceptance that waveform morphology and blood pressure (BP) differ considerably between the central aorta and peripheral arteries, it is clear that BP measurements in the peripheral arteries cannot serve as a direct substitute for their central counterpart [1]. 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, in population-based studies [2-4] and hypertension trials [5], to be the better predictor of cardiovascular outcomes than cuff BP. There have been substantial research efforts to develop non-invasive estimating methods for CBP, mainly based on the technique of applanation tonometry [6-8]. Subsequently, the application of the CBP concept has been furthered through the development of the cuff-based techniques for the non-invasive estimation of CBP [9, 10].

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* This work was supported in part by National Science Council (NSC 96-2314-B-010 -035 -MY3), Ministry of Education, Aim for the Top University Plan (96A-D-D131), and a research grant from an Industry-Academia Cooperation between Microlife Co., Ltd., and National Yang-Ming University.

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II. The burgeoning of new CBP devices

A. New challenges on the validation studies

The technical requirement for the noninvasive assessment of CBP has been considerably reduced after the introduction of the novel cuff-based techniques analyzing the oscillometric signals [9]. Such increasing ease rendered by the novel techniques for CBP measurements and their foreseeable application in home BP or even ambulatory BP monitors have led to the burgeoning availability of new devices that report parameters associated with CBP [10]. With the trend of the development of these novel devices, the research community and clinicians have been faced with the challenges in the conduction and interpretation of the validation studies for the accuracy of central BP devices [11]. Although automatic BP monitors are subject to strict validation standards, it remains to be established how to test the measurement accuracy of emerging CBP monitors. It would be prudent to validate the accuracy of the newly developed CBP monitors according to the standards previously defined for the automatic BP monitors. Herein, we summarize the new challenges facing this emerging technology, the “central BP monitors”.

B. Measurement accuracy of non-invasively obtained CBP - a systematic review [12]

To understand the barriers to the application of the CBP concept for the management of hypertension, we performed a systematic review aimed at investigating the measurement accuracy of non-invasively obtained CBP [12]. Studies with adult patients receiving invasive and non-invasive measurements of CBP were meta-analyzed for the agreement between measurements using non-invasive central blood pressure estimating methods compared to invasive corresponding values were considered. After comprehensively searching for all relevant published or unpublished studies and independently assessing the methodological quality of the validation studies, we obtained pooled estimates of systematic and random error from individual study estimates of the mean and standard deviation of differences between the paired measurements. For studies with directly measured peripheral waveforms, or with waveforms calibrated to match invasively obtained aortic

mean blood pressure and diastolic blood pressure, the mean difference of the estimated central blood pressure was small with a mean and standard deviation of difference −1.1±4.1 mm Hg (95% limits of agreement −9.1to 6.9 mm Hg) for central systolic BP (SBP-C). Such calibration procedure is a theoretic practice and used mainly for the proof of concepts. However, the error inflated to −8.2±10.3 mm Hg (−28.4 to 12.0 mm Hg) for SBP-C when the peripheral waveforms were calibrated to cuff BP. The latter calibration procedure is indeed the real world practice. Therefore, current CBP estimating methods are theoretically acceptable with small systematic and random errors according to international standards [13-15]. However, in the real world, there is still substantial room for improvement in measurement accuracy of central BP when cuff BP is used to calibrate the peripheral waveforms.

C. Measurement accuracy of non-invasively obtained central pulse pressure

As shown in Figure 1, the estimation of PP-C by using cuff pulse pressure (PP) was characterized by a proportional systematic bias, the underestimation at high BP and overestimation at low BP, which actually results from the measurement errors of cuff SBP and DBP when referenced to the corresponding invasive BP [12, 16, 17]. As a result, the measurement accuracy for central pulse pressure (PP-C) is particularly vulnerable to the above calibration errors [12, 16].

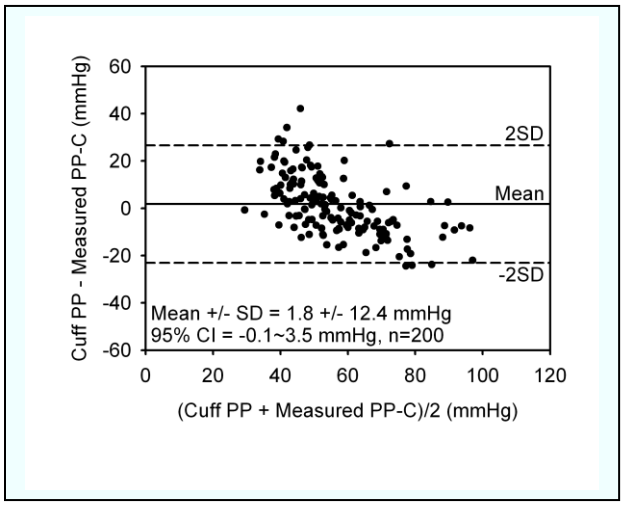

Figure 1. Bland-Altman analysis combining measurements (n = 200) examining the agreement between the invasively measured central aortic pulse pressure (PP-C) and the cuff pulse pressure (PP). Modified from Am. J. Hypertens., 2012, 25, (11), pp. 1162-1169)

Using dual sensor high-fidelity Millar Catheters (model SSD-1059; Millar Instruments, Houston, TX), we obtained invasive central aortic and brachial pressure waveforms simultaneously for constructing a generalized transfer function. We have demonstrated clearly that with the use of a GTF technique to produce estimates of SBP-C and PP-C, the errors are equivalent to those of the oscillometric BP monitor in the estimation of brachial SBP and brachial PP [16, 18], which is proportional to the magnitude of BP [19, 20].

III. Validation Standard for CBP Monitors

As several new technologies for central BP estimation are being developed and require validation, to examine the accuracy of CBP monitors, consensus of the professional society has been requested to format the standardized validation protocols considering the following requirements: [21]

A. Reference standard (comparator):

Choosing the reference standard for the validation studies is a weighty issue. For automatic BP monitors, the reference gold standard is the auscultatory method, Korotkoff sound, to measure arm BP. As for CBP measurement, it might be an acceptable practice to use the most widely used device as a reference comparator given its accuracy is proved. However, since the real gold standard for CBP measurements ought to be invasive BP measurement at ascending aorta, the measurement accuracy of the "surrogate gold standard" measured with any "well-established" devise should be investigated against the invasively measured CBP. As demonstrated in our recent systematic review and meta-analysis [22], the error of the non-invasive central BP measurement by SphygmoCor was −8.2±11.6 mm Hg (95% limits of agreement −30.9 to14.5 mm Hg) for estimating central SBP, −15.4±10.2 mm Hg (−35.3 to 4.6 mm Hg) for central pulse pressure, and 9.3±9.8 mmHg (−9.9 to 28.4 mmHg) for central DBP. Apparently, adopting the CBP estimates as gold standards by SphygmoCor is questionable. In this regard, we suggest using invasive BP as a "true reference standard" and adhering to AAMI's suggestions by conducting the invasive measurement with either a saline-filled catheter or an external pressure transducer with tip in situ [13]. The pressure transducers in the contemporary catheterization laboratories are accurate in pressure measurements, though probably not 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 CBP

monitors, in which high-frequency waveform details, such as inflection points, are of less concern.

B. *Validation process (how many patients and other requirements):*

Except for ESH-IP [14], AAMI [13]and BHS [15] both request 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 shall be made [13]. The device shall 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. Any validation studies should attempt to satisfy the above minimal requirement.

C. *Calculation of errors:*

According to SP10, 2009 [13], the measurement error against intra-arterial BP should be determined as the following process:

"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 shall 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, 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."

This is an easily confusing part and should be clarified that the error-determination using intra-arterial BP as a reference standard is actually different from the traditional method to determine the errors between paired measurements. Further consensus may be required for the validation standards regarding the error-determination process for CBP monitors.

D. *Diagnostic thresholds*

Although BP is continuously distributed, and its relation to cardiovascular risk has been suggested to be continuous [23], clinicians rely on a diagnostic reference range to classify patients as normotensive or hypertensive for further management. Appropriate diagnostic thresholds should be studied to facilitate the clinical application of the new CBP monitors.

IV. Conclusion

With advances in computational science and biomedical engineering, interest in the development of new devices for the noninvasive estimation of CBP has been reignited. We summarized here the barriers and challenges to the clinical application of this new technology. Improved calibration practice, consensus regarding specific protocols, guidelines, and official recommendations for the validation, and diagnostic thresholds for these new CBP monitors are indispensable and urgently demanded.

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