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# The Noninvasive Measurement of Central Aortic Blood Pressure Waveform

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Yang Yao, Lu Wang, Liling Hao, Lisheng Xu,  
Shuran Zhou and Wenyan Liu

Additional information is available at the end of the chapter

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## Abstract

Central aortic pressure (CAP) is a potential surrogate of brachial blood pressure in both clinical practice and routine health screening. It directly reflects the status of the central aorta. Noninvasive measurement of CAP becomes a crucial technique of great interest. There have been advances in recent years, including the proposal of novel methods and commercialization of several instruments. This chapter briefly introduces the clinical importance of CAP and the theoretical basis for the generation of CAP in the first and second sections. The third section describes and discusses the measurement of peripheral blood pressure waveforms, which is employed to estimate CAP. We then review the proposed methods for the measurement of CAP. The calibration of blood pressure waveforms is discussed in the fourth section. After a brief discussion of the technical limitations, we give suggestions for perspectives and future challenges.

**Keywords:** central aortic blood pressure, generalized transfer function, second systolic pressure, N-point moving average, adaptive transfer function, blind system identification, calibration

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## 1. Introduction

For a long time, central aortic pressure (CAP) and brachial artery pressure were considered the same by clinicians. However, blood pressures in the proximal aorta and brachial artery are different due to wave reflection, the systolic blood pressure (SBP), and pulse pressure (BP) increase from the aorta to periphery, while diastolic blood pressure (DBP) and mean artery pressure (MAP) just decrease 1–2 mmHg toward the peripheral arteries [1–3].

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CAP is a better indicator of central hemodynamic stress that is propagated to the peripheral vasculature and target organs, such as the brain and kidneys [4]. Peripheral vasculature and target organs are directly exposed to CAP instead of brachial blood pressure. Measurement of CAP can provide more clinically useful information about cardiovascular system beyond brachial blood pressure. First, recent evidence suggested that CAP may be more strongly related to cardiovascular outcomes [5–15]. For example, central pressure has been shown to have a closer correlation with surrogate measures of cardiovascular disease [6]. Second, CAP responds differently to certain drugs from brachial blood pressure [16–18]. For example, Conduit Artery Function Evaluation (CAFE) which is frequently cited as an example of differential effects of interventions on central and peripheral pressure [16] demonstrated that CAP provides a superior measure of hemodynamic load on the heart and central organs. Besides hypertension, CAP also provides insights into the prevention, diagnosis, and treatment of cardiovascular diseases including coronary artery disease, stroke, myocardial infarction, and heart failure.

Invasive measurement of CAP is considered the “gold standard,” while this method is unsuitable for use in routine screening of large populations or clinical diagnosis. In recent years, there is increasing interest in noninvasive measurement of CAP, evidenced by multiple methods proposed and more and more devices commercialized. This chapter discussed current methodologies and devices for CAP estimation.

## 2. Pulse wave reflection

The arterial tree is made up of dispensable tubes, which transfers the blood from the heart to the periphery. Along these tubes, blood pressure wave, generated by the heart, transmits to the periphery (forward wave) and is reflected back (reflected/backward wave). At different sites along the arterial tree, the forward and reflected waves meet at different times of a cardiac cycle, forming different blood pressure waveforms. This explains the difference in pulse wave contour along the arterial tree. The determinant of the time when the forward and reflected waves meet is the pulse wave velocity (the speed at which the pressure wave transmits in arterial tube). Pulse wave velocity is determined by arterial stiffness, which does not change much in brachial artery with aging or among subjects. This lays the theoretical foundation of using generalized transfer function to estimate aortic pulse wave from radial/brachial pulse wave. Whereas, it does change in central arteries with aging, hypertension, and exercise among subjects, which leads many researchers to seek accurate and practicable adaptive or individualized methods to estimate CAP.

## 3. Methods of pressure wave recording

### 3.1. Applanation tonometry

Applanation tonometry was applied to the measurement of arterial pressure waveforms and has been used ever since. It flattens the arterial wall with a flat pressure sensor, eliminating

the tangential pressures and exposing the sensor to the pressure within the artery [19]. The most widely used device employing this method is the Millar applanation tonometry (Millar Instruments, USA). The applanation tonometry is feasible to accurately record pressure waveforms in the radial artery and carotid artery.

A device using arrayed sensors was used [20–23] and commercialized by Nippon Colin and Omron health statistics companies. The device records all the pressure waveforms detected by the sensors and automatically selects the one with the highest quality. This automatic method makes the ubiquitous measurement of radial blood pressure waveform and estimation of CAP possible. The fixed sensor can reduce the effect of movement produced by the operator, less depending on the operator's skill. In these two cases, the recording is more or less related to the operator's skill, and a reproducibility study is essential for each operator in order to guarantee the measurement quality. The watch-type tonometer developed by BPro (HealthSTATS, Singapore) is expected to enable ambulatory tonometric pressure monitoring.

Note that the pressure measured noninvasively using an applanation tonometry is not identical to that invasively measured. The pressure applied to flatten the arterial wall and compress overlying tissues should be taken into account. The tonometric pressure wave should be calibrated using brachial arterial pressures.

### **3.2. Brachial cuff-based measurements**

More recently, a number of brachial cuff-based devices have appeared to assess CAP. Mobil-O-Graph (I.E.M. GmbH, Germany), Vicorder (Skidmore Medical Ltd., UK), WatchBP (Microlife Corp, Taiwan, China), and BPLab (Petr Telegin, Russia) estimate CAP from the ordinary oscillometric pulse volume recording (diastolic oscillometry) data. In some devices, such as DynaPulse (Pulse Metric Inc., USA), Arteriograph (TensioMed Ltd., Hungary), and BP+ (Uscom Ltd., Australia), supra-systolic brachial cuff plethysmography is used to acquire supra-systolic recordings to estimate CAP. Supra-systolic recordings of oscillometric pulse waveform are made with a cuff pressure above SBP so that the brachial artery is totally occluded. SphygmoCor XCEL and Oscar 2 with SphygmoCor record the blood pressure waveform under sub-diastolic blood pressure. Some devices may offer the advantage of acquiring CAP, ambulatory blood pressure monitoring (ABPM), as well as ambulatory assessment of CAP which may further improve risk stratification. Although some validation studies have been reported, the theoretical validity of the use of a simple cuff as a pressure sensor is not fully understood. Moreover, demonstrative clinical data supporting its accuracy seem to be inadequate. Therefore, the clinical validity of such devices should be evaluated in the future before being used as a clinical tool.

## **4. Methods for central pressure estimation**

The invasive method directly records the blood pressure waveform in the ascending aorta using a pressure-sensing catheter during cardiac catheterization. This method can continuously provide accurate blood pressure waveform and is considered the "gold standard." However, the invasive method is only applicable during catheterization, not appropriate for

routine high-throughput screening of CAP. Recently since the 1990s, noninvasive methods have been introduced and validated for the assessment of central blood pressure. An overview of the related commercial devices is described in **Table 1**.

#### 4.1. Direct method (simple substitution)

Pressure waveforms in the ascending aorta and carotid artery are similar. Carotid pressure is often used as a surrogate measure for CAP [24, 25]. This method directly measures pressure waveform in common carotid artery by applanation tonometry and calibrates the waveform by the mean and diastolic pressure (being identical to that in brachial artery). PulsePen (DiaTecne s.r.l., Italy), Complior Analyze (Alam Medical, France), and NIHem (Cardiovascular Engineering Inc., USA) employ this method.

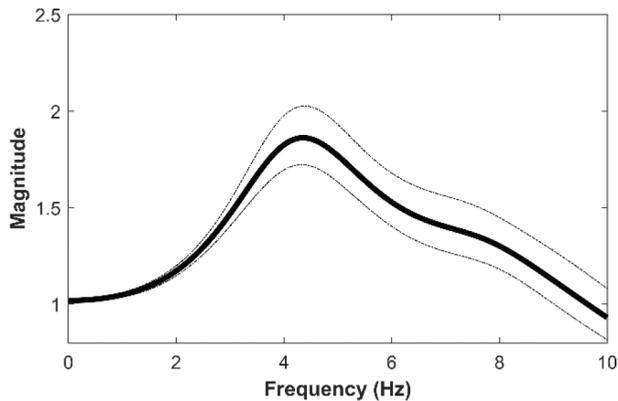
Despite the similarity of the aortic and carotid pulse wave, the amplitude of the augmented pressure wave in the ascending aorta is much higher than that in the carotid artery [19], which affects the calculation accuracy of some cardiovascular parameters like the augmentation index (AI).

#### 4.2. Generalized transfer function (GTF)

This approach assumes that the relationship between central aortic and brachial/radial blood pressure waveforms keeps the same among all subjects (or a set of subjects with similar physiological and pathological characteristics). This relationship is modeled by a generalized transfer function. This generalized transfer function is employed to reconstruct the central pressure waveform from brachial or radial pressure waveform [26, 27]. This is the most well validated [28] and the most widely used method so far. **Figure 1** demonstrates the generalized transfer function produced from 26 subjects. The transfer function is a low-pass filter that compensates for the boost in high frequency components of the pressure waveform as it travels from central aorta to the periphery. This method can provide not only quantitative CAP but also central aortic pressure waveform, allowing further analysis to access more cardiovascular parameters and predict cardiovascular status. The GTF method was first embedded in SphygmoCor (AtCor Medical, Australia), the first device accepted by US Food and Drug Administration (FDA) for the estimation of CAP.

The CAP determined by the GTF method is highly correlated with the brachial pressure used for calibration. Input errors of GTF-brachial pressure values result in a quantifiable effect on its output-CAP. The transfer error by the GTF depends on heart rate and BP levels, which should be taken into account when applying GTF to populations with different hemodynamic conditions [30].

The validity of the GTF method in estimating central arterial pressures was evaluated [28]. The generalizability of GTF has been questioned [31], especially in some special hemodynamic conditions (chronic kidney disease or arterial stiffness) [32]. In addition, not all methods that generate GTFs are equally accurate [33].



**Figure 1.** Frequency response of GTF produced from 26 subjects (the area between the dash-dot lines is the 95% confidence interval) [29].

### 4.3. Second systolic pressure of periphery (SBP2)

Central SBP can be estimated directly from the properly calibrated brachial or radial pressure waveform. The evidences indicate that the reflected wave peak recorded in the periphery approximates to central SBP, since pressure gradients in the arterial system are relatively small during late systole and the late systolic shoulder represents the dominant peak in most adults from midlife onward [34, 35]. Therefore, for older adults, central aortic systolic blood pressure can be calculated [28] via a regression equation employing the second systolic peak as an independent variable [36, 37]. The method is used by Omron HEM-9000AI (Omron Healthcare, Japan), which records the radial pressure waveforms by tonometry, Arteriograph and WatchBP, which calculate central SBP from the brachial cuff pressure.

One drawback of this method is that it does not work when the second peak of a brachial/radial pressure waveform disappears (which often happens in the old or in patients with hypertension or arterial stiffness). The performance of this method in estimating CAP depends on the morphology of brachial/radial pressure waveform [38]. For example, central aortic SBP may be inaccurate in younger individuals with early, non-augmented peak systolic pressure [39]. Besides, this method also suffers the calibration error.

### 4.4. N-point moving average (NPMA)

As mentioned above, the GTF method can be regarded as applying a low-pass filter to the brachial/radial pressure waveform. A simplified approach for assessing CAP is the N-point moving average (NPMA) method, which is a kind of first-order low-pass filter, removing all higher frequency-related pulse wave features, which are typically related to wave reflections,

and, therefore, providing only central aortic SBP instead of aortic blood pressure waveform. This method is also a generalized method as the GTF method does; it suffers the intersubject and intra-subject variability. The accuracy of NPMA cannot be superior to that of GTF method. This method is embedded in BPro device and A-Pulse CASP application software (HealthSTATS, Singapore). It does not provide an estimated central aortic blood pressure waveform.

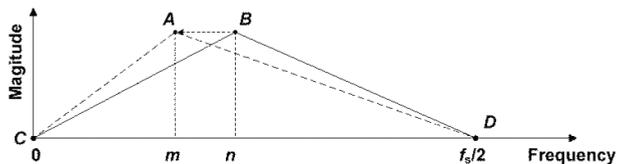
#### 4.5. Adaptive transfer function (ATF)

The fundamental assumption of the GTF method is that the relationship between central aortic and the peripheral pulse waves remains the same in different subjects or in different status of one subject, while, as mentioned before, central arterial stiffness differs with aging, hypertension, or exercise, which changes the relationship between central aortic and brachial/radial pressure waves. Several adaptive transfer function methods were proposed trying to tune the generalized transfer function and derive more reliable CAP [29, 40].

For example, in our previous work, using aortic and brachial pulse waves derived from 26 patients who underwent cardiac catheterization, generalized transfer functions (GTF) were derived based on the autoregressive exogenous model. Then for each individual, the GTF was tuned by its peak resonance frequency, as shown in **Figure 2**. The optional peak resonance frequency for an individual was determined by regression formulas using brachial systolic blood pressure. Another work by Swamy [40] used similar method and validated the method in dogs during multiple interventions.

#### 4.6. Individualized transfer function (ITF)

The GTF method does not account for intersubject or intra-subject variability of the transfer function. Individualized or quasi-individualized methods were proposed in recent years [41–43]. These methods primarily employ a physical transmission line model and focus on the individualization of pulse transit time, which is the main determinant of the aorta-brachial and aorta-radial model. Till now, none of the ITF methods are fully validated by invasive data and unfortunately rarely used in clinical practice [44].



**Figure 2.** Diagram of adaptively adjusting the GTF to the desired ATF. The solid line indicates the GTF, and the dotted line indicates the desired ATF. A and B indicate the peaks of the desired ATF and GTF, respectively. M and n are the peak resonance frequencies of the desired ATF and the GTF, respectively [29].

#### 4.7. Blind system identification (BSI)

The blind system identification (BSI) method reconstructs the input from two or more outputs. In the estimation of central aortic pressure waveform, BSI reconstructs the central aortic pressure waveform based on two peripheral pressure waveforms [45–50]. This method is fully individualized, without the need of measuring or estimating pulse transit time. The main drawback of this method is that it requires extra measurement of peripheral pressure waveforms. The two aorta-periphery models should not be similar in order to provide enough information, which added the inconvenience of clinical application.

### 5. Calibration

The tonometry waveforms in carotid artery are calibrated to MAP and DBP which are similar throughout the arterial system, whereas SBP varies from the proximal artery to the periphery [1–3]. The calibration of tonometry waveforms in carotid artery are calibrated to brachial SBP and DBP. Because of variable amplification of the pressure waveform as it travels from the brachial to the radial recording site, the calibration of the radial waveform with brachial SBP and DBP leads to neglect of brachial-to-radial amplification, which may be sufficiently high to be of practical importance [51–54]. This results in underestimation of radial systolic, mean, and pulse pressure, whereas diastolic pressure is comparable between brachial and radial sites [53, 55]. Since the radial waveform is improperly calibrated, the derived aortic pressure waveform will have systolic, mean, and pulse pressures underestimated. And the difference between central and brachial pressures is overestimated. Thus, incorrect calibration simultaneously underestimates central pressure and overestimates central-to-brachial pressure amplification. In order to decrease calibration errors, the calibration of tonometry waveforms in radial artery with brachial MAP and DBP may be preferable.

The calibration of tonometry waveforms with brachial MAP and DBP also has errors. One error is the inexact MAP obtained. Using brachial blood pressure and a formula to estimate brachial mean pressure is not acceptable because of high variation in the form factor of the brachial pressure waveform which can affect the accuracy of calibration. The maximum amplitude algorithm, which is commonly employed in oscillometric devices to estimate mean arterial pressure, is susceptible to errors that are related to arterial stiffness [56–58]. Another error is related to the inaccuracy of brachial cuff blood pressure used to calibrate which will be inevitably transferred to the resulting CAP.

To sum up, all current methods for estimating CAP are critically dependent on concurrent assessment of conventional peripheral blood pressure for calibration. The brachial blood pressure is used as the source of calibration in all the techniques of estimating CAP. The noninvasive oscillometric blood pressure devices are known to underestimate systolic and overestimate brachial diastolic blood pressure [59, 60]. Estimates of central pressure based on these incorrect estimates of brachial blood pressure will be proportionally confounded. The auscultatory blood pressure, which represents the gold standard measure of peripheral blood pressure, also has error similar to the oscillometric device [61].

## 6. Limitations

### 6.1. Calibration error

Till now, all the available noninvasive methods and devices suffer the calibration error in the estimation of CAP. This means that the performance of these noninvasive methods largely depends on the measurement of peripheral blood pressures [53, 62]. That is why measurements from various methods or devices vary widely. In studies that performed direct comparisons of existing devices, agreement between devices is suboptimal [59, 63, 64]. New noninvasive methods should be introduced to get rid of calibration error, and the accuracy of peripheral blood pressure measurement should be improved.

### 6.2. Lack of CAP-based standard diagnostic criteria

Most standard diagnostic criteria for hypertension are based on brachial blood pressures. However, there are no standard diagnostic criteria available based on CAP. Clinicians should consider providing CAP-based standard diagnostic criteria for hypertension and some other cardiovascular risks.

## 7. Perspectives and future challenges

Central aortic pulse waves contain a vast amount of physiological and pathological information regarding cardiovascular system [65, 66]. Many approaches have been attempted to estimate aortic pressure waveform or CAP noninvasively. However, these techniques are either not fully validated or not accurate enough in estimating CAP compared with the invasive method. Their applications in clinical practice are limited. CAPs derived from different devices are not consistent, making it impossible to substitute for each other clinically. Therefore, these noninvasive methods not only need further improvement but also further clinical validation. There are basically two problems to be solved.

### 7.1. Getting rid of calibration error

As mentioned above, most of the current noninvasive methods suffer calibration error. Novel methods are required to get rid of the calibration error. And the accuracy of current methods for blood pressure measurement should be improved.

### 7.2. Individualized model for estimating central pressure waveform

Both the mathematical models and physical models are mostly used to establish an average model and apply it to each individual. The difference between individuals inevitably brings in error. The parameters of mathematical transfer function have no clear physical meaning. It is not easy to individualize them. One thing we can do is to calculate a transfer function for each specific population with similar physiological status (such as the same gender, the same generation, or those with the same diseases). The physical models are built on the basis of the

mechanical properties of cardiovascular system. The parameters included in the models have a clear physical meaning. Some of them are potentially available via direct measurement or estimation. But many of these parameters are not easily available. In recent years, although some researchers have presented individualized methods, they are either not convenient or do not show much improvement compared with GTF methods. Besides, most of them are not fully validated. Novel convenient individualized method with fully validation is recommended.

## A. Appendices

Device company	Site of record	Method of waveform recording (Sensor)	Method of estimation	Calibration	Invasive validation/ FDA approval
PulsePen DiaTecne s.r.l., Italy	Carotid artery	Applanation tonometry, Single, manual	Simple substitution	Brachial cuff MAP/DBP	[67]/no
Complior Analyse Alam Medical, France	Carotid artery	Applanation tonometry, Single, fixed	Simple substitution	Brachial cuff MAP/DBP	[68]/no
NIHem Cardiovascular Engineering Inc., USA	Carotid artery	Applanation tonometry, Single, manual	Simple substitution	Brachial cuff MAP/DBP	[69]/no
HEM-9000AI Omron Healthcare, Japan	Radial artery	Applanation tonometry Arrayed [40], fixed	SBP2 + regression	Brachial cuff SBP/DBP	[34, 37, 39, 70]/no
BPro+A-Pulse CASP HealthSTATS, Singapore	Radial artery	Applanation tonometry Single, fixed(watch type)	N-point moving average	Brachial cuff SBP/DBP	[71, 72]/yes
Gaon Hanbyul Meditech, Korea	Radial artery	Applanation tonometry Single, fixed	GTF	Brachial cuff SBP/DBP	[73]/no
SphygmoCor CVMS AtCor Medical, Australia	Radial artery	Applanation tonometry Single, manual	GTF	Brachial cuff SBP /DBP	[27, 28, 62, 70, 71, 74–77]/yes
SphygmoCor XCEL AtCor Medical, Australia	Brachial artery	Sub-diastolic brachial cuff plethysmography	GTF	Brachial cuff SBP/DBP	[78]/yes
Oscar 2 with SphygmoCor SunTech Medical, USA	Brachial artery	Sub-diastolic brachial cuff plethysmography	GTF	Brachial cuff SBP/DBP	Yes/yes

Device company	Site of record	Method of waveform recording (Sensor)	Method of estimation	Calibration	Invasive validation/ FDA approval
cBP301 Centron Diagnostics, UK (acquired by SunTech Medical)	Brachial artery	Brachial cuff plethysmography	GTF	Brachial cuff SBP/DBP	[79]/yes
Mobil-O-Graph I.E.M. GmbH, Germany	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff SBP/DBP	[74]/yes
Arteriograph TensioMed Ltd., Hungary	Brachial artery	Supra-systolic brachial cuff plethysmography	SBP2 + regression	Brachial cuff MAP/DBP	[80, 81]/no
Vicorder Skidmore Medical Ltd., UK	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff MAP/DBP	[62, 82]/yes
BPLab Petr Telegin, Russia	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff SBP/DBP	No/no
BP+ Uscom Ltd., Australia (acquire Pulsecor Ltd., Cardioscope II)	Brachial artery	Supra-systolic brachial cuff plethysmography	Physical model Brachial supra-systolic waveform	Brachial cuff SBP/DBP	[83]/no
DynaPulse Pulse Metric Inc., USA	Brachial artery	Supra-systolic brachial cuff plethysmography	Physical model	Brachial cuff SBP/DBP	Yes/yes
WatchBP Microlife Corp, Taiwan, China	Brachial artery	Brachial cuff pulse volume plethysmography	(SBP2, DBP, As, Ad) + regression	Brachial cuff SBP/DBP	[84, 85]/yes
ARCsolver+ VaSera VS-1500 Austrian Institute of Technology, Austria	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff SBP/DBP	Yes/yes

As, area under systolic pressure trace; Ad, area under diastolic pressure trace.

**Table 1.** Statistics and comparison of noninvasive CAP measuring device.

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## Conflict of interest

The authors declare no conflict of interest.

## Author details

Yang Yao<sup>1</sup>, Lu Wang<sup>2</sup>, Liling Hao<sup>1</sup>, Lisheng Xu<sup>1,3\*</sup>, Shuran Zhou<sup>1</sup> and Wenyan Liu<sup>1</sup>

\*Address all correspondence to: [xuls@bmie.neu.edu.cn](mailto:xuls@bmie.neu.edu.cn)

1 Sino-Dutch Biomedical and Information Engineering School, Northeastern University, Shenyang City, Liaoning Province, China

2 School of Computer Science and Engineering, Northeastern University, Shenyang City, Liaoning Province, China

3 Key Laboratory of Medical Image Computing, Ministry of Education, Beijing, China

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