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Basis of Monitoring Central Blood Pressure and Hemodynamic Parameters by Peripheral Arterial Pulse Waveform Analyses*

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Abstract— **In hypertension clinics, central blood pressure (CBP) should be estimated, instead of directly measured, by the "signal processing" of a noninvasive peripheral pressure waveform. This paper deals with the data obtained in our three separate studies focusing on a major estimation method, i.e., radial artery late systolic shoulder pressure (rSBP2)-based CBP estimation.**

***Study 1*: Using a wave separation analysis of precise animal data of pressure wave transmission along the upper-limb arteries, we first demonstrate that pulse pressure amplification is largely attributable to local wave reflection alone.**

***Study 2*: A frequency component analysis of simultaneously recorded human central and radial artery pressure waveforms showed a predominance of lower (1st+2nd) harmonic components in determining the central augmentation peak amplitude. The features of a central pressure waveform, including its phase property, may contribute to the less-altered transmission of augmentation peak pressure to rSBP2.**

***Study 3*: Comparisons of noninvasive rSBP2 with direct or estimated central systolic blood pressure (cSBP) revealed broad agreement but also augmentation-dependent biases. Based on the features of the biases as well as the counterbalanced relationship between pulse pressure amplification and the transmission-induced alterations of augmentation peak amplitude observed in Study 2, we propose an improved cSBP estimate, SBPm, the simple arithmetic mean of rSBP2 and peripheral systolic blood pressure.**

I. Introduction

Recent medical and technical advances have enabled the noninvasive monitoring of central aortic blood pressure (CBP) and hemodynamic parameters. Although several CBP estimation devices using brachial cuff oscillometric pulse waveform recordings have very recently become available, the devices have not yet been fully validated [1, 2]. We will thus discuss mainly the CBP estimation methods based on well-validated radial artery tonometry with a special focus on the basis of the late systolic shoulder pressure in the radial artery (rSBP2) as a CBP estimate, because its mechanism is still unclear and there may be room for improvement.

First we'll position the radial artery pressure waveform analysis in the brief overview of CBP estimation methods as the background of our studies. We'll then report our efforts to elucidate the mechanical basis of central aortic systolic blood pressure (cSBP) estimation using rSBP2.

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II. Background of Our Studies on rSBP2

It is well known that peripheral systolic blood pressure (pSBP) is usually higher than cSBP due to pulse pressure amplification [3, 4]. In the clinical treatment of hypertension, however, this phenomenon has long been ignored, and brachial cuff sphygmomanometric blood pressure (BP) has been used as a reliable alternative to CBP until recently. As we cannot directly access the central aorta noninvasively, CBP should be estimated by some "signal processing" of a noninvasive peripheral pressure waveform that can be regarded as the output signal of the arterial system. The input signal is a central aortic pressure wave, which travels along the arterial tree. Naturally, a generalized pressure transfer function (GTF) of the upper limb arterial tree can be of use to estimate CBP within somewhat limited generalizability [5–7]. This estimation method first became available as the SphygmoCor® device (AtCor Medical, Sydney, Australia). It enabled assessments of CBP in large-scale clinical trials such as the Conduit Artery Function Evaluation (CAFE) study [8]. That study demonstrated a significant difference in the CBP (cSBP)-lowering effects between patient groups treated with different antihypertensive regimens even though peripheral BP levels were comparably lowered, and suggested the superiority of CBP to cuff brachial BP as a cardiovascular prognostic marker in hypertensive patients. The results of the CAFE and other studies [9, 10] reminded clinicians of an undeniable difference between CBP and brachial BP as well as its clinical importance, especially when a patient is treated with vasodilatory antihypertensive drugs (which are frequently prescribed), and the results also facilitated clinical needs to assess CBP. However, the exact mechanism underlying the phenomenon in which pSBP is higher than cSBP, i.e., pulse pressure amplification, is not yet fully understood and has not been demonstrated based on actual data, although a model-based simulation study was performed by Karamanoglu et al. [11].

We therefore investigated detailed pressure wave transmission along the upper-limb arteries in rabbits (Study 1). The animal study was required because it enabled us to acquire highly precise simultaneous measurements of pressure and flow at multiple arterial sites for the wave separation analysis, which has been practically impossible in humans. The peripheral artery size of rabbits allowed the study. The similarity of rabbit arterial pressure waveforms to those of humans are visually evident when temporal scaling is considered (Fig. 1).

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The distal radial artery is currently regarded as an optimal site to obtain precise peripheral pressure waveforms when arterial applanation tonometry is used, because, unlike the other arteries, the radial artery runs shallow beneath the skin and is fixed on the radial bone [1, 2]. The radial artery pressure waveform parameter, rSBP2, has been reported to approximate [12, 13] or closely correlate with central aortic augmentation peak pressure (APP; usually equivalent to cSBP) [2, 14, 15]. rSBP2 has been already used to estimate cSBP in the HEM-9000AI® device (Omron Healthcare, Kyoto, Japan). Although rSBP2 is determined at the second peak time of the 4th derivative of the measured waveform in this device, the mechanism for its validity has never been established based on actual data [2]. In Study 2 therefore, we attempted to elucidate the mechanism responsible for rSBP2 being a close estimate of APP.

The Anglo-Cardiff Collaborative Trial (ACCT), which like some other studies showed that rSBP2 is grossly equivalent to GTF-derived cSBP, pointed out a tendency toward underestimation of cSBP by rSBP2 at lower BP levels [13]. We observed similar findings in clinical data, which led us to propose a simply improved CBP estimate using rSBP2 in Study 3.

III. Our Studies of Radial Artery Pressure Waves

A. Methods

***Study 1*:** In 21 anesthetized rabbits (5 normal and 16 hypercholesterolemic with varied degrees of atherosclerosis), we recorded simultaneous pressure and flow waveforms at the right proximal subclavian artery just after branching from the brachiocephalic artery and the distal site of the ipsilateral brachial artery. Highly precise recordings of pressure and flow waveforms were obtained with a high-fidelity catheter-tipped micromanometer (Mikro-Tip® SPS-320, Millar Instruments, Dallas, TX, USA) and an ultrasonic flowmeter (Transonic Systems, Ithaca, NY, USA) (flat frequency response up to 100 Hz for both devices). Measurements were performed at a basal condition and after the administration of vasoactive agents (angiotensin II 30–40 ng/kg/min, sodium nitroprusside 20–30 μg/kg/min). Finally, 40 data sets were available for the analysis. Pressure waves were decomposed into forward and backward traveling component waves at each measurement site according to Westerhof's method [16] using characteristic impedance determined by a discrete Fourier transformation (DFT)-based impedance analysis.

***Study 2*:** Invasive central aortic (PAo) and tonometric radial artery (PRa) pressure waveforms were simultaneously recorded in 20 patients during cardiac catheterization with step-wise pacing rate alterations to change the extent of augmentation or wave shape. We performed a DFT-based frequency component (for each harmonic) analysis using the final 74 data sets to determine the contribution of each harmonic component to the pressure wave amplitude at specific time points: T1 (radial artery systolic peak timing) and T2 (rSBP2 timing, usually close to the central augmentation peak timing). Since the calibration error relating to the inaccuracy of brachial cuff BP measurement is the common unresolved problem for all CBP estimation methods [2, 17–19], we re-calibrated the noninvasive peripheral (radial) pressure waves to invasive micromanometric mean and diastolic pressures.

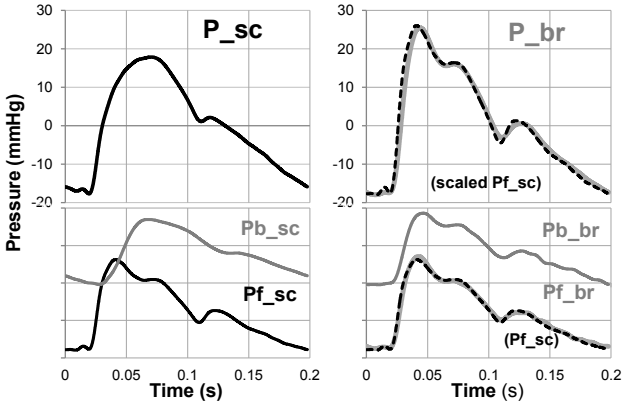

Figure 1. Representative subclavian (P_sc) and brachial (P_br) pressure waves and their forward (Pf) and backward (Pb) component waves in a hypercholesterolemic rabbit.

***Study 3*:** We compared the noninvasively determined radial artery systolic pressure parameters, pSBP and rSBP2, with invasively measured cSBP using the same data as in Study 2. Adding noninvasive PRa data obtained from 30 patients during a pacemaker clinic, we also compared 153 noninvasive rSBP2 data in total with the corresponding GTF-derived cSBP estimates. These comparisons consisted of the Bland-Altman (B-A) plot analysis and its modification, in which the horizontal axis was replaced by radial augmentation index (rAI) to investigate the augmentation dependence of CBP estimation biases.

B. Results and Data Interpretations

***Study 1*:** Fig. 1 shows, in its upper panels, the simultaneously recorded and averaged pressure waveforms measured at proximal subclavian (P_sc) and distal brachial (P_br) arteries in a 12-month-old hypercholesterolemic rabbit. In the lower figure panels, forward (Pf) and backward (Pb) component waves determined at each measurement site are shown. The conduction time delay was eliminated to adjust the upstroke time. In the right lower panel, Pf_sc (superimposed dashed line) and Pf_br seemed nearly identical without any additional modification. This suggests that Pf enters into the subclavian artery from the aorta and travels down to the periphery of the upper limb without large distortion. More interestingly, as shown in the Fig. 1 right

TABLE I. Comparison of Subclavian and Radial Pressure and Component Waves

		Pf_Sc vs. Pf_Br	Pf_Sc* vs. P_Br	P_Sc vs. P_Br
Correlation	**Mean**	0.99	0.98	0.96
	SD	0.01	0.02	0.02
	P**	<0.001	<0.001	
RMSE (mmHg)	**Mean**	1.03	1.79	2.79
	SD	0.49	0.58	0.93
	P**	<0.001	<0.001	

* Pf_sc was scaled so that its RMS became identical to that of P_br.
** Compared to "P_Sc vs. P_Br".

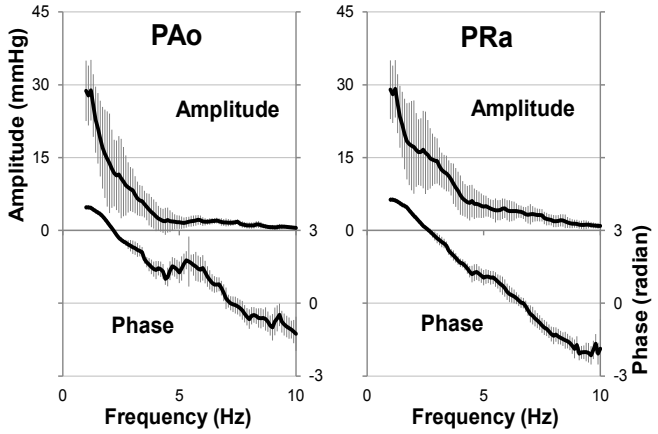

Figure 2. Amplitude and phase properties (mean±SD) of pooled DFT spectra of central aortic (PAo) and radial artery (PRa) pressure waves.

upper panel, an appropriately scaled Pf_sc (dashed line) can be made superimposable on P_br. Reflected Pb_br is also similar to and in-phase with Pf_br as well as time-adjusted Pf_sc.

We evaluated these waveform similarities in all data by determining the correlation coefficients and RMS of differences between the specified waveform pairs (TABLE I). The results were consistent with the typical findings shown in Fig. 1, implying that the forward running component wave (Pf), first determined just after the branching of the subclavian artery from the central aorta, propagates distally being less affected by vascular tapering, progressive stiffening or attenuation, and that Pf determines the peripheral pressure waveform by adding its corresponding backward/reflected wave (Pb) with a negligible time delay. It is of interest that the peripheral (radial in humans) pressure waveform is already determined as a Pf when it enters the proximal subclavian artery just after branching from the aorta/brachiocephalic artery.

More importantly, these findings ultimately suggest that pulse pressure amplification and waveform distortion due to pulse wave propagation are largely attributable to wave reflection at the local arterial periphery. It may also indicate the validity of the "parallel-tube model" proposed by Mukkamala's group [20, 21] as the basis of an adaptive transfer function method for central aortic pressure waveform estimation. That model consists of parallel uniform elastic tubes corresponding to all peripheral arteries instead of a conventional single tapering tube or multi-branched elastic tubes such as anatomical models [11]. The all-parallel tubes arise at the same aortic root rather than the aorta at the branching site, so that a measured arterial site such as the radial artery can be modeled as one of the parallel tubes, in which loss-less transmission and reflection of a pressure wave occur.

TABLE II. HARMONIC COMPONENTS OF CENTRAL AORTIC PRESSURE AT T1 AND T2, AND THEIR CHANGES DUE TO PRESSURE WAVE PROPAGATION

Harmonic #		H1	H2	H3	H4	H5	H6
Frequency (Hz)	**Mean**	1.4	2.8	4.2	5.6	7.0	8.4
	SD	0.2	0.4	0.6	0.8	1.0	1.2
PAo(T1) (%)	**Mean**	63.3	24.7	8.7	3.3	3.6	0.9
	SD	16.9	17.6	9.9	5.5	8.2	4.8
PAo(T2) (%)	**Mean**	79.4	19.3	−3.0	0.8	4.2	1.7
	SD	17.2	15.7	9.9	5.8	4.2	3.3
ΔP(T2) (mmHg)	**Mean**	0.7	−1.1	−2.5	−2.4	−0.6	0.5
	SD	1.7	3.8	2.9	1.7	2.0	1.1
ΔP(T2-T1) (mmHg)	**Mean**	−4.4	6.4	6.6	3.8	1.8	0.8
	SD	3.8	4.9	3.2	2.1	1.9	1.3

TABLE III. DIFFERNCES (BLANT-ALTMAN BIASES) BETWEEN RADIAL ARTERY SYSTOLIC PRESSURE PARAMETERS AND INVASIVE CSBP

cSBP			pSBP-cSBP	rSBP2-cSBP	SBPm-cSBP
Invasive	**Bias** (mmHg)	**Mean**	14.8 [a]	−11.6 [b]	1.6 [c]
		SD	7.9	6.5	3.2
	rAI dependence	**r**	−0.70	0.44	0.42
			p<0.001	p<0.001	p=0.002
		β*	−0.37	0.19	−0.09
GTF-delved	**Bias** (mmHg)	**Mean**	12.7 [d]	−1.4 [e]	5.7 [f]
		SD	5.6	4.4	1.9
	rAI dependence	**r**	−0.76	0.86	−0.11
			p<0.001	p<0.001	ns
		β*	−0.25	0.23	−0.01

* β denotes the regression slope coefficient.
Bias differences between a-b, a-c, b-c, d-e, d-f, and e-f are significant (p<0.001)

***Study 2*:** Fig.2 depicts the pooled DFT-based Fourier transformation spectra of PAo and PRa. The standard deviations (SD) of the phase spectra representing the individual differences are remarkably small (< 5% of 2π) over the lower frequency range up to around 3Hz for both pressure waves. The pulse conduction-induced phase changes (after the simple time delay was eliminated) are small for frequencies <4 Hz as well. Amplifications defined as amplitude differences between PRa and PAo are evident except for lower frequencies up to 1.3 Hz, which corresponds to the first harmonic frequency. An individual harmonic component analysis of PAo showed that the first (H1) plus second (H2) harmonic components at T2 determine >95% of the central augmentation peak amplitude (APA) (TABLE II). For rSBP2, a significant negative correlation was observed between ΔH2+H3 and H4+H5+H6 (r = −0.68; p<0.001; where ΔH2 denotes the pulse conduction-induced change in H2), suggesting a partially counterbalanced relationship between them. These features may contribute to the transmission of APP to rSBP2 with a smaller alteration (ΔP(T2)) due to pressure wave propagation.

***Study 3*:** The results of the B-A biases and their rAI dependence are summarized in TABLE III. rSBP2 shows smaller mean biases than pSBP with invasively measured as well as GTF-derived cSBPs. However, the comparison with invasive cSBP exhibited evident underestimation, as reported

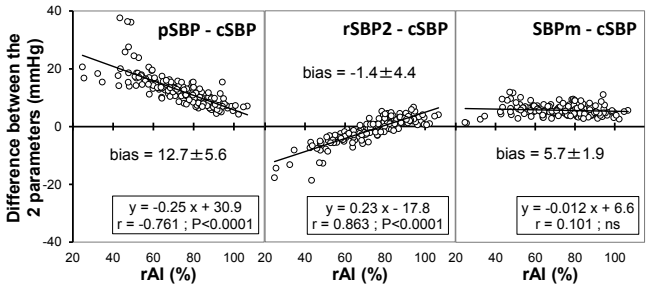

Figure 3. Modified Blant-Altman plot of differences between radial artery systolic pressure parameters and GTF-delived cSBP.

by Hickson et al. [13]. This might be because our invasive study subjects included patients with lower rAI (67.8±17.2% vs. 85.8±13.7%). Fig. 3 shows the modified B-A plot of PRa parameters and GTF-derived cSBP estimates (corresponding to the lower half of TABLE III). As clearly shown in the figure, rSBP2 exhibits systematic biases inversely dependent on the extent of augmentation (rAI), causing the underestimation of cSBP (center panel). This relationship was turned out to be nearly counterbalanced by that of pSBP (left panel). This finding is also consistent with that obtained in Study 2 (TABLE II); i.e., corresponding deviations of wave propagation-induced alterations in harmonic components between APP and rSBP2 (ΔP(T2)) and between APP and pSBP (ΔP(T2−T1) = pulse pressure amplification) seem to be partially counterbalanced. We therefore propose a new improved cSBP estimate named SBPm (the arithmetic mean of rSBP2 and pSBP). As also shown in Fig. 3 (right panel) and TABLE III (right column), the SBPm showed not only a reduction of consistent bias by elimination of its rAI-dependence but also the reduced variance (SD) of biases.

IV. Conclusions

Our data suggest the importance of local pressure wave reflection as the major determinant of peripheral pressure waveform and pulse pressure amplification, whereas a central pressure waveform is largely determined by aortic wave reflection from the systemic reflection sites, which determines APP. Our findings support the modeling of peripheral arteries with uniform elastic tubes with reflection such as the "parallel tube model" [20]. Our frequency component-based characterization of PAo, which is the input signal to a peripheral arterial tree, suggests less altered transmission of central APP to rSBP2. However, the equivalence of APP and rSBP2 is imperfect, the extent of which depends on the augmentation (i.e., systemic reflection) status. Finally, we introduce a simple solution, SBPm, to overcome the imperfectness of rSBP2 as a cSBP estimate based on our findings on pressure wave reflection and propagation.

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