In Silico Validation of Non-Invasive Arterial Compliance Estimation and Potential Determinants of its Variability

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Summary

Arterial compliance (AC) is an important cardiovascular parameter characterizing mechanical properties of arteries. AC is significantly influenced by arterial wall structure and vasomotion, and it markedly influences cardiac load. A new method, based on a two-element Windkessel model, has been recently proposed for estimating AC as the ratio of the time constant τ of the diastolic blood pressure decay and peripheral vascular resistance derived from clinically available stroke volume measurements and selected peripheral blood pressure parameters which are less prone to peripheral distortions. The aim of this study was to validate AC estimation using a virtual population generated by *in silico* model of the systemic arterial tree. In the second part of study, we analysed causal coupling between AC oscillations and variability of its potential determinants – systolic blood pressure and heart rate in healthy young human subjects. The pool of virtual subjects (n=3818) represented an extensive AC distribution. AC was estimated from the peripheral blood pressure curve and by the standard method from the aortic blood pressure curve. The proposed method slightly overestimated AC set in the model but both ACs were strongly correlated ($r=0.94$, $p<0.001$). In real data, we observed that AC dynamics was coupled with basic cardiovascular parameters variability independently of the autonomic nervous system state. *In silico* analysis suggests that AC can be reliably estimated by noninvasive method. The analysis of short-term AC variability together with its determinants could improve our understanding of factors involved in AC dynamics potentially improving assessment of AC changes associated with atherosclerosis process.

Key words

Arterial compliance • Cardiovascular model • Arterial blood pressure • Causal analysis • Volume-clamp photoplethysmography

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Introduction

Arterial compliance (AC) is an important characteristic of the mechanical and structural properties of arterial tree [1,2]. Heart and vessels are anatomically and functionally closely connected resulting in a significant influence of AC on cardiac performance (ventricular-arterial coupling) [3].

AC is defined as a slope of relation between blood pressure and volume in the arterial system. AC can change significantly during aging process. This change results from several mechanisms, including elastin fragmentation, collagen cross-linking alterations and dysfunction of the endothelial and vascular smooth muscle cells [4,5]. In addition, decreased AC is associated with physiological states mostly accompanied by increased sympathetic activity (e.g. cognitive load, orthostasis [5-11]). In the clinical practice, AC or its reciprocal value – arterial stiffness – are used to assess

atherosclerotic process progression with lower AC values indicating more developed atherosclerosis [12,13]. Increased arterial stiffness (or decreased AC) has important pathophysiological consequences: impairment of buffering Windkessel effect on pulsatile blood flow resulting in an increased pulse pressure with its consequences (e.g., increased damage of blood vessels) and an increased speed of pulse wave propagation with a return of reflected pulse wave to the heart during ventricular systole potentially leading to systolic arterial hypertension and an increased cardiac load [1-4,9].

Therefore, it is not surprising that several noninvasive methods for AC estimation were developed during last several years (for review see Svec *et al.* [11]). One of the approaches enabling to estimate AC and its dynamics on a beat-beat basis is a method employing the quantification of diastolic decay of peripheral (brachial artery) blood pressure. Based on the two-element Windkessel model, the rate of this decay is characterized by time constant τ equal to a product of AC and peripheral vascular resistance (PVR). Thus, AC estimation is possible for each heart beat from beat-beat values of time constant τ and PVR. However, this method is limited by the requirement to invasively record a central (aortic) blood pressure curve for time constant τ estimation. This limitation was overcome by the introduction of novel method of τ estimation from the brachial arterial blood pressure curve where only parameters which are known to be robust against distortions due to pulse wave reflections significantly affecting the shape of blood pressure curve are used for τ estimation. As an important advantage, this method is applicable on the peripheral blood pressure curve obtained by volume-clamp photoplethysmographic method [14,15].

Till now, this novel method of time constant τ was verified only on a small group of laboratory animals (swine) [16]. Therefore, the aim of the first part of this study was to verify the preciseness of τ and subsequent AC estimation using time decay method with time constant τ estimated from brachial arterial blood pressure curve. To obtain central and peripheral blood pressure and blood flow curves, *in silico* model of arterial system with preset AC values was used [17]. After verification of AC estimation, the second part of the study was focused on the spontaneous short-term AC variability assessment, including quantification of the strength of causal associations between AC and its potential determinants – heart rate (HR) and systolic blood pressure (SBP). Beat-to-beat AC oscillations were recorded together with basic cardiovascular measures during standardized protocol with supine rest and passive orthostasis phases.

Methods

In silico validation study

Study model

Central (aortic) and peripheral (from brachial artery) blood pressure and blood flow curves were generated by *in silico* one-dimensional (1-D) model of vascular system [17]. Preciseness of the generated model curves (shape of curves and values of parameters derived from these curves, including systolic and diastolic blood pressure, stroke volume) were quantitatively and qualitatively validated against *in vivo* recordings [17,18]. Modelled vascular system was composed from all main arteries including detailed representation of cerebral and coronary circulation finally resulting in 103 arterial segments included in the model. More detailed mathematical description of the model is presented in Reymond *et al.* [17].

Simulations with various preset parameters of the model related to heart and systemic circulation (e.g. vascular geometry – length and cross-sectional area of individual segments, PVR, AC) parameters resulted in a database of virtual subjects (n=3818) with single beat blood pressure and blood flow curves for each segment of modelled vascular system. Modifications of input model parameters were performed by random Gaussian sampling applying data distributions taken from previous human studies [19-23]. Basic cardiovascular measures (SBP, diastolic blood pressure (DBP), mean blood pressure (MBP) and pulse pressure) derived from simulated aortic and brachial artery curves of individual virtual subjects were compared with reference values for normotensive [9] and hypertensive human subjects [24]. Virtual subjects with cardiovascular measures within 99.5 % of confidence interval were used for further analysis. Distribution of modelled cardiovascular parameters are presented in Table 1. Notably, AC values set in the model were distributed in a wide range 0.7-3.6 ml/mm Hg.

Data analysis

Model with set input parameters generated blood pressure and blood flow curves of single heart beat in aorta and brachial artery. Central (aortic) time constant τ_a was derived by standard method from aortic blood

pressure and blood flow curves. Firstly, we used blood flow curve to find a time instant of the diastolic phase onset – we set this time instant as the time when blood flow curve after systolic phase decreased to zero. As the second step, the logarithm of diastolic phase of corresponding blood pressure curve was calculated and its slope was found. Finally, reciprocal value of slope was multiplied by -1 resulting in τ_a value.

Table 1. Cardiovascular parameters distribution in modelled virtual human subjects (n=3818), according to Bikia *et al.* [25].

Parameter	Mean value ± SD
Brachial SBP [mm Hg]	134.5±24.1
Brachial DBP [mm Hg]	77.3±21.3
Brachial PP [mm Hg]	57.2±22.6
Mean BP [mm Hg]	94.5±20.3
Aortic SBP [mm Hg]	122.5±23.7
Aortic DBP [mm Hg]	80.5±21.5
Aortic PP [mm Hg]	42.0±19.4
Stroke volume [ml]	81.2±8.0
Heart rate [bpm]	73.3±14.9
Aortic impedance [mm Hg.s/ml]	0.056±0.012
Systemic AC_{set} [ml/mm Hg]	1.12±0.45
PVR [mm Hg.s/ml]	0.98±0.21
Carotid-femoral PWV [m/s]	8.1±1.0
Carotid-radial PWV [m/s]	10.2±1.3

SD – standard deviation, SBP – systolic blood pressure, DBP – diastolic blood pressure, PP – pulse pressure, BP – blood pressure, AC_{set} – arterial compliance, PVR – peripheral vascular resistance, PWV – pulse wave velocity, bpm – beats per minute.

For estimation of peripheral (brachial) time constant τ_b, we used brachial blood pressure curve applying the method of Arai *et al.* [14]. Estimation of τ_b is based only on parameters which are not influenced by distortion due to pulse wave reflection – cardiac cycle duration (T_i) measured between present diastolic arterial pressure value DBP_i and preceding DBP value (DBP_{i-1}), mean arterial pressure during this cardiac cycle (MBP_i) and time interval from the onset of systolic increase of blood pressure (time instant of DBP_{i-1} occurrence) to the time instant of the immediately following systolic blood pressure peak (indicated as Ts_i) (Fig. 1). Using stroke volume (SV) calculated from central (aortic) blood pressure curve (later in the real data recording for the second part of this study substituted by SV derived from impedance cardiography) and MBP calculated from brachial artery blood pressure curve by integration, we calculated PVR value. As the next step, AC from brachial blood pressure curve (AC_{arai}) was estimated in accordance with two-element Windkessel model as the ratio of time constant τ_b and PVR. Finally, we compared estimated AC values from brachial data (AC_{arai}) with preset AC values (AC_{set}) considering 3818 pairs of values each derived for one virtual subject.

Physiological study – determinants of short-term AC variability

Subjects and study protocol

In the second part of study, a group of 39 healthy volunteers with body mass index in a normal range (22 women, 17 men; age range: 15-25 years, median age: 18.7 years). Exclusion criteria for participation in this study included the presence of cardiovascular (e.g. arterial hypertension), endocrine (e.g. thyroid gland disorders), respiratory (e.g. bronchial asthma) and metabolic diseases (e.g. diabetes mellitus). Participants were instructed not to use substances influencing the autonomic nervous system or cardiovascular system activity for 24 h before the measurement. Female subjects were examined in the proliferative phase (6-13th day) of their menstrual cycle. Examination was performed in a quiet room during morning hours (8-11 am) with a room temperature 22-25 °C.

Participants were positioned on the tilt table (Electric tilt table model 900-00, CNSystems, Austria) with the feet in contact with the footboard at the end of the table and restraining strap secured at the thigh level to provide subject support and safety. The study protocol consisted of two phases: supine rest (15 min, REST), and head-up tilt (HUT, the subject was tilted to 45 degrees on the motor driven tilt table for 8 min to evoke mild orthostatic stress). During the whole measurement, the volunteers were asked to avoid disturbing movements and speaking. There were no signs of presyncope in any subject during the orthostatic challenge. The subjects breathed spontaneously without any effort to control breathing rate or tidal volume. The frequency of breathing in all subjects was in the range of high-frequency oscillations (minimal breathing rates during examination protocol were 0.25 Hz). The study was approved by Ethical Committee of the Jessenius Faculty of Medicine, Comenius University, and all participants provided written informed consent.

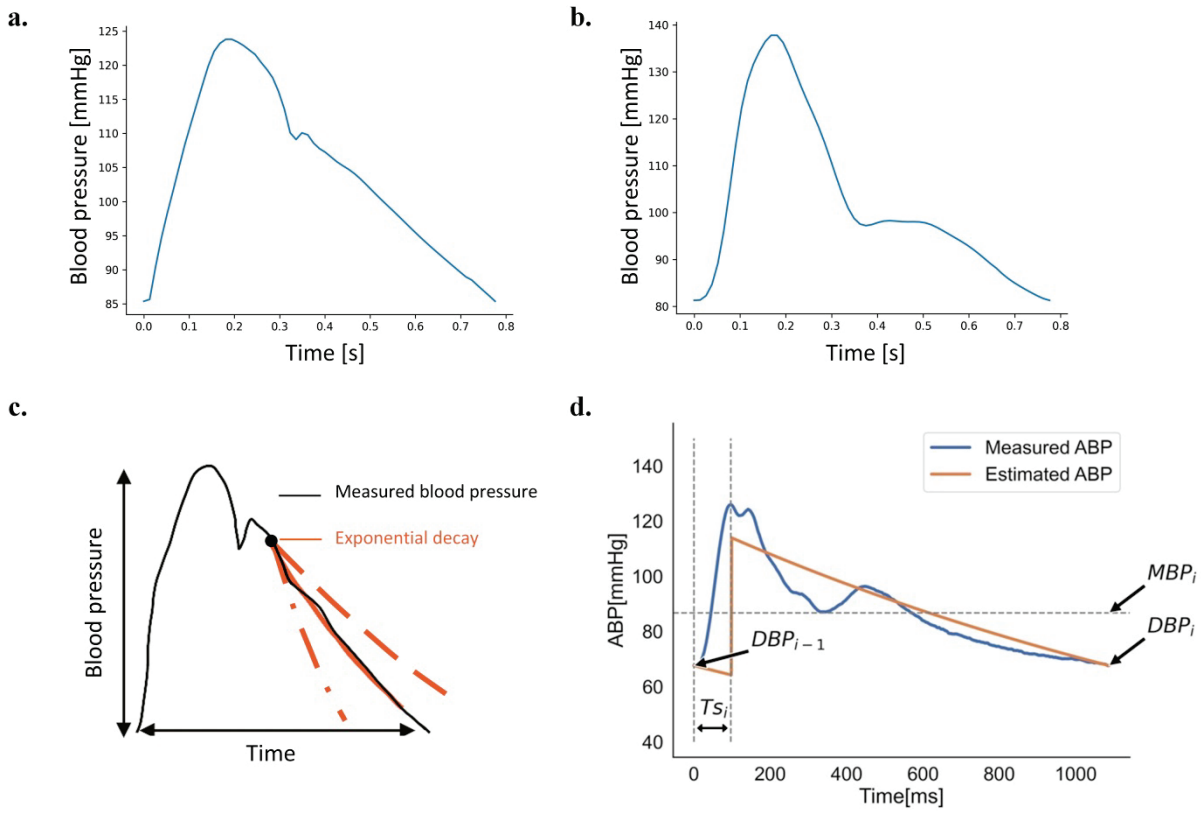

Fig. 1. Examples of aortic (**a**) and brachial artery (**b**) blood pressure curves generated by applied *in silico* model. (**c**): Exponential decay (with indicated starting point) is illustrated by modelled exponential full line curve (in red) fitted to measured blood pressure decay (in black). Its steepness is characterized by time constant τ – from mathematical theory, τ is equal to the time to reach ~37 % of the potential extent of this decay. Furthermore, the effect of varying τ is illustrated – dashed line corresponds to an increased τ value, dash dotted line represents a decreased τ value. In panel (**d**), parameters used for time constant τ estimation from peripheral blood pressure curve are illustrated.

Data recording and cardiovascular parameters estimation

During examination, we simultaneously and non-invasively recorded finger blood pressure curve using volume-clamp photoplethysmography method (device Finometer Pro, FMS Netherlands). This curve was corrected to brachial artery values by calibration procedure employing arm cuff (return to flow calibration procedure). From brachial artery blood pressure curve, parameters (diastolic blood pressure, systolic blood pressure, time constant τ) were estimated using a procedure of Arai *et al.* [14] (Fig. 1d).

To calculate AC from time constant τ, we firstly derived PVR from cardiac output and mean brachial blood pressure. For cardiac output measurement calculated as a product of HR and SV, we used ECG signal from CardioFax ECG-9620 (NihonKohden, Japan) recorded using horizontal bipolar thoracic lead to obtain RR intervals – a reciprocal value of heart rate. For SV measurement, impedance cardiography was used (CardioScreen 2000, Medis GmbH, Germany). Finally, AC was calculated as a ratio of time constant τ and PVR. All recorded signals were digitized at a sampling rate of 1 kHz (PowerLab 8/35, ADInstruments, New Zealand).

From both phases of study protocol, we selected 300 beats long quasistationary segments for each subject. To enable relaxation of the subject at the beginning of first phase and to minimize the effect of transient phase between REST and HUT phases on data analysis, the analyzed segment for REST started 8 min after beginning of this phase, and HUT segment started 3 min after position change.

Assessment of causal relations between AC and other cardiovascular parameters requires a continuous recording of given parameters inside analyzed segment with a minimal number of artifacts. Impedance cardiography is very sensitive to movement artifacts and the resulting signal is also significantly influenced by the contact of electrodes with the body surface of examined person. Due to this limitation, it was not always possible to detect important reference points on impedance cardiography derived curve needed for SV estimation for

all heart beats in the analyzed segment. It resulted in missing AC values. We included to analysis only segments with less than 15 missing AC values and with no more than 3 missing AC values in a row. All missing values in these recordings were substituted by cubic spline interpolation. Recordings not fulfilling above mentioned criteria were excluded from the analysis.

Data analysis

AC variability and causal relations strength was analyzed in frequency domain using a method based on spectral decomposition of autoregressive processes [26,27]. While AC variability was expressed as spectral power (P_S), strength of relation between two time series was quantified as spectral causal coherence (SC) taking values between 0 (no interconnection) and 1 (very strong interconnection). Applying Granger causality concept, SC value was calculated as the last step. Unlike for variability magnitude assessment, where only one time series (in this case AC) is considered to estimate a linear autoregressive model, two time series are used in causality assessment – the source (potential determinant of AC – HR or SBP) and the target time series (AC). Resulting values of P_S and SC were calculated in low frequency (LF; 0.04-0.15 Hz) band only to minimize the effect of ventilation on the assessed parameters. For more detailed description of the spectral decomposition method used to calculate P_S see Sparacino *et al.* [28]. The calculation of SC was described in more detail in Krohova *et al.* [29].

Statistical analysis

Normality of assessed variables distribution was tested by Shapiro-Wilk test. Correlations between analyzed variables in the first part of study (τ_a vs. τ_b; AC_{arai} vs. AC_{set}) were calculated by Spearman correlation coefficient (rho) due to non-Gaussian distribution of all variables. In the second part of the study, we used paired *t*-test or Wilcoxon test (for data with Gaussian and non-Gaussian distributions, respectively) to compare two phases of the examination (REST vs. HUT). Results were considered statistically significant for P values below 0.05.

Results

In silico model – validation of AC method estimation

Time constant τ_b calculated from peripheral modelled curves (values τ_b (mean ± standard deviation (SD))=1.17±0.56 s) underestimated central (aortic) time constant τ_a (1.72±0.84 s; $p<0.001$) but both values were closely correlated ($r=0.98$; $p<0.001$; Fig. 2a). Correlation between these two time constants was closer if τ values were lower (narrower part of scatterplot for lower values of τ indicating faster blood pressure decay). As seen from graph, this part of scatterplot mostly corresponded to virtual subjects with arterial hypertension.

In contrast, AC_{arai} (1.48±0.50) reached higher values compared to AC_{set} (1.12±0.45; $p<0.001$). Both values were strongly significantly correlated ($r=0.94$; $p<0.001$; Fig. 2b). Their mutual relation is characterized by linear function:

$$AC_{set} = 0.84\, AC_{arai} - 0.12 \qquad (1)$$

Similarly to time constants relation, correlation between AC_{set} and AC_{arai} was closer for lower range of values corresponding to virtual subjects with elevated arterial blood pressure.

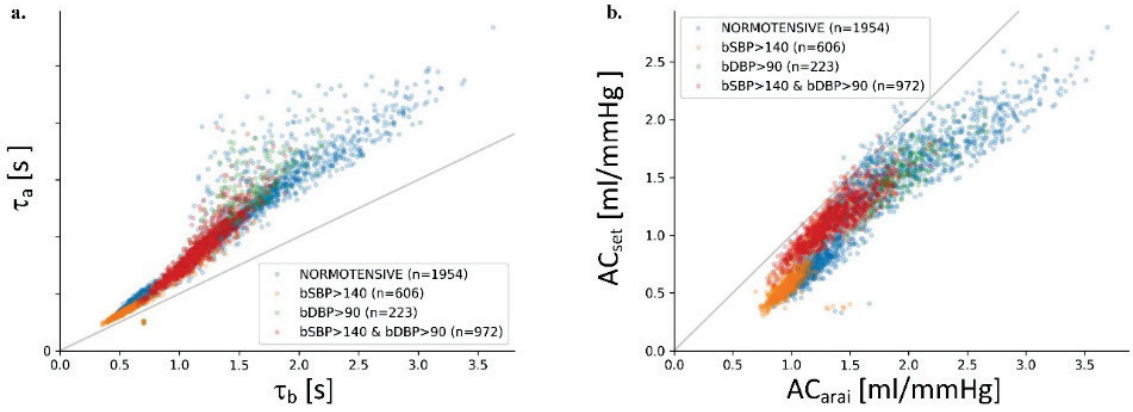

Fig. 2. Scatterplots of relations between assessed parameters – time constant of diastolic blood pressure decay (**a**) and arterial compliance (**b**) derived from central (aorta) and peripheral (brachial) artery of 3818 virtual subjects. Gray line – line of identity. τ_a – time constant estimated from aorta by standard method; τ_b – time constant estimated by novel method of Arai *et al.* [14]; AC_{set} – preset value of arterial compliance for 1-D model of vascular system; AC_{arai} – arterial compliance estimated by two-element Windkessel model using τ_b; bSBP – systolic pressure in brachial artery; bDBP – diastolic pressure in brachial artery.

Short-term AC variability

Mean values of assessed measures (AC, SBP and HR) are illustrated on Figure 3. As a response to passive orthostasis (from REST to HUT), AC and SBP significantly decreased and HR increased.

Figure 4 presents the spontaneous variability of AC in frequency domain (in LF band). We observed a significant increase in LF variability magnitude during HUT.

Spectral coupling strength (SC) between potential determinants of beat-beat AC variability (SBP or HR) and AC was non-zero in majority of subjects (Fig. 5). No significant change in SC (either from SBP to AC, or from HR to AC) was observed as a response to orthostasis.

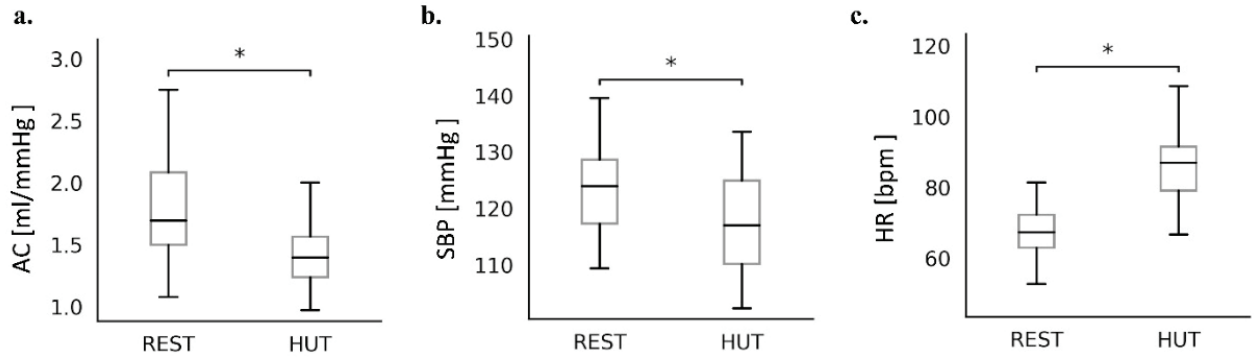

Fig. 3. Box plots (**a**) illustrating mean arterial compliance (AC), (**b**) systolic blood pressure (SBP) and (**c**) heart rate (HR) values during two phases of examination (supine rest – REST and head-up tilt to 45 degrees – HUT); bpm – beats per minute; * indicates significant between phases difference.

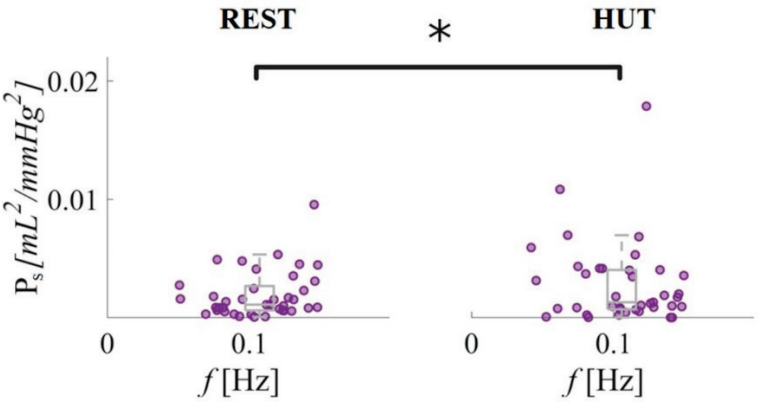

Fig. 4. Spectral power P_s of spontaneous AC oscillations in low frequency band at supine rest (REST) and during head-up tilt (HUT). Each point represent one study participant, *x* coordinate of each point represents a frequency of maximal spectral power; * indicates significant differences between phases in P_s.

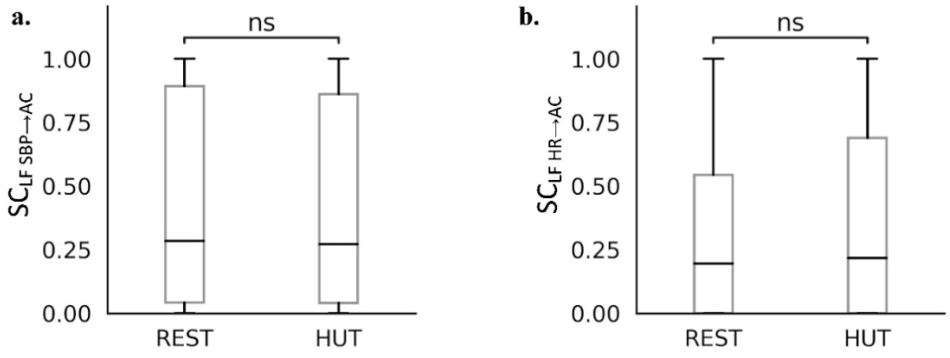

Fig. 5. Box plots representing spectral coupling (SC) in low frequency band (LF) between arterial compliance (AC) and its potential determinants – heart rate (HR) (**a**) and systolic blood pressure (SBP) (**b**). bpm – beats per minute; *ns* indicates non-significant difference between phases.

Discussion

In the first part of study, we tested *in silico* the preciseness of AC estimation from the rate of diastolic blood pressure decay based on two-element Windkessel model. To substitute central blood pressure curve from aorta requiring invasive recording, we used peripheral blood pressure recordable non-invasively by volume-clamp photoplethysmography method calibrated by return to flow method. The time constant τ characterizing blood pressure decay was estimated from this brachial artery blood pressure curve using a method of Arai *et al.* [14] relying only on characteristics with the assumed minimal distortion due to a peripheral measurement site. From brachial artery derived time constant, AC value was calculated by its ratio with PVR. As the standard values for comparison, we used diastolic blood pressure decay time constant τ estimated by standard method from central (aortic) arterial blood pressure curve and preset AC value being one of the input parameters of 1-D *in silico* model of vascular system [17].

Although absolute values of both measures derived from peripheral artery were significantly different from standard values, peripheral artery derived measures were closely correlated with their standard values. It indicates that non-invasively estimated AC values from peripheral (brachial) artery can be used for the analysis of interindividual differences and intraindividual changes in AC. Closer correlation was observed mostly for AC values corresponding to patients with lower compliance pointing towards a possibility to reliably assess changes of AC in patients with arterial hypertension where AC is usually lower. Furthermore, the close correlation indicates the possibility to assess short-term AC changes reflecting various autonomic nervous system states. Indeed, results of previous studies demonstrated the ability of this method to assess short-term changes in AC [11]. This approach allows to estimate time constant τ and AC value for each heart beat separately and to assess their variability potentially reflecting sympathetic vascular control [11,30]. An availability of non-invasively recorded beat-beat AC variability could open a new window to assess interactions between basic hemodynamic variables and vascular characteristics on the beat-beat basis as shown in the second part of this study.

The major limitation of the first part is that data used for verification of novel method of time constant and AC estimation were obtained by computer simulation. However, even if the computer simulation should be considered as a simplified model of vascular system, our results indicate close association between AC estimated from peripheral blood pressure curve and a value set in the model. To validate this method on real data requires invasive recording of central blood pressure curve and so far it was performed only in a pilot study on a small group of swine. Nevertheless, we consider our analysis as a next important step in the process of validation of this method to estimate AC in human.

AC is a dynamical parameter reflecting not only vascular structural properties but it is significantly influenced by other cardiovascular parameters [2,3,11]. As shown in our previous study, the relation between AC and blood pressure can be shifted as a result of the changed autonomic nervous system state [11,31] indicating a significant effect of vasomotion on the short-term changes in AC. To support this concept, our recent study confirmed the presence of 0.1 Hz oscillations in AC often found in vasomotion [30].

To better understand the dynamics of AC variability and to elucidate its further mechanisms, it is important to quantify the effect of other cardiovascular parameters potentially influencing AC. With the introduction of non-invasive beat-beat estimation of AC and after its verification in the first part of this study, it was possible to analyze short-term AC variability and closeness of causal connections between AC and its potential determinants.

We quantified the variability of AC and coupling strength between AC and its potential determinants (SBP, HR). During orthostasis (HUT phase), AC and SBP decreased and HR increased. These observations are in agreement with the baroreflex mediated response – a shift of blood to lower parts of body during passive orthostasis caused blood pressure decrease. Baroreflex response to this change in arterial blood pressure included a decreased parasympathetic activity and an increase in sympathetic activity [32]. It should be stressed that AC decreased despite blood pressure decrease typically associated with AC increase [20]. It indicates the importance of vasomotion in observed AC change independent from blood pressure shift.

Low frequency oscillations in PVR reflect vasomotion in arterioles mediated by sympathetic branch of autonomic nervous system. Their magnitude increased during states characterized by increased sympathetic activity [33]. These oscillations reflect sympathetic control of smooth muscles in arterioles where

norepinephrine kinetics and slow nerve conduction in sympathetic nerves play an important role in their origin [34]. Smooth muscle cells are also present in large elastic arteries significantly influencing AC value on a short-term time scale [35]. Analogically, we assume that observed increase of AC variability in LF band during HUT could be also mediated by sympathetic activity increase.

AC is often considered as an index reflecting structural changes in vessels, most often associated with atherosclerosis. However, this interpretation is complicated by an influence of other parameters – in this context considered as confounding factors. Except above mentioned effect of sympathetic control avoidable by standardization of conditions during measurement (supine rest, relaxed state), effects of blood pressure [36] and heart rate [37] should be also considered.

An importance to analyze given cardiovascular parameter dynamics in the context of other interconnected parameters is stressed by the emergence of new field in physiology – network physiology [38,39]. In this field, the tools of bivariate and multivariate time series analysis are employed to better characterize direct and indirect connections in the whole network of interacting variables [40].

Inspired by this approach, we focused on the quantification of the causal relations strength between AC and its potential determinants: i.e. interactions from heart rate to AC and from SBP to AC. Nonzero values of SC indicate that AC is significantly on a short-term time scale influenced by both SBP and HR. We suggest that these interactions are of mechanical origin demonstrated by their independence on autonomic nervous system state (no significant differences in SC values between REST and HUT phases). Although mechanism of SBP influence on AC is well known – an increased stretch in arterial wall is associated with an increased stiffness [20], the mechanism responsible for an influence of HR on AC is less understood. It is assumed that the time for arterial wall relaxation after ventricular ejection is shorter during tachycardia. Therefore, the arteries are more stretched at the end of diastole resulting in a decreased AC [37].

Conclusions

We verified a method of non-invasive AC estimation based on the peripheral blood pressure curve available to non-invasive recording. Our results employing computer model of vascular system indicate the ability of this method to estimate AC from brachial artery pressure curve. This method of AC estimation enables to assess inter- and intraindividual variations in AC indicating its potential in cardiovascular research and future clinical application. Furthermore, an ability to estimate AC on a beat-beat basis opens a new window to assess interactions between this vascular characteristic and other interconnected variables. It was demonstrated by the presence of spectral coupling between AC and SBP or HR. We suggest that analysis of short-term AC variability together with its determinants could improve our understanding of factors potentially involved in AC dynamics. Quantification of AC in the context of its potential determinants changes will lead to more objective and reliable assessment of long-term changes in AC associated with aging or atherosclerosis process.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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References

1. Klabunde R. *Cardiovascular Physiology Concepts*. Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011, 243 p.
2. Westerhof N, Stergiopulos N, Noble MI, Westerhof BE. *Snapshots of Hemodynamics: An Aid for Clinical Research and Graduate Education*. Springer, 2018, 314 p. https://doi.org/10.1007/978-3-319-91932-4
3. Monge Garcia MI, Santos A. Understanding ventriculo-arterial coupling. Ann Transl Med 2020;8:795. https://doi.org/10.21037/atm.2020.04.10
4. Butlin M, Tan I, Spronck B, Avolio AP. Measuring Arterial Stiffness in Animal Experimental Studies. Arterioscler Thromb Vasc Biol 2020;40:1068-1077. https://doi.org/10.1161/ATVBAHA.119.313861
5. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Cardiol 2007;50:1-13. https://doi.org/10.1016/j.jacc.2006.12.050

6. Hasegawa M, Rodbard S. Effect of posture on arterial pressures, timing of the arterial sounds and pulse wave velocities in the extremities. Cardiology 1979;64:122-132. https://doi.org/10.1159/000170585
7. Huijben AM, Mattace-Raso FU, Deinum J, Lenders J, van den Meiracker AH. Aortic augmentation index and pulse wave velocity in response to head-up tilting: effect of autonomic failure. J Hypertens 2012;30:307-314. https://doi.org/10.1097/HJH.0b013e32834f09ee
8. Matsumura K, Noguchi H, Rolfe P, Yamakoshi T, Matsuoka Y. Differential Effect of Two Mental Stress Tasks on Arterial Stiffness. Japan Psychol Res 2019;61:249-261. https://doi.org/10.1111/jpr.12235
9. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 2005;46:1753-1760. https://doi.org/10.1016/j.jacc.2005.07.037
10. Vlachopoulos C, Kosmopoulou F, Alexopoulos N, Ioakeimidis N, Siasos G, Stefanadis C. Acute mental stress has a prolonged unfavorable effect on arterial stiffness and wave reflections. Psychosom Med 2006;68:231-237. https://doi.org/10.1097/01.psy.0000203171.33348.72
11. Svec D, Czippelova B, Cernanova Krohova J, Mazgutova N, Wiszt R, Turianikova Z, Matuskova L, Javorka M. Short-term arterial compliance changes in the context of systolic blood pressure influence. Physiol Res 2021;70(Suppl 3):S339-S348. https://doi.org/10.33549/physiolres.934838
12. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274:H500-H505. https://doi.org/10.1152/ajpheart.1998.274.2.H500
13. Nagai Y, Helwegen J, Fleg JL, Beemer MK, Earley CJ, Metter EJ. Associations of aortic Windkessel function with age, gender and cardiovascular risk factors. Ultrasound Med Biol 2001;27:1207-1210. https://doi.org/10.1016/S0301-5629(01)00445-8
14. Arai T, Lee K, Stenger MB, Platts SH, Meck JV, Cohen RJ. Preliminary application of a novel algorithm to monitor changes in pre-flight total peripheral resistance for prediction of post-flight orthostatic intolerance in astronauts. Acta Astronautica 2011;68:770-777. https://doi.org/10.1016/j.actaastro.2010.10.008
15. Svec D, Javorka M. Noninvasive arterial compliance estimation. Physiol Res 2021;70(Suppl 4):S483-S494. https://doi.org/10.33549/physiolres.934798
16. Arai T, Lee K, Cohen R. A novel algorithm to continuously monitor change of total peripheral resistance using peripheral arterial blood pressure values for prediction of orthostatic intolerance. *Proceedings of the International Astronautical Congress Glasgow,* 2008.
17. Reymond P, Merenda F, Perren F, Rufenacht D, Stergiopulos N. Validation of a one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol 2009;297:H208-H222. https://doi.org/10.1152/ajpheart.00037.2009
18. Reymond P, Bohraus Y, Perren F, Lazeyras F, Stergiopulos N. Validation of a patient-specific one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol 2011;301:H1173-H1182. https://doi.org/10.1152/ajpheart.00821.2010
19. Devereux RB, de Simone G, Arnett DK, Best LG, Boerwinkle E, Howard BV, Kitzman D, ET AL. Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons >/=15 years of age. Am J Cardiol 2012;110:1189-1194. https://doi.org/10.1016/j.amjcard.2012.05.063
20. Langewouters GJ. *Visco-elasticity of the Human Aorta in Vitro in Relation to Pressure and Age*. Krips Repro, 1982, 221 p.
21. Lu Z, Mukkamala R. Continuous cardiac output monitoring in humans by invasive and noninvasive peripheral blood pressure waveform analysis. J Appl Physiol (1985) 2006;101:598-608. https://doi.org/10.1152/japplphysiol.01488.2005
22. Segers P, Rietzschel ER, De Buyzere ML, Stergiopulos N, Westerhof N, Van Bortel LM, Gillebert T, Verdonck PR. Three- and four-element Windkessel models: assessment of their fitting performance in a large cohort of healthy middle-aged individuals. Proc Inst Mech Eng H 2008;222:417-428. https://doi.org/10.1243/09544119JEIM287
23. Wolak A, Gransar H, Thomson LE, Friedman JD, Hachamovitch R, Gutstein A, Shaw LJ, ET AL. Aortic size assessment by noncontrast cardiac computed tomography: normal limits by age, gender, and body surface area. JACC Cardiovasc Imaging 2008;1:200-209. https://doi.org/10.1016/j.jcmg.2007.11.005

24. Bordin Pelazza B, Filho SRF. Comparison between Central and Brachial Blood Pressure in Hypertensive Elderly Women and Men. Int J Hypertens 2017;2017:6265823. https://doi.org/10.1155/2017/6265823
25. Bikia V, Rovas G, Pagoulatou S, Stergiopulos N. Corrigendum: Determination of aortic characteristic impedance and total arterial compliance from regional pulse wave velocities using machine learning: an in silico study. Front Bioeng Biotechnol 2024;12:1345502. https://doi.org/10.3389/fbioe.2024.1345502
26. Baselli G, Porta A, Rimoldi O, Pagani M, Cerutti S. Spectral decomposition in multichannel recordings based on multivariate parametric identification. IEEE Trans Biomed Eng 1997;44:1092-1101. https://doi.org/10.1109/10.641336
27. Pernice R, Sparacino L, Nollo G, Stivala S, Busacca A, Faes L. Comparison of frequency domain measures based on spectral decomposition for spontaneous baroreflex sensitivity assessment after Acute Myocardial Infarction. Biomed Signal Process Control 2021;68:102680. https://doi.org/10.1016/j.bspc.2021.102680
28. Sparacino L, Pernice R, Barà C, Švec D, Javorka M, Faes L. Spectral analysis of the beat-to-beat variability of arterial compliance. *2022 12th Conference of the European Study Group on Cardiovascular Oscillations (ESGCO)*. 9-12 Oct 2022. https://doi.org/10.1109/ESGCO55423.2022.9931352
29. Krohova J, Faes L, Czippelova B, Pernice R, Turianikova Z, Wiszt R, Mazgutova N, Busacca A, Javorka M. Vascular resistance arm of the baroreflex: methodology and comparison with the cardiac chronotropic arm. J Appl Physiol (1985) 2020;128:1310-1320. https://doi.org/10.1152/japplphysiol.00512.2019
30. Sparacino L, Antonacci Y, Bara C, Svec D, Javorka M, Faes L. A method to assess linear self-predictability of physiologic processes in the frequency domain: application to beat-to-beat variability of arterial compliance. Front Netw Physiol 2024:4:1346424. https://doi.org/10.3389/fnetp.2024.1346424
31. Nardone M, Incognito AV, Millar PJ. Evidence for Pressure-Independent Sympathetic Modulation of Central Pulse Wave Velocity. J Am Heart Assoc 2018;7:e007971. https://doi.org/10.1161/JAHA.117.007971
32. O'Leary DD, Kimmerly DS, Cechetto AD, Shoemaker JK. Differential effect of head-up tilt on cardiovagal and sympathetic baroreflex sensitivity in humans. Exp Physiol 2003;88:769-774. https://doi.org/10.1113/eph8802632
33. Javorka M, Czippelova B, Turianikova Z, Lazarova Z, Tonhajzerova I, Faes L. Causal analysis of short-term cardiovascular variability: state-dependent contribution of feedback and feedforward mechanisms. Med Biol Eng Comput 2017;55:179-190. https://doi.org/10.1007/s11517-016-1492-y
34. Janssen BJ, Malpas SC, Burke SL, Head GA. Frequency-dependent modulation of renal blood flow by renal nerve activity in conscious rabbits. Am J Physiol 1997;273:R597-R608. https://doi.org/10.1152/ajpregu.1997.273.2.R597
35. Stergiopulos N, Westerhof N. Determinants of pulse pressure. Hypertension 1998;32:556-559. https://doi.org/10.1161/01.HYP.32.3.556
36. Cohen J, Pignanelli C, Burr J. The Effect of Body Position on Measures of Arterial Stiffness in Humans. J Vasc Res 2020;57:143-151. https://doi.org/10.1159/000506351
37. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. Hypertension 2002;39:1083-1087. https://doi.org/10.1161/01.HYP.0000019132.41066.95
38. Ivanov PC. The New Field of Network Physiology: Building the Human Physiolome. Front Netw Physiol 2021;1:711778. https://doi.org/10.3389/fnetp.2021.711778
39. Ivanov PC, Liu KKL, Bartsch RP. Focus on the emerging new fields of Network Physiology and Network Medicine. New J Phys 2016;18:100201. https://doi.org/10.1088/1367-2630/18/10/100201
40. Charleston-Villalobos S, Javorka M, Faes L, Voss A. Editorial: Granger causality and information transfer in physiological systems: basic research and applications. Front Netw Physiol 2023;3:1284256. https://doi.org/10.3389/fnetp.2023.1284256