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Maģistrālo artēriju fotopletizmogrāfija un tās pielietojumi hemodinamiskā stāvokļa raksturošanai

Conduit Artery Photoplethysmography and its Applications in the Assessment of Hemodynamic Condition.

Zinātnisko publikāciju kopa

Scientific papers

Rīga, 2015

Anotācija

Promocijas darbā ir izstrādāta maģistrālo artēriju fotopletizmogrāfijas metode artēriju pulsāciju optiskam pierakstam, arteriālo hemodinamisko parametru novērtējumam.
Secīgos pilota pētījumos izstrādāts pulsāciju reģistrācijas protokols, un veikti mēriekārtu/metodiskie uzlabojumi, kas nodrošina stabilu un noturīgu fotopletizmogrāfijas signāla pierakstu. Demonstrēta iespēja iegūt arteriālo elasticitāti raksturojošus parametrus, izmantojot fotopletizmogrāfijas signālu laika aizkaves (pulsa viļņa izplatīšanās laiks) unilaterālā gultnē un fotopletizmogrāfijas signāla formas (atvasinājuma un Gausu aproksimācijas parametri) analīzi. Pretstatot referentām elasticitātes novērtējuma metodēm, parādīts maģistrālo artēriju fotopletizmogrāfijas potenciāls patstāvīgā diagnostiskā pielietojumā.
Izstrādāts artēriju fotopletizmogrāfijas reģistrācijas standartizācijas paņēmiens, kas, vadoties pēc transmurālā artērijas spiediena, mērījuma reāllaikā norāda uz optimālo sensora piespiedienu. Šis paņēmiens validēts pētot ārēji izraisīto faktoru (sensora piespiediena spēks) un iekšēju hemodinamisko stāvokļu (perifērā vaskulārā pretestība) maiņas ietekmi uz femorālā artērijā reģistrēta fotopletizmogrāfijas signāla formas parametriem.
Veikta artēriju fotopletizmogrāfijas pielietojuma validācija asinsrites fizioloģijā – maģistrālo artēriju vazomociju detektēšanā un preklīniskā pētījumā septiskiem intensīvās terapijas pacientiem. Rezultāti demonstrē fotopletizmogrāfijas metodes jutību un atbilstību klīniskiem pielietojumiem.
Izstrādāts arteriālās pulsācijas formas parametrizācijas paņēmiens, kas saista fizioloģiskās pulsa komponentes ar aproksimācijas modeļa komponentēm.
Galvenie rezultāti prezentēti 5 starptautiskās konferencēs, un publicēti 8 zinātniskie raksti recenzētos nozares izdevumos, no tiem 4 - žurnālos ar aprēķinātu impaktfaktoru.

Atslēgas vārdi: maģistrālā artērija, fotopletizmogrāfija, arteriālā elasticitāte, metodes standartizācija, pulsa formas kvantifikācija, vazomocija, sepse

Abstract

The doctoral thesis features the development of a conduit artery photoplethysmography technique for an optical recording of arterial pulsations and the evaluation of arterial hemodynamic parameters.
Consecutive pilot studies have developed a wave registration protocol and methodical improvements as well as improvements of measuring equipment that ensure a stable and consistent recording of photoplethysmography signal. The work demonstrates the possibility to receive parameters characterizing the arterial stiffness by using photoplethysmography signal in a unilateral vascular bed by means of pulse time delay (time of pulse wave propagation) and the analysis of the photoplethysmography waveform (derivation and Gaussian approximation parameters). Contrasting referent methods of arterial stiffness evaluation demonstrates the potential of conduit artery photoplethysmography in a constant diagnostic application.
In this work a technique for arterial photoplethysmography registration standardization was developed which, based on the transmural arterial pressure, points at the optimal sensor push. This technique was validated by studying the impact of alteration of externally induced factors (probe contact force) and internal hemodynamic conditions (peripheral vascular resistance) on the photoplethysmography waveform parameters registered in the femoral artery.
The arterial photoplethysmography application's validation in blood circulation physiology was performed in detecting conduit artery vasomotions and a pre-clinical trial for intensive therapy patients. The results demonstrate the sensitivity of arterial photoplethysmography method and its conformity with clinical applications.
An arterial waveform parameterization was developed relating the physiological wave components with components of approximation model.
The main results are presented in 5 international conferences and 8 scientific articles are published in peer-reviewed publishings. 4 of these were featured in journals with an impact factor.

Keywords: conduit artery, photoplethysmography, arterial stiffness, method standardization, waveform parametrization, vasomotion, sepsis

Promocijas darbā iekļauto publikāciju saraksts

List of scientific papers included in the Thesis

P1 Effect of probe contact pressure on the photoplethysmographic assessment of conduit artery stiffness, Grabovskis A., Marcinkevics Z., Rubins U., Kviesis-Kipge E., J. Biomed. Opt., 0001;18(2), 2013, (10.1117/1.JBO.18.2.027004) (IF=3.66)

P2 Two-Stage Multi-Gaussian Fitting Of Conduit Artery Photoplethysmography Waveform During Induced Unilateral Hemodynamic Events, J. Biomed. Opt., 035001;20(3), 2015, (10.1117/1.JBO.20.3.035001) (IF=3.66)

P3 Aortic stiffness in patients with early sepsis, S. Kazune, A. Grabovskis, E. Strīke and I. Vanags, Critical Care, 18(1) p:136, 2014, (10.1186/cc13326) (IF=5.04)

P4 Bilateral difference of superficial and deep femoral artery haemodynamic and anatomical parameters, Z. Marcinkevics, Z. Lukstina, U.Rubins, A. Grabovskis, J.I. Aivars, Artery Research, 7(3)201:10, 2013, (10.1016/j.artres.2013.09.001) (H=11)

P5 Assessment of conduit artery vasomotion using photoplethysmography, K. Kanders, A. Grabovskis, Z. Marcinkevics, J.I. Aivars, Proc. SPIE 9032, 90320L, 2013, (10.1117/12.2044705)

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P8 Usability of photoplethysmography method in estimation of conduit artery stiffness, A.Grabovskis, Z.Marcinkevics, Z. Lukstina, M.Majauska, J.I. Aivars, V. Lusa and A.Kalinina, Proc SPIE, Vol. 80900X, 2011, (10.1117/12.889801)

Journal of Biomedical Optics

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Effect of probe contact pressure on the photoplethysmographic assessment of conduit artery stiffness

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Effect of probe contact pressure on the photoplethysmographic assessment of conduit artery stiffness

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Abstract. Currently, photoplethysmography (PPG) is a frequently studied optical blood pulsation detection technique among biophotonic and biomedical researchers due to the fact that it shows high potential for estimating the arterial stiffness (AS). The extraction of diagnostically useful information requires standardized measurement procedure with good repeatability. However, the effects of a crucially important factor—the optimal contact pressure (CP) of the probe—are often ignored. Also, CP values are not reported to evaluate those effects. It is hypothesized that AS estimated from PPG pulse wave 2nd derivative parameter b/a is strongly inconsistent when recorded at nonoptimal probe CP. Our pilot study confirmed this during *in vivo* PPG recordings from conduit artery sites on five healthy subjects at variable probe CP (0 to 15 kPa) by using 880 nm reflectance type sensor, force transducer, and PPG alternating current (AC) signal pulse area derived optimal CP criterion. The b/a values, calculated from PPG with variable CP, showed variation >300 percent. In contrast, at the optimal CP, the b/a showed high repeatability (coefficient of variability <5 percent). The effect has been explained with exponential pulse pressure-volume relationship model which indicates the optimal CP range. © *2013 Society of Photo-Optical Instrumentation Engineers (SPIE)* [DOI: 10.1117/1.JBO.18.2.027004]

Keywords: arterial photoplethysmography; arterial stiffness; probe contact pressure; transmural pressure.

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1 Introduction

Inadequate alterations of arterial stiffness (AS) are known to be a timely, determinable indicator of endothelial dysfunction.[1] AS is a term widely used by clinicians to describe the elastic properties of the arterial wall and is directly proportional to the Peterson modulus.[1,2] Recent studies demonstrate that the stiffness of the conduit arteries is recognized as an important contributor to the development of cardiovascular disease as well as an independent predictor of cardiovascular morbidity and mortality, which includes hypertension and end-stage renal disease in general population.[3–5] The noninvasive assessment of AS consists of three main approaches, which include pulse wave velocity (PWV) measurement, pulse pressure or blood flow waveform analysis, and distensibility measurements of arterial pressure and diameter.[6] Photoplethysmography (PPG) is a simple, and promising, optical method for the stiffness evaluation using the signal pulse wave contour analysis and aforementioned PWV approaches even though the optical collection of reliable physiological information from the conduit arteries is still a challenging and controversial issue. There are a limited number of papers related to this technique.[7–10] The oldest, and most investigated, method for stiffness assessment is the PWV determination as it was suggested to be the gold standard.[11] However, this seemingly reliable method has many disadvantages such as the requirement of recording from two distant arterial sites, the lack of a precise definition to what constitutes the foot of the waveform and errors in the calculation of the path length between the optical probes. Moreover, PWV, itself, is sensitive to changes in heart rate (HR), blood pressure, and to the small changes in the arterial wall properties which may not be detected between individuals as the data generated can often show a considerable scatter for a given age range.[12–14] The other way to determine the optical measurement of AS is to use the pulse waveform derived parameters such as reflection and augmentation indexes. Still, many authors have a controversial opinion about the use of these indexes in the assessment of AS.[6,15] The promising, and comparatively new, AS characterizing index is the b/a ratio which is computed from the PPG AC pulse wave 2nd derivative peaks, a and b, as shown in Fig. 1. Proposed by Hashimoto et al., this index demonstrates a good correlation with AS changes altered by age, hypertension, and other vascular risk factors, and have been proven in many other studies.[16–19] However, there are reports of PWV and b/a indicating atherosclerotic alterations differently, yet providing valuable information concerning vascular modifications of aging.[20] Due to apparent simplicity of the measurement and commercially available equipment, the majority of published optical AS assessment studies shows the tendency to use the PPG by applying the probes on the fingertips and ear lobes, the diffuse and arterio-venous anastomoses rich vascular beds which are largely influenced by local temperature changes and sympathetic nervous system.[21–24] In contrary, few papers describe the procedure of AS assessment from superficial conduit arteries using PPG technique.[7,19] Hence, the lack of standardization in the PPG recording procedure and, particularly, in

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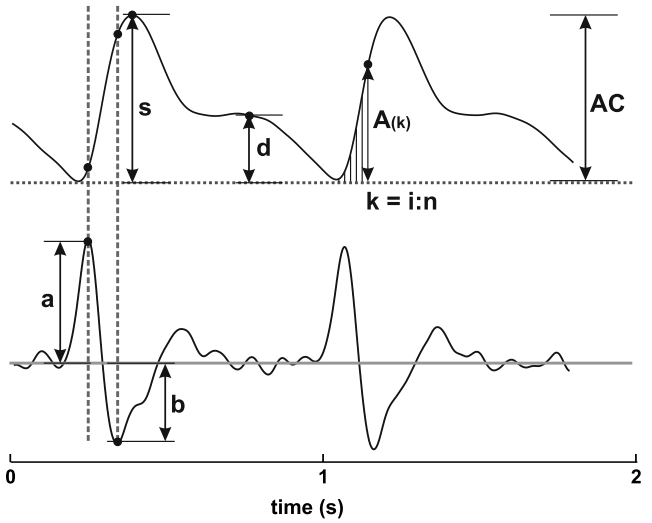

Fig. 1 PPG alternating current (AC) pulse waveform contour consisting of signal samples A_k; systolic peak amplitude s, diastolic peak amplitude d, 2nd derivative extremes a and b.

the unknown PPG probe CP conditions, may cause an inconsistency in the results when the pulse wave contour analysis derived parameters are computed.[25] In case of PWV, this has been explained by analyzing the tissue elastic properties beneath the PPG probe, similar to this study.[26] To the best of our knowledge, there were a few studies addressing the standardization issue and, currently, there are no papers suggesting any standardized criterion of the PPG probe CP except our previous pilot study results.[27,28] Current study focuses on development of methodology to achieve more reliable and valid PPG recordings. The aim of this study was to verify the effect of the PPG probe CP on the value of stiffness related parameter b/a and to clarify whether the previously developed optimal pressure parameter (OPP) can be used for a reliable recording of b/a.[28]

We hypothesized that the stiffness related PPG pulse wave parameter b/a is strongly inconsistent when recorded at nonoptimal probe CP.

2 Methodology

Five young and healthy subjects (3 male, 2 female, 23 ± 2 years old) were enrolled in this pilot study with their informed consent. This study was approved by the Scientific Research Ethics Committee of the University of Latvia, Institute of Experimental and Clinical Medicine. To perform measurement trials in resting conditions, subjects were held in a comfortable, supine position in a quiet and comfortable (23°C to 25°C) environment. The experimental setup and the design of PPG equipment were similar to those reported in our previous study revealing the OPP, as shown in Fig. 2.[28]

The PPG probe was placed on the skin over the three palpable pulse arterial sites (posterior tibial a., femoral a., popliteal a.), consecutively, in different recording trials, repeating the same procedure three times. The probe was fastened with the custom assembled micro-thread manipulator (UniSlide, Velmex Inc.) joined to film-type force transducer (FlexiForc A201, Tekscan) to provide variable CP recording.

Prior to the probe positioning, the arterial region (planned recording site) was insonated with an ultrasound system (Titan, Sonosite; L38 Linear array 10–5 MHz) by an experienced sonographer to reveal any abnormalities or peculiarities which might potentially interfere with a normal arterial site PPG recording as well as to measure the depth and diameter of artery. The stability of the systemic hemodynamic parameters, during the whole experiment, were confirmed by measuring the arterial blood pressure and heart rate by an oscillometric pressure monitor (UA-767Plus30, A&D Instruments) every 2 min. After the ultrasound examination and the determination of the location of the suitable arterial site by mechanical palpation, a single PPG probe was positioned on the skin over the conduit artery. During the recording, the probe CP was slowly increased to the maximum (which was determined by a complete disappearance of the PPG AC pulsations) or reduced until the probe lost contact with the skin. The data acquisitions, of both the PPG signal and force transducer signal, were performed simultaneously at a 4 kHz sample rate and analyzed offline with dedicated Matlab software "PPG Waveform Analysis" (Univ. of Latvia, IAPS, Rubins et al.). The stiffness related waveform parameter b/a was calculated from the 2nd derivative of PPG signal.

For indicating probe CP where PPG is being recorded in the conditions of unloaded arterial wall, OPP was calculated by Eq. (1) during signal processing in beat-per-beat manner:

$$\mathrm{OPP} = \frac{d}{s}\frac{1}{(n-1)}\sum_{k=1}^{n} A_k, \tag{1}$$

where d/s is the diastolic to systolic peak ratio of the PPG signal and $k = i{:}n$ are the samples of each PPG AC pulse; A_k is the amplitude of each sample of PPG AC signal, as shown in Fig. 1.

3 Results

All the subjects examined with the ultrasound imaging showed a normal geometry of the arterial tree at the PPG recording sites and systemic hemodynamic parameters were held constant during PPG measurement procedure (HR $= 68 \pm 5$ BPM; systolic pressure (P_{sys}) 118 ± 8 mmHg; diastolic pressure (P_{dia}) 78 ± 5 mmHg). The depths and diameters of the arteries differed among the subjects and the measurement sites. The smallest diameter and depth were observed for the posterior tibial artery (diameter: 2.1 to 3.2 mm; depth 3.2 to 5.2 mm), the medium values were for the femoral artery (diameter: 6.1 to 8.1 mm; depth 10.4 to 30.2 mm), and the highest values for the popliteal artery (diameter: 7.7 to 9.1 mm; depth 8.6 to 20.5 mm). The literature confirmed our results while

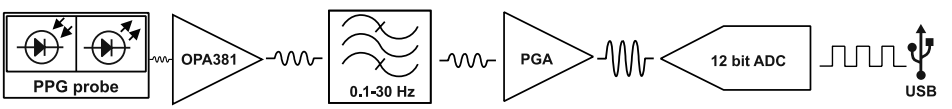

Fig. 2 Schematics of the PPG apparatus: a transimpedance amplifier (OPA381, Texas Instruments) based reflectance type PPG sensor with a photodiode (BPW34-FA, Osram, peak spectral response: 880 nm), an active 1st order feedback circuit 34 Hz low-pass filter, and the 875 nm LED (SIR91-21C/F7, Everlight, 400 mW, a transmission angle 20 deg, diameter 1.9 mm). The probe was connected to custom designed biosignal amplifier with an integrated band pass filter, consisting from 0.1 Hz 2nd order high-pass and 30 Hz 6th order low-pass filters.

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indicating the difference in diameter between the genders and the difference of age.[29] The obtained PPG waveforms were typical for the particular arterial sites and were similar to those reported by Sapoznikov, Loukogeorgakis and our research group.[7,9,10] The optimal probe CP values significantly differ at each recording site ($p < 0.05$). Consequently, the highest optimal CP values were observed for the popliteal artery (15.2 ± 4.0 kPa), medium for the femoral artery (11.8 ± 2.9 kPa), and the lowest values for the posterior tibial artery (10.9 ± 3.1 kPa), mean $\pm$ sd. These results are in accordance with the ultrasound examination data in which they confirm the relationship of the arterial depth and the amount of underlying tissue.

Overall, we observed a 300 percent to 400 percent variation of the stiffness related parameter b/a during the incremental and decremental change of probe CP (states A, B, and C), as depicted in Figs. 3 and 4.

As expected, the b/a values obtained at the optimal probe CP showed a negligible measurement site dependency (CV < 6%), popliteal artery (0.66 ± 0.08), femoral artery (0.69 ± 0.09), and posterior tibial artery (0.73 ± 0.09), mean $\pm$ SD as shown in Fig. 5. Such data represents the b/a values corresponding to the conduit AS of young and healthy subjects that can be explained by a similar compliance of the muscular type arteries. Similar results are illustrated in another prominent study.[16] That can be explained by a similar compliance of the muscular type arteries.

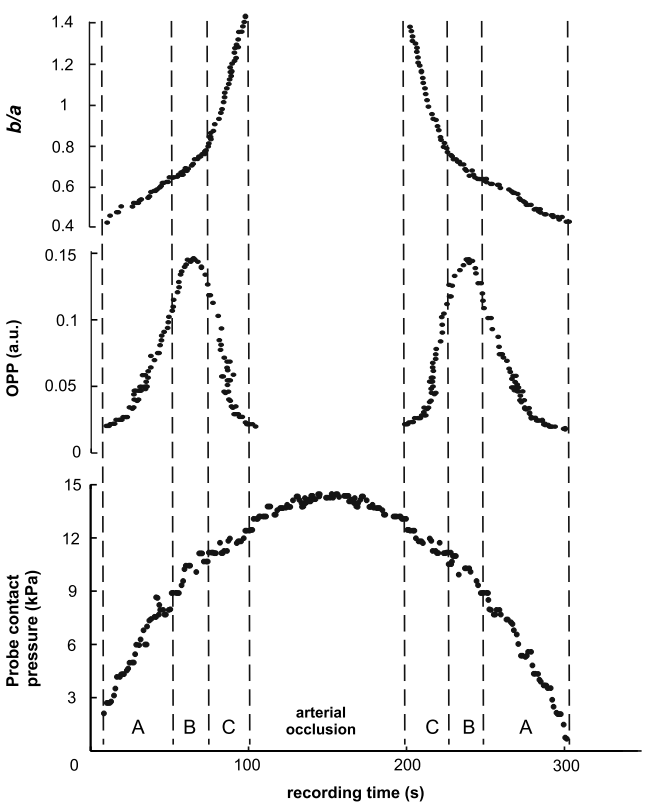

Fig. 3 Representative example of one subject: PPG recorded from the femoral site. The variable probe contact pressure (CP) (bottom curve) induced changes of the PPG AC waveform parameters: optimal pressure parameter (OPP) and 2nd derivative amplitude ratio b/a, which is related to arterial stiffness. The probe CP is partly conducted to the arterial wall. The OPP maximum indicates zero transmural pressure where the external pressure affecting the arterial wall P_{effect} is equal to the mean arterial pressure (MAP), state B, providing repeatable, standardized measurement conditions. It also indicates the conditions of the unloaded artery wall and optimal CP value. At state A probe CP is insufficient, intra-arterial pressure exceeds the external pressure and the transmural pressure is positive, while in state C transmural pressure is negative and the P_{effect} is between MAP and systolic pressure. The PPG pulse wave contours, corresponding to each measurement state (A, B and C), are illustrated in Fig. 4.

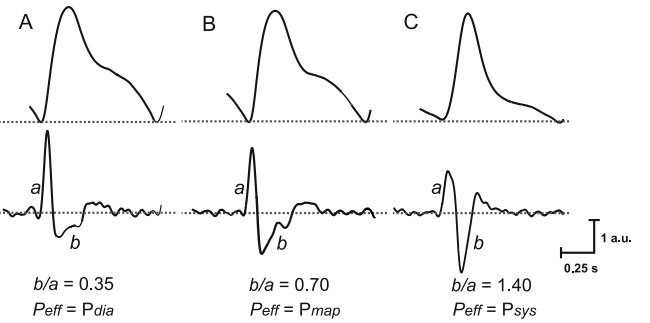

Fig. 4 PPG AC pulse wave and the corresponding 2nd derivative parameter b/a, recorded from one subject. States A, B, and C are in accordance with probe contact pressure condition states in Fig. 3, and P–V relationship in Fig. 6.

The difference between b/a values at states A and B is not significant ($p < 0.05$). A significant b/a error, compared to optimal CP conditions, arises only if the PPG signal is being recorded at conditions where P_{effect} is higher than the MAP, state C ($p < 0.001$; one way repeated measures analysis of variance). This is consistent with our own previous observations during measurements of arterial bed PPG (unpublished data).

4 Discussion

More detailed explanation of our results can be made by using the arterial P–V relationship model. According to the Marey's criterion, the OPP maximum indicates, on the PPG measurement conditions, where the arterial wall is unloaded (the P_{effect} equals to MAP and PPG AC pulse area reaches maximum value).[30] Instead of the mean PPG AC pulse area, we used area derived parameters, OPP, which additionally reflects the relationship between the systolic and diastolic wave of the PPG signal and is uncoupled from the DC component fluctuations. The probe CP influence, on b/a, could be explained by

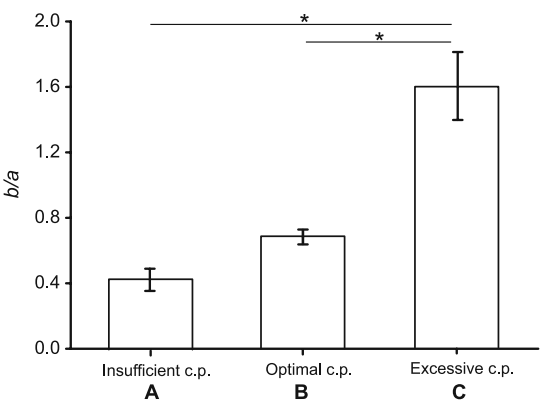

Fig. 5 Representative example of b/a values calculated from PPG signal from one subject, three measurement sites, at all three contact pressure (CP) states (A—insufficient CP; B—optimal CP, refers to maximum OPP; C—excessive CP, Fig. 3) expressed as mean $\pm$ sd. Significant difference is marked by asterisks ($*P < 0.05$).

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the exponential model proposed by Raamat and Baker.[31,32] The model describes the arterial volume (V) dependence on the transmural pressure, P_{transm}, by the system of equations:

$$V = \begin{cases} V_{\text{bal}} e^{\frac{C_{\text{bal}}}{V_{\text{bal}}} P_{\text{transm}}} & for\ P_{\text{transm}} \le 0 \\ V_{\text{sys}} - (V_{\text{sys}} - V_{\text{bal}}) e^{\frac{C_{\text{bal}}}{V_{\text{sys}} - V_{\text{bal}}} P_{\text{transm}}} & for\ P_{\text{transm}} \le 0 \end{cases}, \tag{2}$$

where V_{bal} and C_{bal} are the arterial volume and compliance at the zero transmural pressure, while V_{sys} is the arterial volume at systolic pressure.

Numerous studies show the direct relationship between the oscillating arterial volume and the PPG signal AC waveform[33,34] and, therefore, from this, we associate the arterial P–V relationship with PPG pulse wave.

To explain the b/a dynamics near its peak values in Fig. 3, the PPG AC waveform should be examined by realizing the zero transmural pressure, $P_{\text{transm}} = 0$, at the upper limit state, systolic pressure, which is the highest pressure value within the pulse cycle. Then, the arterial wall is unloaded only at the peak of the pressure wave while, at all other times, it will be constricted by the excess pressure imposed by the state C in Figs. 3 and 6.

In the state of zero transmural pressure, arterial volume is always equal to V_0. During the state A, over one pulse period, oscillating volume of artery is above the level $V_0 = V_{\text{sys}}$ at C, thus, it is smaller than oscillating volume of artery during the state B which is in accordance to Marey's criterion of maximum oscillations at the MAP.

At the state C, the arterial compliance C_{bal} reaches its maximum value only at systole which produces the steeply rising PPG waveform and maximum b/a value, state C, at the Figs. 4 and 6.

During the optimal state B, the oscillating arterial volume, Fig. 6 crosswise, and the mean PPG AC area (and the OPP) reaches maximum, as shown in Fig. 3(b), which produces a more rounded and smooth waveform related to the zero transmural pressure at the MAP, as shown in Fig. 4(b).

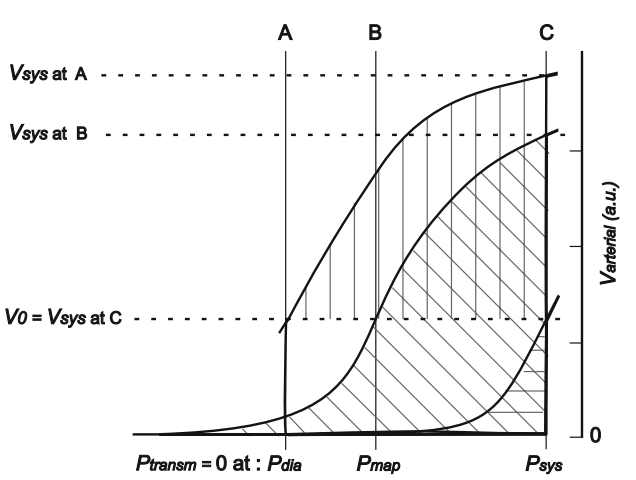

Fig. 6 P–V relationship at the different zero transmural pressure ($P_{\text{transm}} = P_{\text{arterial}} - P_{\text{effect}} = 0$) conditions. P_{transm} is zero at: P_{dia} (state A), MAP (state B) and P_{sys} (state C). Each state corresponds to its specific oscillating arterial volume (vertically, crosswise and horizontally hatched areas, respectively) producing PPG AC signal.

Hereby, the reliability of the OPP criterion was elegantly shown in our experiment during the incremental and decremental change of the probe CP, whereas, the b/a value returned within 5 percent tolerance between both cases. The same was observed for the optimal probe CP value. Being dependent on the measurement site, it returned within the same tolerance both incremental and decremental CP cases.

Overall, it indicates that our measurement is repeatable. Our suggestion to use the PPG waveform parameter, such as the OPP, is based mainly on the evidence of the close tolerance of repeated maximum values (usually CV < 5%) every time when CP is optimal. Our observations show that even if the OPP amplitude maximum values vary more, the AS parameter b/a and probe CP values, returned from the analysis, are only slightly different (CV < 8 percent). This suggests that decreasing the probe CP from the maximum to the optimal is correct when the OPP reaches the next maximum instead of the value of the previous one. The variable probe CP induced notable changes to the PPG parameters OPP and b/a. Parameters display similar values during increment and decrement of probe CP within the measurement trial, thus, confirming the consistency of measurement conditions. This should be considered as the most important reason why the noninvasive contact-manner PPG measurements should be performed in the controlled probe CP conditions. Currently, this factor is still not properly acknowledged and often disregarded while designing the experimental protocol.

So far, OPP range is being calculated offline after the measurement trial, which allows only a fraction of PPG pulses that corresponds to its maximum value to be selected (selection criteria). By improving the data acquisition software with real-time OPP computation, initial OPP range assessment could be added to the experimental protocol prior to performing physiological measurements, thus, ensuring that signal is recorded in standardized conditions.

5 Conclusions

We conclude that, in the case of an uncontrolled probe contact pressure, PPG waveform derived parameters, particularly b/a, are inconsistent. Therefore, the results obtained in such measurement trials should be interpreted with precaution. Our present findings can be considered a step toward standardization of probe contact pressure and more reliable recording of contact-manner PPG signal.

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Two-stage multi-Gaussian fitting of conduit artery photoplethysmography waveform during induced unilateral hemodynamic events

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Abstract. Photoplethysmography (PPG) is an optical technique with high diagnostic potential, yet clinical applications remain underdeveloped. Standardization of signal recording and quantification of waveform are essential prerequisites for broader clinical use. The aim of this study was to utilize a two-stage multi-Gaussian fitting technique in order to examine the parameters of conduit artery PPG waveform recorded during increasing the unilateral regional vascular resistance (RVR). This study was conducted on 14 young and healthy volunteers; various external compressions (ECs) were performed by inflating a tight cuff at 0, 40, 80, and 200 mmHg, while registering femoral PPG (wavelength 880 nm), diameter, blood flow linear velocity (vascular ultrasound), and the arterial pressure (Finapres) during the states of the baseline, partial, and total arterial occlusion, and resultant reactive hyperemia. An increase of the EC elevated the arterial stiffness (AS) and the unilateral distal RVR, and caused a shift of the fitted multi-Gaussian parameters: a decreased delay between reflected and traverse wave components and an increased ratio of their amplitudes. It was concluded that two-stage multi-Gaussian waveform quantification demonstrates an approach potentially extending the use of arterial site PPG in the assessment of diagnostically useful markers e.g., the RVR and the AS. *© 2015 Society of Photo-Optical Instrumentation Engineers (SPIE)* [DOI: 10.1117/1.JBO.20.3.035001]

Keywords: arterial photoplethysmography; waveform decomposition; Gaussian function; external compression.

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1 Introduction

Photoplethysmography (PPG) is a well-recognized optical technique for noninvasive arterial pulsation detection. It was originated in the beginning of the 20th century and is still a burgeoning field of biomedical engineering currently presented in numerous R&D and application studies. However, despite its high diagnostic potential, PPG has yielded clinical applications only in a few specific areas such as the assessment of blood oxygenation known as the pulse oximetry or, in minor cases, as the technique for vascular tone/age estimation from the pulse waveform. Such PPG utilization is being reported in several prominent reviews.[1,2] In conventional applications, PPG is registered from diffuse vascular beds e.g., distal phalanxes or the earlobe, comprising small caliber arterioles, venules, and capillaries.[1,2–4] There are only a few reports describing PPG signal recording from superficial conduit arterial sites[5–7] that could potentially gain more specific information of the hemodynamics e.g., the arterial stiffness (AS).[8] The major reasons for the limited use of PPG in the routine clinical assessment of the vascular state are the waveform quantification and measurement procedure standardization issues. Among several studies on such PPG waveform quantification, there is a lack of reports on single period PPG (SPPPG) waveform dynamics during hemodynamic maneuvers, such as altering the regional vascular resistance (RVR), increasing the blood flow shear, and others, particularly on the PPG signal obtained from superficial conduit artery sites. A literature review reveals that our study is one of the few addressing this issue. A similar procedure utilizing ultrasound (US) to examine the pulsations of femoral artery distension and blood flow velocity during manipulations of RVR has been reported by Heffernan et al.[9] It is generally accepted that the rising distally performed external compression (EC) quantitatively mimics an increase of unilateral RVR and such provocation of hemodynamic response is utilized in physiologic research.[9,10] Peripheral vascular resistance is recognized as an important indicator of different infectious syndromes, diseases, and general vascular age. Therefore, understanding the RVR relationship to SPPPG waveform and its potential quantification has a crucial role in the extension of clinical applications of PPG[11] and brings motivation to this preliminary study.

Generally, the accepted approach in the assessment of hemodynamic parameters from the single arterial pulse waveform is a segregation of its feature points (FPs). Prominent studies have already described the extraction of FP from SPPPG waveform[4,12] or its derivatives,[13] or by fitting various types, combinations, and numbers of analytic functions.[14,15] In cases of a damped, monotonically decreasing diastolic part, existing models often reveal limited operating range and inconsistent calculation of FP.[16] Meanwhile, the similarity of a single hemodynamic wave component, i.e., the left ventricle ejection volume profile and the Gaussian function profile, has previously been reported and utilized[17,18] and can also be visually noticed.[19]

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Recent studies employ a multi-Gaussian model for fitting the peripheral pulse waveform[20–22] guided by the criterion of minimal root-mean-square error (RMSE). An approximation of the SPPPG waveform with four Gaussian functions has also been demonstrated by our group highlighting its advantages over the derivative analysis.[17] However, such previous studies were predominantly focused on fitting accuracy rather than the relevance of actual physiological pulse waves to Gaussian model components, while only a single case mentions their possible pertinence.[18] Apparently, based only on the minimal RMSE criterion, the multi-Gaussian model cannot be used for such an explanation, as the variability of pulse waveform contour causes chaotic dissipation of the fitted components.

Our results indirectly indicate that in designing a reliable Gaussian-based hemodynamic model, boundary conditions for the pulse component positioning and scaling are required.

The present study explores the potential of conduit artery PPG in evaluating the hemodynamic events. The aim of this study was to utilize a two-stage multi-Gaussian fitting technique in order to examine the parameters of conduit artery SPPPG waveform recorded during increasing the unilateral RVR. We hypothesized that by altering the leg's RVR and AS via the tight EC test, femoral pulse waveform transforms, and this resonates in a component shift of SPPPG waveform and fitted multi-Gaussian model.

2 Methods

This study was approved by the Ethics Committee of the University of Latvia, Institute of Experimental and Clinical Medicine, and, with their informed consent, it was performed by enrolling 14 subjects (6 male, 8 female, 25 ± 5 years old). To ensure adequate vascular response, the subjects were asked to refrain from caffeine drinks and active workload for at least 8 h prior to the experiment. In order to improve PPG signal quality, isolate uncontrolled conditions and simplify the palpation of the arterial site for correct PPG/US probe location, enrolled subjects were ectomorph body type (body mass index <20) nonsmoking and normotensive. During the procedure, subjects were held in supine position in a quiet, warm (23°C to 25°C) and comfortable room.

The study protocol included data acquisition of different modalities at the rest, during and after the provocation test; signal processing and hemodynamic parameter calculation, and statistical analysis, Fig. 1.

To provoke regional hemodynamic responses in the femoral artery and distal arterial bed, the study protocol comprised five consecutive measurement states (MS) induced by various tight ECs with CC17 Contoured Thigh Cuff, E20 Inflator and AG101 air supply (D. E. Hokanson, Inc., USA): the baseline MS1 at the rest conditions with 0 mmHg external cuff pressure, the states of partial arterial occlusion MS2 and MS3 (40 and 80 mmHg cuff pressure, each for 15 s), total arterial occlusion MS4 (200 mmHg cuff pressure for 300 s), and the resultant reactive hyperemia (RH) MS5 monitored for the first 30 s, similar to that described by Heffernan et al.[9]

During the aforementioned MS, three different signal modalities were simultaneously recorded: PPG ($\lambda = 880$ nm) from the femoral artery site close to the inguinal ligament utilizing the optimal sensor contact force approach;[23] simultaneous Doppler and B mode US 12L-RS, LOGIQe (GE Medical Systems, USA), positioned approximately 1 cm distally to the PPG probe, recording both the longitudinal section of the artery (diameter d) and the profile of blood flow time averaged mean (TAM) velocity v, Fig. 2; and systolic, diastolic and mean blood pressure values acquired from Finometer Model2 in a beat-per-beat manner and calibrated to brachial arterial pressure (Finapres Medical Systems, The Netherlands).

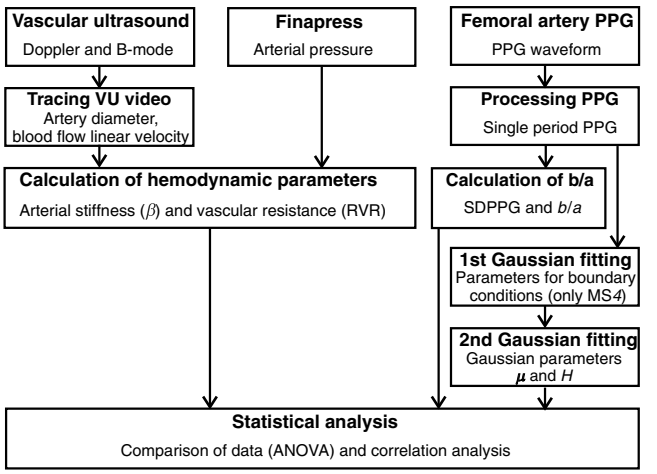

Fig. 1 Flowchart of the performed protocol. β and b/a – local arterial stiffness indices; RVR – regional vascular resistance; SDPPG – second derivative of PPG waveform; MS4 – measurement state of total arterial occlusion; H – Gaussian peak amplitude, μ – Gaussian peak time delay in the waveform.

Data analysis was performed offline in three major steps. First, artifacts of US data were excluded and both the blood flow and diameter traces were determined from the US videos by a custom made MATLAB® US image recognition software.[24] Then, PPG processing was performed by stating the valid range of SPPPG waveform length equal to the median absolute deviation $T\text{mad}_{\text{state}}$ in each of the MS from the corresponding dataset; hence, valid and ectopic waveforms were determined and separated by the criterion:

$$|T_{\text{state}} - T_{\text{ins}}| < T\text{mad}_{\text{state}}, \tag{1}$$

where T_{state} is the median pulse duration within each MS and T_{ins} is the duration of the inspected pulse within the same MS. Then, the returned, i.e., valid SPPPG waveforms were resampled at 1 kHz to 1 s length with a spline interpolation technique and normalized to 1 a. u.

A comparison of amplitudes of valid waveforms from all MS was performed in every sample $j|_0^{1000}$. Inspected SPPPG waveform amplitude a_j was compared to the mean amplitude within each MS A_j and the waveform was excluded if the squared difference exceeded the RMSE at any of the waveform samples:

$$(A_j - a_j)^2 > \text{ARMSE}_j, \tag{2}$$

where ARMSE_j is an RMSE of the same inspected SPPPG waveform at the sample j, thereby picking SPPPG waveforms that characterize each state of the performed measurement. Subsequently, one representative SPPPG waveform per MS was calculated as the median contour of each MS dataset. In the second step, all processed data were merged in a single data array in beat-per-beat manner (synchronized time series). Third, the parameters describing the induced hemodynamic response were calculated and stored in a .mat file for statistical analysis. During each MS, the RVR was graded as

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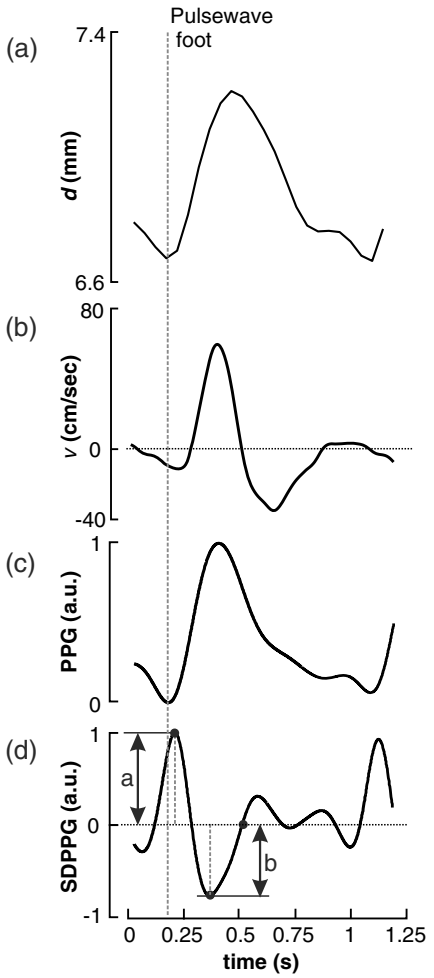

Fig. 2 Typical example of femoral artery pulsation waveforms during the rest conditions (MS1): (a) diameter *d*, (b) blood flow linear TAM velocity *v*, (c) both acquired simultaneously with US; (d) single period arterial PPG and its second derivative SDPPG. SDPPG inflection points *a* and *b* are used for the assessment of the local arterial stiffness.

$$\mathrm{RVR}_{\mathrm{femoral}} = \mathrm{MAP}/Q, \tag{3}$$

where Q is the total femoral blood flow and MAP is the mean arterial pressure,[25] while the changes of local AS were estimated with the referent index β:[26]

$$\beta = \frac{\ln(p_s/p_d)}{(d_s - d_d)/d_d}, \tag{4}$$

where p_s, p_d and d_s, d_d are the values of blood pressure and lumen diameter at systole and diastole, respectively. The pulse wave reflection index[9] was calculated as the ratio of retrograde to anterograde TAM velocity $v_{\mathrm{ret}}/v_{\mathrm{ant}}$ derived from the US signal, while an already approved indicator of local AS - SPPPG second derivative (SDPPG) index b/a[13] was calculated from the PPG signal in all MS.

Meanwhile, in order to manage SPPPG decomposition and waveform parameterization, preprocessed representative waveforms of each subject (one per every MS) were approximated with multiple (2 or 4) one-dimensional Gaussian functions in two fitting stages. In the first stage, the MS4 waveform was fitted with 2 Gaussians: $g_n(t, H, \mu, \sigma)$ where $n = 2$ is the number of Gaussian functions fitted in the SPPPG wave, H is the Gaussian peak amplitude, μ is the peak time delay in the waveform, and σ is the wave width, by solving the system of equations for the multi-Gaussian model $f_G(t)$, Fig. 3:

$$f_G(t) = \sum_n H_n e^{-\frac{(t-\mu_n)^2}{2\sigma_n^2}}. \tag{5}$$

Model parameters were estimated by the weighted least-squares method, minimizing the weighted sum of squared residuals:[27]

$$\sum_{j=1}^{1000} (\mathrm{SPPPG}_j - f_{Gj})^2 \to 0. \tag{6}$$

During the fitting the accuracy was estimated and demonstrated as residual graphs, Fig. 3.

The values of Gaussian parameters H, μ, and σ at this stage were set to boundary condition variables, and the second fitting stage was performed on all but MS4 waveforms by repeating the same approach (5–6) with $n = 4$ in compliance with the boundary conditions to determine Gaussian localization in the SPPPG signal in order to associate them to physiologic pulse wave components. Based on the assumptions of femoral site pulse wave component morphology, mentioned in Sec. 4, to the best of our knowledge, we hereby stated such boundary conditions for the first time. The time difference between both Gaussians $g1$ and $g3$ $\mu_3 - \mu_1$ was defined constant in all MS. Meanwhile, during all but MS4, the time difference between Gaussian pairs $g1 \sim g2$ and $g3 \sim g4$ was equal within the same MS: $\mu_2 - \mu_1 = \mu_4 - \mu_3$. During MS4, it was assumed $\mu_2 - \mu_1 = \mu_4 - \mu_3 = 0$ i.e., the SPPPG waveform during total arterial occlusion was fitted with two Gaussians. During the second fitting stage, four Gaussians were locked in a pair of double-Gaussians $g1 + g3$ and $g2 + g4$ allowing for varying only the time delay $\mu_2 - \mu_1$ and the Gaussian amplitudes that were allowed varying as $H_1 > H_2 > H_4$ and $H_1 > H_3 > H_4$ within the same MS.

Following this procedure, the variables derived from the SDPPG and the multi-Gaussian model were used to estimate the effect of EC on the SPPPG pulse contour and also to assess and validate the changes of leg local and regional AS. First, the values of both local AS indices - b/a and β were compared in all MS. Meanwhile during all but MS4 the regional AS of leg's arterial bed was indicated with the pulse transit time (PTT) $\mu_2 - \mu_1$ of the traverse pulse wave components i.e., $g1$ and $g3$ reaching the endpoint of leg arterial tree and traveling backwards to the PPG probe as $g2$ and $g4$ respectively. Leg peripheral wave reflection properties were described as a ratio of the reflected wave component to its systolic traverse origin, i.e., H_2/H_1 and intended to compare to the $v_{\mathrm{ret}}/v_{\mathrm{ant}}$.

The statistical analysis of the aforementioned parameters was performed on SigmaPlot by comparing the sets of data series by one way ANOVA. The relation of parameters was determined by Pearson correlation.

3 Results

Data from the US indicated the effect of EC on the RVR, expressed as mmHg/ml/ min. RVR obtained at the femoral site varied within the subject group from 0.57 ± 0.11; 0.97 ± 0.18, and 1.11 ± 0.20 at the MS1, MS2, and MS3, respectively, and

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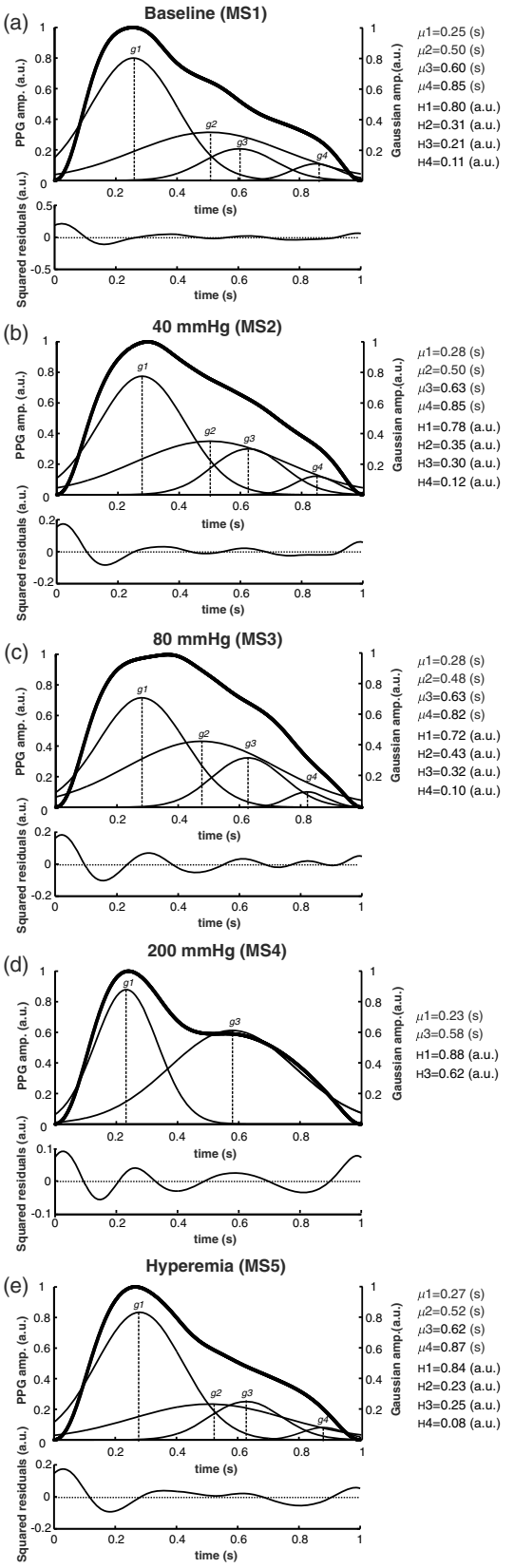

Fig. 3 Representative example (one subject data) of femoral SPPPG waveforms and the fitted Gaussians (upper plots) and the squared residuals (bottom plots) at the measurement states MS1 to MS5, influenced by the distal tight compression: (a) the baseline, (b) and (c) partial arterial occlusions 40 and 80 mmHg of cuff pressure, (d) total arterial occlusion at 200 mmHg, and (e) hyperemia; Gaussian components $g1$ to $g4$, and their respective peak amplitude H and time delay μ tabulated beside.

reached 3.36 ± 0.34 during MS4. In MS5, the release of the cuff caused RH and RVR to drop to 0.10 ± 0.02. Here and hereafter values are expressed as mean $\pm$ standard error of the mean (SEM.) Such RVR alterations were accompanied by significant changes of the v_{ret}/v_{ant}: consequently it increased from 0.392 ± 0.051 during MS1, to 0.747 ± 0.032 at MS2, and 0.820 ± 0.056 at MS3. The v_{ret}/v_{ant} during MS4 was 0.606 ± 0.056, however, due to the artificial pulse wave reflection conditions and the

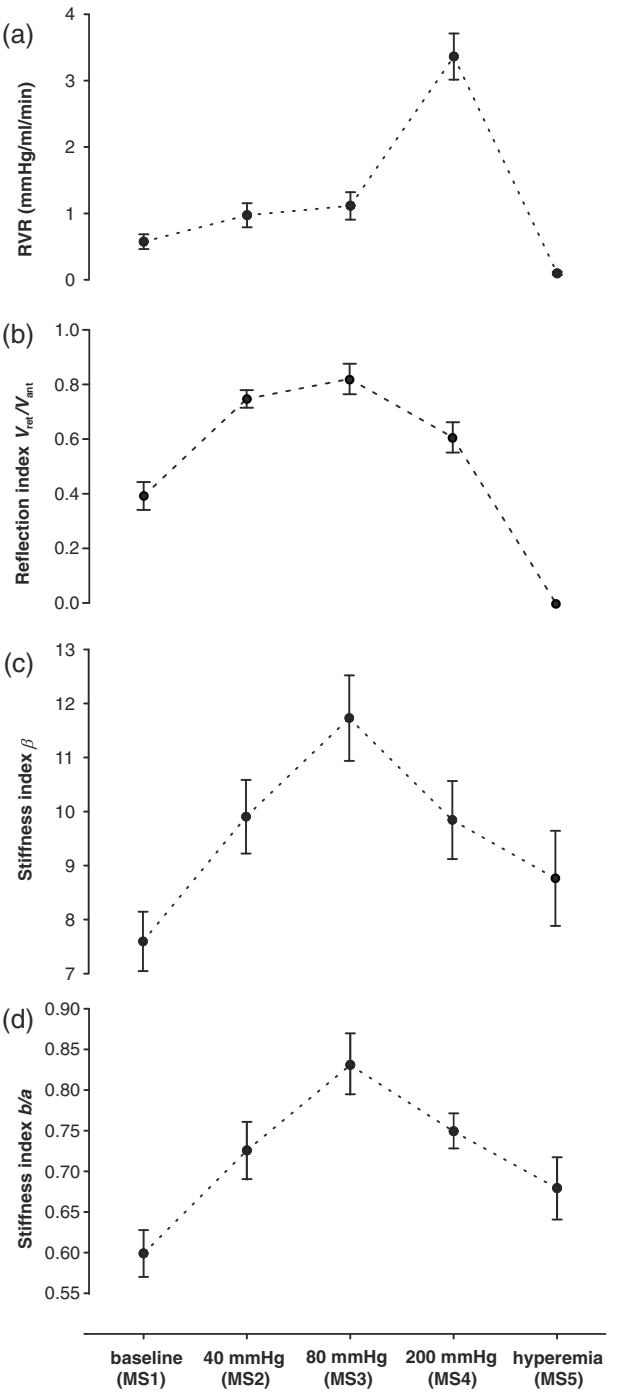

Fig. 4 Femoral artery regional hemodynamic parameters within the subject group at different external cuff pressures, data points, and error bars represent the mean $\pm$ standard error of the mean (SEM): (a) regional vascular resistance RVR; (b) pulse wave reflection index v_{ret}/v_{ant}; (c) local arterial stiffness indices β, and (d) b/a obtained by US and PPG techniques, respectively.

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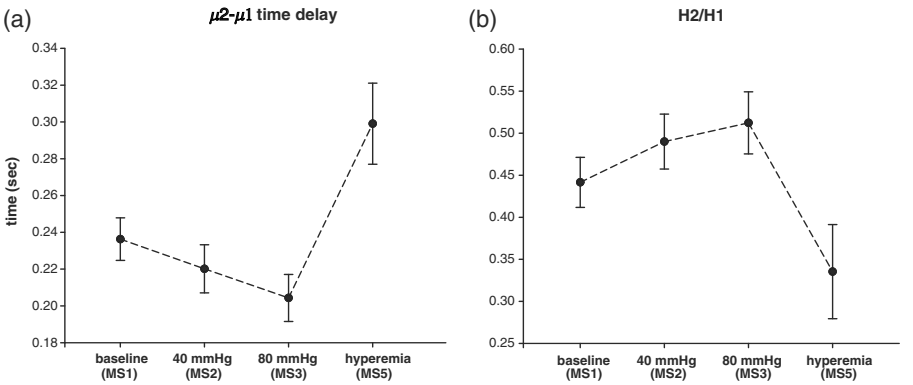

Fig. 5 The time delay between the traverse $g1$ and reflected $g2$ waves: (a) components $\mu_2 - \mu_1$ decreases while their amplitude ratio, (b) H_2/H_1 increases during all but MS4 measurement state, indicating an augmentation of distal vascular tone and resistance during raising external compression, data points, and error bars represent the mean $\pm$ SEM.

diminished blood flow velocity, it should be cautiously interpreted. During the RH in MS5 there is an absence of the retrograde blood flow component, thus the v_{ret}/v_{ant} was 0.

Meanwhile, a high correlation between the b/a and β at all the performed MS ($r = 0.97$, $p < 0.001$) was observed, proving the conformity of both local AS measures derived from PPG and US techniques, Fig. 4.

Four-Gaussian model parameters exhibited the changes of the SPPPG waveform, depending upon the EC: $\mu_2 - \mu_1$ declined from 0.236 ± 0.011 during the MS1 to 0.220 ± 0.013 and 0.204 ± 0.012 during partial arterial occlusions MS2 and MS3; while, on the contrary, H_2/H_1 increased from 0.442 ± 0.030 to 0.490 ± 0.033 and 0.51 ± 0.037 during the same MS of rising EC. Then, both parameters demonstrated a mutually inverse response to the RH: $\mu_2 - \mu_1$ increased to 0.299 ± 0.022 while H_2/H_1 dropped to 0.335 ± 0.056, Fig. 5.

4 Discussion

Our computed hemodynamic parameters during the performed maneuvers showed a similar systemic response to the EC as reported by Heffernan et al.[9] In addition to their performance, we calculated the numeric value of the leg's RVR in each MS and noticed only minor RVR changes between the baseline (MS1) and partial occlusions (MS2 and MS3). In those same MS with raising EC, both local AS indices b/a and β obtained by PPG and US showed an augmentation as expected. However, RVR demonstrated significant alterations during the arterial occlusion (MS4) and RH (MS5). The obtained values of local AS indices b/a and β showed good conformity with the previous results.[9,28]

Regarding the wave reflective properties of leg vasculature, rising RVR causes an augmentation of the reflected wave component expressed through the H_2/H_1. We refer it to as the v_{ret}/v_{ant}, while Heffernan et al describe this effect through the negative area of a pulse pressure wave. We share the view of the risen EC effect on the wave reflection through the diminished capacitance, i.e., reservoir function, thus constricting blood flow discharge into the periphery.[9]

As to the PPG waveform parametrization, the novelty of this study mostly relies on the MS4 conditions providing the necessary PPG waveform for the initial stage of fitting the Gaussians. We thereby assume that the femoral SPPPG pulse wave during MS of the total distal arterial occlusion in a sense represents an aortic pulse, as the peripheral vascular compliance is uncoupled by the inflated pressure cuff and serves as an artificial high vascular resistance reflection site. Such femoral pulse wave consists of two traverse waves: an ejection wave in the systole $g1$ and its re-reflection $g3$ in the diastole emerging between the bifurcation and aortic valve, Fig. 3(d). The pulse wave in this MS condition is not damped by the peripheral blood flow discharge and represents the combination of properties of heart function (pulse duration) and aortic elasticity (aortic PTT). We considered the $\mu_3 - \mu_1$ to correspond to the double bifurcation-to-aortic valve PTT of relevant subjects, which corresponds to the published data.[29] During the MS4, the PTT in the path probe-cuff-probe is close to zero due to their close proximity, while the pulse waves from all other MS contain reflected components $g2$ and $g4$ traveling from the endpoint of the leg periphery with a noticeably longer PTT. Indeed, a half of $\mu_2 - \mu_1$ as well as $\mu_4 - \mu_3$ during all but MS4 waveforms is also close to the PTT values of the pulse wave traveling from femoral to tibial sites at rest conditions.[5,30] If $\mu_2 - \mu_1$ is associated with the regional leg AS, it follows that the arterial tone augments during partial ischemia. Such an increase of AS in the distal vascular bed during EC trials has previously been reported.[31] $\mu_2 - \mu_1$ thereby consists of PTT components from the sites both distal and proximal to the cuff, and describes the total response of leg vasculature to the EC. Based on these assumptions, each fitted Gaussian is associated to the corresponding pulse wave component, and, by locking them in a pair of double-Gaussians – traverse double-wave $g1 + g3$ and reflected double-wave $g2 + g4$, the morphology of femoral artery pulsation waveform is described. Because of the locking, the fitting accuracy is sometimes sacrificed while the fitting accuracy obtained by a single double-Gaussian during MS4 meets previously obtained residual values.[17]

5 Conclusion

The femoral PPG waveform parameters derived from two-stage multi-Gaussian fitting quantitatively characterize their alterations upon the rising distal external compression causing a wide range hemodynamic events. The attempt of associating the Gaussians with pulse wave components demonstrates a new approach potentially extending the use of the arterial site PPG technique in the assessment of diagnostically useful clinical markers such as the peripheral vascular resistance and the arterial stiffness.

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Aortic stiffness in patients with early sepsis

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Introduction

Go to:

Acute and chronic systemic inflammatory conditions are associated with aortic stiffening. Carotid-femoral pulse wave velocity (PWV), a marker of aortic stiffness, increases in patients with inflammatory diseases and independently correlates to levels of C-reactive protein (CRP). The effects of massive inflammatory response in early sepsis on mechanical properties of the aorta have not been investigated. The objective of the current study was to prospectively assess aortic stiffness in patients with early severe sepsis and septic shock and relate it to inflammatory and haemodynamic variables and outcome.

Methods

Go to:

We recruited patients meeting criteria for severe sepsis and septic shock within 24 hours of admission to ICU. After haemodynamic stabilisation, PWV was recorded at inclusion and after 48 hours using dual-channel plethysmography. Severity of illness was assessed with APACHE II and serial SOFA scores, haemodynamic and inflammatory parameters (CRP, procalcitonin and fibrinogen) recorded. A 28-day follow-up was performed to distinguish between survivors and nonsurvivors.

Results

Go to:

Twenty consecutive general ICU patients (six with severe sepsis and 14 with septic shock) were enrolled in the study; median age 59 years (IQR 56.5 to 72), APACHE II score 17 (13 to 20.5), SOFA score 5 (IQR 4 to 9). At 28 days, six patients had died. Median initial PWV was 10.4 (IQR 6.9 to 12.1) m/second in patients with severe sepsis, and 6.8 (IQR 5.3 to 7.5) m/second in patients with septic shock ($P = 0.13$). After 48 hours, PWV in the severe sepsis and septic shock groups had become similar, 9.3 (IQR 7.3 to 11.1) m/second and 9.2 (IQR 7.8 to 13) m/second respectively ($P = 0.96$). PWV had significantly increased in survivors (7.8 to 12.3 m/second) ($P = 0.04$) versus nonsurvivors (6 to 7.8 m/second) ($P = 0.69$). Higher PWV correlated with increasing systolic pressure and lower CRP levels ($r = 0.73$, $P = 0.01$).

Conclusion

Go to:

In early sepsis, aortic stiffness is decreased in patients with greater disease severity, and in survivors increases to median levels within 48 hours. The main factors associated with lower pulse wave velocity are lower systolic pressure and higher CRP levels. The association of high serum CRP levels with low aortic stiffness in patients with sepsis does not match data described in the literature [1].

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Bilateral difference of superficial and deep femoral artery haemodynamic and anatomical parameters

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KEYWORDS
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Abstract Clinically revealed, non-uniform distribution of peripheral vascular diseases throughout the arterial tree suggests that haemodynamic forces can modulate the endothelial dysfunction. In the present study the bilateral differences of deep (DFA) and superficial (SFA) femoral artery blood velocity waveform parameters were examined in relation to artery ramification patterns and subject anthropometry. Young, sedentary women ($n = 25$; age 21.2 ± 3.6 years) were enrolled. Anthropometric data as well as systemic cardiovascular parameters (arterial pressure, heart rate and cardiac output) and Doppler velocity spectrum of SFA and DFA were instantly registered in rest conditions. The study revealed a slight and mutually independent anatomical and morphometric asymmetries of femoral arteries in paired legs which were fluctuation type (do not display any directional tendency). Also bilateral asymmetry of artery haemodynamic parameters was related neither to subjects' anthropometric nor artery anatomical parameters. The magnitude of haemodynamic asymmetry is larger for retrograde linear velocity, retrograde shear rate and oscillatory index — parameters which reflect peripheral resistance of microcirculatory bed and thus has a rather functional origin. Possibly, the observed unilateral changes of femoral artery haemodynamic parameters of young healthy and sedentary women could be considered as a sign of potential genesis of artery structure pathological changes in older age.
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Introduction

A recently apparent fact is the crucial role of endothelium in the control of vascular functions. Clinically revealed, non-uniform distribution of peripheral vascular diseases throughout the arterial tree[1–3] suggests that localised factors, such as haemodynamic forces, can modulate the endothelial function. Contemporary studies suggest that atherosclerosis occurs mainly in artery regions that experience disturbances in blood flow such as: low flow, flow separation, flow reversals and turbulence[4,5] and the most prone site for atherogenesis is the bifurcation of common femoral artery.[6,7] A number of previous studies have shown significant impact of the arterial geometry on local arterial haemodynamics.[8,9]

Over several decades, extensive studies regarding the morphometry and anatomy of the femoral arteries in paired legs were carried out using cadaver dissection, magnetic resonance imaging (MRI) and computer angiography (CT-angio) techniques.[10–13] However in prediction and further prevention of atherogenesis, in addition to investigation of morphometric parameters, the assessment of endothelial function is crucially important.

One of the most common and widely used vascular examinations still remains to be the ultrasound Doppler. Despite the fact that Doppler blood flow measurement in the lower extremities has become a routine procedure in the past years, little is known about existing bilateral differences of blood flow velocity waveform in the femoral arteries and its association with factors such as the geometry of the arterial tree, daily physical activity level and the anthropometric parameters.

In the present study we examined bilateral differences of deep (DFA) and superficial (SFA) femoral artery blood velocity waveform parameters (artery haemodynamic parameters) in relation to artery ramification patterns and subject anthropometry in resting conditions.

We hypothesised that the geometry of the arterial tree would account for the observed asymmetry of artery haemodynamic parameters in paired legs.

Methods

Subjects

A group comprising twenty five women in age 21.2 $\pm$ 3.6 years was enrolled in the study. All subjects were informed about forthcoming procedures and gave written informed consent. Prior to experiment the subjects compiled the questionnaire in which physical activity level and personal health history were assessed. The women enrolled in study were young healthy non-smokers with a sedentary life style (students performing moderate physical activity 5—7 h per week, most of the day time spent in seated posture). All measurement procedures were performed during the follicular phase (days 5—14) of their menstrual cycle, (oral contraception was allowed). All testing was completed in an air-conditioned laboratory at a temperature of 24—26 °C in one day. Twelve hours prior to experiment subjects were refrained from exercise, alcohol and caffeine. Study protocol was approved by the Review Board at the University of Latvia and conformed to the EU standards according to the Declaration of Helsinki.

Anthropometric measurements

The anthropometric measurements were taken by the same investigator to ensure reliability. Weight and height measurements were performed, and BMI was calculated. Skinfold data were obtained using a digital skin-fold calliper *Plicometer* (*Gima*, *Italy*) and recorded to the nearest 0.2 mm. The circumferences of the limbs were measured using a non-elastic tape measure (cm) (*Hokanson Inc. USA*) and followed the Anthropometric Indicators Measurement Guide.[14] Quadriceps muscle mass was estimated using anthropometric muscle volume measurement reported previously.[15,16]

Ultrasound examination and monitoring of systemic haemodynamic parameters

All measurements were performed during rest conditions on subjects in a dorsal recumbent position with slightly extended (30°) and comfortably supported legs. Beat-to-beat changes in systolic (P_{sys}), diastolic (P_{dia}) and mean arterial blood pressure (P_{mean}), cardiac output (CO) and heart rate (HR) were measured from the left middle finger using finger photoplethysmography system *Finometer* (*MIDI*, *FMS*, *Netherlands*). In addition to ensure higher reliability of measurements, brachial arterial pressure and heart rate were acquired by an electronic sphygmomanometer *UA-787*(*A&D Inc.*, *Japan*) from the right upper arm at a 3 min repetition rate. The ultrasound examination procedures were performed sequentially on left and right legs in order to acquire imaging data of the superficial femoral (SFA) and deep femoral (DFA) arteries. Prior to Doppler measurements, branching and geometry of femoral arteries were assessed in B-mode. A high-resolution portable Doppler ultrasound system *Titan*(*Sonosite*, *USA*) equipped with a linear array transducer L38 operating at imaging frequencies of 5—10 MHz and DVI frame grabber (*DVI2USB Epiphan Systems*, *Canada*, at 25 fps, resolution 640 $\times$ 480 pixels) was utilised in this study. A series of transverse and longitudinal images of the arteries were acquired by scanning a triangle distally from the iliac artery, approximately 4 cm above inguinal ligament. All video data were recorded to AVI file for further offline analyses. After collecting the data regarding geometry of the femoral arteries the Doppler velocity measurements were performed.

Blood flow velocity was recorded from the proximal straight portion of the superficial and deep femoral arteries at the insonation angle of 60° with a sample volume encompassing the entire lumen. During recording the B-mode and Doppler mode were switched intermittently, resulting in a frame sequence containing a short series of B-mode vessel diameters and Doppler velocity waveforms.[17] In such a manner 3—4 min long recording fragments were obtained twice from each leg and each artery, with at least 15 min time interval between recordings.

Further analyses (artery wall-tracking and waveform edge-detection) of ultrasound video sequence (AVI file) were performed using a Matlab (*MathWorks Inc.*) based

custom developed dedicated analyses software, *Artery_Ultrasound*, developed by our group.[17]

Examination of artery morphometric and haemodynamic parameters

All the data acquired in this study has been assigned to codenames and treated by an investigator who has not been involved in other experiment procedures.

Off-line data analyses were performed in three major stages: in the first, B-mode ultrasound image sequences were processed in order to estimate the branching of the femoral triangle, in the second detailed analyses of the Doppler velocity waveform and diameter changes were performed, and the final stage provided processing of systemic haemodynamic variables joining them in a beat-to-beat manner to the systemic haemodynamic variables acquired by *Finometer Midi*. Four qualitative artery morphometric parameters were assessed during offline analyses: 1) Type of origin of DFA regarding ramification direction — five principal directions proposed,[18] Table 1, 2) Origin of the lateral circumflex artery (LCA) and 3) Medial circumflex artery (MCA) — origin either DFA or CFA accordingly, 4) The distance to the origin of the lateral or medial circumflex femoral artery from the origin of DFA accordingly.[19]

An automated computation of the artery haemodynamic parameters (Doppler velocity waveform indices)[20] and baseline diameter (average diameter over period of measurement time in rest conditions) have been performed. The resolution for diameter measurements has been considered 0.17 mm, which was selected based on reproducibility of within-subject measurements in our laboratory- which is slightly higher than reported by others.[21] The following haemodynamic parameters were selected and included in further analyses:

1) Average mean velocity (V_{Mean}) — by averaging the entire Doppler spectrum.
2) Time averaged antegrade velocity (V_{Ant}) by averaging the antegrade part of Doppler spectrum.
3) Time averaged retrograde velocity (V_{Ret}) by averaging the retrograde part of Doppler spectrum.
4) Peak systolic antegrade blood velocity (V_{Max}) computed as the highest velocity measured in the Doppler spectrum of a cardiac cycle;
5) Peak retrograde velocity (V_{Min}) — computed as the lowest velocity value in the Doppler spectrum of a cardiac cycle;
6) Mean volumetric blood flow (Q) — calculated from the product of the arterial cross-sectional area, obtained from artery diameter (D) and V_{Mean} using the following equation: $Q = 1/4 \times \Pi \times D^2 \times V_{Mean} \times 60$;
7) Time average shear rate ($S_{V_{mean}}$) $S_{V_{mean}} = (4 \times V_{Mean})/(D)$.
8) Antegrade shear rate ($S_{V_{ant}}$) was calculated from time averaged antegrade velocity.[22]
9) Retrograde shear rate ($S_{V_{ret}}$) was calculated from time averaged retrograde velocity.[22]
10) Oscillatory shear index (OSI) was computed as described by[23] from shear rates according to equation :$OSI = |S_{V_{ret}}|/|S_{V_{ant}}| + |S_{V_{ret}}|$. This dimensionless parameter can be used as an indicator of the magnitude of oscillation and may range from 0 to 0.5, where a value of 0 corresponds to a unidirectional shear rate throughout the cardiac cycle, whereas a value of 0.5 represents pure oscillation with a time average shear rate equal to zero.
11) Systolic acceleration time (T_{ACC}) — computed as the time from the start of flow to the forward flow peak;
12) Systolic deceleration time (T_{DEC}) — computed as the time from the forward flow peak to the reverse flow peak.

Statistics

Statistical analyses have been performed on *SigmaPlot* (*Systat Software. Inc., USA*) and *Matlab* (*Mathwork. Inc., USA*) software. Thirty data points (corresponded to 30 heart beats) from each subject were randomly selected from 2 to 4 min data fragments containing artery waveform and systemic haemodynamic data for further statistical analyses. Within-subject comparisons of bilateral difference of artery diameter, waveform parameters and systemic haemodynamic variables were assessed by repeated measurement analysis of variance (RM ANOVA) with a post-hoc Tukey test comparing four data sets (two legs, two repetitions). In addition, the effect of size difference between artery waveform parameters in paired legs was examined using Cohen's d test. A significant effect has been considered at $d \geq 1.2$.[24] The degree of parameter asymmetry between legs was assessed using paired leg parameter ratios,-bilateral asymmetry ratios. The leg with higher parameter values were denoted as a denominator, thus giving parameter lower value/parameter higher value. Calculated in this manner, the *bilateral asymmetry ratio* lies between zero (absolute asymmetry) and unity with maximum symmetry when paired parameters are exactly equal.[25] The determination of possible association between asymmetry of ramification pattern and asymmetry of artery haemodynamic parameters were made using general linear model analyses (GLM). Associations between degree of asymmetry and subject anthropometric parameters were evaluated as Pearson's correlation coefficients (r). Data are provided as means ± SEM or percentages. The p value at <0.05 was considered statistically significant.

Results

Subjects anthropometry

Anthropometric measures of subjects left and right legs did not differ (accuracy ± 1 mm) therefore only single leg measures have been selected for further volume and muscle mass calculations. The mean values of study group were following: height 1.68 ± 0.06 m, (range 1.53—1.78 m); weight 56.75 ± 5.6 kg (range 48—67 kg); BMI 20 ± 1.61 kg/m^2 (range 17—23 kg/m^2); thigh volume 7.18 ± 1.98 L, (range 2.6—10.5 L); calf volume 2.29 ± 0.45 L, (range 1.2—3.2 L); calculated *m.quadriceps* mass 2.54 ± 0.61 kg, (range 1.15—3.58 kg).

Table 1 Bilateral comparison of femoral artery ramification patterns.

Parameters	Cases on the left side	Cases on the right side
Aspect of DFA origin		
Posterolateral 	58.33%	37.5%
Posterior 	29.16%	58.33%
Lateral 	8.33%	4.16%
Posteromedial 	4.16%	0%
Direct LCA origin		
From DFA 	95.83%	91.66%
From CFA 	4.16%	8.33%
Direct MCA origin		
From DFA 	91.66%	95.83%
From CFA 	8.33%	4.16%
DFA length		
0—10 mm	41.67%	41.67%
11—20 mm	41.67%	45.83%
21—30 mm	16.67%	12.5%

Ultrasonography acquired anatomical characteristics of femoral arteries in paired legs ($n = 25$). Table illustrates aspect of deep femoral artery (DFA); classification of[18], distance of origin of Medial or lateral circumflex from origin of DFA represents straight segment of DFA.

Artery ramification patterns

Statistical analyses revealed significant laterality of femoral artery ramification patterns in paired legs. Thus in one third of all cases (33.3% cases) we observed asymmetric DFA origin. On the right side in the majority of cases (58% cases) the deep femoral artery originated at the *posteriolateral* aspect of the common femoral artery but on the left side at posterior aspect (58% cases), while other aspects were found less frequently, as seen in Table 1.

We found no noticeable differences in the origin of the lateral circumflex artery (LCA) and medial circumflex artery (MCA) on both sides- that is, the difference between left and right sides were only in 12.5% cases. One fifth (20.5%) of all examined women showed bilateral difference of the deep femoral artery segment length (distance from the origin of the deep femoral artery to the first branching). However there was not any relation between subject anthropometric parameters and artery ramification patterns.

Artery diameter

The femoral arteries diameters of (SFA and DFA) were different on the right and left sides. In 70% of cases bilateral differences of DFA baseline diameter were observed and 72% in SFA baseline diameter. The larger SFA diameter on the right side was observed in 65% of woman and the larger DFA diameter on the left side in 54%.

There were no notable relations between artery diameter and subject anthropometric parameters, except subject weight and right SFA diameter ($r = 0.45$; $p = 0.02$). A group comprising young women demonstrated similar asymmetry degrees for both arteries (DFA:0.95 $\pm$ 0.06; SFA:0.92 $\pm$ 0.07). However the SFA artery showed a slight tendency to be less asymmetric.

Systemic haemodynamic parameters

In the entire sonographic examination protocol (four trials) all systemic cardiovascular parameters showed high stability (paired *t*-test; $P < 0.001$). However for some parameters there was a slight intersubject variability. The average values representing the subject group were as follow: systolic arterial blood pressure (P_{sys}) 118.35 $\pm$ 7.15 mmHg, range 101.35—125.69 mmHg; diastolic arterial pressure (P_{dia}) 67.50 $\pm$ 6.19 mmHg, range 60.77—75.96 mmHg; mean arterial pressure (P_M) 87.31 $\pm$ 6.76 mmHg, range 76.58—100.97 mmHg; heart rate (HR) 70.66 $\pm$ 11.00 bpm, range 60.05—90.83 bpm, cardiac output (CO) 4.89 $\pm$ 0.98 L/min, range 3.15—6.46 L/min and total peripheral resistance (TPR) 1100.04 $\pm$ 248.78 dyn, (range 882.45—1480 dyn).

Artery haemodynamic parameters

In general, arterial haemodynamic parameters varied between the subjects and between the paired legs within an individual. Analyses (RM ANOVA) revealed that in 95% subjects at least one haemodynamic parameter differed within paired legs. Considering that arterial pressure, heart rate and cardiac output were equal, there was a convincing difference ($p < 0.05$) between the arterial haemodynamic parameters recorded from arteries on contralateral sites, and there were no differences of parameters obtained ipsilateraly. Individual values of arterial haemodynamic parameters in paired legs for both SFA and DFA are depicted in Fig. 1, whereas computed magnitudes of bilateral differences differ across parameters, as illustrated in Table 2.

Correlation and GLM analyses did not confirm statistically significant relations or interactions between femoral artery asymmetry as a factor or any anatomical differences (factor 2) in paired legs.

Moreover we did not observe any significant correlation between the magnitude of bilateral ratios for artery haemodynamic parameters (either SFA or DFA), and artery diameter, except in an inconsiderable correlation ($r = 0.4$; $p = 0.04$) in few cases when the haemodynamic parameters were directly calculated from diameter data, such as blood flow (product of linear velocity and crossectional area).

Discussion

To date there are a relatively small number of studies regarding bilateral asymmetry of the large conduit arteries.[26—28]The present study revealed a slight, hence statistically significant, haemodynamic, anatomical and morphometric asymmetry of femoral arteries in paired legs of young and healthy women with a sedentary life style (students). To the best of our knowledge, this is the first study utilising an ultrasonography method for bilateral assessment of femoral artery anatomy (ramification) and its possible impact on asymmetry of artery haemodynamic and morphometric parameters.

While comparing the anatomical differences of arteries, the most significant asymmetry was observed in the types of origin of deep femoral artery, as can be seen in Table 1. The results are consistent with the findings obtained in previous studies exploiting cadaver dissection techniques.[18,19,29] According to our study the most common site of origin of the deep femoral artery was from the posterolateral aspect of the common femoral artery and the distance from origin of the deep femoral artery to the first perforating artery (straight segment) was in the range of 11—30 mm, showing slight bilateral asymmetry.

Despite many variations of LCA and MCA branching patterns[30] which are described in literature, in the present study branching patterns were grouped in two most frequently observed types: 1) LCA and MCA origin from DFA; and 2) LCA and MCA origin from CFA. Relatively small asymmetry was observed in the origin of lateral circumflex artery and medial circumflex artery — most women have these arteries originated from DFA, as also reported else where.[10,11,19,31,32] Contrary results have been obtained in the study on a population of Turkish people employing CT Angiography ($n = 300$) — women demonstrated more cases of LCA and MCA originated from CFA.[33]

Observation regarding female artery diameter data implies that the detected bilateral difference was significant even in the case when the selected discrimination criterion

(value) was relatively low (3% difference; which corresponds to approx. 0.17 mm) in comparison to SFA diameter changes during routine FMD test; which is approximately 3—7% from basal level.[34,35]

However, experiments performed in the Thijssen laboratory, have much lower variation and potentially higher discrimination criterion (1.5%),[21,36] which is closer to the variability used in our study. Conversely, in the studies assessing asymmetry of vertebral arteries performed by Mysior et al. the discrimination criterion was set to 25%, which corresponds to 0.5 mm[37] and taking into account such tolerance, healthy subjects couldn't exhibit differences in diameters on both body sides. Similar to ours, recent studies confirm the relationship between femoral artery (SFA and DFA) diameters and body mass(weight),[38] but no relationship with the thigh volume and muscle mass.[39] We can hypothesize that the weak or absent correlation between variations of different artery morphometric parameters suggest that the observed anatomical and morphometric asymmetries are fluctuation type (rather

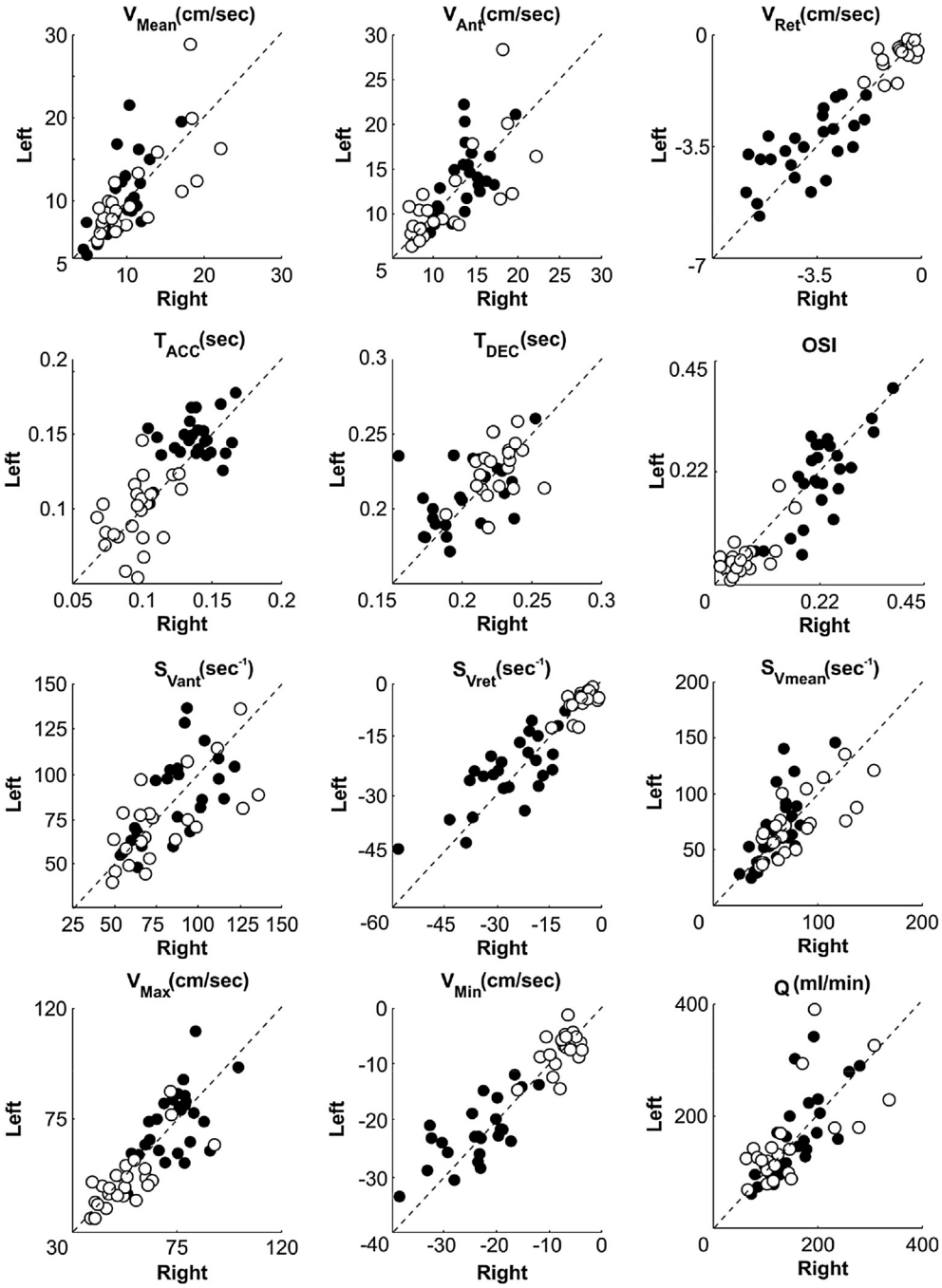

Figure 1 Scatter graph illustrates subjects ($n = 25$) individual mean values of haemodynamic parameters (see Table 2) obtained from superficial (black circle) and deep (white circle) femoral arteries on both sides. Dotted line indicates entire bilateral symmetry, deviation from line- increasing degree of asymmetry.

Table 2 Assessment of femoral artery haemodynamic parameters asymmetry degree.

Haemodynamic parameters	SFA artery		DFA artery	
	% Asym.	Bilat. ratio.	% Asym.	Bilat. ratio.
Linear velocity V_{Mean} (cm/sec)	69%	(0.80 ± 0.13)	66%	(0.81 ± 0.12)
Antegrade linear velocity V_{Ant} (cm/sec)	71%	(0.86 ± 0.10)	71%	(0.82 ± 0.11)
Retrograde linear velocity V_{Ret} (cm/sec)*	65%	(0.80 ± 0.12)	40%	(0.64 ± 0.24)
Acceleration time T_{ACC} (sec)	73%	(0.90 ± 0.08)	46%	(0.85 ± 0.13)
Deceleration time T_{DEC} (sec)	50%	(0.92 ± 0.08)	16%	(0.94 ± 0.05)
Mean shear rate $S_{V_{mean}}$ (s^{-1})	65%	(0.79 ± 0.13)	75%	(0.80 ± 0.12)
Antegrade shear rate $S_{V_{ant}}$ (s^{-1})	57%	(0.83 ± 0.10)	50%	(0.81 ± 0.11)
Retrograde shear rate $S_{V_{ret}}$ (s^{-1})*	77%	(0.76 ± 0.13)	66%	(0.62 ± 0.27)
Blood flow Q (ml/min)	65%	(0.81 ± 0.12)	63%	(0.77 ± 0.16)
Peak linear velocity V_{Max} (cm/sec)	54%	(0.88 ± 0.07)	75%	(0.89 ± 0.08)
Minimal linear velocity V_{Min} (cm/sec)	58%	(0.84 ± 0.10)	54%	(0.73 ± 0.20)
Oscillatory index OSI*	31%	(0.79 ± 0.09)	67%	(0.61 ± 0.24)

Percent of cases showing statically significant bilateral difference of femoral artery (SFA and DFA) haemodynamic parameters (% asym.) and mean value of degree of asymmetry (bilat. ratio). As the bilat. ratio tends towards unity (1), symmetry on both sides increases. The group ($n = 25$) mean parameter values ± std are depicted in table. The statistically significant ($P < 0.05$) difference between bilat. ratios of different femoral arteries (SFA and DFA) are denoted by asterisks.

than directional) — they do not display any directional tendency but is a type of developmental instability.[40,41]

Another important issue addressed in the present study was registering basal values of artery haemodynamic parameters (Ultrasound Doppler velocity waveform indices). Interestingly the registration of Doppler waveform parameters in lower legs is yet to become a routine procedure, however there still are a limited number of papers describing quantification of artery haemodynamics utilising Doppler waveform analyses.[20] And very often the reported values differ from author to author. This question is particularly important as novel indices in the near future might have wide clinical implications. Therefore we prioritised obtaining unbiased SFA and DFA artery haemodynamic parameters which would characterise young healthy, sedentary women.

The basal values of femoral artery haemodynamic parameters obtained presently are consistent with those reported in previous studies. Thus, shear rate values of SFA obtained from healthy young volunteers (males and females) by high-resolution magnetic resonance phase contrast blood velocity measurement techniques were similar to ours.[23] This finding is in agreement with Newcomer SC et al.,[22] Thijssen DH et al.[34] However SFA basal mean shear rate reported by Wu et al.[23] utilising MRI was much larger, while in the study of Thijssen DH et al.[35] was slightly lower. Superficial femoral artery oscillatory index basal values were similar in our study and study of Bell J et al.[42] and Wu et al.[23]

Basal shear rates and oscillatory indexes obtained in our study are consistent with those reported by other authors.[43] The possible explanation of minor discrepancies between basal values reported in different studies would be related to the subject group and utilised methodology. Comparing the basal values of haemodynamic parameters in different femoral arteries (DFA and SFA) (see Table 3); they differ, reflecting distinctive properties of vascular beds and peripheral resistances. The degree of bilateral difference (bilateral ratio) of femoral artery flow related parameters identified in the present study was similar to that obtained by Mayrovitz during segmentary thigh blood flow measurement, and (such difference) has been defined as the asymmetry of healthy subjects.[25]

An important finding is that bilateral asymmetry of artery haemodynamic parameters is related neither to subjects' anthropometric nor artery anatomical parameters and the magnitude of this asymmetry is larger for retrograde linear velocity, retrograde shear rate and oscillatory index. As reported in the literature these parameters reflect peripheral resistance of microcirculatory bed.[44] This can be especially marked for DFA, which supply quadriceps muscles and bilateral differences of haemodynamic parameters could be related to functional differences of this muscles.

There is evidence that the microcirculatory vascular bed (density of capillaries, vascular tone of precapillary sphincters, and haemodynamic vascular resistance) in skeletal muscles reflects local morpho- function properties of muscle, which conversely depends on exercising (every day activity) of the muscle, and may not be uniform on paired legs. This assumption is supported by the Study of Lanshammar et al confirming bilateral asymmetry of muscle force and muscle composition in young non-athletic woman.[45]

Contrary to our hypothesis, which postulates that geometry of the arterial tree would account for the observed asymmetry of artery haemodynamic parameters, the significant shear difference in femoral arteries of paired legs indirectly suggests that the observed asymmetry is of rather functional nature. This conclusion is supported by the finding that a lowered basal shear rate indicates to adaptation to exercise and the increased arterial diameter,[46] whereas increased basal shear rate points to adaptation to sedentary life style and reduced diameter.[47] Also it has been shown that physical activity related factors can enhance alterations of mean shear rate, such as vascular resistance of thigh and calf,[48] elevated blood pressure in

Table 3 Comparison of SFA and DFA haemodynamic parameters.

Haemodynamic parameters	SFA artery (mean ± std)	DFA artery (mean ± std)	Significance level
Linear velocity V_{Mean} (cm/sec)	9.60 ± 3.88	10.67 ± 5.02	$p = 0.508$
Antograde linear velocity V_{Ant} (cm/sec)	13.33 ± 3.46	11.29 ± 4.83	$p = 0.001$
Retrograde linear velocity V_{Ret} (cm/sec)	−3.82 ± 1.37	−0.67 ± 0.46	$p = 0.001$
Acceleration time T_{ACC} (sec)	0.14 ± 0.02	0.10 ± 0.02	$p = 0.001$
Deceleration time T_{DEC} (sec)	0.21 ± 0.02	0.23 ± 0.02	$p = 0.001$
Mean shear rate $S_{V_{mean}}$ (s^{-1})	63.93 ± 27.44	79.74 ± 36.88	$p = 0.036$
Antegrade shear rate $S_{V_{ant}}$ (s^{-1})	89.46 ± 25.72	83.21 ± 34.66	$p = 0.080$
Retrograde shear rate $S_{V_{ret}}$ (s^{-1})	−25.10 ± 10.41	−4.91 ± 3.22	$p = 0.001$
Blood flow Q (ml/min)	162.06 ± 64.30	148.35 ± 77.79	$p = 0.224$
Peak linear velocity V_{Max} (cm/sec)	74.02 ± 12.52	52.23 ± 12.38	$p = 0.001$
Minimal linear velocity V_{Min} (cm/sec)	−23.37 ± 6.70	−7.39 ± 3.07	$p = 0.001$
Oscillatory index OSI	0.22 ± 0.08	0.06 ± 0.04	$p = 0.001$

Mean values of haemodynamic parameters for superficial (SFA) and deep femoral (DFA) arteries. Data pooled together from both sides. The sedentary young women group ($n = 25$; 2 sides) mean value ± standard deviation are reported in table. p value refers to a Man–Whitney Rank sum test, significant p values are indicated with bold.

the leg vasculature during seated posture (our subjects were sedentary), and changes of artery curvature.[22,49] That is why a slightly lower (and different) daily activity of one leg and a slightly higher of the other may cause a small, hence statistically significant, asymmetry, which appears negligible in comparison to the bilateral difference of peripheral artery disease patients. We can merely speculate that the presently observed unilateral changes of femoral artery haemodynamic parameters of young healthy and sedentary women could be considered as an origin of potential genesis of artery structure pathological changes later in older age.

Conclusions

Most of the young and healthy women (roughly 80%) leading a sedentary life style exhibited small anatomical (the direction and type of the ramification, morphometric artery diameters) and haemodynamic (blood flow velocity related parameters) bilateral asymmetry of femoral arteries in paired legs.

Limitations of the study

Despite the careful planning of experimental design and the accurate implementation of all procedures, there are still several limitations that may potentially interfere with present findings and therefore results should be interpreted with precaution.

Arterial structure has been detected via sonography; however additional imaging methods (such as CT or MRI) might be used as a reference. Although it is known that a high-resolution ultrasound system used by an experienced specialist can provide results with comparatively high precision concerning the structure and geometry of a large artery,[50] presently most (peripheral artery disease) PAD diagnosis are made using ultrasound Doppler.

This study comprised a relatively small sample size (25 women), which may not fully reflect characteristics of general population. However, use of within a subject comparison design with a large individual sample size (30 beats) and full randomisation may yield to significant results. The powers of the applied statistical tests were verified and always were in the range to consider statistics significant.

Subject anthropometric parameters (muscle mass) were obtained by callipers and a measuring tape and not by more reliable methods such as CT, MRI or DEXA. However there were numerous studies showing that anthropometric methods are valid and their results are closely correlated to CT and MRI.[51,52] Moreover correlation analyses performed in the present study require only relative values of muscle volume and mass, thus errors of absolute values can be neglected.

Ultrasound Doppler imaging method instead of others more prone to operator mistakes has been utilised for measurement of basal values of artery haemodynamic parameters (Doppler waveform derived indices). Special attention has been paid for this issue as it is crucially important for reliable bilateral comparison of femoral artery haemodynamic parameters. To avoid inter observer variability, sonographic scanning on both sides were performed by the same experienced sonographer (Z.M.). Prior to this study our group estimated (CV%) variability coefficients (including: intra observer, ultrasound device, automated analyses software) which were similar or even lower to those reported by Green at al, and Hussain et al. with a slight differences for different femoral arteries and different haemodynamic parameters (for SFA 3%–8%; for DFA 6–12%, depending on measured parameters). The whole experiment design was intended to avoid different confounding factors which might compromise results.

The daily activity level has been obtained by questionnaires, which is a rather subjective method in comparison to techniques such as personal activity monitors. We feel that the women have answered questions truthfully, and even if the data had been slightly different from reality, full time student daily activity level shouldn't differ notably and are considerably lower than those of the trained athletes.

Disclosures

None.

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Assessment of conduit artery vasomotion using photoplethysmography

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ABSTRACT

Vasomotion is a spontaneous oscillation of vascular tone. The phenomenon has been observed in small arterioles and capillaries as well as in the large conduit arteries. The layer of smooth muscle cells that surrounds a blood vessel can spontaneously and periodically change its tension and thereby the arterial wall stiffness also changes. As the understanding of the phenomenon is still rather obscure, researchers would benefit from a low-cost and reliable investigation technique such as photoplethysmography (PPG). PPG is an optical blood pulsation measurement technique that can offer substantial information about the arterial stiffness. The aims of this pilot study were to evaluate the usefulness of the PPG technique in the research of vasomotion and to investigate vasomotion in the relatively large conduit arteries. Continuous 15 minute long measurements of posterior tibial artery wall stiffness were taken. Artery diameter, electrocardiogram, blood pressure and respiration were also simultaneously registered. Fast Fourier Transform power spectra were calculated to identify unique stiffness oscillations that did not correspond to fluctuations in the systemic parameters and thus would indicate vasomotion.
We concluded that photoplethysmography is a convenient method for the research of the vasomotion in large arteries. Local stiffness parameter b/a is more accurate to use and easier to measure than the pulse wave velocity which describes stiffness of a segment of an artery. Conduit arteries might exhibit a low amplitude high frequency vasomotion (9 to 27 cycles per minute). Low frequency vasomotion is problematic to distinguish from the passive oscillations imposed by the arterial pressure.

Keywords: conduit artery, low frequency oscillations, photoplethysmography, pulse wave velocity, spectral analysis, stiffness, vasomotion, b/a

1. INTRODUCTION

Blood vessels exhibit vasomotion – spontaneous oscillation of vascular tone[1]. The phenomenon has been observed in small arterioles such as in the skin microcirculation[2] as well as in the large conduit arteries[3]. Diameter of a blood vessel can change because of the surrounding layer of smooth muscle cells. For example, if the tension of the smooth muscle layer increases, stiffness of the artery wall will accordingly increase and depending on the systemic blood pressure, the blood vessel will more or less constrict. The recent findings have shed some light on the cellular mechanism of the spontaneous oscillations of the smooth muscle tone[4], however, the physiological role of the phenomenon still remains unclear. It is proposed that vasomotion might have a role in tissue oxygenation when perfusion is compromised and therefore it might have a substantial pathophysiological importance[1]. Vasomotion is generally considered not to be the consequence of heartbeat, respiration or neuronal input and the oscillations have been shown to be generated locally from within the vascular wall in *in vitro* experiments. However, the influence of a central mechanism is also hinted by the somehow controversial finding of synchronous diameter oscillations in contralateral arteries[5]. The presence of vasomotion can be demonstrated directly by continuous measurements of diameter changes in blood vessels using vital microscopy or ultrasonography, and indirectly by measuring blood-cell velocity, capillary pressure variations as well as laser-Doppler flow variations[1]. The research in this field is ongoing but the understanding of the phenomenon is still rather obscure. However, the applications of vasomotion monitoring seems to be a promising method of vascular disease diagnostics[6] and researchers would benefit from a reasonable and reliable investigation technique such as photoplethysmography (PPG).
Photoplethysmography is an optical measurement technique that can be used to detect blood volume and blood perfusion changes in the vascular bed[7]. Light traveling through tissue is reflected, backscattered and partially absorbed by different

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substances, including skin pigmentation, and hemoglobin. PPG sensor consists of an IR-LED that radiates into the tissue and a photo detector that measures the intensity of the backscattered or transmitted (depending on the sensor type) light[8]. The intensity of the measured light over time constitutes the PPG signal. PPG has been shown to be a promising technique to use in various clinical measurements[8]. Substantial information about the arterial wall stiffness can also be obtained from the PPG signal[9,10].

Arterial stiffness is the resistance to stretching of the arterial wall – as mentioned above it is related to the vascular tone, but age and the state of health are known to be important determinants as well. Stiffness of a segment of a blood vessel, i.e., **regional stiffness**, can be determined by measuring pulse wave velocity (PWV) which is directly proportional to the average wall stiffness in the segment of artery where the pulse travelled[10]. Pulse wave travels faster in a stiffer artery. Stiffness at an exact point on the artery, i.e. **local stiffness**, can be assessed from the second derivative of the PPG signal[9,11]. Oscillations of the vascular tone reflects in the stiffness and therefore the vasomotion phenomenon could be identified by showing autonomous fluctuation in stiffness which does not have corresponding oscillations of similar frequency in systemic parameters such as arterial pressure, respiration and heart rate. Local haemodynamic variables like stiffness are influenced by various systemic processes such as baroreflex, respiration movements and the beating of the heart. These central influences cause the artery wall stiffness to change periodically in various frequencies which add up and thus the time series of the stiffness is combined. One can distinguish the frequency components of the time series by calculating the power spectrum. The frequency components that are unique to stiffness and thus indicating vasomotion can be found by comparing power spectrum of stiffness to the power spectra of systemic parameters.

The goals of this pilot study were (1) to evaluate the usefulness of the PPG technique in the research of vasomotion and (2) to investigate vasomotion in the relatively large conduit arteries.

2. METHODS

2.1 Experimental design

Five healthy subjects (2 male and 3 female, 20 ± 1 years old) were enrolled in this study. All subjects gave their informed consent. They were asked to refrain from the consumption of caffeine drinks, alcohol or medication for 12 hours prior to the measurement. Measurements were repeated for each subject, approximately one week after the first session. During the measurement the subject was laying in a prone position on an ergonomic bed in a comfortable and quiet environment, at a room temperature of 22 – 25 °C. Continuous 15 minutes long time-series of the PPG signal, electrocardiogram (ECG), mean arterial pressure (MAP), respiration movements and artery diameter were simultaneously registered.

2.2 Assessment of artery wall stiffness

Regional stiffness was determined by measuring PWV for each consecutive heartbeat. Two reflection type PPG probes were securely placed on the subject's right leg and pulse wave signals were registered from the posterior tibial artery. First probe (PPG1) was placed right next to the knee pit, second probe was placed on the ankle (PPG2) – see Figure 1.

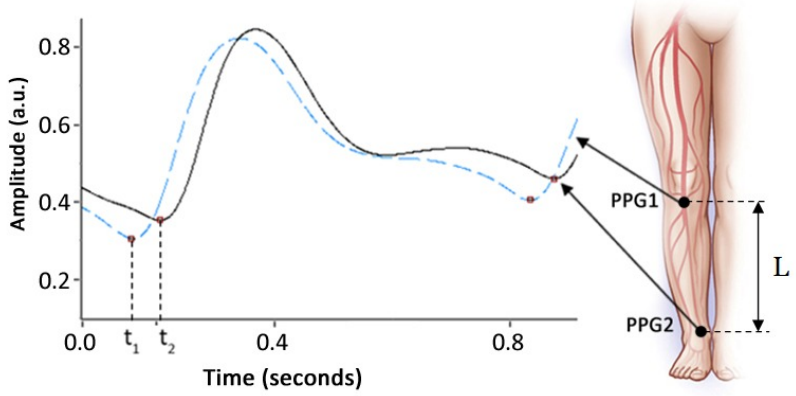

Figure 1. Determination of PWV. Two PPG probes were placed on the posterior tibial artery L cm apart and signals from both sensors were recorded (PPG1 sensor at the knee pit – dashed line, PPG2 sensor at the ankle – solid line). The pulse transit time PTT = $t_2 - t_1$. PWV = L/PTT, where L is the distance between probes.

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The distance in time between the beginning (foot) of both PPG pulse waves is the time the pulse wave travelled from the knee to the ankle (pulse transit time - PTT). PWV was calculated as follows:

$$PWV = \frac{L}{PTT} = \frac{L}{t_2 - t_1} \qquad (1)$$

where PWV – pulse wave velocity, L – distance between PPG probes which is an estimation of the distance the pulse wave travelled, PTT – pulse transit time, t_1 – the beginning (foot) of the PPG1 pulse wave, t_2 – the beginning (foot) of the PPG2 pulse wave.

Local stiffness was determined by calculating the second derivate of a PPG signal from a single probe and measuring the ratio b/a – the absolute value of the ratio of the first and second extremes of the second derivative (Figure 2). Stiffness parameter b/a is strongly related to distensibility and it is inversely proportional to the arterial stiffness at the exact point where the probe is placed[9,11]. In this study b/a was calculated from the signal of the PPG1 probe placed at the knee pit, because it was closer to the ultrasound probe which monitored the artery diameter.

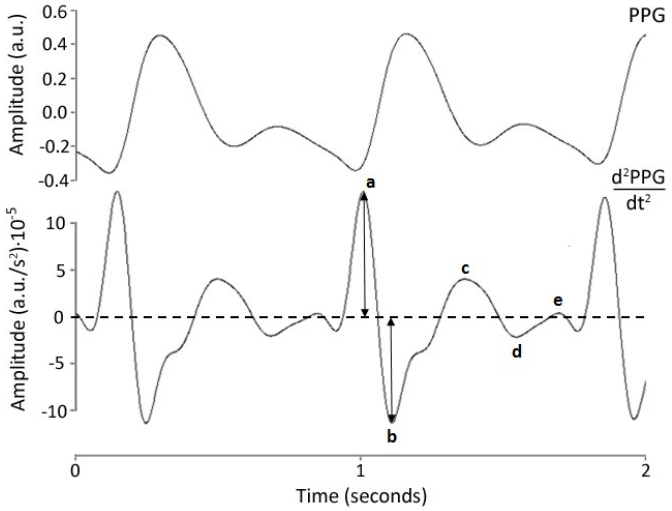

Figure 2. PPG signal (top) and its second derivative (bottom); a, b, c, d and e extremes are shown. Stiffness parameter b/a is obtained from the ratio of a and b amplitudes (|b/a|).

2.3 Materials and data acquisition

PPG signal recordings were performed by using a custom-made four channel PPG bio-amplifier (*Institute of Atomic Physics and Spectroscopy, Latvia*). Electrocardiogram was registered by using an ECG sensor T9306M (*Thought Technology, USA*). Mean arterial pressure was measured by „Finometer Midi" (*FMS, B.V., Netherlands*). Respiration was registered by the SA9311M probe (*Thought Technology, USA*). All analogue signals were acquired using USB-6211 data acquisition board (*National Instruments, USA*) with a 1 kHz sample rate and stored on a PC using "LabVIEW" software. Artery diameter was assessed by using "TITAN" ultrasound system (*SonoSite, USA*) – the video stream of the artery longitudinal section was continuously recorded on a PC via DVI2USB grabber (*Epiphan Systems, USA*) using "VirtualDub" application (25 fps, 600 Kbps compression, Microsoft MPEG-4 codec) and later analyzed using software developed in "Matlab" environment specially for this purpose.

2.4 Data processing and analysis

All data processing was done with software developed by authors within the "LabVIEW" environment. Before feature extraction the recorded PPG signal was filtered with an 8 Hz low-pass FIR filter (511 taps) using the forward-backward method to avoid time lag. PPG AC beat waveform processing algorithm[7] was utilized to find the foot of a PPG pulse wave signal. Multiresolution wavelet analysis was used to find the first two extremes of the second derivative of the PPG signal for the calculation of b/a; the same tool was also used to detect R peaks in ECG signal for the calculation of RR intervals. MAP was calculated by the "Finometer Midi" device.

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Power spectra were calculated using the built-in algorithms of "LabVIEW". Before the calculation of Fast Fourier Transform (FFT) the time series were made equidistant by linear 1 kHz interpolation. DC component (f = 0 Hz) of the spectrum was removed by detrending the time-series using wavelet analysis tools – threshold frequency of 8 mHz was chosen as it is the smallest observed vasomotion frequency[12]. Power values were expressed in normalized units (n.u.) by dividing them with the total power in the low frequency (LF) and high frequency (HF) bands (0.008 – 0.45 Hz) and then multiplying by 100[13]. A high value of normalized power signifies the relative dominance of the fluctuations. In this study LF band was defined as 0.008 – 0.15 Hz which is a combination of the conventional very-low frequency (VLF) and LF bands. HF band was 0.15 – 0.45 Hz. Power spectra smoothing was done by 23-point Henderson moving average to better identify separate frequency components.

2.5 Identification of vasomotion

Vasomotion is a phenomenon with periodicity and thus it should appear in the power spectrum of stiffness and maybe even in the power spectrum of the artery diameter. To distinguish between spontaneous fluctuations in stiffness, i.e., vasomotion, and fluctuations influenced by systemic factors, the power spectra of stiffness parameters PWV and b/a were compared to the power spectra of MAP, respiration and RR intervals. Frequency components, i.e., peaks, of the power spectra of stiffness parameters were considered unique (and thus spontaneous) if they did not have equivalent systemic frequency components, i.e. power spectrum peaks at the same frequency in MAP, respiration or RR power spectra. The precise frequency of peaks in a FFT power spectrum is not always possible to determine, therefore for two frequency components to be considered to be at similar frequencies (thus not unique), they needed to be within the 6 smallest frequency steps or 6.6 mHz (the frequency resolution of a FFT power spectrum of a 15 minute measurement with sampling frequency F_s = 1 kHz is df = F_s/N = 1.1 mHz). Six frequency steps were chosen because the Henderson moving average filter has six positive weights around the central value and therefore at any frequency the power value is also influenced by six points on each side.

3. RESULTS AND DISCUSSION

3.1 Oscillations of the arterial stiffness

Both regional and local stiffness parameters exhibited oscillations. Examples of stiffness time series and power spectra can be seen in Figure 3. PWV is directly proportional to stiffness while b/a is inversely proportional, so as expected there were some similarities in the fluctuations in both time series with an opposite phase, e.g., where PWV falls, b/a rises (Figure 3A, around 5 sec). However, the frequency content of the oscillations was not identical which indicates that the dynamics of the local stiffness have differences from the dynamics of the whole artery segment (Figure 3B).

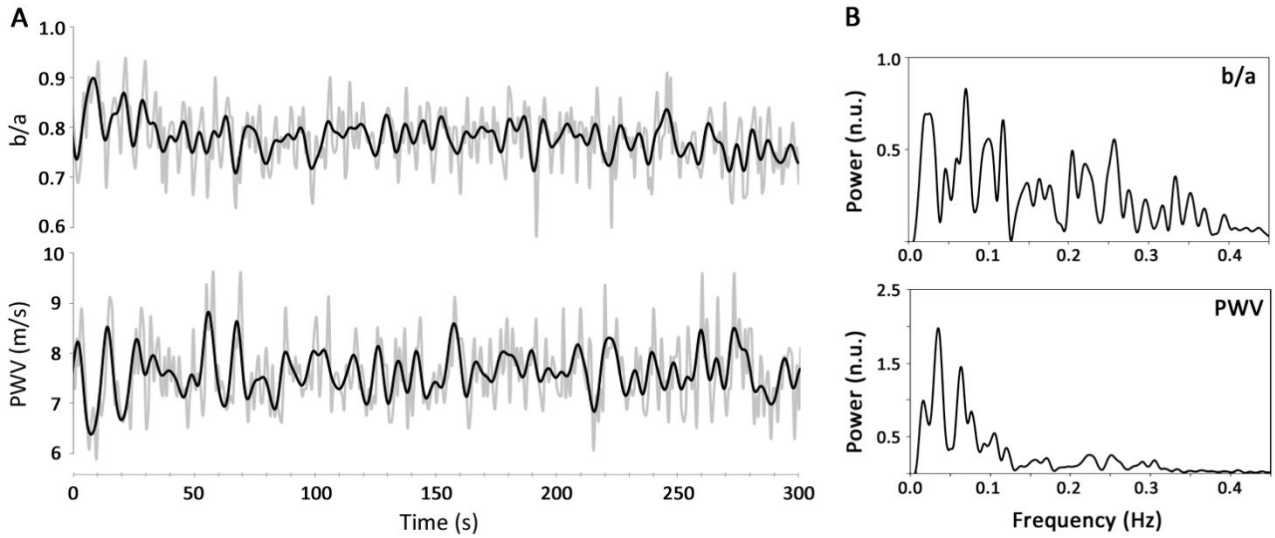

Figure 3. (A) Simultaneous b/a (top) and PWV (bottom) time series for the same subject, 5 min long fragment. Oscillations within LF band (0.008 – 0.15 Hz) are highlighted with a bolder line. (B) Power spectra of b/a (top) and PWV (bottom) of a 15 min measurement for the same subject. Frequency content is clearly different.

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3.2 Values of the stiffness parameters

Local stiffness parameter b/a mean values were between 0.62 and 0.82. The mean b/a for all the group (n = 4) was 0.76 ± 0.09 which is in agreement with the norm for healthy adolescents[11]. For one of the subjects it was not possible to calculate b/a due to poor PPG signal and in further analysis data from the other four subjects was used.
In 6 out of 10 measurements mean PWV was within the norms reported in the literature[14]: 6.5 – 11.9 m/s, group average 8.5 ± 1.6 m/s. In the other 4 measurements PWV was unusually high – over 15 m/s. However, in this study the interest is in relative fluctuations not in the absolute value and, therefore, those measurements could also be included in further analysis (minus the subject with the poor PPG signal).

3.3 Identification of the vasomotion phenomenon

Local stiffness parameter b/a proved to be better for identifying vasomotion, i.e., unique frequency components of the oscillations of arterial stiffness. The unique oscillations of the b/a were found in a broad range between 0.072 and 0.44 Hz while almost all (11 out of 12) of the unique PWV components were in the HF band (Figure 4A). 1 to 7, on average 3 ± 1 unique frequency components could be found in each b/a spectrum. Less ($P < 0.05$) unique frequency components were found in regional stiffness parameter PWV spectra: on average 1.5 ± 1 in each PWV spectrum. The mean normalized power of the unique b/a peaks was significantly higher ($P < 0.05$) than the mean normalized power of the unique PWV peaks (Figure 4B) which shows that the unique b/a fluctuations were relatively more significant than their PWV counterparts. It can be inferred from the data that the oscillations of the local arterial stiffness are less influenced by the systemic processes and that the unique local stiffness oscillations which might indicate vasomotion are with a significantly high amplitude. Furthermore, arterial vasomotion in humans has been reported to be only in the range of 0.01 – 0.05 Hz[3,5] – in our findings only the local stiffness had spontaneous oscillations in this range. Vasomotion in general has been reported to be in the range of 0.008 – 0.30 Hz[12] but this range also leaves out the majority of unique PWV frequency components. It can be concluded that the local arterial stiffness parameter b/a is better suited for the identification of vasomotion than the regional stiffness parameter PWV. As the PWV describes the stiffness of a large segment of the artery, it makes sense that it would be more influenced by the central mechanisms of the cardiovascular system. The spontaneous activity of the smooth muscle cells surrounding the blood vessel might be confined to a smaller area and might not have a significant effect on the propagation of the pulse wave which travels with a considerably high velocity. The usage of parameter b/a is also practically more convenient as only one PPG sensor is required for the measurement, while PWV requires two PPG probes.
The majority (71%) of the unique frequency components of all the arterial stiffness oscillations were found in the HF band. To our knowledge this is the first report of spontaneous oscillations of conduit artery tone in this frequency range. Half of the unique HF components (55%) are out of the reported maximum range of vasomotion at 0.30 Hz[12]. Overall the mean power of the HF components is significantly lower than the mean power of LF components: 0.26 versus 0.53 ($P < 0.05$). The results suggest that the conduit arteries might exhibit a low amplitude high frequency vasomotion with the frequency of 0.15 – 0.45 Hz (9 to 27 cycles per minute).

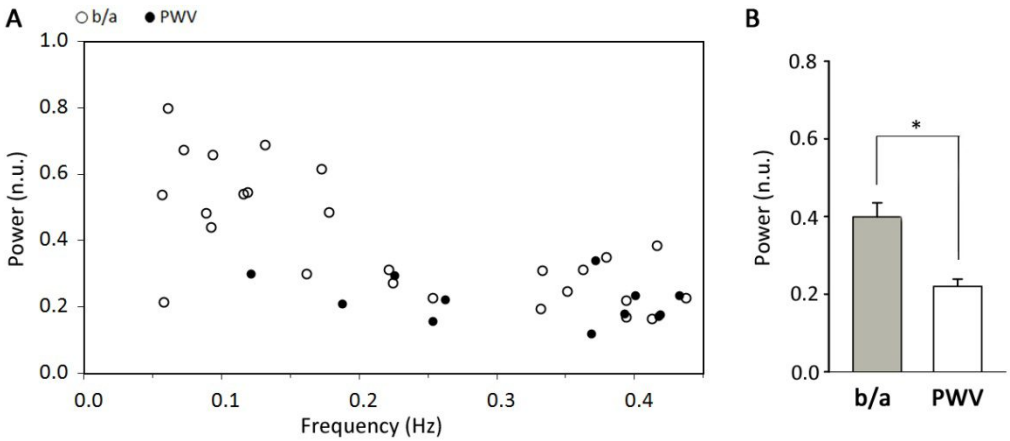

Figure 4. (A) All the unique frequency components of the oscillations of arterial stiffness. (B) The mean normalized power of the unique b/a peaks was significantly higher ($P < 0.05$) than the mean normalized power of the unique PWV peaks.

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Most of the spontaneous b/a oscillations were not accompanied by similar frequency oscillations of the artery diameter (Figure 5). This is not a necessary requirement for vasomotion because it is defined as the oscillation in vascular tone[1] and depending on the arterial pressure the diameter might also stay unchanged if the tension of the muscle cells is insufficient to overcome the intra-arterial force of the pressure. However, the only reports on conduit artery vasomotion provided by Hayoz et al.[3] and Porret et al.[5] have showed oscillations in diameter. In our study artery diameter in general showed a high coherence with the oscillations of MAP (Figure 6). Every MAP power spectrum featured 3 – 5 dominant peaks which turned out to be at almost the same frequencies for all subjects and the oscillations of the artery diameter seemed to reflect all these frequency components. The omnipresent MAP peaks were found at frequencies $f_1 = 0.027 \pm 0.004$ Hz; $f_2 = 0.052 \pm 0.006$ Hz; $f_3 = 0.073 \pm 0.012$ Hz; $f_4 = 0.11 \pm 0.02$ Hz. f_4 in some spectra were closer to 0.10 Hz, in others to 0.12 Hz and in some spectra peaks at both these frequencies were present. f_4 also coincides with the well-known Mayer waves[15]. Frequencies f_1, f_3 and f_4 are already described in an elaborate study by Kuusela et al.[16] where peaks at the same frequencies were found in the systolic pressure oscillations. MAP is a combination of systolic and diastolic pressure, therefore, f_2 might be a component of the diastolic pressure oscillations. The fundamental MAP oscillations cover almost the whole LF range - if vasomotion is also present in the LF range and its frequency is close to one of the MAP frequencies it might be very hard to distinguish vasomotion from the passive oscillations imposed by the arterial pressure.

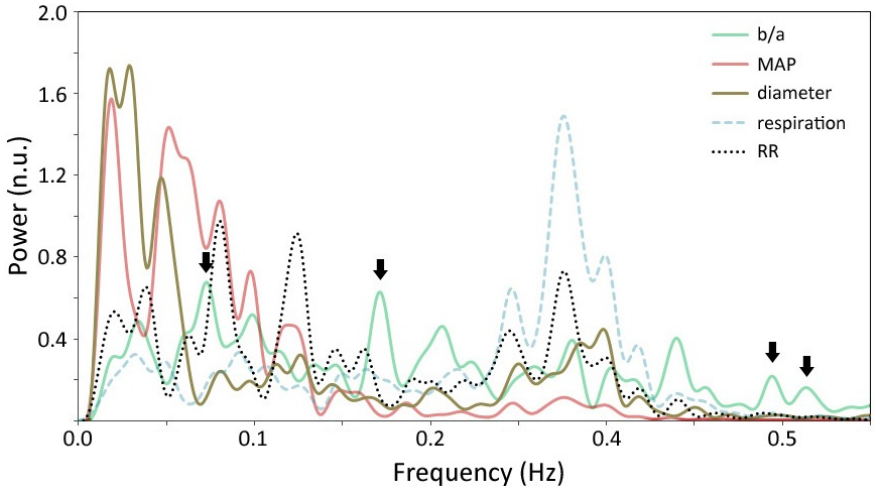

Figure 5. Power spectra of b/a, artery diameter and systemic parameters. Arrows point to the unique frequency components of b/a; note that there are no corresponding diameter frequency components.

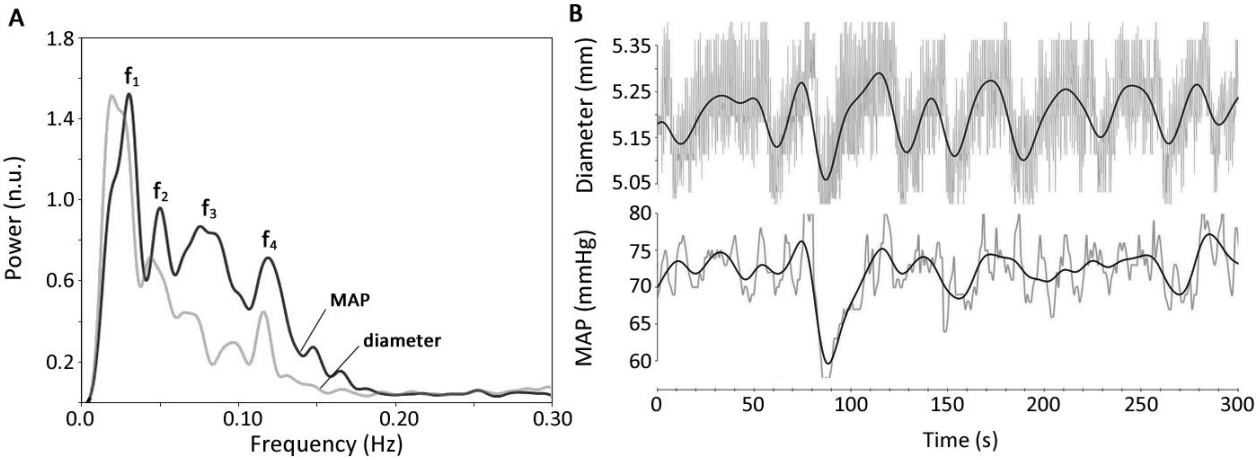

Figure 6. (A) Averaged power spectra of MAP (black) and artery diameter (grey) of the whole group (n = 4); the fundamental MAP peaks are indicated. (B) Example of the artery diameter and MAP time series; slow oscillations ($f < 0.05$ Hz) are highlighted with a bolder line. Note the large amplitude heartbeat pulsations of diameter (lighter line) and the corresponding slow oscillations of diameter and MAP.

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The presence of fundamental LF oscillations of MAP also raises the question whether the aforementioned findings by Hayoz et al. and Porret et al. – artery diameter oscillations of conduit arteries in upper extremities – can be classified as vasomotion. The oscillations in artery diameter observed by them were in the LF range and the amplitude greatly surpassed pulsations of the diameter caused by heartbeat. In our study the pulsations caused by heartbeat were very prominent and only oscillation components in concordance with MAP surpassed them in amplitude (Figure 6B). Furthermore, the fact that the oscillations in diameter where synchronous in contralateral arteries[5] strongly suggests a presence of central influence, e.g., arterial pressure oscillations.

3.4 Limitations and possible improvements of the experimental design

The method of measuring PWV should be improved to minimize the possibility of getting abnormal values. In this study it was observed that sometimes the foot of the pulse wave registered by the first PPG sensor (PPG1) appeared later in time than the foot of the PPG2 pulse wave. As it is physically impossible, a test measurement was performed to check whether the probe contact pressure can influence the time when the foot of the pulse wave appears. Point of reference was the R peak in ECG signal and we measured the distance in time from the R peak to the PPG foot (R-PPT) as a function of the air pressure in an inflatable cushion which presses the PPG probe against the skin. A non linear relationship was discovered: when the probe contact pressure decreased by a critical amount (in this case 160 mmHg), R-PTT started to increase (Figure 7). The maximum increase was 30% (from 196 to 253 mmHg). If the first PPG probe has a too weak contact pressure, the pulse wave will appear later, PTT will be smaller and thus the calculated PWV value will increase dramatically. The effect the probe contact pressure has on the shape of the PPG signal is already described by Grabovskis et al.[17] and now it can be concluded that it also has an effect on the timing of the signal as well. We are now developing a software that would monitor the PPG signal in real-time and alert when the quality of the signal is not optimal.

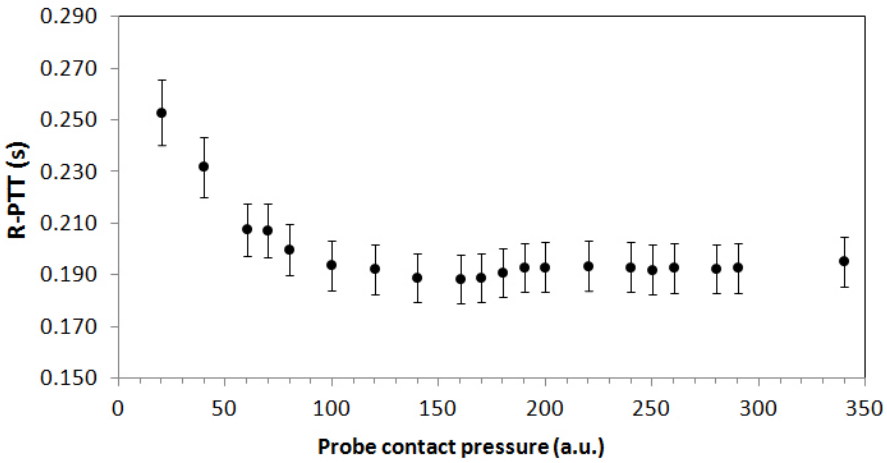

Figure 7. Time distance between R peak of ECG signal and the foot of the PPG pulse wave as a function of probe contact pressure (brachial artery, n = 2).

The study could be improved by using more accurate spectral analysis methods. Biological processes are not perfectly stationary and one process can cause a biological variable to oscillate in various frequencies. These frequencies in the FFT spectrum appear like many narrow peaks close to each other. The peaks can be united into one dominant peak using smoothing algorithms. In this study we used Henderson 23-point moving average, but sometimes the FFT power spectra still featured split peaks – see the first two peaks of the diameter power spectrum in Figure 5 for illustration. Split peaks can lead to wrong interpretation of the data. One way to fix this would be to do stronger smoothing of the spectrum; then the most appropriate algorithm needs to be found. Another way to create smoother spectra is to use auto-regressive (AR) modeling. AR spectrum is smoother and the peaks are less ambiguous. Such an approach is used in the study of the fine features of systolic pressure power spectrum by Kuusela et al.[16] where AR and Wigner-Ville distribution spectra were used in conjunction with FFT spectrum to create the most accurate representation of the pressure oscillations in the frequency domain.

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Smoother spectrum would allow using more quantitative approach to comparing spectra. Analysis in this study was done more qualitatively rather than quantitatively – a specific criterion was devised and employed to distinguish between unique and not-unique peaks. However, spectral analysis allow to calculate coherence which does the same thing quantitatively – it shows how much two signals cohere at a certain frequency. However, in this study the peaks were apparently not accurate enough and coherence could not be used because the calculations gave erroneous results (e.g., low coherence where two peaks where at very close but not exact frequencies).

4. CONCLUSIONS

Photoplethysmography is a convenient method for the research of the vasomotion phenomenon in large arteries. It is more accurate to use and easier to measure the local stiffness parameter b/a derived from the PPG signal than pulse wave velocity that describes stiffness of a region of an artery. Conduit arteries might exhibit a low amplitude high frequency vasomotion with the frequency of 9 to 27 cycles per minute. Low frequency vasomotion (< 9 cycles per minute) is problematic to distinguish from the passive oscillations imposed by the arterial pressure. The timing of the PPG pulse wave can be affected by the probe contact pressure.

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Photoplethysmography system for blood pulsation detection in unloaded artery conditions

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ABSTRACT

Photoplethysmography (PPG) is an optical method of blood pulsation recording and has been extensively studied for decades. Recently PPG is widely used in the medical equipment for patient monitoring and in laboratories for research and physiological studies. In spite of the technological progress in the field of medical equipment, there are no generally accepted standards for clinical PPG measurements up to date. One of the most important factors affecting PPG waveform is the contact pressure between tissue and PPG probe. The aim of the current study was to develop and evaluate a system for software-assisted PPG signal acquisition from the unloaded artery. Novel PPG waveform derived Optimal Pressure Parameter (OPP) has been proposed as the reliable indicator of unloaded artery condition. We affirm that PPG measurements provided in balanced transmural arterial pressure conditions might serve as a reference for the unification of contact manner optical plethysmography methods. It is a step forward towards the standardization of the PPG methodology, and showed that the maximal value of the OPP, obtained in the particular experimental trial, indicates the optimal PPG probe contact pressure at that moment. Our developed system has been validated in the experimental series and showed the possibility of determining the correct PPG contact pressure value with high repeatability. It is concluded that this system can provide the necessary feedback to perform reliable PPG signal acquisition from the unloaded conduit artery.

Keywords: arterial photoplethysmography, probe contact pressure, transmural pressure, unloaded artery wall, optimal pressure parameter

1. INTRODUCTION

Photoplethysmography (PPG) is an optical measurement technique that can be used to detect blood volume and blood perfusion changes in the vascular bed [1, 2]. Light traveling through tissue is reflected, backscattered and partially absorbed by different substances, including skin pigmentation, and hemoglobin. The intensity of either transmitted or backscattered light could be measured by a photo detector, depending of the sensor type and recording mode [3]. In general, photoplethysmography signal is composed of two components – the alternating part (AC component) of total absorbance due to the pulsations of the arterial blood and absorbance due to venous blood, and the non-pulsatile component (DC component) regarding the constant amount of arterial blood and other constant tissue optical factors such as skin pigmentation and hemoglobin [4]. In spite of the relatively simple and well-developed signal acquisition technique, the origins of PPG signal are rather complex. The variations of blood volume and the changes of the red blood cell orientation during pulsatile blood flow have been suggested as important factors [5].

With the technology utilized in commercially available medical devices, PPG has shown widespread clinical applications for non-invasive recording of different physiological variables, such as hemoglobin saturation, heart rate, arterial pressure, and cardiovascular indexes, such as Ankle brachial index (ABI) and reflection index (RI) [1]. A number of studies suggest to PPG waveform parameters as being the indicators of the arterial stiffness and vascular reactivity [6]. Some authors propose using PPG signal parameters for the assessment of endothelial function with a Flow mediated dilation (FMD) test [6 – 9]. PPG signal commonly is being recorded from the digits and the ear lobes. Still, there are some notable studies emphasizing the potential of the PPG for assessment of the conduit artery function. There were a few papers concerning PPG signal acquisition from the skin over the conduit artery – arterial PPG [10 – 13]. Despite the high value of physiological and diagnostic information obtained from the conduit arteries, arterial PPG technique, same as the commonly used peripheral PPG, stays relatively complicated and uncertain because of weak standardization of the recording procedure. Previous research identified the factors affecting PPG recording, including the probe attachment to the tissue, the contact force, pulse rate, signal amplifier and LED parameters, mechanical movement artifacts, subject posture and breathing, wakefulness, room temperature and many other [14, 15].

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Up to date there are no generally accepted standards for clinical or fundamental research PPG measurements. And there are a limited number of studies regarding the standardization of PPG recording [14]. Therefore, it is necessary to seek for a solution towards the establishment of the PPG recording standardization.
The aim of this pilot study was to develop and evaluate a novel system for software-assisted PPG signal acquisition from an unloaded artery. The system incorporates a high-sensitivity low-noise amplifier and the software. The unique embedded algorithm performs real-time computing necessary for the adjustment of optimal PPG probe contact force, thus ensuring correct recording conditions when the artery wall is unloaded and the intravasal and extravasal pressure is balanced. The measurement approach proposed by us could potentially be a step forward, promoting further standardization of PPG signal recording conditions.

2. METHODS

2.1 Measurement system

Probe design and fastenings

The PPG sensor (fig. 1) was built on the basis of the precision, hi-speed transimpedance amplifier (Opa 381, Texas Instruments) with a low-noise low-input bias current (3 pA) for correct circuiting with a photodiode (BPW34-FA, Osram, daylight filter, active surface area: 7mm^2, peak spectral response wavelength: 880nm). The feedback circuit was designed as the 1st order active low-pass filter for about 30 Hz (47 kOhm, 470nF)
To provide sufficient tissue illumination according to measurement conditions, an up to 400 mW 880 LED was used (SIR91-21C/F7, Everlight, peak wavelength 875 nm, a transmission angle 20°, diameter 1,9 mm)

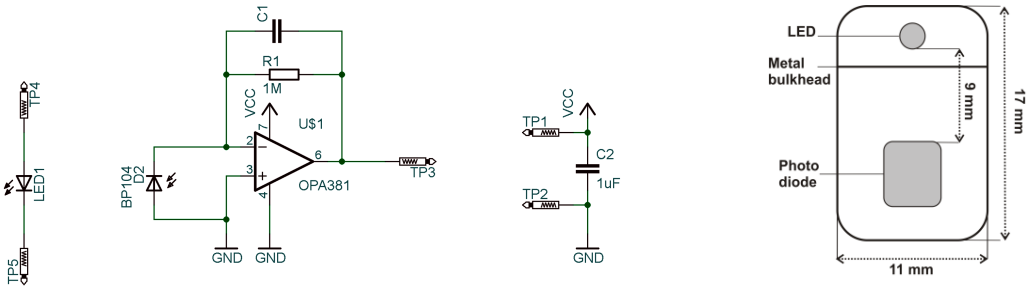

Figure 1. PPG sensor probe and circuit design

PPG probe was fabricated in the dimensions of 11 mm width to 17mm length with a distance of 9mm between the IR LED and PD. The PCB board in the probe was sealed with epoxy resin, and its surface was polished (abrasive grain size P2500). To perform a probe contact pressure adjustment and positioning, two types of fasteners were fabricated. The first: custom assembled micro-thread manipulator (UniSlide, Velmex Inc.) arm with a 360 degree adjustable ball-head bolt for the PPG measurement from popliteal and femoral arteries. The second: a custom made Velcro-strip-attached pneumatic cushion, attached to a precisely controlled air inflation system (AG101, Hokanson) for PPG probe placement over posterior tibial artery. The range of the tissue compression with the fastenings was around 12 – 16 mm for the tissue over the femoral artery, 3 – 5 mm over the tibial posterior and 10 – 12 mm for the popliteal arteries, relative to the level of relaxed tissue.

Data acquisition system

PPG sensor was connected to a custom made biosignal amplifier with an integrated band pass filter and DC remover (fig. 2). The signal was smoothed by the 34 Hz 6th order low-pass active filter (-72dB @ 160 Hz, matched to 12-bit dynamic range of ADC) and the 0,1 Hz 2nd order high-pass filter. The analogue PPG signal output was amplified to a required ADC level by a low-noise programmable gain amplifier microchip (PGA4311, Texas Instruments). The intensity of

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probe LED light source was controlled by a LED driver (LM3595, National Semiconductor). Circuit design, power supply, and sensor wiring was implemented in accordance with the medical equipment directive 93/42/EEC.

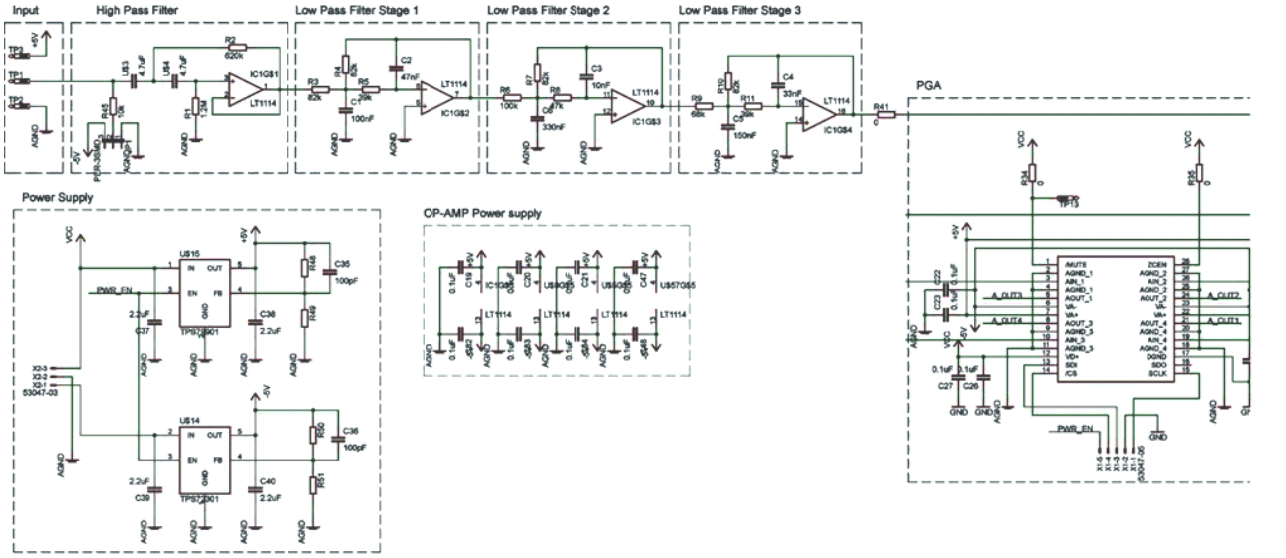

Figure 2. Circuit design of the PPG amplifier

Contact force detector

The contact force between the PPG probe and the tissue over the conduit artery site was controlled by a thin film-type force transducer (FlexiForc A201, Tekscan), inserted between the parallel planes of the PPG probe and the fastener. To provide an adequate signal acquisition, force transducer was connected to a miniature custom-made amplifier with an adjustable offset and gain, and calibrated to pressure units. During the recording, both PPG and contact pressure signals were fed to the 12-bit ADC module (LA2USB, Rudnev-Shilajev) for simultaneous data acquisition and real-time processing.

Real-time signal processing software

Signal processing was performed in real-time by single precision floating point arithmetic (32-bit float). Data acquisition was performed at a 4 kHz sample rate. Signal processing was performed by a digital symmetrical FIR filter with linear phase response for constant delay at all frequencies (8001 taps, 1 sec delay to input signal). The purpose of the software was to acquire the raw PPG signal, to identify the PPG pulse foot (in beat-to-beat manner) and systolic and diastolic peaks. The software incorporates a unique signal processing algorithm, which is implemented with an application software interface (Windows API, Microsoft).

PPG AC beat waveform processing algorithm

PPG signal *S* has been acquired with 12-bit precision, buffered and processed sample-by-sample, as shown in the signal processing state machine chart, (fig. 3). Processing starts in the state *Wait Beat*, where current sample of the signal's *S* 1st derivative *S'* is compared with an exponentially decaying threshold. The algorithm passes to state *Start* where the value of *S'* exceeds the threshold and reaches the maximum and then zero value, where the *S* systolic peak maximum is recognized. When *S'* changes its sign to negative, state *Peak S* is entered where algorithm waits until *S''* becomes positive. Processing continues within state *Wait S''<=0* until *S''* changes its sign to negative again. Depending on the sign of *S'*, the algorithm passes to state *WaitS'<=0* (if *S'* >0) or *PeakD* (if *S'*<=0). By entering state *Peak D*, the algorithm recognizes *S* value as the diastolic peak. In the case of entering state *WaitS'<=0,* the algorithm waits till *S'*

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becomes negative and also enters state *PeakD*. Both of these states can return to the state *WaitS''<=0*, if *S''*, the current value exceeds the maximum value previously fixed at this state in the current PPG beat. The algorithm stays in the state *PeakD*, until the previously calculated time *Timeout* runs out. *Timeout* is calculated from the foot of PPG beat to *PeakS* and adding 2 periods of this length.
The foot of the current PPG beat is detected by the last negative or zero *S'* value before entering the state *Start* (the beat being detected). The state *Start* resets the maximum fixed value of *S''*, and can be entered from any other state, if the next beat is detected. After the time *Timeout* has run out, the algorithm passes to the initial state *WaitBeat*.

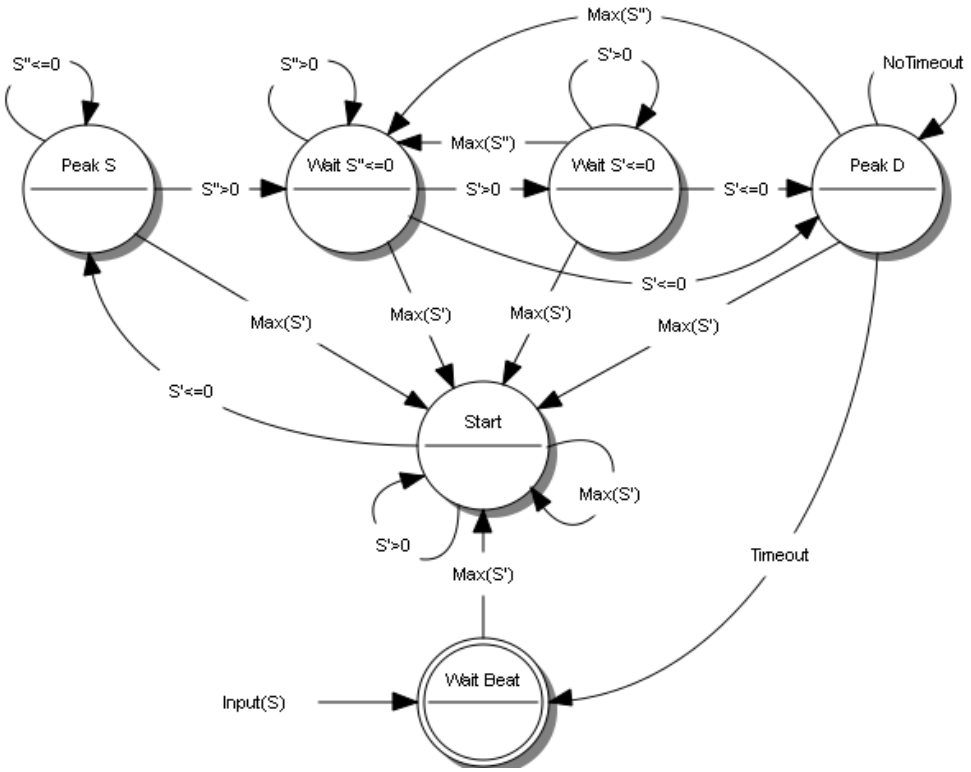

Figure 3. State machine of PPG foot and systolic/diastolic peak detection

2.2 Experimental design and the subjects

In this pilot study we focused on the investigation of parameters indicating the optimal contact pressure between the PPG probe and the tissue over the conduit artery. The experiment was carried out so that the influence of the confounding factors would be maximally reduced - hemodynamics influencing physiological factors, such as alterations of arterial blood pressure, heart rate and arterial tone were avoided. Healthy and normotensive subjects (3 male, 2 female, 28 ±6 years old) were enrolled in this study. The measurement protocol, personnel and devices were approved by the Scientific Research Ethics Committee of the University of Latvia, Institute of Experimental and Clinical Medicine. All subjects gave their informed consent. They were held in a supine position in a comfortable and quiet environment, at a room temperature of 23 – 25 degrees Celsius. All the measurements were performed during resting conditions. To verify the stability of systemic hemodynamic parameters during PPG signal recording, arterial blood pressure and heart rate were monitored with an oscillometric blood pressure monitor (UA-767Plus30, A&D Instruments). To provide correct recording, prior to the positioning of the PPG probe, the geometry and location of the arteries were examined with a portable Ultrasound system (Titan, Sonosite; L38 Linear array 10-5 MHz). After an ultrasound examination and location of the correct arterial site by a mechanical palpation, a single PPG probe was positioned on the skin over the conduit

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artery (fig. 4). During the recording the probe contact pressure was slowly increased to the maximum (the maximum was determined by a rapid disappearance of PPG AC pulsations) and decreased until the probe lost the contact with the skin. The measurement was repeated in three arterial sites (posterior tibial a. site, femoral a. site, popliteal a. site) consecutively in different recording sets, repeating the same measurement. The experiment time was approximately 25 - 35 minutes per subject, ensuring no frustration or stress.

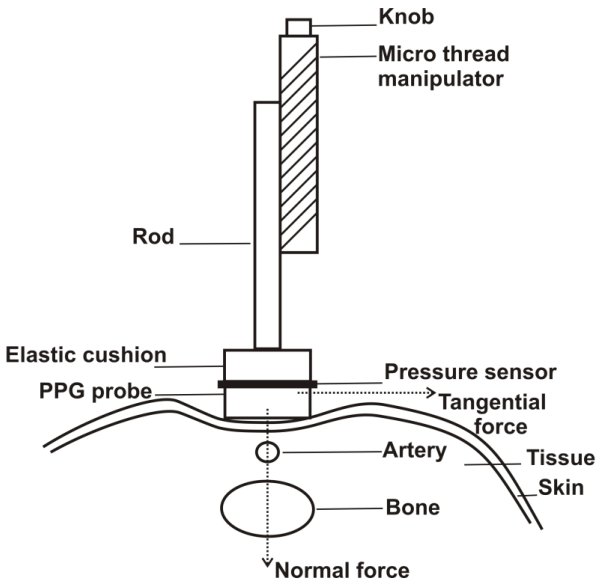

Figure 4. Experimental setup of the PPG measurement – probe contact pressure was adjusted by a micro-thread manipulator and controlled by a FlexiForce transducer. The optimal pressure was assessed by real-time PPG signal waveform analysis.

2.3 Calculations

We were looking for a PPG waveform derived parameter that would indicate the conditions of balanced transmural pressure in the conduit artery and surrounding tissue. Performing the measurements in the conditions of unloaded artery wall could serve as the standardized way of PPG signal acquisition. Relevant studies suggested the PPG AC component dependence on the force applied by the PPG probe [13]. By considering the information from the literature and the evidence obtained in our previous research [13, 14, 16], we calculated a time-averaged mean PPG amplitude A_m (fig. 5), instead of systolic amplitude or normalized pulse area (eq. 1).

$$A_m = \frac{1}{n-i}\sum_{s=i}^{n} A_s \qquad (1)$$

where $s=i:n$ are samples of each PPG AC beat, A_s – amplitude of each sample of PPG AC signal.

To describe the PPG signal waveform dependence on variable contact pressure, the PPG derived index – Optimal Pressure Parameter (OPP) was calculated from the A_m and the diastolic to systolic peak ratio d/s (eq. 2).

$$OPP = A_m \frac{d}{s} \qquad (2)$$

Prior to the calculation of the OPP the values of A_m and d/s were smoothed by median filter.

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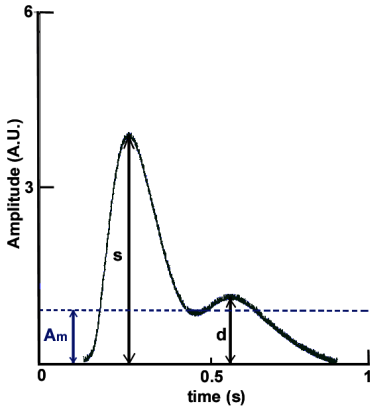

Figure 5. Time-averaged mean PPG amplitude A_m was selected to describe the PPG signal AC amplitude.

3. RESULTS AND DISCUSSION

In evaluation of the custom-designed PPG system and OPP, the low-noise and artifact free PPG signal was acquired from three arterial sites (femoral artery, popliteal artery, posterior tibial artery) of five subjects. Measurements were supported by the real-time OPP guidance software, thus allowing to perform controlled probe contact force adjustments, resulting transmural pressure conditions. The Ultrasound Doppler examination of the arteries revealed normal arterial structure, with appropriate flow velocity profile in all three measurement sites for all subjects. The depth and the diameter of the arteries differed from subject to subject, however, in general, the smallest diameter and depth were observed for the posterior tibial artery (diameter: 2.2- 3.0 mm; depth 3.3-5.2 mm); the monitoring of the popliteal artery returned medium values (diameter: 6.2- 8.1 mm; depth 10.4-30.1 mm), and the largest values showed the femoral artery parameters (diameter: 7.6 – 9.1 mm; depth 8.6-20.4 mm). The literature report confirmed our results, while indicating the difference in diameter between the genders, and the different age [17]. The number of subjects in our group (n=5) was not sufficient to observe such differences in the thickness of the tissue above the monitored arterial site or within the genders. Moreover, the purpose of artery inspection was to exclude any abnormalities in arterial structure.

The waveform of the obtained PPG signal differed depending on the PPG probe contact pressure (fig. 6). Insufficient pressure resulted in an inadequate contact and consequently low-signal AC amplitude. PPG signal recording in excessive pressure conditions lead to an undersized AC amplitude and distorted the waveform caused by the occluded artery beyond the PPG probe. Optimal contact pressure resulted in a high AC amplitude and diastolic to systolic peak ratio.

In addition, the PPG signal from femoral artery was flatter with a less pronounced diastolic peak, the signal from popliteal artery site had a higher diastolic peak amplitude and a more prominent dicrotic notch, while the signal from posterior tibial arterial site typically has a two-hump waveform with a noticeable dicrotic notch and diastolic peak-resembling the shape of the PPG signal from the digits. These observations are in agreement with the previous studies, revealing that the pulse waveform changes as it travels toward the periphery and undergoes amplification and alterations in its shape and temporal characteristics [18, 19] In these papers the authors had reported pressure pulse instead of PPG pulse wave, however it was pointed out that the pressure pulse has similarities to the pulse of the PPG signal [3].

During the measurement all subjects displayed steady-state values of systemic hemodynamic variables. The arterial pressure was similar for all volunteers, (systolic: 118±4 mmHg; n=5) however the length of the cardiac cycle (foot-to-foot interval) slightly differed from subject to subject (920±192 ms; n=5). Steady systemic hemodynamic parameters are crucially important to this study, as the alterations of the mean arterial pressure might unpredictably disturb the established balance between external pressure exerted by the PPG probe, thus modifying the transmural pressure.

When evaluating the effect of PPG probe contact pressure over the conduit arteries to the signal contour derived OPP, we found the maximum of OPP parameter to be a reliable indicator of unloaded artery wall conditions, where the transmural pressure is close to zero and the PPG signal recording is a manageable process. An example of the raw PPG signal waveform is shown below (fig. 7). This figure depicts the changes of OPP reflecting PPG probe contact pressure on the

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tissue over the conduit artery. The optimal probe contact pressure is considered at the point where OPP reaches its maximal value.

Within a subject and at the same measurement site, the coefficient of the variation of the optimal pressure calculated from three successive recording trials was less than 3%, indicating a relatively high repeatability.

As it can be understood from the origins of OPP, its maximum value comes from a sufficient signal AC amplitude and high diastolic to systolic peak ratio. During the measurement, it was possible to observe the PPG pulsations with a high diastolic peak and marked dicrotic notch.

Other studies also suggest that the maximum oscillation occurs when the extravasal pressure is equal to the mean arterial pressure (MAP). Thus, if the extravasal pressure remains at the level of the MAP, the artery can be considered to be in a grossly unloaded condition [20].

The optimal probe contact pressure for particular arterial sites varied across the subjects. However, we observed a tendency that the lowest value was for the posterial tibial site, medium value for femoral artery site, and the highest contact pressure value for popliteal artery site (table 1). Considering different properties of tissue over the artery, we assume that probe contact pressure might differ even in the situations when the mean arterial pressure and the arterial stiffness are similar. Presumably, these differences could be explained by different mechano-elastic properties of the tissue between the artery and the probe. Moreover, the depth and the diameter of an artery in the PPG recording site varied across the subjects. We can also speculate about the contribution of arterial stiffness; however, we do not possess data concerning this parameter in our current experiment. Thereby, it is more likely to associate the optimal contact pressure of the probe with the mechano-elastic properties of the surrounding tissue, even if the mean arterial pressure and heart rate maintain stable.

Table 1. Subject and measurement site dependence on optimal probe contact pressure.

Subjects	**PPG probe Optimal contact pressure (kPa)**		
	posterior tibial a	**popliteal a**	**femoral a**
1.	9.1±0.1	11.6±0.1	10.9±0.1
2.	12.5±0.2	17.03±0.2	10.1±0.2
3.	7.2±0.1	11.4±0.1	8.6±0.1
4.	15.3±0.1	21.1±0.1	16.2±0.1
5.	10.4±0.2	15.0±0.2	13.4±0.2

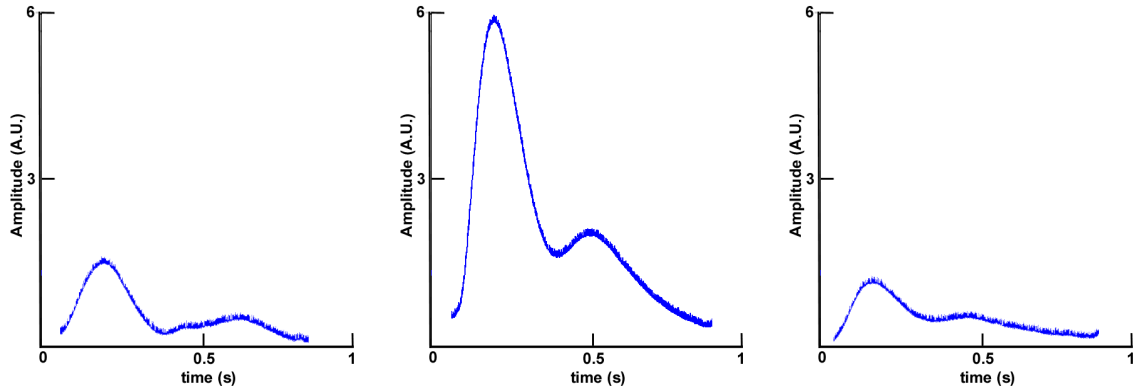

Figure 6. Typical example of arterial PPG waveform recorded at different probe contact pressures; insufficient pressure (left), optimal pressure (middle) and excessive pressure (right); Signals acquired during the same measurement trial.

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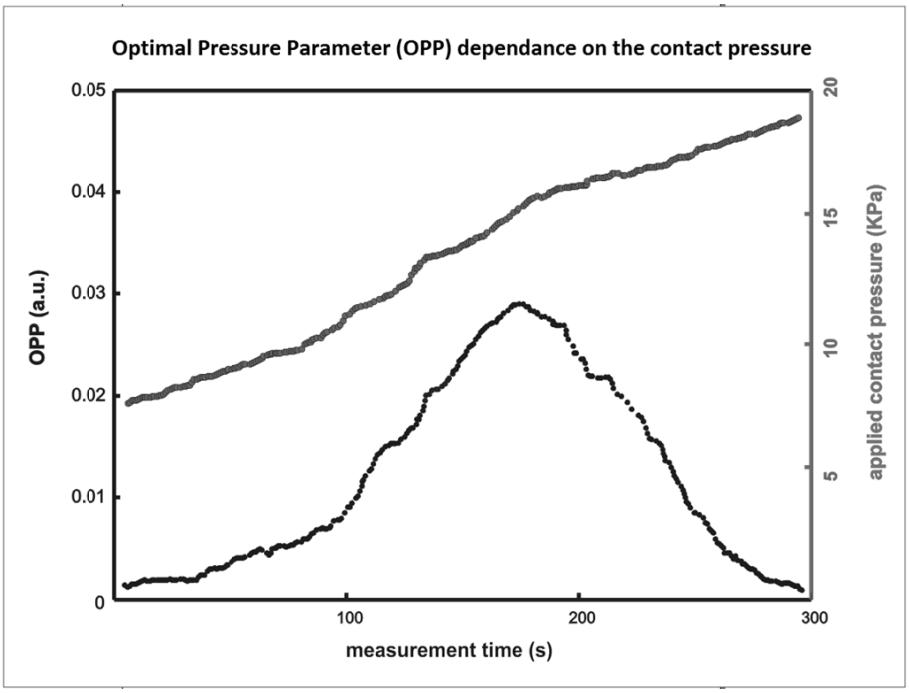

Figure 7. Typical example of PPG recording from popliteal a. during one trial; the lower curve represents changes of OPP depending of the PPG probe contact pressure over the artery. The maximal value of OPP (0.03 a.u.) indicates optimal PPG probe contact pressure (15 KPa).

4. CONCLUSIONS

We have developed a novel PPG measurement system for standardized signal recordings from the skin over the conduit artery (arterial PPG). The maximal value of the PPG derived parameter OPP can be used as a reliable indicator of the optimal probe contact pressure where the artery wall is unloaded. We conclude that the system can provide the feedback necessary to perform reliable PPG recording in balanced transmural pressure conditions.

ACKNOWLEDGMENT

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Reliability of Hemodynamic Parameters Measured by a Novel Photoplethysmography Device

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Abstract— **Three channel photoplethysmography (PPG) signal pulse wave studies of the leg's conduit arteries during rest conditions were performed. The obtained data of each channel showed similar values, proving arterial PPG as a reliable and repeatable method to assess arterial waveform parameters. A validation experiment was carried out by acquiring signals from three identical IR PPG sensors, which were placed on different sites over the leg's conduit arteries during rest conditions. Coefficients of variation (CV) were calculated at a 95% confidence interval by comparing results of each subject during multiple attempts. This data processing leads us to certain criteria of improvements in our methodology. Results show that the arterial PPG technique can give trusted and accurate information about the changes in hemodynamics, and therefore, makes it promising for early diagnostics of vascular disease.**

Keywords **— conduit arteries, photoplethysmography, pulse wave velocity, second derivative.**

I. Introduction

Photoplethysmography (PPG) is a well known, non-invasive, optical method used for detecting blood pulsations. Currently PPG measurements are typically performed by recording signals from defused vascular beds, such as fingertips and ear lobes, thus providing information about their microcirculation and tone of the small arteries [1]. There were attempts to obtain PPG signals from the large conduit arteries since 1971, when Weinman and Sapoznikov first described continuous measurement of the arterial pulse wave velocity (PWV) [2]. Later studies were focused on methodological and PPG device validation [3], and comparison of PWV obtained by PPG in healthy subjects and patients [4]. Despite the potential clinical value, arterial PPG has not become a widely used method among researchers and clinicians. The reasons are the lack of available, commercial versions of arterial PPG sensors and the protocol for receiving correct measurements. Also, there are methodological and technical difficulties in its application which requires highly skilled personnel.

Our studies are related to the arterial health assessment using PPG waveform analysis.

To our knowledge, the PWV and wave form parameter assessment using three site arterial PPG, has not been previously performed.

Therefore, the aim of this study was to verify the usability of the arterial PPG technique for measuring multiple pulse wave parameters which refer to local and regional arterial stiffness which is an independent predictor of cardiovascular events [5].

II. Materials and Methods

A. Subjects

Youthful (18 to 26 years old) volunteers (2 males, 4 females) with a healthy lifestyle, body mass index from 16.2 to 25.9 kg/m^2 and no signs or symptoms of cardiovascular diseases were enrolled in this study. All of the subjects gave their informed consent to participate. The Scientific Research Ethics Committee of the University of Latvia, Institute of Experimental and Clinical Medicine approved the research protocol.

B. Equipment and Experimental Design

Every volunteer was subjected to three attempt series, each five minutes long. During the experiment, a subject was held in a supine position on an ergonomic pedestal at room temperature (24°C) in quiet and comfortable conditions. Prior to data recording, the PPG sensors were placed while the subject adapted. The volunteers were cautioned not to intake any caffeine or eat a meal within 2 hours before the experiment.

Physiological measurements require an accurate and easy to use PPG signal measuring device, which ensures low signal noise, and high spatial and temporal resolution. One of the novelties of this study is the usage of identical PPG sensors and custom fastening strips for their attachment to multiple sites of the leg arteries, instead of measuring the

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pulse transit time between these sites with different methods – ultrasound, ECG, sphygmogram etc. In physiological measurements, we are looking to achieve an accuracy higher than 8 %, therefore same type of sensor applications with common device clock is required, instead of using different types of pulsation detection methods with unknown hardware delay times.

Such PPG devices are not produced commercially, hence we designed a laboratory-made prototype. This prototype is a custom made 3-channel digital PPG device (sampling rate: 1 kHz per channel; 875 nm LED; photodiodes with visible light filter and peak spectral response wavelength of 880nm). Originally this device was designed for scientific purposes, which require an analog signal output to one common data acquisition system. Therefore, the digital PPG signals were converted using a 12-bit eight-channel DAC. The device has an integrated LED driver that provides stable power throughout the battery discharge range. LEDs were typically driven by 55 ± 15 mA (5 mA stepping), so that no perceptible warming of the upper tissue layer was produced. A special screening barrier for the photodiode was made within the sensor to lower the influence of ambient light. The design of the scheme is based on a photodiode discharge time measurement using a 32-bit timer built into a microcontroller [6].

The only filter integrated in the design is a second order Butterworth low pass filter with the cut off frequency of 42Hz at 3dB. This filter did not distort the signal shape and phase because the typical bandwidth of the PPG signal is 0.05 – 40Hz. The measured noise level of the device is -30 to -40dB compared to the PPG signal level.

Three custom-made, reflection type PPG probes were developed and adapted to meet criteria necessary for the measurements of arterial blood pulsation from the skin over the conduit artery. This provided the ability to take contact PPG measurements virtually from any site of superficial arterial tree. The PPG method is very sensitive to tissue motion and to the sensor-to-tissue contact force [7]. Therefore, to prevent signal artifacts, the arterial PPG sensors were fastened with custom-made holders.

Sensors were placed as follows: S1 over femoral a. near the groin, S2 over popliteal a. in the popliteal fossa, and S3 over posterior tibial a. near the ankle (Fig. 1.). Distances between sensors were noted to derive the pulse wave velocities from the pulse transit time (PTT) – delay time of the pulse wave reached all three PPG sensors consecutively (S1-S2 for thigh, S2-S3 for calf, S1-S3 for both thigh and calf). The analog signals from the PPG device were captured by a 12-bit ADC USB data acquisition module at 1 kHz per channel, and stored in a PC.

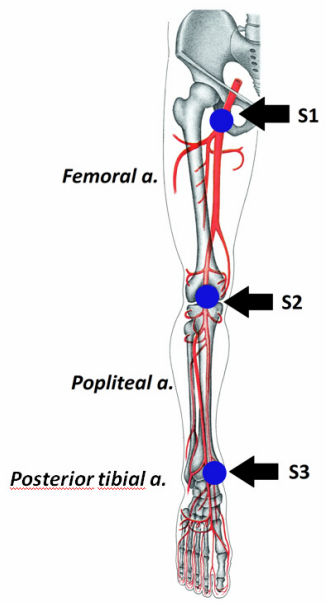

Fig. 1 Placement of PPG sensors during experiment

Later, the PPG signals were processed offline with custom developed Matlab software (signal smoothing with wavelet and Savitsky-Golay filters to reduce signal artifacts and ADC stepping noise.); foot-to-foot PTT was computed in a beat-per-beat manner, and second derivative waveform parameter *b/a* of PPG signal was calculated by using a well-known method of a normalized amplitude ratio *b/a* of the second derivative shape [8] (Fig. 2.).

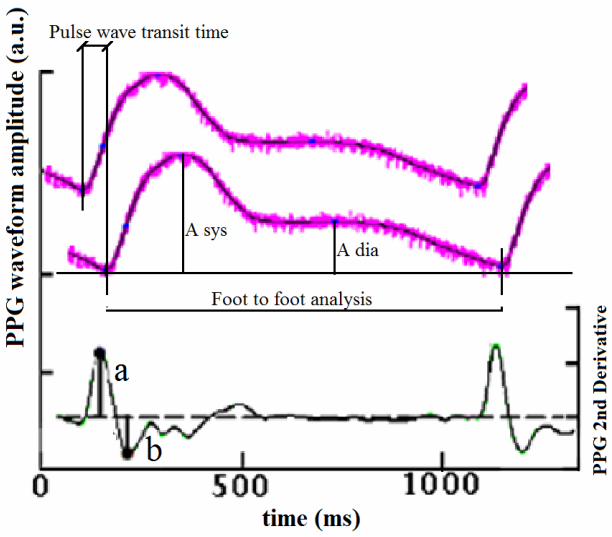

Fig. 2 PPG Waveform analysis parameters: pulse wave transit time (PTT), 2nd derivative parameter *b/a*, and diastolic to systolic peak amplitude ratio A_{dia}/A_{sys}

Every single beat of the PPG waveform was also analyzed by a pulse peak amplitude ratio parameter – a ratio of amplitudes of systolic and diastolic components of pulse wave.

The measure of variability of PPG parameters between different measurement times and other factors were assessed by computing coefficients of variation (CV) in %.

III. Results and Discussion

High quality PPG recordings were acquired from each subject and from each of the arterial sites (Fig. 3.).

However, in some cases it was difficult to obtain the low noise signals from the S2 site. Partly, that could be explained by the anatomical peculiarities of the subject and the ability to achieve the correct position over the artery with the PPG probe.

Different subjects showed diverse parameter values, reflecting acceptable individual inter-subject variability, yet, there was a good agreement within all three attempts for each subject, thus proving ability to obtain repeatable signal (Table 1).

The most reliable results were obtained for PWV measured between the sites S1 and S3 (coefficient of variation 4±1%) which represents the total limb PWV and could be explained by more precise sensor location on these sites. While the PWV data obtained for calf and thigh were less reliable, 11±7% and 10±3%, respectively. The precision of the thigh and calf PWV largely depended on sensor positioning on the polpiteal fossa, over the artery.

The average variability between different measurements (three times) for parameter *b/a* is 7±4%, which is acceptable, considering that its calculation is sensitive to signal-noise ratio and consequently on processing software settings (smoothing level, filter settings).

The variability of A_{dia}/A_{sys} ratio (8±3%) was similar to that of parameter *b/a*.

Table 1 Summary of parameters acquired during all three measurements: the coefficient of variation in % of PWV, second derivative waveform parameter *b/a*, and pulse peak amplitude ratio parameter A_{dia}/A_{sys}

Subject	Sex	PWV (S1-S2)	PWV (S2-S3)	PWV (S1-S3)	*b/a*	A_{dia}/A_{sys}
1	F	9%	15%	5%	10%	8%
2	F	14%	5%	3%	8%	11%
3	F	12%	6%	2%	12%	12%
4	M	11%	23%	5%	2%	5%
5	F	7%	5%	4%	5%	5%
6	M	5%	11%	4%	7%	8%

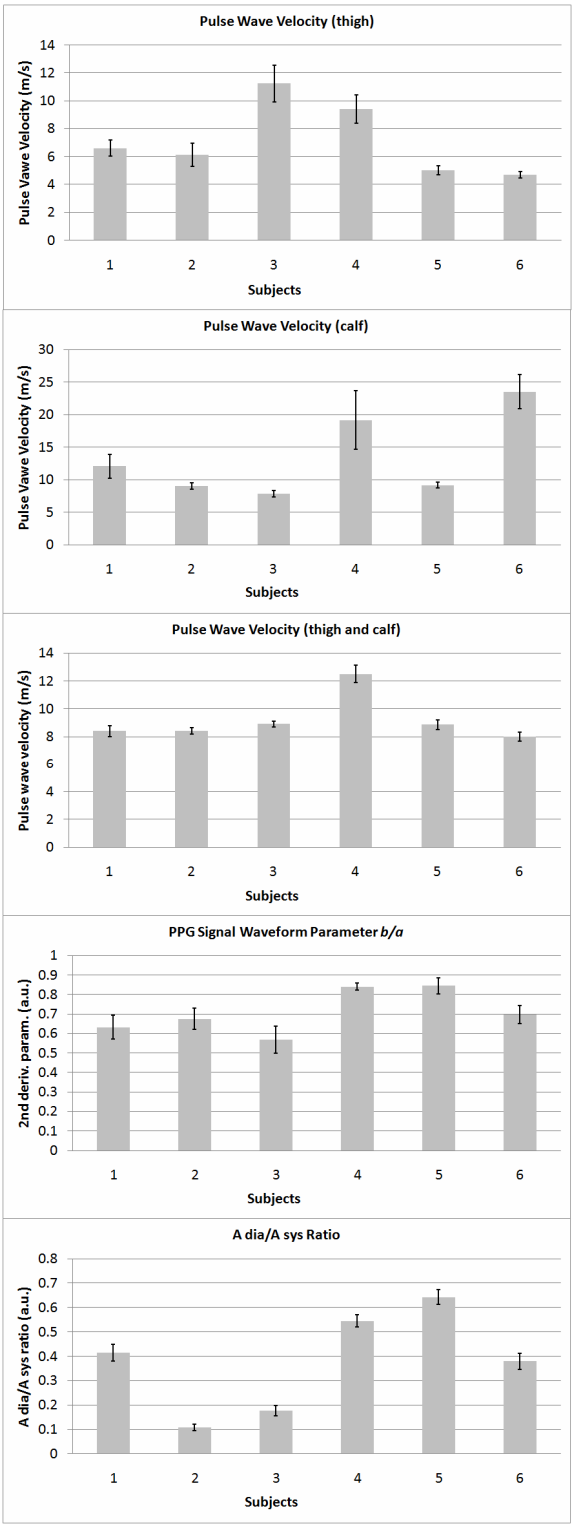

Fig. 3 Obtained mean values and standard deviations for six subjects of all measured parameters for three attempts.

IV. Conclusions

The measurements and standardisation protocol for PPG recordings provided a good reliability. The possible sources in dispersion of pulse wave measurements were the contact force, the precise positioning and the orientation of PPG probe, as well as the settings in signal processing software – the level of signal smoothing and applied filters. Arterial PPG seems to be a promising, reliable and convenient method, which can be used in equipment for early diagnostics of vascular disease.

Acknowledgment

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Usability of photoplethysmography method in estimation of conduit artery stiffness

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ABSTRACT: Three channel photoplethysmography (PPG) signal waveform studies of leg conduit arteries during a provocative occlusion test were performed. PPG waveform second derivative amplitude ratio and arterial pulse wave velocity values showed significant correlations with ultrasound (US) reference method of local and regional arterial stiffness (AS), showing the ability to use PPG for AS change quantitative assessment.

Keywords: *arterial photoplethysmography, arterial stiffness, pulse transit time, arterial occlusion test*

1. INTRODUCTION

Arterial stiffness (AS) is an independent predictor of cardiovascular events and may serve as an indirect indicator of endothelial dysfunction. Disorders of the arterial system's response to inconsistent loads, stress level, or blood supply, can be considered as early signs of vascular and endocrine disease, such as diabetes, stenosis, and atherosclerosis. Early diagnostics of arterial dysfunction and monitoring of AS changes is increasingly noticed as a potentially high field of applied medicine and device development. In recent years, more attention has been focused on studies of AS because the assessment of AS is increasingly used in clinical applications [1]. AS disorder, particularly in lower limbs, may be a key factor in later exacerbation of peripheral arterial disease, and necessity of serious treatment and rehabilitation, or surgical aid, such as arterial bypass grafting.

These aspects and the demand of non-invasive and reliable diagnostic methods lead us into studies of arterial stiffness assessment technique. Currently, arterial dysfunction is mostly assessed by mechanical - pressure cuff based plethysmography methods [2]. Meanwhile our interest is focused on developing both devices and software to assess usability of photoplethysmography (PPG), and prove its stability and reliability in detection of AS changes.

Research was carried out using PPG, the optical method which is non- invasive, non- intrusive, and has the ability to be widely adapted for specific needs. Particularly, we were looking to obtain signals from sensors that were placed over various conduit arterial sites, thus measuring AS directly from congeneric part of arterial system, not involving diffuse zone of blood circulatory system, like fingertips. Also, it was for the usage of a single type method and source of signal, to avoid different delay timing effects from the hardware and human physiology.

Another issue addressed in this paper is the development of an optimal experimental design for measurement of AS changes in healthy subjects. Every medical measurement must be taken as a physiological experiment, considering all the precautions – isolating unwanted effects, minimizing human made artifacts and creating correct environment. We offer an experimental protocol, which demonstrates the possibility to reach adequate repeatability of the measurements, thus showing the limits of the usability of the PPG method.

There were many attempts to derive AS from a finger PPG waveform, and there are only a few studies concerning AS being estimated by a PPG signal recorded from the skin over conduit arteries – arterial PPG [3]. That mainly is explained by the technical difficulties of fastening PPG sensors, finding correct sites of the arterial system, as well as the lack of suitable hardware equipment.

In this study we used an arterial PPG method to estimate regional and local AS of the leg conduit arteries, by measuring the pulse wave transit time (PTT) and analyzing PPG waveform.

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Objective:

The aim of this study was to prove and test the usability of the arterial PPG signal waveform and PTT analysis to assess arterial stiffness changes in the leg conduit arteries.

Another aim was to compare the values computed from the PPG signal to those obtained by B-mode ultrasonography (US) and beat-per beat blood pressure.

2. MATERIALS AND METHODS

2.1. Subjects

Young (22 ± 3 years old), healthy volunteers (5 male, 8 females, total 13 trials) with a healthy lifestyle, body mass index ranging from 16.2 to 25.9 kg/m^2 and no signs or symptoms of cardiovascular diseases were enrolled in this study.

All of the subjects gave their informed consent to participate in the study. The Scientific Research Ethics Committee of the University of Latvia, Institute of Experimental and Clinical Medicine approved the research protocol.

2.2. Experimental design and protocol

To record the PPG signal, a custom made 3-channel digital PPG device prototype was used (sampling rate: 1 kHz per channel, 920 nm IR LED, IR spectrum photodiodes, 12-bit DAC and analog outputs). The design of the scheme was based on a photodiode discharge time measurement using a 32-bit timer built into a microcontroller [4]. Analog outputs were filtered by a second order Butterworth low pass filter with the cut off frequency of 42Hz at 3dB. This filter did not distort the signal shape and phase because the typical bandwidth of the PPG signal is 0.05 – 40Hz. The measured noise level of the device is -30 to -40dB compared to the PPG signal level.

Three custom-made reflection type PPG sensors were developed to meet the criteria necessary for the measurement of arterial blood pulsation from the skin, over the conduit artery. Sensor photodiodes and capacitor values were selected, by adapting each sensor to specific part of lower limb. This provided the ability to take contact PPG measurements virtually from any site of the superficial arterial tree. The PPG method is very sensitive to tissue motion and sensor contact force. Therefore, to prevent signal artifacts, the arterial PPG sensors were fastened with custom made holders. To fasten the PPG sensor at tibial posterior a., a custom Velcro-type holder and pneumatic force transducer were developed. The sensor placed on popliteal a. was fastened by a microthread equipped holder, enabling the sensor to be fixated to all the volunteers with different body types (Fig 1.).

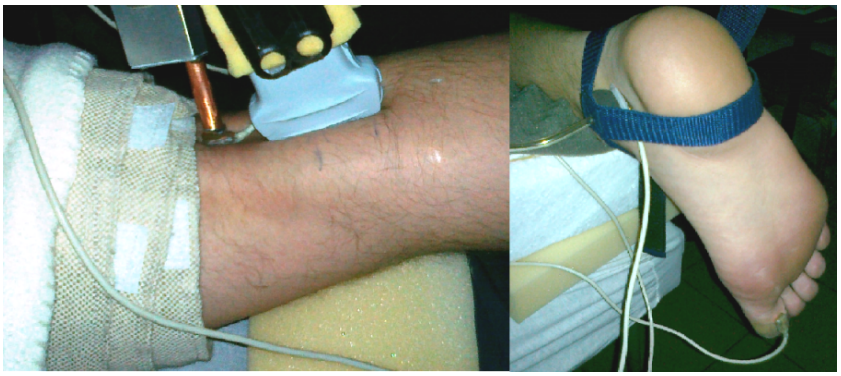

Fig. 1. Custom made holders of the arterial PPG sensors. Measurements of popliteal a. done with a PPG sensor (left side) and a distally located ultrasound probe. PPG sensors fastened with a Velcro holder over the tibial posterior a. and on the hallux (right side).

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Sensors were placed as follows: S1 on femoral a., S2 on popliteal a. and S3 on tibial posterior a. (Fig.2.).

As for reference methods, ultrasound imaging (a US probe distal to the femoral flow divider; SonoSite Titan, L38/10-5MHz, B-mode) and a beat- per beat pressure monitoring (Finometer model-2, FMS) were used for the measurement of the arterial diameter and the arterial blood pressure during the entire experiment. To manage with US probe, a custom flexible probe holder was designed. Mechanical pulsations of conduit arteries demand flexible, but stable fixation that can hold the US probe calmly to the tissue for the complete measurement. The applied provocation test – arterial occlusion, usually causes pressure cuff and limb motions, so personnel presence and minor corrections are obligatory. Continuous blood pressure monitoring requires a stable microcirculation state and to maintain the hand microcirculation in a sufficient level, the room temperature was held at least 26°C. The Finometer probe is located on the right arm's index finger and its PPG sensor is very sensitive to tissue temperature.

Volunteers were subjected to a provocation test (alter AS changes), which consisted of a rapid 10-minute posterior tibial a. occlusion performed by inflating a pneumatic cuff up to 100 mmHg over systolic pressure (Hokanson Instruments). During the experiment, the subject was held in a supine position on an ergonomic pedestal at room temperature in quiet and comfortable conditions. Prior to recording, all sensors were placed while the subject adapted. The pre-test data was recorded during the rest conditions, after that an operator performed the arterial occlusion of blood circulation distal to the knee joint. Following the ten minute occlusion period, the cuff was deflated and circulation restored. Thus, during recovery period, it was possible to observe arterial responses and alteration of AS (Fig.3.).

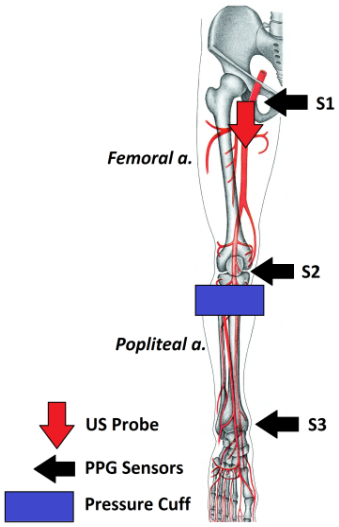

Fig. 2. Placement of the sensors during experiment.

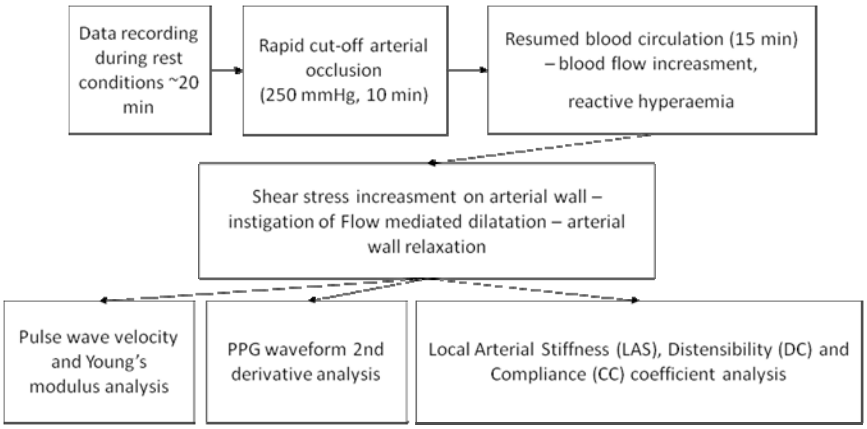

Fig. 3. Schematics of the design of the experiment. Arterial occlusion procedure (provocation test) serves as the targeted provocation test.

2.3. Signal processing and data analysis

The analog signals from PPG and Finometer were captured simultaneously by a 12-bit ADC USB data acquisition module at 1 kHz per channel, and stored in a PC. Synchronously, video signal from the US device was passed to a DVI frame grabber (DVI2USB, Epiphan Systems Inc), and captured at a 25 fps frame rate, then stored in an AVI file. Later, the PPG signal was processed offline with custom developed Matlab software (signal smoothing with wavelet and Savitsky-Golay filters to reduce signal artifacts and ADC stepping noise). PTT and waveform second derivative parameters were computed for each PPG signal in a beat-per beat manner (Fig. 4. left). All recorded signals were synchronized and exported with common timing, so arterial response changes could be assessed by calculating AS parameters during the recovery process.

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US video was processed with another custom made Matlab software (segment artery boundaries) to obtain beat-per beat arterial diameter changes (Fig. 4. right).

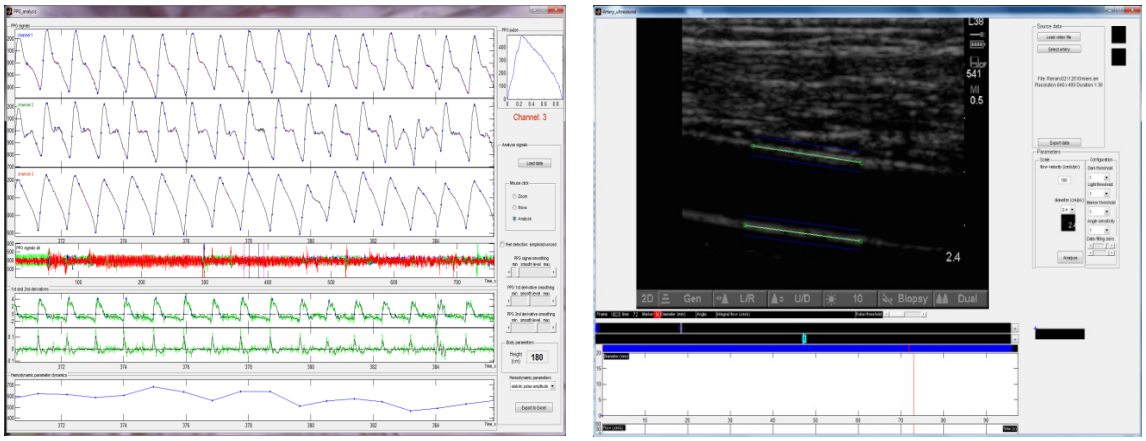

Fig. 4. Data analysis software – PPG pulsation analysis (left) and US video processing (right) software (Matlab). Pulse time shifts and waveform second derivative amplitude values were computed from all three arterial sites. Artery pulsations were computed by a brightness gradient method.

2.4. Calculations

1. Regional AS (RAS) was estimated by PTT shift analysis [5] from the PPG signal between S1 and S2 or S2 and S3. Elastic Young's modulus E (Pa) was computed by the Moens-Korteweg equation (1),

$$E = \frac{D^2 \rho d}{PTT^2 h} \qquad (1)$$

where D – distance between sensors, ρ – blood density (1060 kg/m^3), d – artery diameter, PTT – pulse transit time between sensors, h – artery wall thickness.

Elastic Young's modulus E (Pa) can be calculated by Moens-Korteweg equation under the assumptions that there are no significant changes in the vessel area and the artery wall thickness in observed region of the arterial circulatory bed. Typically, the diameter of popliteal a. is 5.7 ± 0.8 mm.

Changes of local AS (LAS) from each PPG data channel were estimated by waveform analysis (Fig. 5.), by using a well known method of normalized amplitude ratio b/a of the second derivative shape [6]. The parameter b/a is derived from the early systolic component of the pulse waveform, and shows elastic properties of the large conduit arteries – the arterial wall response to blood flow from the heart. Parameter b/a can be used for assessing AS changes during a single measurement and dynamic range of the artery wall elastic properties.

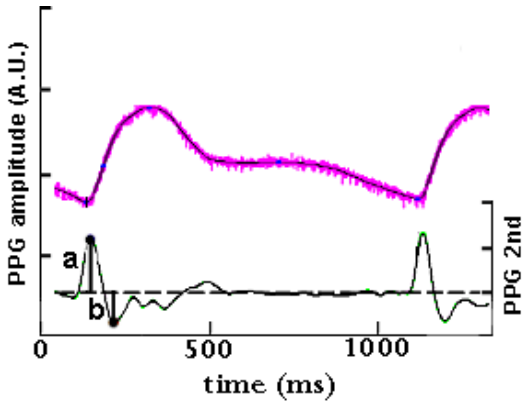

Fig. 5. PPG pulse wave (top) and second derivative (bottom). Waveform parameter b/a ratio was computed as a ratio of first (a) and second (b) extreme point amplitude. Changes of b/a characterizes arterial tone during the early systolic phase.

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LAS was also calculated by the equation (2) of the proved distensibility coefficient (DC) method [7], and compared with the results obtained from the PPG signal analysis,

$$E = \frac{d}{h \cdot DC} \quad \text{where} \quad DC = \frac{2 \cdot \Delta d \cdot d + \Delta d^2}{PP \cdot d^2} \qquad (2)$$

where *DC* is distensibility coefficient, *Δd* – amplitude of artery diameter pulsations, *PP* – difference between systolic and diastolic pressure, obtained by beat- per beat pressure monitor. The amplitude of the artery diameter pulsations greatly depends on the precise selection of observed segment of artery.

3. RESULTS

Results showed relations between the arterial PPG and reference method values:

- The relation between femoral artery LAS (DC method) and RAS (PPG PTT S2-S1) showed a significant correlation ($r = 0.980$; $p < 0.0001$) during the recovery period (Fig. 6.).

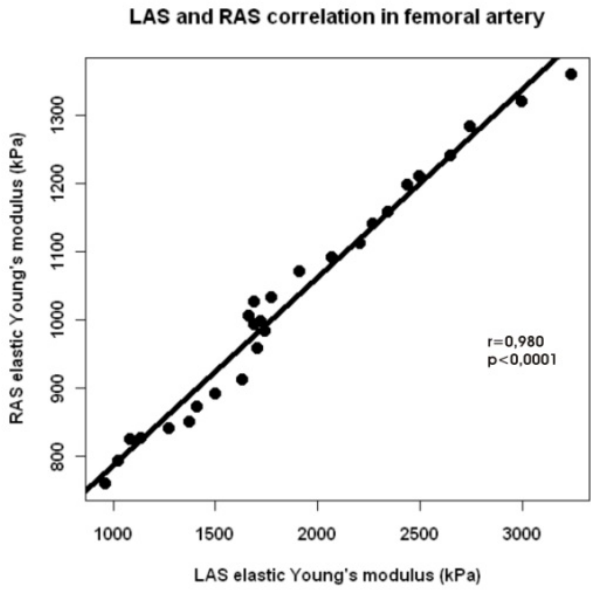

Fig. 6. Representative example of data from one subject. Relationship between changes of absolute values of Young's modulus, describing local arterial stiffness (LAS) and regional arterial stiffness (RAS) of femoral artery during recovery period. Artery stiffness changes are reflected both in artery diameter fluctuation amplitude and pulse transit time changes, thus proving PPG usability.

- There was also a strong correlation within the hemodynamic parameters of the sensor's (S3) PPG signal distal to the pressure cuff. PPG PTT (S3-S2) showed a significant correlation ($r = -0.916$; $p < 0.0001$) with the PPG waveform second derivative parameter b/a (S3), (Fig. 7.).

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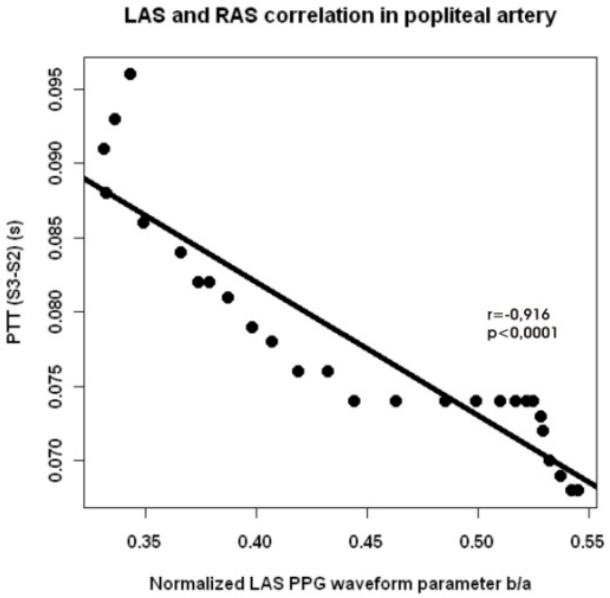

Fig. 7. Representative example of the data from one subject. PPG signal (S3 and S2) parameter – pulse transit time PTT, and PPG waveform (S3) parameter *b/a* show opposite responses of arterial stiffness during the post-occlusion recovery period.

• Both femoral artery LAS methods – the PPG waveform (S1) second derivative analysis and the reference DC method showed a correlation (r = 0,729, p < 0,0001), thus a single channel, single site arterial PPG application seems to be promising for LAS assessment (Fig. 8.).

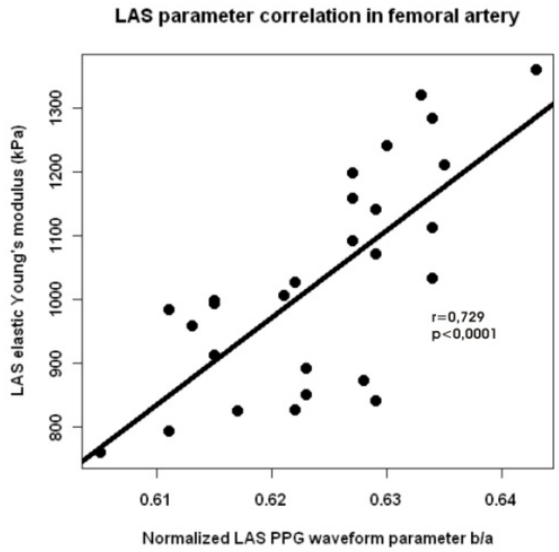

Fig. 8. Representative example of the data from one subject. PPG signal waveform parameter *b/a* (S1) describes local arterial stiffness changes of the femoral artery and correlates with the femoral artery local stiffness – Young's modulus' absolute value was obtained by the reference DC method.

4. DISCUSSION

The major findings of this study are that the PPG method can be used for both local and regional AS detection. Great importance has been made to obtain blood pulsation biosignals that reflect the correct information about the processes we are interested in. Mostly, available devices and described studies are based on combining different methods such as an EKG, US imaging and the automated oscillometric technique. Our goal is to obtain information about the PWV changes within one technique. Revealed correlations demonstrate that arterial occlusion, as from the targeted provocation test, causes AS changes which can be safely and reliably detected by the PPG method. US imaging currently is considered the most reliable method to assess AS locally. We show the possibility to assess AS both locally and regionally by using the optical PPG method.

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The investigated vascular bed areas distal and proximal to the occlusion cuff show a different reaction to the provocation test. The femoral artery response to the distal occlusion was a reduction of the AS immediately after circulatory recovery. On the contrary, the lower leg artery occlusion during relaxation and blood circulation restored and the tension returned to the values inherent in peaceful conditions. The US method showed that the femoral artery diameter increased by ~7% in the 200 seconds after circulatory recovery

5. CONCLUSIONS

The obtained results convincingly show significant correlation between the arterial photoplethysmography waveform parameter *b/a* and the arterial stiffness value changes obtained by the arterial photoplethysmography pulse transit time and pulsatory fluctuations of the artery diameter. Hence arterial stiffness assessment by photoplethysmography waveform analysis seems to be a promising, reliable and convenient method, which can be used in equipment for early diagnostics of vascular disease.

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