TRANSLATING PHOTOPLETHYSMOGRAPHIC PERIPHERAL PULSEWAVE ANALYSIS: BRIDGING THEORY TO CLINICAL PRACTICE FOR THE UTILIZATION OF A REMOTE PATIENT MONITORING SYSTEM

PhD thesis booklet

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Table of Contents

1. Introduction

Cardiovascular diseases remain the leading cause of global mortality. Beyond overt clinical events, subtle alterations in cardiovascular regulation, vascular function, and cardiac performance may precede disease manifestation by years, highlighting the importance of physiological markers suitable for early detection and repeated, non-invasive assessment. Photoplethysmography (PPG) is a simple optical method capable of recording peripheral pulse waveforms that reflect the interaction between cardiac ejection, arterial properties, wave reflection, and autonomic regulation. Pulse wave analysis (PWA) of PPG signals provides timing- and morphology-based indices related to vascular compliance, systolic and diastolic function, and cardiovascular dynamics. Understanding how these peripheral waveform features relate to central hemodynamic processes is therefore a key physiological question with translational relevance.

The primary focus of this thesis is the physiological interpretation of peripheral pulse wave morphology. It aims to explore how conventional and novel PPG-derived parameters reflect underlying cardiovascular function under resting conditions in healthy subjects and how they relate to established echocardiographic measures. Due to the limitations of available PWA devices at the start of this work, a dedicated PPG recording and analysis framework (SCN4ALL) was developed as a research-enabling tool to support reliable signal acquisition and flexible parameter extraction. The studies presented combine methodological rigor with a physiology-driven approach. By analyzing pulse wave morphology, timing indices, and derivative-based parameters in relation to echocardiographic reference measures, this work contributes to a clearer understanding of what peripheral PPG signals can - and cannot - reveal about cardiovascular function, supporting their rational use in research and longitudinal assessment contexts.

2. Objectives

Study 1 - Physiological stability and variability of PPG-based peripheral pulse wave parameters

- To quantify the technical contribution to variability in PPG-derived pulse wave parameters using artificially generated pulse wave signals under identical measurement settings, in order to distinguish device- and algorithm-related effects from physiological behavior
- To assess short-term intra-subject physiological variability of selected PPG-derived hemodynamic parameters in healthy volunteers during repeated measurements under strictly standardized conditions
- To compare intra-subject variability with inter-subject variability across individuals measured under identical protocols, thereby identifying parameters that primarily reflect individual physiological differences
- To evaluate the influence of anatomical measurement site on pulse wave morphology and derived parameters, using simultaneous recordings from four different fingers (left/right index and ring fingers)

Study 2 – Relationship between peripheral pulse wave features and central cardiac function

- To investigate the association between PPG-derived timing parameters and echocardiographic measures of left ventricular ejection time (LVET)
- To explore whether distinct pulse wave morphological features correspond to echocardiographic indicators of systolic and diastolic cardiac function
- To identify PPG-derived parameters that demonstrate the closest physiological alignment with established echocardiographic measures, without implying direct clinical interchangeability

3. Methods

The custom-made PPG system consists of a Bluetooth-connected transmission pulse oximeter (Berry BM1000 Shanghai Berry Electronic Tech Co., Ltd., Shanghai, China); 200 Hz sampling rate, 32-bit ADC) and a mobile application that records 140-second digital volume pulse (DVP) signals and uploads them to a secure cloud server (Amazon Web Services, Amazon Web Services EMEA SARL, 1855 Luxembourg, Luxemburg).

The PPG signal is bandpass-filtered (0.1–10 Hz, 4th-order Butterworth), and segmented into pulse cycles. Fiducial points are identified on the primary waveform and its derivatives to compute morphological and pulse rate variability parameters. Cycle means are calculated automatically, with results displayed on a physician web platform and exported for analysis.

Ethical approval numbers for Study 1 and 2, respectively: 120/2018, 120/2018-3.

Methods - Study 1

Artificial signal repeatability
Artificial DVP signals generated by a simulator (MS100 SpO_2 Simulator, Contec Medical Systems Co., Ltd., Qinhuangdao, China) were measured 5x, under three settings (Normal, Geriatric, Weak) using five different pulse oximeters of the same type.

Intra-subject variability
Ten healthy adults (5M/5F, 19–35 y) underwent ten repeated 140-second measurements under standardized morning conditions (quiet room, seated, left index finger, altogether 30-40 minutes per person).

Anatomical site variability
Twenty-five healthy adults (17M/8F, 19–49 y) underwent parallel 140-second measurements on left/right index and ring fingers using four oximeters.

Statistical analysis
Coefficient of variation (CV) quantified signal analysis repeatability (<2% threshold) and test–retest variability (<10% threshold). Intraclass correlation coefficients (ICC, linear mixed-effects model) assessed inter-finger

reproducibility and the contribution of interpersonal differences.

Methods - Study 2

PPG recording

Thirty-seven healthy adults (18–60 y, BMI 18–25 kg/m²) underwent 140-second PPG measurement (right index finger) during standard transthoracic echocardiography, using the SCN4ALL system.

Echocardiography

2D echo performed with a GE Vivid E95 (4Vc-D transducer- GE Vingmed Ultrasound, Horten, Norway), obtaining LV-focused, ECG-gated views at ≥50 fps. LV volumes, function, and Doppler parameters were measured; global longitudinal strain was derived using speckle-tracking (Autostrain LV, TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany).

Parameters

20 PPG parameters were analyzed, including conventional indices (ET(PPG), Crest Time, b/a, stiffness index) and new parameters (Dicrotic Notch Index, early left ventricular ejection time-1, -2).

Statistical analysis

Pearson or Spearman correlations assessed associations between PPG and echo parameters ($p<0.05$, $r/\rho>0.4$ reported). Bland–Altman analysis quantified agreement between ejection time measurements with echocardiography and PPG, with calculation of bias and 95% limits of agreement.

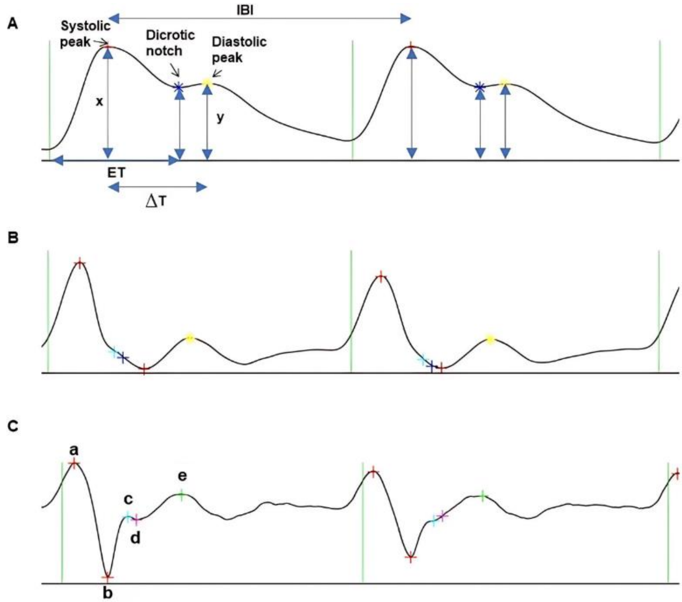

Figure 1 - **Representative pulse wave recording by the SCN4ALL system**. Original pulse curve (panel A), and its first-, (panel B) and second derivative curves (panel C). Abbreviations: IBI: inter-beat-interval, x: relative height of the systolic peak, y: relative height of the diastolic peak, ΔT: time difference between systolic and diastolic peak (ms). a,b,c,d and e points: fiducial inflection points on the second derivative. Adapted and modified from Kulin et al. https://doi.org/10.3390/app10227977, licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

4. Results

Study 1

Artificial signal repeatability

- CV values for all parameters under normal artificial signal conditions were <1%, confirming high stability.
- Under abnormal conditions (high heart rate (HR), low amplitude), most parameters remained stable except those dependent on second derivative PPG's (SDPPG) c–d point detection (SDPPG Ageing Index and d/a ratio), which became unreliable.

Intra-subject variability

- Core parameters – SDPPG b/a ratio, left ventricular ejection time index (LVETi), mean interbeat interval, stiffness index, and mean HR — showed CV <10%, indicating strong short-term reproducibility.
- Most SDPPG parameters, like Ageing Index (CV: 13.6%), d/a ratio, and c–d point detection ratio showed higher variability, suggesting greater sensitivity to subtle waveform changes.

Anatomical variability

- ICC exceeded 99% for mean interbeat interval, mean HR, and LVETi; most other parameters showed ICCs of 80–90%, indicating minimal influence of finger selection compared with inter-individual differences.

Study 2

Ejection time

- Left ventricular ejection time ET(echo) correlated significantly with ET(PPG) ($r=0.648$, $p<0.001$), Crest Time ($r=0.567$), eLVET2*[1] ($\rho=0.496$), and DNi* ($r=-0.496$).
- Bland–Altman analysis showed a mean bias of +95 ms for ET(PPG) (limits of agreement: 54–136 ms) without proportional bias.

Systolic function

- LV-EDD and LV-ESD correlated moderately with Ageing Index ($r\approx-0.51$) and, to a lesser degree, with b/a and d/a ratios.
- GLS correlated with DNi* (r=0,5), representing the first reported link between PPG waveform morphology and ventricular strain.

Aortic parameters

- DNi* showed moderate correlations with aortic root diameter ($\rho=0.48$), Ao-VTI ($p=0.44$), and LVOT-VTI($p=0.40$), supporting its possible relationship with aortic mechanics and ventriculo-arterial coupling.

Diastolic function

- Strongest associations were observed between MV-A and eLVET2@75*($\rho=0.57$) or b/a ratio ($r=0.52$), Crest Time@75 ($\rho=0.52$) and between E/e′-lat and LVETi ($r=0.42$).

[1] *: newly defined PPG parameters

5. Conclusions

This dissertation summarizes two initial studies aimed at improving the physiological interpretation of selected PPG-based pulse wave parameters measured using the SCN4ALL system. The first study characterized the physiological stability and sources of variability of peripheral pulse wave parameters under standardized conditions, while the second examined their association with central cardiovascular structure and function as assessed by echocardiography. The results presented here were obtained from healthy individuals with normal cardiac functions and provide ground for future clinical studies and later, applications.

Study 1 – Physiological stability and variability of PPG-based peripheral pulse wave parameters

- The custom-built system demonstrated excellent repeatability under controlled conditions: measurement variability remained below 2% across devices when recording artificial pulse signals with proper signal quality.

- A novel contribution was the introduction of the "c-d point detection ratio" as a quality control metric to assess the trustworthiness of second-derivative-based parameters. This parameter supports the selective interpretation of features like the Aging-index and d/a ratio. Their use should be limited to measurements with sufficient c-d point detection ratios.

- Key pulse wave parameters - including b/a, stiffness index, left ventricular ejection time index, and mean interbeat interval - showed low intrapersonal variability (CV < 10%) in short-term repeated measurements on healthy subjects, identifying the most robust parameters from the aspect of hemodynamic stability, under standardized conditions.

- Parallel measurements on four different fingers showed strong within-subject agreement, with intraclass correlation coefficients exceeding 0.80 for all investigated pulse wave parameters, indicating that finger-related anatomical variability contributes only minimally to overall pulse wave variability. For longitudinal or repeated measurements, it is therefore recommended to consistently perform follow-up recordings on the same finger to minimize even minor inter-finger differences.

- The consistently high intraclass correlation coefficients further indicate that the majority of observed variability originates from true interindividual differences rather than short-term intraindividual fluctuations related to measurement location.

Study 2 – Relationship between peripheral pulse wave features and central cardiac function

- PPG-derived ejection time showed a moderate-to-strong association with echocardiographic left ventricular ejection time ($r = 0.648$, $p < 0.001$), with a systematic mean offset of +95 ms relative to echocardiography, indicating that peripheral timing-based pulse wave features reflect central systolic timing under standardized measurement conditions.

- Both newly defined parameters such as eLVET2 @ 75 and established PPG-derived metrics including the Aging index and b/a demonstrated moderate and significant associations with echocardiographic measures of chamber dimensions, diastolic filling pressure, and atrial contraction, consistent with peripheral pulse wave morphology being sensitive to variations in central cardiac structure and filling dynamics.

- The Dicrotic Notch Index (DNi) showed consistent moderate associations with aortic root diameter, LVOT-VTI, and global longitudinal strain, indicating a potential sensitivity to properties related to aortic mechanics and ventriculo-arterial interaction.

Overall Conclusion and Future Outlook

Upon the publication of further PPG related research, future potential of the method (with the SCN4ALL system, as a potential tool) is the paradigm shift: from the occasional medical measurements to daily or continuous data recording. There is high chance that trend analysis of daily measurements and insights from Big Data and pattern evaluation will overcome the known limitations of the peripheral pulse wave analysis on the long run - especially as this is a more affordable technology than the current expensive medical systems to assess hemodynamics, leading to a more reachable and inclusive healthcare even for the low socioeconomic areas and remote places of Earth.

Ongoing studies and collaborative projects using the SCN4ALL system are underway in multiple clinics and academic centers across Europe - including Hungary, Greece, and the Netherlands - to gather further data and determine which medical settings and patient groups may benefit most from the regular use of this approach.

6. Bibliography of the candidate's publications

Publications tightly related to the dissertation:

Kulin D, Antali F, Kulin S, Wafa D, Lucz KI, Veres DS, Miklós Z. Preclinical, multi-aspect assessment of the reliability of a photoplethysmography-based telemonitoring system to track cardiovascular status. *Appl Sci*. 2020;10(22):1–17. doi:10.3390/app10227977

IF: 2.679

Kulin D, Antali F, Horváth M, Kulin S, Kulin S Jr, Miklós Z, Szűcs A. Evaluating photoplethysmography-based pulsewave parameters and composite scores for assessment of cardiac function: A comparison with echocardiography. *Physiol Int*. 2025;112(3), 229-247. doi: 10.1556/2060.2025.00675

IF: (article published after the submission)

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IF: 3.847

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IF: 1.6

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IF: 4.8

Publications referenced in, but not strongly related to the dissertation:

D. Kulin, M. Várfalvi, and S. Kulin, “Digital Support for Family Health Protection by Health Visitors: The ‘Health Visitors for a Healthy Generation and Nation’ Project,” *Aranypajzs*, vol. 2, no. 1, pp. 19–24, 2023. DOI: 10.56077/AP.2023.t1.2

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