Preclinical Assessment of a Novel Cardiovascular Telemedicine System

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Research

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Preclinical Assessment of a Novel Cardiovascular Telemedicine System

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Abstract

Background: Introduction of telemonitoring systems to patient care which provide extensive information about the cardiovascular status of the patient is a promising direction to reduce cardiovascular morbidity and mortality. Our team has developed a telemedical system which is based on the photoplethysmographic detection of the digital arterial pulse wave. The system incorporates a cloud-based automated algorithm which analyses the pulse contour to provide 15 scientifically established parameters for versatile characterization of cardiovascular function. The aim of the current study was to assess the variability of the measurements to test the applicability of the tool before clinical use. We assessed the repeatability of the measurements by detecting stable artificial signals,

and also test-retest variability by repeatedly examining the pulse contours of healthy individuals under standardized conditions.

Results: Most contour parameters (stiffness index, reflection index, left ventricular ejection time index and mean interbeat intervals) are measured with high repeatability (coefficients of variation (CV) < 1% for each parameter), and exhibit acceptable intrapersonal fluctuations (CVs <10%). However, some parameters derived from the second derivative of the pulse wave seem to be more variable (aging index, *d/a* ratio). This is explained by the typical alterations of the pulse wave under specific circumstances, which cause the flattening or complete disappearance of *c* and *d* inflections on the second derivative.

Conclusion: Our measurements proved that our telemonitoring system detects and analyses digital pulse contours with high accuracy and highlighted that second derivative parameters should be interpreted cautiously. We recommend the evaluation of these parameters only in those measurements where *c* and *d* points are detected reliably. Pulse contour parameters are stable in healthy individuals under standardized conditions, which allows detection of subtle abnormal alterations by the remote surveillance system.

Key words

arterial pulse contour analysis, cardiovascular telemedicine system, photoplethysmography, digital volume pulse, measurement error

Background

Despite the enormous effort invested in research and in development of new treatments to break the dominance of cardiovascular diseases in morbidity and mortality statistics, they are still among the leading causes of death [1][2]. A potential breakthrough could be achieved by launching extensive home surveillance programs which allow close follow-up of cardiovascular patients. The pandemic months of COVID-19 underlines the need for reliable telemedicine surveillance tools. In order to reduce the need for personal visits to outpatient clinics, thus reducing the chance of infection of the highest risk population. Telemedical systems exploiting recording and analysis of the peripheral arterial pulse wave could offer a proper solution. [3]

The pulse wave is a pressure wave that is initiated by cardiac ejection and runs through the arterial system. The pulse wave's amplitude and contour are influenced by the dynamics of cardiac function, elasticity of the arteries, and the pressure augmentation caused by the superimposing reflected pressure wave. [4] The latter is highly affected by the tone of the resistance vessels. All these factors are dependent on the current status of the autonomic nervous system. Cardiovascular (CV) conditions (both physiological and pathological) have implications on one or more determinants of the pulse wave, and hence cause well-defined characteristic changes in its shape and propagation velocity. [5][6][7][8][9][10] Therefore, by detecting the changes of pulse wave contour, it is possible to establish the cardiovascular status of the patient. Incorporation of reliable pulse wave analysis in home monitoring systems may allow remote supervision of disease progression, improvement, and applied therapy successes in cardiovascular patients.

Development of a telemonitoring system requires the incorporation of a measurement that is non-invasive, easy-to-use for the patient, convenient, timesaving, and still reliable. The detection of digital volume pulse (DVP), recorded by the photoplethysmographic (PPG) method is a perfect option to track the pulse wave, as it fits these requirements. The principle of PPG is to emit light to the tissues of the

finger from a LED light source and to detect the reflected or transmitted light by a photodiode. The amount of absorbed light is proportional to the volume of tissue below the detector. Vessel diameter and blood volume in the arteries change with pulsation, and so does the amount of absorbed light. This causes fluctuations in the intensity of the detectable reflected/transmitted light, which allows detection of a continuous DVP. [3][11] The shape of the DVP is identical to the pressure pulse.

Mathematical analysis of the pulse wave and DVP is well established in the literature. Several parameters derived from the raw curve, and from its first and second derivatives have been identified as measures of various elements of cardiac and vascular function. Alterations of these indices have been associated with cardiovascular pathologies such as arterial stiffness, atherosclerosis, hypertension, aging, diabetes, coronary heart disease and heart failure [11][12][13][14][15][16][17] [18][19].

Our research team has developed a telemedicine system (SCN4ALL ver.1.0, E-Med4All - Europe ltd.), which utilizes pulse curve detection and analysis, and is designed to monitor the users' cardiovascular conditions on a daily basis. The system is based on DVP registration. The analysis of the continuously recorded pulse wave is completed immediately upon the measurement. The cloud-based algorithm we elaborated to perform data analysis calculates 15 different pulse contour parameters, which all provide relevant information about the CV condition of the user. The results are all displayed on an internet platform, released for the physician's review. (Figure 1)

The innovation is ready for introduction to clinical research and application. However, to set out feasible research questions, and to formulate precise instructions as to the circumstances of application, we need to define the precision and the suitability of our system to detect subtle abnormal alterations in pulse contour parameters. The ultimate aim of this study is to determine the calculated pulse contour parameters' variability under standard conditions. This variability may be attributable to measurement errors of our telemedicine system on the one hand, and to the physiological intrapersonal variability of the DVP, on the other. Although these types of errors may limit the

interpretation and validity of measurements, information about testing pulse wave analysis systems for these errors is scarce in scientific literature [20][21]. In the present study we used a multidirectional methodological approach to address both aspects and focused on selected parameters which have well-reported medical significance based on scientific literature.

In order to determine the variability caused by measurement error of our telemedicine system, we used a simulator that generates artificial pulse signals which could be detected by a photoplethysmograph. We repeatedly recorded and evaluated the signal with our system.

Our CV functioning constantly adapts to the changing environment. Changes of our CV status are reflected by the pulse wave morphology. In order to enhance the accuracy of the measurements, we need to standardize the circumstances of the examination (e.g. resting conditions, ambient temperature, body position, time of the day, time from last meal, coffee, smoking and physical activity) [22][23][24][25]. However, even under standard conditions there is a physiological intrapersonal variability in the pulse contour parameters, which determines the size of the minimum pathological alterations which are detectable by DVP analysis. In our study we also addressed defining this intrapersonal physiological variability in healthy individuals. For this purpose, we measured test-retest variability under standard conditions. Moreover, we also aimed to clarify whether using different fingers for the measurement has influence on the measured parameters.

Methods

Subjects

Healthy, informed, consented volunteers participated in the study. Volunteers who smoked, received any kind of medication, were pregnant or had BMI > 30 were excluded. The study was approved by the

Regional and Institutional Committee of Science and Research Ethics at Semmelweis University (approval number: 120/2018).

Measurements with the SCN4ALL system

In each investigational protocol pulse wave detection and analysis were performed by the 1.0 version of the SCN4ALL telemedicine system (E-Med4All Europe Ltd.). Pulse wave was recorded as DVP detected by a transmission pulse oximeter (Berry Pulse Oximeter, Shanghai Berry Electronic Tech Co., Ltd, Shanghai, China). The device communicates via Bluetooth connection with a mobile application which initiates and terminates the 2-minute-long data acquisition and transmits the recording to a cloud-based automated algorithm which has been developed by our research group. (Figure 1.)

Place holder for Figure 1

Signal preprocessing by the algorithm starts with upsampling the 200-Hz sampling frequency of the device to 1 kHz. In order to condition the PPG signal a digital band pass filter - fourth order Butterworth - with -3dB points at 0.1 Hz and 10 Hz is applied. Then the algorithm identifies the pulse cycles. Afterwards, within each cycle particular distinct points of the DVP (primary curve, first and second derivatives) are identified. Then contour parameters are computed for every individual cycle. The means of all cycles are displayed as results on an internet platform for the physician as mean ± 2x standard deviation. Data are stored at a cloud-based server (Amazon Web Services, Amazon Web Services EMEA SARL, 1855 Luxembourg, Luxemburg) equipped with safe data protection which conforms to the applicable regulations. The automatically calculated parameters that this study focuses on are: *mean interbeat interval* (IBI - ms), *heart rate* (HR 1/min), *stiffness index* (calculated as the height of the subject over pulse transit time PTT – m/s [5][11]), *reflection index* (the ratio of the amplitude of the diastolic peak to the amplitude of the systolic peak); *left ventricular ejection time*

index (LVETI - ejection time (ET) normalized for heart rate using the formulae LVETI = 1.7 × heart rate + ET, and LVETI = 1.6 × heart rate + ET in males and females, respectively [13]), *b/a* (parameter relating the amplitude of the second wave of the DVP second derivative to the first wave), *d/a* (ratio of the fourth and first inflection points of the second derivative of the DVP), aging index (a parameter derived from the amplitudes of inflections of the second derivative of the DVP as *b-c-d-e/a* [26]), and *c-d* point detection ratio (a value that specifies the percentage of those pulse cycles in the 2-minute recording in which *c* and *d* points of the second derivative were successfully identified by the algorithm) (Figure 2).

Place holder for Figure 2

Protocols

Variability due to measurement error

In order to explore the size of the variability in the measured parameters which is attributable to measurement error of our telemedicine system (combined error of DVP recording, data processing and analysis), we recorded artificial signals generated by a pulse simulator device (MS100 SpO2 Simulator, Contec Medical Systems Co., Ltd., Qinhuangdao, China). Beside the generation of high-quality, physiological simulated pulse signals ("normal" - SpO_2: 98%, heart rate: 55/min), the simulator offers signals which model frequent signal variants, 'Abnormal 1' (titled 'geriatric' in the simulator's software) (SpO_2: 92%, heart rate: 95/min) and the 'Abnormal 2' titled 'weak' in the software (SpO_2: 90%, heart rate: 95/min) signal settings. The latter simulates the pulse wave when the detectable signal is of low-intensity. (Figure 3.) We performed 5 repeated measurements for each signal setting ('Normal', 'Abnormal 1', 'Abnormal 2') with 5 different pulse oximeters of the same product release.

Place holder for Figure 3

Intrapersonal variability at standard conditions

To define the size of variability caused by physiological fluctuations of CV functioning, which still remains after standardizing the measurement conditions, we performed 10 repeated 2-minute-long measurements on 10 young healthy individuals (M/F: 5/5, Age: 19-35, Mean ± SD: 25.3 ± 4.3) at standard conditions. The course of successive measurements took approximately 30 minutes. We defined 'standard condition' as the set of measurement conditions which we recommend our users to keep when they perform their daily morning measurements during follow-up. Criteria of standard conditions: measurement takes place in a quiet room at room temperature; in the morning hours at least two hours after the last meal and coffee; in a sitting, resting position, with hands held quietly on a table. Moreover, consumption of energy drinks and alcoholic beverages, and intensive physical activity on the day of the measurement were avoided in this study. For these measurements the pulse oximeter was placed on the left index finger.

Parallel measurement on 4 fingers

To investigate whether different anatomical disposition of the fingers comprises additional variability in the measured pulse contour parameters, we placed 4 pulse oximeters on 4 fingers (left and right indices and ring fingers) and made parallel 2-minute measurements. We made 2 consecutive pulse recordings on 25 healthy individuals (M/F: 17/8; Age: 19-49, Mean ±SD: 29.4 ± 8.4), and took the average of the 2 measurements for each individual.

Data analysis and statistics

Cycles with irregular duration and unusual morphology were automatically excluded from the analysis by the algorithm (< 5%). Afterwards, the means of values calculated for the individual pulse cycles of

the 2-minute-long recording were calculated for each parameter. For the present analysis, means were exported from the system in spreadsheets. These mean values were used for further characterizations. The descriptive statistics are presented as mean with its 95% confidence interval. To estimate variability between measurements and intrapersonal variability we used Coefficient of Variation (CV = (SD/mean x 100) x (1+1/4n) where n is the sample size) [27]. For repeatability measurements, we predefined the criterion of acceptance for CV as 2%, whereas for test-retest variability measurements as 10 %. At the 4-finger measurements we calculated intraclass correlation coefficients (ICC) to show the correlation between fingers and assess the contribution of interpersonal variability to overall variability. The ICC calculation was based on a linear mixed effect model. All statistical analyses were performed by using IBM SPSS Statistics for Windows, version 26 (Armonk, NY: IBM Corp.)

Results

Determination of measurement error by the telemedicine system was assessed by detecting stable artificial signals generated by a pulse oximeter simulator. The overall measurement error may be produced by the data analyzing algorithm, the measurement error of a single pulse oximeter as well as by the variability due to using different pulse oximeter devices to detect the pulse signals. Firstly, in order to assess the combined contribution of the algorithm and the error of a single pulse oximeter to the overall measurement error, we detected the normal pulse signals of the simulator with a single, randomly chosen pulse oximeter and repeated it 5 times (Table 1. Normal condition, 1st column). The results showed that the measurement was stable: the CI was very close to the mean of the 5 measurements, and the coefficient of variation was below 1% for each calculated variable.

Then we randomly chose 4 other pulse oximeters of the same release, and repeated the measurements as described above. Then we averaged the results of the 25 measurements. These

showed that the output data had low variability as evidenced by narrow CI-s and small (lower than 1%) CV-s for each parameter (Table 1. Normal condition, 2nd column).

After proving that our system detects and analyzes normal pulse signals reliably, we repeated the measurements described above with signal presets of the simulator, which simulate abnormal conditions. For this purpose, we used the 'Abnormal 1' and the 'Abnormal 2' presets. The former preset of the simulator generates a signal with high heart rate (95/min). In this setting, the reliability of pulse detection and analysis was similar to the 'Normal' condition except for the calculation of aging index and *d/a* parameters - as the second derivative of this preset has no detectable c and d points. (Table 1. 'Abnormal 1' condition)

The 'Abnormal 2' signal preset mimics a condition, when the signal is of low intensity (a typical source of error in DVP detection). Similar to what we observed with the 'Abnormal 1' signals, the results of these measurements also showed stable detection and analysis for most parameters, except for the aging index and the *d/a* ratio - for the same reasons as in Abnormal 1. (Table 1. 'Abnormal 2' condition)

Test-retest variability was assessed to evaluate intrapersonal variability of the pulse wave parameters under standard conditions. For this purpose, resting measurements were repeated 10 times in 10 healthy individuals. After calculating the coefficient of variation for each individual, the CV-s of the 10 subjects were averaged. The mean CV-s are presented in Table 2. These show that *b/a*, left ventricular ejection time index, mean interbeat interval, stiffness index and mean heart rate are parameters which remain stable under standard measurement conditions (CV-s are lower than 10%). However, aging index is slightly (CV: 13.6%), whereas *d/a* along with *c-d* point detection ratio are highly variable even when measured under unchanged conditions.

In order to assess how the detected intrapersonal variability relates to interpersonal variability, for each sequential measurement time point, we demonstrated the mean of measurements obtained

from the 10 subjects with confidence intervals on Figure 4. along with the individual graphs of the subjects. The graphs show that for each parameter, individual curves look parallel and show no trend, only random fluctuations could be noticed. The mean curves show no trends or extremes, and have homogenous confidence intervals. The variability of the individual curves among measurements and the variability between the individual curves look comparable.

Place holder for Figure 4

Concomitant measurements on 4 different fingers were also performed in 25 individuals to test how slightly different anatomic disposition of the fingers affects the detected pulse wave parameters. The results are summarized in Table 3. The mean of the measurements of the 4 fingers are presented, showing no relevant difference between the fingers. Moreover, the intraclass correlation coefficients were over 99% for mean interbeat interval, mean heart rate, left ventricular ejection time index indicating that the effect of using different fingers for measurement is negligible. The ICCs for stiffness index and *c-d* point detection ratio were about 90%, and were over 80% for reflection index, *b/a, d/a* and aging index. These confirm that the effect of using different fingers on variability is much less than that of the interindividual differences for these parameters, too (see Table 3 for exact values for the different parameters).

Discussion

Home monitoring of cardiovascular patients is a promising approach in patient care which is expected to gain ground in the upcoming decades and may constitute a relevant breakthrough in primary and secondary prevention of cardiovascular diseases. Implementation of non-invasive simple

measurements, which give a deep insight to the momentary cardiovascular condition of the patient allowing extensive evaluation, and reliable fast data analysis are all basic requirements for such telemedical systems. Our research group has developed a telemonitoring system which utilizes digital photoplethysmographic pulse detection and provides relevant practical information for the caregivers by calculating numerous pulse contour parameters. Professional utilization of a new system in research and in clinical practice demands accurate knowledge of measurement errors as they highly influence clinical evaluation. Nonetheless, in-depth evaluation of such errors is not abundant in scientific literature [20] [21]. This study was designed to assess the size of all relevant potential measurement errors of our system including estimation of repeatability of the telemonitoring system measurements (using stable simulated artificial signals), and to estimate the variability caused by alterations in physiological and anatomical circumstances of the examination (including test-retest variability measured on human subjects). With this multidirectional approach, we gave an in-depth description of errors and highlighted the potential limitations of the system prior to its first introduction to clinical research.

The repeatability of the measurements of our telemonitoring system was assessed by calculating the variability of the DVP parameters obtained from successive measurements of stable artificial pulse signals, which simulated healthy pulse waves and were generated by a pulse oximeter simulator device. Such variability can be caused by measurement errors of the pulse oximeter instrument and also the automated algorithm analyzing the detected pulse wave. The combined effect of these 2 factors on measurement variability was investigated by testing the agreement between the results of 5 successive measurements performed by the same randomly chosen pulse oximeter device. The variation was smaller than the predefined 2% criterion of acceptance for each parameter (Table 1. 'Normal' condition). Afterwards, we extended the investigation to 4 additional instruments with which we performed the same measurements. We pooled the 5x5 measurements and calculated the overall CV-s, which now reflect the combined variation caused by measurement error of a single pulse oximeter, analysis by the algorithm, and also the 'inter-instrumental' variability of several pulse

oximeters of the same product. The CV-s calculated in this way were also below the limit of acceptance (Table 1. 'Normal' condition), showing that measurements are highly repeatable, even if different pulse oximeters are used.

The pulse oximeter simulator also offers abnormal pulse signals. We repeated the measurements with these settings, too. 'Abnormal 1' setting generates a pulse signal of high heart rate and almost totally absent second derivative *c-d* points, whereas 'Abnormal 2' a signal simulates a weak pulse wave (e.g. similar to that observed in case of vasoconstriction due to cold). Second derivative *c-d* points are absent in this setting as well. With these settings the calculation of most parameters was still highly repeatable (CV% below 2%). However, detection of *c* and *d* points became less reliable. In accordance with that, *c-d* point detection ratio, the parameter which expresses the percent of those pulse cycles in which *c* and *d* points are recognized by the algorithm, fell below 5% for each setting (Table 1. 'Abnormal 1' and 'Abnormal 2' condition). This increased the variability of all those parameters, which are derived from *c* and *d* values, namely aging index and *d/a*.

This indicates that improvements of the automated algorithm may be needed in order to make identification of second derivative *c* and *d* points more reliable. However, literature data suggest that this may have limitations. (Reviewed by M. Elgendi [28]). Pulse wave analysis was originally extended to the second derivative of the DVP by Takazawa *et al.* [14]. They defined notable points of the curve which facilitate understanding of the pressure wave. Since then, several research groups have related the height of the *b, c* and *d* waves to the *a* wave to create measures which can index vascular pathologies (vascular aging, hypertension, arterial stiffness) and predict cardiovascular endpoints [14][29][30][31]. However, detection of *c* and *d* inflections has become reportedly a challenge for automated algorithms as their position and amplitude change along with pathophysiological alterations of the PPG [28]. Although attempts to make *c-d* point detection more precise are inevitable, we also propose to use *c-d* point detection ratio as a tool which aids clinical assessment of parameters derived from the second derivative. If *c-d* point detection ratio reaches a certain value, we

can reliably use parameters derived from the second derivative to support patient evaluation, however, when it is low, these parameters should be neglected. Determination of the minimum *c-d* point detection ratio which allows valid second derivative parameter interpretation requires further studies, however, based on our preliminary observations it is around 30 % (data shown). Moreover, in the follow-up of a patient, a sudden or progressive change in *c-d* point detection may be a warning for pulse wave abnormalities.

Pulse contour parameters may vary continuously even in healthy individuals, since the activity of the underlying physiological processes constantly fluctuates while the body adapts to common everyday challenges (such as physical and mental activities, changes in body posture, environmental temperature, food ingestion etc.). This potential variability may limit the usefulness of pulse wave monitoring by increasing the threshold for detectability of subtle pathological alterations. In order to enhance the precision of pulse contour analysis we need to advise the users to do their everyday measurements under standardized conditions. This standardization does not require any particular cooperation from users, the recommendations are as simple as those for blood pressure measurement and are confined to those conditions which have been reported to influence pulse contour parameters. [22][23][24][25] Measurements should be performed in a quiet room at room temperature; in the morning hours, preferably at least two hours after the last meal and coffee; in a sitting, resting position, with hands held calm on a table. Speaking, moving and mental activity (e. g. reading, watching TV) should be avoided during data collection. Naturally, this standardization does not remove variability completely. In order to judge how the given pulse contour parameter may support clinical decision, we defined this remaining variability by measuring test-retest variability. The output contour parameters of our telemedical system show minimal test-retest variability for most of the parameters, namely for *b/a*, left ventricular ejection time index, mean interbeat interval, stiffness index and mean heart rate (CV-s are lower than 10%; Table 2). Consequently, these parameters are suitable for patient follow-up, as deviation of a measurement from the ordinary individual value of the patient is not likely to be caused by normal intrapersonal variability, but rather indicates pathological alterations.

However, parameters derived from *c* and *d* points of the second derivative of the DVP are more variable (aging index, *d/a*). This concurs with the relatively high variations in *c-d* point detection ratio of consecutive measurements. This also confirms that aging index and *d/a* should only be involved in clinical evaluation, when *c* and *d* points are reliably detected by the algorithm, otherwise their applicability is questionable (see above).

In our study, we also provided preliminary data on the interpersonal variability of the studied contour parameters (Figure 4.). Based on our observations we can conclude that interpersonal and intrapersonal variabilities of the studied parameters are in the same range for healthy individuals when measurements are performed under standard conditions. This indicates that deviations from normal ranges may reflect DVP, - and hence cardiovascular - abnormalities both at individual (when compared to other results of the same patient) and at population level (when data are compared to values of healthy individuals). However, larger studies should be conducted to define the normal reference ranges for the contour parameters computed by our telemedicine system. Reference ranges for these parameters are scant in the literature, and they have only limited validity for larger populations [5][14] [31][32][33] [34][35][36][37].

In our study we also tested how different anatomical disposition of the fingers affects the results of pulse contour analysis. It is not a question that we recommend our users to use the same finger for each measurement. However, it may occur that for some reason they use another finger sometimes. Therefore, we need to be aware whether this error causes significant alterations of the output results. We could observe that in healthy individuals there was no clinically relevant difference in pulse contour parameters when measured parallel on index and ring fingers of the 2 hands. The calculated ICCs showed that the effect of using different fingers on variability of the outcomes is much less than the effect of interpersonal differences. Therefore, changing to different fingers does not constitute relevant measurement error. However, we need to keep in mind that pathological alterations and

diseases of the supplying arterial tree may have an impact on blood flow of the digital arteries. For this reason, at the first patient visit it is recommended to record pulse signals on several fingers on both sides and analyze whether there are differences in the output parameters.

Conclusion

In this study we completed the preclinical assessment of a novel pulse wave analysis based telemonitoring system. We used a multidirectional approach to explore and characterize the possible measurement errors in depth. We showed that our system is capable of measuring most common pulse contour parameters (e.g. stiffness index, reflection index, left ventricular ejection time index) with high precision. Moreover, under standardized conditions test-retest variability in healthy individuals is also negligible for these variables. These allow high fidelity evaluation of these parameters and detection of small pathological alterations. However, correct evaluation of some parameters derived from the second derivative of the pulse wave (i.e. aging index, *d/a*) can be violated by pathophysiological alterations of the pulse wave which make *c* and *d* point identification difficult. For elimination of this error, we recommend the introduction of *c-d* point detection ratio in pulse wave analysis and consideration of second derivative parameters only if its value is acceptable. In summary, we can claim that our system operates reliably with acceptable measurement errors, and meets the requirements set for medical devices.

Figure legends

Figure 1. Outline of the SCN4ALL telemedicine system. Peripheral arterial pulse wave is detected by a transmission pulse oximeter. The device communicates via bluetooth connection with a mobile

application which initiates and terminates the 2-minute-long data acquisition and transmits the recording to a cloud database. A cloud-based automated algorithm calculates the pulse contour variables which are reported to the dashboard of the physician, and in brief form, to the mobile application of the user.

Figure 2. Pulse contour parameters calculated by the SCN4ALL system. Representative pulse wave recording (panel A), and its first (panel B) and second derivative curves (panel C). ET represents ejection time measured as the duration between the foot of the pulse wave and the dicrotic notch. PTT stands for pulse transit time which is the duration measured between the systolic and diastolic peaks of the curve. IBI represents interbeat interval, which is the pulse duration measured from peak to peak. 'x' and 'y' are amplitudes of the systolic and diastolic peaks, respectively, and are used for calculation of the reflection index as x/y. 'a', 'b', 'c', 'd', and 'e' points represent notable inflection points of the second derivative curve.

Figure 3. Representative recordings obtained on a healthy individual and the pulse oximeter stimulator. Panel A shows representative recording of one of our healthy subjects. Panel B shows recording of an artificial pulse wave generated by the 'Normal' setting of the pulse oximeter simulator. Recordings of panel C and D demonstrate pulse waves generated by the 'Abnormal 1' and 'Abnormal 2' signal settings of the pulse oximeter simulator device. Both are high heart rate signals (95/min) and are characterized by disappearance of 'c' and 'd' inflections of the second derivative curve. 'Abnormal 2' setting was a low-intensity signal, but was still recorded accurately with the system.

Figure 4. Graphs demonstrating the relationship between interpersonal variability and intrapersonal variations of the computed pulse contour parameters. Measurements were performed on 10 healthy volunteers 10 times repeatedly under standardized conditions. Means (± confidence intervals) are

405 presented (red solid line) for each consecutive measurement along with individual measurement data
406 (black lines). Individual lines are similar to each other and to the average line. The variability of the
407 individual curves among measurements and the variability between the individual curves seem to fall
408 in the same order of magnitude.

409

410 Declarations

411 Ethics approval and consent to participate

412 The study was approved by the Regional and Institutional Committee of Science and Research Ethics
413 at Semmelweis University (approval number: 120/2018). All subjects consented to participate in the
414 study.

415

416 Consent for publication

417 Not applicable

418

419 Availability of data and materials

420 The data that support the findings of this study are available from E-Med4All Europe ltd., but
421 restrictions apply to the availability of these data, which were used under license for the current study,
422 and so are not publicly available. Data are however available from the authors upon reasonable
423 request and with permission of E-Med4All Europe ltd.

424

Competing interests

DK, FA, KIL, SK and ZsM are in financial terms with E-Med4All Europe Ltd (DK and SK as co-owners, FA as employee and KIL and ZsM as subcontractors). DSV and DW did not receive compensation for their contribution by financial or any other means.

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Authors' contributions

DK had a relevant contribution to the design of the study, performed the examinations and drafted the manuscript. FA performed repeatability measurements and contributed to data analysis and manuscript preparation. SK made substantial contributions to conception and substantively revised the manuscript. DW performed test-retest measurements and made figures. KIL did the majority of data and statistical analysis. DSV contributed to statistical analysis and substantively revised the manuscript. ZsM contributed to conception, supervised the implementation of measurements and data analysis, substantially contributed to outlining and finalization of the manuscript. All authors read and approved the final manuscript.

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Authors' information (optional)

Not applicable

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Tables

Table 1. **Results of repeatability measurements.**

	Normal				**Abnormal 1**				**Abnormal 2**			
	n=5		*n=25*		*n=5*		*n=25*		*n=5*		*n=25*	
Variables	*Mean[CI]*	*CV(%)*	*Mean[CI]*	*CV(%)*	*Mean[CI]*	*CV(%)*	*Mean[CI]*	*CV(%)*	*Mean[CI]*	*CV(%)*	*Mean[CI]*	*CV(%)*
Aging index	-1.13[-1.14; -1.12]	0.41	-1.14[-1.14; -1.13]	0.57	-3.37[-4.45; -2.29]	27.1	-3.12[-3.46; -2.79]	26.1	-3.71[-4.60; -2.81]	20.4	-3.84[-4; -3.69]	9.9
b/a	-1.78[-1.79; -1.78]	0.26	-1.79[-1.79; -1.78]	0.32	-1.59[-1.59; -1.59]	0.29	-1.59[-1.60; -1.59]	0.32	-1.60[-1.60; -1.59]	0.36	-1.60[-1.59; -1.56]	0.33
c-d point detection ratio (%)	100[100; 100]	0	100[100; 100]	0	0.60[0.08; 1.28]	95.9	0.44[0.23; 0.65]	116	2[0.48; 3.52]	64.3	2.70[2.25; 3.19]	42.2
d/a	-0.75[-0.75; -0.74]	0.77	-0.75[-0.75; -0.75]	0.37	-0.48[-1.01; -0.06]	95.9	-0.35[0.18-0.52]	116	-0.64[-1.09; -0.20]	58.7	-0.71[-0.79; -0.63]	26.9
Left ventricular ejection time index (ms)	552[552; 554]	0.22	553[552; 553]	0.27	462 [461; 462]	0.06	462[462; 462]	0.05	462[462; 463]	0.06	462[462; 463]	0.07
Heart rate (1/min)	55[55; 55]	0	55[55; 55]	0	95[95; 95]	0	95[95; 95]	0	95[95; 95]	0	95[95; 95]	0
Interbeat interval (ms)	1089[1089; 1089]	0	1089[1088; 1090]	0.21	631[631; 631]	0	631[631; 631]	0.19	630[630; 631]	0.07	631[631; 632]	0.18
Reflection index (%)	35.5[35.5; 35.6]	0.13	35.5[35.5; 35.6]	0.11	32.7[32.7; 32.8]	0.12	32.7[32.7; 32.8]	0.13	32.8[32.6; 32.9]	0.35	32.8[32.7; 32.8]	0.42
Stiffness index (m/s)	4.62[4.62; 4.63]	0.10	4.62[4.62; 4.63]	0.26	7.34[7.34; 7.34]	0	7.34[7.33; 7.34]	0.18	7.34 [7.33; 7.36]	0.16	7.34[7.33; 7.35]	0.34

Means (and confidence intervals - CI) and coefficients of variation (CV) of pulse contour variables measured by the SCN4ALL telemedicine system. In order to evaluate repeatability of the measurements by the system, we detected and analyzed artificial pulse signals generated by a pulse oximeter simulator device. 3 different signal settings of the simulator were selected (Normal, Abnormal 1, and Abnormal 2). For each setting, measurements were repeated 5 times with a single randomly chosen pulse oximeter (n=5 columns), then these measurements were supplemented with the repeated measurements on 4 other pulse oximeters of the same release (n=25 columns, showing the results of 5x5 measurements).

Table 2. **Results of test-retest variability measurements.**

Pulse contour variables	CV % [CI]
Aging index	13.6[4.78; 22.5]
b/a	3.84[2.13; 5.55]
c-d point detection ratio (%)	33.6[17.1; 50.1]
d/a	83.9[9.5; 177]
Left ventricular ejection time (ms)	1.30[0.75; 1.84]
Heart rate (1/min)	3.19[1.99; 4.39]
Interbeat interval (ms)	3.23[2.11; 4.35]
Reflection index (%)	7.43[2.79; 12.1]
Stiffness index (m/s)	4.34[2.20; 6.48]

Intrapersonal variability of pulse contour parameters measured by the SCN4ALL telemedicine system. Measurements were performed on 10 healthy volunteers 10 times repeatedly under standardized conditions. Coefficient of variation (CV) for the results of the consecutive measurements was calculated for each individual. Afterwards, individual CV-s were averaged and are presented in the table along with confidence intervals [in brackets].

Table 3. **Results of measurements performed parallel on 4 separate fingers on 25 healthy individuals.**

	Left index finger	**Left ring finger**	**Right index finger**	**Right ring finger**	**ICC**
	n=25	*n=25*	*n=25*	*n=25*	
Pulse contour variables	*Mean[CI]*	*Mean[CI]*	*Mean[CI]*	*Mean[CI]*	
Aging index	-1.29[-1.46; -1.13]	-1.30[-1.47; -1.13]	-1.34[-1.15; -1.12]	-1.47[-1.17; -1.25]	0.81
b/a	-1.21[-1.26; -1.152]	-1.22[-1.29; -1.16]	-1.25[-1.312; -1.20]	-1.24[-1.30; -1.17]	0.83
c;d point detection ratio (%)	33.8[25.3; 42.4]	31.3[23.1; 39.5]	31.9[22.9; 40.8]	32.3[23.9; 40.78]	0.90
d/a	-0.15[-0.24; -0.06]	-0.16[-0.26; -0.07]	-0.17[-0.29; -0.06]	-0.10[-0.21; -0.01]	0.82
Left ventricular ejection time index (ms)	148[56; 240]	148[57; 240]	147[56; 238]	147[56; 237]	>0.99
Heart rate (1/min)	70.6[67.1; 74.2]	71.0[67.5; 74.2]	70.9[67.4; 74.4]	71.0[67.4; 74.5]	>0.99
Interbeat interval (ms)	862[817; 906]	862[818; 908]	862[816; 907]	861[817; 907]	>0.99
Reflection index (%)	62.2[59.2; 65.1]	60.8[57; 64.6]	61.5[58.4; 64.5]	61.3[57.6; 65.0]	0.81
Stiffness index (ms)	7.74[7.37; 8.10]	7.71[7.32; 8.10]	7.58[7.20; 7.97]	7.59[7.13; 8.05]	0.90

For each individual, 2 consecutive 4-finger measurements were taken, and the average of the 2 was used for further calculations. The results of the 25 subjects were averaged for each finger separately, and presented in the table with confidence intervals [*CI* in brackets]. Intraclass coefficients were calculated to assess correlation of results within the same individuals.

Figures

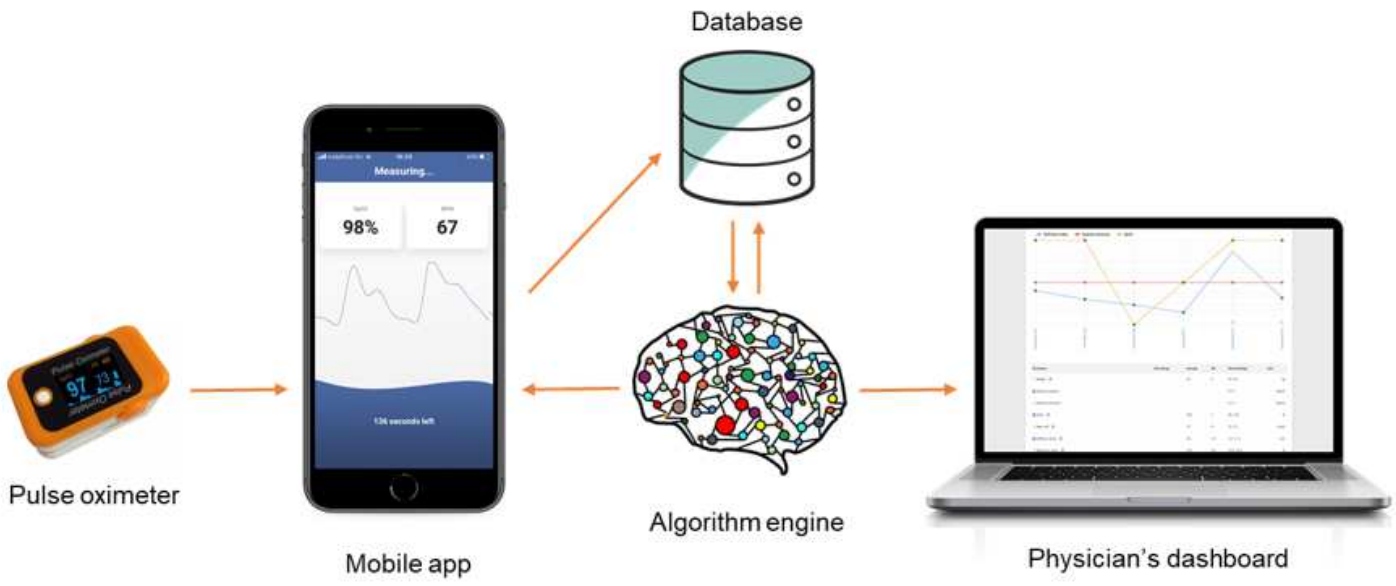

Figure 1

Outline of the SCN4ALL telemedicine system. Peripheral arterial pulse wave is detected by a transmission pulse oximeter. The device communicates via bluetooth connection with a mobile application which initiates and terminates the 2-minute-long data acquisition and transmits the recording to a cloud database. A cloud-based automated algorithm calculates the pulse contour variables which are reported to the dashboard of the physician, and in brief form, to the mobile application of the user.

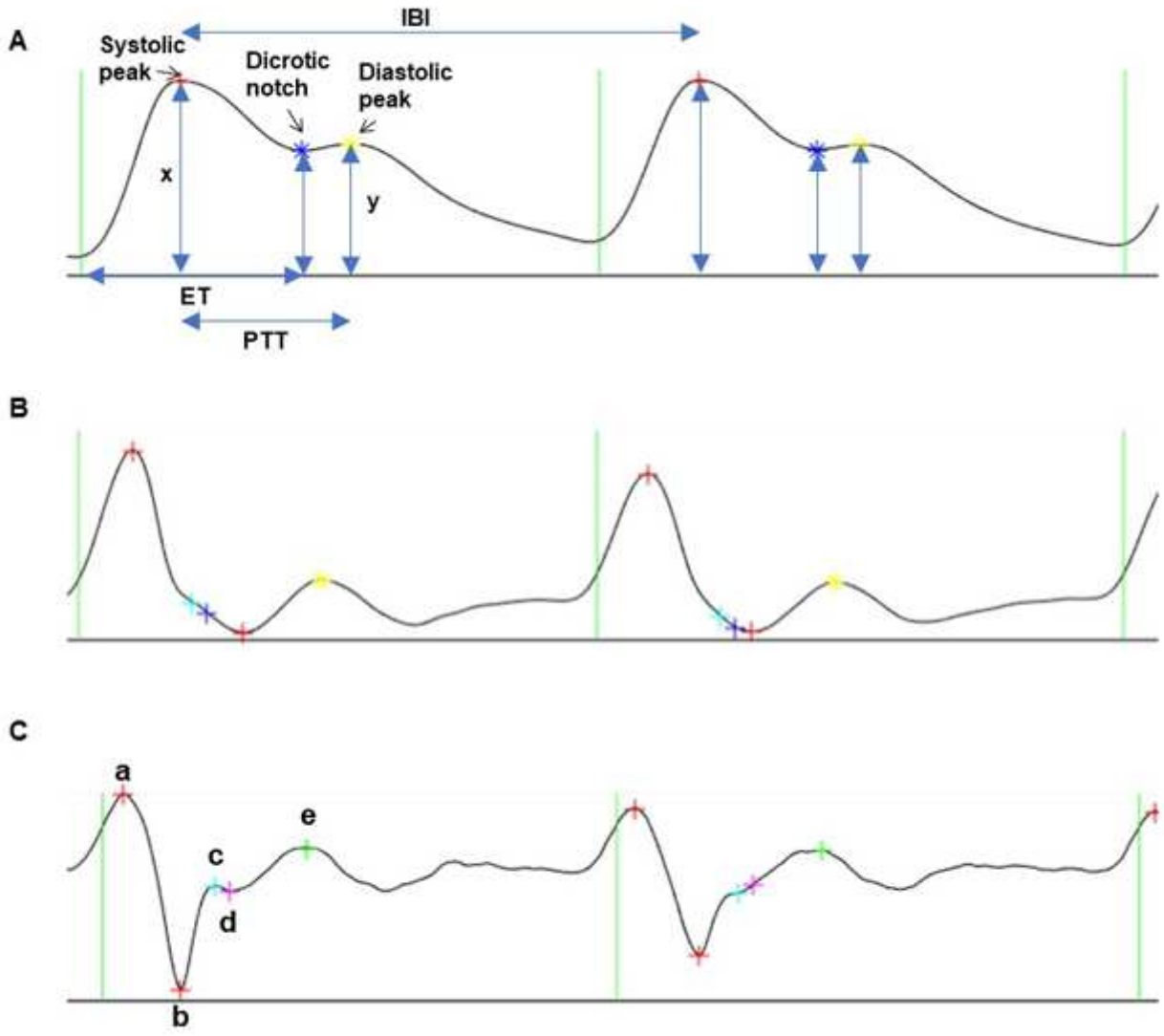

Figure 2

Pulse contour parameters calculated by the SCN4ALL system. Representative pulse wave recording (panel A), and its first (panel B) and second derivative curves (panel C). ET represents ejection time measured as the duration between the foot of the pulse wave and the dicrotic notch. PTT stands for pulse transit time which is the duration measured between the systolic and diastolic peaks of the curve. IBI represents interbeat interval, which is the pulse duration measured from peak to peak. ‘x’ and ‘y’ are amplitudes of the systolic and diastolic peaks, respectively, and are used for calculation of the reflection index as x/y. ‘a’, ‘b’, ‘c’, ‘d’, and ‘e’ points represent notable inflection points of the second derivative curve.

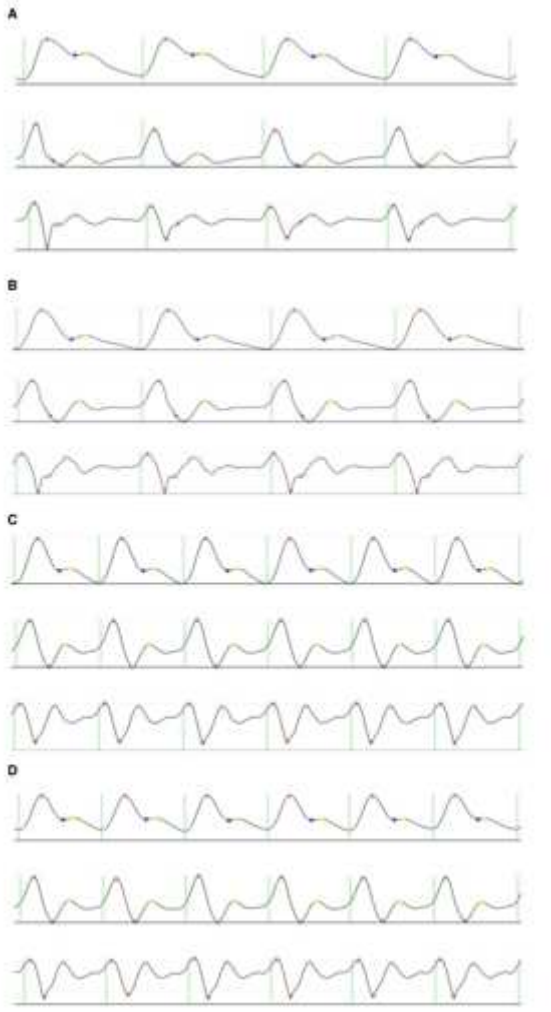

Figure 3

Representative recordings obtained on a healthy individual and the pulse oximeter stimulator. Panel A shows representative recording of one of our healthy subjects. Panel B shows recording of an artificial pulse wave generated by the ‘Normal’ setting of the pulse oximeter simulator. Recordings of panel C and D demonstrate pulse waves generated by the ‘Abnormal 1’ and ‘Abnormal 2’ signal settings of the pulse oximeter simulator device. Both are high heart rate signals (95/min) and are characterized by disappearance of ’c’ and ’d’ inflections of the second derivative curve. ‘Abnormal 2’ setting was a low-intensity signal, but was still recorded accurately with the system.

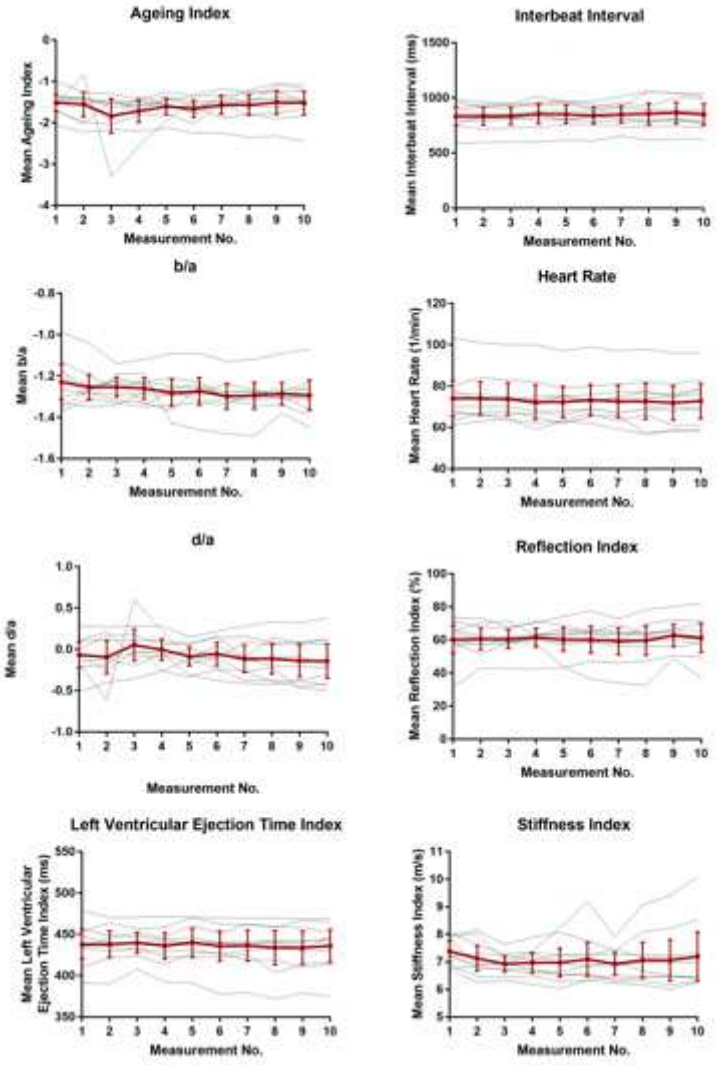

Figure 4

Graphs demonstrating the relationship between interpersonal variability and intrapersonal variations of the computed pulse contour parameters. Measurements were performed on 10 healthy volunteers 10 times repeatedly under standardized conditions. Means (± confidence intervals) are presented (red solid line) for each consecutive measurement along with individual measurement data (black lines). Individual lines are similar to each other and to the average line. The variability of the individual curves among measurements and the variability between the individual curves seem to fall in the same order of magnitude.