A novel method for continuous, non-invasive, cuff-less measurement of blood pressure: evaluation in patients with non-alcoholic fatty liver disease

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Abstract*—*Objective: **One promising approach for a continuous, non-invasive, cuff-less ambulatory BP monitor is to measure the pulse wave velocity or the inversely proportional pulse transit time (PTT), based on electrical and optical physiological measurements in the chest area. A device termed IsenseU-BP+ has been developed for measuring continuous BP, as well as other physiological data. The objective of this paper is to present results from the first clinical evaluation with a wide range of patients. The study was set up to verify whether IsenseU-BP+ can be used to measure raw signals with sufficient quality to derive PTT.** ***Methods:*** **The test protocol, run 23 times on 18 different patients with non-alcoholic fatty liver disease, includes both supine measurement at rest as well as measurements during indoor cycling. Changes in PTT were compared with the BP changes measured using validated reference sensors.** ***Results:*** **IsenseU-BP+ measured signals with good quality during rest on 17 of 18 patients despite the high diversity in age, body shape and BMI. Evaluation during cycling was difficult due to a lack of good reference measurements.** ***Conclusion:*** **IsenseU-BP+ measures PTT with high quality during supine rest and exercise and could therefore be suitable for deriving non-invasive continuous BP, although evaluation during exercise was limited due to inaccurate reference BP measurements.** ***Significance:*** **Continuous, non-invasive measurement of BP would be highly beneficial in a number of clinical settings. Systems currently considered gold-standard for the investigation of hypertension carry considerable limitations which could be overcome by the method proposed here.**

***Index Terms*—cuff-less blood pressure, pulse transit time, pulse wave velocity, unobtrusive sensing, hypertension**

I. Introduction

Hypertension (elevated blood pressure (BP)) is the major risk factor for early mortality in Western society. It is estimated to contribute to around 12.8% of all deaths, and globally affects 40% of adults aged 25 and over, according to the World Health Organization [1]. Treating systolic BP (SBP) and diastolic BP (DBP) to below 140/90mmHg is associated with a reduction in cardiovascular complications [2]. Increasingly, the medical community is also focusing on blood pressure variability [3] and nocturnal BP in the assessment and treatment of hypertension. Point BP measurements taken in the clinic tend to be inadequate or misleading due to diurnal variation and the so-called "white-coat hypertension". The clinical practice for 24-hour ambulatory monitoring is to use cuff-based equipment with a unit for control and data storage usually worn on a lanyard around the neck. Typically, point measurements are restricted to three times an hour during daytime and once an hour overnight. There are considerable limitations to this method: the equipment is usually only validated at rest [4] and patients are instructed to sit down when the measurements are taken. This means that measurements are not representative of the full range in BP over the 24-hour period. The monitoring interferes with patients' activities of daily living, and a large group of patients finds the cuff inflation uncomfortable and disruptive. This is problematic overnight, in particular, when the cuff inflation can disturb the patient's sleep and can, itself, impact the BP.

One approach for a continuous, non-invasive, cuff-less ambulatory BP monitor is to measure the pulse wave velocity or the inversely proportional pulse transit time (PTT). Several studies based on different technical solutions shows correlation between PTT and BP [5]-[11], but improvements are necessary. Most of the studies measured the time from ECG R-peak to the pulse wave reached a peripheral artery. This time measurement includes both PTT and part of the pre-ejection period, which is the period from start of the depolarization of the heart, represented with the ECG-Q wave, to the aortic valve opening. Both the pre-ejection period and the PTT vary with blood pressure, and combining the two makes extraction of blood pressure values difficult [12]. Including the pre-ejection period also makes the measurements dependent on posture [13]. Also, in most studies, as well as in commercially available devices [14], a peripheral point such as the finger or earlobe is used. Measuring PTT peripherally means that vasoconstriction

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(narrowing of the blood vessels resulting from contraction of the muscular wall of the vessels) can affect the results [15]. Vasoconstriction can, for instance, be caused by exercise or temperature changes. Alternatively, measuring the distal pulse on the chest makes the system less vulnerable to vasoconstriction. Sola et al. have demonstrated a chest sensor system complying with the British Hypertension Society requirements of Grade A BP monitors for mean arterial readings [16]. They measured PTT from the opening of the aortic valve to the internal thoracic artery, just after it arises from the subclavian artery. However, they did not show a fully integrated device, and only present results for healthy subjects at rest in the supine position.

IsenseU-BP+ is a fully integrated, compact and unobtrusive wearable sensor unit that measures impedance cardiography (ICG), plethysmography (PPG) and single-channel electrocardiography (ECG) on the chest, and extracts PTT by combining these three signals. To our knowledge, IsenseU-BP+ is the first device aiming to measure BP changes with all components and processing integrated within a single, small unit strapped around the chest, thereby making it truly unobtrusive in daily life. In tests performed on healthy volunteers with normal range BMI using handgrip movement to change blood pressure, it has been verified that IsenseU-BP+ can be used to monitor blood pressure changes [17]. The hypothesis behind the present work was that IsenseU-BP+ can be used to measure PTT in a patient population with both genders and varying age, body shapes and body mass index (BMI). The objective of the present work is therefore to explore the effect of body habitus on device performance. A population with non-alcoholic fatty liver disease (NAFLD) was chosen because this is a diverse patient group that is likely to benefit from closer monitoring of many health parameters, including BP. The protocol involved steady state supine testing as well as indoor cycling. Cycling was included to investigate whether measurement of PTT during activity is feasible and to investigate the system's responsivity to BP changes during exercise.

II. Materials and Methods

A. *Description of IsenseU-BP+*

IsenseU-BP+ resembles a pulse belt with the addition of three standard ECG electrodes. A sketch showing sensor locations as well as an image of the body worn device is given in Fig. 1. Mechanically, the device was designed to be comfortable for both genders of all weights, with rounded edges and smooth surfaces. The electronic compartment has an elliptic-like shape with a major axis length of 12.5 cm, and minor axis height of 4.5 cm. The sensor module is attached to a standard textile belt with integrated electrodes that is strapped around the torso, and this design ensures that the PPG sensor connects to the chest with a reproducible force each time. IsenseU-BP is built around a 32-bit ARM Cortex-M3 microcontroller (Cypress PSoC® 5LP), and provides wireless communication by Bluetooth. A large internal flash memory allows data logging when the device is not connected. Three primary sensors are used to derive BP parameters:

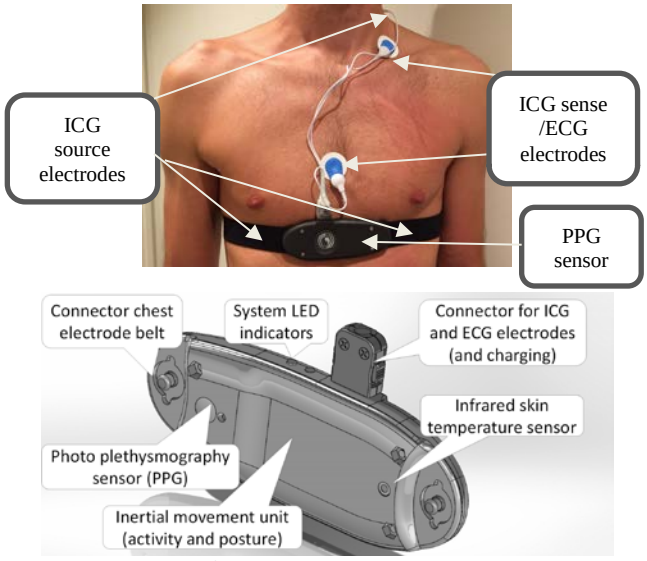

Fig. 1. Top: Sketch of IsenseU-BP+ wearable device showing sensor locations. Bottum: The IsenseU-BP+ wearable device with electrodes.

1) A single-channel (2-electrode) electrocardiogram (ECG) circuit is used for detecting the 'R' peak, and as source for the heart rate (HR).
2) Electrical impedance of the heart region throughout the cardiac cycle is monitored using impedance cardiography (ICG). This is a four-point measurement, using two electrodes to source an AC current (1mA RMS, 60 kHz), and two sense electrodes.
3) Changes in the blood flow at the chest surface are detected by PPG. A green LED (570nm) sends light pulses into the skin, and the returned light is detected by a photodetector. The LED and detector are mounted approximately 6 mm apart on the rear side of the device.
In addition, detailed movement and posture tracking by a 9-axis inertial motion unit as well as skin temperature on the chest by an infrared temperature sensor are measured by the system.

Electrode locations were chosen based on work by Patterson [18] and in-house testing informed by previous work carried out by Tan et al. [19] on electrode placement with the Physio Flow® [20] impedance cardiograph device for measuring cardiac output. The ICG current source uses the two chest-belt electrodes in parallel, and one electrode behind the neck. To reduce the number of electrodes, the same electrodes are used for both ICG and ECG sensing. The sensing electrodes are high quality disposable electrodes that are glued to the skin and connected with single wire conductors to the device. This configuration limits mechanical strain on the electrodes during movement. The sensing electrode positions were also chosen because they are affected relatively little by the body's natural movements. This design makes the ICG system more robust towards motion artifacts. The PPG sensor located at the chest measures the blood flow in superficial skin capillaries. The blood flow has therefore travelled a distance in muscular arteries that could be affected by vasoconstriction. It is estimated that that approximately 2/3 of the travel time is in muscular arteries and 1/3 in elastic arteries. The impact of vasoconstriction, and especially the

effect of temperature, is, however, significantly lower than with finger or earlobe measurements. The current position was chosen based on the highly prioritized requirement of an easy-to-use device.

Fig. 2displays the raw signals during rest (Fig. 2A) and during cycling (Fig. 2B) for test 8. The raw signals (ECG, PPG, ICG) from IsenseU-BP+ have previously been compared against validated reference sensor signals, see [17] for more information. In the current work the sampling time of the raw data (ECG, ICG, PPG) was 4 ms, data was collected and logged with Bluetooth disabled, and filter settings were held constant. An online algorithm was implemented in IsenseU-BP+ to find online PTT but parts of the data was also post-processed using Matlab to be able to explore the quality of online PTT.

B. Calculation of pulse transit time

The characteristic features for the ECG, PPG and ICG signals used in the online PTT algorithm are illustrated in Fig. 2A. Distal time for the PTT calculation is derived from the PPG signal. It is set at the foot of the pressure wave, defined as the intersection of the tangent through the minimum PPG and the tangent through the maximum slope of the PPG, during each cardiac cycle. The proximal time is found from the ICG signal. The ICG target proximal point is the ICG-B point, which indicates the opening of the aortic valve. The ICG-B point is however difficult to locate in individual cycles in ICG signals recorded during activity [21]. In this work, we have chosen an approach were the B-point is estimated based on the time gap (in ms) between the ECG-R wave and the ICG-C peak (the maxima on the ICG curve), T_{RC}. The time gap between ECG-R wave and ICG-B point (T_{RB}), and thereby the timing for the ICG-B point, is estimated using the formula described by van Lien et al. [22]: $T_{RB} = -15 + (0.7*T_{RC})$. The equation for PTT is then given for each cycle:

$$PTT = T_{RPPG} - T_{RB} = T_{RPPG} - (-15 + (0.7*T_{RC}))$$
$$PTT = T_{RPPG} + 15 - (0.7*T_{RC}).$$

Here T_{RPPG} is the time gap from ECG-R to the PPG foot. Even though this method does not estimate the pre-injection period with the accuracy required by van Lien et al. (changes less than 3.5 ms in individual heart cycles), the precision of the ICG B-point detection was judged sufficient for the intended use of the IsenseU-BP+ device. Lien et al. had a mean difference between the actual pre-ejection period and estimated pre-ejection period of +8ms/-4ms. Approximately half of the error was due to using a fixed value for the period from the onset of cardiac depolarization until ECG-R. The error in the individual heart cycle RB period in their study was then +4ms/-2ms. We have considered an averaged PPT value, and, assuming the error in B detection had a random component, we found that the averaging decreased the error. A change in mean blood pressure of 10 mmHg is expected to give a change in PTT of about 8ms-16ms [21]. Their calculations were based on PTT values in the range 100ms to 200ms. Thus, the error caused by this method for ICG-B point detection will influence the possibility to detect small changes in blood pressure, and the beat-to-beat variation. For changes in the range evaluated during activity in this study (>20 mmHg and averaged over 10 heart cycles) the error of the ICG-B point detection were judged acceptable [17].

C. Test Protocol

The IsenseU-BP+ study was carried out in conjunction with a study where patients with NAFLD underwent exercise testing exploring the effects of exercise on underlying liver fat at Newcastle University. The overall study, as well as the device study, were granted a favorable ethical opinion by the Black Country Research Ethics Committee.

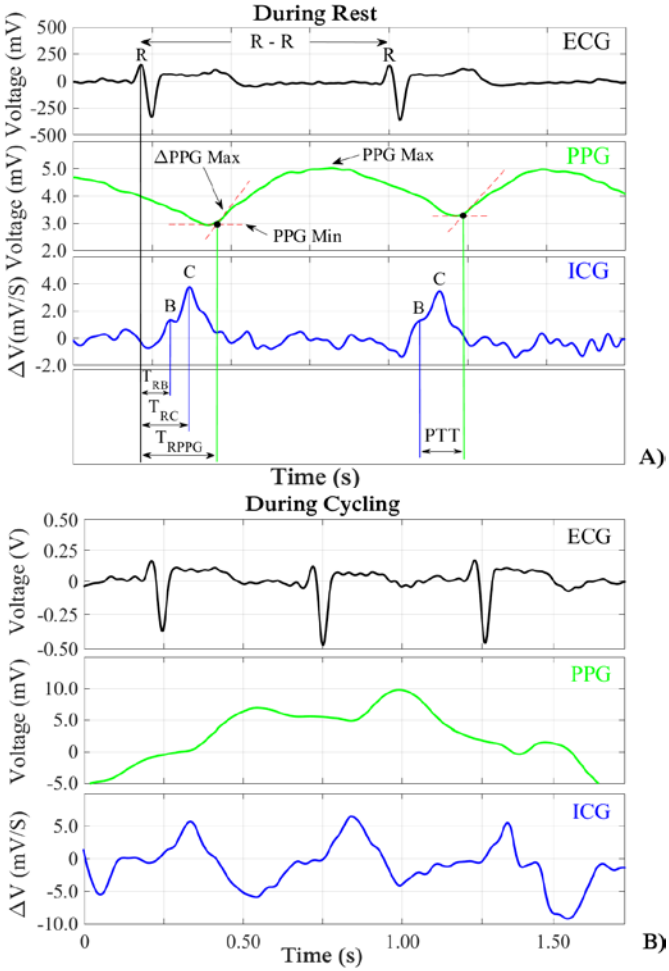

Fig. 2. Fig. 2A displays raw data from test 8 during rest, it also illustrates the characteristic features of ECG, PPG and ICG signals used for detection of distal and proximal time from PPG and ICG signals. Fig. 2B displays raw signals from the same patient during cycling.

All patients had previously undergone maximal exercise testing allowing calculation of maximal VO2 consumption and anaerobic threshold. Beat-to-beat continuous HR and BP monitoring were performed during a 10 minute supine rest. Following this, patients were subject to physical activity on a Lode exercise bike. The test setup during rest and exercise are shown in Fig. 3. After a warm-up period of five minutes, patients exercised at 50% of their maximum intensity for 60 minutes, followed by a final supine rest period of 5 minutes. During exercise and the end rest period, point blood pressure measurements were measured a total of six times using a brachial sphygmomanometer cuff: 1) before exercising began, 2) after the warm-up, 3) at the middle and 4) end of exercise,

and at the 5) start and 6) end of the post-exercise rest period. The time to acquire the reference cuff BP measurements varied between 20 and 60 seconds.

D. Reference sensors

During the initial supine rest period, continuous non-invasive BP monitoring using finger cuffs and intermittent monitoring with a conventional brachial cuff were carried out using the Task Force monitor (Task Force (TF), CN Systems, Austria, http://www.cnsystems.com/products/task-force-monitor). This device provided autonomic function data (HR variability,

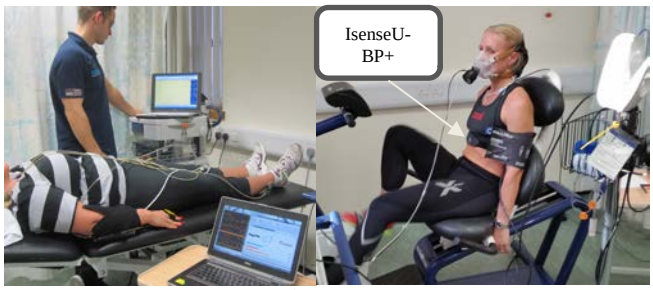

Fig. 3. Test setup during rest (left) and exercise (right). IsenseU-BP+ can be seen on the picture to the right, but are hidden under the shirt on the picture to the left. The rest of the instruments seen are the reference measurement systems.

baroreflexsensitivity etc.) as well as beat-to-beat blood pressure (SBP, DBP and MAP). The BP monitor of the TF system, CNAP®, measures the pressure in the finger and correlates this with the brachial cuff measurement. Studies show that CNAP® is precise compared to arterial BP measurements for MAP and DBP, but with greater variation in SBP [23][24]. However, TF can only be used while lying down. During cycling, BP was therefore measured using a conventional brachial sphygmomanometer cuff (Spot Vital Signs, Welch Allyn, USA). The patients were told to keep their arm and upper body as still as possible while measuring the reference BP. The cuff manufacturer states cuff accuracies of ± 5 mmHg (mean error) and 8 mmHg (standard deviation). This cuff is however not designed to be used during activity, so the real accuracy is probably poorer than this. The cuff only measures SBP and DBP, not MAP. In the activity phase, MAP has therefore been estimated using the formula: MAP = DBP + 1/3(SBP-DBP). This formula has been shown by MacDugall et.al [26] to be valid throughout exercise, while others claim that it underestimates the impact of SBP [27].

E. Statistical methods

To define the relationship between PTT and MAP, a linear correlation has been assumed, and the least square regression method has been used to find the best linear fit. To evaluate the fit of the line, the R values (based on R2 calculations) have been calculated.

III. Results

A. Fitting of IsenseU-BP+ on persons with a wide range of body habitus

The protocol was conducted 23 times on 18 different patients, five of whom were tested twice. Detailed patient characteristics are given in Table I. IsenseU-BP+ could be easily fitted to all patients despite varying body habitus.

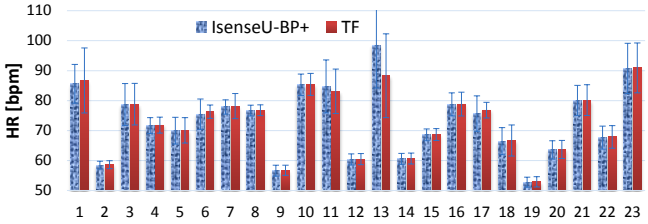

Fig. 4. Mean HR during rest for all patients with standard deviation error bars, comparing data measured by IsenseU-BP+ and the TF.

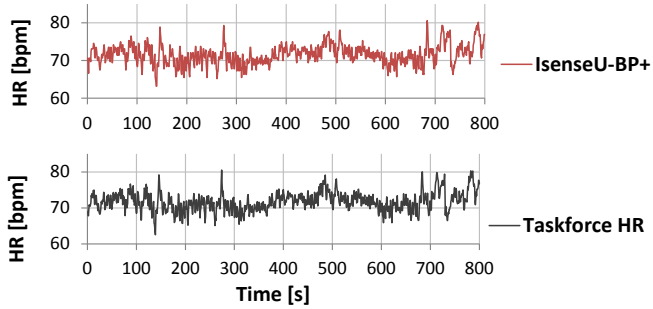

Fig. 5. Comparison of HR measured by IsenseU-BP+ and TF during rest (test 4).

B. Verification of heart rate measured by IsenseU-BP+ during rest

Mean HR and standard deviation for each patient measured by IsenseU-BP+ and TF in the supine resting phase are displayed in Fig. 4. A typical trace comparing HR measured by IsenseU-BP+ and TF (test 8) is showed in Fig. 5. The IsenseU-BP+ electrode positions used in this study are optimized for ICG, and are therefore suboptimal for measuring HR. This is due to the location of the two ECG electrodes. They are both placed centrally on the chest. The QRS therefor has an abnormal shape, and for many users the amplitude of the R-peak is low. Despite this, the tests show that IsenseU-BP+ is able to measure HR with the desired beat-to-beat level accuracy. HR measured by IsenseU-BP+ and the TF reference sensor are nearly identical for all tests with only negligible differences most likely due to the differences in filtering and signal processing.

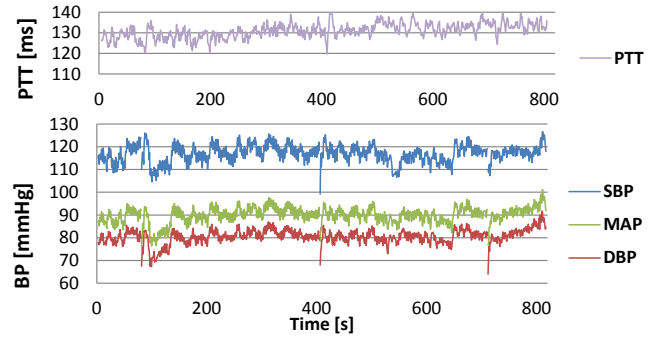

Fig. 6. Reference BP and PTT from the initial phase (test 5) where the patient is laying down resting, this means that the blood pressure and PTT should be stable. The fluctuations that are seen in the graphs is likely due to limitations in the measurement accuracy of the sensors (for example movement artefact's is an important source of error). A running average of 5

C. Measurements of pulse transit time and blood pressure during rest

BP was stable during rest for all patients, and this was also

true for PTT. Fig. 6 displays a typical data from the patient laying down resting, the small fluctuations in TF reference BP parameters and PTT are probably due to limitation in the measurement accuracy (for example movement artifacts is an important source of error). We had one sample for each heart beat, but as discussed later, the sampling rate used in these tests (250 kHz) was too low to provide a beat-to-beat PTT accuracy. A five sample running average has therefor been used in the plot. In order to assess the quality of the PTT-data the fraction F of valid PTT measurement data have been defined as follows: F = valid PTT data divided by total amount of measured PTT data. Valid PTT data is defined as: 50ms < PTT < 170ms (200ms for test 20 which had a higher mean PTT) and ΔPTT = max ± 25ms. At rest, FRest was high with an average of 90%, with the exception of two tests, (test 6 and 17), see Table I. The two outliers were both from the same patient, and the poor FRest (48% and 27%) were due to high noise levels in the PPG signal. In Fig. 9, FRest versus BMI for all patients are displayed, and it shows that high BMI does not correlate with low FRest. Table II shows mean values of all BP parameters together with corresponding relative standard deviation. There was no correlation between BMI and the variation (standard deviation) in PTT or BP measurements (see Fig. 7). A significantly higher standard deviation was observed for the reference BP in test 13, but BMI for this patient was close to the average value (29.1 kg/m2).

D. Measuring pulse transit time during activity

Complete data sets during cycling were collected for 16 tests, including retest of 4 patients. For the remaining 7 tests, data is missing for the final test stages (final minutes of steady state cycling and cool down) due to premature system setup combined with operator errors.

The general trends during testing were that SBP and MAP were stable during the supine resting phase and then increased during the warm-up period, increasing further to the middle of exercise. Following this, either a slight further increase or a plateau was observed until the end of exercise. After exercise, both the SBP and MAP returned to the pre-exercise level during the final rest period. The variation of PTT and $T_{RB}/T_{RPPG}/T_{RC}$ followed the opposite trend: When SBP and MAP increased, they decreased. Most patients had only small variations in DBP throughout the test period. A typical pattern of variation during the test for PTT and reference BP parameters together with HR during the whole test is given in Fig. 8 (test 15). The PTT data quality indicator parameters FRest and FCycl have been plotted as a function of BMI for both rest and cycling in Fig. 9. Numbers are given in Table I.

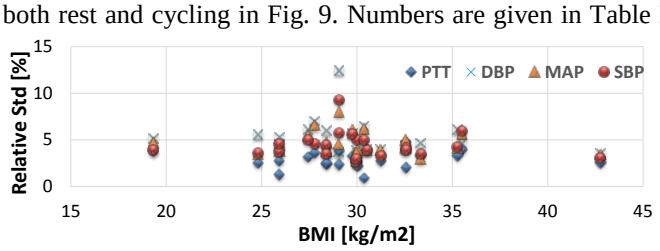

Fig. 7. Relative standard deviation of PTT, MAP and SBP (standard deviation/ mean value) versus BMI for all tests during supine rest state.

TABLE I – PATIENT CHARACTERISTICS WITH GENDER, AGE[YEAR], WEIGH[KG], BMI [KG/M^2], VO2 MAX [ML/KG*MIN] AND QUALITY OF DATA REPRESENTED BY F_{REST} [%] AND F_{CYCL}[%].

Id	Gender	Age	Weight	BMI	VO_2 Max	F_{Rest}	F_{Cycl}
1	M	55	110	35.5	16	95	ND
2	M	67	94	30.0	30	99	57
3	F	69	49	19.3	16	77	42
4	M	43	93	30.0	24	98	58
5	M	52	114	31.2	19	97	65
6	F	42	82	32.6	19	48	44
7	M	47	137	42.8	21	97	23
8	M	63	108	33.3	12	73	41
9	M	55	84	24.8	32	99	67
10	M	27	84	25.9	29	100	77
11	M	31	92	30.5	26	100	65
12	M	68	83	29.8	20	97	83
13	M	48	89	29.1	25	87	77
14	M	44	108	35.3	30	97	66
15	M	39	88	27.8	31	83	68
16	M	60	91	29.0	24	100	65
$17*_6$	F	42	82	32.6	19	27	38
18	M	47	92	28.4	32	98	53
$19*_2$	M	67	94	30.0	30	99	49
20	F	59	72	30.4	19	100	54
$21*_{10}$	M	27	84	25.9	29	100	71
$22*_{18}$	M	47	92	28.4	21	95	53
$23*_{11}$	M	31	84	27.4	15	99	65

$*_X$ retest of a patient x, ND = no data

TABLE II – PTT[MS] AND REFERENCE BP [MMHG] DURING REST - AVERAGE VALUES AND RELATIVE STANDARD DEVIATION (STANDARD DEVIATION/MEAN) [%].

ID	PTT AVE	SBP AVE	DBP AVE	MAP AVE	PTT %ST	SBP %ST	DBP %ST	MAP %ST
1	126	125	86	96	4.0	5.9	4.6	5.6
2	118	116	79	89	2.6	2.6	2.8	2.7
3	139	118	70	80	3.8	3.9	5.1	4.6
4	125	119	78	89	2.2	5.0	3.6	3.9
5	131	117	81	90	2.7	3.3	4.0	3.9
6	143	124	77	90	4.8	4.1	4.4	5.0
7	105	146	103	113	2.6	3.0	3.6	3.4
8	140	128	95	103	3.3	3.5	4.7	3.0
9	110	114	73	86	2.5	3.6	5.6	3.5
10	105	142	98	111	2.7	3.7	5.3	3.9
11	108	112	78	90	2.5	3.8	4.6	4.1
12	105	111	69	77	3.3	5.6	5.7	6.1
13	116	114	85	94	3.8	9.3	12.4	8.0
14	135	146	101	113	3.3	4.2	6.1	4.2
15	149	127	81	96	3.6	4.5	7.0	6.5
16	115	123	84	92	2.4	5.7	3.7	4.5
$17*_6$	148	132	85	99	2.0	3.9	4.3	4.1
18	147	126	93	102	2.4	4.4	6.0	4.7
$19*_2$	149	114	77	86	2.7	3.0	3.9	3.6
20	166	129	72	85	0.9	5.0	6.5	6.1
$21*_{10}$	103	133	90	102	1.3	4.5	4.6	4.5
$22*_{18}$	136	132	93	104	2.5	3.5	3.7	3.8
$23*_{11}$	106	120	81	93	3.1	5.0	6.1	5.5
AVE	**127**	**125**	**84**	**95**	**2.8**	**4.4**	**5.1**	**4.6**
MIN	**103**	**111**	**69**	**77**	**0.9**	**2.6**	**2.8**	**2.7**
MAX	**166**	**146**	**103**	**113**	**4.8**	**9.3**	**12.4**	**8.0**

$*_X$ retest of a patient x

E. Correlation and prediction of blood pressure

The correlations between inverse PTT and SBP/MAP/DBP have been calculated for all full datasets (16 sets). PTT was estimated for every heart beat by IsenseU-BP+ (by the method described in II.B), but to reduce random variation and be able to compare with the reference BP measurements that takes 20s-50s, an average of 30 samples has been used for the

IsenseU-BP+ measurements. The mean value has been used for the rest period. Even though the quality of the reference measurements are low due to cycling induced movement noise, high correlation (correlation coefficients R > 0.70) was found between SDB/PTT in 10 of 17 tests, between MAP/PTT in 7 of 17 tests and between DBP/ PTT in only 3 of 16. Details are given in Table III. Table III also shows two columns that indicates the quality of the data: Qual.Ref is the subjectively assessed quality of the reference cuff data where the evaluation was based on whether or not the BP followed the expected pattern or not. Qual.PTT gives an assessment of the quality of the PTT data based on the observed noise in the PPG signal. Linear regression data for three of the tests, which showed a high correlation between SBP and PTT (tests 5, 8 and 18 randomly picked of the group of high correlation), are shown in Fig. 10.

It is of interest to analyze whether measurements done on a specific patient is reproducible from day to day. For one of the patients who did repeat testing, BP was predicted from the PTT data recorded on the second day (test 22) based on the regression model derived from the first day (test 18). This was only done for one patient due to low quality data for the other retested patients. Fig. 11 shows a Bland-Altman plot comparing predicted and measured values (TF reference data) for MAP and SBP during rest for in test 22. The prediction is based on the linear regression model derived in test 18 by plotting PTT and BP to find the linear regression line (linear equation). The relationship between BP and PTT for this patient is given by the equation SBP = -1.22PTT + 299. This linear equation was then used in test 22 to convert the PTT values to predicted SBP and MAP. A moving average of 20 samples was used for each point. The deviations between predicted and measured values are small and inside the measurement accuracy of the TF device. The mean predicted value for SBP was 134 mmHg, the measured value was 132 mmHg. For MAP the mean predicted value was 103 mmHg, the measured value was 104 mmHg.

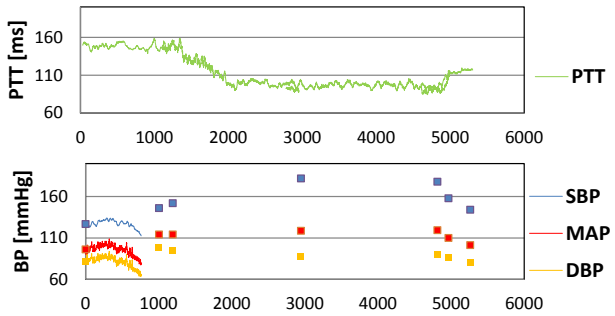

Fig. 8. PTT measured by IsenseU-BP+ and reference BP (SBP, DBP and MAP) measured by TF in the beginning, then point measurements during cycling (test 15).

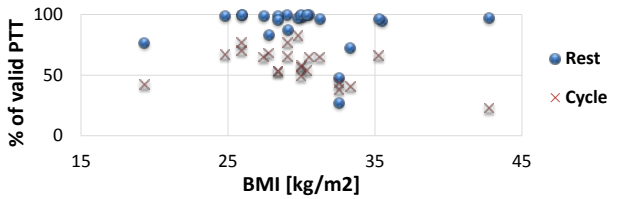

Fig. 9. Fraction of valid PTT versus BMI for all tests during rest (F_{Rest}) and activity (F_{Cycl}).

TABLE III – CORRELATION (R) BETWEEN INVERSE PTT AND MAP/SBP/DBP, VARIATON (VAR[MMHG]) OF PTT, SBP, DBP INCLUDING A SUBJECTIVE ASSESSMENT OF THE QUALITY OF REFERENCE (QUAL REF) AND PTT (QUAL. PTT) DATA.

Patient Id	R SBP	R MAP	R DBP	Var MAP	Var SBP	Var DBP	Qual Ref**	Qual PTT***
18	0.97	0.97	0.89	55	94	23	OK	OK
22*$_{18}$	0.97	0.96	0.70	24	53	12	OK	OK
5	0.92	0.89	0.22	21	40	12	OK	OK
9	0.88	0.78	0.10	21	49	9	OK	OK
15	0.87	0.59	0.20	24	59	18	OK	OK
8	0.85	0.82	0.12	31	53	26	OK	OK
10	0.83	0.25	0.39	16	28	18	OK	OK
13	0.78	0.62	0.36	34	52	28	OK	OK
20	0.78	0.81	0.28	31	66	13	OK	OK
2	0.75	0.63	0.06	24	44	13	OK	OK
3	0.64	0.73	0.83	53	77	33	LOW	OK
17*$_{6}$	0.54	0.29	0.66	9	26	22	LOW	LOW
14	0.53	0.45	0.00	25	44	16	LOW	OK
19*$_{2}$	0.34	0.56	0.58	30	49	18	LOW	OK
23*$_{11}$	0.26	0.45	0.64	16	16	21	LOW	OK
6	0.19	0.08	0.00	29	30	29	LOW	LOW

*$_X$ retest of a patient x, ** subjectively assessed based on expected values, *** subjectively assessed based on observed noise

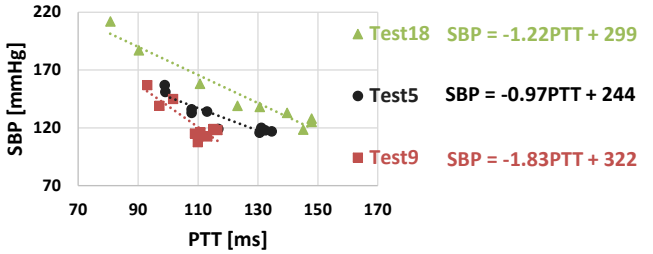

Fig. 10. Relationship between SBP and PTT, both graphical and by equation in test 5, 9 and 18.

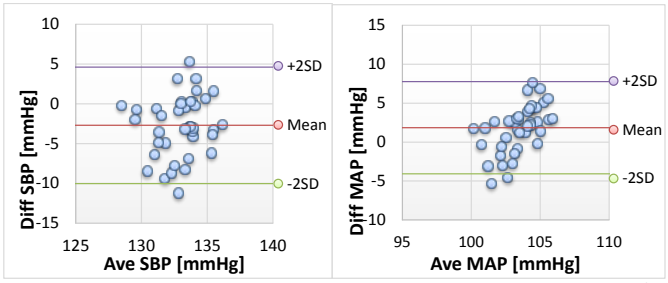

Fig. 11. Bland-Altman plot comparing predicted and measured values for MAP and SBP during rest (test 22). The predicted values were found using a linear calibration factor derived from previous testing of the same patient on a different day (test 18). The relationship between BP and PTT for this patient is given by the equation SBP = -1.22PTT + 299.

IV. DISCUSSION

A. *Measurement of pulse transit time and patient diversity*

It was hypothesized that IsenseU-BP+ was able to measure data on all patients, despite difference in gender, age, body shape and BMI. The patients were a heterogeneous group; age varied between 27 and 69 years, both genders were present and BMI varied from 19.3 (normal weight) to 42.8 kg/m2 (very severely obese). Still, it was found that IsenseU-BP+ has a form factor that were suited for all patients in the study. This is probably due to a small sized compartment, an adjustable belt and electrodes that can be placed freely. PTT during rest was measured with high quality; the average value of good

samples was 90%. This result is impressive for this diverse patient group. The exception was in test 6 and 17 where the test subject was the same female patient with BMI slightly above the average. The reason for the low FRest in this patient was noise in the PPG raw signal; this can probably be solved with an optimized PPG sensor (discussed below).

B. Correlation between pulse transit time and blood pressure

To be able to correlate PTT with BP parameters, a change in BP must be induced. There are several ways to induce BP changes; using drugs, stress, hand grip dynamometer, activities such as cycling, or immersion of hands or feet in ice cold water [9]. In the present work, indoor cycling was used since we wanted to explore if measuring PTT during activity is feasible. Cycling is a harmless, easy way for the patient to change BP, and could therefore be part of a calibration regime.

The result show that the fraction of valid PTT samples was significantly reduced during cycling (FCycl mean value = 58%) compared to while rest (FRest mean value = 90%). This is due to movement artifact from cycling and breathing, which is more pronounced while exercising than while laying still. A possible solution for measuring during every-day activities could be to use data from the activity sensors to identify favorable, low activity periods to measure PTT, or more advanced use of detailed activity data to remove noise from the PPG and ICG raw signals.

FCycl was lowest in the test that involved the patient with the highest BMI (test 7). This patient had a low noise PPG signal at the beginning of the cycling period, but at the end the PPG signal became very noisy. The location of the sensor may have shifted during the cycling to a less favorable location. It is reasonable to believe that this can happen more easily for obese people than those with normal weight.

SBP, DBP and MAP values are all clinically relevant BP parameters. According to the Moens-Kortweg equation [25], estimation techniques based on pulse wave velocity (and its inversely proportional PTT) provide estimates of MAP and not SBP or DBP. However, others have reported good correlation with SBP. In this present study, the best correlation with PTT was found between PTT and SBP/MAP, see Table III. Low correlation was found between DBP and PTT. High correlation ($R > 0.7$) was found between PTT/MAP and PTT/SBP for several patients. The slope of the PTT – MAP linear regression line differs between persons and individual calibration functions will be needed. This finding is the same as reported by Solá et al. [16].

In order to achieve a good calibration between PTT and BP precise reference measurement are needed. However, there are no non-invasive methods that are able to measure accurate BP during activity. Accuracy of the reference sensor used during cycling was too low, and resulted in a poor correlation with PTT for several patients. The reason is that the cuff is not meant to be used during activity, and even small movements can lead to large errors [28] [23]. Even though the patients were asked to sit as still as possible with their upper body during the measurements this was not sufficient. For several patients, the operator had to measure BP several times in order to get a measurement. An option would have been to make the patient stop cycling while taking the measurement, which would have made it easier to measure BP. However, that would cause a decrease in heart rate and BP, and BP would be unstable during the measurement period, which is relatively long (30seconds-2minutes). Among the patients with medium and low correlation ($R<0.7$) between PTT and MAP (10 patients) and SBP (7 patients), 5 are assumed to be due to low quality of the cuff reference data. Low quality was set subjectively based on how the BP was expected to change based on the HR and test protocol. Low quality was only marked if the BP decreased while the HR increased, and there might be poor data not marked by this procedure. For MAP, there is also an uncertainty in the equation used for calculating MAP from DBP and SBP, and this may be one reason for poorer correlation with MAP than SBP.

Despite the low quality reference data Fig. 11 indicates that it is possible to predict BP with good quality for a patient based on a model derived on a previous day, indicating that a calibration method is feasible, but a large evaluation study with repeating tests is needed to confirm this. A larger scale correlation study between PTT and BP is also needed. This protocol had also a limited amount of reference cuff BP measurements per subject, and this can lead to misleading calculations of correlation. An improvement to the protocol would have been to have a longer rest period at the end while measuring cuff BP and PTT. One challenge is the method used to induce change in BP. From our experience, changing the BP by hand grip is a better method than cycling.

C. Clinical application and recommendation for further work

An effective method for continuous, non-invasive, measurement of BP would be highly beneficial in a number of clinical settings. Systems currently considered gold-standard for the investigation of hypertension carry considerable limitations which could be overcome by the method proposed here. Derivation of BP from beat-to-beat data enables continuous monitoring, rather than limited point measurements, ensuring a true representation of the entire period of investigation. Current continuous BP monitors (such as the reference method used here) are restricted to measurements carried out at rest. By contrast, IsenseU-BP+ performed well even during exercise for several test persons. Potential application for the in-patient setting could be desirable over current invasive (“arterial-line”) techniques. In addition to the in-patient applications, the device clearly has considerable potential in ambulatory (out-patient) BP logging applications for hypertension and cardiovascular logging applications.

The sampling rate used in these tests (250 kHz) was too low to provide beat-to-beat PTT accuracy. As discussed in [8] and [9], this requires a sampling rate of 1kHz. With the present sampling rate, it was difficult to find the exact time for the maxima of the ICG curve; this could easily be shifted 1-3 samples. A time offset of 8 ms corresponds to about 10 mmHg offset in BP [17]. However, the result is still valid for longer time estimates by averaging over several PTT samples. The

sampling rate can be changed in the present HW version of IsenseU-BP+ by modifying the embedded software.

Only basic signal processing with fixed filter settings were used in these measurements. More advanced signal processing using e.g. adaptive filtering will provide improved raw signals for deriving PTT. More robust and accurate algorithms for estimating PTT from raw data should also be developed and evaluated. A relatively simple online algorithm has been used to derive PTT and correlate with BP. The work by Ding et al [10] indicates that combining other features from PPG signal traces in addition to PTT could potentially be a better way to estimate BP and adding features from the ICG trace could further increase the accuracy.

The PPG sensor of IsenseU-BP+ has been shown to be sensitive to small changes in position as well as pressure on the skin, meaning that during breathing and activity the sensor can move slightly, especially for persons with a high BMI. Initial analysis suggests that this is caused by low signal quality due to suboptimal placement of the PPG sensor and filtering of the PPG signal to reduce breathing artefact. This is the same that is found by Mukkamala et al.[9]. Filtering to remove the breathing artefact without influencing PPG foot detection must be further improved. In this device, the PPG sensor has a single LED, while others have suggested advanced arrays of LEDs and detectors [16]. A second LED could be added to the IsenseU-BP+ in the present design, otherwise if this is not sufficient the PPG sensor must be refined through hardware improvements.

V. Conclusion

IsenseU-BP+ measured PTT with good quality during supine rest for all but one patient, despite a heterogeneous patient group. These results are promising; taking into account the known weaknesses of currently available test equipment, and indicate that measurement over longer periods, across a wide range of BMIs, without disturbing the patient is possible.

More noise was induced during cycling, but it was still possible to measure PTT with sufficient quality in many of the patients. In future the activity sensors could be used to identify optimal periods for measurements, and could even be used for motion artefact suppression.

Refinements, in particular to improve PPG signal quality, should lead to improvements so that a high quality, beat-to-beat resolution of BP can be reliably achieved.

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