An Unobtrusive Wearable Device for Ambulatory Monitoring of Pulse Transit Time to Estimate Central Blood Pressure

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Abstract: There is a clinical need for improved ambulatory, frequent and unobtrusive monitoring of blood pressure and cardiac parameters like systolic time intervals. Truly unobtrusive wearable devices combining impedance cardiography with other sensors may be one possible solution. The IsenseU-BP+ device presented in this article measures single channel ECG, impedance cardiography and photo plethysmography at the chest. The device also measures activity and posture, as well as skin temperature. In this study, we report on the possibility to use these signals to measure pulse transit time for estimating blood pressure changes. Six subjects has been tested. Four of them showed good correlation between PTT and mean arterial pressure while two of the subjects had too low signal to noise ratio in the photoplethysmography signal for good estimation of PTT. Thus these results show that the quality of the raw data is promising for calculating a pulse transit time that shows good coherence with mean arterial pressure.

1 INTRODUCTION

High blood pressure, hypertension, is estimated to cause about 13% of the total of all deaths world wide. In 2008 40% of adults aged 25 and over suffered from hypertension globally (World Health Organization Global Health Observatory (GHO) data on raised blood pressure, n.d). Raised blood pressure levels represent a major risk factor for coronary heart disease and stroke. The risk increases with increasing blood pressure level. Treating systolic blood pressure and diastolic blood pressure to get below 140/90 mmHg, is associated with a reduction in cardiovascular complications (Mancia et al., 2013). Increasingly, the medical community is also focusing on blood pressure variability (Rothwell et al., 2010) and the night level blood pressure in the assessment and treatment of hypertension. For a person with high and poorly controlled blood pressure, the pressure often varies significantly throughout the day, as well as between days. Point measurements taken in a doctor's office therefore tend to be inadequate or even misleading. For ambulatory monitoring to evaluate the variation during day and night at home the state of the art is to measure blood pressure over a 24-hour period with cuff-based equipment. Typically, point measurements are taken three times per hour during daytime and once per hour during sleep. The equipment is usually validated at rest only (O'Brian et al., 2010). Patients are instructed to sit down when the measurements are to be taken, thereby interfering with daily living. A significant group of the patients finds the cuff inflation stressful and disturbing, and this is particularly a problem during night. Thus, there is a need for better ambulatory blood pressure measurement equipment.

One approach for a new cuff-less ambulatory blood pressure system is to measure the pulse wave velocity or the inversely proportional pulse transit time (PTT). Assumed correlation between blood pressure and PTT is based on the Moens-Korteweg equation (Nichols and O'Rourke, 2005), which describes how the pulse wave velocity of elastic tubes are associated to structural arterial stiffness. The average pressure of the arterial wall defines the stiffness and therefor PTT should correlate better with Mean Arterial Pressure (MAP) than systolic and diastolic blood pressure. Different technical solutions have been proposed and several studies show correlation between PTT and blood pressure (a good summary was given in Buxi et al., (2015)).

Several 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 (Muehlsteff, Aubert and Shuett, 2006). Including part of the pre-ejection period also makes the measurement dependent on posture (Muehlsteff, Aubert and Morren, 2008). Impedance cardiography (ICG) can be used to detect aortic valve opening and therefore the pre-ejection period can be excluded from the measurements. ICG is a diagnostic method based on measurement of the electrical properties of the biological tissues applied to the thorax region. Changes in impedance on each heartbeat reflect changes in blood volume in the great vessels, but the origin of the signal is complicated and not well understood (Patterson, 2010).

In most of the studies estimating blood pressure based on PTT, as well as in commercially available devices (ViSiMobile, n.d.), a peripheral point at the finger or earlobe is used. Using e.g. the finger allows vasoconstriction (narrowing of the blood vessels resulting from contraction of the muscular wall of the vessels), to affect the results (Budidha and Kyriacou, 2014). Vasoconstriction can be caused by e.g. exercise or temperature changes. Measuring the peripheral pulse on the chest makes the system less vulnerable to vasoconstriction. Sola et al. (2013) have demonstrated a chest sensor system complying with the British Hypertension Society requirements of Grade A blood pressure monitors for MAP readings. PTT in Solà et al.'s system is measured from opening of the aortic valve to the internal thoracic artery, just after it arise from the subclavian artery. However, only a prototype setup, that is not fully integrated, is shown and only results for subjects at rest in supine position were presented.

This paper introduces a new, compact and unobtrusive wearable sensor device intended for long term continuous blood pressure estimations. This device, IsenseU-BP+, is to our knowledge the first fully integrated device aiming for estimating blood pressure, with ECG, ICG and photo plethysmography (PPG) sensors as well as all necessary electronics and processing; everything combined in one small unit strapped around the chest which make it truly unobtrusive in daily life. Results from tests that compares the individual sensor signal quality to reference sensors are

presented, followed by PTT measurements and an evaluation of how these correlates with changes in blood pressure.

2 MATERIALS AND METHODS
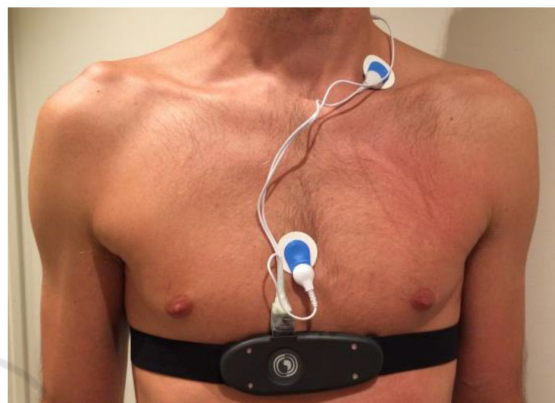
2.1 The IsenseU-BP+ Device

Figure 1: The IsenseU-BP+ wearable device with electrodes.

Physically, the device resembles the heart rate monitor commonly used during exercise, but with the addition of three standard ECG electrodes. The electronic compartment has an elliptic-like form with a major axis 12.5 cm, and minor axis of 4.5 cm. An image of a subject wearing the device is shown in figure 1. The device is built around a 32-bit ARM Cortex-M3 microcontroller (Cypress PSoC® 5LP), and provides wireless Bluetooth communication. The Bluetooth Serial Port Profile is implemented for live transmission of all data, and a Continua Health Alliance based Health Device Profile implementation is made for exchange of a sub-set of the data. An internal flash memory allows offline data logging. The belt is a commercially available off-the-shelf belt with rubber electrodes.

There are three primary sensors:

1) A single-channel (2-electrode) ECG circuit detecting the electrical activity of the heart

2) ICG that monitors variations in the electrical impedance of the heart region during the contraction cycle. This is a four-point measurement, using two electrode sets for sourcing a weak AC current (1mA RMS, 60 kHz), and two sense electrodes.

3) A PPG sensor detecting changes in the blood flow at the chest. A green LED (570nm) sends light pulses into the skin, and the returned light is measured by a photodetector. The LED and the
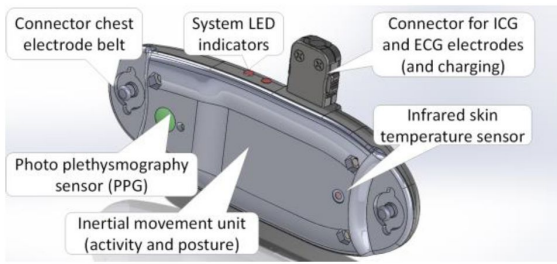
Figure 2: Drawing of the IsenseU-BP+ wearable device with sensors.

Figure 3: Detection of distal and proximal time from PPG and ICG signals. (PEP – pre ejection period of the heart).

detector are mounted approximately 6 mm apart on the rear of the device. The PPG sensor location at the chest, will make the measurements less affected by vasoconstriction than when measuring at the finger.

To reduce the number of electrodes, the same electrodes are used for both ICG and ECG sensing. One of these electrodes is located at or close to the lower part of sternum and the other close to the left collarbone. The ICG current source uses the two chest-belt electrodes in parallel in addition to an electrode behind the neck. Electrode locations optimize the ICG signal rather than the ECG signal. Locations are selected after in-house testing based on work by Patterson (2010) and inspired by the testing done by Tan, Lai and Hwang (2006) on electrode placement with the Physio Flow® impedance cardiograph device for cardiac output (Physioflow, n.d.). The position of the sense electrodes gives a non-standard ECG waveform, but does not influence the detection of the R-peak of the ECG signal or the R-to-R distance or variation. Figure 2 shows a drawing of IsenseU-BP+ with sensor locations. Mechanically, the device was designed to be comfortable for both genders of all weights, with rounded edges and smooth surfaces. The prototype was made by rapid prototyping with laser sintered plastic (PA2200).

PTT was measured from the ICG-B point (see figure 3) to the point of pulse arrival seen in the PPG signal. The ICG-B point indicates the opening of the aortic valve. In this work a method for ICG-B point estimation described by Van Lien et al. (2013) was used. Even though this estimation method did not estimate pre-ejection period with the accuracy required by van Lien et al. (2013), the precision of the ICG-B-point detection was judged sufficient for this first evaluation of using IsenseU-BP+ to estimate blood pressure changes. The RC interval was first computed as the time between the R-peak of the ECG and the C point of the ICG trace (RC in ms) Thereafter, the time from R-peak to B (RB in
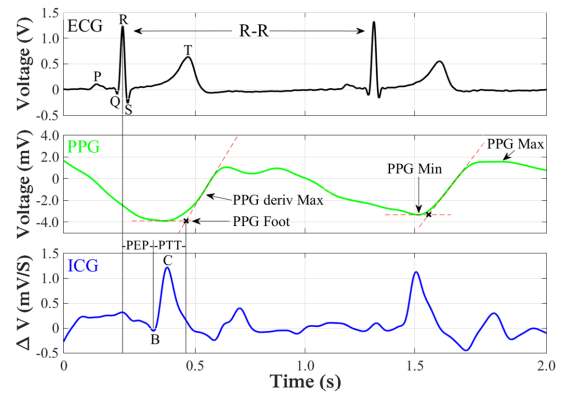
ms) was calculated according to van Lien et al (2013), RB = -15 + (0.7*RC). Knowing the timing of the R peak and the RB distance, the time of the B-point is found. The distal time was found from the PPG signal as the foot of the pressure wave. This was defined for a heart cycle by the intersection of the tangent through the minimum PPG and the tangent through the maximum slope of the PPG. Finally, PTT was calculated as the difference between time of the PPG_{Foot} and the B-point. The characteristic points for the signals are shown in figure 3.

2.2 Test Setup

According to the Norwegian Health Research Act, no approval by committee for medical and health research ethics was needed for these tests. For storing personal data, an approval from the The Data Protection Official for Research under the Personal Data Act/Personal Health Data Filing System Act was obtained.

The IsenseU-BP+ ICG and ECG sensors were compared to a BioNomadix system (BioPac Systems, Inc., Goleta, CA, USA). The fields of two ICG sensors applied at the same time may affect the result of the sensors, and therefore the testing with the two systems was done sequentially. The sampling rate for IsenseU-BP+ sensors was 250 Hz, while for the BioNomadix system it was 1 kHz. The Nonin finger signal was captured with a 100Hz low pass filter, and BioNomadix ECG and ICG with a 20Hz filter. IsenseU-BP+ sensors were captured ufiltered. Both IsenseU-BP+ and BioPac system was attached before the test started. The subjects rested for 5 minutes to minimize changes in heart rate. For ICG the same electrodes were used for both systems. For BioNomadix ECG the electrodes were in pulse

belt position with ground on the right hip. ICG and ECG with the BioNomadix system as well as PPG signal from a Nonin 8000AA finger clip sensor (Nonin Medical, Inc, Plymouth, MN, USA) were recorded for 1 minute, while the IsenseU-BP+ device was turned off. When the BioNomadix units were turned off, its wires for ICG was switched with the IsenseU-BP+ electrode wires. IsenseU-BP+ were turned on for recording of ICG, ECG and PPG for 1 minute.

IsenseU-BP+ was tested for correlation between PTT and blood pressure on six healthy volunteers, three men and three women, aged 25 to 45. The persons were in supine position with upper body slightly elevated (~10 degrees.). Blood pressure changes were induced using an isometric handgrip manoeuvre. The reference system used for measuring blood pressure was the CNAP® Monitor 500 HD (CNSystems Medizintechnik AG; Graz, Austria). This system is precise compared to arterial blood pressure measurements for MAP and diastolic blood pressure, but with some variation for systolic blood pressure (Ilies et al., 2015; Wagner et al., 2015). Jamar® Plus+ Digital Hand Dynamometer (Patterson Medical /Samsons' Preston, Warrenville, IL, USA) was used to define the maximum grip force of the right hand and to monitor the grip force during the handgrip tests. Target handgrip force during test was 30% of maximum force. The CNAP® system was calibrated according to the instruction manual using the integrated upper arm cuff immediately before the tests were started. The test protocol started with a 5 minutes rest period in supine position, followed by three periods of handgrip exercise lasting for minimum 3 minutes each, and with at least 1.5 minutes intermediate rest. At the end, the subject rested until blood pressure was stable before he/she raised and a final upright measurements were done. The CNAP® system was recalibrated when standing up.

2.3 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 R^2 calculations) and root mean square values for each point to the regression line, has been calculated.
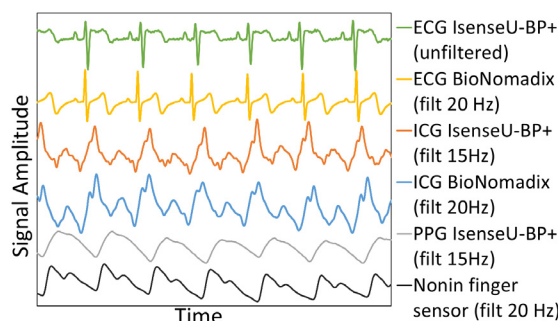

Figure 4: Comparing approximately six seconds ECG, ICG and PPG from IsenseU-BP+ with ECG and ICG from BioNomadix and PPG from Nonin finger sensors. The BioNomadix signals and Nonin finger sensor signal was recorded prior to the IsenseU-BP+ signal.
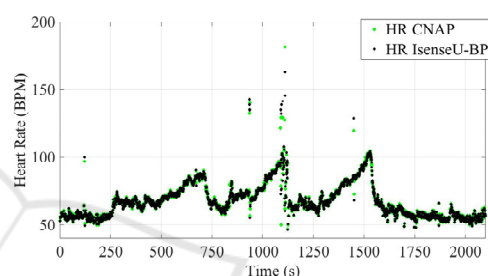

Figure 5: Comparing IsenseU-BP+ and CNAP® heart rate (HR) for subject 5.

3 RESULTS

3.1 Verification against Reference Sensors

As simultaneously recording of the ICG raw signals with the two systems is not possible, raw data have not been quantitatively compared, only a qualitative comparison of signal form was done. Figure 4 show data from subject 1. ECG, ICG and PPG data from the middle of the recording with reference sensor signals are compared to signals from IsenseU-BP+. The signals were scaled to show approximately the same amplitude. The figure shows IsenseU-BP+ ICG and PPG filtered using a 15Hz 4th-order Butterworth filter.

IsenseU-BP+ calculates heart rate from the ECG R-peak-to-R-peak interval. Figure 5 compares heart rate from IsenseU-BP+ and heart rate detected by the finger cuff in the CNAP® equipment for subject 5. The figure shows the test with three handgrip manoeuvres that increase the heart rate and blood pressure.
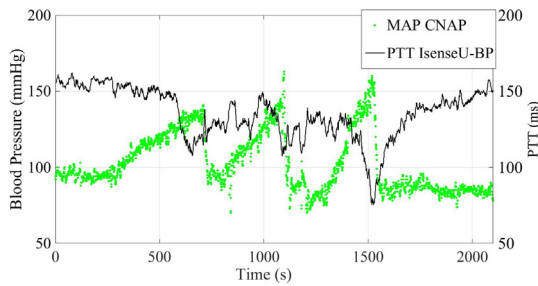
Figure 6: MAP (green) from CNAP® reference equipment plotted together with PTT (black) from IsenseU-BP+ equipment. Plotted PTT is a moving average of 10 samples/heart cycles, while MAP shows every heart cycle. Data is from subject 5.
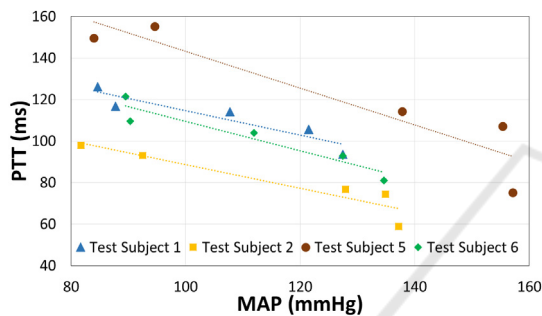

Figure 7: Average PTT plotted versus the corresponding MAP, for the start and end rest periods, and the elevated blood pressure peaks for subject 1, 2, 5 and 6.

3.2 Correlation between PTT and Blood Pressure

Six subjects completed the test protocol for correlation study. In this first test it was however only possible to estimate PTT with a reasonable low level of noise in four of the six data sets, and only results from these four data sets are further analyzed. Possible reasons for the noise are discussed in subsection 4.1.

Figure 6 shows the estimated PTT from IsenseU-BP+ and MAP from the CNAP® reference equipment through a complete test for subject 5. For PTT the moving averages of 10 heart cycles was plotted. MAP values was plotted for every heart cycle. Figure 7 shows PTT versus MAP for five different periods of the test: The rest period before handgrip manoeuvre, the three blood pressure peaks during the handgrip manoeuvres and the rest period after the handgrip manoeuvre. During the handgrip manoeuvre, the MAP values used was the maximum moving average of 10 heart cycles and the PTT was the, minimum moving average in the same peak

Table 1: R-values for linear fit of PTT as function of MAP, RMS values for MAP to the fit line, and slope and interception for the line. Subject 3 and 4 had too much noise.

Subject #	R-value linear fit	Average RMS value	Slope	Interception
1	0.93	4.2	-0,6	173,4
2	0.93	5.0	-0,6	145,4
5	0.93	11.0	-0,9	231,9
6	0.95	4.4	-0,7	180,4

(within ±15s from the detected MAP peak). For the start and end rest periods, an average MAP of approximately 30 seconds with stable blood pressure and a corresponding average PTT value was used. The figure shows a linear relation between MAP and PTT. Table 1 summarize the R-values for linear fit of the regression lines, as well as the average root mean square values for the measured PTT value's deviation from the line.

4 DISCUSSION

4.1 Detection of the Characteristic Points and Heart Rate

In figure 4 a representative part of the signals from IsenseU-BP+ is compared to signals from reference systems. The ECG R-peak is less prominent with the IsenseU-BP+ location of electrodes. For all subjects ECG R-peaks were easily detectable, both for using as a guide for detection of the ICG-C-peak, and for calculating of heart rate based on R-R interval. Figure 5 compares the heart rate detected by the IsenseU-BP+ device and the CNAP® system. There are some divergent heart rate measurements for both systems, but the periods with divergent measurements were similarly detected by both systems and was probably realistic. These results shows that the use of combined ECG and ICG sense electrodes are acceptable. ICG signals in figure 4 were recorded with the same electrodes and have similar shape. The IsenseU-BP+ ICG signal had some noise, even though IsenseU-BP+ had a lower filter frequency in this plot. The subject had a double ICG-C peak and this is more clearly seen in the BioNomadix recording and may be due to the lower filter frequency and lower sampling rate used for IsenseU-BP+ in this study. For the detection of the ICG-C peak, the quality of the ICG signal from IsenseU-BP+ was similar to BioNomadix, but the lower sampling rate decreased the resolution. The

IsenseU-BP+ ICG signal quality was not evaluated for direct detection of B-point.

van Lien et al (2013) did not find the estimation of ICG-B point through RC distance to be precise enough for pre-ejection period estimation. They were looking for changes in order of 3.5 ms in individual heart cycles. In the laboratory/ ambulatory study they 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 onset of depolarization of the heart till ECG-R. The error in the individual heart cycle RB period in their study was then +4ms/-2ms. We have looked at an averaged PPT value and assuming the error in B detection had a random component, the averaging decreased the error. A change in mean blood pressure of 10 mmHg is expected to give a change in PTT about 8ms-16ms (Proenca et al., 2010). Their calculations was 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 in this study (>20 mmHg and averaged over 10 heart cycles) the error of the ICG-B point detection was judged acceptable.

Figure 4 shows that during supine rest the quality of the PPG signal is good. The PPG-foot is as sharply defined when measured at the chest as at the finger. It was observed that quality of the chest PPG signal vary with small changes in location of the sensor as well as with the pressure towards the skin. Breathing will cause changes in the level of the PPG signal. In this study, 2 out of the 6 subjects had high noise in their PPG foot detection. Initial studies of these data indicates that this is caused by low signal quality due to none-optimal placement of the PPG sensor, and filtering of the PPG signal to reduce breathing artefacts. Filtering to remove the breathing artefacts without influencing the PPG foot detection must be further improved. In this device, the PPG sensor has only one LED, while others have suggested advanced arrays of LEDs and detectors (Solà et al., 2011). For a more robust PPG foot detection during movement an improvement in the PPG sensor and better algorithms for motion artefact suppression are required.

4.2 IsenseU-BP+ as a Device for Estimating Blood Pressure

To evaluate blood pressure, physicians usually relates to all the three blood pressure values;

systolic, diastolic and mean. According to the Moens-Kortweg equation (Nichols and O'Rourke, 2005) estimation techniques based on pulse wave velocity, and its inversely proportional pulse transit time, provides estimates of MAP and not systolic or diastolic pressure, since the average pressure of the arterial wall defines the structural arterial stiffness. Based on this, this study focus on MAP. Others have however reported good correlation with systolic blood pressure.

Measured PTT and MAP versus time are plotted for subject 5 in figure 6. These data indicates that the measured PTT response is delayed compared to the pressure measured with the finger cuff. This may be due to measurements at different locations. Central blood pressure changes may differ from peripheral blood pressure changes. Further work is needed to investigate this delay, whether it shows a real physiological difference or if it is caused by a weakness in the algorithms that detects the characteristics point in the raw signal. MAP during rest before the test is higher than after the test. This decrease was observed for several subjects and may be due to a drift in the CNAP® reference equipment. The first part of the test lasted 35 minutes with no recalibration of the CNAP® reference system during the test. The default recalibration, with arm cuff, interval of the CNAP® equipment is 15 minutes. This possible small drift has not been judged critical for these initial tests to verify the design of the IsenseU-BP+ device.

The PPT values in range 80ms-180ms are reasonable compared to the overall value of 95ms presented by Solà et al. (2013). IsenseU-BP+ detects the PPG signal further away from the heart than the system made by Solà et al. (2013).

Muehlsteff, Aubert and Morren (2008) have found that when the person changed posture form lying to sitting the pre-ejection period increased significantly (25-45 ms) while blood pressure was stable or slightly increased. We found a slight decrease in PTT when subject rose corresponding to an expected slight increase in blood pressure, thus the PTT measurements was not dependent on posture (results not shown).

Figure 7 and table 1 show good correlation between PTT and MAP for the four subjects evaluated (two excluded due to noise in PPG measurements as discussed in section 4.1). The number of points in the regression analysis was however low, and there were also an uncertainty in the MAP measurements. To increase the confidence in the regression parameters, a test set-up that gives more points per person is needed.

The maximum of the moving average CNAP® MAP and the minimum the moving average IsenseU-BP+ PTT, within ±15s of the time for maximum MAP, are used in the plot. The maximum MAP and minimum PTT do not match exactly in time (as seen also in figure 6); this may be related to the different location of the sensors but has to be further investigated. The current version of the equipment was not intended for beat to beat comparison of values and hence this approach is judged acceptable. With more stable changes in blood pressure, a longer averaging period could be used. The slope of the PTT – MAP linear regression line differs between persons and individual calibration functions will be needed. This is the same as reported by others (Solà et al., 2013).

As seen from the RMS values in table 1 subject 5 has significantly higher RMS values. This is mainly caused by eight subsequent high values of individual heart cycle MAPs in the middle blood pressure peak. These values, which differ from the shape of the curve, can be seen in figure 6. During the same blood pressure peak, also divergent heart rate measurements were observed with both systems (figure 5). Excluding these eight MAP values lowers the RMS values to the level of the other subjects (not shown).

According to the British Hypertension Society standard, a blood pressure device falls into the category Grade A if it complies with a cumulative percentage (CP) of the readings within ±5mmHg > 60%, CP at ±10 mmHg > 85% and CP at ±15 mmHg > 95%. This standard is defined for systolic and diastolic blood pressure, and is mostly used for cuff based equipment measuring slow changes in blood pressure (measurement time is 20s-60s). The hand grip manoeuvre test induced pronounced changes for a short period of time and therefore it was only possible to average about ten heart beats (5s-10s). The subjects in this test was only tested once, therefor there are not enough data to calculate the calibration curve, and subsequently see how a new dataset fits into this. Calculating the error for the points used to make the calibration curve 85% of the measurements are within 10 mmHg, 90% of the measurements are within ±15mmHg, but only 25% within 5 mmHg. Max deviation are 20 mmHg. The MAP estimations diverging most from the estimated relationship are caused by the high MAP readings for test subject 5 described in the former section. The test setup with short periods of induced high blood pressure and test equipment measuring on different locations of the body, makes the result vulnerable for short time deviations and anomalies.

This must be taken into account when planning a more thorough verification test.

These results are very promising taking into account the demanding tests and the known weaknesses in the current version of test equipment. The raw signal sampling rate used in this study are too low and more work has to be done to improve the signal filtering (adaptive filtering) and algorithms for B-point detection. These changes may be implemented in the embedded software in the device. It may also be necessary to improve the PPG sensor through hardware improvements, the IsenseU-BP+ is prepared for a second LED. In addition, there are some uncertainties in the reference measurements when it comes to calibration and differences between central and finger blood pressure.

Based on this it is reasonable to assume that the estimation of PTT and correlation with MAP can be further improved, and that a grade A classification is possible with the current design. These improvements may also make the equipment suitable for studying beat-to-beat variations.

5 CONCLUSIONS

We have presented IsenseU-BP+, a new compact wearable device suitable for both female and male users. The first testing shows that it is feasible to make an easy to use device to monitor blood pressure changes and possibly additional heart parameters. More effort has to be put into the PPG sensor design and the signal processing algorithms for characteristic point's detection to get stable and reliable results for a wide variety of persons. Testing during activity is also needed. The device has to be tested on a wide range of persons (different gender, age and BMI) to show that a manageable calibration regime for PTT to blood pressure calculation is feasible.

ACKNOWLEDGEMENTS

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