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## Technology Development for Simultaneous Wearable Monitoring of Cerebral Hemodynamics and Blood Pressure

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## Abstract

For many cerebrovascular diseases both blood pressure (BP) and hemodynamic changes are important clinical variables. In this paper, we describe the development of a novel approach to noninvasively and simultaneously monitor cerebral hemodynamics, BP, and other important parameters at high temporal resolution (250 Hz sampling rate). In this approach, cerebral

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hemodynamics are acquired using near infrared spectroscopy based sensors and algorithms, whereas continuous BP is acquired by superficial temporal artery tonometry with pulse transit time based drift correction. The sensors, monitoring system, and data analysis algorithms used in the prototype for this approach are reported in detail in this paper. Preliminary performance tests demonstrated that we were able to simultaneously and noninvasively record and reveal cerebral hemodynamics and BP during people's daily activity. As examples, we report dynamic cerebral hemodynamic and BP fluctuations during postural changes and micturition. These preliminary results demonstrate the feasibility of our approach, and its unique power in catching hemodynamics and BP fluctuations during transient symptoms (such as syncope) and revealing the dynamic features of related events.

#### Index Terms—

Cerebral hemodynamics; NIRS; brain monitoring; wearable devices; cuffless blood pressure monitoring; multi-modality

## I. Introduction

FOR many cerebral vascular diseases (CVDs)—such as stroke, traumatic brain injury, and syncope—both blood pressure and hemodynamic changes (including blood perfusion/ volume and oxygenation) are important features associated with the occurrence and development of their pathological status. For example, strokes are actually defined by their hemodynamic fingerprints: hemorrhagic stroke features extra-vascular blood pooling, whereas ischemic stroke features reduced tissue oxygenation levels due to insufficient perfusion. Hypertension can lead to pathological cerebral hemodynamic conditions well before the occurrence of strokes, as well as additional damage to brain and other organs. A recent landmark NIH study, the Systolic Blood Pressure Intervention Trial (SPRINT), found that more intensive management of high blood pressure (120 mmHg target systolic pressure), below the commonly recommended blood pressure target (140 mmHg), significantly reduced rates of cardiovascular disease, and lowered risk of death (www.sprinttrial.org). Noninvasive measurement and monitoring of both blood pressure and hemodynamic changes are therefore important in the prevention, early detection, diagnosis and treatment efficacy evaluations of CVDs and TBIs.

Wearable long term monitoring of cerebral hemodynamics and blood pressure has numerous advantages over single-shot clinical examinations. In terms of blood pressure, single shot BP measurements are subject to [1] BP variability and easily affected by environmental error such as the "white-coat" effect [2] and technical operational errors [3]–[6]. Noninvasive ambulatory blood pressure monitoring (ABPM) provides significant improvement over single shot clinic BP measurements [1], [7], allowing better characterization of BP during everyday activities, including sleep. Most importantly, the findings correlate more strongly than clinic BP with target organ damage, CVD risk, and long-term patient prognosis [8]–[18]. In terms of cerebral hemodynamics, cerebral blood flow is stabilized by compensating fluctuations of systemic blood pressure, a mechanism named "cerebral autoregulation" (DCAR) when dynamic

features are considered. CAR is important for the normal functioning of the brain [19], and is impaired following both stroke [20]–[22] and traumatic brain injury (TBI) [23], [24]. Autoregulation estimates have shown predictive value for determining outcomes in TBI patients [25], [26]. Vascular capacity to regulate cerebral perfusion is also compromised by microvascular disease associated with aging, hypertension and diabetes [27]–[29]. Noninvasive assessment of cerebral vasoregulation is largely lacking in medical diagnostics and acute care. Studies have also shown that DCAR can be evaluated using introduced BP change, but also using spontaneous blood pressure fluctuations [30], [31]. To estimate and monitor cerebral autoregulation during people's activities, first we need to develop wearable technology that can simultaneously monitor blood pressure and cerebral hemodynamics.

Long term ambulatory monitoring during people's daily activities provides the opportunity to catch transient events with unpredictable onsets, for example syncope, hemorrhagic conversion of stroke. Synchronized and simultaneous monitoring of both cerebral hemodynamics and blood pressure, together with other auxiliary parameters such as actigraphy and ECG, can provide a much more complete measure of cerebrovascular conditions, and help us understand those pathological events in-depth.

Such ambulatory multi-modality monitoring is technically challenging. To date there are several long term ambulatory near infrared spectroscopy (NIRS) monitoring devices developed by academic institutions and companies, and preliminary results have been reported [32]–[35]. However, none of the existing systems incorporate simultaneous blood pressure recordings. One of the major challenges of simultaneous hemodynamics and blood pressure monitoring is that current noninvasive BP technologies are unable to provide the temporal resolution (>20 Hz), accuracy, and form factor for simultaneous and continuous monitoring with cerebral hemodynamics.

Cuff-based blood pressure measurement-the primary clinical and home BP monitoring tool -includes inflation and deflation of the cuff for each point of BP measurement, and it takes minutes for the blood vessels to fully recover from a cuff-based BP measurement. Cuffbased BP monitoring technology is therefore considered slow and obtrusive, not suitable for wearable continuous monitoring scenario. Cuffless BP technologies have strong potential to meet the above requirements, such as pulse transit time (PTT) and tonometry based methods. The PTT method has received much attention over the recent decades because of its capability to track BP change, as well as its advantages as a noninvasive, continuous and most importantly cuffless tool for BP measurement [36]-[42]. PTT is currently the focus for most academic and industrial efforts for cuffless BP monitoring. However, while PTT-based BP monitoring is able to provide an evaluation of systolic and diastolic blood pressure during each heartbeat (~1 Hz), it is still in-adequate to provide the temporal resolution and details of BP fluctuation needed to synchronize with cerebral hemodynamics recordings for the evaluation of the dynamic features of CAR. In addition, the relationship between pulse transit time and blood pressure is not yet fully developed, with challenges in terms of accuracy and calibration. Factors that adversely affect PTT calibration include: motion artifacts, changes in sensor contact force, temperature, and vascular muscle tone [37], [41]-[44].

Tonometry is one of the other major noninvasive techniques that provide continuous blood pressure measurements. The principle and modeling of arterial tonometry has been well studied [45]–[49]. In general, a pressure transducer (tonometer sensor) is placed over the artery (with sufficient bony support) to compress it until the vessel is flattened against the bone but not occluded (applanation). The tonometer on the skin surface can then measure arterial blood pressure via contact pressure. Traditional tonometry uses large arteries such as the radial artery for BP monitoring. Unfortunately, it suffers from difficulties including optimal localization of the artery as well as maintaining stable and precise applanation pressure given its limited bony support.

To date the accuracy of these cuffless methods are not comparable to BP devices using cuffs, and to the best of our knowledge none of them have passed clinical test similar to standards (such as AAMI SP10, EN 1060–4, ISO 81060–2) or protocols (such as BHS, EHS-IP) used to test BP devices utilizing cuffs. There has not been a technical breakthrough in recent years. At the same time, because of the numerous advantages of cuffless BP technology, IEEE has recently published a new standard 1708 ("IEEE Standard for Wearable, Cuffless Blood Pressure Measuring Devices") to help promote the development of cuffless BP technology.

In the past several years we have been developing novel cuffless BP technologies. Compared with noninvasive BP measurements at the arm or wrist (over big arteries such as radial artery), we found that for unobtrusive BP measurements, smaller superficial arteries have advantages. Operations (compression, occlusion) on a large artery require significant pressure and a relatively large device. Our approach is to instead use the superficial temporal artery (STA), which has several advantages as an optimal location for unobtrusive BP measurements: (1) The STA is easy to identify and localize; (2) it is well-supported by the underlying bone structure; (3) it does not require a cuff or much pressure to compress or occlude (we have demonstrated quality STA tonometry data with less than 50 gram-force of pressure-similar to the pressure from regular eyeglasses-which does not cause much discomfort during long term monitoring); (4) tonometry at STA can provide complete waveform data (20+ Hz bandwidth) for BP monitoring; (5) the STA moves much less than a wrist, and hence is less susceptible to motion artifacts during ambulatory monitoring; (6) no other BP technologies provide a BP measurement at the brain level, which is critical for monitoring of cerebrovascular status and stroke prevention. BP measurements at STA has been preliminarily explored [50], demonstrating the feasibility of BP measurement at STA. Based on these advantages and preliminary work, we have designed and developed novel superficial temporal artery tonometry (STAT) prototypes for conducting wearable cuffless BP monitoring at STA [51], [52].

Gravity is an important influence on BP, as it imposes numerous cardiovascular and neurohumoral changes on the human body. The associated physiological adaptation to postural and body position changes leads to fluctuations in blood pressure, heart rate, perfusion and other parameters. Postural changes can also influence the symptoms of various diseases involving not only the circulatory system but also other systems (respiratory, digestive, osteoarticular etc.) [53]. Thus, development of technologies to objectively and quantitatively measure of cerebral hemodynamics and blood pressure

during the gross body movements required during postural changes can provide a powerful tool to help us understand the interaction between gravity, body position, and people's physiological or pathological status, especially those related to cardiovascular and cerebrovascular diseases.

Micturition (or post-micturition) syncope is fainting during or, more commonly, immediately after urination due to a severe drop in BP [54], [55]. Micturition syncope is most common in older men and usually occurs at night after a deep sleep. It is hypothesized that micturition syncope is related to vasodilation that occurs when getting up and standing at the toilet or that occurs at the rapid emptying of a full bladder. This is thought to result in a sudden drop in blood pressure via the vasovagal response [56], [57]. The exact cause of micturition syncope isn't fully understood however, in part due to lack of appropriate monitoring techniques. We have not found any published ambulatory blood pressure or cerebral hemodynamic monitoring results during micturition. Development of a dynamic (high temporal resolution) monitoring technology thus has potential to significantly help with the understanding, diagnosis and management of patients with micturition syncope.

In this paper, we further explore the feasibility of synchronized continuous monitoring of BP, cerebral hemodynamics, systemic hemodynamics, ECG and actigraphy for brain function evaluation, and demonstrate its features in example conditions for which ambulatory multi-modal cerebral monitoring is useful, including postural change and micturition responses. Here ECG is the standard parameter for cardiac conditions, and is one of the two essential components for calculating PTT based BP. Actigraphy can be used to distinguish wakefulness and sleep [58], [59], and also provides quantitative measure of the level of activity and movement. In addition, accelerometer readings can be used for the identification and correction of motion artifacts [60]. The details of the prototype system we developed are described in detail in this paper. Typical postural change and micturition test results on a healthy subject are reported, as demonstrations of the feasibility and potential of this new approach's promising power in the diagnosis and management of cardiovascular and cerebrovascular diseases.

## II. Methods

The design and development of the prototype, ambulatory multi-modality cerebral monitoring system, namely MCMS-1, is based on our previous projects and experience in hemodynamics measurement, BP measurement, and wearable monitoring technologies [43], [50], [61]–[64]. The human studies were approved by the Massachusetts General Hospital institutional review board.

#### A. Sensors in the MCMS-1 System

The sensors included in the MCMS-1 prototype include: (1) NIRS based cerebral and systemic hemodynamic sensors, (2) an STA tonometry sensor, and (3) ECG and (4) accelerometry sensors. PTT is calculated from the synchronized ECG and NIRS signals, whereas accelerometry is recorded to monitor the orientation and motion of the sensor suite.

The NIRS-based cerebral and systemic hemodynamic sensors, ECG electrodes and actigraphy sensors are shown in Fig. 1. The structure of our hemodynamics sensor pad has been previously reported [63]. Briefly, to monitor cerebral and systemic hemodynamics, a dual wavelength (785 nm and 830 nm) laser diode was used as the light source (Axcel Photonics, Inc.), and two OPT101 photodiodes (Texas Instruments, Inc.) were used as detectors. Laser power at each wavelength was about 3.5 mW (constant during the monitoring period), under the maximum permissible exposure (MPE) standards for skin illumination. An optical diffuser was used to expand the laser beam profile and reduce spatial density of the light. Systemic hemodynamics was acquired from a sourcedetector pair with 1.1 cm separation, while the cerebral hemodynamics was acquired from source-detector pair at 3.8 cm separation. NIRS based on diffusion theory and modified Beer-Lambert law is used to calculate the concentration change of oxygenated hemoglobin (O<sub>2</sub>Hb) and de-oxygenated hemoglobin (HHb) [61], [63], [65]–[72]. ECG was acquired through standard chest leads and Ag-AgCl electrodes. Since we know the cerebral hemodynamics and blood pressure can be affected by body postural position (e.g., sitting upright, supine) and different activities (sleep, sports etc.), an accelerometer, ADXL325 (Analog Devices, Inc), was implemented to sense body position/orientation, and to provide actigraphy measurements.

STAT is the major modality for BP monitoring using MCMS-1. For STAT, we developed a lightweight wearable BP sensing module that can be easily attached to a regular pair of eyeglasses, a head band, or to headphones. The structure of the BP sensing module can be seen in Fig. 2. This BP sensor module was developed using 3D printing. Two important features are incorporated in the design of the BP sensor module to achieve successful STA tonometry: (1) Optimized positioning of the blood pressure sensor. This was achieved by fine tuning of the STA localization in both *x* and *y* directions. (2) Adjustable external pressure for tonometry, achieved by screw-controlled adjustable hold-down pressure. The piezoresistive blood pressure sensor has a sensing area of 14.5 mm in diameter, sensing range of 0 ~ 300 mmHg, 5 KOhm overall resistance (of the resistor sensor bridge), with a sensitivity of 250  $\mu$ V/mmHg. Preliminary tests revealed that most glasses have enough elastic force to provide the hold-down pressure needed; and the hold-down pressure can remain relatively stable for hours.

Our current STA tonometry design does not require strict applanation pressure, but instead relies on initial cuff based BP calibration using a wrist blood pressure meter (BPW-360BT Premium Wrist Blood Pressure Monitor, Homedics) to convert tonometer readings to blood pressure. BP calibration is performed with the wrist BP meter held at the heart level. In principle, blood pressure measurement depends both on the pressure generated at the heart and on the transmission line characteristics of the arterial system, plus the hydrostatic difference between the BP measured at the heart level and BP measured at the heart level. Given a calibration measurement at the heart level, and assuming constant hydrostatic pressure difference between heart and head level, the final BP results should represent the traditional heart level measurements that we are familiar with.

To validate the accuracy of STA tonometry, we have performed preliminary comparison with the gold standard methods including cuff-based sphygmomanometer (attached to the

left arm) and also Nexfin (finger volume-clamp method for beat-to-beat arterial pressure monitoring) [51]. This test on 4 subjects (10 measurements each) showed that the mean arterial BP percent error (comparing with cuff-based BP) using STA tonometry is 7.7% (7.0 mmHg), while using Nexfin the error is 7.3% (6.6 mmHg). The results from these two continuous noninvasive BP techniques were very close.

#### B. Wearable Recording System

The block diagram of the wearable prototype MCMS-1 recording system can be found in Fig. 3, it is based on the NINscan systems described in our previous studies [61], [63]. This fully wearable system provides data acquisition and recording of all the sensors of MCMS-1, with one tonometry channel, four optical channels to measure tissue hemodynamics, one differential ECG channel, and two accelerometer channels. The STA tonometry channel has a bandwidth of up to 50 Hz. The actigraphy channels can measured +/-5 g and have a bandwidth of 40 Hz, whereas the single ECG has a frequency range of 0.1–40 Hz. All data acquired are stored in 512 M byte of on-board memory. The system is controlled by a low power MSP430 family microcontroller. All eight analog signals are strictly co-registered, digitized by a 12 bit A/D converter and sampled at 250 Hz. Powered by 3 AA size lithium batteries, this system can continuously acquire data from all sensors for more than 24 hours. The system also includes two event buttons for users to mark the onset of special events, conditions or symptoms. This allows us to associate the systemic and cerebral hemodynamics with different types of body positions and daily activities, such as sleep, work, sports, riding elevators and even driving. When data acquisition is complete, the wearable recorder is connected to a computer via USB 2.0 for data download and analysis; 10 hours of recording generates 144 Mb of data. The dimensions of this wearable recorder are  $68 \times 132 \times 24$  mm<sup>3</sup>, about the size of a person's palm, and weighs less than 350 grams (including batteries and sensors).

#### C. Data Analysis Algorithms

Data analysis for BP, hemodynamics and other parameters are performed in the Matlab environment using algorithms we developed. The raw 250-Hz NIRS data are offsetcorrected and further digitally low pass filtered at 5 Hz (in addition to the instrument filter). Then, for hemodynamics analysis, we converted optical measurements to relative changes in the concentration of HHb and O<sub>2</sub>Hb, we used the modified Beer-Lambert Law [73]–[76]. The differential path length factor (DPF) used in the calculations can be measured directly or based on Monte Carlo simulations with common head structure and tissue optical properties [69]. When the multiple source-detector separation configuration is used, common mode interference cancellation can be achieved via adaptive filtering [67], [69], [70].

For BP analysis, our prototype MCMS-1 STA tonometry provides continuous beat-to-beat BP readings at 250 Hz sampling rate. After we acquire the tonometry measurements, we perform a search to identify the peaks and valleys of each heartbeat, followed by cubic interpolation to acquire smooth systolic and diastolic BP curves. The tonometry sensor used in our prototype MCMS-1 is larger than the STA; this enables easy localization of STA, but it makes quantification and absolute BP measurement difficult, as the results are affected by individual differences (vessel size, tissue elasticity etc.). To address this problem, we used

readings from a wrist-mounted cuff-based device to calibrate the STA tonometry readings. That is, the tonometry readings and the wrist BP readings are mapped by linear relationship:

$$BP = kU + b \tag{1}$$

Here BP is the blood pressure measurement, U is the tonometer output, k and b are the linear conversion coefficients, which is acquired through BP calibration. During calibration, the wrist BP meter is held at the heart level, and the readings from the wrist BP meter are used to calculate the coefficients in the linear mapping equation.

To minimize errors from possible hold down pressure drift, low sample-rate BP measurements from PTT method is combined with STA tonometry. The combination of PTT and STA tonometry consists of two steps: first drift in STA tonometry is evaluated by comparing the STA tonometry results with several cuff based BP measurements after the initial calibration. If the drift is larger than the threshold (e.g., 5 mmHg), then the drift correction is conducted. ECG and NIRS were used together for PTT based BP measurements, which in turn were used for STA tonometry drift correction.

PTT is the time taken by the arterial pulse pressure-wave propagating from the heart to a peripheral site; in our MCMS-1 prototype, the ECG measurement and the NIRS hemodynamics measurements are strictly co-registered, and PTT is calculated as the time interval between the R wave peak of electrocardiogram (ECG) and a characteristic point of blood volume signals acquired from NIRS measurements [36], [40]–[42].

The fundamental principle of PTT-based BP method [36], [40]–[42] is based upon the pulse wave velocity (PWV) recording through the Moens-Korteweg (M-K) equation:

$$PWV = \sqrt{\frac{Eh}{\rho d}} \tag{2}$$

which relates PWV with the elastic modulus of vessel wall *E*, blood density  $\rho$  and arterial dimension properties such as vessel thickness *h* and arterial diameter *d*. PWV is inversely related with PTT, i.e., *PWV* = *K*/*PTT*, where *K* is the distance between heart and certain peripheral site; and *E* can be exponentially correlated BP through the following equation [77]:

$$E = E_0 e^{\gamma P} \tag{3}$$

where  $E_0$  is the elastic modulus at zero pressure;  $\gamma$  is a coefficient depending on particular vessel, and *P* is BP. Therefore, PTT can be translated into BP with an initial calibration under the assumption that h/d remains constant.

For the hold-down pressure drift correction using PTT measurements, we used frequency domain data fusion. Our experiment shows that after calibration PTT method is good for low frequency BP measurements (e.g., < 0.005 Hz), however not responsive to BP fluctuations at higher frequencies. STAT, on the other hand, demonstrate low frequency baseline drift (e.g., due to unstable hold down pressure), but good response for dynamic BP fluctuation.

Therefore, in this paper, we combine the low frequency component from PTT and high frequency component from STAT to correct possible STAT baseline drift and generate the final BP measurements. BP data from PTT and STA tonometry signals were divided into two different frequency components, separated at 0.005 Hz. We thus extracted and combined the STA tonometry data above the 0.005 Hz cutoff with the PTT frequency data below the 0.005 Hz cutoff to achieve the final BP time course. The block diagram of the multimodality BP algorithm is shown in Fig. 4.

Heart rate carries important information and can be calculated from either ECG or NIRS signal. We have implemented both ECG and NIRS based heart rate algorithms based on methods published in Physionet (www.physionet.org). Two channels of accelerometer readings were recorded and converted to gravity units (g values) using the linear characteristics provided by the manufacturer.

#### D. Human Subject Testing

To demonstrate the feasibility of our MCMS-1 prototype for simultaneous ambulatory cerebral hemodynamics and blood pressure monitoring, we performed ambulatory tests during people's daily activities. The test settings can be seen in Fig. 5. The subject wore a pair of regular glasses with the STA tonometry module attached. The tonometry sensor was positioned above the STA, on left side of the head. The optical hemodynamics probe was secured via its adhesive surface and a head band on the forehead, over the left prefrontal cortex (midway between 10/20 position F3 and Fp1). ECG and body position/ motion (sensors located on the chest and upper abdomen) were simultaneously recorded, and all channels were sampled at 250 Hz. The recorder was carried in the subject's pocket. During the data collection period, the subject performed regular activities including working, walking around, making phone calls, rest room breaks, plus several postural changes. Event buttons were pressed to log the precise timing of different events. BP calibration was performed using wrist blood pressure meter. At the beginning of the recording, an event button integrated in the NINscan 4 box was pressed at a specific time on the subjects' watch which was used to keep the activity log. This way the NINscan recording time and the diary time could be synchronized. Subjects were asked to press event buttons and keep a simple diary to record the beginnings and ends of consecutive activities during the entire data collection period. Few restrictions were placed on the subjects' activities during the ambulatory recording. The most significant one was to avoid getting the device and probe wet (e.g., washing).

To demonstrate the unique capabilities of wearable MCMS-1, we specifically monitored three healthy subjects during activities including micturition and postural change (from stand to low squat, specifically). In the low squat position, the subjects kept feet flat, sat on his/her heels, with arms holding around shins. During testing, the subjects rapidly moved from this low squat to standing position (or vice versa), and remained still at the target position for 30 seconds. Event buttons were pressed when the subject changes from one position to the other.

## III. Results

In all three subjects we ran, we saw our technology sensitive to reveal blood pressure and hemodynamic changes associated with different types of activities. Here we present results from a healthy subject (Fig. 6 to 8), a 43 year old male with baseline BP of 128/84 mmHg (measured by the wrist cuff blood pressure meter).

A result of two hour's ambulatory blood pressure monitoring is shown in Fig. 6. In our data analysis flow, an overview of the full dataset for the ambulatory monitoring test is always the first step, it help us to identify each events (individual tests), make sure the signal quality of the recordings is good, and identify obvious drifts and artifacts. In this recording, data collection was initiated at 19:35 and completed at 21:38 in the evening. Cuffless blood pressure monitoring measured at STA, cerebral hemodynamics, systemic (scalp) hemodynamics, heart rate and accelerometer recordings during the activity were recorded and displayed in the figure. Fig. 6 provides an overview of the data collected in one ambulatory test, and can be used to ensure signal quality and the low frequency or trend of signal changes. During the two hour ambulatory recording, the subject pressed the two event buttons 51 times, indicating the onsets and offsets of the various activities and events during the ambulatory monitoring, including working, walking around, making phone calls, rest room breaks, plus several postural changes. The timings of the events and activities (labeled as E1 or E2) were all precisely logged into the memory and shown in this figure. Together with the subjects' diary, different events and activities can be accurately identified, and their associated cerebral blood pressure and hemodynamics, systemic hemodynamics, cardiovascular features were calculated.

Several interesting spontaneous or introduced blood pressure fluctuations were captured during the ambulatory recording; here we present the details from two of these: postural change and micturition.

#### A. Cerebral Hemodynamic and Blood Changes Associated With Stand-To-Low Squat Test

A series of stand-to-low squat events are shown in Fig. 7. In this test, the subject performed postural change (between squat and stand positions). Moving rapidly from low squat position to standing position takes about 1 sec, as measured from the accelerometer readings shown in Fig. 7E. MCMS-1 recording revealed dynamic changes in all parameters monitored. As seen in Fig. 7A, systolic and diastolic BP increased from 125/87 mmHg to a peak of 160/130 mmHg when changing from standing to low squat position. This initial transient BP overshoot, which lasted approximately 15 seconds, was followed by a new equilibrium of 145/110 mmHg, a ~20 mmHg blood pressure increase. When moving from the low squat position back to standing, the transient BP decrease reached a valley of 90/55 mmHg, and it again took approximately 15 seconds for blood pressure to return to a stable baseline level. The overall local blood pressure fluctuation at the STA, from peak to valley, was as large as 70 mmHg. It should be emphasized that this is a transient maximum BP fluctuation during a highly dynamic process, recorded at high temporal resolution that reveals detailed dynamic BP fluctuation features, we therefore expected that it would be higher as compared to the stable static values. To explain the results physiologically, when subjects moved from low squat to standing, because of the pressure change in the chest

and abdomen, the returning blood volume to the heart decreased temporally, this in turn reduced the stroke volume from the heart, leading to lowered blood pressure. For healthy subjects, the reduced blood pressure evokes their automatic blood pressure feedback control mechanism to help bring the blood pressure back to normal level. This is done through blood pressure sensors located at the aortic arch and carotid sinus, related responses from the central nervous system, adjustment from the vascular resistance, and elevated heart rate. Indeed, as shown in Fig. 7D, the heart rate increased from 60 bpm to 80 bpm when the subject stood up from a low squat position.

The most important findings from this preliminary test were in the cerebral blood volume and systemic blood volume changes associated with the related blood pressure fluctuation. As can been seen from Fig. 7B and 7C, scalp (systemic) blood volume demonstrated more than 15  $\mu$ M decrease when the subject stood up, with an initial transient of an additional  $10 \mu M$  decrease. Compared with the systemic blood volume change, cerebral blood volume change was much smaller (about 7 µM, half of the scalp HbT change), and demonstrated no overshoot to complement the  $-10 \,\mu M$  transient in the scalp hemodynamic signal. On the other hand, when the subject changed from standing position to low squat position, cerebral blood volume demonstrated a much more gradual increase. It took 30 seconds for the blood volume increase to complete, compared with the 8 second fast response shown in the systemic blood volume change, which also demonstrated the initial transient. In both directions (increase or decrease), the cerebral hemodynamics had the appearance of a highly regulated change, similar to a low pass filter. This agrees well with the well-known cerebral autoregulation function, and can be analyzed mathematically using transfer function and other methods [32], [33]. In other words, our MCMS-1 platform appears sensitive to people's cerebral autoregulation, including both its static and dynamic features, which could potentially be used in the diagnosis of TBI and other diseases.

#### **B. Micturition Response**

The details of the cerebral blood pressure and hemodynamics, systemic hemodynamics, heart rate and accelerometer recordings associated with micturition are shown in Fig. 8.

From Fig. 8B and 8C, we see a gradual increase of scalp HbT by 5  $\mu$ M and a 2  $\mu$ M increase in cerebral HbT increase over the 35 seconds of micturition period. This is followed by a sharp drop of 8  $\mu$ M in scalp HbT and 4  $\mu$ M in cerebral HbT in the next 5 seconds. That is, most of the hemodynamic fluctuation within the head happened around the completion of micturition. From Fig. 8A, we see a gradual 20 mmHg increase of systolic and diastolic blood pressure during micturition, followed by a significant BP fluctuation (35 mmHg from valley to peak in systolic BP) right after. Heart rate decreased from the base line of 85 bpm to a valley of 70 bpm during micturition, (likely due to vagal excitation during micturition). This heart rate valley was followed by a large heart rate increase and fluctuation around the end of the micturition, with the peak reaching up to 93 bpm. In other words, almost all parameters—BP measured at STA, cerebral/scalp hemodynamic and heart rate—demonstrated the largest fluctuations around the completion of micturition, which agrees with the fact that most micturition syncope happens immediately after urination. Notice here that the subject remained relatively still during and 10 seconds after micturition,

as can be seen from Fig. 8E, indicating these fluctuations were not caused by body position change.

### IV. Discussion

In this work, we have developed an MCMS-1 prototype to simultaneously monitor cerebral hemodynamics, blood pressure, ECG, actigraphy during people's daily activities. Our preliminary human subject tests demonstrated the feasibility of the multimodality cerebral monitoring, and suggest its potential in diagnosis and management of CVD and TBI. Since the goal of this work was to demonstrate the feasibility of the technology (simultaneous monitoring of cerebral BP and hemodynamics), rather than targeting any specific applications, no statistical analyses were conducted.

To the best of our knowledge, this is the first demonstration of continuous blood pressure, cerebral and systemic hemodynamics fluctuations during micturition maneuver and postural change. The consistency between the results from multiple modalities supports the reliability of our recordings, and also suggests the advantage of multi-modality blood pressure measurements. Our recording of the micturition response, measured with BP at STA and hemodynamics on the forehead, demonstrates MCMS-1' power in catching transient events with high temporal resolution could be important for analysis of pathological symptoms such as syncope.

Comparison of the current BP technologies and STAT is shown in Table I; as can be seen, STAT is the only method that is able to provide noninvasive continuous BP monitoring in a wearable form, especially suitable for cerebral autoregulation evaluations during activities. Comparison of technologies for cerebral hemodynamics is show in Table II. Currently there are several methods to study cerebral hemodynamics and the mechanism of cerebral autoregulation (CA) [78]-[81]. Positive emission tomography (PET) can give estimates of cerebral blood volume (CBV), regional cerebral blood flow (rCBF), cerebral metabolic rate of oxygen (CMRO2) and mean transit time (MTT); Magnetic resonance imaging (MRI) provides relative estimates of CBV. However, it cannot provide absolute CBV measurements and may be inaccurate when there is breakdown of the blood brain barrier [78]. Both PET and MRI are poorly suited for long-term measurements, because they require the subject to lie still, and in the case of PET also ionizing radiation and poor temporal resolution limit applicability [82]. Although fMRI can image cerebral hemodynamics with high spatial resolution, the high cost, low temporal resolution and poor mobility limit its frequent use. Transcranial Doppler ultrasonography (TCD) permits the noninvasive measurement of blood flow velocities in the basal brain arteries [83], [84] under assumption that the size of the blood vessel remains constant. It is suited for monitoring global cerebral blood flow (CBF), and does not reveal rCBF, because it focuses on the hemodynamics measure in major arteries but not in the microvasculature. However, it is insensitive to blood oxygenation changes [82], [85]. In addition, positioning of the TCD probe for the correct artery and stable hemodynamic measurements requires significant training and experience.

NIRS allows tracking the concentration changes of both  $O_2Hb$  and HHb in venous, capillary, and arterial blood comprising the sampling volume [86]. It is comfortable, portable, and has

relatively low equipment cost, compared to fMRI and PET [35], [87]. Because the changes in concentration of hemoglobin from NIRS measurements are directly proportional to the variation of CBV [88], [89], NIRS has been used to estimate the CBV [90]–[92], which is linearly correlated to rCBF when the MTT does not change.  $O_2Hb$  is considered the most sensitive indicator of changes in rCBF in NIRS measurement [93]. Furthermore, NIRS has high temporal resolution and better tolerance to head motion that precludes studies of higher-intensity exercise.

Wearable BP monitoring is the primary challenge for combined cerebral hemodynamics and blood pressure measurements, as none of the existing BP technologies have the form factor and temporal resolution needed for this purpose. With our novel STA tonometry and PTT based drift correction, we preliminarily achieved wearable BP monitoring with high temporal resolution. STA tonometry typically exhibits more drift (due to unstable hold down pressure) but excellent temporal resolution, whereas PTT approach generally exhibits minimal drift but poor temporal resolution, and that is the reason why we sought to combine these two techniques. Our experiments show that as the STAT approach is sensitive to low frequency hold down pressure drift while PTT approach suffers poor dynamic response, when BP is measured using only STAT or PTT respectively, the MAD can be >15 mmHg (depending on the test conditions); however, when the two approaches are combined, the goal of MAD <7 mmHg can be routinely reached.

PTT, as well as STAT, has many factors that differ from person to person. In order to solve this problem, in our experiments initial calibration using a gold standard (e.g., cuff-based BP measurements) is required at the beginning of the BP monitoring. Most individual differences will be cancelled during the calibration process.

In this manuscript we only performed preliminary tests on healthy subjects without introduced BP fluctuations; and the BP readings were calibrated using initial cuff-based BP measurements. Further validating this new BP technology will require additional clinical validation tests. A first step would be to monitor outpatients with a Peñás type device (e.g., NIBP100 BIOPAC Systems, Inc) and a cuff-based ABPM device (e.g., CF-3001, Chancefine, Inc) for non-invasive gold-standard continuous BP measurement as compared to MCMS-1. A second step would be to monitor inpatients already undergoing invasive arterial blood pressure (ABP) monitoring, and will also equipped with NIBP100 and MCMS-1. Subject selection would presumably proceed as per IEEE 1708 Phase 1 testing (Table I therein), including (1) 20 healthy, pre-hypertensive or hypertensive out-patients, with target BPs distributed as per Phase 1 testing in IEEE 1708 (i.e., 5 normals, 5 pre-hypertensive, 5 stage 1 hypertensive and 5 stage 2 hypertensive individuals), and (2) 20 intensive care inpatients undergoing invasive ABP monitoring for clinical reasons; these participants are expected to exhibit notably fluctuating BPs consequent to disease and drug or other therapy administration. As per IEEE 1708, mean absolute percentage difference (MAPD) <5 mmHg for systolic, mean and diastolic pressures will indicate successful BP monitoring.

In principle, there is hydrostatic difference between the blood pressure measured at the head level and blood pressure measured at the heart level. Although STA tonometry measures blood pressure at the level of the temple, the approach we took is to calibrate

this against regular BP readings at the heart level, therefore the final BP results are still for the traditional heart level. For certain vascular diseases (e.g., carotid artery stenosis), the "constant hydrostatic difference" assumption may not hold precisely. Further investigation and validation of the STA tonometry approach and such exceptions remain to be fully investigated.

Different dynamic temporal features from blood pressure and cerebral hemodynamic monitoring during postural changes showed MCMS-1' significant potential in dynamic cerebral autoregulation analysis. The micturition response is a mixture of many changes, including those from muscle, abdomen/chest pressure, nervous and vascular reactions. The micturition response measured by MCMS-1 suggests a more detailed and more complicated pattern then the simple "drop of blood pressure" hypothesis, with gradual changes occurring during micturition, and substantial swings in multiple parameters at the completion of micturition response and micturition syncope, and to test the performance limits of the parameters measured. The purpose of our preliminary tests on healthy subjects here was to demonstrate the capability of MCMS-1 and the feasibility of using MCMS-1 in syncope diagnosis.

There are still several limitations in our technology, and we are doing our best to remove those limitations step by step, as well as to find applications that are suitable for our technology at each step. For example, external calibration using a wrist BP meter can be uncomfortable or inconvenient. Currently we are developing ways to reduce the need for cuff-based BP calibration (e.g., using stepped compression and multi sensor tonometry for hold down pressure drift correction); and our ultimate goal is to totally remove external calibration (e.g., replace it with step motor controlled or hydrostatic based selfcalibration). So far, our human subject tests show that although not desired, a short initial calibration and a couple of calibrations during BP monitoring can be tolerated. In fact, almost all cuffless BP technologies, such as PTT, require initial calibration, and sometimes calibration during and after the BP monitoring. We are also testing other clinical applications including surgical and post-surgical monitoring where calibrations are allowed so that the measurement accuracy can be assured.

It could be an issue or restriction if the subject is not used to wearing glasses, especially for long term monitoring during activities. Our current solutions to this problem are: (1) reducing the monitoring time. For example, CAR evaluation usually can be done in less than an hour, therefore no further cerebral monitoring will be required. (2) For applications where long term monitoring is absolutely needed, for example to catch transient syncope episodes, if the subject is not used to eyeglass type of STAT headgear, we have also developed other wearable forms, such as hairband and headband (see Fig. 9) to meet the need. We hope by providing subjects with multiple choices, long term monitoring can be accepted, performed comfortably and successfully.

Our system was designed to simultaneously record multiple channels at 250 Hz sample rate. For cerebral hemodynamic evaluation, such high temporal resolution is needed in several aspects: (1) To measure and evaluate dynamic cerebral response to rapid blood

pressure changes (e.g., associated with sudden body position change, in milliseconds); (2) For reliable blood pressure measurements. PTT method rely on accurate QRS detection to calculate blood pressure and the beat-to-beat variation of pulse transit time is in the scale of milliseconds. (3) For noise reduction. In order to remove 60 Hz line interferences, which may happen during long term monitoring in real life environment, practically we need >120 Hz sampling rate to avoid aliasing, and to further identify and remove the interference.

Real-time signal processing and display of results, prevention, early detection and alarm for pathological conditions are important for many applications. The wearable data recording system used in this manuscript did not support real time display and processing; however currently we are testing a new system [94] that has embedded Bluetooth module that supports real time display and alarms, and the result will be reported in the future.

## V. Conclusions

This paper reports the development of an ambulatory multi-modal cerebrovascular measurement prototype. The system enables the recording of people's cerebral hemodynamics (changes in tissue total hemoglobin concentrations), blood pressure, ECG, and body postural position/motion simultaneously and continuously at 250 Hz sampling rate, during (and without restriction to) their daily activities. This is the first time continuous cuffless blood pressure (at the brain level) is included in the wearable multimodality monitoring, and it enables important brain function studies such as cerebral autoregulation. Application of this unique technology in the prevention and diagnosis of cerebral vascular diseases (such as stroke and Alzheimer's disease) is currently underway, and the results will be reported in the future. The system also features event buttons to enable precise co-registration of multi-modality recordings with the events of interest during the blood pressure monitoring. Preliminary feasibility tests show that this system is capable of revealing cerebral hemodynamic changes associated with blood pressure fluctuation during different types of activities. We have also presented the first simultaneous ambulatory BP and hemodynamics recording of postural changes and the micturition response, which demonstrates its unique power of capturing hemodynamic and blood pressure fluctuations during transient events with great temporal details.

Our preliminary tests demonstrated MCMS-1' potential for measuring continuous, ambulatory cerebral hemodynamics and blood pressure, even under rapid-motion conditions. It also highlights the feasibility of conducting symptom-capture studies. This suggests the potential suitability of MCMS-1 for assessment and monitoring of cerebrovascular and cardiovascular diseases, and analysis of symptoms like syncope. Further work can include improvements in sensor and measurement stability, thorough validation of the system, enhancements of the data fusion algorithm, and developing novel algorithms to reveal dynamic cerebral autoregulation during different physiological or pathological conditions. The ultimate goal of this work is to develop a novel technology for wearable, multimodality brain monitoring. Future versions of MCMS-1 will take full advantage of the latest information technologies, its power can be enhanced by wireless communication capabilities with devices such as smart phones, and the result can be directly integrated into

online health record systems. If successful, we expect this approach could lead to significant changes in cardiovascular health care.

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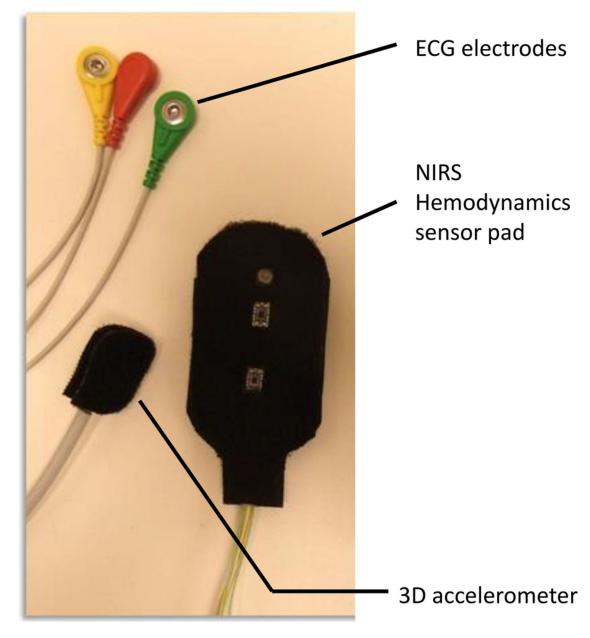
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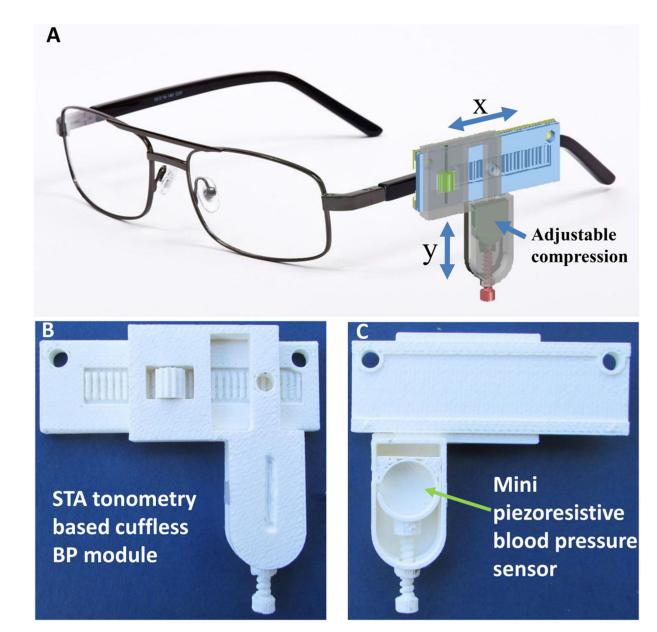
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## Fig. 1.

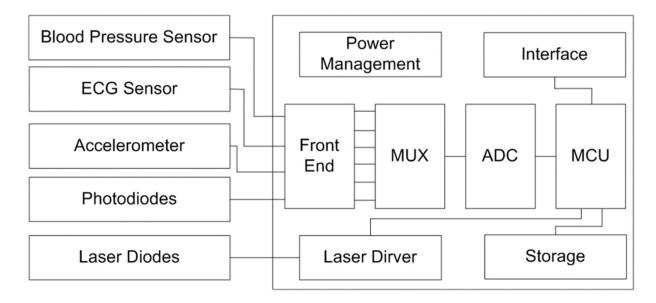
NIRS based cerebral hemodynamic sensors, ECG and 3D accelerometer sensors used with the MCMS-1 prototype.

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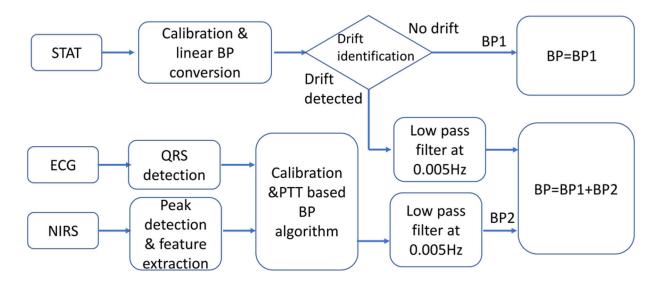
#### Fig. 2.

Design of the BP sensor module attached to a regular pair of eyeglasses that allows stable skin contact, flexible positioning of the sensor, and adjustable compression level. (A) Attachment of the BP sensor module to a regular pair of glasses; (B) Front and (C) back view of the structure of the wearable BP sensor module.



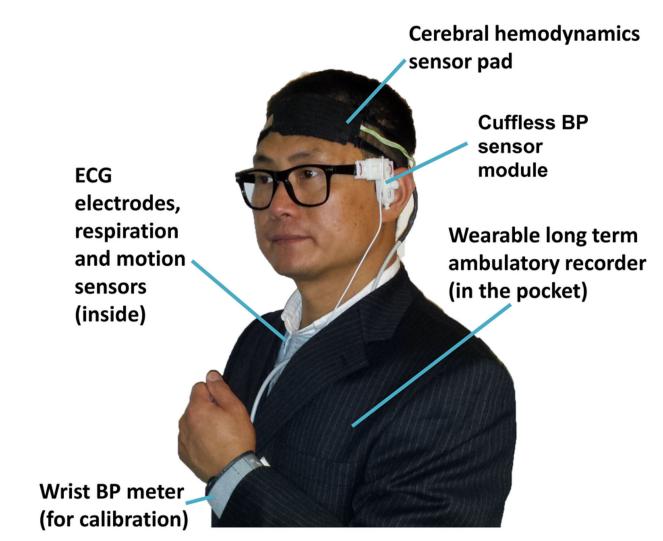


Block diagram of the wearable data recording system for the MCMS-1 prototype.



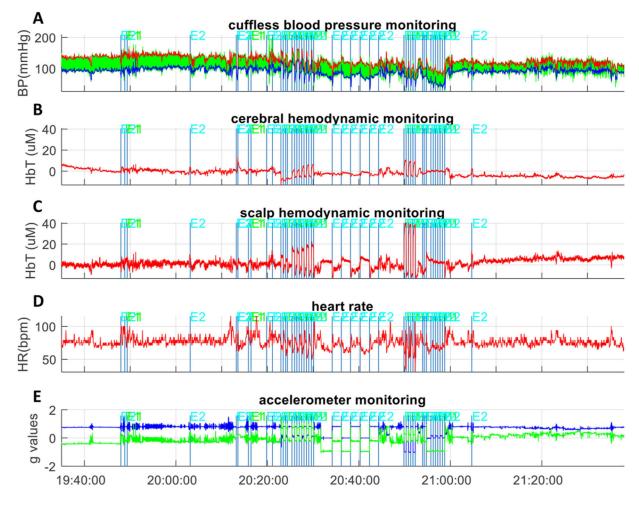


Multimodality BP Monitoring algorithm: STAT with PTT based drift correction.



**Fig. 5.** Wearable AMMCMS monitoring.

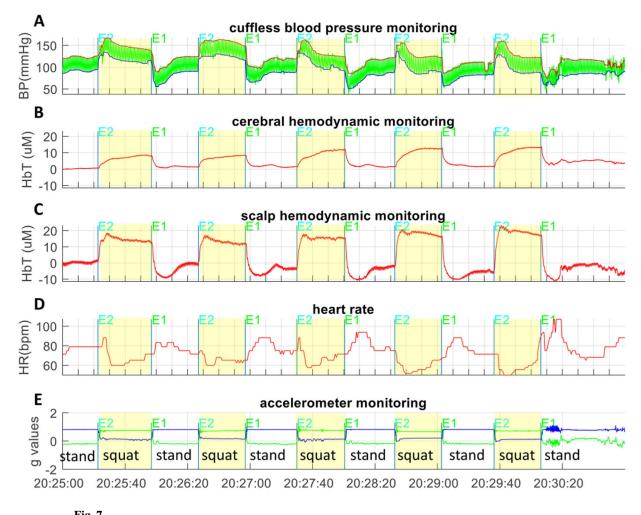
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#### Fig. 6.

Two hour AMMCMS recording. A) Cuffless blood pressure monitoring. The middle curve is the real time blood pressure curve acquired at 250 Hz sampling rate; the top and bottom outlining envelope curves are the systolic and diastolic BP. B) Total hemoglobin (HbT) concentration measured from the far source-detector pair (3.8 cm separation) of the NIRS probe, with superficial layer interference removed to reveal the cerebral HbT change. C) HbT measured from the close source-detector pair (1.1 cm separation) of the NIRS probe, revealing the non-regulated scalp hemodynamics and representing general systemic hemodynamic change. D) Heart rate calculated from NIRS channels. E) Two channel of accelerometer readings, indicting activity level and body positions. Accelerometer output has both a static component (from earth gravity) and a dynamic component (from sensor acceleration), and the two lines in E correspond to one vertical and one horizontal acceleration vector, that is, two out of the three accelerometer outputs. Event marks E1 and E2 were pressed by the subject and indicated the onsets or offsets of specific activities or tests.

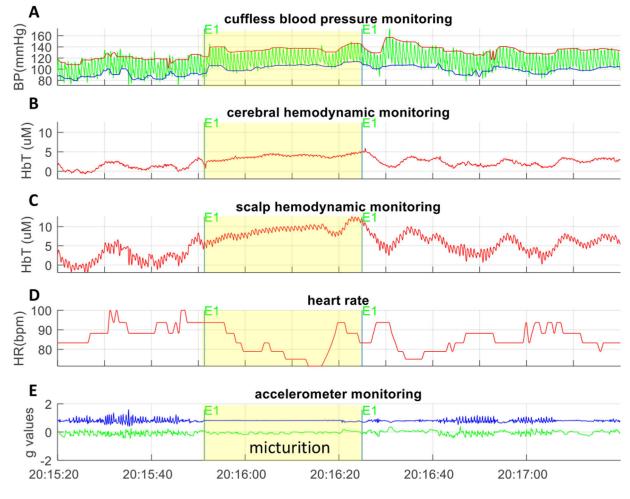
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### Fig. 7.

Postural change (stand-to-low squat) test result using the prototype MCMS-1 system. The shaded sections indicate the low squat body positions.

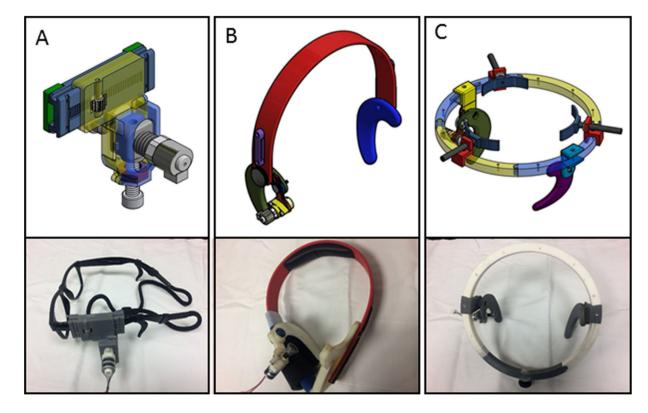
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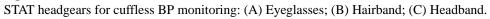
#### Fig. 8.

Dynamic blood pressure, cerebral and systemic hemodynamics and heart rate monitoring for the micturition response. The highlighted segment indicates the actual urination period.

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Comparison of Current BP Technologies.

|                     |  | Features  |               |                        |                                     |             |          |
|---------------------|--|---|---------------|------------------------|-------------------------------------|-------------|----------|
| Methods             | Advantages   | Limitations   | Accuracy      | Data Rate              | Equipment Cost Labour Cost Wearable | Labour Cost | Wearable |
| Arterial line       | GS for IM; CM  | Risk to the patient; Requires trained personnel to place<br>appropriately   | High          | >20Hz                  | High (>\$10K)                       | Medium      | No       |
| Peñás               | Convenient; IM; CM   | Expensive: Affected by factors such as cold extremities, vasopressors; Needs calibration via another method                               | Medium        | >20Hz                  | High (>\$20K)                       | Medium      | No       |
| Korotkoff           | Clinical GS for IM; cheap; No<br>risk to patient           | Relies on trained personnel; Subjective method with<br>possible human error; Cuff sizing error; NON-CM                                    | Medium        | 1 reading per<br>10min | Low                                 | High        | No       |
| Oscillometric       | Convenient; cheap; Requires<br>little to no operator skill | Cuff sizing error; NON-CM   | Medium        | 1 reading per<br>10min | Medium                              | Medium      | No       |
| PTT (photometric)   | IM; beat-to-beat monitoring;                               | Not fully developed to correlate pulse transit time to<br>blood pressure  | Low           | Beat-to-beat<br>(~1Hz) | low                                 | Low         | Yes      |
| STAT                | IM; CM   | Needs calibration via another method; optimization of probe location takes time   | Medium        | >20Hz                  | low                                 | Low         | Yes      |
| CM: Continuous moni | itoring: IM: invasive monitoring: GS                       | CM: Continuous monitoring: IM: invasive monitoring: GS: "gold standard": In 6 <sup>th</sup> column. "Low": < \$ 0.5K: "Medium": < \$ 10K. | m": < \$ 10K. |                        |                                     |             |          |

#### TABLE II

Comparison of Current Methods for Measurements of Cerebral Hemodynamic

| Methods | Features |             |          |                      |                   |  |
|---------|----------|-------------|----------|----------------------|-------------------|--|
|         | rCBF     | Portability | Low cost | High time resolution | Area of expertise |  |
| TCD     | 0        | 0           | 0        | 0                    | CBFV              |  |
| PET     | •        | 0           | 0        | 0                    | CBV/rCBF/MTT      |  |
| fMRI    | •        | 0           | 0        | 0                    | CBV/rCBF/MTT      |  |
| NIRS    | •        | •           | •        | •                    | O2Hb/CBV/rCBF     |  |

Symbol  ${\scriptstyle \bullet}$  means the method has this attribute, while  ${\scriptstyle \circ}$  means no.