NONINVASIVE PHOTOPLETHYSMOGRAPHIC MONITORING OF PULSE WAVE VELOCITY AND VASCULAR STIFFNESS FOR HYPERTENSION APPLICATIONS

By

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ABSTRACT OF THE THESIS

NONINVASIVE PHOTOPLETHYSMOGRAPHIC MONITORING OF PULSE WAVE VELOCITY AND VASCULAR STIFFNESS FOR HYPERTENSION APPLICATIONS

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Cardiovascular diseases are the leading cause of death globally. These usually have two main types of risk factors namely modifiable risk factors and non-modifiable risk factors. Among these, hypertension is the primary risk factor. Accurate noninvasive monitoring of hypertension in high risk patients is therefore essential in order to tackle or prevent their cardiovascular diseases.

In terms of hemodynamics, increased vascular stiffness has been recognized as the main contributing factor to hypertension. This leads to the observed increase in pressure pulse propagation velocity, or pulse wave velocity, in conduit arteries. Thus, a method that can afford continuous noninvasive monitoring of vascular stiffness will be clinically desirable. To achieve this, the current investigation provides a new method of application of a photoplethysmograph (PPG) that employs light emitting diodes of visible wavelengths coupled with new ambient light detectors for optimal recording of propagating pulses. PPG sensors are placed at two different superficial arterial sites (Dual PPG) for monitoring pulse transit time (PTT) and hence pulse wave velocity (PWV) in patients. Data were simultaneously recorded in a human model, sampled by means of a

Biopac System and selective filtering was applied to enhance the signal-to-noise ratio. Vascular stiffness is obtained as elastic modulus through the Moens-Korteweg formula. Interventions were imposed to observe induced changes in vascular stiffness. Results show that our current design is accurate for continuous monitoring of vascular stiffness changes. Measured pulse wave velocities agree well with clinically reported values for different arterial sites, such as ear lobe artery to radial artery and brachial artery to index finger artery. The light-weight, low cost, continuous and noninvasive PPG design can be used for future routine screening of vascular stiffness. This can be used to predict hypertension, its severity in terms of structural changes, and potential evaluation of therapeutic efficacy of anti-hypertensive drugs in hypertensives.

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Firstly, I would like to thank my thesis advisor Dr. John K-J. Li for his guidance, support and encouragement without which this thesis would not have been completed.

I would also like to thank my parents, teachers, friends and colleagues whose contributions towards making me a better person in all my endeavors can never be underestimated.

Also, this thesis work is dedicated towards trying to help all those people who need such devices for enabling them to improve their health, especially people in need like my late grandmother.

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Chapter 1: Introduction

1.1 Risk Factors for Cardiovascular Diseases

It is well known that cardiovascular diseases (CVD) are the leading cause of death globally. They generally have two main risk factors i.e. modifiable risk factors and non-modifiable risk factors.

1.1.1 Modifiable Risk Factors

Modifiable risk factors account for a majority of CVD. As the name suggests, such factors are controllable which can help in treatment or even prevention of CVD. These include high blood pressure or hypertension, increased blood glucose levels, physical inactivity, obesity and tobacco consumption. Hypertension accounts for the most number of CVD occurring globally followed by others (Mendis S, et.al. 2011).

Hypertension

Hypertension can be defined as raised blood pressure levels during systole (contraction) and diastole (relaxation) of the heart. The blood pressure corresponding to systole is called systolic pressure which is the maximum blood pressure during one contraction of the heart in a cardiac cycle. On the other hand, the blood pressure corresponding to diastole is called the diastolic pressure which is the minimum blood pressure during one relaxation of the heart in a cardiac cycle. Blood pressure is measured as a ratio of systolic pressure to diastolic pressure in mmHg (millimeters of mercury). Typically, a ratio of 120/80 mmHg is considered clinically standard for a normal healthy adult. People with systolic pressures greater than 140 mmHg and diastolic pressures greater than 90 mmHg are considered to be hypertensive as defined by the American Heart Association (AHA).

Nearly 1 billion people suffer from hypertension worldwide. Of these, almost two-thirds reside in developing countries. By the end of the next decade, the World Health Organization (WHO) states that around 1.56 billion adults will be hypertensive. People with hypertension are also more vulnerable to other complications such as diabetes and stroke (Sowers JR, et.al. 2001). It is also one of the most prominent causes of premature deaths on the planet. It is a real growing problem. Hypertension can also be associated with Coronary Artery Disease (CAD). CAD is the result of deposition of plaque in the arteries supplying blood to the heart. This blocks blood supply to the heart which increases the risk of heart attacks and strokes. With hardening and thickening of arteries, the channel for blood flow becomes narrower leading to hypertension. Hypertension often goes undetected for a long time, like a "silent killer", because of the lack of warning signs and symptoms. Hence accurate, noninvasive and continuous monitoring of blood pressure is essential for optimal diagnosis and treatment.

1.1.2 Non-modifiable Risk Factors

Non-modifiable risk factors are the exact opposite of the modifiable ones. Unlike modifiable risk factors, non-modifiable risk factors cannot be altered. These include age, gender and family history.

With increasing age, CVD becomes increasingly more prevalent. As a person gets older, the muscles of that person's heart undergo physiological changes. They become stiffer. The ability of the heart to relax between successive cardiac cycles decreases. This leads to more workload and wear related to the heart chambers. Such age related factors may make the CVD worse and its treatment more difficult. CVD is more commonplace among males as compared to females. After menopause though, the risk of CVD among females

is similar to that among males. The risk of CVD is higher if there has been an occurrence of CVD in a person's family (Mendis S, et.al. 2011). As non-modifiable risk factors cannot be customized actively and voluntarily, they are not of much use in trying to treat or prevent CVD in patients.

1.2 Invasive and Noninvasive Monitoring Methods

Generally, there are two main methods of monitoring blood pressure, invasive (direct) and noninvasive (indirect).

1.2.1 Invasive Methods

The invasive or direct method incorporates the use of an intra-arterial catheter for measurements. This method, however, is not practical due to its invasiveness and its failure to be applied to large groups of patients not showing any symptoms (Perloff D, et. al. 1993).

1.2.2 Noninvasive Methods

The noninvasive or indirect methods make use of auscultatoric or oscillometric devices for monitoring blood pressure. Such methods rely on the pressure readings obtained during the collapsing of arteries using inflatable cuffs.

Auscultatoric measurement devices determine blood pressure by monitoring Korotkoff sounds which result due to rapid blood flow through a partially collapsed artery. In conjunction with an inflatable cuff, a mercury manometer is also used in this method. The steps involved in this method are as follows. First, the inflatable cuff is placed around the upper arm of a patient. The upper arm is raised to the level of that patient's heart. The cuff is then inflated till the pressure in it increases to about 30mmHg greater than systolic pressure (typically till around 160 mmHg). The pressure in the cuff is then slowly decreased. When arterial blood starts flowing in the artery, it creates a pounding pulse sound first. The pressure at which this sound first occurs is the systolic pressure. The pressure in the cuff is then further decreased till when no sound can be heard. The

pressure at this point is taken as the diastolic pressure. The sounds can be detected using a stethoscope.

In oscillometric measurement devices, an electronic pressure sensor, a cuff and a numerical display are used. The cuff is inflated automatically in this device by an electrically operated pump and valve system. The cuff may be fitted on the wrist or on the upper arm. The cuff is inflated to a pressure higher than systolic pressure and then decreased till it falls below the diastolic pressure, similar to the auscultatoric method. Corresponding raw data is recorded. The raw data gives the values for systolic and diastolic pressures. Systolic pressure is the point at which oscillations in the raw data start while diastolic pressure is the point after which they stop. This can be achieved using either a fully automatic or a semi-automatic monitor.

The use of ultrasound and MRI as indirect blood pressure monitoring methods has also been tested. However, there are many drawbacks involving these methods. MRI use takes up a lot of time. The lack of availability of an MRI system everywhere and its cost are also hindrances. Hence, this method is currently being used in research environments only (Mackenzie IS, et.al. 2002). Even ultrasound use for this purpose is not free of impediments. Firstly, its use is limited to only larger and more accessible arteries. Secondly, it has limited resolution. Also, device operator errors play a significant role in measurement quality using this method. This has led to concerns regarding its reproducibility. Even though ultrasound is noninvasive, it is not easily portable. Thus, even the use of ultrasound for monitoring blood pressure has been restricted to research only (Mackenzie IS, et.al. 2002).

There are a lot of errors which can be pointed out in manual blood pressure measurement methods. These include observer errors such as digit preferences or decimal point estimations, lack of attention, speed of cuff deflation and hearing deficits. In addition, there are also "methodological" errors such as not accounting for beat-to-beat variations in each pulse (Smulyan H, et. al. 2011). Another important component of measuring blood pressure manually is an understanding of the Korotkoff phases. The Korotkoff phases have been classified as 5 phases. Phases I, IV, and V are integral to obtaining an accurate blood pressure reading. Automated oscillometric devices remove the observer errors which can occur with manual measurement methods but still have some constraints. Oscillometric devices have been criticized for their inaccuracy. This can be a big disadvantage in measuring blood pressure in hypotensive, hypertensive and trauma patients (Skirton H, et.al. 2011). For example, in one study, mean systolic and diastolic blood pressures were significantly greater using the auscultatoric method than those obtained while using the automated oscillometric technique (Landgraf J, et.al. 2010). These findings can have important clinical implications as they may falsely indicate hypertensive patients' need for more treatment even though they might have been already treated satisfactorily.

Regardless of whether a manual or an automated method is used, accurate blood pressure measurement in patients is a key part of clinical medicine and healthcare and must be addressed aptly.

1.3 Arterial Stiffness and Hypertension

With a view to addressing the need for accurately monitoring hypertension in patients, it is essential to understand its relationship with vascular stiffness.

Compliance is a physical property of a material which enables its elastic deformation when force is applied to it. Stiffness is the reciprocal of compliance i.e. the more the compliance, the lesser the stiffness and vice-a-versa.

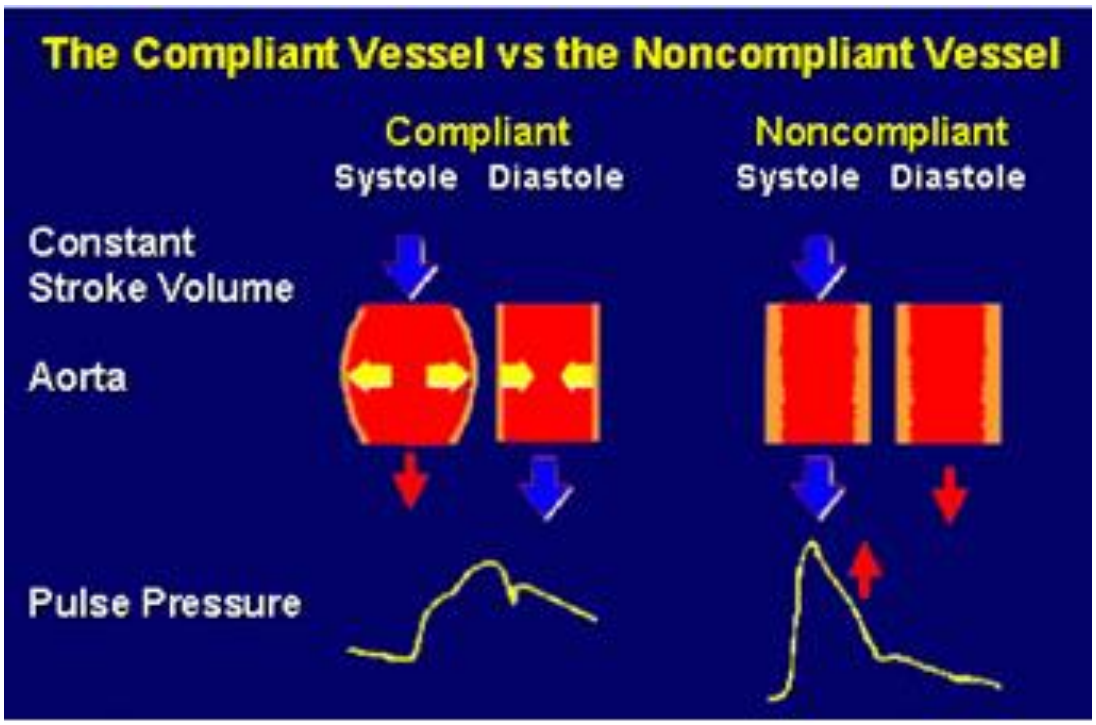

Fig 1.1: Compliance in blood vessels. *Reproduced with permission from Arnett DK*

(Liao D, Arnett DK, et. al. 1999)

Arterial compliance can be affiliated with blood volume and pressure changes. Such changes occurring during the diastolic or the systolic phase of the cardiac cycle can give an indication of compliance.

$$Compliance = \frac{\Delta V}{\Delta P} \tag{1.3.1}$$

where ΔV=change in volume and ΔP=change in pressure.

The existing hypertension monitoring method using the pressure-volume relationship is direct. However, it is invasive owing to catheter-use and hence not desirable in patients (Perloff D, et.al. 1993).

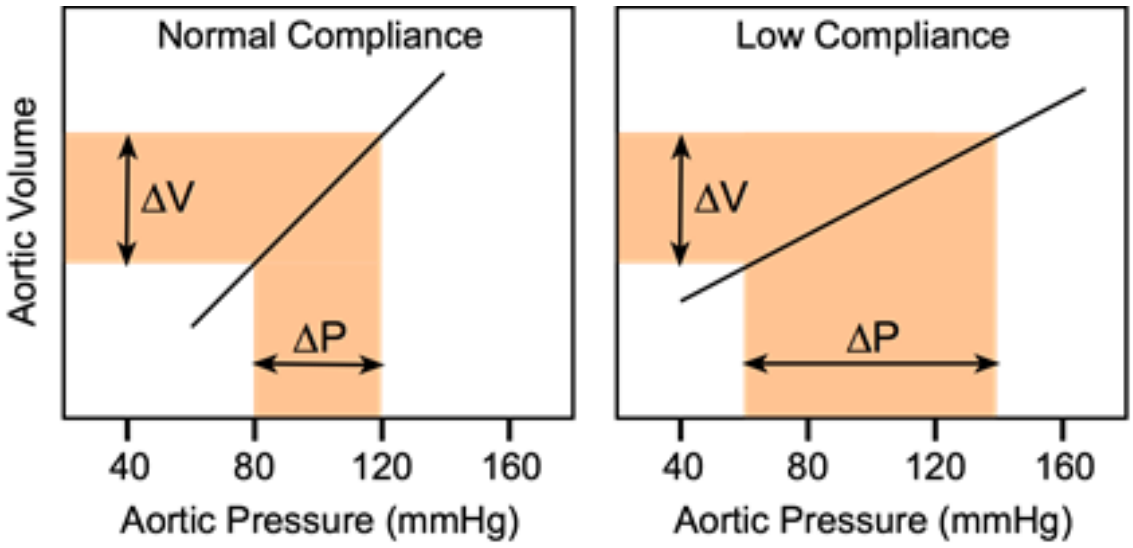

Fig 1.2: Relationship between changes in aortic volume (ΔV) and aortic pulse pressure (ΔP) in aortas having normal compliance and low compliance (high stiffness)

Reproduced with permission from Klabunde RE (Klabunde RE, et.al. 2011)

Arteries possess a dual function in our bodies of having both a conduit behavior as well as a cushioning effect (Marchais SJ, et.al. 1993). The two main components of arterial pressure are the steady component related to mean blood pressure and the pulsatile component related to pulse pressure (Marchais SJ, et.al. 1993). Arterial compliance is associated with the pulsatile component.

Compliance depends on intrinsic elastic properties and is a determinant of pulse wave velocity (PWV). When arterial compliance decreases, the effect of not only the incident pulse pressure waves but also that of the reflected pulse pressure waves increases. This tends to increase the blood pressure. PWV is directly proportional to the arterial elastic modulus given by the Moens-Korteweg formula (Li JKJ, 2004) as follows:

$$PWV = \sqrt{\frac{Eh}{2r\rho}} \tag{1.3.2}$$

where E=elastic modulus, h=wall thickness, r=vessel radius and $\boldsymbol{\rho}$=blood density. Hence, as elastic modulus or compliance of the arteries changes, PWV also changes. As arterial compliance decreases (or arterial stiffness increases), the tendency of systolic hypertension increases (Li JKJ, 2004). Also, the stiffer the artery, the faster is the flow of blood in it, as shown in equation 1.2.2. Thus, arterial compliance and PWV are a direct measure of blood pressure changes (Gribbin, et.al. 1976). Hence, by monitoring arterial compliance we can predict hypertension by comparison of arterial compliance with blood pressure readings for an individual. This can be tested among various types of subjects representing different patient groups (Blacher, et.al. 1999) (Safar ME, et. al. 2002). This can be achieved via pulse wave analysis (PWA) (Cohn JN, et. al. 1995).

1.4 Photoplethysmography as Noninvasive Method

As discussed in the previous sections, the current methods for predicting blood pressure have limitations making it imperative for the inception of a noninvasive and continuous method which can overcome these drawbacks without eliminating any existing benefits. So far, it has been established that continuous monitoring of PWV can be a great indicator for changes in vascular stiffness which correlates with prediction of hypertension. Thus, a technique for monitoring PWV is needed. Photoplethysmography (PPG) is one such optimal technique. A basic PPG monitoring system requires only a few electronic components which mainly include a light source and a matched light detector for measuring changes in light from a target area. It is noninvasive and easy to use as it can be applied at the skin surface for measuring PWV. As discussed earlier, PWV readings can help in prediction of hypertension (Kamal, et. al. 1989).

A typical PPG waveform consists of two main components, a pulsatile AC component and a quasi-DC component. The AC component incorporates the peripheral pulse which is the most recognized feature of a PPG. It is synchronous with each heartbeat and is the target of this method. It is usually superimposed over the quasi-DC component. The DC component varies slowly due to a number of influences such as breathing rate, vasomotor activity and thermoregulation. With suitable electronic filtering and amplification both the AC and the DC components of a PPG can be extracted for subsequent PWA (Foo, 2006).

A PPG pulse has two phases: 1) the “anacrotic” phase which is the rising edge of the pulse and 2) the “catacrotic” phase which is the falling edge of the pulse. The anacrotic phase represents systole whereas the catacrotic phase represents diastole. The PPG pulse

also has a dichrotic notch between these two phases which is indicative of sudden increase in pressure due to the closure of the aortic valve (Hertzman et. al., 1937). For PWV detection using PPG, pulse time duration or pulse transit time (PTT) is an indicator along with pulse width and pulse height (Murray and Foster, 1996).

Light interacts with biological tissue in a complex manner. It consists of a number of optical processes including scattering, absorption, reflection, transmission and fluorescence. The amount of light received by the photo detector can be affected by the blood vessel wall movement, the orientation of red blood cells (RBC) and blood volume. There is a direct association of perfusion with detected signal. The greater the blood volume, the more the light from the source is attenuated. Hence, the smaller will be the amplitude of the detected signal. Wavelength of light used is essential in this method (Cui, et. al. 1990). "This is because of three main reasons: (1) Optical water window: tissue is generally made up of water. Water absorbs light in the ultraviolet and infrared regions of its spectrum. However, there is a window in this absorption spectrum which allows for the transmission of light at the red and infrared wavelengths. Thus, PPG methods make use of light in these regions of wavelength, (2) Isobestic wavelength: uniform absorption by both haemoglobin and oxyhaemoglobin is achieved only at an isobestic wavelength (Gordy and Drabkin, 1957). This is important for accurate readings. (3) Tissue penetration depth: the wavelength of light used also governs tissue penetration depth (Murray and Marjanovic, 1997). Red and near infrared wavelength light used at defined intensities is useful for achieving this."

The general block diagram of a PPG monitoring system can be illustrated as follows:

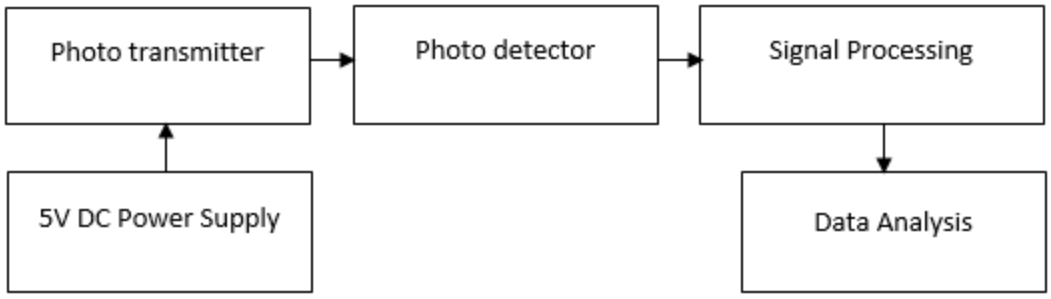

Fig 1.3: General schematic diagram of a photoplethysmographic recording system

PPG systems can be used in two main configuration modes: 1) Transmission mode: where the target area is placed between the photo transmitter and the photo detector and 2) Reflection mode: where the photo transmitter, target area and the detector are placed adjacent to each other. By using two PPG sensors at any two different locations on a patient's body simultaneously, like those at the radial artery and the brachial artery, we can obtain two time varying signals. These sensors enable us to gauge the time difference between the blood flow at these two locations. Knowing this time difference along with the fixed distance between these two locations, the PWV can be calculated from the formula:

$$PWV = \frac{Distance\ between\ two\ sensor\ sites}{Time\ difference\ between\ two\ sensor\ sites\ (\Delta t)}\ \text{m/s} \qquad (1.4.1)$$

Once the PWV is obtained, it can be compared with standard clinical data and help the patients assess their arterial stiffness accurately with a view to predict hypertension. As mentioned in section 1.2, the higher the PWV, the more the hypertension. Thus, using the

dual or bilateral site PPG monitoring technique, PWV at any given instant of time can be calculated noninvasively continuously to successfully predict hypertension in real-time.

PPG recordings from various bodily sites can be analyzed for detection and diagnosis. Some of these recordings have been described in related literature and are as follows:

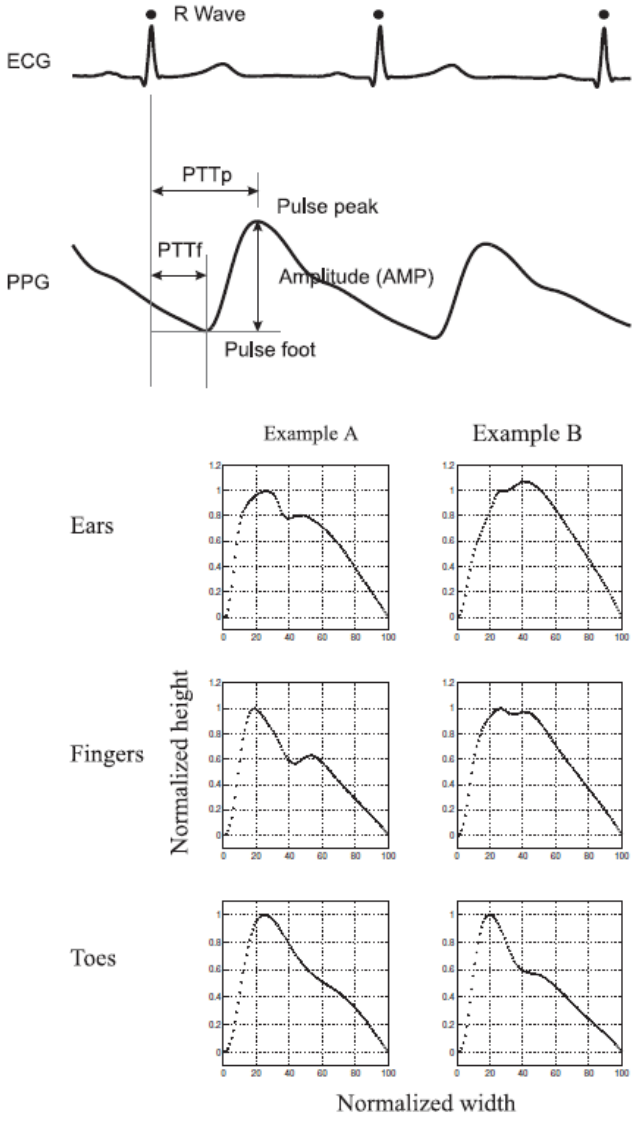

Fig 1.4: Graphic illustration of PPG recordings from various noninvasive sites

Reproduced with permission from IOP (Allen JN, 2007)

Also, there are slight differences in PPG signals recorded from proximal and distal measurement sites as shown below:

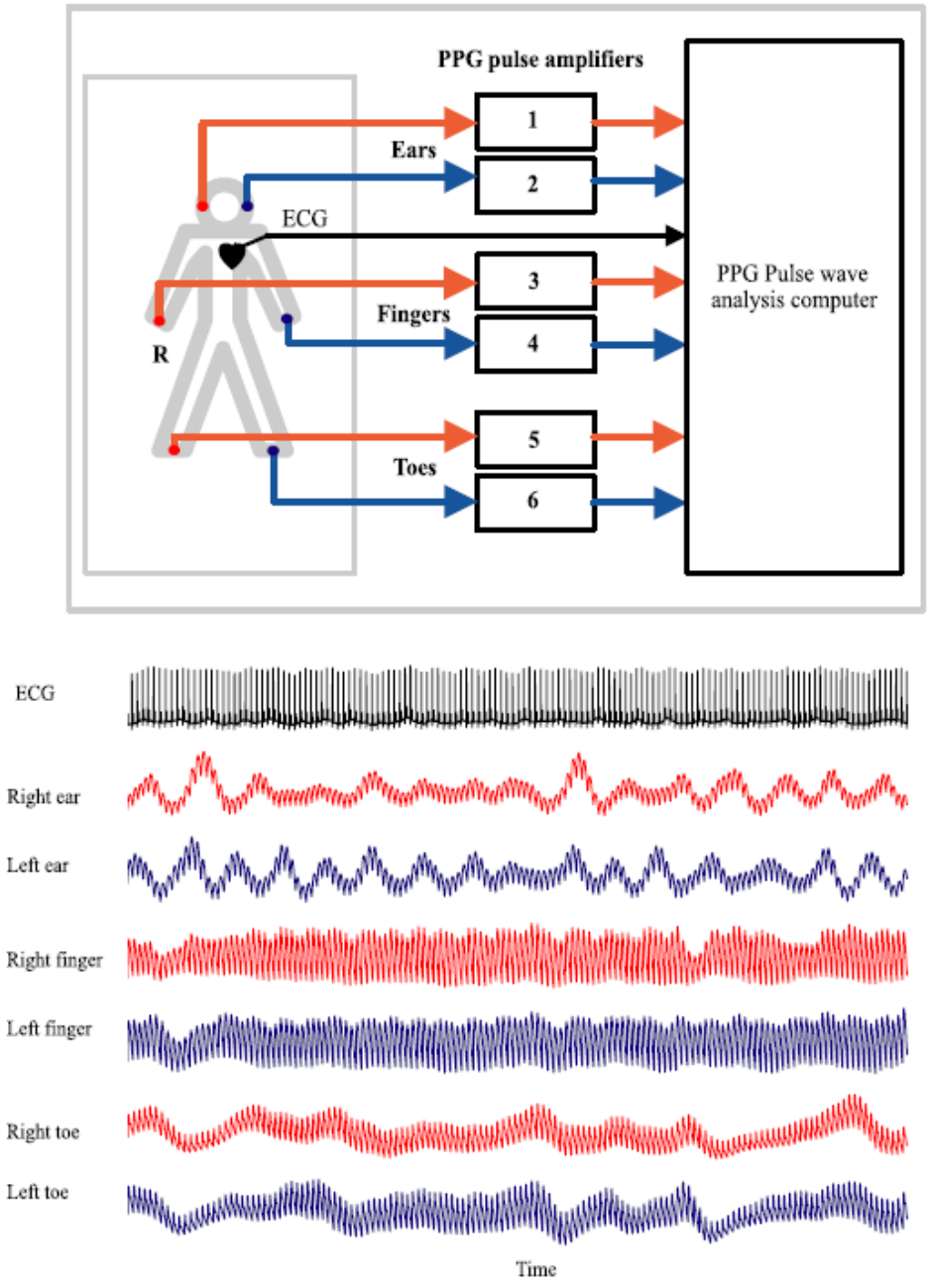

Fig 1.5: Multi-bilateral PPG analysis procedures and recording sites

Reproduced with permission from IOP (Allen JN and Murray A, 2000)

The wide availability of low cost and small semiconductor components and the advancement of computer-based PWA techniques have helped re-enforce this methodology.

Chapter 2: Aims and Significance of the Thesis

2.1 Specific Aims

In the present investigation, a novel design of a dual photoplethysmographic system (PPG) is established for continuous noninvasive monitoring of a vascular stiffness parameter, identified as pulse wave velocity. The overall hypothesis is that vascular stiffness index can be readily obtained through low-cost, portable, noninvasive and continuous monitoring of blood pressure or volume pulsations. To test this hypothesis in a human model, the specific aims are:

1. Employ visible light spectrum for sensing. In this approach, light emitting diodes (LED) of visible wavelengths are coupled with new ambient light photodetectors to establish optimal sensing of pulsations.

2. Dual channel PPGs are designed with matched characteristics for recording of the pulse propagation at two different arterial sites.

3. Selection of arterial sites with sufficient resolution of pulse transit times to allow computation of pulse wave velocity.

4. Explore physiologic changes provoked by interventions that alter pulse wave velocity and corresponding vascular stiffness through the Moens-Korteweg formula.

5. Analyze limitations and potential clinical applications of the current approach and make suggestions for future improvement.

2.2 Significance of the Thesis

Cardiovascular diseases (CVD) are the leading cause of death globally. These can occur due to modifiable as well as non-modifiable risk factors, a majority of which are associated with modifiable ones. Among these, hypertension or high blood pressure is the leading risk factor for CVDs. Monitoring this risk factor accurately can therefore help treat or even prevent CVDs.

Currently, there are two ways of measuring blood pressure. These are invasive or direct method and noninvasive or indirect method. The invasive method is catheter based. Owing to its invasiveness and its inability to be applied to large groups of people at a time, it is not preferred. The noninvasive or indirect methods involve collapsing the artery with an external cuff, providing an inexpensive and easily reproducible way to measure blood pressure. The indirect method can be performed using a manual sphygmomanometer or with an automated oscillometric device. However, even indirect methods have many limitations. Manual methods involve many errors. These can be either due to the observer/operator or due to the method being used. Automated oscillometric devices remove the observer errors that can occur with manual measurements but still have some constraints. The inaccuracy of the oscillometric devices has been criticized. Even the use of MRI and ultrasound machines for monitoring blood pressure is not without limitations. Therefore, this thesis investigates the use of noninvasive sensor monitoring for arterial stiffness via pulse wave velocity which can be utilized for hypertension applications. Compared to current clinical methods for hypertension prediction in patients, which are intermittent, the method used in this thesis would be continuous.

Chapter 3: Methods

3.1 Hardware Components and Electrical Circuit Design

As described in section 1.4, the PPG monitoring method for PWV and vascular stiffness comprises of components including an electrical breadboard, resistors, capacitors, connecting wires, a light-emitting diode (LED), an ambient phototransistor (photodetector), a power supply, connecting probes and an oscilloscope or a computer for output display and signal processing.

Breadboard

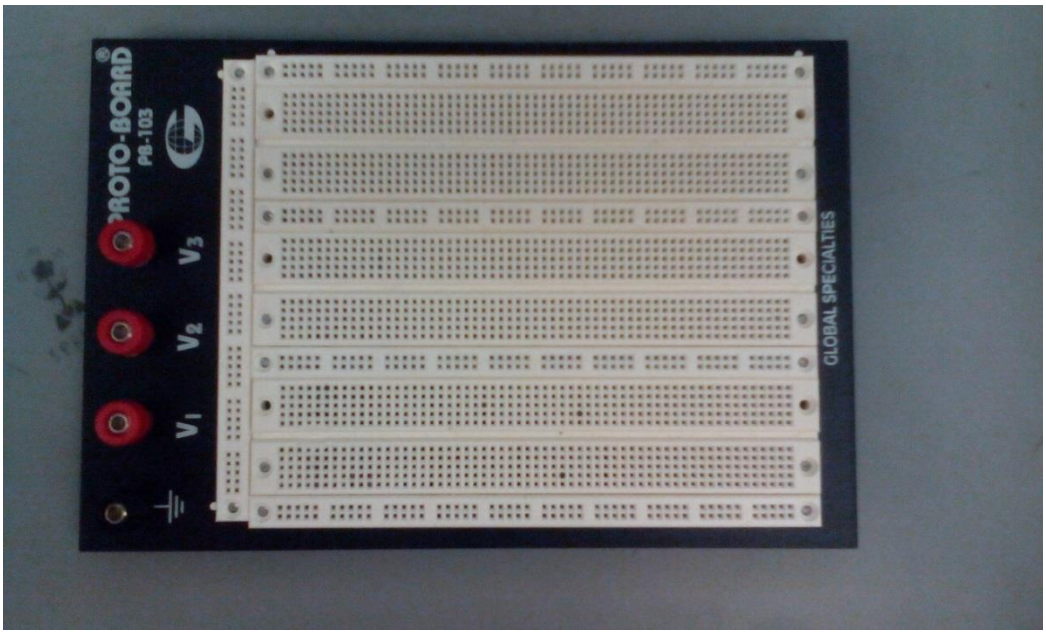

Fig 3.1: Electrical breadboard

A standard solder-less thermoplastic electrical breadboard with 2250 connection points was used.

Power Supply

Fig 3.2: Adjustable DC power supply

An adjustable DC voltage supply with isolation amplifiers was used. 5V DC voltage was required.

Light-Emitting Diode (LED) or Photo transmitter

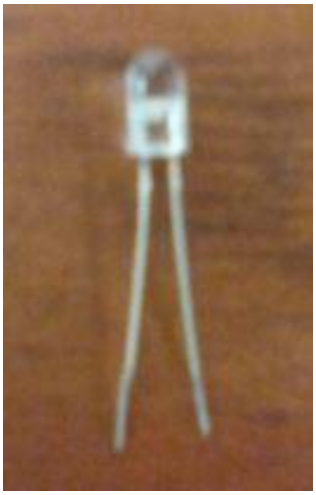

Fig 3.3: Light-Emitting Diode

An LED is a p-n junction diode which emits light when activated. With a suitable supply voltage, the electrons from the cathode (-) of this device recombine with holes in the anode (+) which release photons giving light of a particular wavelength. In Fig 3.3 above, the anode and the cathode can be pointed out as the longer leg and the shorter leg of the component respectively. An LED of 770 nm visible red wavelength was employed. Red or near Infrared light is most useful for hematologic applications.

Photo detector or Photo-transistor

A 5 mm flat ambient light cylindrical photo-transistor was utilized, a new approach to detection.

Fig 3.4: Ambient light photo-transistor *Reproduced with permission from RadioShack* (RadioShack)

A phototransistor is a light sensitive semiconductor device. A phototransistor has a collector, a base and an emitter semiconductor regions. It can be of two types, NPN or PNP, based on the type (p or n) of doping in the semiconductor regions and can be used in three configurations i.e. Common Collector (CC), Common Base (CB) and Common

Emitter (CE). A 5mm flat ambient NPN transistor in CE configuration was used in this design. Also, the ambient transistor was more sensitive in light detection than a non-ambient transistor as observed during trials owing to its extremely low dark current of 0.1 µA.

RC Low Pass Filter

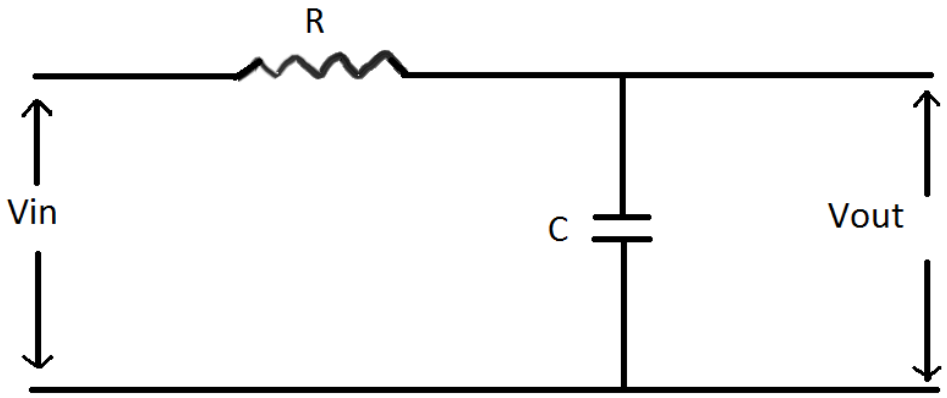

Fig 3.5: Schematic diagram for RC low pass filter

An RC low pass filter passes signals with frequencies lower than a cut-off frequency and attenuates signals with a frequency higher than that cut-off frequency. It removes noise and fluctuations in electronic circuits.

The cut-off frequency is determined by the formula

$$fc = \frac{1}{2\pi RC} \text{ Hz} \quad (3.1.1)$$

where R=resistance and C=Capacitance. Upon testing and analysis, the most useful RC combination was found to be R=1kΩ and C=0.1 to 4.7 µF, which gives a cut-off

frequency of about 48.23 Hz for R=1kΩ and C=3.3 μF. A second-order low pass filter i.e. two low pass filters in "cascade" was used. This gave a steeper roll-off slope, giving a stop-band response closer to the ideal stop band characteristics for this filter as compared to that obtained when using just a first-order filter. Thus, it prevented under-filtration of the signal from the photo detector. However, it was also found that using an order higher than two in this design did not necessarily give better filtration of the signal from the photo detector than that obtained using a second-order filter. This is because the gain and the accuracy of a low pass filter decrease with increasing order and the filtered signal gets distorted for such a filter (Allen JN and Murray A, 2000). Hence, a second-order filter was employed in the designed circuit.

Thus, with the general block diagram and the components outlined above, an overall schematic circuit diagram can be depicted as shown in Fig. 3.6 as follows:

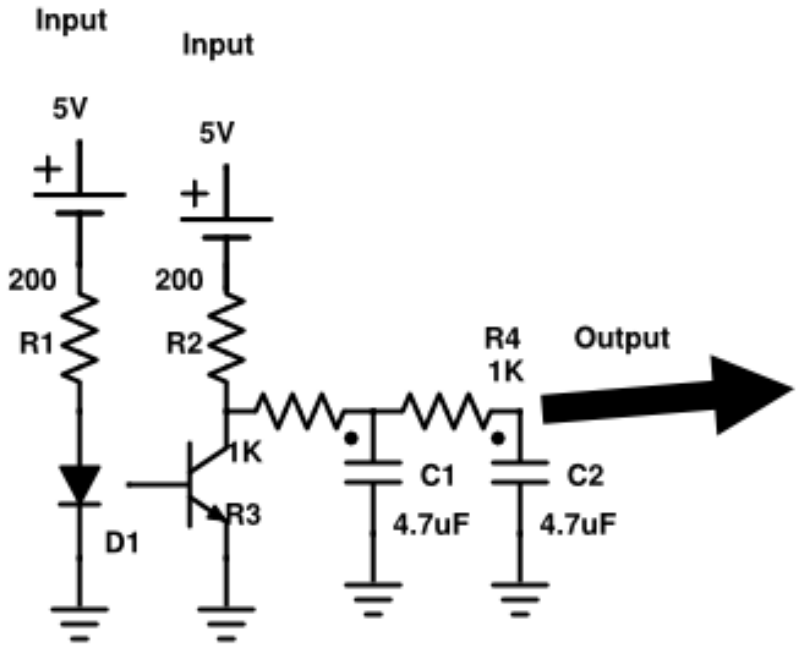

Fig 3.6: Overall schematic circuit design

The resistance values in Fig 3.6 above are in ohms (Ω). The experimental setup was as portrayed below:

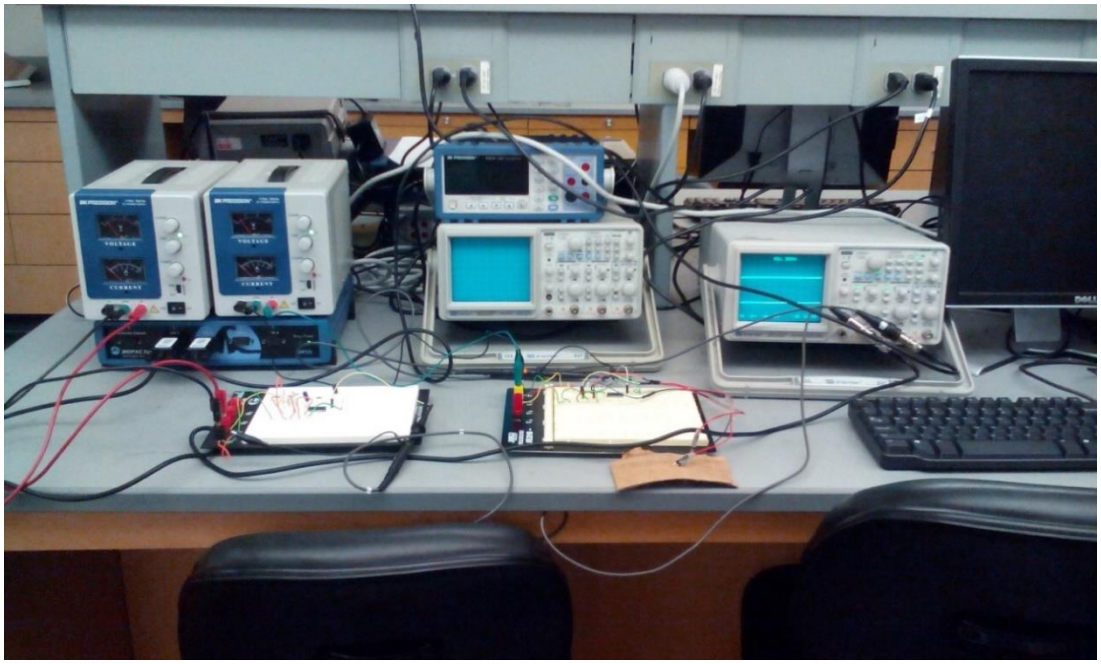

Fig 3.7: Bench-top testing and experimentation with two identically designed PPG (Dual PPG) systems

Here, the circuit in the left portion of the image is the one which was used to obtain PPG signals from the finger artery. On the other hand, the circuit in the right portion of the image was used to obtain PPG signals from the ear lobe artery, the brachial artery and the radial artery. A cardboard cut-out and a black Velcro band were used for fixation and probe support purposes. A similar cardboard cut-out, in the shape of a human ear, was used for ear lobe artery PPG monitoring.

3.2 Software for Signal Acquisition and Analysis

The output signal from the circuit was acquired, processed and analyzed for PWV computation using Biopac®. Biopac® can be easily installed on computers and is readily available in updated versions. It comprises of a data acquisition port and a computer software for analysis called the Biopac Student Lab (BSL) system.

The data acquisition hardware acquires data from external sources using connecting electrodes or transducers. In the PPG monitoring setup, this was accomplished using t-connectors and connecting probes. The BSL system includes in-built universal amplifiers to record and condition electrical signals from different parts of the body (Burgess, et. al. 2003). The acquired data signals have very small amplitudes usually in the range of mV but sometimes can also be in μV. Hence, the BSL system must amplify these signals, filter out unwanted electrical noise and convert them to a set of numbers that the computer can read. These numbers are then displayed as waveforms. The BSL software guides students by sharing onscreen instructions. A detailed lab manual follows the scientific method. Once students have collected data, they use analysis tools to measure the amplitude and frequency, plus a wide range of other values, from the electrical signals (Goodman, et.al. 2005).

3.3 Experimental Aspects

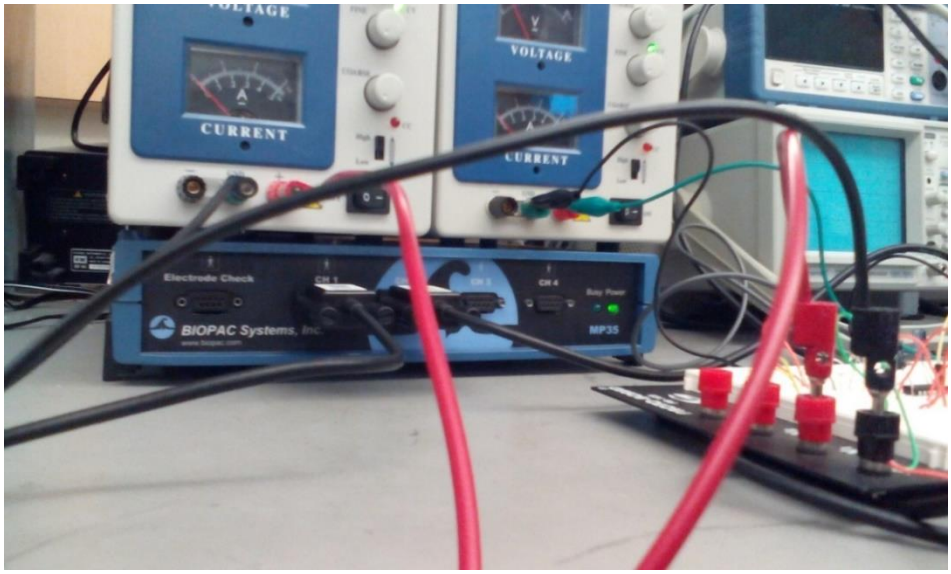

Fig 3.8: Biopac MP36 data acquisition port and its connection with the Dual PPG circuits

As shown in figure 3.8 above, the Biopac MP36 data acquisition port enabled acquisition of data from the two circuits via channel 1 (CH1) and channel 2 (CH2). This is done with the help of connecting probes and a t-connector junction as mentioned earlier.

The steps for data acquisition using Biopac were as follows:

1) The Biopac Student Lab was launched on the computer

2) Create/Record a new experiment was selected

3) Set Up Channels was selected under the MP36 tab on the menu bar of the BSL

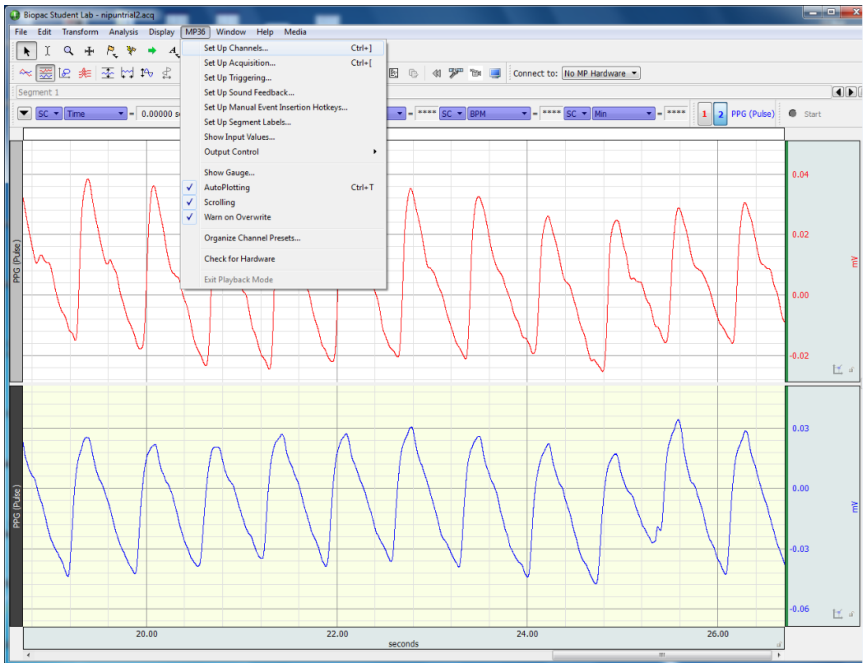

Fig 3.9: BSL settings-Set up channels

4) The two channels (CH1 and CH2) were selected with sampling rates of 2 kHz each. They were labelled as PPG (Pulse). According to the Nyquist theorem (Nyquist, 1928), a sampling rate of around 20 Hz should have been sufficient for this investigation as the highest analog frequency was around 10 Hz. A high sampling rate, such as 2 kHz, was not an issue while using Biopac. However, for a wireless design of this device, and bitrate considerations, a sampling rate of around 20 Hz will have to be used instead. The setup tab on the top right corner was then selected. The channels were autoscaled.

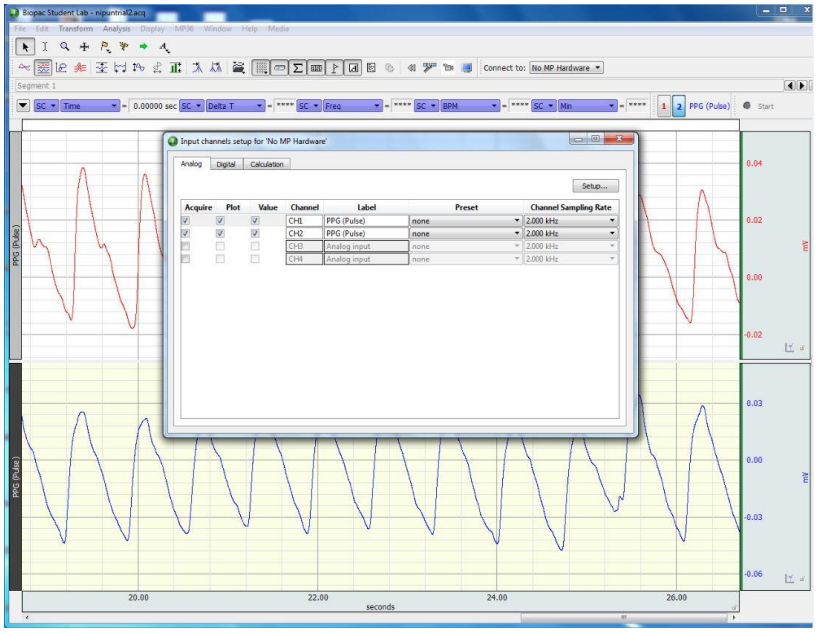

Fig 3.10: BSL settings-Channel selection and sampling rate

5) In this setup tab, digital filters and a gain were applied to the pulse signals (for both CH1 and CH2), the values of which are given in the image below.

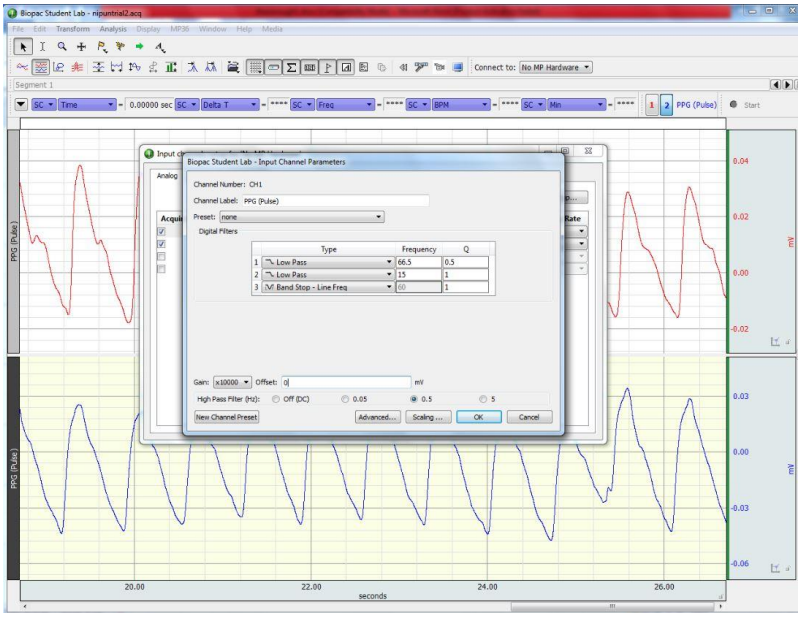

Fig 3.11: BSL settings-Filter and gain selection

6) Next, the MP36 menu was visited again. The Set Up Acquisition option was selected this time.

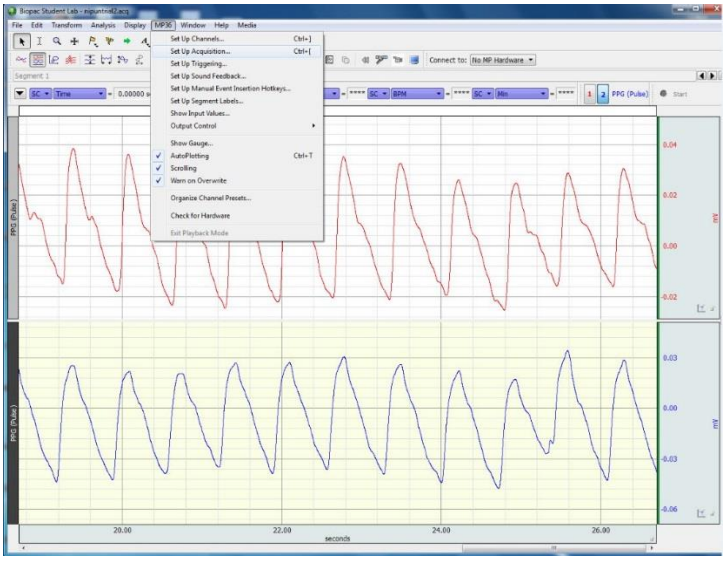

Fig 3.12: BSL settings-Set up acquisition

7) Here, the Acquisition length was fixed to a value as shown below. If there were any changes made in these settings, the Reset button was clicked.

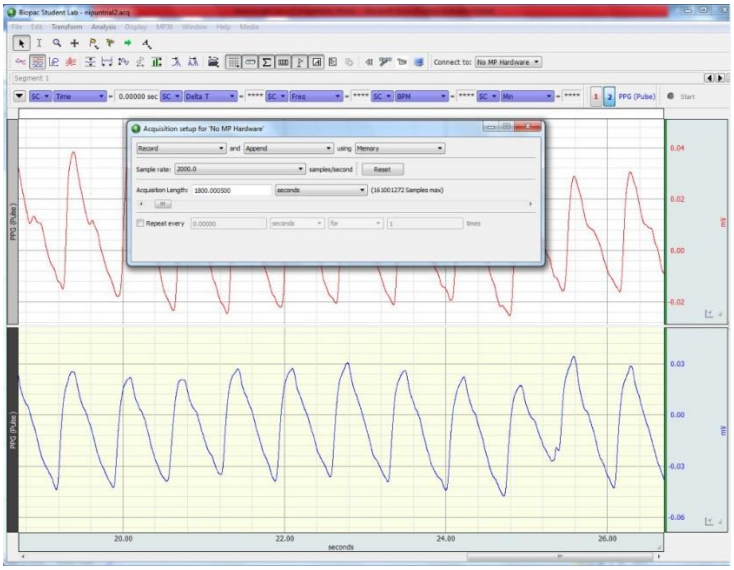

Fig 3.13: BSL settings-Sampling rate and acquisition length

Chapter 4: Results

4.1 Raw Data

Using the designed hardware, Biopac and the data acquisition steps explained in the preceding section, data was ready for analysis and computation. The raw data obtained was as shown below:

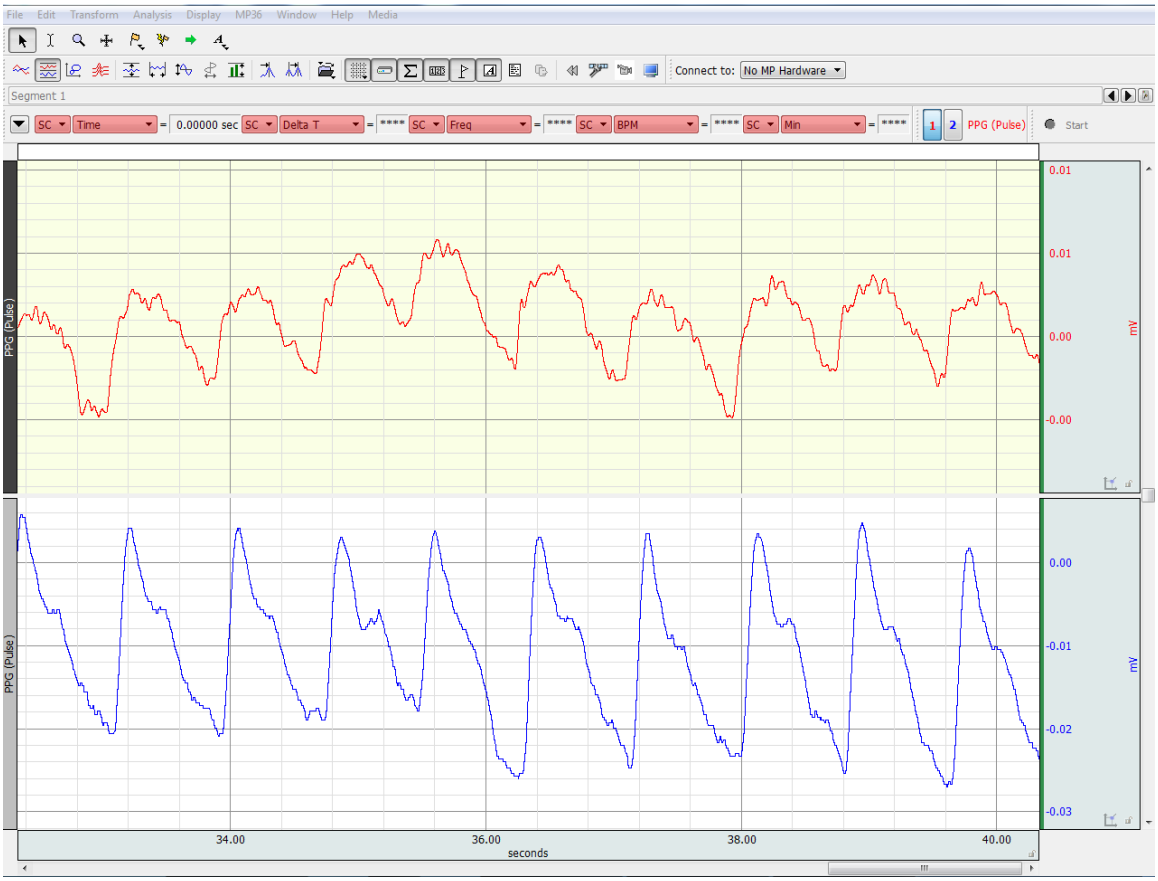

Fig 4.1: Raw PPG data-Red: Ear lobe PPG and Blue: Finger PPG

Figure 4.1 shows the raw PPG data acquired from finger and ear lobe. The pulse in red is from the ear lobe artery while the one in blue is from the finger artery.

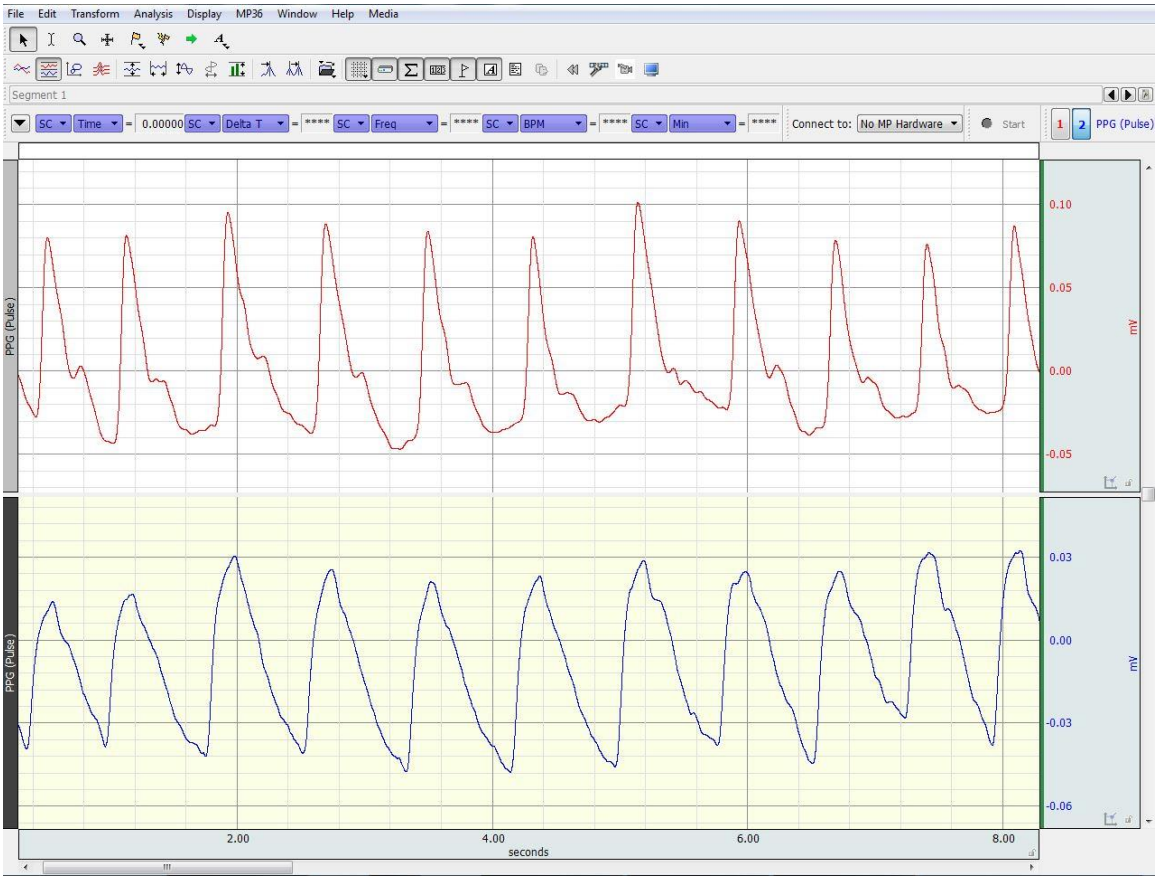

Fig 4.2: Raw PPG data-Red: Finger PPG and Blue: Ear lobe PPG

Figure 4.2 shows another set of raw PPG data acquired from finger and ear lobe. The pulse in red is from the finger artery while the one in blue is from the ear lobe artery.

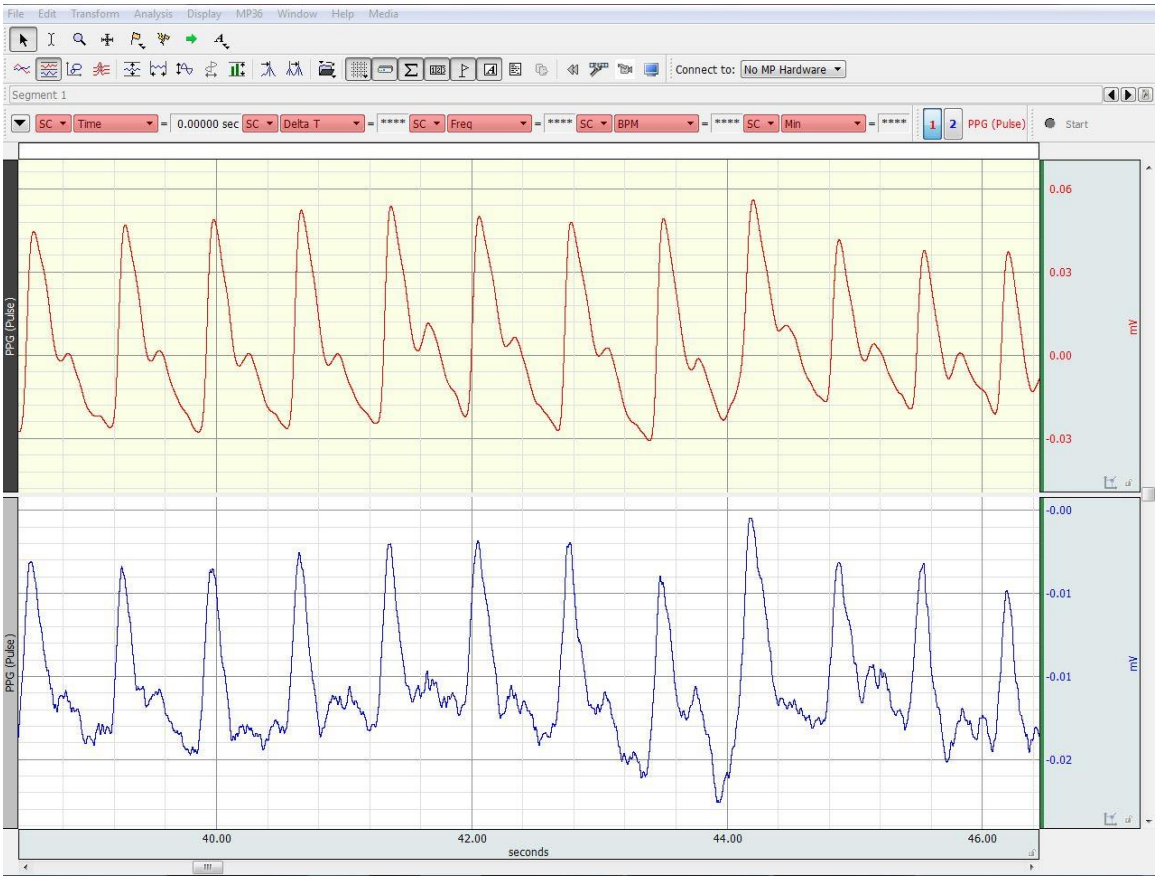

Fig 4.3: Raw PPG data-Red: Finger PPG and Blue: Radial artery PPG

Figure 4.3 above shows raw PPG data obtained from the finger artery and the radial artery at the wrist.

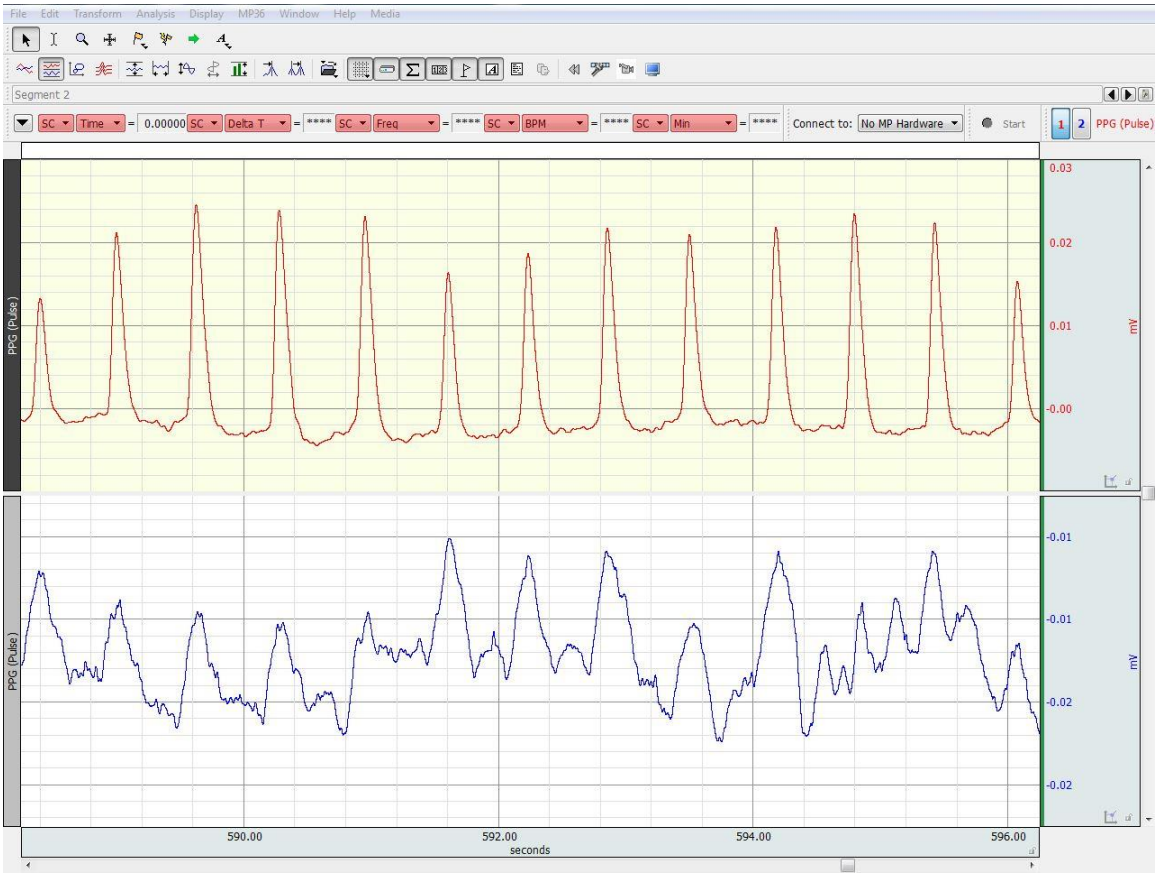

Fig 4.4: Raw PPG data-Red: Finger PPG and Blue: Brachial artery PPG

Similarly, figure 4.4 above shows raw PPG data obtained from the finger artery and the brachial artery at the wrist.

4.2 Case Studies and Analysis

A variety of different signals were obtained in order to accurately assess and confirm the relation between PWV and vascular stiffness.

4.2.1 Measurement at different locations

a) Finger and Wrist

Dual PPG technique was applied to finger and radial artery at the wrist in this case.

Following was the output:

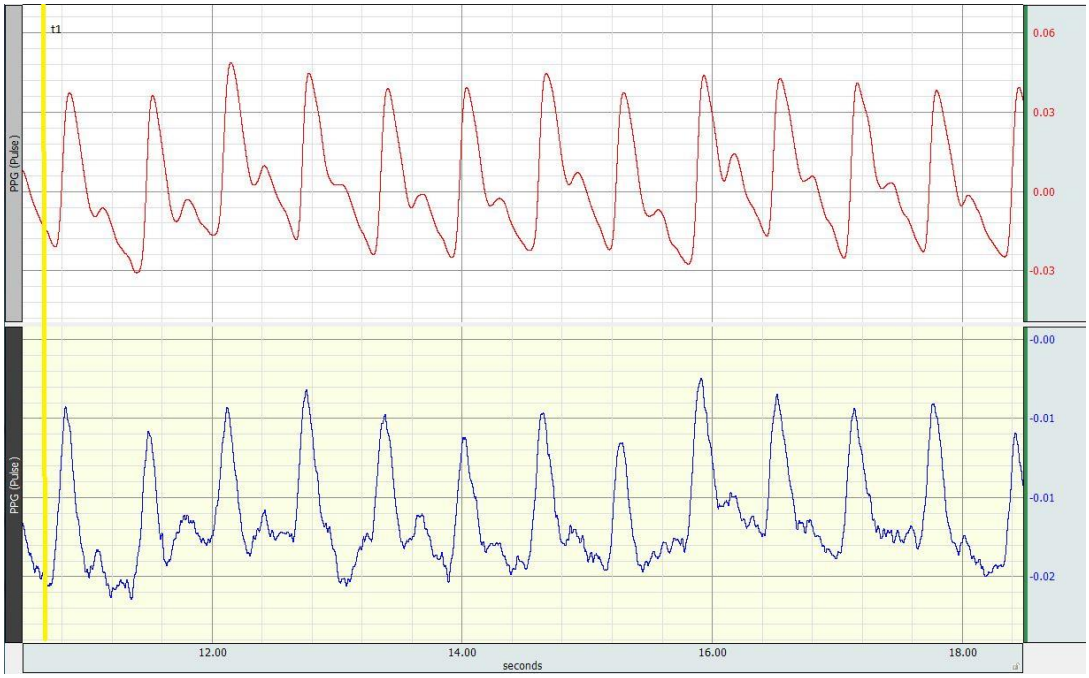

Fig 4.5: Dual PPG at finger and wrist-Red: Finger PPG and Blue: Radial artery PPG

Table 4.1 Results for dual PPG at finger and wrist

Case 1	Finger & Radial					
PTT F (s)	PTT Ra (s)	Delta T	Average	Distance between F and Ra (cm)	PWV (cm/s)	PWV (m/s)
11.3882	11.3386	0.0496	0.06124	18.5	302.0901372	3.0209014
11.9964	11.954	0.0424				
12.6684	12.633	0.0354				
13.2838	13.13	0.1538				
13.9062	13.885	0.0212				
14.5288	14.436	0.0928				
15.1654	15.1158	0.0496				
15.809	15.7666	0.0424				
16.4314	16.37	0.0614				
17.0398	16.976	0.0638				

Thus, for a sample size of 10 in this case, the PWV was calculated to be about 3.021 m/s.

b) Finger and Ear Lobe

Similarly, Dual PPG at finger and ear lobe was as follows:

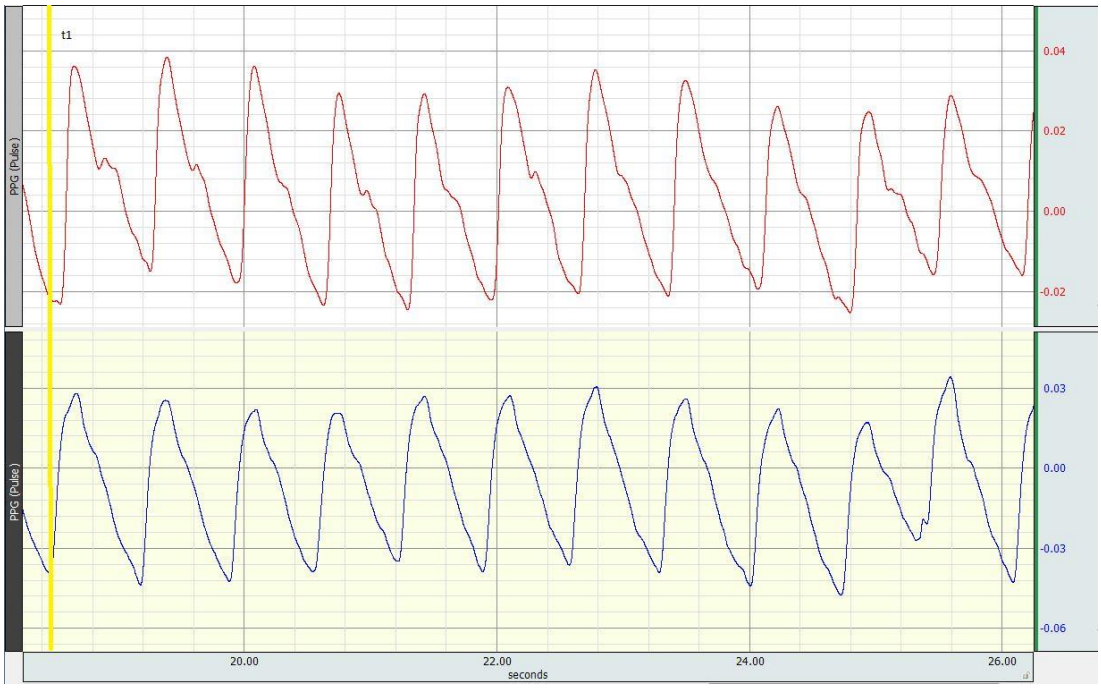

Fig 4.6: Dual PPG at finger and ear lobe-Red: Finger PPG and Blue: Ear lobe artery PPG

Table 4.2 Results for dual PPG at finger and ear lobe

Case 2	Finger & Ear Lobe					
PTT F (s)	PTT EL (s)	Delta T	Average	Distance from aortic arch to F-Distance from aortic arch to Ear lobe (cm)	PWV (cm/s)	PWV (m/s)
19.246	19.1545	0.0915	0.0859	35	407.4505239	4.0745052
19.94	19.869	0.071				
20.612	20.527	0.085				
21.276	21.213	0.063				
21.9485	21.864	0.0845				
22.628	22.55	0.078				
23.3565	23.278	0.0785				
24.0635	23.979	0.0845				
24.792	24.7245	0.0675				
25.45	25.2945	0.1555				

Here, for a sample size of 10, the PWV was computed to be around 4.075 m/s. As mentioned in section 1.4, slight variations in PWV readings occur with change in measurement sites. This was clearly observed in tables 4.1 and 4.2 printed above. However, they are consistent with clinical values and within experimental limitations.

4.2.2 Interventional Variations

Examples of a few interventional variations in PPG have been described in related literature as follows:

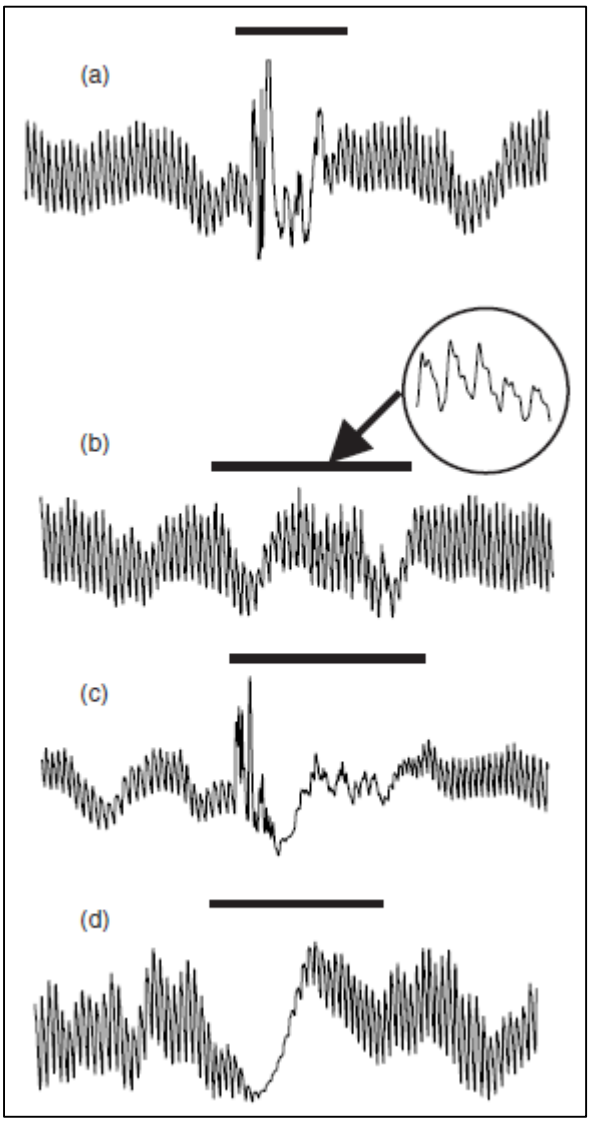

Fig 4.7: PPG data with interventional variations-a) Motion artifact b) Hand/Finger tremors c) Coughing d) Change in breathing pattern *Reproduced with permission from IOP* (Allen JN, 2007)

Recordings were obtained with interventional variations including respiratory changes and motion artifacts. The results of these are given below:

a) Respiratory interventions

For example, holding breath for a few seconds during analysis reduced the amplitude of the signal and showed a longer transit time. Dual PPG at finger and wrist with respiratory intervention can be seen below:

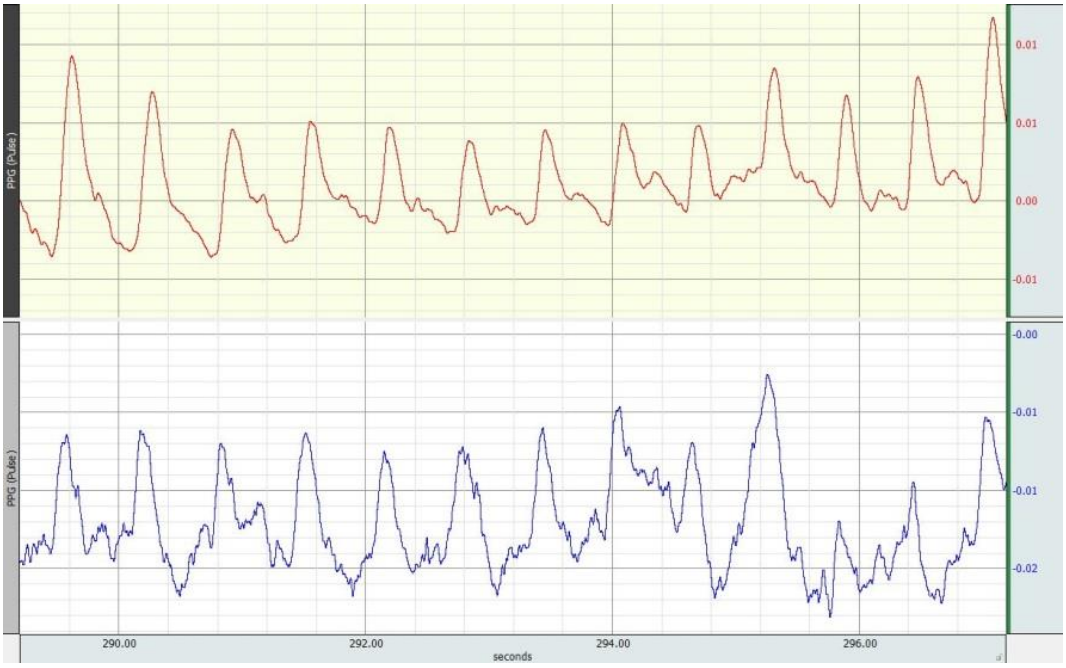

Fig 4.8: PPG data with respiratory intervention of holding breath-Red: Finger PPG and Blue: Radial artery PPG

b) Emotional changes

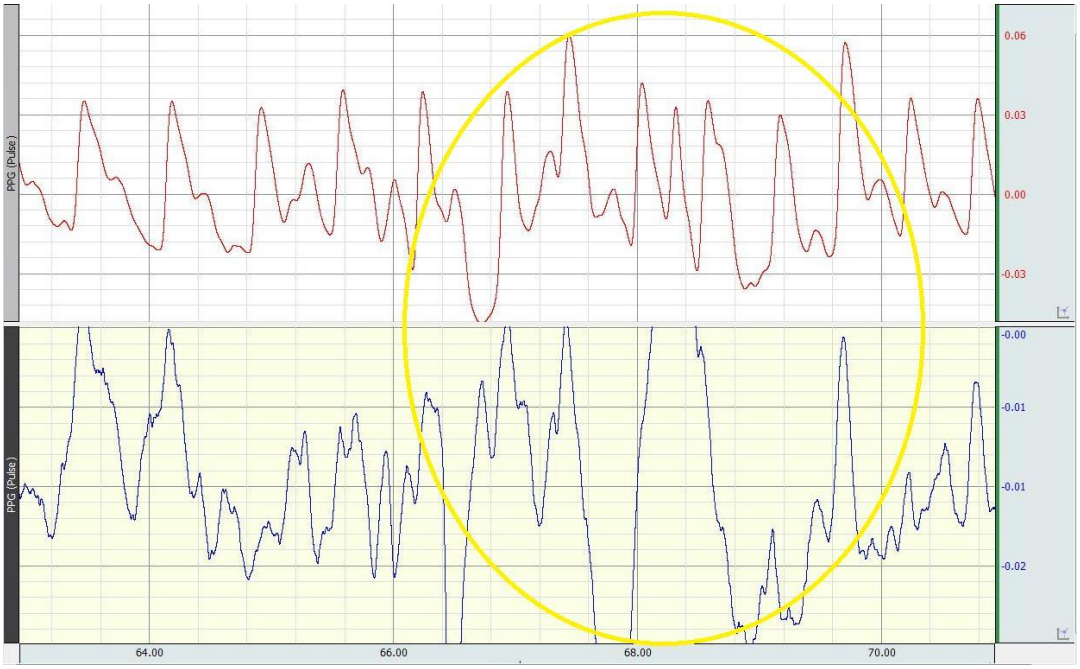

Fig 4.9: PPG data with emotional changes-Red: Finger PPG and Blue: Radial artery PPG

As shown in figure 4.9 above, the Dual PPG at finger and wrist showed an irregular change in pulse pattern due to smiling or laughter of the subject being monitored. This is also the basis for lie-detector tests.

Chapter 5: Discussion

5.1 Limitations

The PPG method described in this paper was not without limitations. This can be analyzed sequentially from component to component involved in this method. Firstly, the consistency of the power supply used is crucial. In a laboratory environment, the adjustable DC voltage supply sufficed for this application. However, in industry, at the time of commercialization (which must be the eventual outcome of such research), it is essential to define a reliable DC battery for consistent voltage supply to this device. Along with accurate battery calculations, Li-ion cell batteries can be used here. Secondly, the matching of wavelength characteristics of the photo transmitter and the photo detector used is absolutely imperative. If unmatched, detection of signals will be impossible, leading to failure of this methodology. With this in mind, the procurement of matched LED and photo-transistor was vital. In relation to photo-transistors used, it was found that their consistency was very troublesome. Also, the advantage of ambient transistors was realized over regular ones. However, while testing the acquired ambient transistors, it was found that consistency of each transistor was questionable with only six to seven working ones out of a total of fifty used in the circuitry. On the other hand, the LEDs used were fairly consistent. Thirdly, during the initial setup, an LM 324 operational amplifier (opamp) was used to amplify the signal. Theoretically, it should have sufficed in amplifying the filtered signal from the ambient transistor to give a clear output signal for processing. However, even upon different amplifier gain combinations, the opamp did not give as clear and amplified an output signal as compared to the output signal given by

the use of a second-order low pass filter. Hence, the opamp was not used in the eventual circuit design.

During data acquisition and analysis, a number of constraints were observed. Motion artifacts and the general awareness of the subject being monitored play a key role in giving accurate signals for analysis. With the light source-detector system being highly sensitive, even small movements of components led to large errors in detected signals. This was not helpful for analysis. Room lighting and available illumination for the setup also play a significant role in accurate data acquisition. As the amount of room lighting was varied, better signals were acquired as the room lighting was decreased. However, an important point to note here is that such effects were more prominently visible while using regular photo-transistors as compared to the ambient ones. This is because, unlike regular transistors, the ambient photo-transistors have very less inherent dark current which helps to reduce the effect of room lighting (or ambient lighting) on detected signals. Also, a black Velcro cuff used for the probe helped to minimize the effect of ambient illumination on readings. The choice of filter cut-off frequency was also found to be fundamental. Excessive filtering distorts the pulse shape whereas too little filtering can result in the DC component dominating over the required AC component. In the experimental setup, Biopac was available for signal processing and analysis. However, the commercialized product will not have the liberty of using Biopac. Hence, the use of microprocessors (such as Arduino boards), which has not been tested and validated yet, could prove to be another begetter of errors. Also, the number of data sets acquired is a major validation factor. In order to accurately validate this method, each case of the case studies should be applied to subjects belonging to different groups (hypotensive, normal,

hypertensive, male, female, etc.). Clearly, the more the number of data sets available, the stronger the validation of use of this method. In addition to the above mentioned potential sources of error, transmission mode PPG was also found to have more restrictions than reflection mode PPG. Thus, PPG configuration used is not trivial while employing this method. The results also substantiated some of these sources of error. Firstly, stability of the design for monitoring PWV at different locations is essential as even a slight movement in placement of the device adversely affects the output signal with noise. This is apparent in figure 5.1 below. Here, the finger artery pulse in blue was steady and hence clearly acquired. However, the brachial artery pulse in red was not clear and was very noisy as the subject's arm was not kept in a steady position and also because the device was not placed firmly on the subject.

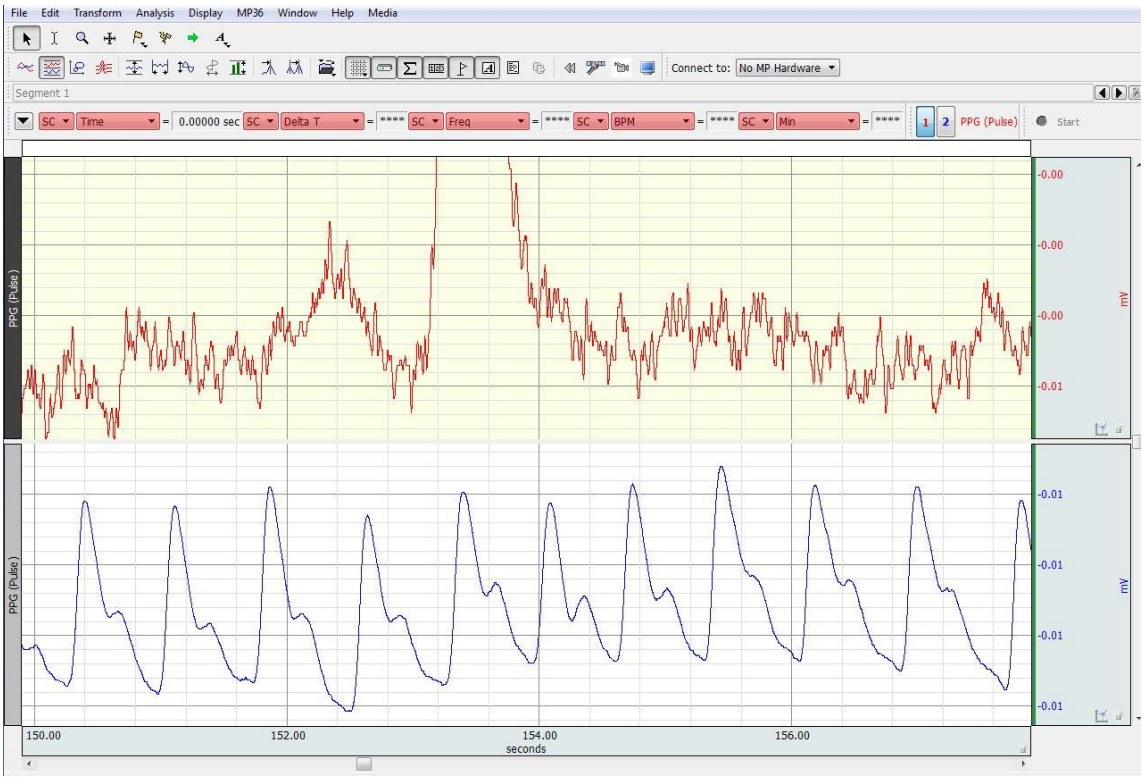

Fig 5.1: Limitation of design instability and resultant noise in acquired PPG-Red: Noisy brachial artery PPG and Blue: Stable finger PPG

5.2 Future Work

While the current method gives meticulous results in computation of PWV using a circuit and Biopac, it can be improved by acquiring more data sets, miniaturizing the circuit, designing a solid housing for the hardware, utilizing a microprocessor with a display screen and comparing the acquired PWV data with blood pressure readings to enable prediction of hypertension continuously. PPG monitoring can be used for other clinical applications as well.

5.2.1 Future designs

The current circuit can be miniaturized using a printed circuit board (PCB) which can be economically designed and printed as a small chip. This can be coupled with a small display screen and a microprocessor for calculating PTT, PWV and displaying it on the screen in m/s. All of this can be easily and cost-effectively accommodated in a wrist band-styled device, the housing of which would have dimensions of 1.25” width x length similar to the length of a wrist watch x height equivalent to the corresponding dimensions of the LED and the transistor so that they fit snugly into it. It would appear similar to a wrist watch. A pair of these devices would be required in tandem to monitor a patient for PWV and with the provision of a user manual showing a table of PWV values and indications for hypertension (Blacher, et. al. 1999), the patient will be able to keep a track of hypertension. Another design which can be utilized is a clip-styled device and a patch-styled device which can be clipped-on to the ear lobe or patched on to the neck for monitoring PWV in the ear lobe artery and the carotid artery respectively. Both of these designs can be implemented using SolidWorks and a 3D printer. Such designs will be more stable than the current one, eliminating artifacts to give accurate PPG signals. Also,

PPG based monitoring is cheaper than ultrasound monitoring making it economical for both commercialization and use (Allen JN, 2007). In addition, vascular stiffness along the conduit arteries being monitored can be accurately located by utilizing the PPG sensors at more than two sites along an arterial pathway. This can help improve the monitoring methodology described in this paper.

5.2.2 Other clinical applications

Monitoring blood pressure

Currently, the PPG technique described in this paper gives us detailed results for tracking PWV and vascular stiffness. However, the ultimate goal of the use of this method should be monitoring of blood pressure of the patients being analyzed. Simultaneous recordings employing both a blood pressure monitor (in mmHg) and a PPG system (for PWV in m/s) of the same subject can help achieve this. This will exactly help relate vascular stiffness and hypertension in a subject in order to facilitate the actual 'monitoring' of hypertension in that subject. Brief tests related to this application were conducted in lab as well. They were brief as the automatic blood pressure monitoring machine used for this purpose started giving error results for heart rate after three readings. However, even though there were only these three readings obtained in relation to this application aspect, they were indicative of the validity of this application. The first two tests herein were conducted on a female subject and the next one was on a male subject. The first test was related to normal resting conditions. In this case, the blood pressure (BP) readings were 111/78 mmHg with heart rate (HR) of 79 beats/min. A corresponding finger PPG signal was acquired here. In test number two, the female subject was asked to hold her breath for a few seconds during measurement. Recordings in this case (with breath held for

those few seconds) showed BP of 90/70 mmHg and an HR of 40 beats/min. The corresponding PPG signal obtained had smaller amplitude values and greater transit time. Test number three involving the male subject in normal resting conditions also showed similar recordings to test number one including BP of 128/85 mmHg, HR of 80 beats/min. and a regular corresponding finger PPG signal. Thus, the data collected herein ratifies this application avenue of the PPG sensor described in this paper. Thus, with more data sets, it will become clearer that the PPG monitoring technique can eventually effectively be used to 'monitor' hypertension in patients.

Venous assessment, assessment of Raynaud's phenomenon, healing potential of tissues and heart rate assessment are a few other applications of this approach. Contour analysis of venous PPG pulses can help in monitoring Chronic Venous Insufficiency (CVI) (Belcaro, et.al. 1998). Raynaud's phenomenon is a condition which adversely affects the blood supply to tips of extremities in extremely frigid regions and also among smokers. Monitoring this phenomenon is also possible using the PPG technique (Allen JN, 2007). PPG can be employed to analyze the healing potential of tissues which is associated with its pulsatile nature i.e. the more pulsatile the PPG signal obtained, the better the healing potential of the tissue being monitored (Lee, et. al. 1979). Also, heart rate of patients can be analyzed by observing their PPG signals. The AC component of the PPG pulse is synchronous with the beating heart and therefore can be a source of heart rate information (Naschitz, et. al. 2004, Payne, et. al. 2006).

In summary, it can safely be said that noninvasive photoplethysmographic monitoring of PWV and vascular stiffness is the technique which can help improve hypertension prediction and, with the required future work, hypertension monitoring as well. This will

enable continuous, noninvasive, low-cost and accurate tracking of hypertension in patients who desperately need such technology for better healthcare.

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