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Model guided improvements in the measurement of continuous non invasive blood pressure

PHD THESIS

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Abstract

Non invasive blood pressure measurement ($NIBP$) is one of the most discussed topics in cardiovascular medicine. Currently, continuous measurement of blood pressure is possible by invasive methods which makes the measurement impractical for the medical doctors and uncomfortable for the patients or it is possible to use special devices which are able to measure blood pressure non invasive continuously but there are still some problems with long time monitoring and comfort for the patient. Each heart ejection gives the blood a pressure force and it creates a pulse wave which travels from the heart to peripheral blood vessels (blood vessel in fingers, toes,...). This pulse wave travels during arterial tree and it depends on arterial properties as elasticity, stiffness or thickness of the artery wall. It will be very useful to describe the relationship between blood pressure, pulse wave propagation in real or very similar conditions as are in real cardiovascular system. It would bring a better knowledge about the behaviour of cardiovascular system and improve approaches to continuous non invasive blood pressure measurement.

Acknowledgement

Foremost, I would like to express my sincere gratitude to my advisors prof. Norbert Noury and doc. Martin Cerny for the continuous support of my Ph.D study and research, for their patience, motivation, enthusiasm, and immense knowledge. Their guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisers and mentors for my Ph.D study.

My sincere thanks go out to all who those have helped me complete this dissertation with whom this project may not have been possible. In particular, I would like to thank my colleagues and friends for some excellent conversations, support, the perceptive comments and their encouragement.

Last but not the least, I would also like to thank my parents and especially my wife for their wise counsel and sympathetic ear. You are always there for me. Finally, there are my five best friends, thank you for standing by me.

Thank you very much, everyone!

Declaration

I declare that my dissertation work of the topic "Model guided improvements in the measurement of continuous non invasive blood pressure" was elaborated independently under the guidance of the dissertation leader and using specialized literature and other information sources, all of which are listed in the literature at the end of the thesis.

In Ostrava on August 15^{th} 2017 .....

Ing. Lukas Peter

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1 Introduction

Contents

The human cardiovascular system is a closed network of blood vessels. This system is one of the most important systems in human body. The world health organization (WHO) defines cardiovascular diseases (CVD) as a group of disorders of the heart and blood vessels. According to the WHO report, $CVDs$ are unfortunately the leading causes of death.

Thus, there are 2 complementary approaches for the evaluation of the functional status of the cardiovascular system. The most immediate method is to monitor the electrical activity of the heart. This is mainly obtained with surface electrodes. (ECG; recordings of body surface potential) which refers the electrical activity of the heart. The normal ECG signal features P wave followed by the QRS complex and T wave successively. The interpretation of the ECG signal is well established for cardiologists to diagnose various heart diseases (e.g., ventricular tachycardia, ventricular fibrillation).

The second approach is to monitor the blood pressure itself, which is the consequence of the electrical activity of the heart. Blood pressure is a key physiological parameter in assessing the circulatory system. It indicates the ability of blood vessels to convert the energy of the blood flow and the force applied by the blood flow through the blood vessels on the arterial walls. On each beat of the heart, the blood is ejected from the ventricle to the aorta. Each ejection puts in motion the volume of blood, which creates a pressure wave travelling from the heart to the peripheral vessels. This pressure wave travels along the arterial tree and its flow depends on arterial properties as elasticity, stiffness or thickness of the artery wall. The dependence of blood pressure on arterial properties makes it a very good indicator of the status of the cardiovascular system. The monitoring of the cardiovascular system is therefore also very important.

Along the vessel pathway, the pressure wave is altered (Fig. 1.1). This is due to a combination of vasomotor tone and peripheral resistance, the ability of store energy of pressure to the blood vessel wall, which is effect of the elastic vessel wall. These lead to different inten-

sity and timing of pulse wave propagation (forward flow) and wave reflection (backward flow) along the pathway [1], [2]. The propagating wave from the ascending aorta overlaps with the reflected wave from the periphery. The central arterial blood pressure (ABP) waveform is hence the summation of the cyclical pressure, the propagated and the reflected pressure waves. This phenomenon also applies to the blood pressure along the rest of the arterial tree and results in different blood pressure wave shapes in different arteries. The blood pressure waveform provides valuable information of the circulatory system of the human body.

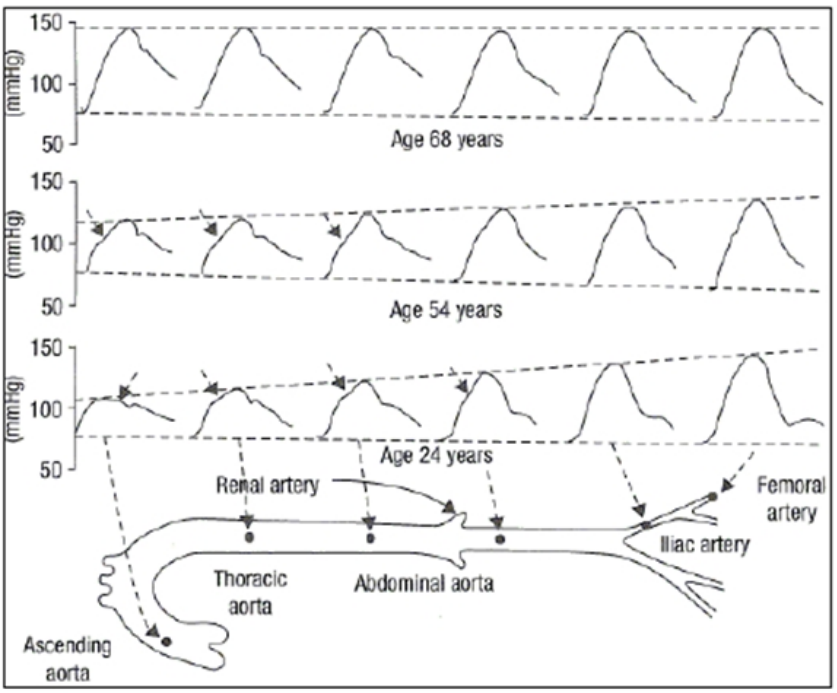

Figure 1.1 Example of modification of blood pressure waveforms while propagating through aorta in different segments of arteries and at 3 different ages.The blood pressure generally increases from central aorta to peripheral segments due to the resistance to blood flow, although this phenomenon is less visible in older subjects while the magnitude of the pressure increases [3].

When talking about non-invasive and continuous measurement methods we mean methods not needing skin penetration and with the possibility to measure blood pressure values on long time periods. There are several approaches to monitor the blood pressure, either continuously or non-continuously, invasively or noninvasively. The standard non invasive and non-continuous blood pressure method is the oscilometric method, which is well suited for ambulatory situations, but only delivers the value of blood pressures at discrete time intervals, typically every 15 minutes. But, as the blood pressure can change more rapidly within minutes, it is sometimes needed to follow it more continuously. The continuous monitoring of blood pressure is mainly achieved through invasive methods (e.g. central pressure catheter). For medical doctors it is necessary to find some method which will measure accurately several parameters of blood pressure (systolic, diastolic, mean blood pressure). Nowadays some methods for continuous non invasive blood pressure measurement exist, each of them have some advantages, but unfortunately also a lot of disadvantages.

There are two possible and clinically used methods for long time non invasive continuous blood pressure monitoring:

Tonometry method The tonometry method is based on applying a controlled force orthogonally to the wall of a superficial artery against a bone.

Volume clamp method This method is still partly occlusive because it uses a small cuff around the finger to maintain constant flow of blood under this cuff during each heartbeat. The device uses an inflatable finger cuff with a built-in photoplethysmography (PPG) sensor and a pressure controller unit placed on the wrist of the arm.

Unfortunately, none of these methods are reliable, accurate and comfortable for patients and adapted for the long time measurement. To ensure a proper and safe measurement of continuous blood pressure wave it is looking for a method which will be **noninvasive, non-occlusive, without supervision, accurate, paintless, comfortable for the patient.**

Possible way how to access blood pressure without using a cuff is to analyse pulse wave which travels the arterial tree. In a non invasive continuous blood pressure monitoring the propagated pulse waves is collected from photoplethysmographic sensors which can be placed at various locations on the surface of the body, although usually on the periphery (fingers, ear lobe or forehead). The amplitude of the pulse wave signal collected from photoplethysmography sensor is non-linearly attenuated due to the elasticity of blood vessel, thus the relationship between attenuation and blood pressure is not straightforward. It is more interesting to investigate the relationship between time propagation of pulse wave and blood pressure value.

Actually, the velocity of pulse pressure waves propagating along the arterial tree depends on the value of blood pressure. Because there is a relationship between pulse wave velocity and blood pressure, there is the same relationship between time of travel and blood pressure which is time of propagation of the pulse wave. The main factors that determine the speed of propagation of the pulse wave, thus, affect timing of propagation, are the elasticity coefficient, the thickness of the arterial wall, the end-diastolic diameter of the vessel lumen and blood density.

Pulse wave which is needed for evaluation of blood pressure is most often measured from the periphery and due to the unique properties of cardiovascular system of each person it is necessary to use equations which includes constants for each person.

The assessment of accuracy depends on many factors, such as the size of the population, the method for signal processing or the reference method for blood pressure measuring (intra artery pressure or auscultatory method). For developing of satisfactory method for non invasive blood pressure measurement ($NIBP$) is it necessary to investigate relationship not only between the propagation of business and blood pressure value, but also between properties of artery system and blood pressure value. Good description of the relationship between properties of artery system and blood pressure value will bring a good background for evaluation of calibration procedure and it helps to improve algorithms for continuous non invasive blood pressure measurement.

1.1 Motivation of Thesis Work

Continuous noninvasive blood pressure measurement devices were developed during the last decade. Nevertheless, the accuracy of these devices has not yet reached the necessary level, since only some of them are clinically validated and most have a questionable accuracy. Pulse wave velocity (PWV) measurement has become broadly used and clinically approved. This method is based on the relationship between blood pressure, properties of the cardiovascular system - mainly the aortic segment - and propagation of the pulse wave through the cardiovascular system.

The evaluation of the relationship between blood pressure value and spreading biological signals through human body was studied experimentally. Unfortunately, up till now there is no satisfactory model for the blood pressure measurement based on pulse wave velocity measurement which can be used in clinical practice. The most successful models are based on Moens-Korteweg equation. This equation is valid only in aortic segment and it is mainly used for the evaluation of some mechanical properties of aorta (elasticity, calcification). Blood pressure as a indicator of risk of cardiovascular diseases is evaluated indirectly.

1.2 Objective of Thesis Work

The main objective of this thesis work is to use analysis propagation and properties of the pulse wave for better prediction of noninvasive continuous blood pressure measurement.

It will be advantageous to make Moesn-Kortewg equation more precise for blood pressure evaluation or to find satisfy and enough accuracy algorithm for noninvasive continuous blood pressure measurement. The following aims detail the main objective:

Background
- To describe the behaviour of the pulse waveform in the human arterial system.
- To provide background in noninvasive blood pressure measurement.
- To verify relationship between propagation of pulse wave and blood pressure value.
- To compare the most common used algorithm for noninvasive blood pressure evaluation.

Developing of physical model of cardiovascular system
- To evaluate all of parts of cardiovascular system.
- To developed and verify physical model of cardiovascular system.

New possible algorithm for noninvasive blood pressure measurement
- To evaluate all of parameters of pulse wave in relationship with hemodynamic parameters.
- To evaluate relationships between pulse wave propagation and blood pressure.
- To describe new possible algorithm for noninvasive blood pressure measurement.
- To compare Moens-Korteweg equation accuracy of alternative algorithm.

Additionally, this thesis work lays the ground work for a future clinical test of the noninvasive blood pressure measurement based on pulse wave propagation.

1.3 Organization of Thesis Work

This thesis consists of 6 chapters.

Chapter 1 describes introduction and the main motivation of this thesis.

Chapter 2 describes our first experiment for the verification of relationship between biological signal propagation and blood pressure. In this chapter we describe the complete measurement setting and developed device which was needed for measurement in clinical conditions.

Chapter 3 presents the current state of the art regarding current knowledge of continuous non-invasive blood pressure measurement. The techniques utilized in non-invasive BP measurement are analysed and compared, referring advantages and disadvantages of those methods.

Chapter 4 investigates and compare the most common algorithms for blood pressure evaluation based on PWV measurement. In this chapter we describe signal analysis of real measured signal from human body and we evaluate the accuracy of measurement. There is also used and compare method of forward and backward pulse wave evaluation. Time delay between forward and backward pulse wave seems to be the main parameter which affecting the accuracy of continuous noninvasive blood pressure measurement.

Chapter 5 describes the settings of physiological model of cardiovascular system which we developed for measurement of pulse wave velocity in vitro but in conditions close to real cardiovascular system. Thanks to this model it is possible to adjust each individual hemodynamics parameters and monitor theirs effects on blood pressure. In this chapter is also described the analysis of measured signals thanks to the physiological model and proposed new algorithm for continuous noninvasive blood pressure measurement.

Chapter 6 is a conclusion of this dissertation thesis with propositions for the future work.

2

Hemodynamics of Arterial System

Contents

The circulatory system provides various organs and tissues with oxygen and nutrition which are essential to metabolism, and the system disposes carbon dioxide and wastes as well. Especially, arterial blood delivers oxygen and nutrition, and its flow is driven by arterial blood pressure (ABP) exerted by the contraction of the left ventricle. The relationship between the blood flow and the pressure is very complex and also highly dependent on the mechanics of vascular structures.

The aorta and large blood vessel have passive function to transfer oxygenated blood from the heart to the periphery, but also ability to depreciate left ventricular stroke volume thanks to viscoelastic properties. Such blood vessels have the task of damping the pulsatile output of the left ventricle and of converting the rhythmic, intermittent and discontinuous activity of the heart into a continuous one. After the stroke volume when blood is ejected into the aorta and the closure of the aortic valve, a large quantity of blood (compare to volume of aorta) has to be stored up in the aorta and the large arteries and to be further released (Windkessel effect) so that proper pressure values are maintained in diastole.

In diastole, when the aortic valve is closed, the aorta which has been filled by the blood, tends to its basal state, which assures blood movement also during diastole. The reason is that potential energy which was stored in the artery walls in systole turns into kinetic energy in diastole. The aorta is acting as a second pump at diastole which is known as the Windkessel effect.

The viscoelastic properties of the large blood vessels depend on the main components of the arterial wall, such are elastin, collagen and smooth muscle. The state and anatomical properties of the arterial wall affect ability to store potential energy of the blood pressure. Under viscoelastic

conditions, the amount of the stroke volume that is stored by the aorta during a systole and continuous into the periphery changes blood pressure value. With a higher stiffness of artery wall the stroke volume is pushed directly to the periphery and the propulsive effect in diastole is reduced. This phenomenon increases the systolic blood pressure, decreases diastolic pressure and increases pulse pressure. An increase in vascular resistance, results in increased systolic and diatoslic pressure values [4].

If cardiovascular is analysed it could be seen, that blood pressure is affected by two distinct but interdependent components.

- A constant component as a mean arterial pressure which depends on **heart rate, stroke volume and systemic vascular resistance**.
- A pulsatile component as a pulse pressure which depends on **the blood pressure wave propagation in both of direction - forward wave and also reflected wave**.

The mechanical properties of arteries can be measured starting from the volume/pressure of an isolated arterial segment. From a general point of view, the mechanical properties of a blood vessel are not linear. They depend on the pressure and on the way, how they are measured. The main property which affects blood pressure and pulse wave propagation is compliance

2.1 Blood flow

Basically the flow (Q) of liquid along the entire rigid tube is given as:

$$Q = A\bar{v} \tag{2.1}$$

Where $\bar{v}$ is the average flow velocity over the ctoss-section of the tube (area A). Therefore the important property of fluid is viscosity originated from shear stress between layers of fluid each of which moves at different velocity. The viscosity (μ) is in relationship with share stress (τ) and shear deformation ($\frac{v}{y}$) which can be also written as a shear velocity ($\frac{dv}{dy}$) as [4], [5]:

$$\tau = \mu \frac{dv}{dy} \tag{2.2}$$

Where shear stress can be also describe as a force (F) per unit area (A):

$$\tau = \frac{F}{A}$$

Because of the viscosity of the fluid and the friction from the tube's wall, a velocity profile of the liquid flow develops to balance the sheer stress with a driving force. In constant laminar flow, the velocity profile ($v(r)$) becomes parabolic and its profile is expressed as:

$$v(r) = v_{max}(1 - \frac{r}{R}^2) \tag{2.3}$$

Where r is the radius from the axis, v_{max} is the maximum velocity, and R is the inner radius of the tube [4].

2.2 Pulse Wave

With each systole the heart ejects some volume of blood, approximately 60 to 100 ml, into the aorta which is filled whit this volume of blood at a approximate pressure 10 kPa (75 mmHg). It affects the pulse wave and its propagation. Pulse wave is spread through arterial system into a pressure wave which based on contraction of blood vessel is then converted into a volume wave (Fig. 2.1).

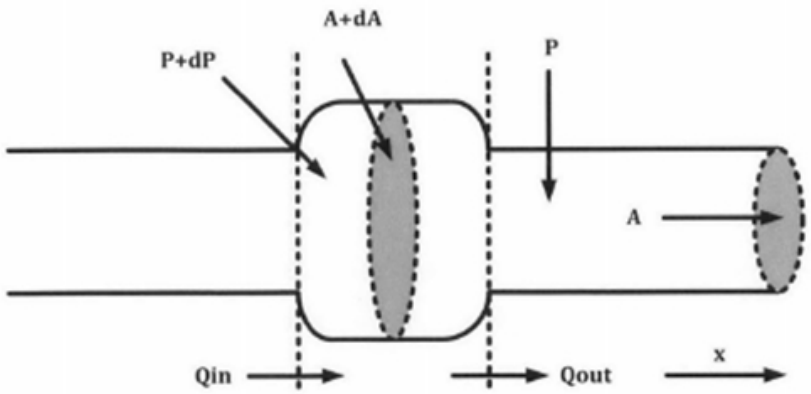

Figure 2.1 Schematic of a pulse wave propagation in elastic tube. It can be seen that the pressure gradient is the function of a longitudinal dimension, the acceleration of the fluid is also the function of a longitudinal dimension, thus causing the flow gradient.

The consequence of the flow gradient is the change of the cross-sectional area by radially expanding the elastic tube under the effect of the pressure, and it is expressed in a continuity based on the equation 2.4.

$$\frac{dQ}{dx} = \frac{dV}{dt} = \frac{dV}{dP}\frac{dP}{dt} \tag{2.4}$$

Where dQ is change in blood flow, dV is change in volume of the vessel and dP is change of pressure because of change of volume (dV). The compliance (C) of the blood vessel is defined as:

$$C = \frac{dV}{dP} \tag{2.5}$$

Compliance represents the change in diameter or in section (the volume) of the artery, at a given pressure level, for a given arterial length. Compliance is the ratio between the change in volume and change in pressure. If there is a good arterial elasticity, small change in pressure results in a significant change in volume [4].

The inverse value of compliance is defined as a coefficient of volume expansion E.

$$E = \frac{dP}{dV} \tag{2.6}$$

It is defined for the vessel in which the circular cross section is assumed to be the ratio of the pressure change dP to volume change dV. Because of the modulus of volume expansion, the blood vessel is able to expand or contract in response to internal pressure change. If there is change in volume of blood push to the blood vessel, blood pressure is also modified accordingly.

Blood flow (cm/s) varies during each cardiac cycle as same as velocity of pulse wave (m/s). A longitudinal pressure wave is launched which turns into a volumetric wave due to vascular expansion. If then the stretching of the vessels was linear in all places, these two waves would equal themselves. The velocity of pressure waves is about $3 - 6m/s$ and are much higher than the blood flow rate that is directly depending on the contraction force of the heart and on the resistance of the vascular bed. The process of the wave is possible to feel as a pulse, as it acts by stretching the wall of the blood vessels, due to the volumetric wave. The volumetric wave can be recorded from the surface of the body with non-invasive plethysmography method. The disadvantage is that the volume wave does not exactly match the pressure wave as a result non-linear vascular extensibility. The pressure wave can only be measured by an invasive method, that is introducing the catheter into the artery [4].

The pressure wave changes during the process by the vascular system. The blood pressure will not only depend on cardiac contraction of the left atrium, but also on elasticity of blood vessels, blood flow, blood vessel resistance and forward and backward pulse wave propagation.

2.3 Reflected Waves

The existence of reflected waves is typical of any hydromechanical system. In cardiovascular system reflected waves appear due to:

- Arterial bifurcation
- Arterial narrowing or bifurcation
- Arterioles (which define the systemic resistance)

At any places where a reflected wave occur , forward pulse wave is divided minimal into two single waves (**continued forward wave and backward wave**). The pressure waveform analysis depends on the relationship between the superposition of the forward and backward pressure waves (Fig. 2.2), the latter arising thanks to reflection of forward wave from the division of artery, and its shape is affected by elasticity of blood vessel. Decrease of stiffness of artery makes the forward wave smaller and backward wave bigger and vice versa.

A backward wave is travelling back to the heart and superimpose the forward wave. In periphery peak is affected by backward wave which affects the systolic blood pressure. In the ascending aorta, if the viscoelastic properties are not deteriorated, the systolic value isn't affected by backward wave and backward wave do not change a systolic value. Backward wave affects

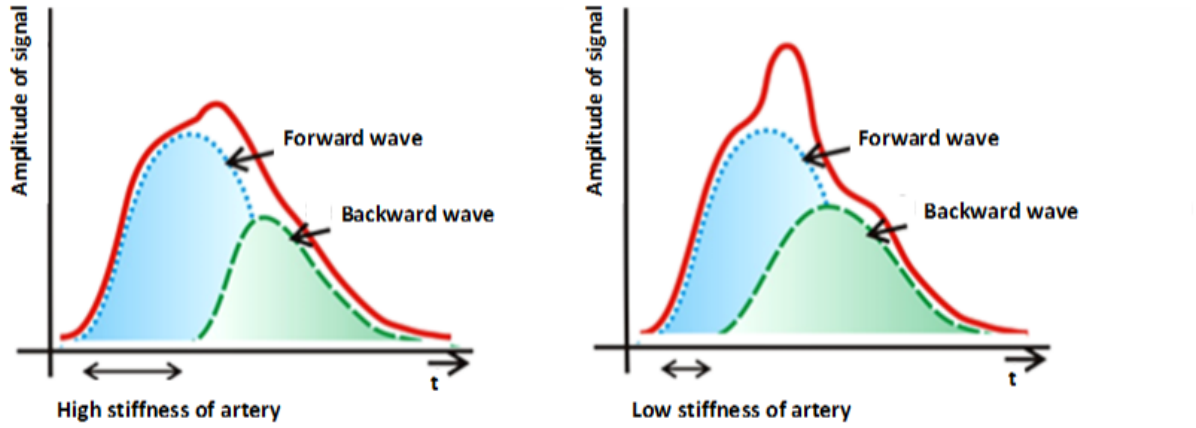

Figure 2.2 Comparison of the shape of pulse wave based on stiffness of artery. Higher stiffness leads to faster waves and faster backward wave which makes blood pressure higher (right figure). Low stiffness leads to a slower backward (left figure) and positively affects blood flow.

diastolic time. Based on this phenomenon it can be understood that central systolic pressure value is lower compare to periphery.

$$Periphery\ ressure\ wave = forward\ wave + backward\ wave$$

$$Central\ pressure\ wave = forward\ wave$$

The factors which affect central blood pressure and pressure amplification phenomenon are **the viscoelastic properties of the large arteries, the propagation of pulse wave, magnitude and variability in reflected waves, length of the aorta, heart rate and the attenuation phenomenon of pressure wave**.

It is possible to measure the propagation of pulse wave by non-invasive methods such photoplethysmography and standard ECG measurement and compare it with non-invasive blood pressure which is mainly measured in discrete time. However in this case it isn't possible to evaluate relation ship for continuous blood pressure monitoring. To investigate the relationship between instantaneous values of blood pressure and propagation time of pulse wave we developed a measurement set up and performed first experiment. Our experimental set up allowed us to measure continuous invasive blood pressure signal, standard ECG signal and pulse wave. It was preliminary evaluated relationship between blood pressure and pulse wave propagation to verify if pulse wave analysis can be potentially used for continuous non-invasive blood pressure measurement.

2.4 Preliminary Experiment

Nowadays is continuous measurement of blood pressure measured mainly by invasive sensors, which is uncomfortable for the patient and like any invasive procedures present some risks. There exists no reliable system enabling non-invasive continuous measurement of blood pressure

($CNIBP$) without limiting the monitored person during common daily activities but they have still some problems with comfort for patients.

Blood pressure value is connected to electrical and mechanical heart functions, condition of vascular system and propagation of biosignals, which are possible to measure without limiting the persons during common daily activities. Clinicians work closely together with engineers to elaborate a reliable, accurate and non-invasive method which would be comfortable for the patient to improve the early detection of symptoms of cardiovascular disorders, and then undertake rapid remedial action for the latent anticipation of sudden cardiac arrest for example [4].

Monitoring and analysing of pulse wave seems to be a promising method to achieve this goal. Parameters of pulse wave provide relevant information about heart rate and also about the good functioning of heart thanks to the information about start and end of systole and, what is very important, information about pulse wave velocity (PWV) and pulse transit time (PTT). PWV and PTT could be used for the evaluation of the stiffness of blood vessel or for the continuous monitoring of blood pressure which is a complex indicator about state of cardiovascular system.

2.4.1 Motivation

The aim of this experiment was to preliminary determine the dependency of the pulse wave propagation on blood pressure. Pulse wave results from the contraction of the left part of heart. A single pulse wave is generated during each cardiac cycle. The cardiac cycle can be defined as the interval between two successive systoles. Most of the time, pulse wave is detected from periphery like fingertip or from places showing good blood perfusion like ear lobe, nose or forehead. This measurement is non-invasive and relatively comfortable for the patient. This is why the diagnostic methods based on processing of pulse wave could end up being a good candidate for the prevention of cardiovascular failure.

In this experiment is pulse wave propagation describe as PTT. Often is PTT described as time in which pulse wave gets from the heart to other places in vascular system. The PTT value at one place is dependent on the parameters of the blood vessels such as elasticity, vascular tissue thickness, vessel diameter and blood pressure value. There are more ways to detect PTT. One of them is to measure the time delay between R-wave from ECG recording and the initial point of pulse wave in same cardio cycle. These parameters can easily be acquired from commonly measured biosignals (ECG and PPG, Fig. 2.3). The sensors for measuring these biosignals are small in size, they are easy to firmly attach to the patient's body and do not bother the patient. Blood pressure measurement using the measurement of PTT is therefore the least demanding for the necessary measurement of biosignals and also the least uncomfortable for the patient.

First experiment was performed in 2013 in Hospital *Nemocnice Podlesi s.r.o. Trinec*[1] and involved one patient. We measured invasive blood pressure wave as a reference value, ECG and PPG. Patient was lying and in the rest. It was measured 5 min time interval. It was evaluated PTT, systolic and diastolic blood pressure value in each cardiac cycle.

[1] http://nemocnicepodlesi.agel.cz/index.html

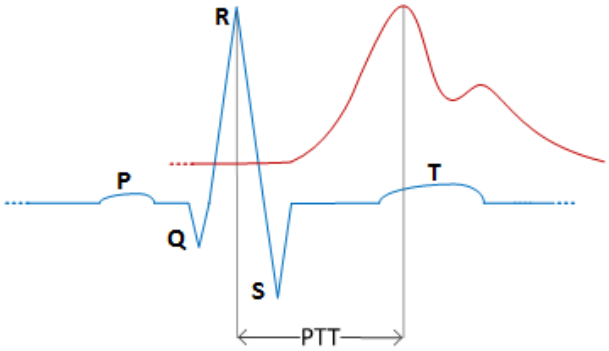

Figure 2.3 Evaluation of pulse transit time as time delay between ECG R-wave and peak of pulse wave.

2.4.2 Current State of CNIBP method

The method of $CNIBP$ measurement based on PTT is described in many scientific papers [6], [7], [8]. There exists several ways to assess blood pressure value that are based on PTT. The blood pressure evaluation using PTT is dependent on the method of taking reference value for blood pressure. Most of literature dealing with the given problem were always conducted as ECG and PPG measurements for PTT evaluation and $CNIBP$ measurement. There exist only few clinical studies, in which central blood pressure was simultaneously measured in invasive way, however this studies dealt mainly with hemodynamic parameters of cardiovascular system

The most common algorithms describing evaluation of BP based on PTT will be more precisely described in Chapter 3. These algorithms are always dependent on constants describing hemodynamic properties of the cardiovascular system.

$$P = \frac{1}{0.7}(\frac{1}{2}\rho\frac{d^2}{PTT} + h\rho g) = \frac{A}{PTT^2} + B \tag{2.7}$$

$$\Delta P = \frac{2}{T_\gamma} + PTT \tag{2.8}$$

$$BP = aPTT + b \tag{2.9}$$

Where T_γ in the first formula and A, B in the second and third formula are characteristics of the cardiovascular system which are specific to each patient. Unfortunately they are not clearly described in the literature and their determination is also unclear.

The hemodynamic properties of the cardiovascular system will differ with each monitored person and therefore it will be very difficult to determine their general evaluation. The algorithms used so far for evaluating the blood pressure based on PTT were always acquired by correlation with the value of non-invasive blood pressure using oscillometric, sphygmomanometric method as reference value of BP or using the continuous blood pressure measurement based on Penaz's method. All the measurements so far have been performed on the patients without cardiovascular problems and therefore the results cannot be considered general and suitable for all kinds of

patients. It is necessary to correlate the acquired PTT value with the more accurate value of blood pressure, i.e. the value of blood pressure measured invasively in order to get more accurate results.

2.4.3 The Measurement procedure

PTT is acquired as the time delay between R-wave from ECG recording and the initial point of pulse wave in same cardiac cycle. We continuously monitored the blood pressure to have a reference value. Invasive blood pressure measurement was performed under supervision of a specialist M.D. because the patient was catheterised during the measurement.

We developed a specific hardware with individual sensors and probes collecting electrical and nonelectrical signals on the body of the patient (ECG, PPG and BP, Fig. 2.4) and also our own embedded software for acquiring, displaying and saving the data.

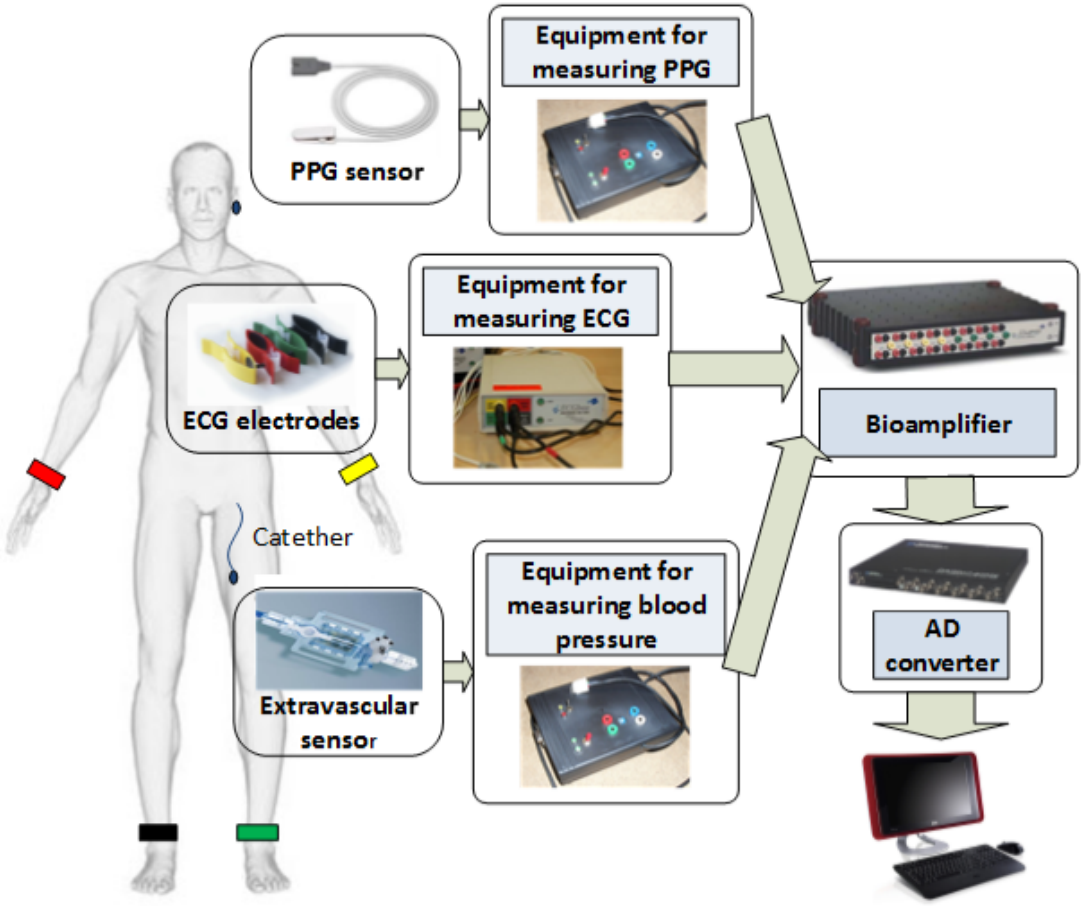

Figure 2.4 Measuring chain. PPG was measured from ear lobe and index finger. It was measured standard one leads ECG and invasive blood pressure wave. Signals were measured with our own developed hardware was connected to a bioamplifier and NI measuring board.

Signals from ECG, PPG and blood pressure wave were recorded at 8 min intervals. Central blood pressure was measured from a catheter introduced at the femoral artery. At the end of the catheter extravascular sensor was attached. 4-lead ECG was measured from the chest. PPG

pulse wave was measured using the sensor at the left ear lobe.

2.4.4 Developed hardware

ECG Signals of electrical activity of the heart were collected with g.ECGbox, which was compatible to the used amplifier. Thanks to this equipment 4 electrodes placed on the patient's chest are sufficient for ECG sensing. The ECG recording was taken from standard Einthoven bipolar leads.

PPG A specific measurement equipment was designed for collecting the photoplethysmography signal from an ear lobe and index finger. The equipment was constructed for universal taking of PPG wave at various parts of the body using a sensor with a standard connector.

The whole equipment was powered by two 9 V batteries so it was not necessary to galvanically isolate the power supply from the patient's circuit.

BP Blood pressure was measured invasively with an extravascular sensor (DPT-6100[2], Fig. 2.5) placed on the extremity of a catheter. This sensor uses a Wheatson resistance bridge and is always connected directly into the monitoring equipment. It was necessary to create hardware interface for measuring the signals at resistance bridge and its consequent connection to AD converter.

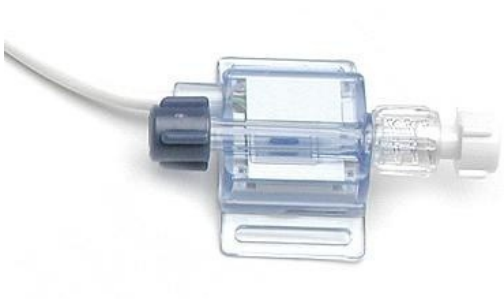

Figure 2.5 Extravascular sensor for blood pressure measurement. This sensor is connected to the catheter which used for invasive monitoring of central blood pressure.

Because the measurement at the resistance bridge is performed in a differential way, it was necessary to reference the signal to the ground. At this step a differential instrumentation amplifier (INA126, Texas Instruments) was used. This amplifier was powered by symmetric voltage. Signal from the resistor bridge was brought to input terminals of the amplifier and the amplified difference at output is referenced to the ground.

It was necessary to insure stable and accurate power supply of the resistance bridge in order to measure the blood pressure precisely because of sensitivity of extravascular pressure sensor 5 $\mu V/V/mmHg$. This power supply was provided by a stabiliser mode from stabilizing diode TL431, which is characteristic by its temperature stability, by which it insures stability of power supply and at the same time it was possible to alter the voltage to a small extent.

[2]https://www.codan.de (2013)

After connecting the sensor it was necessary to calibrate it on an acquired pressure value. This calibration was achieved using a laboratory calibrating device when the acquired pressure value was set and then the voltage coming from chain measuring equipment for measuring blood pressure was subtracted.

Bioamplifier Bioamplifier Bsamp by g.TEC was used during measurement. This amplifier has 16 input channels. Individual channel groups previously configured for measuring biosignals. On the back panel of the model DIP switches for hardware filters of Butterworth type are placed. Filter low pass 200 Hz and high pass 0.5 Hz were set for measuring. A band removal filter centred on the 50 Hz frequency is directly implemented into the amplifier. The settings was same for filters all of measuring channels same. This amplifier insures separation of the sources of signal, i.e. the monitored person from other electronic sources. It was therefore suitable for measuring signals from the human body and certified by manufacturer for measuring biological signals.

AD converter Since the central idea of cufless non invasive methods is based on analysis of transit time of individual variables, synchronisation of each measurements is very important. Therefore individual signal routes in the measurement set up were tested and signal transit times in individual channels of A/D converter were analysed (Fig. 2.6).

Input sensitivity of individual channels is relatively high ($\pm\,10\,V$). Hence a laboratory signal generator was used as a source of signals. The parameters of the tested signal were chosen so as to be very close to actual signals from patients' bodies. A signal at 4 Vpp amplitude, with a repeating frequency 1 Hz and a pulse width of 20 % was brought to all the 16 input terminals at once. From the measured data it was observed that the delay time between the individual channels is undetectable with the chosen signal. The signal was measured with an accuracy of 100 μs. The same results were achieved with a signal of repeating frequency of 10 kHz. The signal was sampled at 1 kHz frequency.

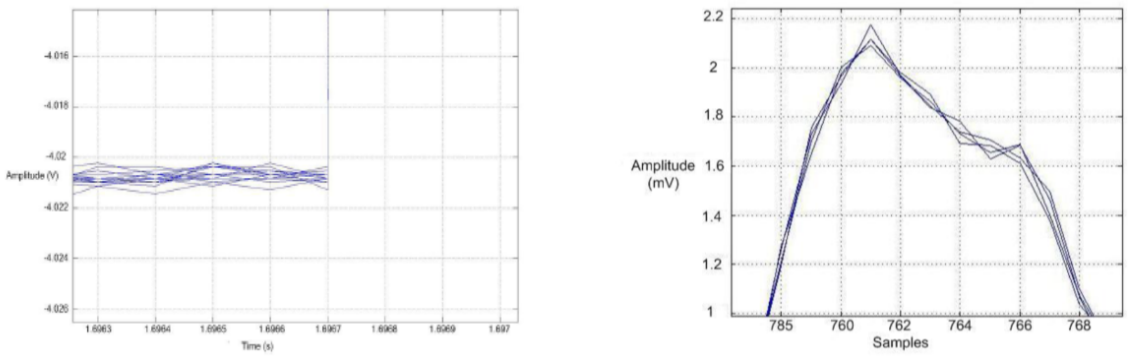

Figure 2.6 Detail of synchronization measurement of all of channels. The left picture is showing synchronization of signals for AD converter. The right picture is showing detail of simulated signal for R-wave for all of channels. There is non significant time difference between channels.

2.4.5 Developed software

The measurement software was developed in LabView environment and it could be divided into two parts:

- A part for acquiring and saving of data
- A part for data processing and evaluation

Acquiring and saving of data In the part for signal reception ii was possible to set the measuring channel of the AD converter, to choose sampling frequency, speed of data drawing and a buffer size. The whole software was primarily designated for saving measured data for consequent processing but nonetheless it is also equipped by a visualisation part, which contains simple filtering of the received signals which are consequently displayed on a monitor.

Because of blood pressure calibration the signal from a pressure sensor is processed entirely separately. For blood pressure measurement it is necessary to use zero adjust. In the moment when the sensor is connected to the applied catheter it is necessary to subtract the immediate voltage value. This value is generated on the sensor before opening of a "three-way valve" (this valve is used for connection of sensor to physiological solution for cleaning of catheter or connection of other liquid) which the sensor is equipped, and it corresponds to absolute pressure.

Signal processing of measured data Acquired signals were saved for off-line analysis. The data were saved into .txt format. Although the text format is the least suitable for saving data because the final document is very large (each 10 minutes approximately 50 MB) it was chosen for a clearer check of the data when displayed in a notepad. The program is also ready to save the data in a binary code.

Signal processing consisted from filtering and modify of signal and from detection of significant points important for evaluation of PTT. It was necessary to use FIR filters, which are stable and do not change the phase of the filtered signal (because the time delays between individual signals were analysed). For each signal was used the same filter settings only the filtered frequency was different. Just signal signal from the pressure sensor was filtered by a simple filter for medium values.

Cut of frequency 30 Hz of low pass filer was used for filtration of ECG signal. For filtration of PPG signal was used cut of frequency 15 Hz. The values of the cut of frequencies were set so as to avoid filtering out the needed frequencies, i.e. 8–22 Hz for QRS and 0.5–15 Hz for PPG.

The programme is created mainly for detection of significant features of individual signals, the R-wave of ECG signal, the peaks of PPG signal and the peaks of blood pressure wave (Fig. 2.7). Wavelet transformation was used to detect the R-wave of ECG signal. Filter Daubechies 4 was chosen as the most suitable decomposition filter used for WT in the detector.

2.4.6 The measurement settings

The biosignals were collected from one person (Male, 62 years old). The patient was still under anaesthesia, was included immediately after the angiography procedure, his pulse, which was

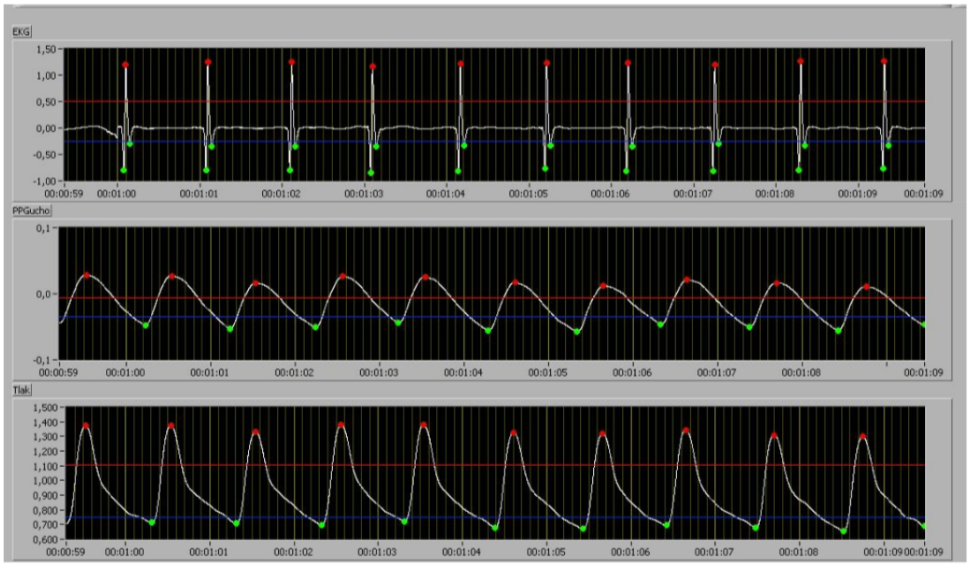

Figure 2.7 Filtered *ECG*, *PPG* and *BP* signal. It can be seen detected significant points for evaluation of *PTT* (R-wave and peaks of *PPG* and *BP* signals)

displayed on the monitoring was in average of 60 bpm. Systolic pressure displayed on the monitoring device was 129 mmHg.It was recorded 8.4 minutes of signals. At this interval, 498 peaks of R-waves were found, corresponding to an approximate value of 60 beats per minute. The value of the systolic pressure measured by extravascular sensor was in range from 127 to 131 mmHg at this interval.

Blood pressure was measured from the femoral artery via a catheter which was connected to extravascular sensor. *ECG* signal was measured from the chest. The *PPG* finger sensor was placed on the left hand finger and the *PPG* earlobe sensor was located on the left ear. The sampling rate for acquiring data was set to 1 kHz. All of this setting was valid for all of measured biosignals.

2.4.7 Analysis of PTT/BP relationship

After the signal processing of the measured data the detection of peaks in the whole measured interval was done for all of the measured signals. In order to statistically evaluate the measured data it was necessary to evaluated *PTT* and *BP* value in each cardiac cycle. It was suitable to use a method of regression analysis which expects relationship between two variables, independent and dependent. To see if there is some significant relationship between blood pressure value and *PTT*, the data was displayed as dependency on cardiac segment (systole to systole).

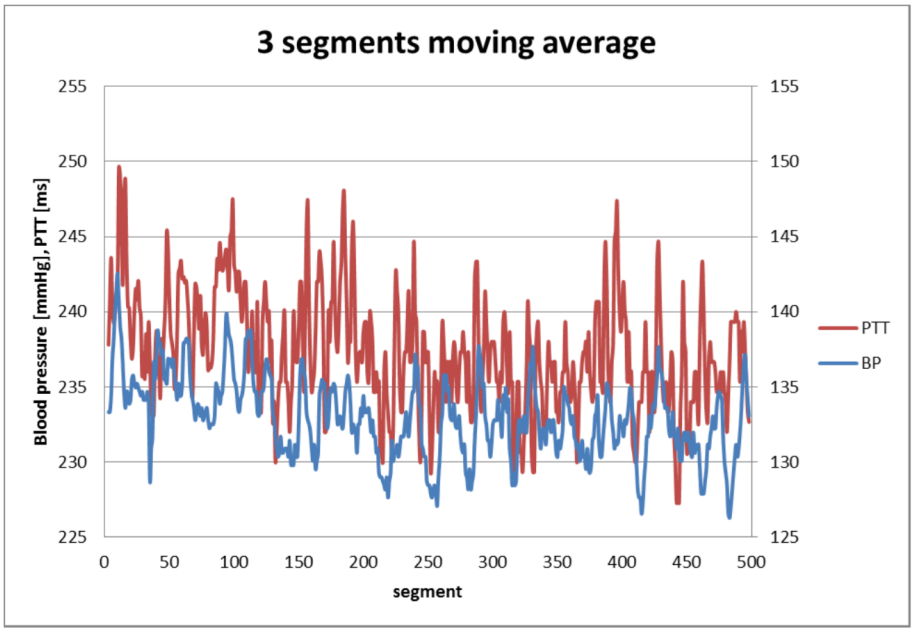

Figure 2.8 Waveform of 3 segment moving average smooth data. The relation ship between PTT and BP is already visible.

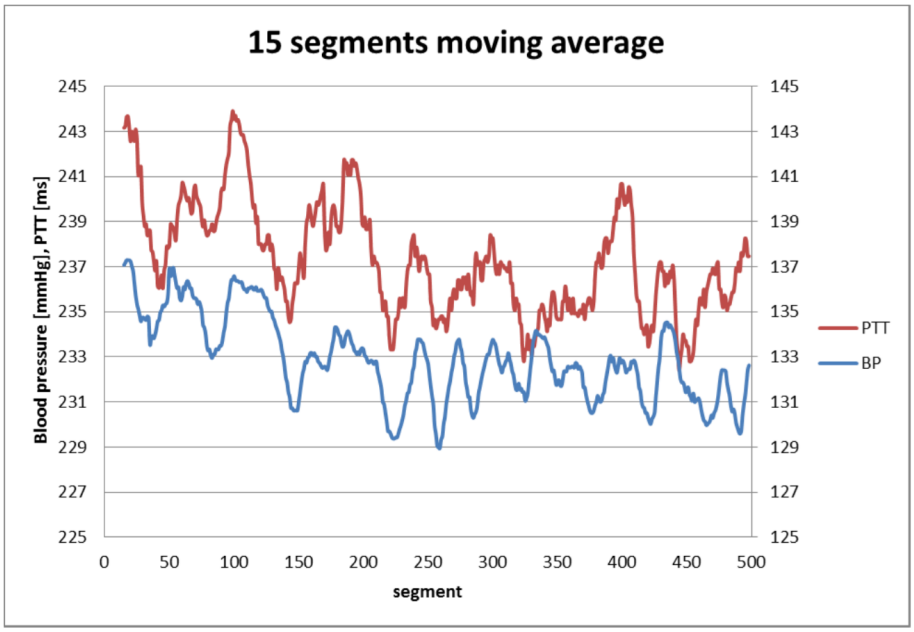

Figure 2.9 Waveform of 15 segment moving average smooth data. The correlation between variations of BP and of PTT is more visible on the waveforms after a 15 segments moving average filter.

A consultation with the cardiologist from a cardiology department of the University Hospital of Ostrava yielded that it is not appropriate to analyse the dependence of instantaneous blood pressure values because these can bring substantial mistakes into analysis. This was confirmed also by the applied regression analysis, in which the dependency of PTT to the blood pressure value was lower than 5 % when computed on the instantaneous values. During the analysis

several windows for moving average of different length were used (Fig. 2.8, Fig. 2.9).

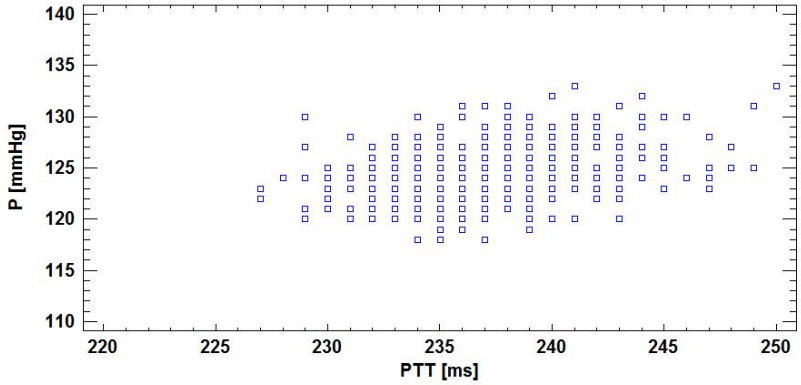

Figure 2.10 Drawn the 3 segments smoothed data into a XY graph to verify if there exist some relationship between PTT and pressure value.

Data were displayed into XY graph (Fig. 2.10). Because there is relatively high variation of PTT time interval for single blood pressure value, data of pressure was processed into range of 2 mmHg and again displayed as XY graph (Fig 2.11).

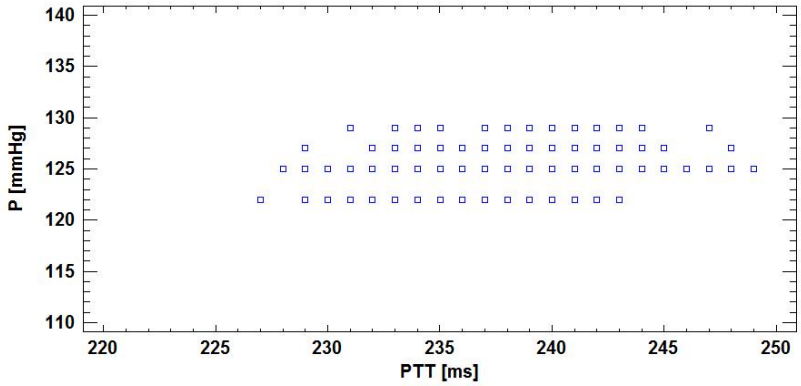

Figure 2.11 Visualisation of blood pressure variations by steps of 2 mmHg. It is difficult to concludeggg about the relationship.

If the multi box plot is displayed for each range of blood pressure, starting from 123 mmHg to 130 mmHg in 2 mmHg steps, it can be seen that increase in PTT value corresponds to increase in blood pressure value.

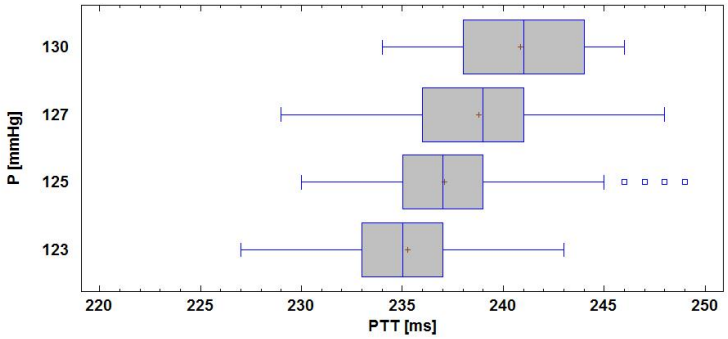

Figure 2.12 Drawn data separate based on a range of 2 mmHg of blood pressure. The relationship isn't so clear.

Table 2.1 Summary statistics for each range of data connected to the figure 2.12.

Range	Count	Average	Standard deviation
122-123	92	235,3	3.3
124-125	162	237.0	3.7
126-127	149	238,8	3.3
130-132	19	240.8	3.3

2.4.8 Results of The Preliminary Experiment

It was assumed a priori that there exist some direct relationship between PTT and blood pressure value. For evaluation of this dependency was used the regression analysis. The regression analysis revealed that accuracy of estimate of the blood pressure value based on the PTT rises with a rising size of moving average window for smooth of data. This is obvious from the above mentioned values of the determination index R-square which indicates what amount of dissipation of the defined variable is defined by a given regression model. When processing with a 3 segments moving average window the index of determination is only 16 % (Fig. 2.8), whereas with a 15 segments the index rises to 46 % (Fig. 2.9).

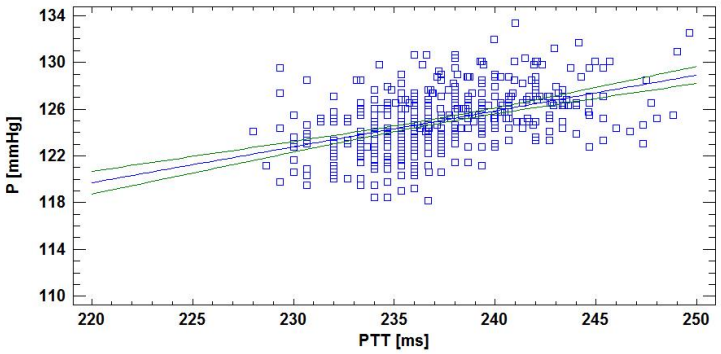

Figure 2.13 The linear model of regression analysis for 3 segments moving average window smoothed data.

Table 2.2 Analysis of variance for regression model of 3 segments smoothed data connected to the figure 2.13.

Source	Mean Square	F-Ratio	P-value
Model	649.5	121.3	0.0000
Residual	5.4		
Correlation coefficient		0.46	
R-square		21.04	percent
Standard error		2.31	
Mean absolute eror		1.82	
Coefficients			
Parameter	Least squares estimate	Standard error	P-value
Intercept	52.04	6.63	0.0000
Slope	0.31	0.03	0.0000

The output shows the results of fitting a linear model to describe the relationship between 3 segments smoothed data of blood pressure and PTT. The equation of the fitted model is:

$$BP = 52.04 + 0.31PTT$$

Since the P-value in the ANOVA table is less than 0.05, there is a statistically significant relationship between blood pressure and PTT at the 95 % confidence level. The R-Squared statistic indicates that the model as fitted explains 21 % of the variability in blood pressure value. The correlation coefficient equals 0.46, indicating a relatively weak relationship between

the variables.

Based on the p-values of the partial t-tests, this equation model can be reduced. Reduction of the model meant neglect the relevant constants contained in equation. For simplicity, the model is written with a substitution equation:

$$Y = \beta_0 + \beta_1 x$$

Subsequently, the null and alternative hypotheses are described:

$$H_0 : \beta_{0,1} = 0; H_A : \beta_{0,1} \neq 0$$

The P-value of the partial t-test for the intercept and for the slope is both 0, which means that in both cases it is negated 0.05 zero hypothesis at the significance level and neither of these values can be dropped out of the model.

Evaluation of the assumption to implement the linear regression model is based on defined conditions. It is necessary to evaluate the normality of residues (Fig. 2.14), the null mean value of residual (Tab. 2.3) and homoskedasticity of residues (Fig. 2.15).

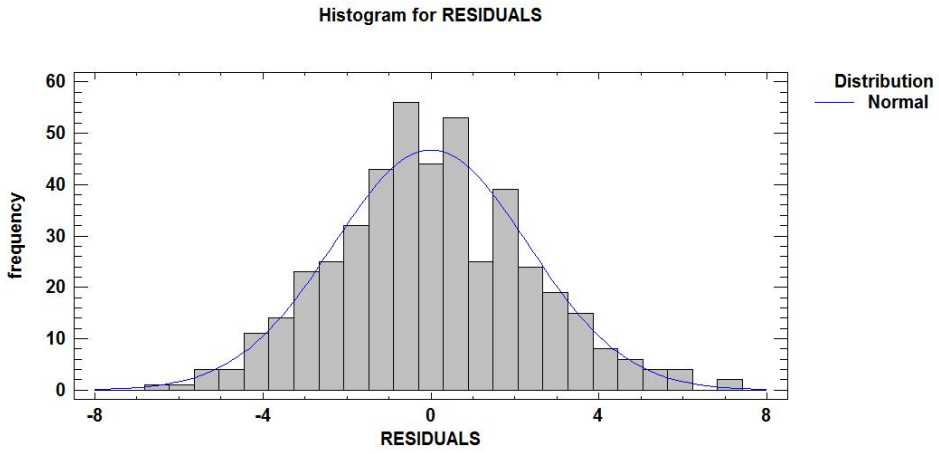

Figure 2.14 Histogram for residuals.

Table 2.3 Residuals analysis for the evaluation of the use of linear regression model.

Kolmogorv-Smirnov test
P-value 0,33
Hypotesis test for residuals
Null hypotesis: mean = 0 Alternative: not equal
P-value 0,99

We tested (Tab. 2.3) whether residuals can be adequately modelled by a normal distribution. Since the smallest P-value amongst the tests performed is greater than or equal to 0.05, we can not reject the hypothesis that residuals comes from a normal distribution with 95 % confidence. Based on the result of the t-test for hypothesis of the null mean value it can not be rejected the null hypothesis for alpha 0.05.

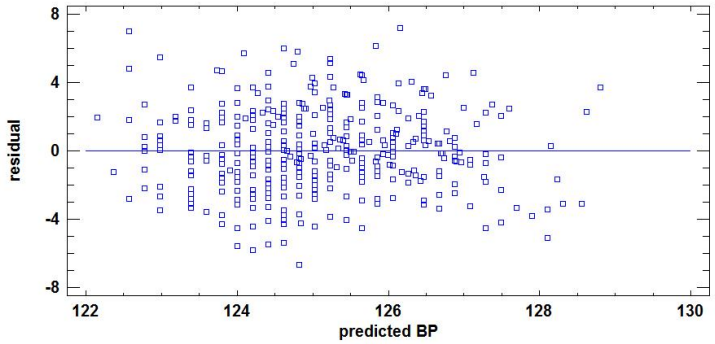

Figure 2.15 The residues are randomly spaced around zero and have no apparent relationship to predicted values are neither systematically increased nor systematically reduced along with the growing with predicted values. Homoskedasticity of the residue has been confirmed.

The analysis was made for different length of moving average window from 3 to 15. Nevertheless after a consultation with doctors from a cardiology department of the University Hospital of Ostrava it was evidenced that the diagnostically suitable time period is 10–20 s maximum delay, which corresponds in this case to the 11 or 15 segments window.

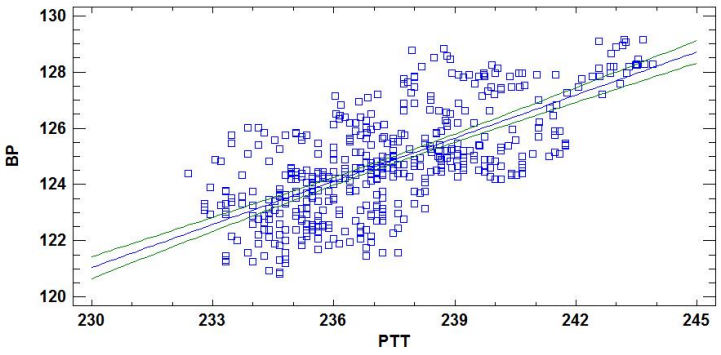

Figure 2.16 The linear model of regress analysis for 15 segments moving average window smoothed data.

Table 2.4 Analysis of variance for regression model of 15 segments smoothed data connected to the figure 2.16.

Source	Mean Square	F-Ratio	P-value
Model	773.6	410.7	0.0000
Residual	1.9		
Correlation coefficient		0.68	
R-square		46.63	percent
Standard error		1.37	
Mean absolute error		1.12	
Coefficients			
Parameter	Least squares estimate	Standard error	P-value
Intercept	3.36	5.99	0.5753
Slope	0.51	0.03	0.0000

With the increase of width of moving average window length there is possible to reach a high degree of accuracy of blood pressure determination (Tab. 2.5).

Table 2.5 Accuracy of non-invasive blood pressure measurement method.

MA (segment)	Correlation coeficient	R-square
3	0.46	21.04
5	0.49	29.41
11	0.65	42.15
15	0.68	46.63
60	0.82	68.17

2.5 Conclusion

The results which were founded in this preliminary experiment showed dependence between PTT and BP, however, it is necessary to expand the study to a statistically significant group of people. In our experiment we involved only one patient. Probably the most important things which results from this experiment is that the relationship between non-invasively measured biosignal and blood pressure exists. In fact it was the aim of this experiment to bring a proof that it is possible to measure blood pressure without a cuff (which means standard auscultatory method) and also without invasive intrusion (placing catheter into human body for continuous measurement).

This approach for the measurement of $CNIBP$ can be an important contribution to a body sensor network for continuous monitoring of the health. It can have applications on short terms for the detection of rapid changes in blood pressure -indicating acute diseases-, or on long terms for the monitoring of the long variations of the status of the cardiovascular system of a person.

For high quality and diagnostically beneficial continuous measurement blood pressure it is necessary to find a method of general and reliable evaluation of the constants determining hemodynamic parameters of the blood stream and consequently apply these values on the algorithm which directly assesses the blood pressure value.

An effective method for measuring blood pressure based on PTT and an algorithm for evaluating for blood pressure value would diagnostically contribute to improving medical care and at the same time it would help to anticipate many physiologically dangerous situations, which are caused by value of blood pressure. For more accuracy analysis is necessary to have possibility monitor continuous blood pressure and to have possibility to change hemodynamics parameters to see, which kind of parameters of pulse wave propagation affects this relationship.

Nowadays some methods, algorithms and devices can be used for continuous non-invasive blood pressure measurement. There are still some problems with calibration and comfort for patient. Description of all of this method, algorithm and devices will be introduce in the next chapter with a comparison of this method and, what is probably the most important part of the next chapter, it will be describe advantages, disadvantages and their weakness.

PUBLISHED

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A.5 PETER, Lukas; CERNY, Martin. Hardware for precise in vivo pulse transmit time CNIBP tests. In: *Applied Electronics (AE), 2013 International Conference on.* IEEE, 2013. p. 1-4.

3

The State of the Art

Contents

Most medical examinations include measuring of blood pressure because it is a very good indicator about the status of the cardiovascular system, and it helps medical doctors to adjust the ideal treatment. It would be very useful to know profile of pressure values during long time period, especially during standard daily activities. It could be used for homecare monitoring and prevention of premature death. Problem is that blood pressure is monitored mainly at discrete time intervals and use an inflatable cuff placed around the arm, which is uncomfortable for the patient. Currently there are a few technical solutions for continuous non-invasive measurement of blood pressure. This review is focused on the description of methods for continuous blood pressure measurement including their limitations and especially is focused on the description method based on pulse transit time. This method could be the most widely used of methods for non-invasive long time monitoring of blood pressure in the future but now there are still a lot of unsolved problems.

3.1 Introduction

On each beat of the heart, the blood is ejected from the ventricular to the aorta. Each ejection produces a force on blood, which creates a pressure wave travelling from the heart to the peripherals vessels. This pressure wave travels along the arterial tree and its flow depends on arterial properties as elasticity, stiffness or thickness of artery wall. The dependence of blood pressure

with arterial properties makes it a very good indicator of the status of the cardiovascular system. The monitoring of the cardiovascular system is therefore very important.

Some cardiovascular diseases are closely associated with the creation of atherosclerosis, in which arterial compliance decreases dramatically with a resulting increase of arterial stiffness [9]. This can induce an increase in blood pressure. It is one of reasons why cardiovascular diseases increase the patient's risk and are one of the leading causes of death.

Blood pressure varies periodically (in the range 40–180 times per minutes) between two extreme values, the maximum systolic value (SP) and the minimum diastolic value (DP), following a temporal pattern (Fig. 3.1) which is important to follow up.

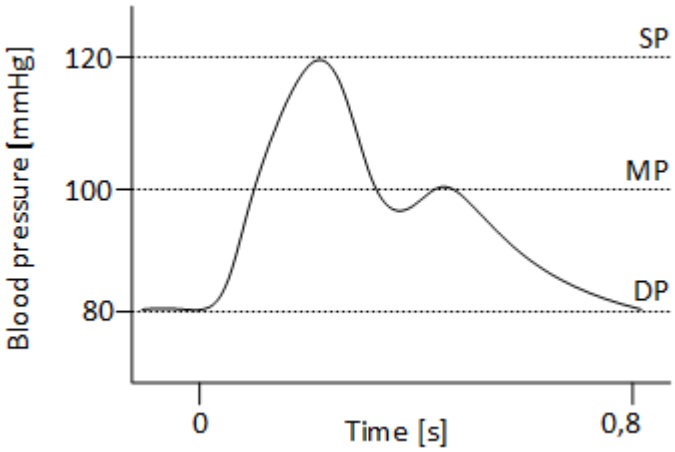

Figure 3.1 Blood pressure wave with main parameters SP – systolic blood pressure, DP – diastolic blood pressure and MAP – mean arterial blood pressure

Additionally, blood pressure values change over time. If the systolic blood pressure is too low ($SP < 90\,mmHg$ [10]) there is bad perfusion of blood in the smallest vessels, which means poor distribution of nutrients and oxygen. If the systolic blood pressure is too high ($SP > 140\,mmHg$ [11]) there is high risk for rupture of vessels. This can damage organs where the circulation of blood is important, as it is the case for liver, kidney, brain or heart.

Extreme values of blood pressures also vary continuously to maintain homoeostasis against variations of external conditions (stress, thermal variations). But if blood pressure values remain out of normal range on long time (e.g. due to cardiovascular system pathologies), it can have lethal consequences for the patient.

The long time continuous monitoring can be very useful to medical doctor for following up the reactions of cardiovascular system in presence of some drugs or medical treatment. It can help the physician to adapt the treatment or to predict a heart failure. Continuous monitoring of blood pressure is useful in many situations, such as in cardiovascular diseases (hypertension), or to prevent falling accidents related to orthostatic hypotension (low pressure).

Therefore, medical doctors need methods to collect information during long time periods and with high accuracy in order to place the best diagnostic. But they want these methods to be unsupervised, not using inflatable cuff which is unpleasant and uncomfortable for long time periods. Non-invasive and long time period blood pressure measurements methods are therefore

highly valuable.

3.2 CNIBP measurement methods

When we consider non-invasive and continuous measurement methods, we mean methods not needing skin penetration and the possibility to measure blood pressure values on long time periods. For medical doctors it is necessary to find some method which will measure accurately several parameters of blood pressure (systolic, diastolic, mean blood pressure). We now present current methods for continuous non-invasive blood pressure measurement, each of them with their advantages and disadvantages. Unfortunately none of these methods are reliable, accurate and comfortable for patient.

3.2.1 Auscultatory and oscillometric methods

The most known and the most widely used non-invasive methods for blood pressure measurements are auscultatory and oscillometric methods. These two methods are commonly used during standard examination at the office of medical doctors. Both methods use a cuff placed around the arm, which is inflated at a pressure higher than the systolic pressure, then slowly deflated (Fig. 3.2).

The auscultatory method is based on listening to Korotkoff's sounds under the cuff, which appear when the cuff pressure equal to the SP and disappear when the remaining pressure equal to DP.

The oscillometric method is based on measuring of the pressure oscillations which appear when the pressure in the cuff equals to the SP, are maximum at the mean pressure, and disappear at the DP [12].

Auscultatory method is the most commonly used for blood pressure measurement. This method is imprecise and user dependent. Additionally this method cannot be used for long time monitoring because medical doctor's supervision is necessary. Blood pressure can be measured only at time intervals, with more than 3 minutes time delay between successive measurements. Therefore auscultatory method is used only during standard examinations.

Oscillometric method is the most commonly used method for non-invasive continuous blood pressure monitoring in Holter's monitoring. Blood pressure is also measured non-continuously at discrete time intervals (every 15 to 20 minutes). When patient is indicated long time monitoring of blood pressure, he leaves the doctor's office with a cuff around the upper arm. During the following days, an automatic device records blood pressure values approximately every 20 minutes with inflating the pneumatic cuff. Finally, the patient returns to the doctor's office where is evaluated hypertensive profile and an appropriate treatment is proposed. The measuring values are accurate but, after a couple of hours, the accuracy decreases and the discomfort of patient increases. Such a measure is not idealistic, because it is uncomfortable, noisy and painful. Especially during night, the periodic inflations of the cuff create sleep arousal and moreover affect blood pressure values [12].

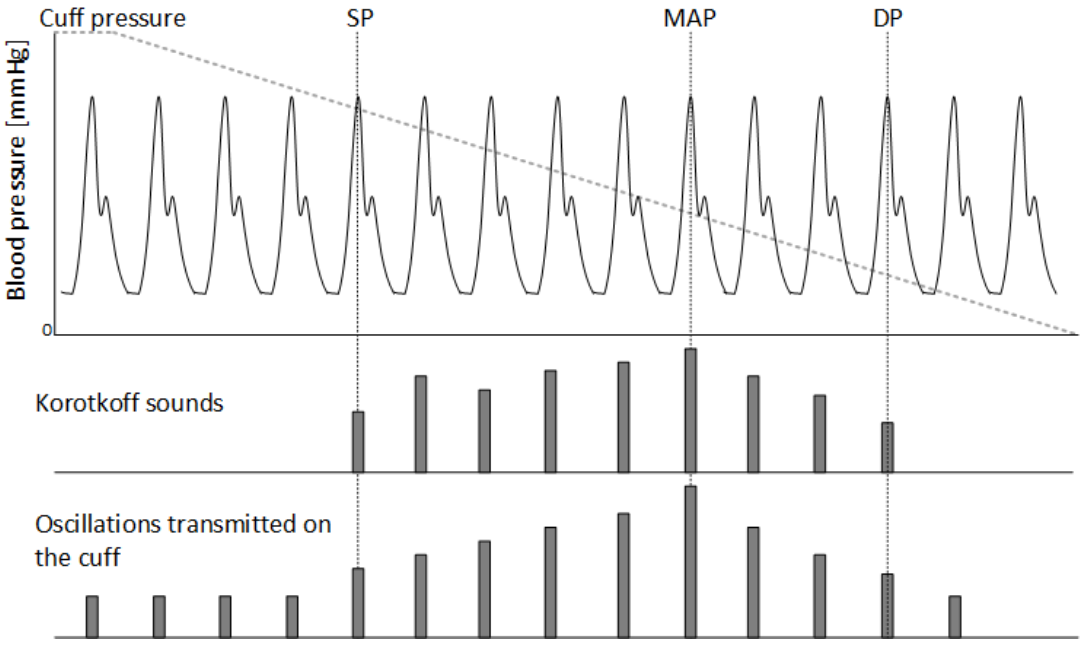

Figure 3.2 Schematic illustration of working principles of auscultatory and oscillometric methods. The first method evaluates the level of Korotkoff sounds, whereas the second method detects the oscillometric vibrations under the brachial cuff.

3.2.2 Tonometry method

The tonometry method is more adapted for continuous monitoring of the blood pressure waveforms. This method is based on applying a controlled force orthogonally to the wall of a superficial artery against a bone.

A force sensor measures the pressure at contact, thus this action on superficial artery produces a local occlusion. It doesn't need a cuff but it needs some supporting device which creates pushing force. The applied force must be small in order not to completely close the artery, as in this case blood pressure is not measured and there is a risk of ischemia. The contact is maintained all through the heart cycle, and thus the applied force changes and follows up the pressure wave [13].

Not only applied force is important for correct measurement. The positioning of the tonometer over the center of the artery is also very important. The difference between correct and wrong placements is millimetres. When sensor will be placement wrong it will lead to non-linear affect blood pressure on the sensor. Blood pressure will not measure correctly.

Tonometry is highly sensitive to motion so it need of a continuous precise positioning of the sensor. So the ideal situation for measurement with tonometry is in the rest position. The accuracy of tonometry method depends on several factors which need to be controlled over time, thus the accuracy decreases rapidly over time without supervision. Device is not comfortable for patient during daily activities.

Currently some commercially available devices are based on the tonometry method: the T-Line[1] (Tensys Medical Inc., USA) and the BPro[2] (Center for Hearts, Canada). But this method

[1] http://www.tensysmedical.com (2005)
[2] http://www.centerforhearts.com (2010)

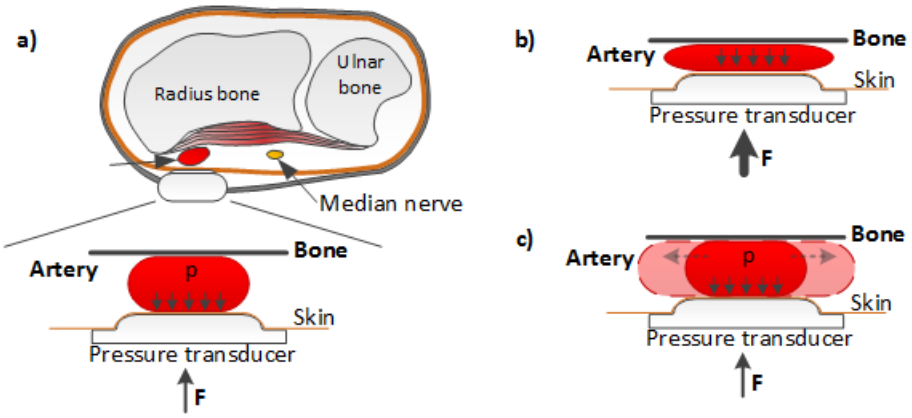

Figure 3.3 Working principle of the tonometry method (a): a superficial artery is compressed against a flat bone. The two main problems with tonometry method are: (b) if applied force is too high the artery is closed and blood pressure cant be measured, (c) when artery moves under sensor, blood pressure is also incorrectly measured.

is not commonly used for blood pressure measurement.

3.2.3 Volume clamp method

The first continual noninvasive method for blood pressure monitoring, was introduced and patented by Czech medical doctor Jan Peňáz in 1969. This method is still partly occlusive because it uses a small cuff around the finger to maintain constant the flow of blood under this cuff during each heartbeat [14]. The device uses an inflatable finger cuff with a built-in photoplethysmography (PPG) sensor and a pressure controller unit placed on wrist of arm.

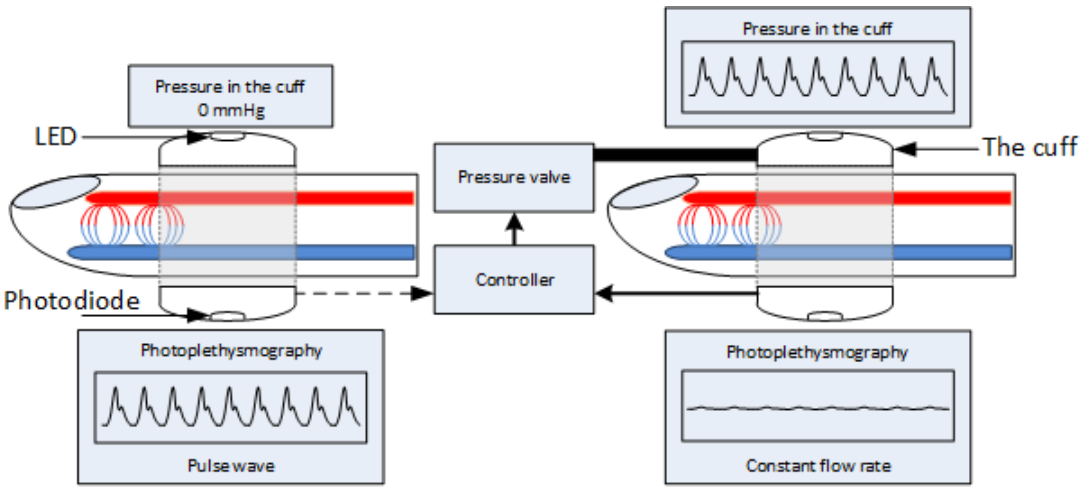

Figure 3.4 Principle of Volume clamp method. The pressure in finger cuff is controlled with measurement of PPG. With low cuff pressure, the PPG wave is fully visible. When the cuff pressure balances the pressure of blood volume in vessel under the cuff, the PPG wave turns to constant.

PPG does not access directly to blood pressure values but can measure blood volume changes in artery. Unfortunately, these volume changes cannot be transformed into pressure values

because of the non-linearity of the elastic components of the arterial wall. PPG measures pulse wave it means changes in volume of blood under cuff. Based on these changes is changing pressure in cuff. If blood volume under a cuff is constant, blood pressure value can be evaluated as pressure value in a cuff. Therefore, the continuously changing pressure, which is applied from the outside of finger, corresponds to the intra-arterial pressure and thus it is an instantaneous, continuous measure for arterial blood pressure [15].

The Finapres (Medical Systems, Amsterdam, Netherlands) was the first commercially available device based on volume clamp methodology, introduced in the early 1980s. Finapres cuff pressure was compared to intra-arterial pressure in a large number of studies and the wave forms obtained using this procedure were found similar to the intra-arterial pressure waves in most subjects. Nowadays the Finapres system is no more available, but alternative devices are based on the same methodology: the Portapres[3] and Finometer (Fianpres Medical Systems, Holland), the Task Force Monitor system[4] (CNSystems Medizintechnik, GmbH) and the ccNexfin[5] (Edwards Lifesciences, California, USA).

Volume clamp method can be used for long time period monitoring of blood pressure waves. Although in 1985, a study about tissue hypoxia revealed an impairing effect on blood circulation in the finger tip on the distal side of the finger cuff. It was found that after applying cuff pressure for one minute oxygen decreased from 97 % to 93.7 % [16].

Continuous measurement of blood pressure is possible with Fianpres technology, but the cuff is still uncomfortable to the patient. Relationship between blood pressure and pulse wave velocity can be a candidate for this measurement.

3.2.4 Pulse wave velocity method

One possible way to access blood pressure without using a cuff is to measure the velocity of propagation of pulse waves along the arterial tree. Actually, the velocity of pulse pressure waves propagating along the arterial tree depends on the value of blood pressure. Indirect measurement of blood pressure was performed by continuously measuring pulse wave velocity [17]. The best site for measuring this velocity is located in the aorta because relationship between PWV and blood pressure is only exploitable in central elastic arteries. But it is difficult to perform non-invasive. It is easier to measure arrival of the pulse wave from the first arteries, which begin at the aorta and are more accessible, the common carotids and the common femoral arteries [17].

Pulse wave velocity (PWV) refers to the velocity of the pressure pulses which are generated during left ventricular ejection, after opening of the aortic valve. Nowadays, clinicians find it important to determine the velocity of those pulses in the aorta, because the velocity of propagation of aortic pressure pulses mainly depends on the elastic and geometric properties of the arterial wall. Actually, the measurement of PWV is the gold standard for investigating arterial stiffness, but it also gives indirect measurements of blood pressure by continuously measuring pulse wave velocity [18].

[3] http://www.finapres.com (2012)
[4] http://www.cnsystems.at (2013)
[5] http://www.edwards.com (2013)

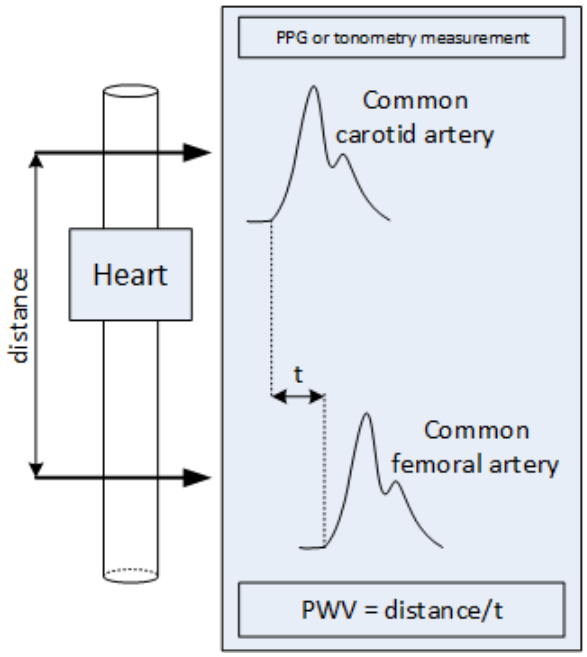

Figure 3.5 Principle of evaluation of pulse wave velocity.

The in vivo determination of aortic PWV is difficult because it is necessary to detect the time of arrival of a pressure pulse at both the ascending aorta and the iliac bifurcation and to precisely measure the travelling distance of the pulses. The aorta is not easily accessible, neither by optical nor by mechanical means. One possibility is to measure arrival of a pressure pulse at two substitute arterial sites which are close to aorta. The best is measured arrival of pulse wave from the first arteries, which start from the aorta and are accessible, the common carotids and the common femoral arteries.

Currently automatic devices are commercially available: the Complior[6] (Alam Medical), the SphygmoCor[7] (AtCor Medical, New South Wales, Australia) and the PulsePen[8] (DiaTecne s.r.l., Milano, Italia).

The Complitor measures pulse transit time as the time delay between carotid pulse wave and femoral pulse wave. The SphygmoCor evaluates the pulse transit time measure from two different time values. The first value is the time delay measured between R-peak from ECG and foot point of carotid pulse wave and, the second value is the time delay measured between R-peak from ECG and foot point of femoral pulse wave.

The PWV measurement method needs to know precisely the distance between sites where signals are collected. Each technique provides different and inconsistent recommendations on how to derive this distance, which is measured manually. These devices require the presence of a skilled operator to manually localize the carotid and femoral arteries. For this reason this measurement is operator dependent and prone to errors.

[6]http://www.complior.com (2013)
[7]http://www.atcormedical.com (2013)
[8]http://www.diatecne.com (2011)

3.2.5 Summary of measurement methods

From the doctors' point of view, the better method for continuous non-invasive blood pressure measurement should offer high accuracy and low risk to patient. From the patient point of view, the idealistic method for continuous non-invasive blood pressure measurement should be comfortable, painless, non-occlusive, needing no supervision and with no risk during long time monitoring. Currently none of the above methods are adapted for long time measurement.

Table 3.1 Comparative point of view of patient and physician of standard non-invasive blood pressure measurement methods.

Medical's criteria				
Method	Periodicity		Accuracy	
Auscultatory	Discrete time		Gold standard for standard control	
Oscillometric	Discrete time		Gold standard for pressure Holter	
Tonometry	Beat-to-beat, continuous		Controversial	
Volume-clamp	Continuous		Controversial	
Pulse wave velocity	Beat-to-beat		Beat-to-beat	
Patient's criteria				
Method	Occlusion	Supervision	Long time monitoring	Comfort on long time
Auscultatory	Total	Yes	Yes	No
Oscillometric	Total	No	Yes	No
Tonometry	Partly	No	Yes	No
Volume-clamp	Partly	No	Yes	No
Pulse wave velocity	No	Yes	No	No

Fortunately, for non-invasive long time period ambulatory and clinical evaluation of blood pressure value another measurement method is proposed, called "Pulse Transit Time (PTT)", which doesn't require a skilled operator, no cuff, and can be used for long time monitoring with a stable comfort for the patient.

3.3 Pulse transit time method

The PTT method is based on the evaluation of the PW velocity from the travel time between two known locations. Because there is a relationship between PWV and blood pressure, there is the same relationship between time of travel and blood pressure.

Practically the PTT is derived from the time delay between the R-wave of ECG and the arrival of pulse wave on finger, which is measured from PPG. The R-wave occurs at the beginning of the heart systole when the blood ejected from heart to aorta creates the pulse pressure wave which further travels to the periphery. Therefore, the R-wave is a good reference for the beginning of the pressure cycle. Additionally, it is easy to detect.

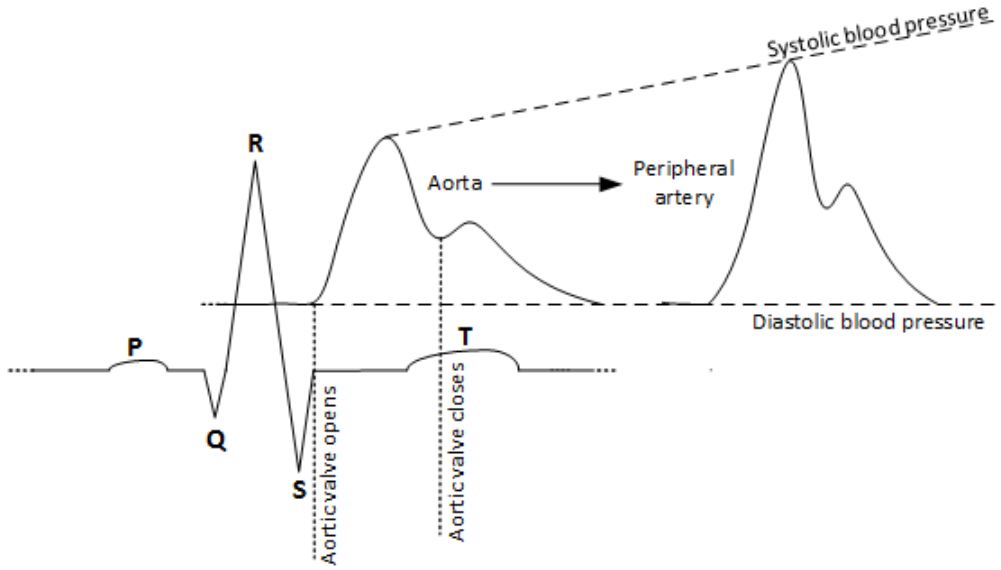

Figure 3.6 Schematic illustration of the signals of ECG and blood pressure wave at the aorta and the PPG wave at the finger.

It was described that elasticity of an artery is related to velocity of the volume pulses propagating through it. Each contraction of the left ventricle ejects the blood from the heart into the arterial system, which affects velocity of the blood and produces a pressure wave which travels along the elastic arteries. It is this pressure wave, not blood flow, which is felt as the pulse beat [19]. The main factors that determine the speed of propagation of the pulse wave, thus affect PTT value, are the elasticity coefficient, the thickness of the arterial wall, the end-diastolic diameter of the vessel lumen and blood density [20]. In 1878, Moens and Korteweg [21] derived a mathematical expression for the velocity of the pulse travelling along an artery as a function of such above described factors.

$$PWV = \frac{D}{PTT} = \sqrt{\frac{tE}{\rho d}} \tag{3.1}$$

Where PWV is pulse wave velocity, D is length of the vessel, PTT is pulse transit time, t is thickness of the vessel wall, d is diameter of the vessel, ρ is blood density and E stands for Young's modulus of the elasticity of the arterial wall [4]. Therefore, this approach was opening the way to access a wide variety of cardiovascular parameters (thickness, elasticity, diameter of vessels) and, from 1878, pulse transit velocity was used as a clinical index of arterial elasticity.

In 1974, Jernstedt and Newcomer [22], presented the first device exploiting changes in PWV to measure blood pressure variations, instantaneously and continuously, over long periods of time with no interruption, reliably, simply and for free body movements. PWV was evaluated from time interval between R-wave of the ECG and the arrival of pulse wave on finger measured with photoplethysmography. Blood pressure was measured with a sphygmomanometer and value of blood pressure was correlated with PWV.

In 1978, relationship between blood pressure and PTT value was investigated under stress

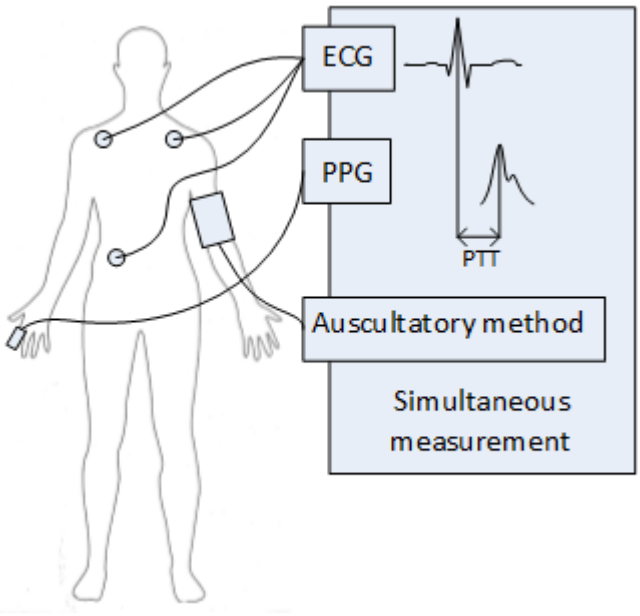

Figure 3.7 Method for blood pressure evaluation based on PTT proposed by Jernsted and Newcomer. The auscultatory method is represented as a control.

conditions including the cold presser or watching pornographic movies. The results showed that PTT covariates with systolic blood pressure (SBP) in most individuals. These high correlations were observed whether SBP was measured indirectly or directly. When some medications were used for blocking the sympathetic innervation of the heart, the level of covariation was significantly attenuated [20].

Until 1981 it has not been possible to obtain the diastolic pressure by seeking a transition in waveform or amplitude of the peripheral pulse. Geddes [17] described new method for indirect measurement of systolic and diastolic blood pressure, with a linear relationship between pulse wave velocity and blood pressure. He also showed that diastolic blood pressure can be monitored continuously using extravascular pulse pickups and time-domain techniques to determine the pulse wave velocity. This method used measurement of the break through time of the pulse beyond the cuff. Pulse of blood pressure was measured on the same artery in different location along the vessel.

In 1988, Pruett *et al.* [23] used a measuring method based on collection of multiple pulse wave velocities and pressure from a single beat of aortic pulses detected at different distances from the left ventricle. Blood pressure was measured invasively with a catheter. It was measured on dogs under anaesthesia. This study showed that the linear relationship between pulse wave velocity and blood pressure, is an approximation that can only be applied with pressure below typical diastolic. In the same year, Okada [24] showed that PTT correlates well with age, gender and systolic and diastolic blood pressure. He recorded two pulse waves from different places, from the fingertip and the toe tip.

In 1991, Geddes [12] showed that Young's modulus E of artery walls is not a constant. There exists an empirical exponential relation between E and the fluid pressure P:

$$E = E_0 e^{\alpha P} \tag{3.2}$$

Where E_0 is the zero pressure modulus, α is a parameter of the vessel ($e = 2.718$, *is Euler's number*). Therefore, the Moens-Korteweg (Eq. (3.1)) can be reformulated to show the relationship between PWV and P:

$$PWV = \frac{D}{PTT} = \sqrt{\frac{tE_0 e^{\alpha P}}{\rho d}} \tag{3.3}$$

During the 1990s and 2000s PWV became a broadly approved method for assessing arterial stiffness; this is still believed to be a good marker for predicting premature death. Dr Roland Asmar investigated the principles of the method, its clinical applications and factors influencing pulse wave velocity. Pulse wave can be measured non-invasive on the skin over the artery between two different places in the arterial tree. Increased blood pressure is associated with increased arterial stiffness and vice versa, which means that the elastic modulus is dependent on pressure. The elastic modulus varies along the arterial three depending on the vascular tonus which makes it difficult to measure PWV accurately [25].

From 2000, Sorvoja et al. proposed a method where a pressure sensor was used to sense radial artery pulsation and a cuff was placed around the upper arm to occlude the brachial artery. Diastolic blood pressure determination was based on either pulse amplitude change or PTT change. The same year was proposed a method based on measuring the beat-to-beat time interval between R-wave in the ECG signal and the onset of photoplethysmography sensor placed on a fingertip. PTT value was correlated with invasive blood pressure value and results showed that systolic blood pressure changes can be tracked using PTT, if the calibration pressure can be measured regularly and if the elasticity of the arterial wall is maintained constant [6]. Especially during ergonometric exercise test when heart rate increases, because the instantaneous heart rate has a strong correlation to systolic blood pressure [26]. It was showed that photoplethysmographic method can be used for noninvasive registration of PTT delay in different regions of human body in comparison to ECG signal [27]. During exercise ECG can be recorded nearly undisturbed whereas photoplethysmographic signal is frequently artefacted by movements of the subject. Movement's artefacts can be reduced by sensor placement. The sensor placements at the ear lobe yields to a minimum of artifacts even though the perfusion at the ear is generally lower than at the finger. PTT was compared to blood pressure measured with standard oscillometric method. As this last technique is sensitive to motion artefacts, the physical exercise is stopped for a minute every two-minute load, in order to take an oscillometric blood pressure reading [26].

In most studies, PTT is evaluated as the time delay between two time markers, one on ECG R-wave detection and another one on the detection of pulse wave in peripheral arteries. There are several possible points to time stamp the PPG wave, either at the foot, the peak or some midpoint between foot and peak. In 2004, Lass *etal.* [28] measured PTT as the time interval between R-wave and 50% of the rising front of PPG wave (where the signal slope is the sharpest) in the same cardiac cycle. This study showed that PTT increases with subjects' age. It could be explained that PTT also includes an electromechanical delay between electrical and

mechanical work of heart. An electromechanical delay is needed to convert the electrical signal into mechanical pumping force and isovolumetric contraction; it is called pre-ejection period (PEP) [19]. PEP is the "pre-ejection period" duration of the isovolumetric ventricle contraction up to aortic valve opening. PEP is a non-constant delay which changes rapidly in response to stress, emotion and physical effort. This period also increases with age.

The same year a human model for dependence between blood pressure and PTT was used. The model was fitted, ignoring or approximating unknown parameters such as the elasticity of arterial wall, heart PEP and blood density. The human model of blood pressure and PTT assumes laminar blood flow from the heart chamber to fingertip. The model estimates the pressure difference between two sites, the heart and the finger. PTT was defined as the time interval between R-wave from ECG and the maximum of PPG wave. Evaluation of blood pressure value from PTT can be described in equation (2.7):

$$P = \frac{A}{PTT^2} + B$$

With the constants A and B are subject dependents [7].

The human PTT-BP model has several limitations. First, the method is sensitive to movement artefacts as is PPG. In case of a movement of the segment where the PPG sensor is located (i.e. the arm), the measured signal will be strongly influenced. Second, this model doesn't include PEP value. Actually, the PEP increases when heart rate is slower. So the PEP value is more significant at slower heart rates, for the same SBP and PPT [7].

In 2006, a study was performed to determine the specific contributions of the PEP and PTT within the pulse wave methodology. The start time of each heartbeat was given by R-wave and the arrival time of the volume pulse by the foot or peak of PPG. In this case, pulse arrival time (PAT) is made up of two parts [29]:

$$PAT = PEP + PTT \tag{3.4}$$

The human PPT-BP model also showed that blood pressure is affected by hydrostatic pressure. Work by Shaltis *etal.* [30] is focused on non-invasive blood pressure measuring based on technique combining a PPG signal with a hydrostatic pressure reference for absolute sensor calibration. They measured blood pressure and PTT simultaneously at different height of the arm and described the effects of hydrostatic changes on the peripheral pressure waveform. Experiment showed that changes in hydrostatic pressure affect waveform morphology. After one year same results were obtained during night-long respiratory sleep studies [31].

Another parameter influencing the measurement of blood pressure from PTT is due to the use of PPG. Actually the photoplethysmogram is affected by the contact force applied to the photoplethysmographic sensor at the measurement site, i.e. finger [32]. The shape of PTT is modified when the contact force increases. The applied sensor contact pressure should be carefully controlled in PTT measurement in order to avoid reducing its significance as a diagnostic tool [33].

To date a lot of works were published on non-invasive blood pressure measurement based on

PPT measurements.

The research group led by Prof Asada at the Massachusetts Institute of Technology (MIT, USA) introduced a ring sensor for PPG and a pulse oximetry monitor, attached around patient's finger for continuous measurement 24 hours a day. The last version of their plethysmography sensor could measure five vital signs on the patient [34].

Another group led by Prof Zhang in Hong Kong investigated the relationship between blood pressure and PTT during different exercises as cold [35], stress or with drugs used for affecting blood pressure value [36]. The exercise tests showed that BP-PTT method could be used in homecare systems for real-time continuous monitoring of blood pressure [37]. The main works were introduced by the research group by prof. Zhang. This group investigated relationships between blood pressure and PWV or PTT. They were the first to present a method for noninvasive and cuff-less blood pressure measurement for telemedicine purposes [38]. This group also described measurements with three different types of PPG rings; they measured ECG from dorsal side of hand [39], proposed a mathematical method to compensate motion artefacts, referred to as stationary wavelet transform [40] or described a calibration method for non-invasive blood pressure measurement [41].

Recently, several methods for cuff-less blood pressure estimation using PTT value were described in the literature. Experiments were conducted on different groups with independent devices used to acquire ECG and PPG and blood pressure simultaneously. The most frequently used method for statistical data analysis is linear regression. The relationship between blood pressure and PTT is based on a linearised version of the Moens-Korteweg equation.

Chen *etal.* [6] described that if changes in thickness and diameter of arterial wall with respect to the change in blood pressure are negligible, and if the change in the arterial wall tonus is slow enough, blood pressure can be evaluated from equation (2.8):

$$\Delta BP = -\frac{2}{\gamma PTT}\Delta PTT$$

Where γ is a coefficient ranging from 0.016 to 0.018 mmHg, which depends on the particular vessel and ΔPTT is the change in the pulse arrival time. A linear approximation, equation (2.9) was proposed by Zhang, for a given subject [8]:

$$BP = aPTT + b$$

Proneça *etal.* [42] proposed a nonlinear equation to evaluate the blood pressure value:

$$BP = a \ln PTT + b \tag{3.5}$$

Whong and Poon [43] in their year study described a relationship between blood pressure, PTT and heart rate:

$$BP = aPTT + bHR + c \tag{3.6}$$

Each of these models was tested in laboratory on test groups of people, to show a very high

dependence of blood pressure value on PTT. Constants (a and b) in each of these models, depend on individual subjects and must be learned from calibration procedures. Calibration methods were studied in several papers [20], [41], [8], [44], [45], [46]. Authors proposed several calibration methods giving similar results.

From 2010, group by Joseph Sóla started work on noninvasive measurement of blood pressure. In their first work they focused on the role of pulse wave velocity in cardiovascular system [47]. They described possibilities of blood pressure measurement based on PWV method. In 2011, they introduced the novel principle of noninvasive pulse wave velocity measurement. They introduced a chest sensor including measurements of ECG, PPG, and phonocardiography and cardiography impedance. Impedance cardiography was used for the detection of opening of the aortic valve, and PPG simultaneously measured to directly evaluate pulse arrival time [48]. In 2012 and 2013, they introduced the principle of noninvasive blood pressure measurement based on their chest sensor [49], which allows to measure beat-to-beat mean arterial pressure value. This sensor can be integrated in a T-shirt to measure accurately, non-occlusive and continuous blood pressure. The chest sensor measures two independent time values: the opening of the aortic valve and the arrival of pressure pulse on the sternum. The ECG is collected from four electrodes placed around the thorax. These electrodes are also included in the chest sensor. The arrival time of PW at the sternum is measured by the multi-channel PPG (the use of multiple PPG channels improves the robustness of PAT estimation). Unfortunately, this method cannot be used during exercise. In this study each subject was to be in supine position and to remain still [50]. These types of measurement are known for their repeatability limitations, introducing uncertainty to the study results.

In 2012, a new wearable device was introduced for continuous heart rate and pulse transit time measurements [51]. This device was placed on the ear and included monitoring of the ECG in single configuration, the ballistocardiogram (BCG) with a triaxial accelerometer and the PPG. Peak time intervals between the ECG, BCG and PPG were extracted and were used for evaluating the PEP value. The BCG is collected from the mechanical waves propagating in the body after the blood ejection during systole. It was demonstrated that BCG can be measured from head [52] and the BCG wave can be used for estimation of PEP value [51].

3.4 Accuracy of methods

From the clinical point of view, the most important features are accuracy and precision of noninvasive blood pressure measurement method. Guidelines were created by *British Hypertension Society (BHS)* and by *Advancing Safety In Medical Technology (AAMI)* to compare any method to the reference intra artery pressure (IAP). According to the $AAMI$ standard, either the mean difference between measurements must be less than 5 mmHg, or the standard deviation must be less than 8 mmHg for 85 % of measurements. The British protocol created four grades, A to D, where A is the most accurate and D is the worst. The grades represent the cumulative percentage of readings falling within 5, 10 and 15 mmHg. To fulfil the BHS protocol, a device or method must achieve at least grade B.

Table 3.2 Accuracy of non-invasive blood pressure measurement method.

Method	Systolic BP Accuracy	Diastolic BP Accuracy	Remarks
Auscultatory	3 ± 1.16 mmHg	1.4 ± 1.36 mmHg	Compared to IAP [53]
Oscillometric	-1.49 ± 5.11 mmHg	0.61 ± 5.89 mmHg	Compared to ABP [54]
	-2.6 ± 9 mmHg	6.1 ± 7 mmHg	Compared to IAP [55]
Tonometry	-1.1 ± 4.1 mmHg	-0.5 ± 2.1 mmHg	Compared to IAP [56]
	-8.2 ± 10.3 mmHg	7.6 ± 8.7 mmHg	Compared to SBP [56]
Volume clamp	6.5 ± 2.6 mmHg	5.4 ± 2.9 mmHg	Compared to IAP [14]
	Difference 5.4 mmHg	Difference -2.5 mmHg	Compared to ABP [57]
	Varies greatly according to time of measurement		
Pulse transit time	Depends upon calibration		
	The relationship between PPT and BP is still controversial		

IAP – intra-arterial pressure, SBP – sphygmomanometer blood pressure, ABP – auscultatory blood pressure

Each non-invasive blood pressure measurement system meets the guidelines before to access the marketplace. Still, the assessment of accuracy dependence on many factors, such as the size of population tested the method for signal processing or the reference method (intra artery pressure or auscultatory method). The most common reference value is the invasive blood pressure value but it could be interesting to compare also to the gold standard non-invasive measurement method.

3.5 Comparative of performances

There is still unsatisfied needs for a cuff less, non-invasive method for the continuous monitoring of blood pressure during anesthesia and in critical-care. Among all candidate methods, pulse transit time (PTT) offers the possibility of fulfilling the requirements (Tab. 3.2).

Table 3.3 Comparison of methods for noninvasive and continuous BP measurements.

Method	Advantages	Disadvantages and limitations
Auscultatory	**Gold standard** for noninvasive blood pressure measuring **The most widely used** method during medical examinations	Measuring only at **discrete time intervals** Needs **medical supervision** **Use of a cuff** **Decreased comfort** of patient on long time monitoring
Oscillometric	Automatic measurement **doesn't need skilled operator** **The most widely used** method for long time monitoring **(Holter's monitoring)**	Measuring only at **discrete time intervals** **Use of a cuff** **Automatic inflation and deflation** is noisy (sleep) and frequent inflation is **painful** **Decreased comfort** of patient on long time monitoring Sensitive to stiffness of the arteries and on the site of measurement
Tonometry	Measuring beat-to-beat pressure values **No need for medical doctor supervision** **Only partly occlusive** method	Needs **continuous control of contact pressure** Needs **continuous control of placement of sensor** Measurement is affected by **movement artefacts** **Accuracy decreases** with length of monitoring **Comfort decreases** with length of monitoring Sensitive to anatomical skin abnormalities
Volume clamp (Penaz)	**Continuously measures BP wave** **No need for medical doctor supervision** **Partly occlusive** method	**The vessel** under the cuff is **still little closed** **Oxygen decrease** in tissue under cuff Needs **continuous control of pressure** in the cuff **Expensive method** **Affected by poor blood circulation in fingers** **Comfort decreases** with length of monitoring Affected by reduced peripheral blood circulation and arteriosclerosis
Pulse wave velocity	Measuring beat-to-beat pressure values Measuring **without cuff** **No need for medical doctor supervision** No need for additional device Gold standard for investigation of arterial stiffness	Needs **measure precisely distance between places** where arrival time of pulse wave is measured **Distance is measured manually** with a ruler at the body surface Need **supervision of skilled medical doctor** to find arteries used for measurement Measurement is artefacted by movements
Pulse transit time	Measuring beat-to-beat pressure values for long time Measuring **without cuff** **No need for medical doctor supervision** **Comfortable for long time measurement** BP value evaluated from **standard biological signals** **Can be used during normal daily activities**	**Needs measurement recalibrations** **Accuracy is influenced by several factors** **A lot of unsolved problems for evaluation** **BP based on PTT**

PTT method can bring benefice because it indirectly evaluates the blood pressure from existing standard biological signals, it does not need medical supervision, it doesn't use uncomfortable cuff and it can offer long time measurement with no risk to the patient. Since 1974, when *PTT* was first used for evaluation of blood pressure value, a lot of works and experiments were done. Still there are a lot of unsolved, or no clearly described, problems.

ECG, *PPG* and blood pressure have been measured simultaneously with different modalities. As the method is based on measurement of very short time delays (milliseconds), it needs precise time synchronization between each device. This synchronization is not described in literature.

PTT-BP values have been compared to blood pressure pressures measured non-invasive on different limbs. But blood pressure values differ on each limb.

Blood pressure and *PTT* were measured during different physical exercises as ergonometric tests. It was shown that relationship between blood pressure and *PTT* can be used for evaluating blood pressure based on *PTT* during exercise. But in real situations, when arms are not still (e.g. with a subject running), the upper limb movements will affect the blood pressure distribution. The blood pressure varies with each position of arms because blood pressure is affected by hydrostatic pressure.

PTT is measured as the time interval between R wave from *ECG* and the time of arrival of pulse wave into the periphery during same cardiac cycle. The time markers on *PPG* waves differ in a lot of experiments. Some use foot or peak of *PPG* wave, other use some point between foot and peak. The peak of second derivation of *PPG* wave is also used as it is the sharpest change in the signal. At present, no comparative study reported which is the most reliable one.

Methods for obtaining *PTT* from *ECG* neglect the electromechanical delay between electrical and mechanical work of heart. During systolic phase there exists a time delay between R waves and the opening of aortic valve, called the pre ejection period (*PEP*). It means that pressure wave doesn't start with R-wave but after a short time delay. The *PTT* time, measured as time delay between R-wave and *PPG* wave, therefore includes the time delay between electrical and mechanical work of heart.

The BP-PTT model based on Moens-Korteweg equation correctly works for a testing group of people and shows high dependence between blood pressure and *PTT*. But if it is used on other group of people it doesn't perform so well. The reason is due calibration for measurement which are not clearly described. Several different calibration methods were proposed but none of them work reliably on each patient.

3.6 Limitations of measurement methods

Whatever the measurement method, the value of blood pressure can be affected by the state of the cardiovascular system and the existence of some pathologies. For the auscultatory method, which is the gold standard in non-invasive blood pressure method, the measurement will be unreliable and may not impracticable with irregular heartbeats caused by cardiac arrhythmia. If the arterial pulse pressure changes rapidly during measurement, the blood pressure monitor would

not be able to obtain a good reading. When the patient is severely shocked or in hypothermia, blood flow will be reduced resulting in weak pulses. If the radial artery pulse is too low, it is not possible to measure blood pressure. A thick layer of fat underneath the skin will have a damping effect on the signal which may be too weak when reaching the sensor in the cuff. In addition, with some diseases such as calcification of artery, sclerosis of artery, it is still possible to feel radial artery pulse even when the cuff is inflated at higher pressure than systolic blood pressure [58].

Most these limitations are applicable to other measurement methods, with some differences. In the oscillometric method, the amplitude of oscillations depends on the stiffness of the arteries and on the site of measurement. Tonometry method is affected by anatomical skin abnormalities (grafts, cysts, scarring, cuts or burns). Volume clamp method and pulse wave velocity method are affected by reduced blood circulation in peripheries and also diseases of arteries such as arteriosclerosis which affects transport pressure or pulse wave during arterial tree.

3.7 Conclusion

In summary, commercial possibilities currently exist for non-invasive monitoring of blood pressure. The devices mostly in used clinically, are based on volume clamp method. But these methods are uncomfortable for the patient for the long term monitoring during normal daily activities. Alternatively, the blood pressure can be evaluated from other biosignals such as ECG or PPG, which can be more conveniently measured from body surface, with no limitation and no disturbance to the patient.

Several authors described the relationship between blood pressure value and PTT. Many authors described different possibilities for evaluation of blood pressure based on PTT. PTT value was compared to other methods, such as invasive blood pressure, volume clamp method, and standard oscillometric method. The results showed high correlation between blood pressure and PTT.

Most experiments were based on signal processing on collections of data. Only a few authors investigated new solutions and devices for blood pressure measurement based on PTT. Currently none of the experiments took into consideration simultaneously all the above described problems. And yet none of the described algorithms and methods is proved reliable.

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4

Comparison of Methods for The Evaluation of NIBP from Pulse Transit Time

Contents

This part of the thesis investigates various methods for the evaluation of $CNIP$B from pulse transit time. It was analysed real signals which was obtained during surgical interventions in Hospital, with invasive measurements of blood pressure waves, and non invasive measurements of pulse waves and ECG signal.

It was shown a relationship between the blood pressure and the propagation of biosignals, electrocardiographic and photoplethysmographic, in human body [20]. In this part of thesis it was investigated this relationship from the analysis of biosignals and central pressure signals which were collected on 16 patients during clinical examinations.

4.1 Introduction

Propagation time of pulse wave is called pulse transit time (PTT) and it was shown it is correlated to the value of blood pressure. When the blood pressure increases, the velocity of pulse wave increases, thus time of propagation decreases. There is a time delay between the electrical activity of heart (ventricular depolarization) and the beginning of the pulse wave, which is called pre-ejection period (PEP). Because this period is included in the time propagation of R-wave, it isn't called PTT but pulse arrival time (PAT) and it is evaluated as equation (3.4).

$$PAT = PEP + PTT$$

For evaluation of PAT it is necessary to collect both ECG and PPG signals. ECG signal is used as time synchronization for correct assignment of each pulse wave to each cardiac cycle. Pulse transit time is defined as the time delay between R-wave arrival and some significant points of the pulse wave from the same cardiac cycle.

Significant points of the pulse wave are most of the time evaluated as the foot, the steepest part and the peak of the pulse wave. The foot of wave is a less reliable marker because the end of diastole can be affected with the inertia of blood vessel's wall which effect is a change in diameter. The shape of the signal depends on the interface pressure between the photoplethysmographic sensor and the skin. The most suitable significant point is the steepest part of wave; it occurs during the systolic cycle when the blood has the highest energy. This point is easily found as the peak of first derivation of signal.

Another method for evaluating the PAT, which doesn't need collection of ECG signal, is based on time analysis of forward and backward pulse waves which is based on wave reflection. When considering wave reflections in the arterial system there are two components of pressure wave: an incident wave travelling away from the origin, and a reflected wave travelling backwards toward the origin. After ejection of blood from the heart, the pulse wave travels straight till the first division of blood vessels, where it divides into three waves, two parts continuing in the forward direction and one part reflected backward to the heart as a backward wave. In a non-pathological affected cardiovascular system, the backward wave positively recombines to the blood flow because it affects the next forward wave during diastole. When the wall of blood vessel is stiffer, the velocity of pulse waves is higher and the backward wave affects the next forward wave during systole and the blood pressure increases. The blood pressure also depends on the time delay between forward and backward waves.

The aorta is a hydraulic system. The pressure wave which is generated by the hear-aorta interaction (forward wave) loses energy along its way. This energy is significant under marked arterial distensibility conditions which is value of arterial compliance in relation to the initial diameter of the artery. It is defined as a relative change in diameter in relation to the change in pressure. It was mentioned above that alteration in the mechanical properties of large arteries causes an increase in systolic blood pressure and a decrease in diastolic pressure, and, a consequence, an increase in pulse pressure. This difference between diastolic and systolic blood pressure becomes more marked because early superposition of the reflect wave. The increase in pulse wave velocity is the main sing of alternation in the viscoelastic properties of the wall of the blood vessel [5]. It means if the forward pressure wave travels faster owing to arterial stiffness, similarly, the backward pressure wave goes back to the heart faster. If vascular elasticity is reduced the two waves meet very early and their superimposition increase systolic value of blood pressure. The systolic peak is strongly affected by the backward waves [4].

4.2 Measurement Settings

It was the continuous invasive blood pressure, simultaneously with PPG and ECG signals during 3–5 minutes on patients after angiology intervention. The experiment involved 16 subjects (10 males and 6 females, aged 57 to 79 years) at the Hospital Trinec Podlesi (Ostrava, Czech Republic), a major cardiology center in the Czech Republic. The patients were lying at rest. Due to the invasive measurement of blood pressure, an ethical committee approval was obtained.

A dedicated hardware and software solution was developed for data collection. Hardware was powered on 9 Volts batteries for safety of patient. The sampling rate was 1000 Hz, higher than standard to detect short time delays between ECG and PPG, in the range of milliseconds.

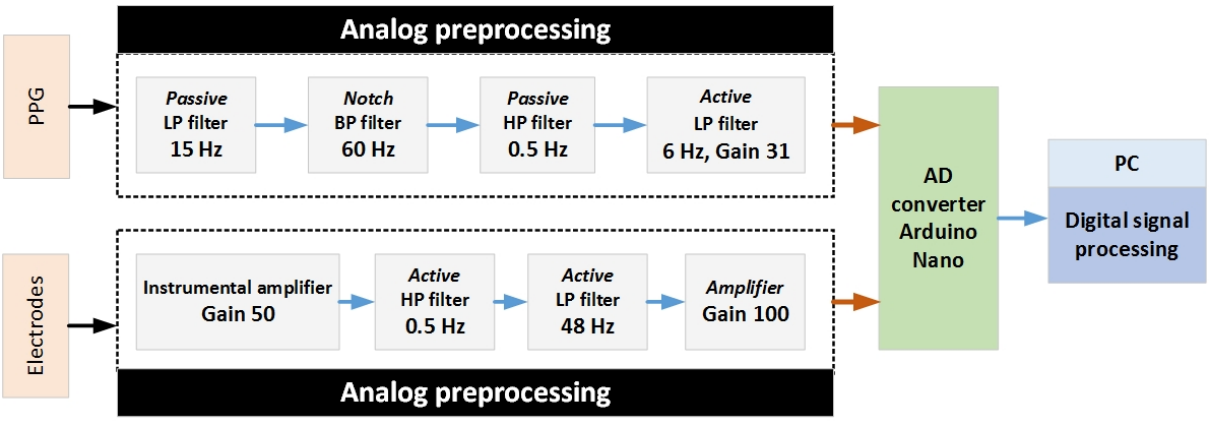

Figure 4.1 Block scheme of the hardware part developed. The device includes PPG channel and ECG channel. Signal from each channel is processed analogically for better digital conversion. A software-controlled multiplexor enables to connect the output of the same amplifier to all channels to evaluate the delay between samples of different channels.

One channel of shortened ECG from chest leads was measured. On half of the patients their PPG was measured from ear lobe and the other half from fingertip of left hand. Blood pressure wave was measured with an invasive extravascular sensor connected to a catheter placed in subclavian artery.

4.3 Evaluation of PAT

Pulse arrival time (PAT) is simply defined as the time interval between the R-wave from ECG signal and some significant point on the PPG wave in the same cardiac cycle. But the literature doesn't report precisely which is the best significant point on PPG wave for a better evaluation of the PAT. Thus we performed a signal analysis to compare the relationships of PAT with blood pressure value, using three different significant points from the PPG signal.

4.3.1 Detection of significant points

Detection of significant points was made in each cardiac cycle. It was necessary to segment signal to individual cardiac cycles. Segmentation of signal was based on detection of R-wave from *ECG*. One cardiac cycle is defined as the period of time between 2 successive systoles; this corresponds to the signal between two successive R peaks. This cycle includes one pulse wave and one pressure wave.

The segmentation is important, not only for the detection of significant points of the pulse and pressure waves but also for the decomposition of these waves into forward and reflected waves and identification of signal processing artefacts on 3D plots (Fig. 4.2 and Fig. 4.3).

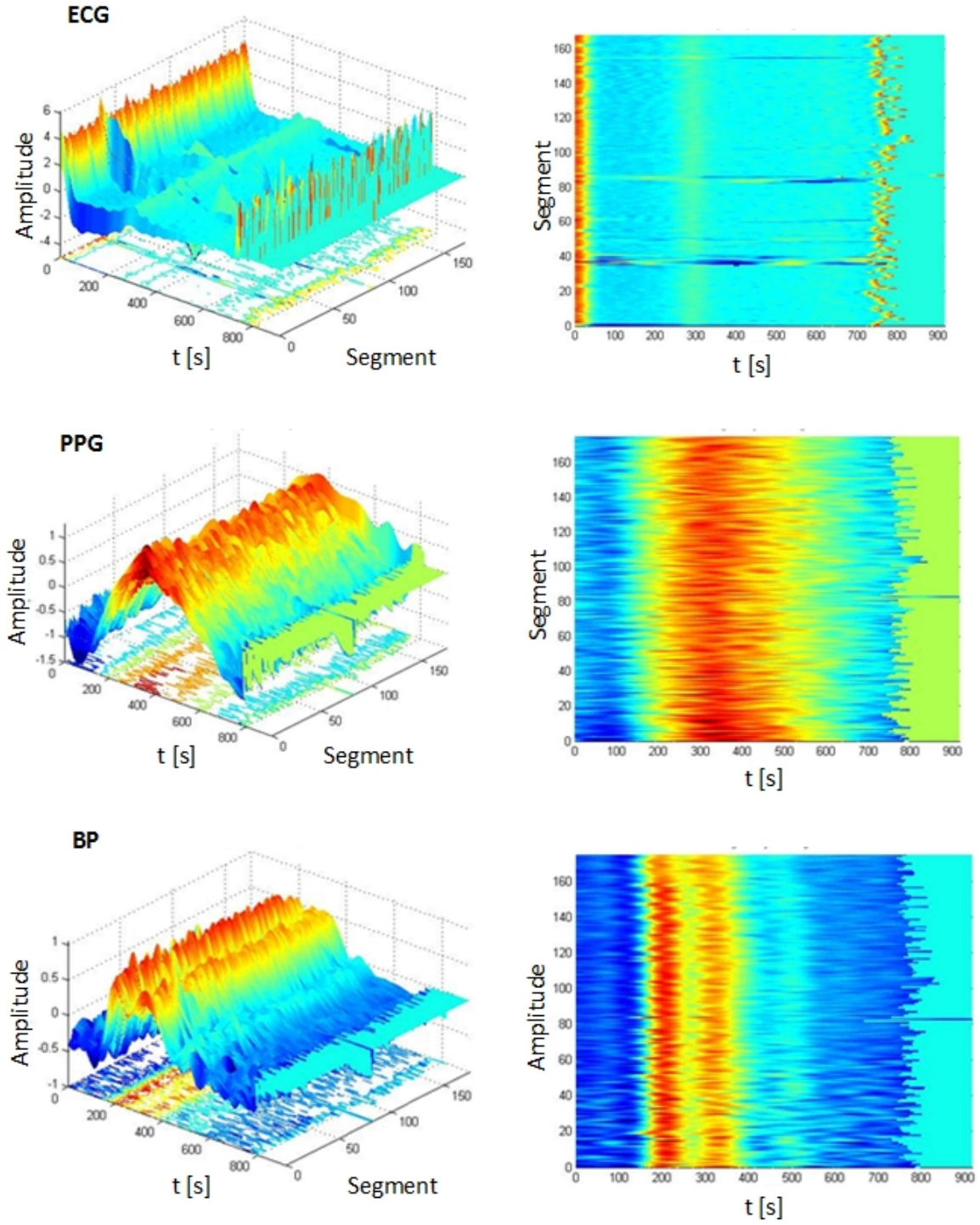

Figure 4.2 Cardiac pathology free patients. 3D plots of ECG, PPG and BP signal (from left to right). One can recognize moving artefacts on ECG which are not visible on the 2 other signals.

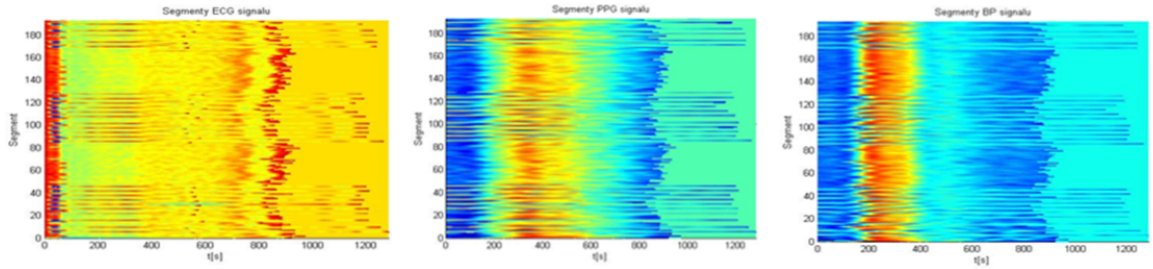

Figure 4.3 Patient with pathology. 3D plots of ECG, PPG and BP signal (from the left site). A pathology of extrasystole can be seen on both 3 measured signals.

The 4 significant points considered on pulse and blood pressure waves were: the start of wave (beginning of systole), the steepest part of systole, the end of systole and the peak of wave (Fig. 4.4). The significant points were evaluated in each segment.

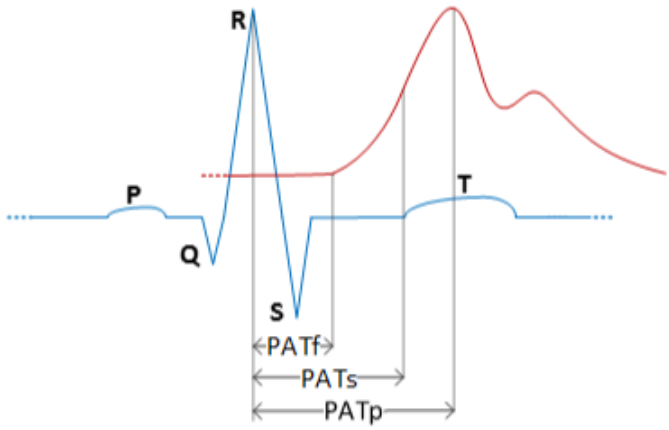

Figure 4.4 Evaluation of PAT as time delay between R-wave of ECG (Blue line) and foot ($PATf$), steepest part ($PATs$) and peak ($PATp$) of pulse wave (red line).

4.3.2 Detection of foot and peak

Detection of foot and peak of wave is based on analysis of first derivation of PPG and pressure signal. Each segment was differentiated, then negative part was removed for better detection of negative and positive zeros. Positive zeros correspond to signal changes from positive to negative values.

It is also possible to detect the end of systole at the smaller peak before peak of wave. This point is possible to find thanks to second derivation. In interval between foot and peak was found last negative zero which means last change of value of signal from negative to positive level.

PPG and blood pressure waves also include the dicrotic notch which is due to the reflection of the wave from aortic valve when it is closed after systole and reflection of forward wave from

deviation of artery. Dicrotic corresponds to the highest value of first negative wave after peak of pulse wave.

4.4 Decomposition in forward and backward waves

Thanks to reflected wave blood pressure increases and blood flow decreases. Decomposition of signal into forward and reflected wave was based on known equations for time dependent wave $Pm(t)$ which is sum of forward wave $Pf(t)$ and reflected wave $Pb(t)$ and it is also dependent on blood flow $Qm(t)$ which is possible to evaluate as algebraic sum of outgoing flow $Qf(t)$ and incoming flow $Qb(t)$.

$$Pm(t) = Pf(t) + Pb(t) \tag{4.1}$$

$$Qm(t) = Qf(t) + Qb(t) \tag{4.2}$$

$Pf(t)$ and $Pb(t)$ can be evaluated thanks to $Pm(t)$ and $Qm(t)$ and the characteristic impedance Zc [59], [4].

$$Qm(t) = ZcPm(t) \tag{4.3}$$

$$Pf(t) = 0.5(Pm(t) + ZcQm(t)) \tag{4.3a}$$

$$Pb(t) = 0.5(Pm(t) - ZcQm(t)) \tag{4.3b}$$

In fact $Pm(t)$ is one pulse wave in time. $Qm(t)$ can be evaluated from the triangular approximation of the blood flow (Fig. 4.5) when flow increases from start of systole to end of systole then decreases till dicrotic, when aortic valve is closed.

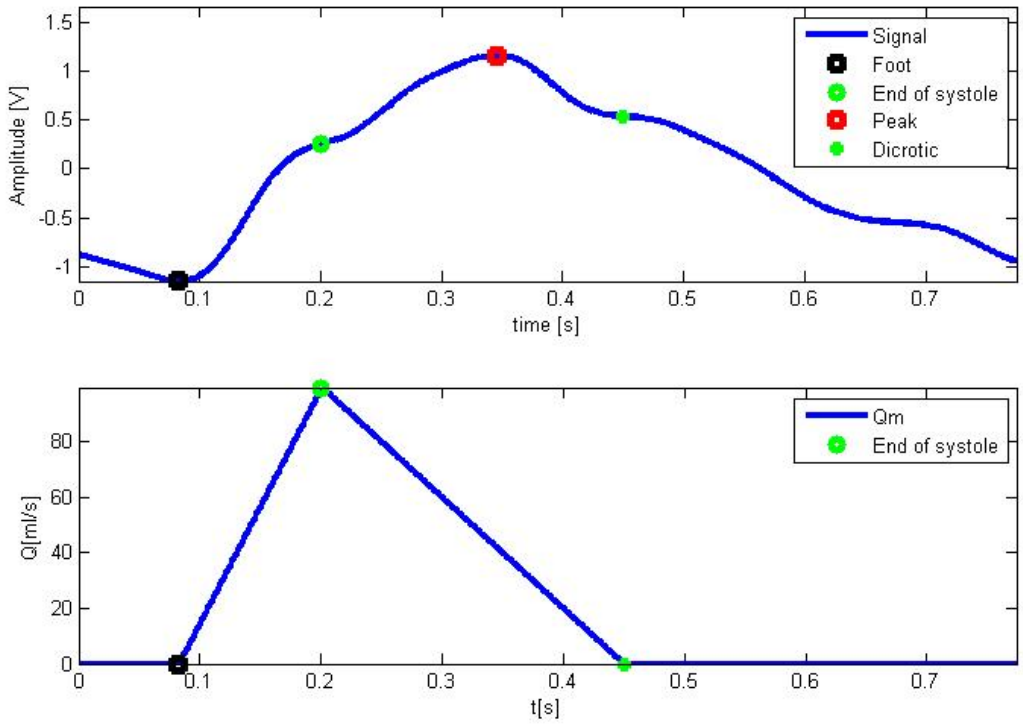

Figure 4.5 One pulse wave and corresponding theoretical profile of blood flow. One segment, one wave, of PPG signal. The significant points are: foot of wave (first green), end of systole (first red), peak of wave (second green) and dicrotic wave (second red).

Characteristic impedance Zc was evaluated as a function of frequency of the Fourier decomposition of $Pm(t)$ and $Qm(t)$ following equations (4.3a) to (4.3b) [60].

$$\frac{d[Pb(t)]}{dt} = 0 \tag{4.4a}$$

$$with 0 \leq t \leq endofsystole \tag{4.4b}$$

$$\frac{d[Pf(t)]}{dt} < 0 \tag{4.5a}$$

$$withendofsystole < t < dicroticnotch \tag{4.5b}$$

$Pm(t)$ and $Qm(t)$ were divided into real and imaginary parts (i.e. individuals sin and cos functions) and it was evaluated the amplitude $Am()$ and phase $Phase()$. Then input impedance was evaluated from:

$$Zc = \frac{Am(Pm)}{Am(Qm)} e^{(i(Phase(Pm) - Phase(Qm)))} \tag{4.6}$$

The forward and backward waves were computed knowing Zc in equations 4.3a and 4.3b.

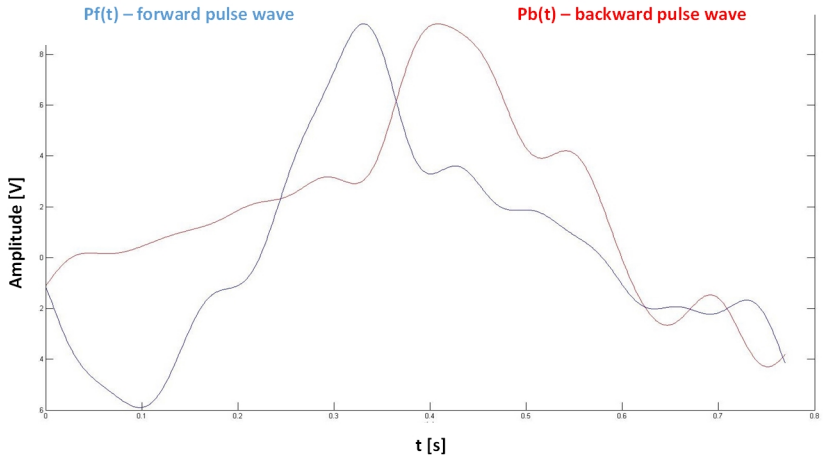

Figure 4.6 Forward (blue) and reflected (red) waves. A time delay is visible between these 2 waves.

Time delay between $Pf(t)$ and $Pb(t)$ was evaluated thanks to cross correlation at half time of maximum of cross correlation [61].

4.5 Summary of Evaluation of PAT

PTT was evaluated as interval between R-wave from ECG and 4 different significant points:

- Foot of wave ($PATf$)
- Peak of wave ($PATp$)
- Steepest part of wave ($PATs$)
- And also as a time delay between forward and backward wave (PTT).

Values of systolic and diastolic blood pressures were taken from pressure waves in each cardio cycle. Values of blood pressure were compared with all of PAT and PTT and with a statistical analysis.

4.6 Statistical Analysis

To establish a statistically significant relationship between pulse wave propagation times and values of blood pressure, we compared the correlations between the systolic blood pressure BPp and value of blood pressure of steepest part pressure wave BPs and the $PATs$, $PATp$ and PTT.

$PATf$ was removed because its detection is difficult due to the pulsation of artery wall during diastole. At this time the artery wall moves back to its original state when the stored kinetic energy returns back to the blood.

Bland and Altman make the point that any two methods that are designed to measure the same parameter (or property) should have good correlation when a set of samples are chosen such that the property to be determined varies considerably. A high correlation for any two methods designed to measure the same property could thus in itself just be a sign that one has chosen a widespread sample. A high correlation does not necessarily imply that there is good agreement between the two methods.

The Bland-Altman plot and analysis is used to compare two measurements of the same variable. That is, it is a method comparison technique if there is needed to evaluate the agreement between a variable X_1 and a second variable X_2 which each evaluates the same variable, such as different algorithm blood pressure measurement based on PTT. The Bland-Altman plot is formed by plotting the differences $X_1 - X_2$ on the vertical axis versus the averages $(X_1 + X_2)/2$ on the horizontal axis. A horizontal line represents the bias between the two tests which is measured by the mean of the differences calculated in the usual fashion as:

$$\bar{d} = \frac{1}{n}\sum_{k=1}^{n} d_k \tag{4.7}$$

Additional horizontal lines, known as limits of agreement, are added to the plot at $mean - 1.96S_d$ and $mean + 1.96S_d$. Limits of agreement between the two tests are defined by a 95 % prediction interval of a particular value of the difference which are computed as follows:

$$\bar{d} \pm 1.96S_d$$
$$where\ S_d = \sqrt{\frac{1}{n-1}\sum_{k=1}^{n}(d_k - \bar{d})^2)} \tag{4.8}$$

The graph displays a scatter diagram of the differences plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the limits of agreement. The limits of agreement (LoA) are defined as the mean difference $\pm 1.96S_d$ of differences. If these limits do not exceed the maximum allowed difference between methods Δ (the differences within mean $\pm 1.96S_d$ are not clinically important), the two methods are considered to be in agreement and may be used interchangeably.

4.6.1 Analysis of Instantaneous Data

The main propose of the analysis of this measurement is to investigated if blood pressure evaluation based on PTT measurement can be used for all of patient. It was investigated by linear regression and Bland-Altman analysis (Fig. 4.7).

Table 4.1 Comparison of the relationships between different *PTT* and blood pressure value collected from linear regression.

	Correlation Coeficient	R-square	P-value
BPp vs. PATp	0.25	6.02	0.0001
BPs vs. PTT	-0.42	17.37	0.0000
BPs vs. PATs	-0.43	18.12	0.0000
BPp vs. PTT	-0.69	47.79	0.0000

Based on Bland-Altman analysis it can e seen that *PTT* method for evaluation blood pressure measurement cannot be used because of its clinical inaccuracy. Nowadays can be acceptable differences in blood pressure measurement method 8 mmHg. It can be seen that bias is almost two times higher.

4.6.2 Analysis of Smoothed Data

Most standard medical devices used for continuous monitoring of blood pressure, are performing a moving average of blood pressure values. When using this method on our series of data we can make visible the relationship between biosignals propagations and blood pressures.

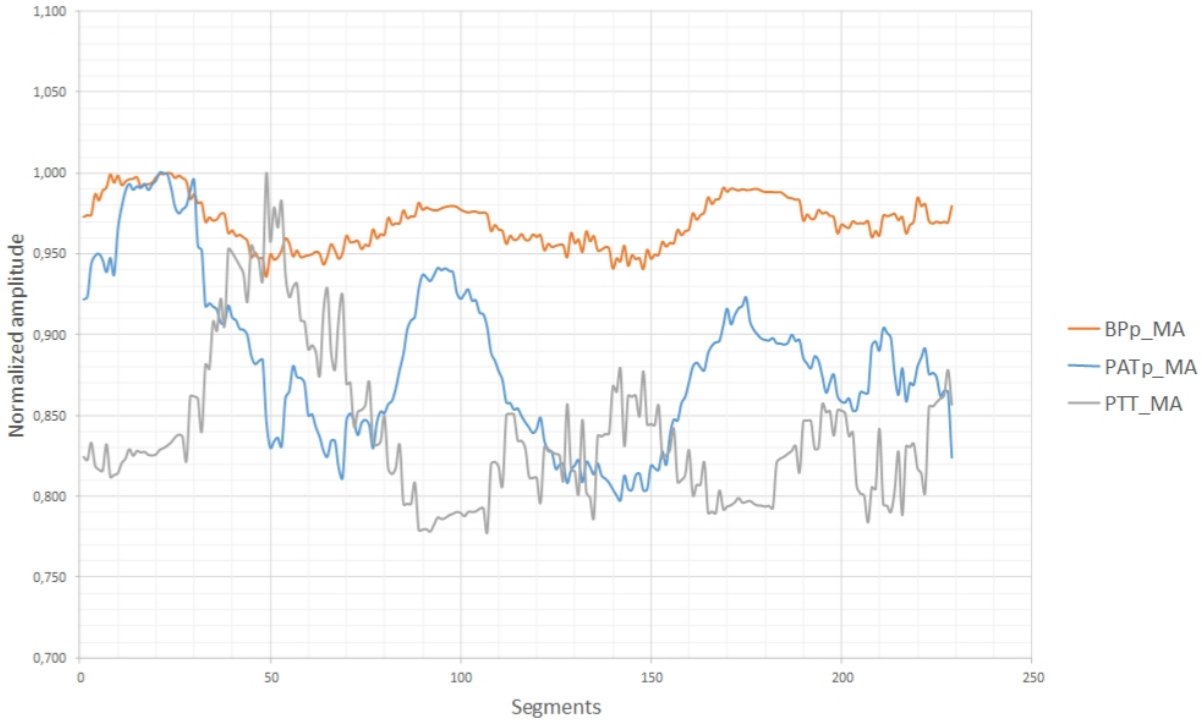

Figure 4.8 Plot of normalized moving average data. It can be seen there is some correlation between signals.

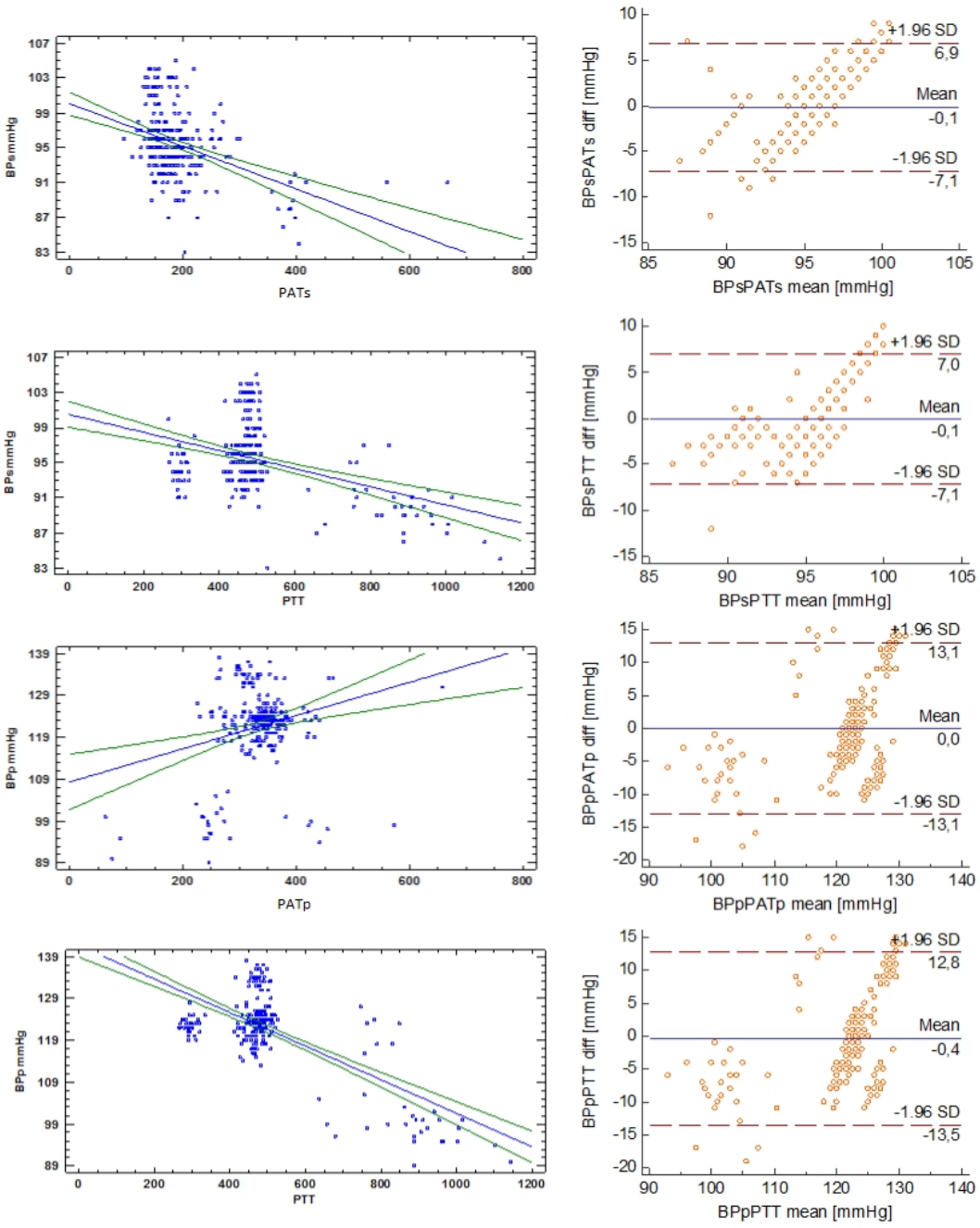

Figure 4.7 Long-time relationship between propagation of biosignals and blood pressure for instantaneous data of subject with cardiac pathology (extrasystole).

With 21 segments window of moving average we can see BP is directly proportional to PAT and inversely proportional to PTT. This is in concordance with the physiology of cardiovascular system.

From reformulated Moens-Korteweg (Eq. 3.3):

$$PWV = \frac{D}{PTT} = \sqrt{\frac{tE_0 e^{\alpha P}}{\rho d}}$$

Where PWV is pulse wave velocity, D is length of the blood vessel, t is thickness, d is diameter and ρ is blood density, E_0 is zero pressure modulus, P is blood pressure, α is a parameter of blood vessel and e is Euler's number, it is clear that when blood pressure (P) increases the PWV also increases but PTT decreases. This relationship is verified (Fig. 4.8) between blood pressure and PTT which is the time delay between forward and reflective pulse waves.

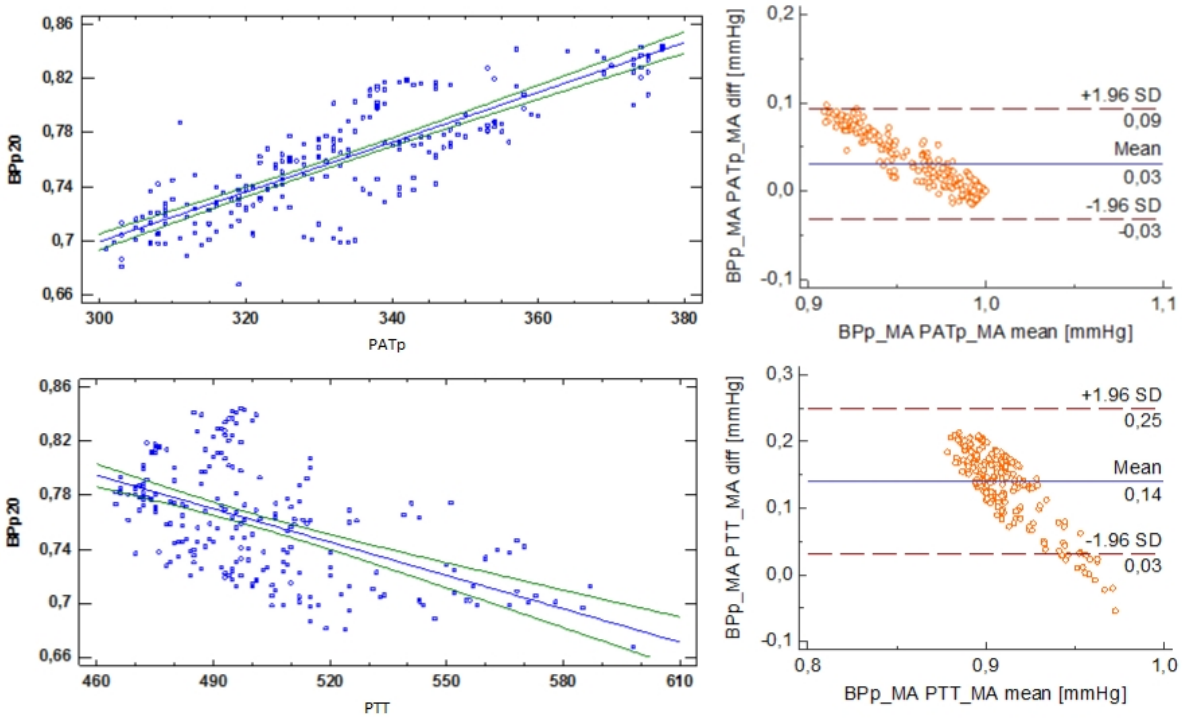

Figure 4.9 Long-time relationship between propagation of biosignals and blood pressure for moving average data of subject with pathology (extrasystole).

4.7 Discussion

Our experiment involved 16 patients at hospital who were monitored their blood pressure together with their ECG and PPG biosignals. We performed the analysis of relationship between

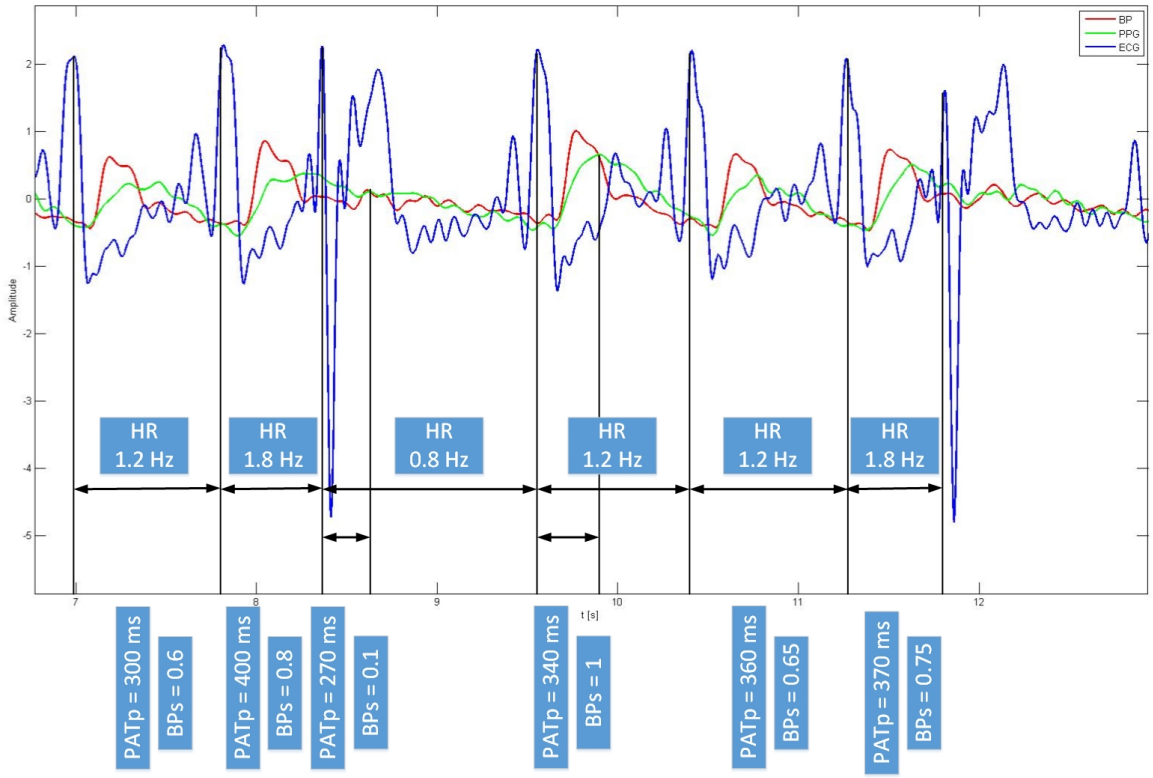

Figure 4.10 Blue curve represented ECG signal with pathology. The red curve represented signal of blood pressure wave. There is seen that after extrasystole is longer time delay to normal systole and after this normal systole is value of blood pressure higher than average value of blood pressure.

propagations of biosignals in human body and blood pressure values. We concluded there is no significant relationship between instantaneous values and thus it isn't possible to use common models of evaluation blood pressure based on PTT for instantaneous data. Better results are obtained when using moving average window for processing of obtained values.

One of the patient had pathology of cardiovascular system – extra systoles. Those signal is interesting because it shows that blood pressure also depends on heart rate. If there is a longer time delay between systoles, blood is given more time to fill the heart and thus immediate systolic blood pressure is higher than average pressure in artery system (Fig. 4.9). When extra systole occur HR increases but heart isn't fully loaded. BP value is much lower than average value but PAT is little different from average PAT (300 ms/0.6 BPsystolic; 270 ms/0.1 BPsystolic). Same problem is for normal systole right after extra systole. The heart has much more blood than during average cardiac cycle, BP is higher than average value but PAT is close to average PAT (300 ms/0.6 BPsystolic; 340 ms/1 BPsystolic).

It means that common model for evaluation of blood pressure cannot be used such simply. There are many factors which must be included such as instantaneous and preceding instanta-

neous heart rate or effect of backward wave. Pulse wave has to be analysed for the increasing accuracy of blood pressure evaluation based on propagation of biosignals.

PUBLISHED

A.1 PETER, Lukas, et al. Comparison of methods for the evaluation of NIBP from pulse transit time. In: Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the. IEEE, 2016. p. 4244-4247. *EMBC2016*

A.2 Peter, L., Foltyn, J., Cerny, M. (2015, January). Pulse wave velocity measurement; developing process of new measuring device. In Applied Machine Intelligence and Informatics (SAMI), 2015 IEEE 13th International Symposium on (pp. 59-62). IEEE.

5 Model of cardiovascular system

Contents

Cardiovascular hemodynamics is one of the most complex and one of the most important system in human body. With recent development of ambulatory and long term monitoring of cardiovascular hemodynamics, it is not only needed to develop communication and monitoring technologies but also to better understand the function in human body in order to develop new sensors approaches better adapted to long term noninvasive monitoring. Because it is infeasible on human or animal directly to adjust individual parameters of cardiovascular hemodynamics at full range, including in pathological situations, it is needed to build some model to have possibility to adjust safely each parameter without any risk. It could be mathematical or electrical model, but in this case it may be difficult to use mathematical model of a new sensor technology or to investigate a new approach of measurement so it is needed a physical model, based on fluidic circuit.

5.1 Introduction

Cardiovascular system is a very important system which is responsible for transport nutrient and oxygen to tissues. As a consequence, the cardiovascular system involves complex relationships between various systems in a living body. Therefore, it is difficult to run experiments with individual control of the different parameters and thus, it is interesting to work with a model.

Nowadays, in developed countries, Congestive Heart Failure (CHF) is one of the major causes of mortality. CHF means that the heart isn't able to pump blood as well as it should.

Certain conditions, such as narrowed arteries in the heart (coronary artery disease) or high blood pressure may cause that the heart is too weak or stiff to fill and pump blood efficiently. Monitoring of arterial pressure is also of main importance in many pathologies. Therefore, it is advantageous to measure blood pressure in real time and on long terms to know instantaneous state of cardiovascular system.

The Cardiovascular system is affected by many factors which makes it very difficult to describe the relationships between hemodynamic and others parameters or pathologies which affected function of cardiovascular system without invasive entrance. State of cardiovascular system is influenced by blood pressure which is determined by various factors. All of these factors are independent - blood flow, stroke volume, geometry of the arterial segment, compliance of the arterial wall, pulse wave velocity, pulse transit time, non-linearity of the arterial tree. The topology of arterial tree is unique for each person so all of these factors has to be determined to have good information about state of the individual cardiovascular system. The biggest problems are due to non-linearity of parameters of cardiovascular system. There are a lot of factors which can affect properties of arterial tree only locally which results in non-linear dependency between blood pressure and properties of the cardiovascular system.

To develop new sensors or new methodology of measurement, one need to be able to vary each parameter independently to correctly understand and describe function and behaviour of cardiovascular system due to its properties. This is not feasible on humans due to high variability and also changing properties of the cardiovascular system to see its work. Also it is not safe. Above all It isn't possible to provoke accidents like ischemia for instance. It is needed to developed model of cardiovascular system to perform test in safe conditions. There already exist some models of cardiovascular system. Mainly mathematical models which are able to simulate almost all of parameters and to watch effect of their changes. This kind of models cannot be used for testing of sensors for measurement of hemodynamics parameters or for experiments in real time just for mathematical simulations to describe relationships in the cardiovascular system. Relationship between hemodynamics parameters of cardiovascular system are difficult to monitor and describe in real conditions of human body. There isn't possibility to change blood pressure, heart rate or stiffness or artery wall and monitor changes in cardiovascular system. A multi-physics simulation of the cardiovascular system is not accessible. For this kind of purpose would be interesting to have some tool which be able to make this experiments without invasive entrance into the human body.

It will be useful to develop some loop which will allow to simulate cardiovascular system with access to the individual physiological parameters and possibilities to adjust independently the hemodynamic parameters or to provoke some pathology and watch their effects on function of cardiovascular system in real time. hemodynamics parameters. This loop should be able to reproduce physiological signal as outputs with real flow and pressure and be very close to real cardiovascular system, it means not only with internal parameters, such as the value of pressure or flow, but also with parameters of the arterial segments such as modulus of elasticity, width of artery wall, curvature of blood vessel and its bifurcations. Such kind of model could be used for description of real relationships between propagation of pulse wave, modulus of elas-

ticity and blood pressure and for testing under variable controlled conditions, the intravascular, extravascular or catheter pressure sensors.

5.2 State of the art of existing cardiovascular models

5.2.1 Extravascular circulation systems

Extravascular circulation systems are the only one artificial systems clinically used to mimic the cardiovascular circulation. This kind of systems are used for extravascular blood circulation during hemodialysis or during heart surgery. These extravascular systems use a pump which produce flow to build short "bridge" between two parts of body. It isn't real cardiovascular models because it isn't so important to evaluate and set all of parameters to be close to real cardiovascular system. It is used for short time solution for extravascular circulation This model doesn't need to reproduce the pulsatile flow.

The extravascular systems are limited in use for our purpose of the modeling of cardiovascular system because they don't propose to adjust the individual parameters separately.

5.2.2 Mathematical models

The mathematical modelling of the cardiovascular system is extremely complex and at the present time no model exists that is able to describe all the parameters of cardiovascular system. This model is based on a simplification of the cardiovascular system into smaller elements, each described by differential equations involving their individual physical properties. It is possible to describe any part of the cardiovascular system its physical parameters as volume, blood flow, blood pressure, stress of arterial wall, modulus of elasticity and others.

To develop precise physical model of the cardiovascular system which can be used for research, training or for testing of sensors is very difficult and is limited to some of cardiovascular conditions. In fact, it isn't possible to build whole physical model of cardiovascular system with all of its parts (due to quantity and length of all of blood vessels). The most common approach is a mathematical model of the cardiovascular system as a whole with an electrical equivalent.

The mathematical model is interesting for understanding some functions of cardiovascular system and its working in ideal conditions. Thanks to mathematical model it is possible to evaluate all changes in potential and kinetic energy which are produced by heart and blood vessels. It is also possible to investigate blood's forces which affect blood vessel walls during each heartbeat; it means to investigate the effect of modulus of elasticity on change in diameter of blood vessel for example. With mathematical model is possible to describe all parameters and all changes in cardiovascular system. Model can be very precise and close to real cardiovascular model.

Unfortunately, everything is modelled by software so it is a more global approach than the fluidic physical model in which is possible to access a particular segment as needed. It is not possible to reproduce real physical parameters such as the pressure or the flow in order to test developed sensors or some heart support devices. For this kind of test, it is necessary to develop

physical cardiovascular models or parts of it, which simulate real conditions of cardiovascular system in real time and which output real pressure and blood flow.

5.2.3 Electrical model

Based on the equivalence between hydraulic and electrical circuits, it was proposed to model the cardiovascular system as an electrical circuit which is based on a merging of lumped parameter method into a numerical model.

The electrical equivalent of physical cardiovascular system helps electrical engineers understand the phenomenon, but there is still need a conversion to work with the physical sensors.

Electrical analogy of the cardiovascular system is called the lumped parameter method (Fig. 5.1).

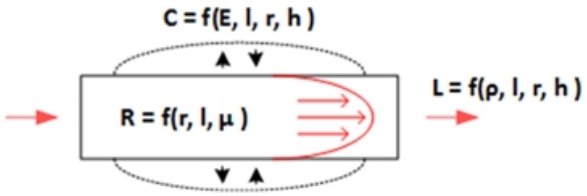

Figure 5.1 Scheme of blood vessel. Resistance is mainly function of diameter, compliance of modulus of elasticity and inertia of density of blood.

Each segment of the cardiovascular system can be simulated through an electrical circuit including a resistor (Eq. 5.1), which refers to the vascular resistance to the flow of the blood travelling through the systemic arterial system, a capacitor (Eq. 5.2) which refers to the elasticity and extensibility (compliance) of blood vessels and an inductor (Eq. 5.3) which simulates the inertia of the blood as it is cycled through the whole system.

In this electrical model, the continuous pulsatile flow (Volume per time unit) is equivalent to a current (Amperes) and the blood pressure (Pascal) is measured through a potential difference (Volts).

$$R = \frac{8l\pi\mu}{A^2}\ [Pa.s/ml] \tag{5.1}$$

$$C = \frac{3l\pi r^3}{2Eh}\ [ml/Pa] \tag{5.2}$$

$$L = \frac{9l\rho}{4A}\ [Pa.s^2/ml] \tag{5.3}$$

Where μ is blood viscosity, l is length of blood vessel, r and A are in respect radius and cross section of blood vessel, ρ is density of blood, h is thickness of blood vessel and E is modulus of elasticity.

Furthermore, the physical values of each 3 parameters of the cardiovascular system (Resistance, Compliance, Inertance) can be translated into the value of their equivalent electrical parameters (Resistance, Capacitance, Inductance) using the following correspondence table:

$$1\ Pa.s/ml = 1\ k\Omega\ (resistance - resistance)$$

$$0.01\ ml/Pa = 1\mu F\ (compliance - capacitance)$$

$$1\ Pa.s^2/ml = 1\mu H\ (inertia - inductor)$$

As we can see, the vascular resistance is directly proportional to the length of the vessel and the viscosity of the blood, and inversely proportional to the radius to the fourth power. The vessel diameter changes due to the contraction and relaxation of the vascular smooth muscle in the wall of the blood vessel. Because of inverse relationship to the radius of the fourth power very small changes in vessel diameter lead to large changes in resistance. Actually the Vessel length does not vary significantly and blood viscosity normally remains within a constant range. Thus It is the resistance which must be overcome to create the blood flow in cardiovascular system.

$$Q = \frac{\Delta p}{R}\ [ml/s] \tag{5.4}$$

The Arterial compliance is the ability of a blood vessel wall to expand and to accommodate surges in blood flow without increased resistance or blood pressure. Veins are more compliant than arteries and can expand to hold more blood. It is an index of the elasticity of arteries and it can be used as an indicator of arterial stiffness. When vascular disease causes stiffening of arteries, compliance is reduced and resistance to blood flow is increased and blood pressure also increase.

$$C = \frac{\Delta V}{\Delta p}\ [ml/Pa] \tag{5.5}$$

Electrical analogy of the cardiovascular system is called the lumped parameter method. The properties of each part of the cardiovascular system can be simulated thanks to an electrical circuit including a resistor, which refers to the flow resistance encountered by the blood as it flows through the systemic arterial system, a capacitor which refers to the elasticity and extensibility during the cardiac cycle and an inductor which simulates the inertia of the blood as it is cycled through the whole system.

Inertia of blood is the resistance of blood to any changes in its state of motion. This parameter describes the tendency of blood to keep moving at a constant velocity. Blood inertia accelerates and decelerates the blood velocity with every heartbeat. It relates pressure drop (Δp) to the rate of change of blood flow (dQ/dt).

$$\Delta p = L\frac{dQ}{dt}\ [Pa.s^2/ml] \tag{5.6}$$

As one can see, the length of the vessel is proportional to compliance (capacity) and inertance (inductance) and therefore, the longer the vessel the higher the compliance and the inertance. The cross section is inversely proportional to the resistance, thus the larger the cross section, the lower the resistance to flow. The blood viscosity only involves in the resistance as a proportional parameter because the more viscous is the blood, the higher is the resistance to the flow. But

the density of blood only affects the inertance as it acts on the inertia of the mass of blood.

We give some real physical properties of 4 selected sections of human aorta in table 5.1. It shows that there is a large variability in the geometrical properties (length, radius), in the intrinsic characteristics (Resistance, Compliance, Inertance) and the physical measurements (Pressure drop, mean velocity).

Table 5.1 Physical properties of different segments of a real human aorta.

	Length $[mm]$	Radius $[mm]$	Thickness $[mm]$	Stiffness $[Pa]$
Aorta Ascendens	40	14.5	1.6	400000
Arcus Aortae	20	11.2	1.3	400000
Aorta Thoracia	209	10	1.2	400000
Aorta Abdominalis	106	5.7	0.8	400000
	R 10^3 $[Pa.s/m^3]$	C 10^{-9} $[m^3/Pa]$	L 10^3 $[Pa.s^2/m^3]$	
Aorta Ascendens	9.2	0.59	66.3	
Arcus Aortae	13.0	0.17	55.6	
Aorta Thoracia	213.0	1.37	181.3	
Aorta Abdominalis	1023.4	0.19	568.9	
	PWV $[m/s]$	v_{mean} $[m/s]$	ΔP $[mmHg]$	
Aorta Ascendens	4.7	0.16	0.1	
Arcus Aortae	4.9	0.27	0.1	
Aorta Thoracia	5.0	0.36	0.2	
Aorta Abdominalis	5.3	1.05	0.8	

The radius of the aorta vessels reduce from central to periphery. To figure this influence, we have computed for different values of the radius, the intrinsic characteristics and physical measurements of the aorta segments.

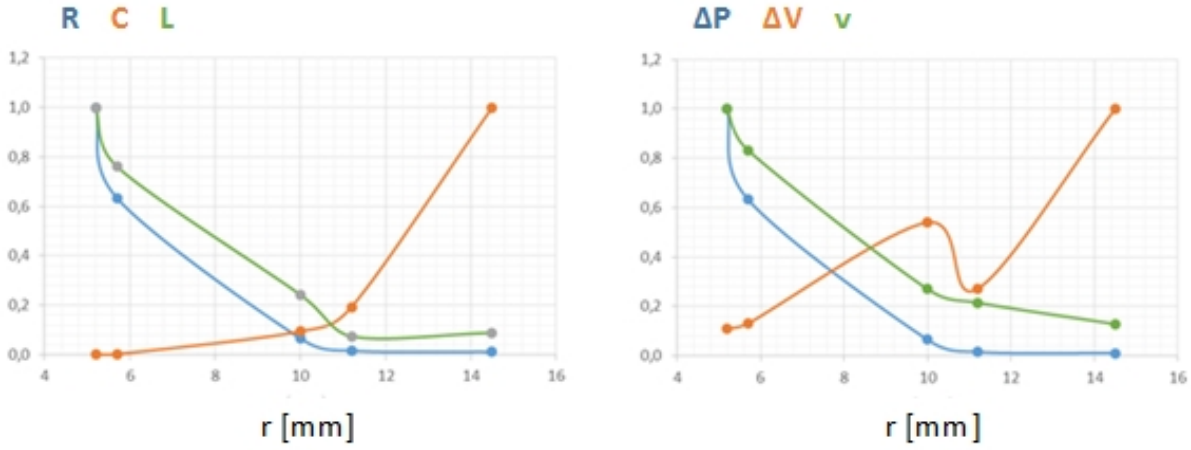

Figure 5.2 It can be seen that when the diameter of vessels reduces, from central to periphery, the capacitance decreases whereas the resistance and inertance increase. As a consequence, the flow reduces, the pressure drops and the velocity increases.

It can be seen that there is a relationship between ability of blood vessel to store energy of blood pressure and blood velocity. If blood velocity increases also pressure wave velocity increases time to storage energy of blood pressure to artery wall is shorter so it means blood pressure increases. When modulus of elasticity increases, compliance decreases. As a consequence, the pulse wave velocity and the blood pressure increase.

Each blood vessel, atrium, ventricle and set of all capillaries and arterioles can be modelled by a functional block consisting of a resistor, an inductance and a capacitor which are evaluated thanks to equations above.

Windkessel model

A model of cardiovascular system can be built with an electrical circuit by using the Windkessel model [62]. It is analogous to the Poiseuille's law for a hydraulic system to describe each part of cardiovascular system as component of an electrical circuit. Three different Windkessel models are available. Each Windkessel model can be used as equivalent of electric circuit for part of cardiovascular system. The Windkessel models include more electrical parts to reproduce more closely the real function of cardiovascular system.

The 2-elements Windkessel model [63] – one resistor, one capacitor to simulate resistance and compliance of blood vessel (Fig. 5.3a). The 3-element Windkessel model [63] (Fig. 5.3b) is based on the two-element Windkessel model with an additional characteristic impedance Z_0. The aortic characteristic impedance Z_0 account for the combined effects of compliance and inertance of the very proximal aorta, and thus forms a link with the transmission line models. The 4-elements Windkessel model [63] is a refinement with an additional inductor to model inertance of blood. In this kind of electrical equivalent of cardiovascular model is possible to describe and observe pressure waves, blood flow in continuous conditions (Fig. 5.3c).

A more accurate description of the pressure-flow relationship may be obtained by including more lumped elements in a lumped model of the cardiovascular system. For example the

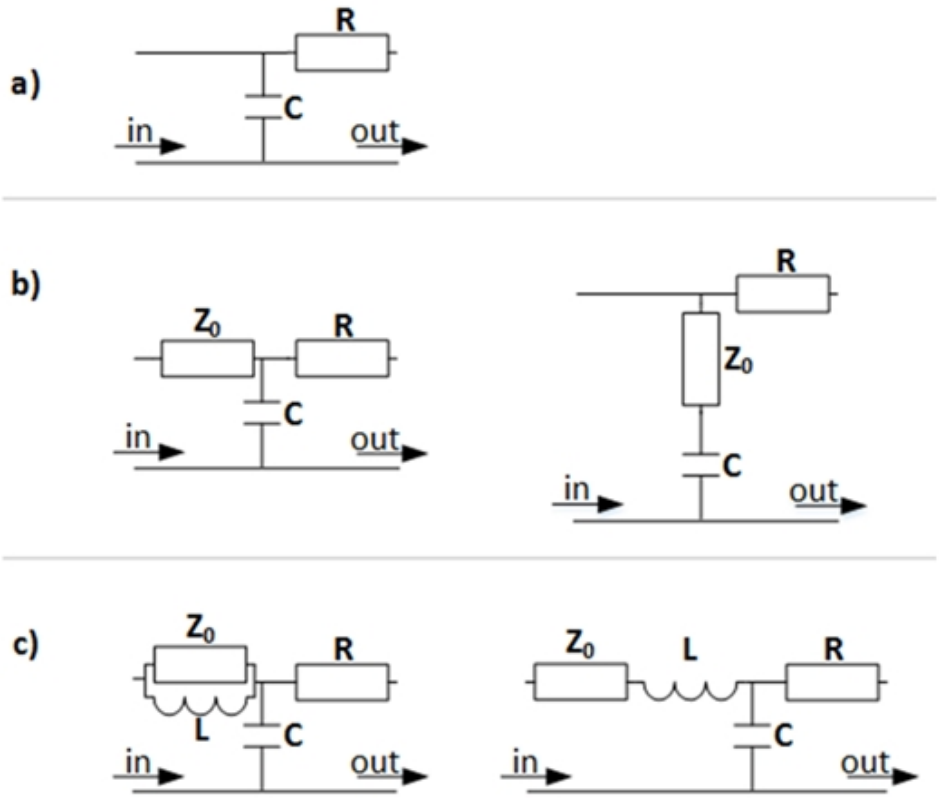

Figure 5.3 a) 2-elements Windkessel model; b) 3-elements Windkessel model by Westerhof and by Buratini; c) 4-elements Windkessel model by Stergiopulos and by Grant.

characteristic impedance Z_0, resulting in a better description of the high frequency modes of the aortic input impedance and accordingly a better prediction of the aortic pressure pulse. Increasing complexity of the lumped models provides better prediction of the pressure-flow relationship. However, as the number of lumped elements increase, the physical meaning and hence the determination of each individual parameter becomes less clear.

5.2.4 Mock circulatory loop method

Multiple mechanical circulatory support devices ($MCSDs$) have been developed in recent decades, including total artificial hearts ($TAHs$) and ventricular assisting devices ($VADs$) [64]. Under long-term support circumstances, a physiological control algorithm is necessary for an $MCSD$ to meet various physiological demands. It isn't possible to test it directly in human body so it is necessary to use some system which will be similar to cardiovascular system. For testing such kind of devices was developed Mock circulatory loop (MCL) [65].

It is an in vitro platform for evaluation of cardiac assistance technologies which can provide valuable insights to physiological control development prior to animal and clinical trials. Utilizing MCL as bench test methods for cardiac assistive technologies necessitates that they must be capable of reproducing the circulatory conditions that would exist physiologically. The flow of the MCL progresses serially through separate elements for arterial resistances, arterial com-

pliances, and venous volume, each simulating a parameter of the circulatory system. All of these parameters can be set continuously in a wide range of physiological and pathological conditions.

Prior to design the MCL elements, it is necessary to use lumped method for mathematical evaluation of properties of elements. Afterwards it is possible to develop MCL which will produce conditions similar to the human cardiovascular system.

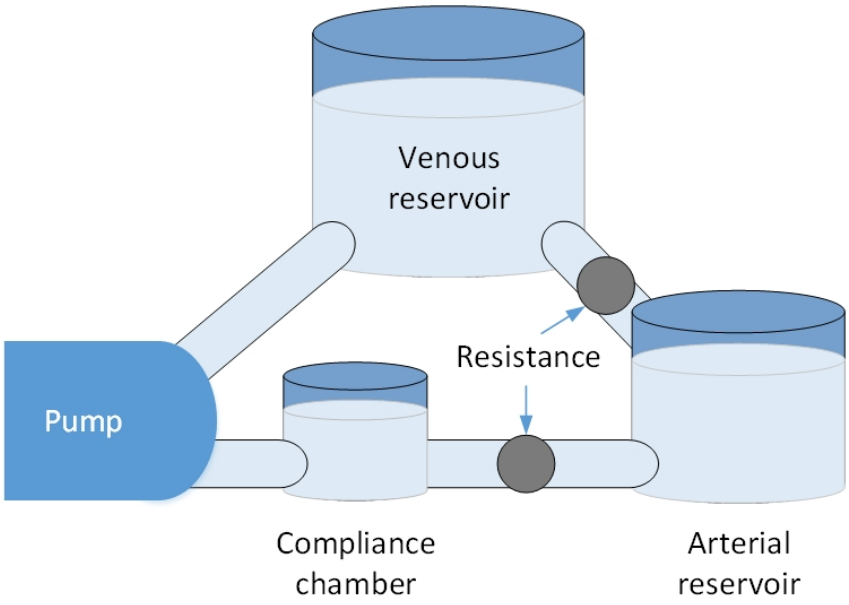

Figure 5.4 A Mock circulatory loop (MCL) consist in arterial and venous reservoirs to simulate compliance and resistance of whole human body, compliance chamber to simulate compliance of aortic segment and to set offset of pressure and adjustable valves to vary resistance to blood flow.

Thanks to MCL is possible to measure pressure and flow changes but without variations of modulus of elasticity and other properties of artery segments. This model was developed to simulate global body hemodynamic properties. It isn't possible to access the relationships between propagation of pulse wave, blood pressure and blood flow in individual segments. Also it isn't possible to test sensors of pressure, flow and other for the monitoring of cardiovascular system in real conditions in different segments of modelled cardiovascular system. Therefore, this model of MCL isn't suitable for testing sensors and for investigation of new approaches to monitor and evaluate state of the cardiovascular system.

5.3 Design of the physical model

We can conclude that only physical models can reproduce in real time the phenomenon, in order to test the newly developed sensors both in normal and extreme situations (hypertension), but also in accidental situations (ischemia can be simulated by clamping the model), with no risk for the patient. It is necessary to combine all possible methods for modeling the cardiovascular system to develop physical model which correctly mimics the behaviour of the cardiovascular system, in order to support future developments for new monitoring approaches of the various

parameters of the cardiovascular system.

There is no existing physical model of cardiovascular system giving the possibility to adjust all the hemodynamics parameters in large ranges of variations. Such kind of model would be beneficent for monitoring changes of pulse wave propagation and blood pressure based on hemodynamic parameters. It isn't possible to build a model of cardiovascular system which includes all blood vessels with their parameters. In human body there are thousand kilometers of blood vessels. It is necessary to make some approximation of some sections of cardiovascular system.

In order to reproduce the pulsatile flow in human body we used a pulsatile pump (Harvard Apparatus [1]) which is currently used in clinical situations as an external heart. This type of pump can simulate the heart of bigger animal with the possibility to change basic hemodynamic parameters. For instance, it is possible to set the stroke volume in the range 5-30 ml, the heart rate in range 0-200 bpm and the ratio of systole to diastole in the range 25/75.

To model the blood vessel segments we used tubes and tubules with given properties like the inner diameter, width of artery wall and modulus of elasticity. Silicone was selected because this material has closest properties to real blood vessel tissues. In addition, we also used PVC and Teflon materials, with different compliance, to open the possibility to simulate pathology of arterial segments and for monitoring the pulse wave properties based on changing in arterial tree.

We modeled the aortic segment as a separate part, for the measurement of pulse wave propagation. Rest of arterial tree was modeled with reservoirs mimicking its resistivity and compliance. The venous tree was simply modeled with a reservoir.

The Liquid we used was water, which viscosity is 1 $mPa.s$ (or 1 cPo), and to further simulate real properties of blood we also used a solution 60 % water and 40 % of glycerine which viscosity is 4 $mPa.s$.

We built a close circulation loop which was based on adjustment of a Mock circulatory loop. We can change some hemodynamics parameters and monitor changes of pulse wave propagation, with the possibility to change blood flow, range of pressure – value of systolic, diastolic and pulsatile pressure only with changing resistivity, compliance of artery segments or heart rate or stroke volume of pulsatile pump.

5.4 The first approach

In our first approach, we investigated the basic relationships of hemodynamics parameters, and patterns reproduction of pulse and pressure waves. It was based on very close model to MCL. We built a model of cardiovascular system which contains segments of aorta from different materials, one reservoir for simulating the compliance of artery tree, one reservoir for simulating compliance and volume of venous tree and one valve to change resistance of artery. Actually it was needed to add one more chamber at the beginning of the model of aorta to simulate the aortic arch which is the biggest energy storage at each systole of the heart. Without this chamber negative blood pressures would appear.

[1] http://www.harvardapparatus.com/pumps-liquid-handling/pulsatile-blood-pumps.html

The first experiment was used for optimizing the pattern of the arterial pressure wave. Thanks to the model it was possible to obtain a wide range of variations of the hemodynamic parameters like stroke volume, frequency, pressure, etc. In addition, this simplified model made it possible to evaluate the influence of material (silicone, PVC) of the vessel on the hemodynamic parameters.

The aortic segment was made of two successive parts with different stiffness, one made of silicone and the second from PVC tube. This setting was used in order to investigate the effect stiffness on the pattern of the pressure wave and its change due to velocity of pressure wave which is connected to ability of the wall of blood vessel to store energy of blood pressure which means also with blood pressure.

5.4.1 Settings of the first experiment

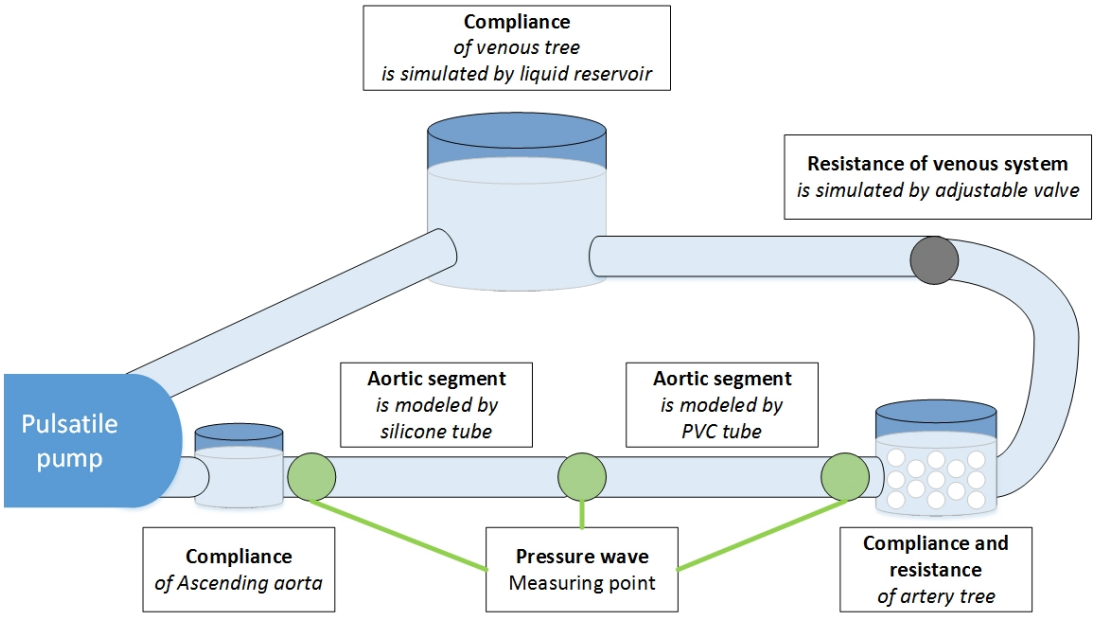

Figure 5.5 Simplified model of cardiovascular system. This model included one chamber as simulator of compliance of aorta, two successive segments with same geometrical properties (diameter, thickness of the wall and length) but with different modulus of elasticity and one chamber as compliance and resistance of artery three.

The compliance of ascending aorta was modeled by seal circular plastic box (diameter 96 mm and height 70 mm) filled with liquid till half level to reach maximum compliance with minimum resistivity (Fig. 5.6)

$$R = \frac{\Delta P}{Q} \sim 0\ \Omega$$

$$C = \frac{\Delta V}{\Delta P} \sim 0.22\ \mu F$$

The first and second segments of aorta, just after compliance chamber, were modelled by silicone and PVC tubes. The modulus of elasticity of materials are rarely available from manu-

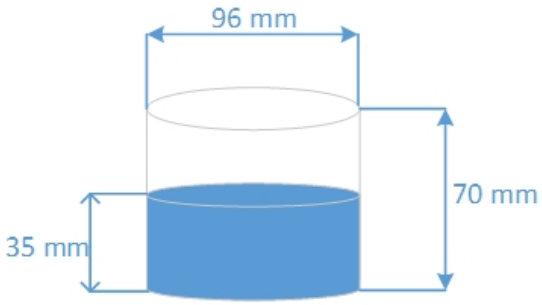

Figure 5.6 Physical model of the compliance of ascending aorta.

facturers' datasheets but they often mention the Shore hardness of their materials.

Thanks to [66] it is possible to compute the modulus of elasticity from Shore hardness. Hardness may be defined as a material's resistance to indentation. The durometer scale was defined by Albert Ferdinand Shore, who developed a device to measure Shore hardness in the 1920s. The term durometer is often used to refer to the measurement as well as the instrument itself. Shore's device was not the first hardness tester nor the first to be called a durometer, but today that name usually refers to Shore hardness.

$$E = 10^{(ShA*0.0235-0.6403)}\ [MPa] \tag{5.7}$$

We can compute the stiffness of the two different tubes we used to simulate different rigidity of blood vessels (Tab. 5.2.

Table 5.2 Stiffness of used materials.

	Shore	Modulus of elasticity [MPa]
Silicone segment	ShA	2.61
PVC segment	ShA	13.25

In the following table, we compare the characteristics of the 2 segments in our model to to the real aorta (Tab. 5.3).

Table 5.3 The comparison of physiological model of aorta and physiological human aorta.

	Silicon/PVC tube	Physiologic aorta]
Length [cm[	30	Range 30–45
Inner diameter [cm]	1.23	Range 1–2.8
Width of wall [mm]	1	Range 0.7–1.6
Modulus of elasticity [MPa]	2.61/13.25	Approximately 0.4

The first two segments of our aorta model were made of silicone and PVC tubes having following properties:

R - Silicon/PVC tube

$$R = \frac{8l\pi\mu}{A^2} = 534\ \Omega$$

C - Silicon

$$E = 2.61\ MPa$$

$$C = \frac{3l\pi r^3}{2Eh} = 0.0126\ \mu F$$

C - PVC

$$E = 13.25\ MPa$$

$$C = \frac{3l\pi r^3}{2Eh} = 0.00245\ \mu F$$

It can be seen that rigid PVC tube present less ability to store energy of pressure within its walls.

The Resistance of arterial tree was modeled by plastic box fulfilled by small glass balls. Resistance of arterial vessel is inversely proportional to the power 4 of the radius of artery (Eq. 5.1). Therefore a little change change in radius causes a large change in resistance. In the human body arterial tree radius of blood vessel is decreasing with distance from the heart. There are also bifurcations associated with the reduction in radius of vessels. Resistance of capillaries are so big, that blood pressure could lead to rupture of one individual vessel. Actually, the total resistance is due to the parallel association of resistance of several vessels, which reduces the total resistance and thus cancel risk of rupture.

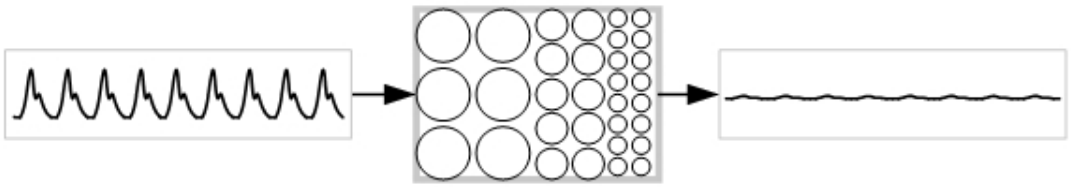

Figure 5.7 Resistance of all arterial tree was modeled by plastic box fulfilled by glass balls. This system converts the flow from a pulsatile to a constant one, together with the drop in pressure from maximum systolic down to 3 mmHg.

Those boxes are small plastic boxes with very rigid wall. The glass balls inside the box, reduce the pulsatility of blood flow to constant, so there is no change in volume.

$$C = \frac{\Delta V}{\Delta P} \sim 0\ \mu F$$

$$mean\ pressure\ in\ front\ of\ the\ box = 107\ mmHg$$

$$mean\ pressure\ afte\ the\ box = 11\ mmHg$$

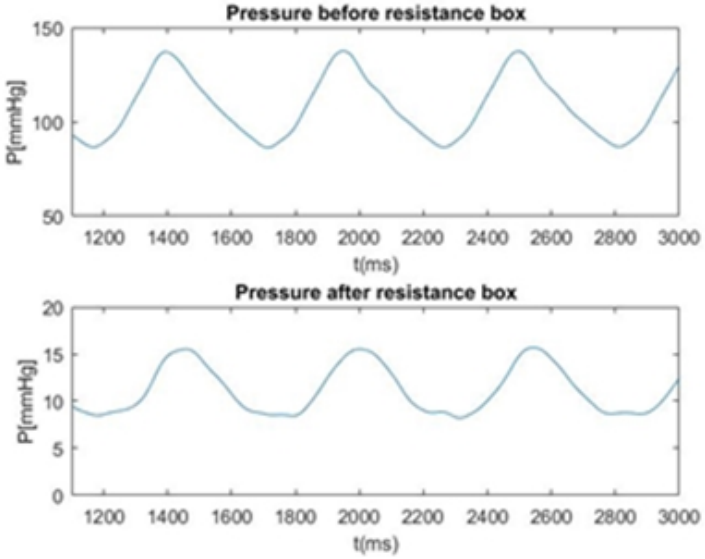

Figure 5.8 Pressure wave measured thanks to model in front of box and behind box. It can be seen that pressure drop is pulsatile pressure wave/pulsatile flow is almost reduced to continuous.

$$pressure\ drop\ due\ to\ the\ box = 96\ mmHg$$

Pressure drop due to the box which simulate vascular resistance is similar to pressure drop in the human body due to vascular resistance.

For all of measuring was set global parameters:

SV = 15 ml/s	Stroke volume
25/75 Pulsatility	25 % of systole, 75 % of diastole in each cardiac cycle
HR = 40–150 bpm	Heart rate was changed continuously

5.4.2 Validation of The Model Compare to The Human Body Aortic Segment

In computations "A" denotes real aorta and "M" denotes model.

Table 5.4 Set and computed parameters

	Aorta	Silicone	PVC
Heart rate [bpm]	90	90	90
Stroke volume [ml]	80	15	15
Cardiac output [ml/s]	120	22.5	22.5
Viscosity [Pa.s]	0.004	0.001	0.001
Length of segment [m]	0.414	0.3	0.3
Average radius of segment [m]	0.0299	0.00615	0.00615
Average thickness [m]	0.0012	0.001	0.001
E - Modulus of elasticity [MPa]	0.4	2.61	13.25
R - Resistance of segment [Pa.s/l]	1318.0	534.3	534.3
C - Compliance of segment [ml/Pa]	0.000152	0.000126	2.45E-5

SVR - systemic vascular resistance

$$SVR = \frac{\Delta P_M}{CO_M} = \frac{Mean\ arterial\ pressure - Mean\ right\ venous\ pressure}{CO_M}$$

Physiological systemic vascular resistance	$12 \pm 2\ mmHg.min/l$
Model vascular resistance water (H_2O)	$74 \pm 7\ mmHg.min/l$
Model vascular resistance glycerine (GLY)	$67 \pm 2\ mmHg.min/l$

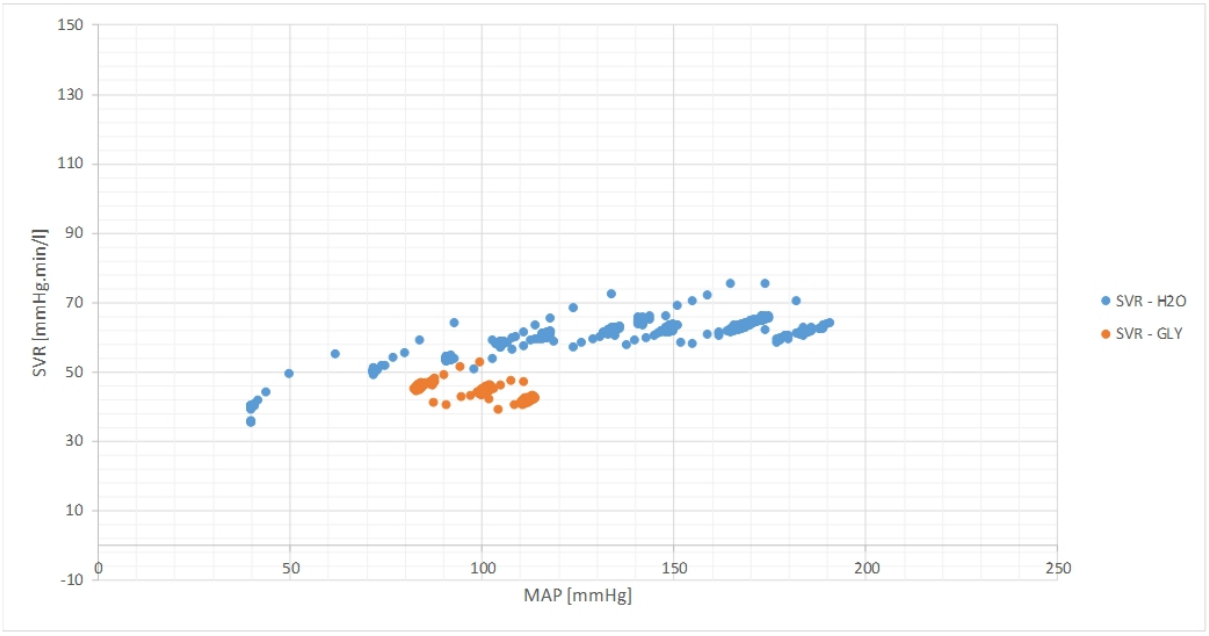

Figure 5.9 Systemic vascular resistance of model based cardiovascular system. It can be seen that it is affected by mean arterial pressure value at lower range of MAP but is almost constant at higher range of MAP.

To obtain the same drop in pressure in our physical model as in the real cardiovascular model it is necessary to adjust cardiac output which is based on heart rate and stroke volume which means it is necessary to adjust stroke volume.

$$CO = \frac{\Delta P}{SVR}$$

Computed value

$$SVR_A \approx \frac{SVR_M}{5}$$

Value for the model

$$\Delta P = SVR_A \cdot CO_A$$

$$\Delta P_A = \Delta P_M$$

$$CO_A \cdot \frac{SVR_M}{5} = CO_M \cdot SVR_M$$

$$\mathbf{CO_A = 5CO_M}$$

Set value

$$SV_A = 5SV_M \rightarrow \mathbf{CO_A = 5CO_M}$$

The set vascular resistance thanks to resistance box and right adjusted stroke volume occur same drop pressure in model as in the human body.

Q - blood flow

Physiological blood flow	$160 \pm 20\ ml/s$
Model blood flow H2O	$283 \pm 105\ ml/s$
Model blood flow GLY	$430 \pm 130\ ml/s$

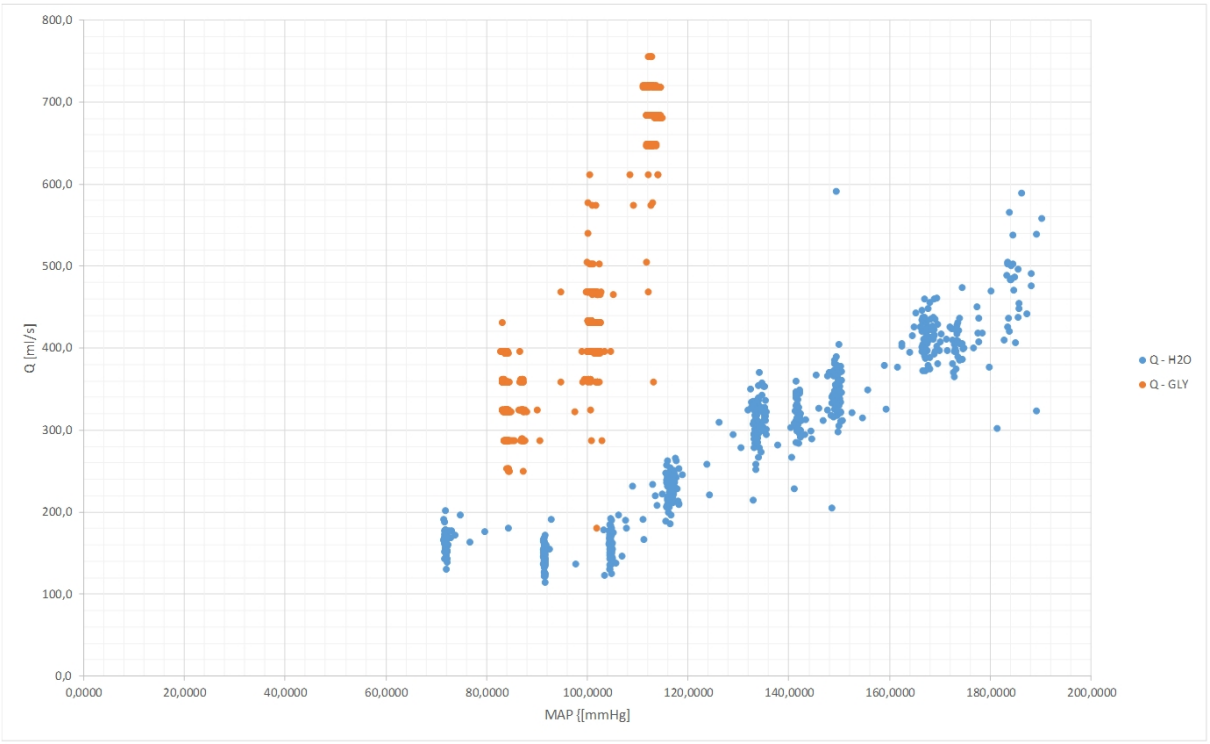

Figure 5.10 The change in blood flow due to mean pressure value. It can be seen that change in blood flow is higher with more viscous liquids.

$$\Delta P = Q \cdot R$$

Computed value

$$R_A \approx 2.5R_M$$

Value for the model

$$\Delta P_A = \Delta P_M$$

$$Q_A \cdot R_A = Q_M \cdot R_M$$

$$Q_A \cdot 2.5R_M = Q_M \cdot R_M$$

$$\mathbf{Q_A} = \frac{\mathbf{Q_M}}{\mathbf{2.5}}$$

Set value

$$\mathbf{Q_A} = \frac{\mathbf{Q_M}}{\mathbf{2.2}}$$

5.4.3 Pulse Wave Analysis

For the analysis of the dependency between pressure value and properties of propagation of pulse wave we evaluated some basic parameters of the blood pressure wave (Fig. 5.11).

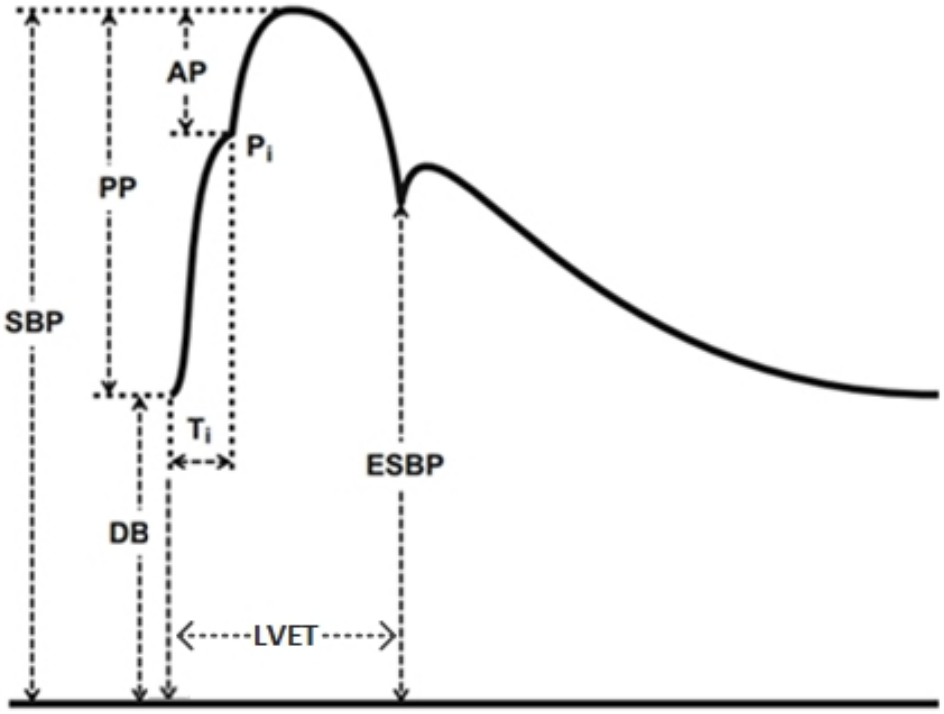

Figure 5.11 Parameters of pulse wave analysis.

Systolic blood pressure	SBP	The maximum blood value in systole
Diastolic blood pressure	DBP	The blood pressure in end diastole
Pulse pressure	PP = SBP - DBP	The systolic diastolic change
Mean arterial pressure	MAP	Mean of the single instantaneous blood pressure values
End systolic blood pressure	ESBP	The blood pressure value at the end of systole, Dicrotic notch
Travel time of the reflected wave	Ti	The time delay of the backward waveform
Blood pressure at inflection point	Pi	The blood pressure value corresponding to the point where the backward wave starts superimposing onto the forward wave

The inflection point (Pi) corresponding to the point where forward and backward waves meet. In most cases it is easily recognize in pulse wave analysis. For the evaluation of this point is used

analysis of the fourth derivative as Pi corresponds to the zero-crossing of the fourth derivative after the first positive peak.

Augmented pressure	AP = SBP - Pi	The increase in blood pressure due to the earliness of the backward wave
Augmentation index	Aix = 100*AP/PP	The percentage increase in blood pressure with regard to pulse pressure

The augmentation index (Aix) is a parameter which provides an indication of the incidence of reflected waves on the total pulse pressure. The factors affecting Aix are basically the same as those affecting central blood pressure. It is affected by Arterial stiffness, heart rate, magnitude and variability in reflected waves, mainly in relation to systemic vascular resistance in the same way as in blood pressure [5].

Left ventricular ejection time	LEVT	Duration of the systolic phase
Diastolic time	DT	Duration of the diastolic phase
Heart period	HP	Duration of the cardiac cycle, corresponding to R-R interval in ECG (start start interval in pressure wave)

Evaluated data were used for the analysis of the model based measurement.

The pulse wave velocity can be used for non invasive evaluation of elasticity of aortic part. It can be also used for indirect blood pressure evaluation but it is inaccurate because there is little information about parameter of each segments of blood vessel such as thickness, stiffness or diameter. Pulse wave propagation is affected by properties of the blood vessel resulting in changes in blood pressure.

For the evaluation of blood pressure based on Moens-Korteweg equation we also need the parameter α which isn't described clearly and which significantly affects blood pressure value (as it can be seen above). This parameter will be probably also affected by hemodynamic parameters.

PWV - pulse wave velocity

As seen in Chapter 3, the PWV can be computed knowing the modulus of elasticity (Eq. 3.1):

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

With the elasticity modulus set to:

$$E_{silicone} = 2.61MPa$$

$$E_{PVC} = 13.25MPa$$

Set value

$$\mathbf{E_A} = \frac{\mathbf{E_{silicon}}}{\mathbf{6.5}} = \frac{\mathbf{E_{PVC}}}{\mathbf{33.1}}$$

Computed value

Aorta	Silicone	PVC
PWV=4.97 m/s	PWV=14.57 m/s	PWV=32.8 m/s

Based on the Moens-Korteweg equation it can be seen that PWV should be should be constant for a constant conditions (modulus of elasticity, geometrical dimensions). Pulse wave propagation is based on changes in blood pressure, which means it cannot be constant. We must used edit Moens-Korteweg equation which is dependent on blood pressure value. The main problem is constant α which is defined for each blood vessel separately. Other constant like thickness and stiffness can be evaluated thanks to calibration of measurement.

$$PWV = \sqrt{\frac{E_0 e^{\alpha P} h}{2\rho r}}$$

For the known average pulse wave velocity in the aorta 4.97 m/s can be α evaluated as:

$$\alpha = \frac{1}{P} ln(\frac{2\rho r PWV^2}{E_0 h}) \tag{5.8}$$

With expectation of predefined blood pressure values and known constant values such thickness and stiffness, α can be experimentally defined.

BP [mmHg]	α	PWC [m/s]
105	0.011299	4.5
110	0.010786	4.7
115	0.010317	4.8
120	0.009126	4.9
130	0.009126	5.1
140	0.008475	5.4
160	0.007415	6.0

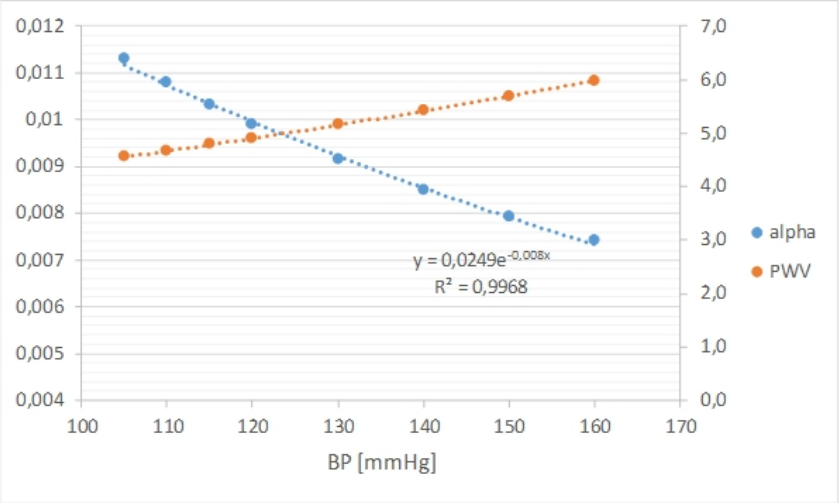

Figure 5.12 The α parameter is not a constant value and it is changing with pulse pressure velocity changing. Evaluated parameter of α was used for evaluation of PWV in the model.

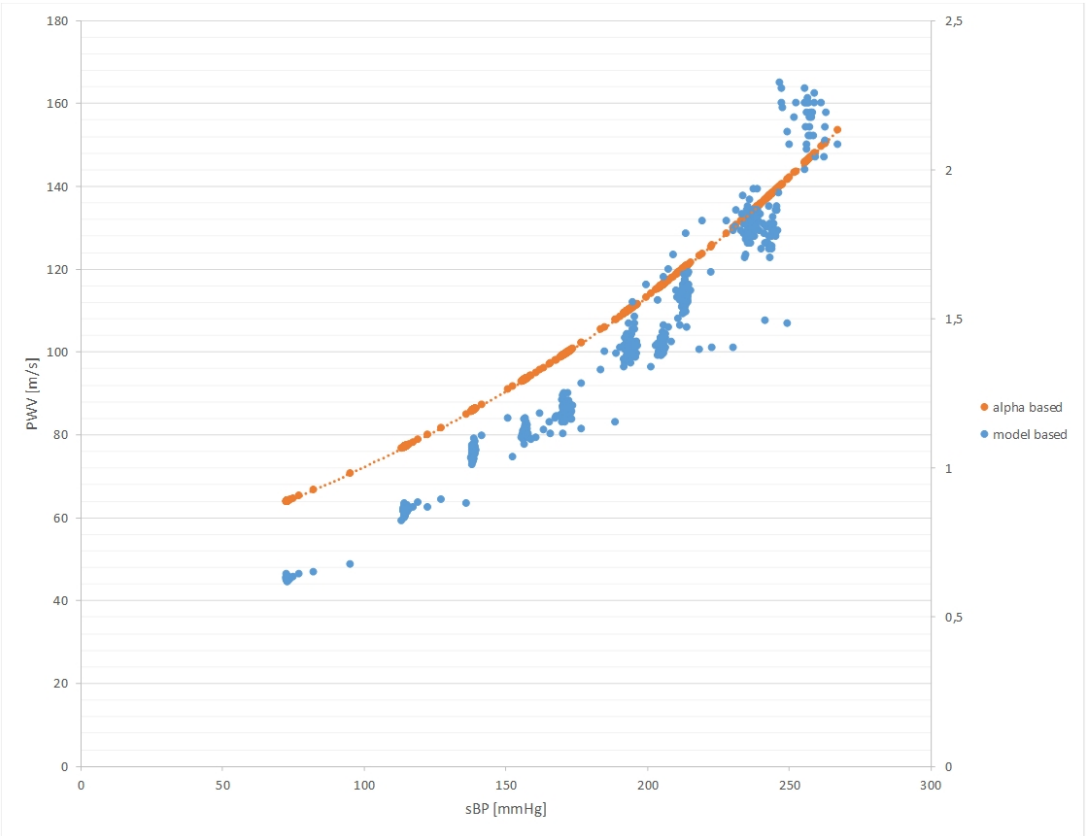

Figure 5.13 The PWV evaluated thanks to α parameter for physiological aorta which was used for evaluation of the PWV in the model and PWV evaluated directly from the developed model of cardiovascular system.

The relationship between blood pressure and constants can be writen as:

$$P = e^{\alpha P} = \frac{2\rho r PWV^2}{E_0 h}$$

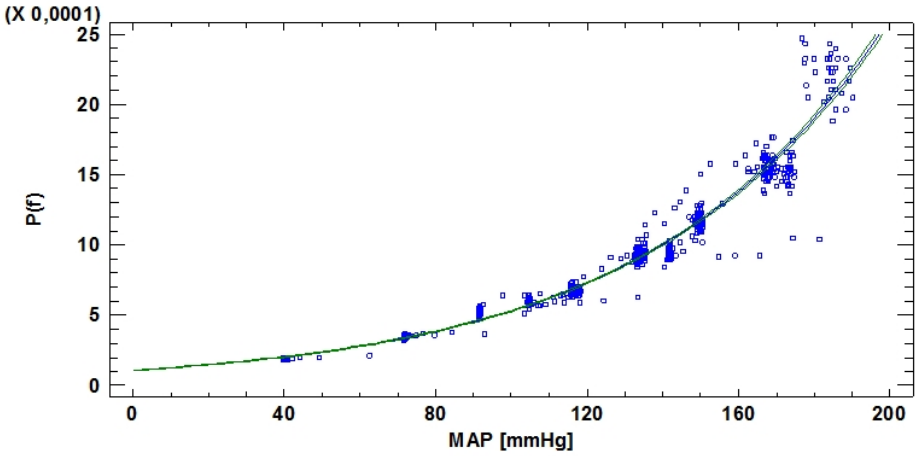

Figure 5.14 The function $e^{\alpha}P$ is called as function of pressure based on blood pressure. There is a visible relationship between MAP and $P(f)$. This relationship can be evaluated in ideal conditions when all of properties of artery segment are known. Evaluation is based on regression analysis.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**-9.13915**	0.01147	-796.492	**0.0000**
Slope	**0.015966**	0.000089	178.444	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	279.558	279.558	31842.36	**0.0000**
Residual	6.0841	0.00878		
Corelation Coefficient		**0.9893**		
R-squared		97.87 percent		
Standard Error		0.0937		
Mean absolute Error		0.0687		

The R-Squared statistic indicates that the model as fitted explains 97.87% of the variability in alpha after transforming to a reciprocal scale to linearize the model. The correlation coefficient equals 0.989293, indicating a relatively strong relationship between the variables. The standard error of the estimate shows the standard deviation of the residuals to be 0.0936986. This value can be used to construct prediction limits for new observations by selecting the Forecasts option from the text menu.

The stiffness and thickness, diameter and density are constants, which describe properties of cardiovascular system which affect pulse wave propagation (as its compliance and ability to store kinetic energy into the wall of blood vessel) It seems that instantaneous blood pressure is affected by pulse wave velocity and constant of α. The question is, how is parameter α itself affected by

hemodynamic parameters as heart rate, pulse transit time between forward and backward wave and amplification of blood pressure in each pressure wave. Could it be evaluated based on these parameters?

The same questions should be asked for the pulse wave velocity and its dependency on the hemodynamics parameters. For evaluation of PWV is necessary to know distance between measured points. Little errors in the evaluation of this distance, can bring increasing errors during long time measurements.

For the evaluation of PWV and α is necessary to know precise cardiovascular parameters which are not possible to measure in standard conditions (thickness of artery wall, modulus of elasticity, etc.). Pulse wave propagation is also affected by this parameters. It is possible to analyse time travel of pulse wave, systolic and diastolic intervals, attenuation and heart rate. These parameters are measured very easily and could reflect all of properties of blood vessels which can affect blood pressure value.

5.4.4 Evaluation of α

$$\alpha = \frac{1}{P} ln(\frac{2\rho r PWV^2}{E_0 h})$$

$$\alpha = \frac{1}{P} ln(K \cdot PWV^2)$$

Effect of HR

The parameter α is affected by the heart rate (Fig. 5.15). The dependency is same for both liquid (Fig. 5.16).

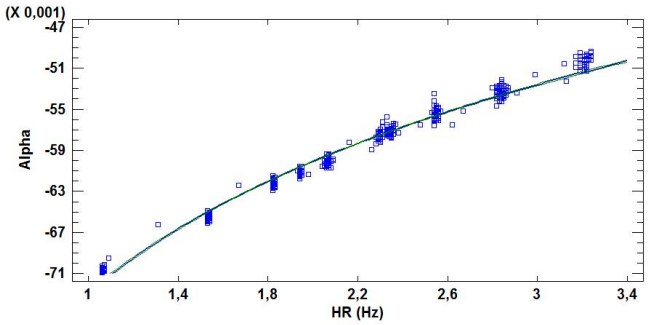

Figure 5.15 It was previously evidenced the relationship between variations in blood pressure and heart rate. In mots cases, when heart rate increases, pulse wave increases and the blood pressure increases as well. The change in HR affects also α parameter.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**-0.0725**	0.0000094	-766.861	**0.0000**
Slope	**0.01803**	0.0001186	-151.995	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	0.018	0.018	23102.4	**0.0000**
Residual	0.00054	7.795E-7		
Corelation Coefficient		**-0.9854**		
R-squared		97.10 percent		
Standard Error		0.00088		
Mean absolute Error		0.0006		

Parameter α can be describe with dependency on HR as:

$$\alpha = \mathbf{a} - \mathbf{b} \cdot \mathbf{lnHR} \tag{5.9}$$

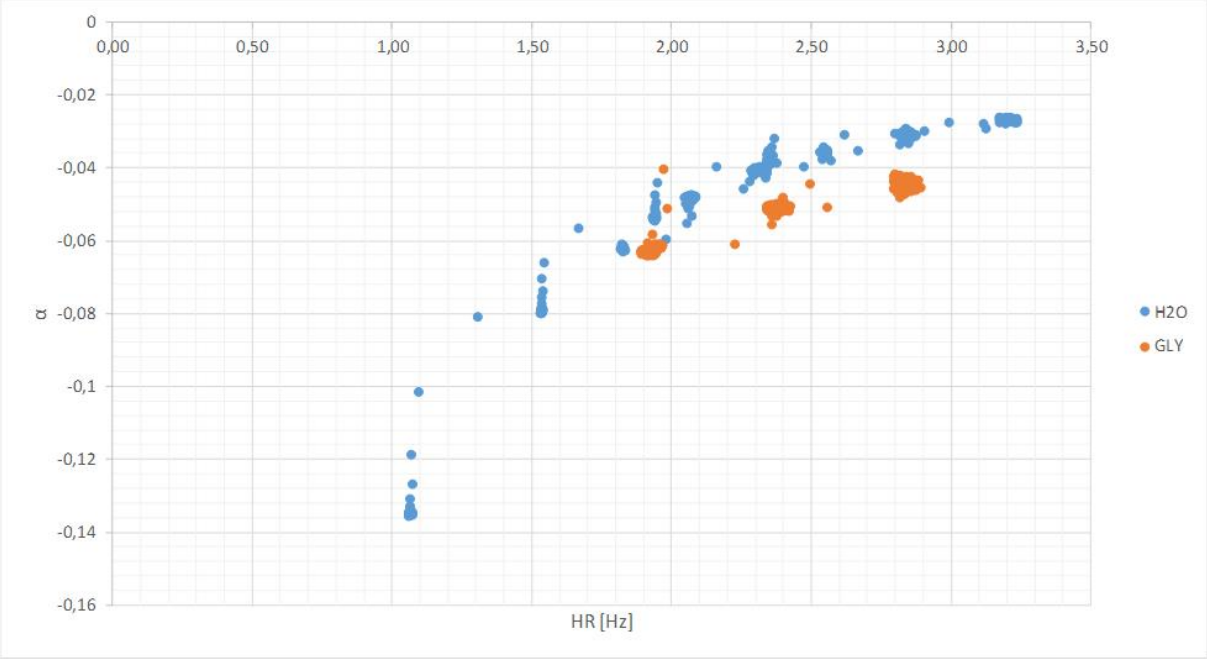

Figure 5.16 Relationship between alpha and HR can be described equally for water (H_2O) and glycerine (GLY).

Effect of time delay of backward wave

Another parameter which affect blood pressure value is attenuation of pressure wave based on backward and forward superimposition. Backward wave affects systolic phase of pressure wave.

It is also dependent on properties of blood vessel wall as stiffness, thickness and diameter. Time delay between forward and backward wave is evaluated at the inflex point (Fig. 5.11). Time delay affects alpha parameter, this phenomenon can be seen for both liquid (Fig. 5.18).

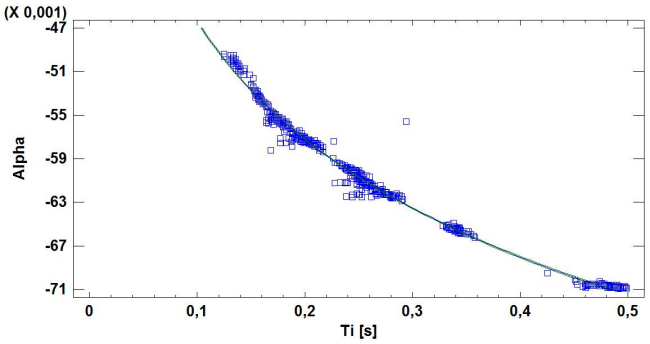

Figure 5.17 It can be seen significant relationship between alpha parameter and time travel of backward wave. Alpha parameter affects blood pressure as was mentioned above but it is obvious that alpha itself is affected by other hemodynamic parameters.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**0.0255**	0.00035	73.46	**0.0000**
Slope	**-0.0156**	0.000064	-244.3	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	0.019	0.019	59698.4	**0.0000**
Residual	0.00022	3.203E-7		
Corelation Coefficient		**-0.994**		
R-squared		98.8 percent		
Standard Error		0.00056		
Mean absolute Error		0.00032		

Parameter α can be described with dependency on Ti as:

$$\alpha = \mathbf{a} - \mathbf{b} \cdot \mathbf{lnTi} \tag{5.10}$$

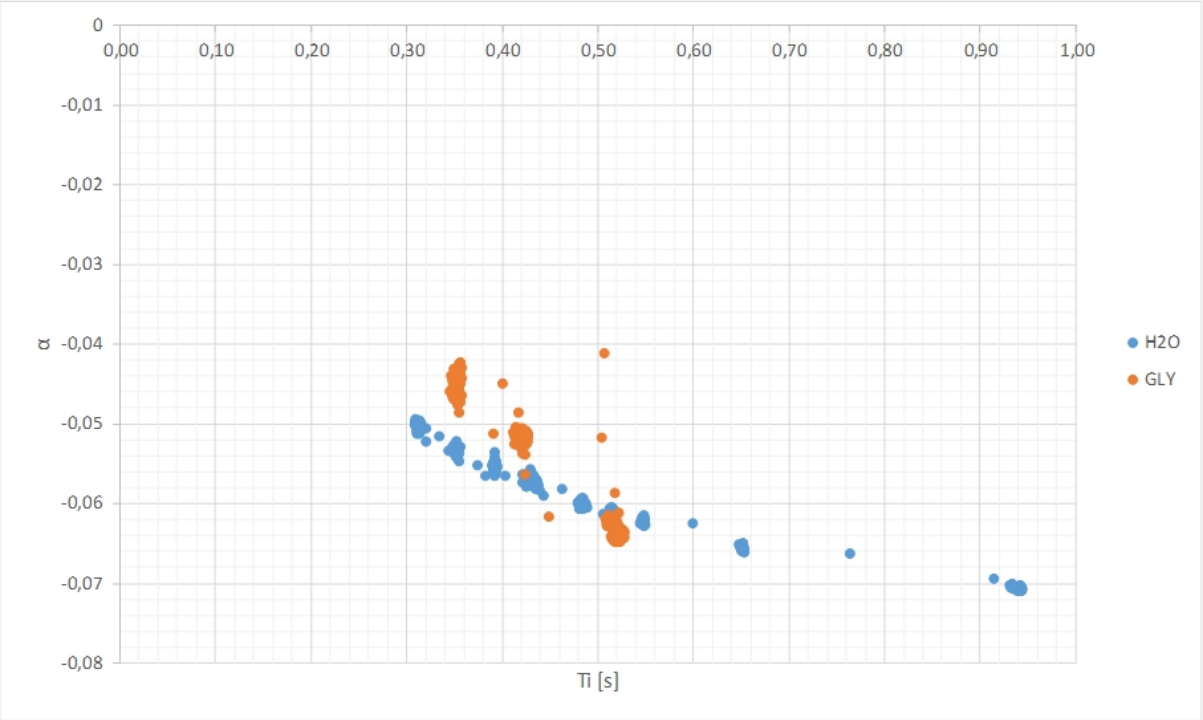

Figure 5.18 Relationship between alpha and Ti can be describe equally for water (H_2O) and glycerine (GLY).

Effect of systolic augmentation

One important parameters which can be evaluated form pulse wave is the augmented pressure (AP, see Fig. 5.11). Under different arterial stiffness conditions, there is early superimposition of backward waves onto the forward wave, causing a localised increase in systolic blood pressure. Augmentation index should be useful parameter to quantify the role of wave reflection in high blood pressure values.

$$Augmentation(AXi) = SBP - Pi$$

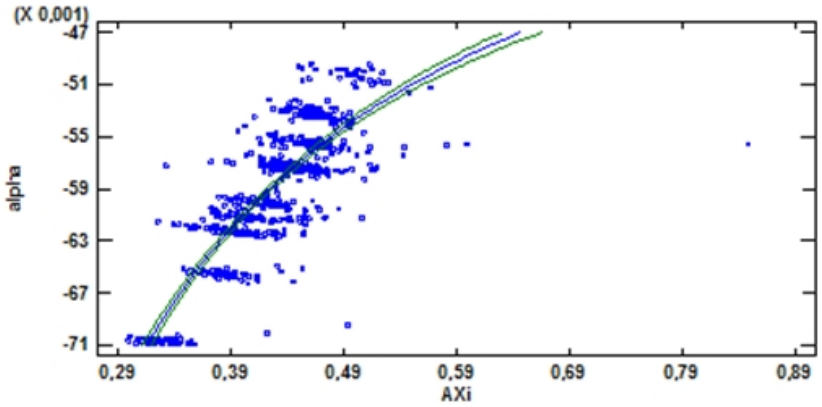

Figure 5.19 The relationship between α parameter and augmented pressure.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**-0.024**	0.00086	-28.08	**0.0000**
Slope	**-0.015**	0.00036	-40.86	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	0.014	0.014	1669.7	**0.0000**
Residual	0.0057	8.1E-6		
Corelation Coefficient		**-0.84**		
R-squared		70.6 percent		
Standard Error		0.0029		
Mean absolute Error		0.0022		

The relationship between alpha parameter and augmented pressure isn't so clear. Augmented pressure is one of the parameter which has to be evaluated. This parameter substitute evaluation of modulus of elasticity. It shows the ability of the blood vessel to absorb pressure force into the wall. In the human body there is a tissue around blood vessels which affects its ability to expand due to pressure. The model was without this options so the relationship isn't so clear. This relationship has to be investigate also under this set up. Relationship between augmented pressure and alpha parameter for water and glycerine can be seen in figure 5.20

Parameter α can be described with dependency to AXi as:

$$\alpha = \mathbf{a} + \frac{\mathbf{b}}{\mathbf{AXi}} \tag{5.11}$$

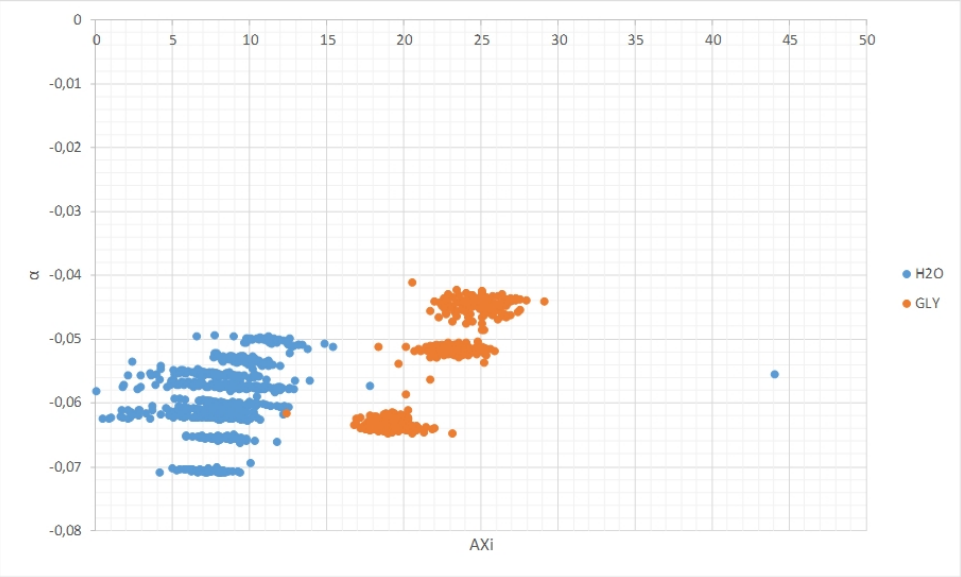

Figure 5.20 Relationship between alpha and AXi can be describe equally for water (H_2O) and glycerine (GLY).

Heart rate, time delay of backward pulse wave and attenuation pressure are parameters which affect parameter alpha.

$$\alpha = A + B \cdot ln(HR)$$

$$\alpha = C - D \cdot ln(Ti)$$

$$\alpha = E - \frac{F}{AXi}$$

Where A, B, C, D, E and F are calibration constants which has to be obtain from calibration measurement. For evaluation of relationship we can simplified this equation and combine constant.

$$3\alpha = A + B \cdot ln(\frac{HR}{Ti}) - \frac{F}{AXi}$$

$$\alpha = \frac{\mathbf{1}}{\mathbf{3}}(\mathbf{A} + \mathbf{B} \cdot \mathbf{ln}(\frac{\mathbf{HR}}{\mathbf{Ti}}) - \frac{\mathbf{F}}{\mathbf{AXi}}) \tag{5.12}$$

Dimensional analysis

$$\alpha = [\frac{1}{s} \cdot s + \frac{1}{Pa}] = [\frac{1}{Pa}]$$

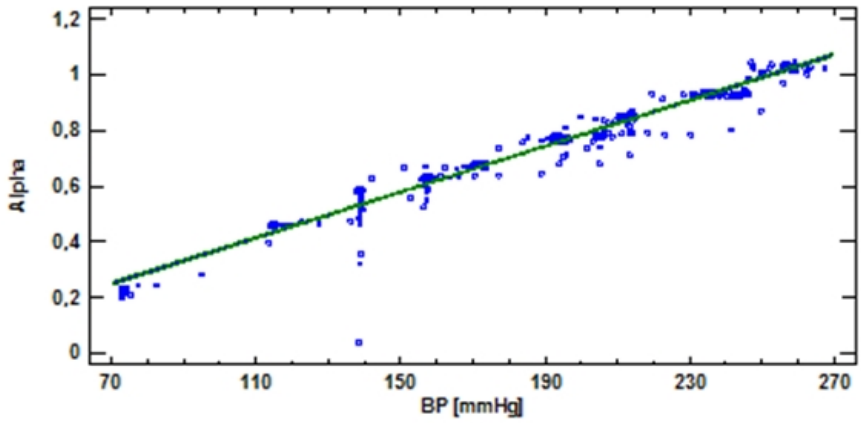

Figure 5.21 Relationship between evaluated alpha and BP. Alpha is evaluated thanks to pulse wave analysis and time propagation of pulse wave. It is possible to evaluate alpha without information about properties of cardiovascular system as stiffness and thickness because this information is reflected by change in pulse wave propagation.

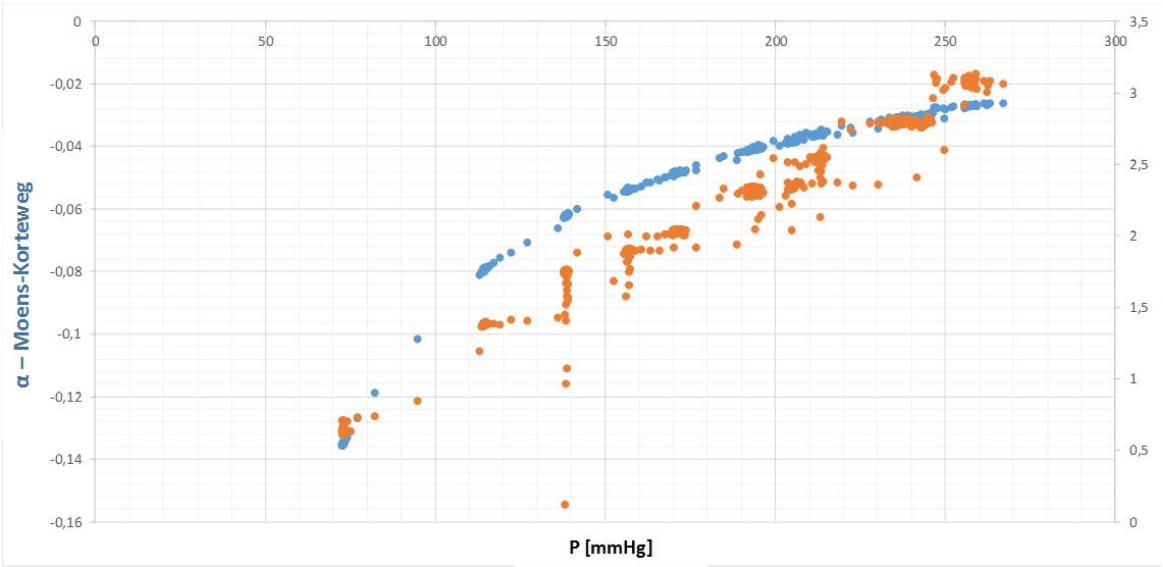

Figure 5.22 Comparison between alpha parameter which was evaluated thanks to Monens-Korteweg equation and which was evaluated thanks to analysis. It can be seen that alpha evaluated thanks to analysis seems to be close to original value. Evaluated alpha parameter is more in linear dependence to pressure value.

5.4.5 Evaluation of PWV

From the Moens-Korteweg equation can be pressure value evaluated as:

$$P = \frac{1}{\alpha} ln(\frac{2\rho r PWV^2}{E_0 h})$$

It can be seen that alpha parameter can be evaluated thanks to pulse wave analysis. The equation can be split into 2 parts, one part is constant and the second part depend on the value of blood pressure:

$$K = \frac{2\rho r}{E_0 h}$$

$$Presure\ as\ a\ function\ of\ PWV\ -\ P(PWV)$$

Pulse wave velocity is defined from the distance which pulse wave has to travel within a time delay $\frac{D}{PTT}$. Distance is constant, parameter which is changing is PTT. Pulse wave velocity is affected by the artery properties which affect the time propagation of backward wave and its effect on attenuation of pressure value and also pulse wave velocity will be affected by HR as mentioned earlier.

Effect of systolic time fraction

Pressure wave velocity is affected propagation of backward wave. How does pulse wave velocity affect the time of propagation of backward wave to the whole systolic phase? If pulse wave velocity is changing, the time of propagation of backward wave should change also which affects the systolic phase.

$$systolic\ time\ fraction\ (STF) = \frac{time\ of\ systole}{time\ of\ backward\ wave\ propagation}$$

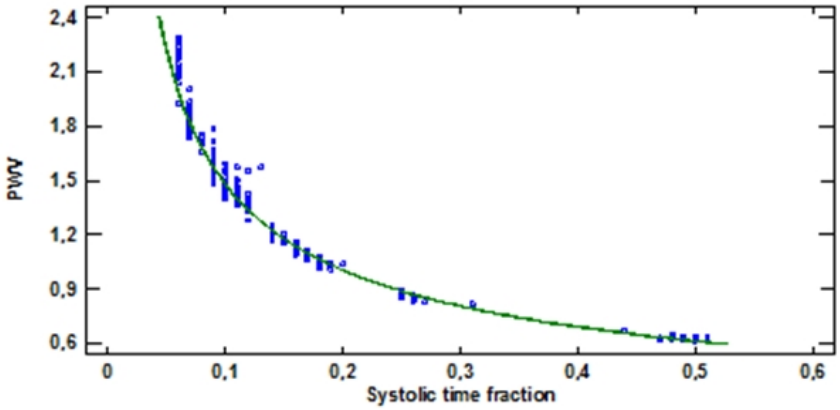

Figure 5.23 The relationship between pulse wave velocity and effect of the range of time propagation of backward wave and systolic phase which occur augmentation of pressure value.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**-0.092**	0.00301	-30.56	**0.0000**
Slope	**2.43**	0.0075	323.5	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	60.54	60.54	104658	**0.0000**
Residual	0.401	0.00058		
Corelation Coefficient		**0.99**		
R-squared		99.34 percent		
Standard Error		0.024		
Mean absolute Error		0.018		

The relationship between pulse wave velocity and effect of time propagation of backward wave to systolic phase can be describe as:

$$\mathbf{PWV} = \frac{\mathbf{1}}{\mathbf{a} + \mathbf{b}\sqrt{\mathbf{STF}}} \tag{5.13}$$

Effect of time delay of backward wave

The relationship between pulse wave velocity and propagation time of the backward wave to systolic phase can be described as:

$$\mathbf{PWV} = \frac{\mathbf{1}}{\mathbf{a} + \mathbf{b} \cdot \mathbf{Ti}} \tag{5.14}$$

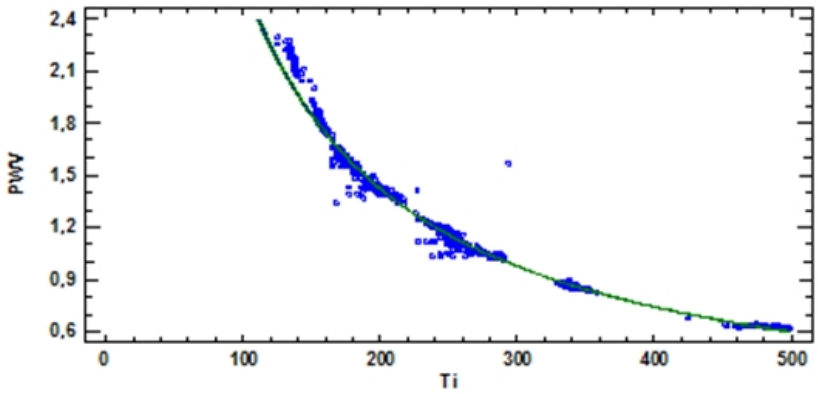

Figure 5.24 The relationship between pulse wave velocity and backward wave time propagation. Pulse wave velocity is affected by the backward wave as well as blood pressure value.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**0.059**	0.00289	19.82	**0.0000**
Slope	**0.0032**	0.000012	278.15	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	60.4	60.4	77365.9	**0.0000**
Residual	0.54	0.00078		
Corelation Coefficient		**0.99**		
R-squared		99.11 percent		
Standard Error		0.028		
Mean absolute Error		0.017		

Time delay of backward pulse wave and systolic time fraction are parameters which affect parameter alpha.

$$PWV = \frac{1}{A + B\sqrt{STF}}$$

$$PWV = \frac{1}{C + D \cdot Ti}$$

$$2PWV = \frac{1}{A + B\sqrt{STF}} + \frac{1}{C + D \cdot Ti}$$

$$\mathbf{PWV} = \mathbf{0.5}\left(\frac{\mathbf{1}}{\mathbf{A} + \mathbf{B}\sqrt{\mathbf{STF}}} + \frac{\mathbf{1}}{\mathbf{C} + \mathbf{D} \cdot \mathbf{Ti}}\right) \tag{5.15}$$

Dimensional analysis

$$PWV(t) = [\frac{1}{s}]$$

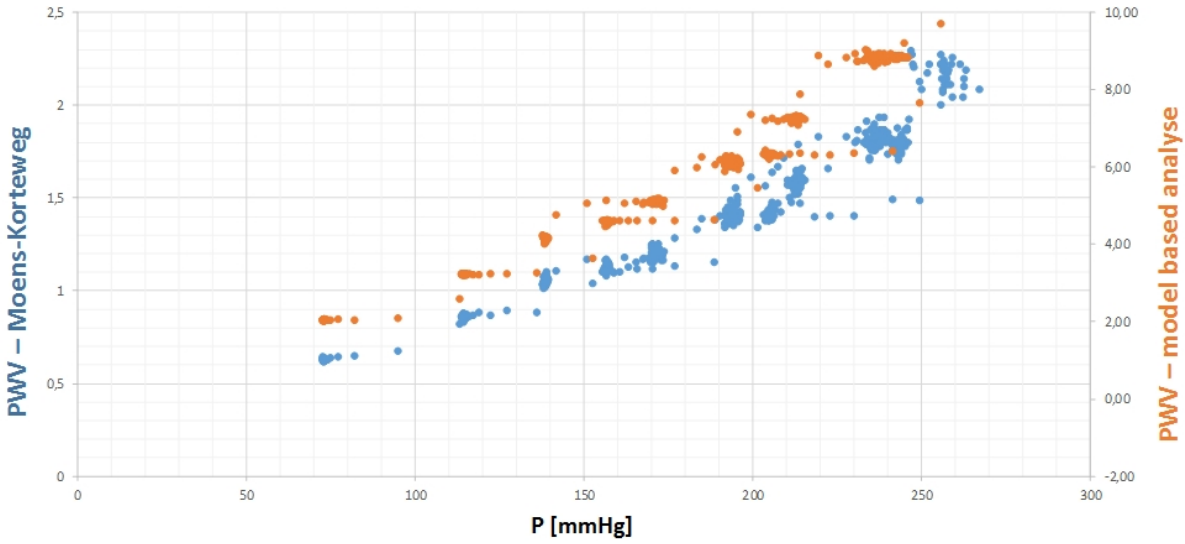

Figure 5.25 Comparison between pulse wave velocity based on Moens-Korteweg equation and pulse wave velocity as a function of time propagation of pulse wave.

Pulse wave velocity analysis is based on how the pulse wave propagation is affected by the properties of cardiovascular system. It should not depend on the distance of propagation. Blood pressure is evaluated thanks to Moens-Korteweg equation where is for the accuracy evaluation necessary to know properties of cardiovascular system. It is very difficult to evaluate stiffness and thickness of each segment of artery in the human body, in fact it is impossible to get these constant for this equation. These constant affect propagation of pulse wave through cardiovascular system, which means that only their mean values can be determined, indirectly from the propagation of the pulse wave.

5.5 Comparison of algorithms

Pressure based on Moens-Korteweg equation	Pressure based on adjusted Moens-Korteweg equation	Pressure based on pulse transit time
$P = \frac{1}{\alpha} ln(\frac{2\rho r PWV^2}{E_0 h})$	$function\ of\ P = \frac{1}{\alpha} ln(PWV)$	$P = A + B \cdot PTT$

If we remove the outliers, the relationship between P and PWV is roughly logarithmic, as in the Moens-Korteweg equation but without any reference to the intrinsic properties of the cardiovascular system.

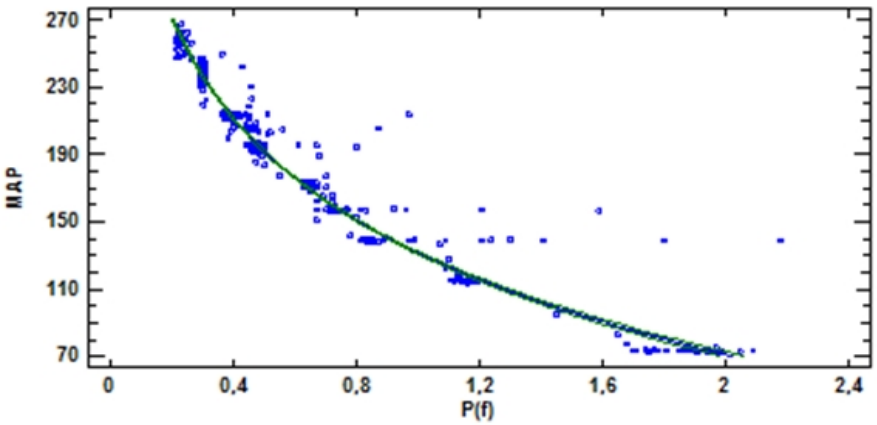

Figure 5.26 Function of blood pressure evaluated thanks to propagation of blood pressure.

Coeficients				
Parameter	*Least Squares Estimate*	*Standard Error*	*T Statistic*	*P-Value*
Intercept	**131.37**	0.48	274.04	**0.0000**
Slope	**-86.9**	0.6	-143.4	**0.0000**
Analysis of Variance				
Source	*Sum of Squares*	*Mean Square*	*F-Ratio*	*P-Value*
Model	1.7E6	1.7E6	20567.7	**0.0000**
Residual	58287.3	84.5		
Corelation Coefficient		**-0.98**		
R-squared		96.75 percent		
Standard Error		9.19		
Mean absolute Error		5.4		

Relationship between evaluated pressure function and blood pressure can be describe as:

$$\mathbf{MAP} = \mathbf{a} - \mathbf{b} \cdot \mathbf{ln}(\mathbf{function\ of\ P}) \tag{5.16}$$

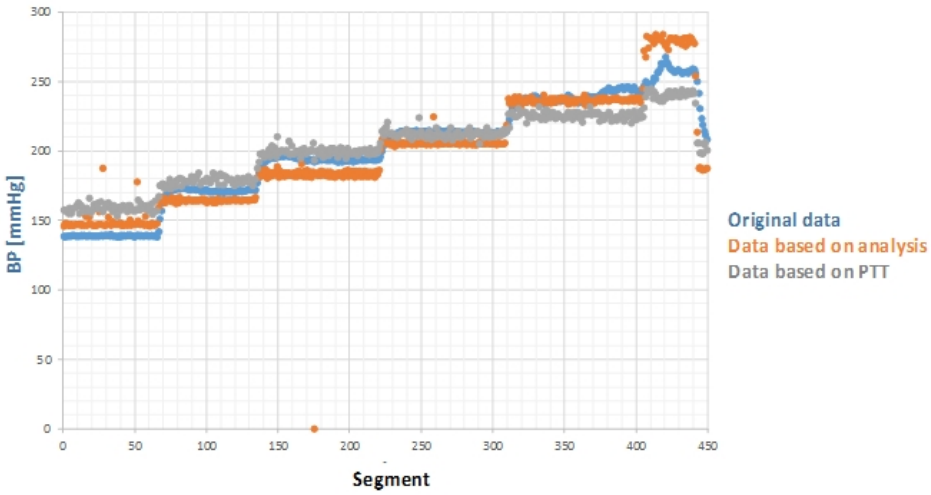

Figure 5.27 Comparison between original pressure value and evaluated pressure thanks to *PTT* algorithm and new proposed algorithm. The first approach of the model.

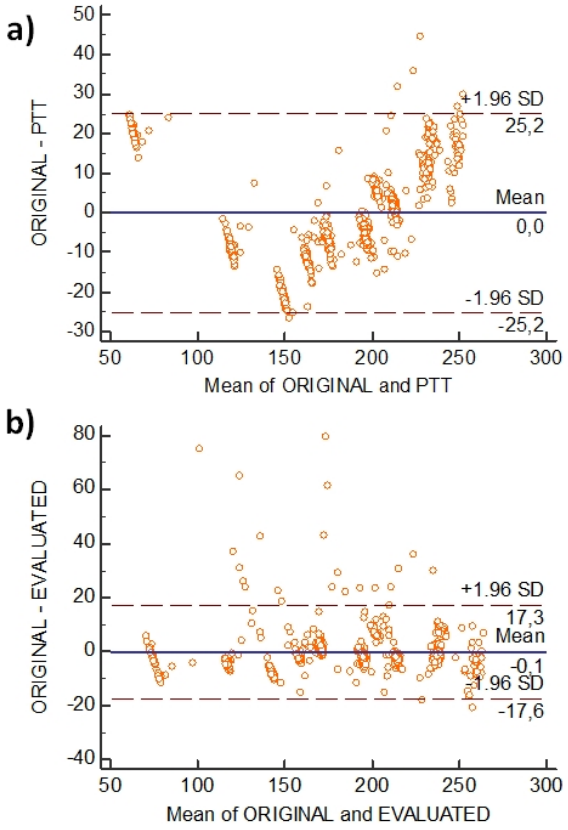

Figure 5.28 Bland-Altman comparison between two algorithms for the evaluation of blood pressure value. a) comparison between pressure evaluated by the algorithm based on *PTT* and original measured pressure. It can be seen some trend in absolute error. b) comparison between pressure evaluated by the new proposed algorithm. The mean difference value between these two algorithm is almost 0. Bias is quiet large, due to outliers.

5.6 Upgrade of the first approach

To obtain results closer to real cardiovascular system we modified and completed some parts to our model.

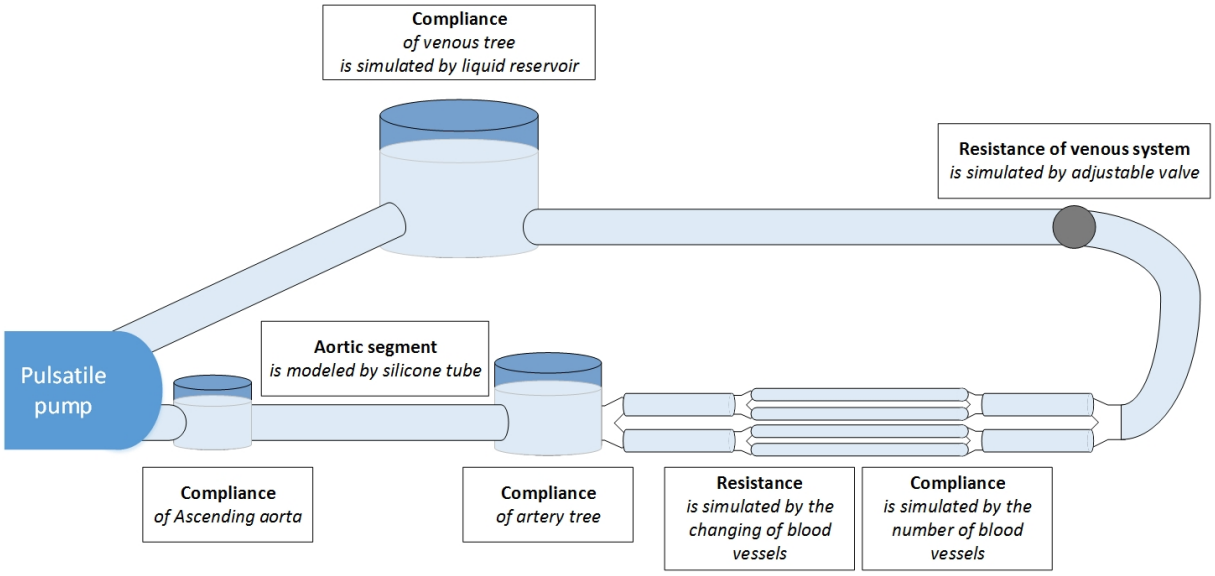

Figure 5.29 Pressure waves were measured by standard extravascular pressure sensors. In this model we also used catheter for measurement of central pressure wave.

First we changed our aortic part to a replica of the physical model of aorta. This model was created from a magnetic resonance image of real aorta and then printed into a 3D plastic model (Fig. 5.30 and Fig. 5.31).

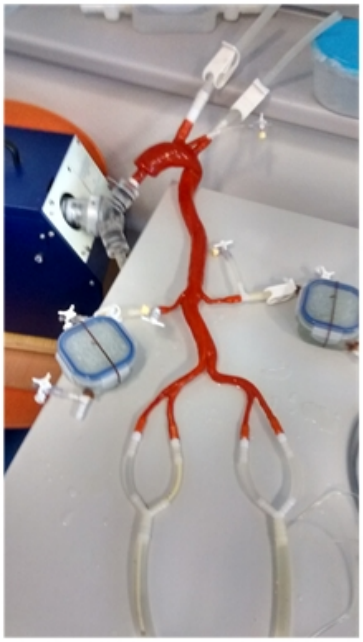

Figure 5.30 Setting of the model with physical model of aorta.

This plastic matrix was then coated with liquid silicone. When the silicone solidified, the plastic part was removed. We used silicon with Young's modulus 0.77 MPa, width of artery wall approximately 1 mm.

Resistivity of artery system was simulated with a box filled with small glass balls of different diameters into simulate physiological conditions. In human body each blood vessel is divided to two blood vessels with smaller diameter and higher resistivity. It this case the blood pressure should be higher which means that capillary with diameters of micrometers could collapse due to high blood pressure values. Fortunately, with decreasing diameter of blood vessel there is an increase in their number. Because of the number of capillaries the total resistance increases. The high resistance in capillaries decrease of blood flow which enables to transport nutrients and oxygen to tissue. Glass small balls with different diameters simulate this physiological process.

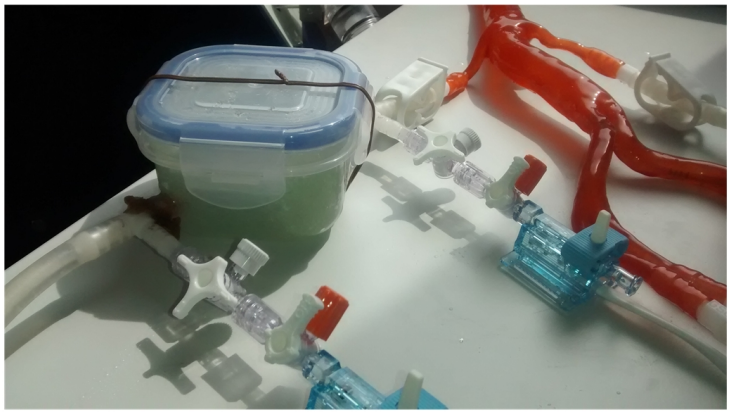

Figure 5.31 The model was extended also of "kidneys" which are simulated as boxes full of small glass balls with diameter less than 1 mm.

The liquid used was water with 40 % of glycerine to mimic the density and viscosity of real blood. This kind of liquid has same properties as real blood – viscosity 4, density 1095 kg/m^3.

This setting was used for the validation of the evaluated algorithm. We performed a pulse wave analysis same as in previous description to evaluate the properties of the pulse wave. After that was compared the relationship between alpha parameter and pulse wave velocity function and pressure value in this model.

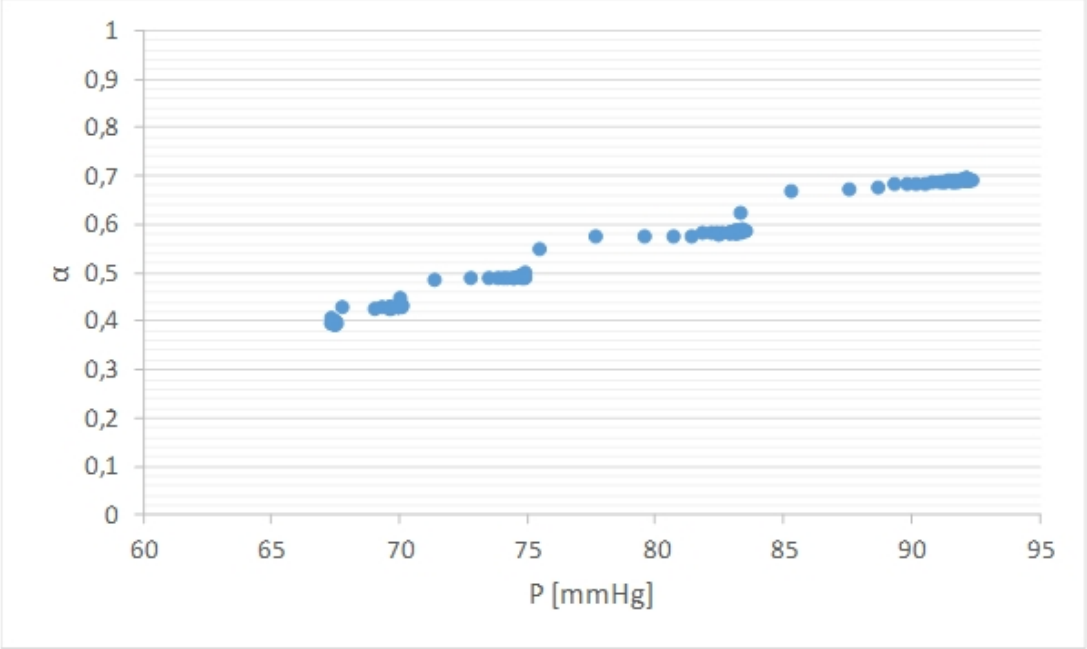

Figure 5.32 It can be seen close relationship between the alpha parameter and pressure value as in the first approach based model setting.

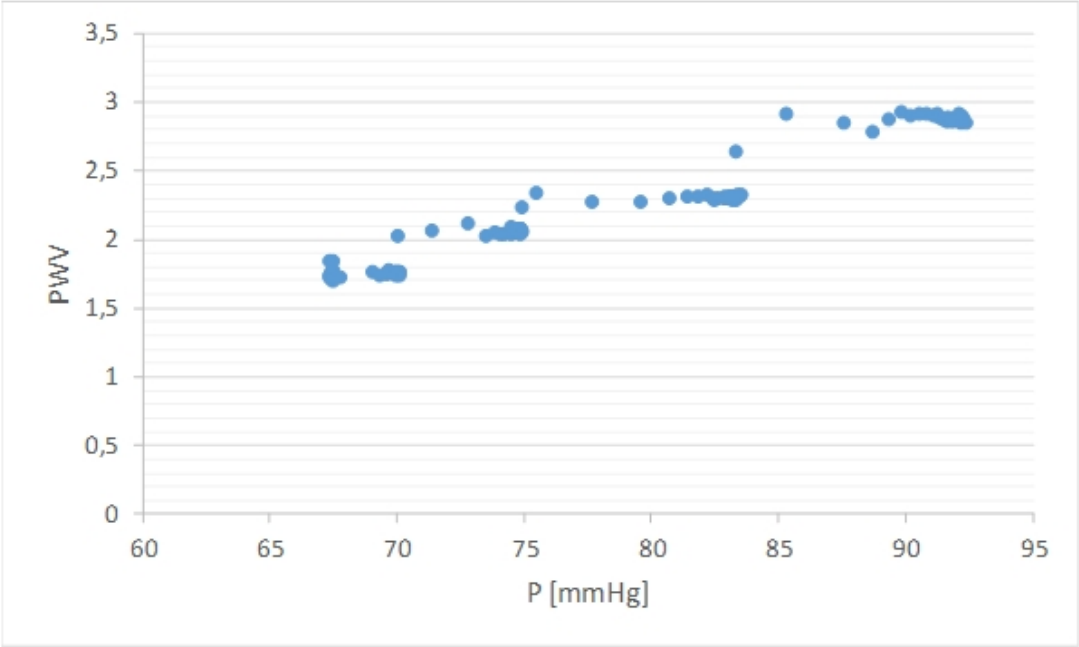

Figure 5.33 The relationship between pulse wave velocity function and pressure value is as same as in the first approach model.

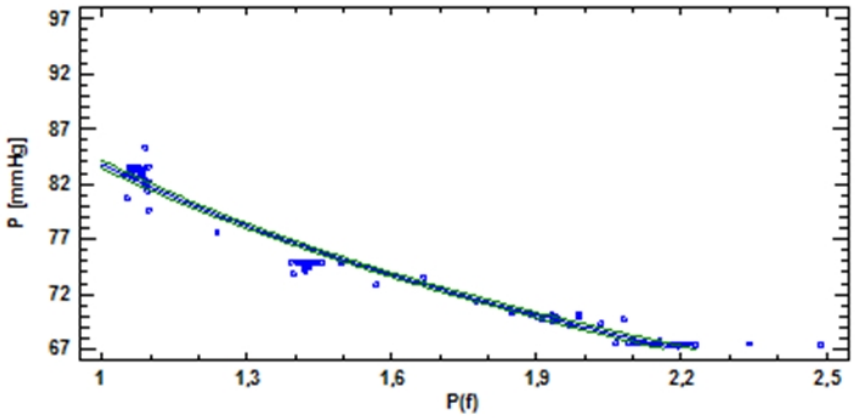

Figure 5.34 The relationship between pressure function and arterial pressure is as same as in the first approach model.

The new algorithm based on propagation of pulse wave was applied. Algorithm works quite well for a large range of pressure. It reflects changes in pressure and indirectly evaluates pressure values.

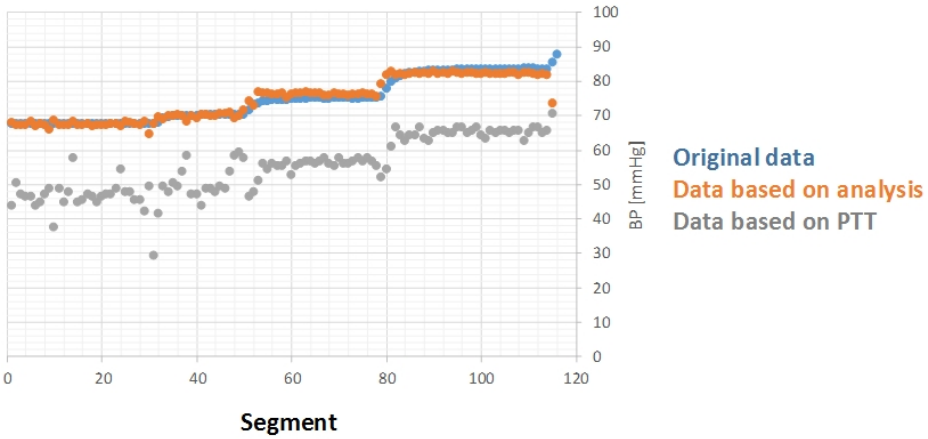

Figure 5.35 Comparison between original pressure value and evaluated pressure thanks to *PTT* algorithm and new proposed algorithm. Upgraded model.

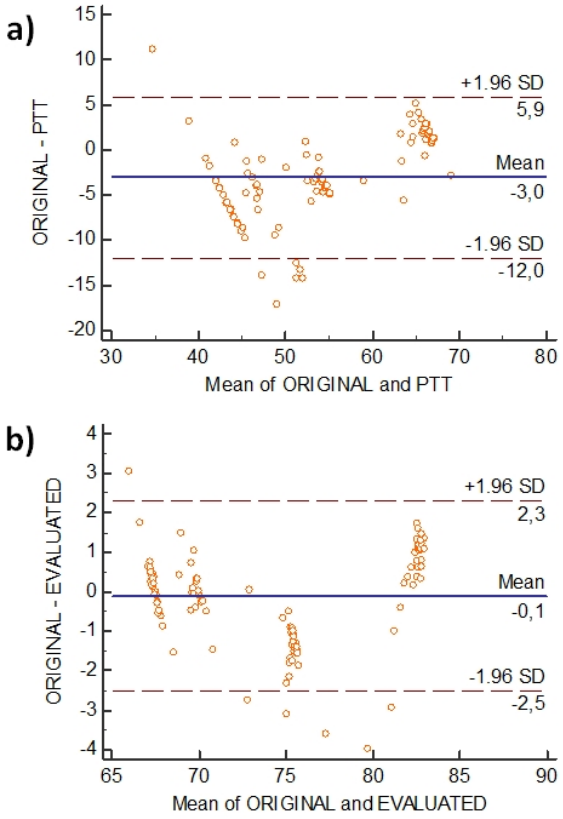

Figure 5.36 Bland-Altman comparison between two algorithms for the evaluation of blood pressure value. a) comparison between pressure evaluated by the algorithm based on *PTT* and original measured pressure. There can be seen systematic error. b) comparison between pressure evaluated by the new proposed algorithm. The mean difference value between these two algorithm is almost 0.

For the evaluation of the constant it is needed calibration. Calibration itself affect accuracy of indirect evaluation. For the same signal was made calibration from first 20 seconds of measurement. After that, evaluated calibration constants and at the end evaluated pressure wave based on this calibration.

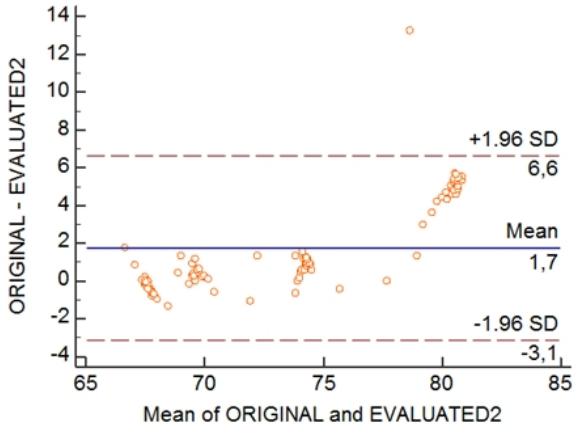

Figure 5.37 Comparison between original pressure values and values after using calibration procedure. There is differences between both values which shown that calibration procedure will be another important part which will affect pressure value.

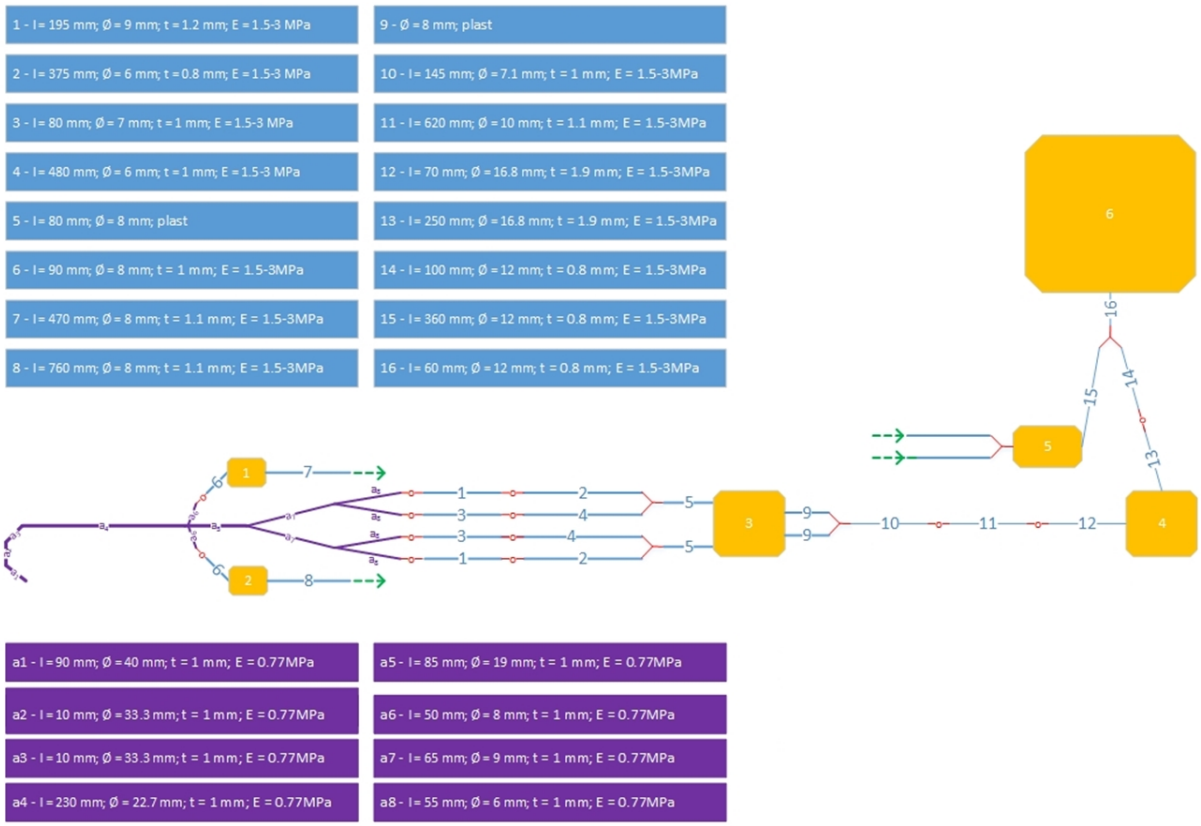

Figure 5.38 Detailed setting of the model.

5.7 Conclusion

We can now confirm that we can evaluate the instantaneous blood pressure from the propagation parameters of the derivated biosignals. This analysis of the dependency of propagation of pulse wave and blood pressure can not involve signals collected on real human because of small

variability during measurement. For this kind of purpose we developed physical model of cardiovascular system. System was validated and compared to the real human cardiovascular system. It is smaller than real cardiovascular system but parameters of each part were set to make model condition close to the real human body.

Thanks to this model we could perform the analysis of the main factors which affect blood pressure and pulse wave propagation. Based on this analysis was evaluated equation which describe blood pressure value based on propagation of pulse wave and its conditions.

We investigated relationship between pulse wave propagation and its effect to blood pressure. From analysis of pulse wave is possible to evaluate noninvasive blood pressure value. All of investigation were done thanks to our model which simulate hemodynamics parameters close to real human body.

In the human body there is a tissue around blood vessels which affects theirs ability to expand due to pressure. It has to be next upgrade of this model, to simulate this kind of environment as a some substance which will simulate human tissue.

6

Concluding remarks and future directions

The thesis has successfully concluded the aims set out in the first chapter. One of the main aims of this thesis was to build physic model of cardiovascular system. The model was built in two settings. First one was arranged as a simplified model based on silicone and PVC tubes and parts which simulate a resistivity. It was validated and compare to real human cardiovascular system. Thanks to this model were measured signals in same condition as in human body. It was possible to change hemodynamic parameters to change pressure inside the system. Afterwards measured signals were analysed. It was evaluated the all of needed parameters from the pulse wave which are affected by the properties of the cardiovascular system. In this chapter major results are summarized and potential future directions of this research work are given.

6.1 Conclusion of the thesis

This thesis started with experiment which described and preliminary proved the relationship between propagation of biological signal, as pulse wave, and blood pressure value. We measured standard biological signals as ECG and PPG and invasive blood pressure simultaneously.

The first experiment was performed in the hospital and one patient was involved. We preliminary evaluated the relationship between noninvasive signals and blood pressure. Such relationship exists but it was shown that it will be necessary to analyse not only propagation of pulse wave but also effect of state of cardiovascular system to propagation of pulse wave.

It was described nowadays the commonly used methods for measurement blood pressure and compared it with possible indirect measurement based on pulse wave propagation. This chapter shown, that nowadays exist some possibilities of noninvasive blood pressure measurement which are based on pulse wave propagation but results are still controversy and it is necessary to improve accuracy of this indirect evaluation.

In this chapter we shown the most often used algorithm for $NIBP$ evaluation. All of algorithm have some weakness. For the precise evaluation of $NIBP$ thanks to these algorithm is necessary to known some constants or parameters which are not possible to measure in normal condition, most of time it is necessary invasive measurement. The possibility of noninvasive evaluation of these parameters has to be found.

Another experiment shown that pulse wave propagation is affected significantly by the hemodynamic parameters of cardiovascular system and into the evaluation should come information about heart rate. It was also investigated the best point from the pulse wave for evaluation pulse transit time. Mainly it was confirming, that analysis of pulse wave is needed to improve indirect evaluation of blood pressure measurement.

Thanks to the analysis of signals from second experiment we shown than blood pressure is also affected by hart rate and it has to be included into investigation.

For such kind of investigation and evaluation is needed a lot of measurement and measurement with possibility of changing properties of cardiovascular system to investigate how is pulse wave affected by the properties of cardiovascular system. It was developed simplify model of cardiovascular system with same hemodynamic properties as the real human cardiovascular system. Thanks this model was possible to analysed pulse wave and its relationship with pressure.

Because of existing Moens-Korteweg equation which can be write as pressure dependency and which is used for the evaluation of state of the aortic segment as a gold standard based on pulse wave velocity measurement there should be strong relationship between propagation of pulse wave and blood pressure. This equation consists from parameters of artery as stiffness, thickness and diameter. These parameters aren't possible to get from the human body, so for the using this equation is needed to replace they by the parameters which can describe properties of artery and can be evaluated just form propagation of pulse wave. These parameters were analysed and it was proposed alternative equation for indirect blood pressure evaluation. This equation was validated by the model which was based just on the tubes and afterwards on the model which was based on physic model of aorta. Proposed equation describe relationship between propagation of pulse wave and blood pressure very precisely.

At the end was equation used for the comparison between nowadays the most discuss equation based on pulse transit time measurement. Both of these algorithm was used on real measurement signal and compare its error in comparison to real blood pressure value.

Whole analyse shown that equation can be used very precisely, same as the Moens-Korteweg equation but without knowledge about parameters of aorta or blood vessel. But it is obvious that big role of this equation will have calibration which will be needed before each measurement of blood pressure. Calibration method has to be investigate.

Thanks to our developed physical model we shown that it is possible to produce in real time the real pressure waves in human so as to test real time sensing methods of cardiovascular properties and it is possible to evaluate those cardiovascular properties from the propagation temporal parameters of the pulse wave. These two objective bring us possibility to investigate the relationships between hemodynamics parameters, pulse wave propagation and blood pressure in *invitro* conditions. We were able to describe all of conditions and theirs effect to blood pressure. We successfully described the new algorithm for indirect $NIBP$ evaluation. There are still possibility to improve our model.

6.2 Future directions

The main theme of this work was to develop a physical model of cardiovascular system, very close to real condition to have possibility measure pulse wave propagation as in human body and analyse it with pressure value and thanks it improve the indirect of continuous noninvasive blood pressure measurement. As mentioned earlier, there are many hemodynamic factor which can affect pulse wave propagation and also the process of calibration of measurement to personalized measurement for each patient have to be investigate. For such kind of analysis has be model improved:

1 It has to be investigated the effect of tissue pressure. The aortic segment can be close into the box fulfilled by the material close to the density of tissue. In this box will be possible to change pressure which makes change in the pressure which affect the aorta. It will simulate change in pressure due to the physical activity or stress.

2 It has to be investigated the process and methodology of the calibration o this measurement. This parameter makes the biggest error. It could be used some predictive model which will be able to allow for all of not only hemodynamic parameters but also physical condition.

List of Abbreviations

BP ..... Blood pressure

MAP ..... Mean arterial pressure

ABP ..... Arterial blood pressure

CNIBP ..... Continuous noninvasive blood pressure measurement

PWV ..... Pulse Wave Velocity

PTT ..... Pulse Transit Time

PAT ..... Pulse Arrival time

PEP ..... Pre ejection period

ECG ..... Electrocardiography

PPG ..... Photoplethysmography

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Publications on the subject of the dissertation

A.1 Peter, L., Noury, N., Cerny, M., Nykl, I. (2016, August). Comparison of methods for the evaluation of NIBP from pulse transit time. In Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the (pp. 4244-4247). IEEE.

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B.1 Cerny, M., Klinkovsky, T., Petrik, J., Peter, L., Penhaker, M., Kasik, V. (2017, January). Defibrillator educational devices. In Applied Machine Intelligence and Informatics (SAMI), 2017 IEEE 15th International Symposium on (pp. 000333-000336). IEEE.

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Other results

Prototype

C.1 Ing. Lukáš Peter , Ing. Martin Černý Ph.D., Ing. Martin Augustynek: Osmi-kanálový fotopletysmograf. FEI VŠB-TU Ostrava, 2013

Software

D.1 Ing. Lukáš Peter , Ing. Martin Černý Ph.D., Ing. Martin Augustynek: Software pro záznam pulsní křivky z osmikanálového fotopletysmografu. FEI VŠB-TU Ostrava, 2013

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