THESIS ON NATURAL AND EXACT SCIENCES

Optical pulse wave signal analysis for determination of early arterial ageing in diabetic patients

KRISTJAN PILT

TALLINN UNIVERSITY OF TECHNOLOGY
Technomedicum
Department of Biomedical Engineering

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Supervisor: Professor **Kalju Meigas**, PhD, Department of Biomedical Engineering, Technomedicum, Tallinn University of Technology, Estonia

Co-supervisor: Professor **Margus Viigimaa**, MD, Department of Biomedical Engineering, Technomedicum, Tallinn University of Technology, Estonia

Reviewed by: Professor Emeritus **Hiie Hinrikus**, DSc, Department of Biomedical Engineering, Technomedicum, Tallinn University of Technology, Estonia

Opponents:

Defense of the thesis:

Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any academic degree.

/Kristjan Pilt/

LOODUS- JA TÄPISTEADUSED

Optilise pulsilaine signaali analüüs arterite varase vananemise määramiseks diabeedihaigetel

KRISTJAN PILT

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List of Publications

I **Pilt K**, Meigas K, Viigimaa M, Temitski K, Kaik J (2010) "An experimental measurement complex for probable estimation of arterial stiffness", *In: Proceedings of 30th Annual International Conference of the IEEE EMBS, Buenos Aires, Argentina, August 31 – September 4*, 194-197 (DOI: 10.1109/IEMBS.2010.5627925).

II **Pilt K**, Meigas K, Ferenets R, Kaik J (2010) "Photoplethysmographic signal processing using adaptive sum comb filter for pulse delay measurement", *Estonian Journal of Engineering*, 16: 78-94 (DOI: 10.3176/eng.2010.1.08).

III **Pilt K**, Ferenets R, Meigas K, Lindberg L-G, Temitski K, Viigimaa M (2013) "New photoplethysmographic signal analysis algorithm for arterial stiffness estimation", *The Scientific World Journal*, vol. 2013, Article ID 169035, 9 pages (DOI: 10.1155/2013/169035).

IV **Pilt K**, Meigas K, Temitski K, Viigimaa M (2012) "Second derivative analysis of forehead photoplethysmographic signal in healthy volunteers and diabetes patients", *In: IFMBE Proceedings of World Congress on Medical Physics and Biomedical Engineering, Beijing, China, May 26-31*, 410-413 (DOI: 10.1007/978-3-642-29305-4_109).

V **Pilt K**, Meigas K, Ferenets R, Temitski K and Viigimaa M (2013) "Photoplethysmographic signal waveform index for detection of increased arterial stiffness", *Manuscript submitted*

Author's Contribution to the Publications

In publication I the author built PPG and piezoelectric signal modules and compiled the devices together into one working unit. In addition the author carried out the experiments and data analysis and developed the concept of the LabView recording program. In publication II the author developed the algorithm of adaptive comb filter and implemented it in MATLAB. In addition the author was carrying out all the experiments, simulations, and data analysis. In publication III the author developed the SDPPG signal analysis algorithm, processed all the signals and carried out data analysis. In addition the author participated in planning of the experiments and conducted the 75% of the signal recordings from the subjects in cooperation with other members of the group. In publication IV the author processed all the signals, carried out data analysis, and conducted 90% of the experiments in cooperation with other members of the group. In publication V the author processed all the signals and carried out data analysis.

Approbation

- Method and device for long term variability monitoring of cardiovascular parameters based on registered electrocardiograph and pulse wave signals; Priority number: P201100016; Priority date: 09.03.2011
- 11th Mediterranean Conference of the Medical and Biological Engineering and Computing, Ljubljana, Slovenia, June 26-30, 2007.
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- 14th Nordic-Baltic Conference on Biomedical Engineering and Medical Physics, Riga, Latvia, June 16-20, 2008.
- 30th Annual International Conference of the IEEE EMBS, Vancouver, Canada, August 20-24, 2008.
- 11th Biennial Baltic Electronics Conference, Tallinn, Estonia, October 6-8, 2008.
- 31st Annual International Conference of the IEEE EMBS, Minneapolis, USA, September 2-6, 2009.
- 11th International Congress of the Medical Physics and Biomedical Engineering, Munich, Germany, September 7-12, 2009.
- 12th Mediterranean Conference on Medical and Biological Engineering and Computing, Chalkidiki, Greece, May 27-30, 2010.
- 32nd Annual International Conference of the IEEE EMBS, Buenos Aires, Argentina, August 31 – September 4, 2010.
- 12th Biennial Baltic Electronics Conference, Tallinn, Estonia, October 4-6, 2010.
- 15th Nordic-Baltic Conference on Biomedical Engineering and Medical Physics, Aalborg, Denmark, June 14-17, 2011.
- 5th European Conference of the IFMBE, Budapest, Hungary, September 14-18, 2011.
- World Congress on Medical Physics and Biomedical Engineering, Beijing, China, May 26-31, 2012.
- 13th Biennial Baltic Electronics Conference, Tallinn, Estonia, October 3-5, 2012.
- International Symposium on Biomedical Engineering and Medical Physics, Riga, Latvia, October 10-12, 2012.
- 35th Annual International Conference of the IEEE EMBS, Osaka, Japan, July 3-7, 2013.

Introduction

The cardiovascular diseases are the leading cause of death globally according to the WHO global status report (Alwan et al 2011). The largest number of people dies annually due to cardiovascular diseases than from any other of cause. In 2008 about 17,3 million people died due to cardiovascular diseases, which constitutes 30% of all global deaths. However, most of the cardiovascular diseases can be prevented through healthy lifestyle. The major behavioral risk factors of cardiovascular disease are smoking, immoderate use of alcohol, obesity and physical inactivity.

The prevention and treatment of cardiovascular disease is based on 'risk factors', which are known to cause harm to arterial system, such as elevated blood pressure, high level of cholesterol and blood sugar, and smoking. However, a considerable number of cardiovascular events happen each year in subjects who do not qualify for treatment based on such guidelines (Herrington et al 2004). Therefore, a lot of effort has been put into research to develop methods, which would enable more accurately to identify the subjects with high risk from general population. Early diagnosis and treatment of cardiovascular disease could provide treatment benefits and reduce the cost to society (Perk et al 2012).

Diabetes is not a cardiovascular disease, but more than 75% diabetic patients die because of the causes related to atherosclerosis. The premature increase in stiffness of the arteries in case of diabetes patients is often explained through accelerated cardiovascular ageing. With early diagnosis of the atherosclerosis the disease can be decelerated through treatment and lifestyle change. Therefore, it is essential to detect the early changes in the arterial walls of diabetes patients.

The aortic PWV, which is an index of aortic stiffness, has already entered to the guidelines for hypertension of the European Society of Hypertension as providing extra cardiovascular risk prediction besides classical risk factors (Mancia et al 2007). However, the atherosclerosis involves the whole cardiovascular system and changes in smaller arteries can arise even earlier. The assessment of peripheral arteries may enable earlier detection of atherosclerosis (Cohn J N 2006).

Different methods and devices are developed to estimate arterial stiffness (Laurent et al 2006, Woodman et al 2005). Usually the measurements are time consuming, uncomfortable for subject and a trained operator is needed. The user independent, rapidly performed and inexpensive noninvasive technique is needed for the arterial stiffness estimation.

The general aim of this study was to investigate the possibilities to detect the premature increase in cardiovascular ageing using non-invasive optical method and pulse waveform analysis. Furthermore, to compare the effectiveness of developed method and algorithms with recognized and in clinical practice used methods in differentiating between the patients with normal and higher arterial stiffness.

In the first part of study (Publication I) the measurement complex, which includes the modules for synchroneous recording of optical pulse wave signals from different segments of arteries, was compiled and tested. The synchronous recording of the signals is essential for the PTT and PWV estimation. In addition the

measurement complex enables recording of other physiological signals, which are relevant to the cardiovascular system evaluation and arterial stiffness estimation from different segments of arteries. In publication II an algorithm was developed algorithm for motion caused noise suppression in the recorded optical signal providing significant improvement of the signal quality.

In the second part of study the waveform analysis of the recorded optical signals has been carried out in order to determine the features of the signal characteristics for increased arterial stiffness and, consequently, estimating the premature increase in cardiovascular ageing. Publication III introduces the new pulse waveform analysis algorithm for finger signal providing the differentiation between the subjects with normal and increased arterial stiffness. In publication IV the optical signal from forehead has been investigated by using the algorithm and optical waveform index developed in publication III, for the differentiation of subjects with higher arterial stiffness. The aim of publication V was to compare the effectiveness of the developed optical waveform index and arterial stiffness index used in commercial clinical devices in differentiating patients with increased arterial stiffness.

Abbreviations

AGI – ageing index
AIx – augmentation index
ECG – electrocardiography
HDL – high-density lipoprotein
IMT – intima-media thickness
LDL – low-density lipoprotein
LED – light emitting diode
MRI – magnetic resonance imaging
NO – nitric oxide
PEP – pre-ejection period
PPG – photoplethysmography
PPGAI – PPG waveform augmentation index
PTT – pulse transit time
PWV – pulse wave velocity
SDPPG – second derivative photoplethysmography
SNR – signal to noise ratio
WHO – World Health Organization

1. Anatomy of arteries and pathogenesis of artherosclerosis

1.1. Anatomy of arteries

The structure of arterial vessel wall is heterogeneous and can be generally divided into three layers: *tunica interna* (*intima*), *tunica media* (*media*), *tunica externa* (*externa*) (figure 1). The thickness and the structure of the layers vary depending on the type of artery. The inner layer contributes minimally to the total thickness of the vessel and it is in contact with blood. The innermost layer of *intima* is endothelium, which is a thin layer of cells that covers the whole surface of the cardiovascular system. The smooth surface of the endothelial cells enables efficient blood flow by reducing surface friction. In addition it prevents the blood coagulation inside the vessel. The next layer in *intima* is basement membrane, which consists of collagen fiber. This layer provides physical support base for epithelial cells of endothelium. The outermost layer of the *intima* is *internal elastic lamina*, which forms a thin sheet of elastic fibers around the inner layers (Tortora and Derrickson 2011).

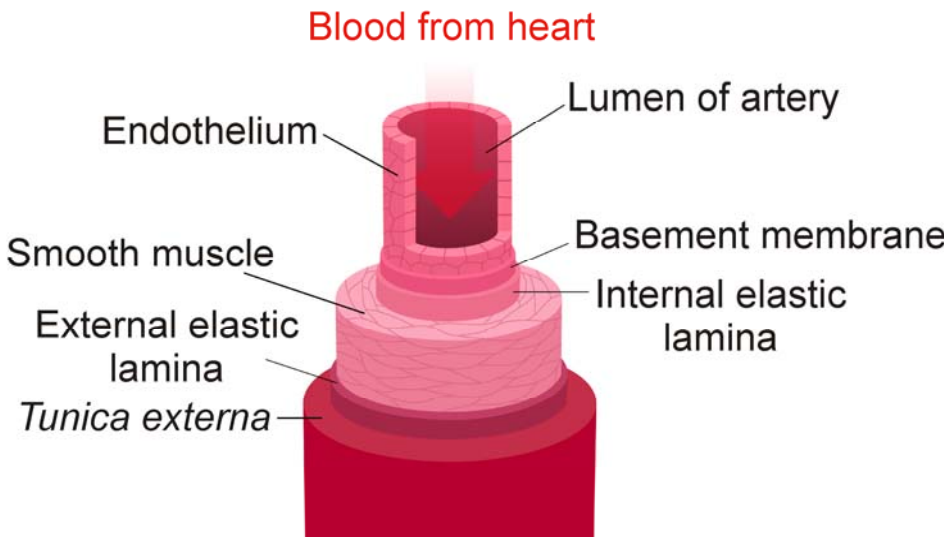

Figure 1. The anatomy of artery [CC: By Kelvin Song, http://creativecommons.org/licenses/by/3.0/].

The structure of *tunica media* is more complex and its composition varies the most among different arterial vessels. This layer is relatively thick in most vessels and it consists of smooth muscle cells, which are connected together with the net of elastin and collagen fibers (Dobrin 1999). This construction prevents the damage to the wall of the arterial vessel at high transmural pressures. The main purpose of the muscular cells in the wall is to change the diameter of the vessel's lumen.

Vasoconstriction (decrease in the diameter) and vasodilatation (increase in diameter) is typically caused by parasympathetic intervention or in response to blood pressure.

The outer layer of arterial vessel, *tunica externa*, is separated from *tunica media* by the external elastic lamina, which consists of elastin and collagen. In addition this layer contains numerous nerves. Especially, in larger vessels this layer contains small blood vessels that supply the tissue of the vessel wall. In addition, this layer connects the vessel to the surrounding tissue (Tortora and Derrickson 2011).

Arteries have normally high compliance, which means that in the case of a small increase in transmural pressure causes the stretch in the wall without tearing. The elasticity of the arterial vessel wall is determined by several components. The passive (without using biochemical energy) elastic components of the *tunica media* are collagen and elastin. Collagen has higher Young's modulus ($\sim 10^8$Pa), than elastin ($\sim 3 \cdot 10^5$Pa) (Nichols and O'Rourke 2005). The elastic fibers of the vessel wall enable to stretch themselves more than two times from the initial length and they dominate the wall behavior at the low strain levels. Collagen starts to dominate at the higher strain levels. In addition, the layer of smooth muscle cells enables to change noticeably the elasticity of the arterial wall.

Largest arteries, such as aorta and branches of aorta, in the body are the most elastic. Those arteries have the largest diameter (>10mm) and relatively thin wall (1/10 of the diameter) compared to the overall size of the vessel (Avolio 1980, Westerhof et al 1969). In these vessels the tunica media is dominated by elastic fibers. Those vessels help to propel the blood onward, due to the high elasticity, while the aortic valve is closed and the ventricles are relaxing. The aorta stretches due to the blood ejection from heart into the cardiovascular system. Due to the stretch of the vessel the elastic fibers stores the mechanical energy (potential energy). It is followed by the recovery of the vessel diameter and the stored potential energy in the wall is converted into kinetic energy of the blood.

The muscular arteries, also called as conduit arteries (e.g. brachial, femoral, radial, etc.), contain more smooth muscle and fewer elastic fibers than elastic arteries. The lumen diameter of muscular artery is between 0.1mm up to 10mm and wall thickness comprises about 25% of the diameter (Avolio A P 1980, Westerhof et al 1969). The muscular arteries are less elastic due to the reduced amount of elastic fibers. In addition the muscle tissue is able to maintain state of partial contraction. This reduces the elasticity or increases the stiffness of the artery.

1.2. Pathogenesis of atherosclerosis

Thickening and stiffening of the arteries is considered arteriosclerosis. The arteries stiffen with healthy ageing and disease. Atherosclerosis is the specific form of the arteriosclerosis, which is endovascular inflammatory disease, resulting in a build up of a plaque (Cavalcante et al 2011). The disease is triggered by the chemical or physical damage of the endothelial cell layer. The damage can be caused by one or multiple of following factors: physical damage or stress due to hypertension, turbulent blood flow in the branch points of arteries, free radicals

(reactive oxygen species) in blood caused by smoking, high concentrations of LDL in blood (hyperlipidemia), constantly high blood glucose levels in blood, high concentrations of homocysteine in blood (Libby 2002a).

In case of healthy arteries the blood cells in blood do not stick to the endothelial cells. Due to the above mentioned reasons the endothelial cell layer gets damaged and mostly LDL starts to pass through endothelial cells and accumulates in the *intima*. Oxidation of LDL in the arterial wall is caused by the exposure to NO, and some enzymes. Oxidized LDL is toxic and this initiates an inflammatory process. (Libby et al 2002a). The cell surface adhesion molecules (VCAM-1) are produced due to the injury of endothelial cells and oxidative stress (Li et al 1993, Huo and Ley 2001). Monocytes respond to inflammation process and start to stick and infiltrate through endothelium cells into media (Crowther M A 2005). After entering to the *intima* the monocyte interact with stimuli. Through formation of macrophages and foam cells the lipid and end products of the cells are collected between *intima* and *media* layers of the artery.

In case the process continues the fatty streaks starts to form to the wall of artery and it is the first visible sign of atherosclerosis (Libby et al 2002a). It can be seen in most of people by the age of 20 in the surfaces of the aorta and carotid arteries as a yellow hue (Strong et al 1992). It is part of the ageing process. In addition smooth muscle cells migrate through *internal elastic lamina* and accumulate, which leads to built-up of extracellular matrix in plaque and fatty streaks turn into fatty fibrous lesions. In the next stages fibrosis continues and sometimes with smooth cell death. This leads to fibrous cap formation over the lipid core. The fibrous cap consists largely of collagen and elastin. This represents the reaction by the body to heal the lesion. Formed fatty streaks may turn into atherosclerotic plaques or remain stable and even regress (Libby 2002a, 2002b).

Continued plaque growth caused by an accumulation of LDL within the intima causes the external elastic membrane to expand. This compensatory luminal enlargement (Boutouyrie et al, 1992) and wall thickening (Cheng et al 2002 and Zieman et al 2005), known as an arterial remodeling, allows the vessel to maintain normal or sufficient lumen area and blood flow.

However, as a plaque increases the artery can no longer compensate by expanding outward and the plaque begins to foray into the lumen. Usually it occurs, when plaque thickness reaches about 40% of the lumen diameter (Glagov et al 1987). Rupture of plaques may occur due to the biomechanical and hemodynamic stresses (Cloves and Berceli 2000). Plaques that contain a large lipid core and covered by a thin fibrous cap rupture more easily (Hennerici 2004).

The lipid core comes in a contact with a blood, when a fibrous cap ruptures. From this stage the formation of a thrombus or clot starts. The thrombus may partially or totally block an artery causing a sudden reduction in blood flow. Partial blockage of the lumen may cause the symptoms of angina. Complete blockage of the vessel lasting more than two to four hours may cause an acute event such as myocardial infarction (Naghavi et al 2003).

Healing of the vessel may also take place. Plaque rupture with subsequent healing is believed to be the major mechanism by which atherosclerotic lesions progress and narrow the lumen. Plaques that heal generally have a higher fibrotic composition than before making them more stable and less prone to future rupture (Waxman et al 2006).

At early ages the atherosclerotic fatty plaques are seen mainly in the carotid, and femoral arteries (Tuzcu 2001, Stary 2003). Atherogenic inflammation may appear in any arteries, but the disease is marginal in upper limb, renal and other muscular arteries (Stary et al 1992). However, it has been reported that atherosclerosis and increase in the stiffening of arteries are strongly associated at various locations in the vascular tree (van Popele 2001).

There are number of risk factors for atherosclerosis, which include age, hypertension, hypercholesterolemia, smoking, diabetes mellitus, physical inactivity, adiposity. In addition the biochemical risk factors of atherosclerosis are reduced HDL-cholesterol and elevated LDL-cholesterol, lipoprotein, C-reactive protein, and homocystine (Smith et al 2011).

2. Premature arterial stiffness in diabetes patients and importance of its early detection

The insulin is hormone, which is produced by the β-cells in the pancreas. The rise in blood sugar excites the secretion of the insulin to the circulation. Insulin receptors in muscle and fat cells are binding insulin, which triggers the process, where the glucose from the blood stream is entered into the fat and muscle cell.

Type I diabetes results from a lack of insulin in blood. It is caused by autoimmune process, which destroys the β-cells and due to that glucose cannot enter into fat or muscle cells. This causes the glucose rise in blood resulting over time with hyperglycemia. Type I diabetes is also called as insulin-dependent diabetes.

Type II diabetes is primarily caused by the insulin resistance, which is caused by the dysfunctional interaction between insulin and its receptor. Despite sufficient levels of insulin the glucose is not entered into fat and muscle cells. Increased glucose levels in blood leads to hyperglycemia and endothelial cell dysfunction. Type II diabetes is also called as non-insulin dependent diabetes.

Diabetes augments the process of atherosclerosis by a variety of mechanisms. Increased blood sugar has two effects on endothelium as part of atherosclerosis. The hyperglycemia increases the production of free radicals, which are highly reactive molecules that causes damage and premature death of endothelial cells (Hudson et al 2005). In addition the accumulation of advanced glycation end products in endothelial cells increases oxidative stress, which minimizes the availability of NO. Otherwise NO enables blood vessels to relax. Oxidative stress subsequently encourages the formation of fatty streaks in the wall of artery (Creager et al 2003, Rask-Madsen and King 2007).

Exercise and good diet brings faster blood flow through blood vessels contrary to diabetes. The force along arterial walls, which is created by fast and steady blood flow, has been shown in recent studies to protect arteries from atherosclerosis. It has been found that physical force can be a key player in function, which is capable to change biochemical processes (Woo et al 2008).

The progression of diabetes mellitus is closely connected with hypertension, renal disease and different forms of cardiovascular diseases. Diabetes is not vascular disease, but more than 75% diabetic patients die because of the causes related to atherosclerosis. However, about 70% of diabetic patients do not take it seriously that they are at high risk for cardiovascular disease (Hurst and Lee 2003). However, with early diagnosis of the atherosclerosis the disease can be decelerated through treatment and lifestyle change.

Elastin and collagen ratio determines the stiffness of the artery wall. Vascular ageing through endothelial dysfunction and elastic fiber degeneration leads to progressive arterial stiffness and atherosclerosis development. Arterial stiffness has been considered one of the risk markers of early cardiovascular disease.

It has been found that arterial stiffness is increased with diabetes mellitus type I (Llauradó G et al 2012) and type II (Urbina et al 2010). Diabetic vascular disease can be explained through the accelerated ageing of the arteries. In earlier studies have been noticed that calculated cardiovascular age, based on aortic stiffness changes, increases with diabetes mellitus about 8.9 years in case of diabetes type I (Ravikumar et al 2002) and 11.1 years in case of diabetes type II (Cockroft and Wilkinson 2002). Higher arterial stiffness in diabetes patients through measurement of aortic pulse wave velocity and aortic augmentation has been also confirmed in the earlier studies (Brooks et al 2001, Wilkinson et al 2000a, Cruickshank et al 2002).

Hypertension is connected to the increase of arterial stiffness and is part of development of the diabetes mellitus (Sowers et al 2001). Arteries of diabetes patients compared to the healthy arteries are more exposed to the injuries caused by high blood pressure and more often rupture or occlude occur (Williams 1999). Due to that the damage is caused often to retina, brain and kidneys (Safar et al 2004). However, the consequences can be effectively avoided through the blood pressure reduction. In large studies (HOPE and LIFE) it has been shown that benefit in the reduction of cardiovascular mortality was achieved by lowering the blood pressure (Yusuf et al 2000, Dahlöf et al 2002). Thus, the rapid monitoring of blood pressure in diabetes patients is strongly recommended (Solomon 2003, Rydén et al 2013).

3. Non-invasive methods for evaluation of arterial stiffness

Nowadays, there has been developed several indices for the evaluation of the cardiovascular system. Generally, they are addressed to the assessment of arterial stiffness either systemically, regionally or locally (Pannier et al 2002). Due to several reasons the stiffness of arterial wall is closely connected with development and progression of cardiovascular diseases. Firstly, the pathogenesis mechanism of isolated systolic hypertension (increased systolic blood pressure) includes increase

in arterial stiffness (Cohen et al 2011). Secondly, the stiffness of the arteries determines the ability of the vessel to accommodate ejected blood from the heart. Thus, increased arterial stiffness imposes the higher left ventricle afterload (Chirinos and Segers 2010). Thirdly, the increased pulse pressure, which is connected to the increase of aortic stiffening, may damage the organs such as the brain and the kidney (O'Rourke and Safar 2005). Fourthly, different biologic processes are connected with arterial stiffness, which causes the cardiovascular diseases (Franklin 2008). Increase in arterial stiffness is caused by aging and accelerated due to the propagation of the diseases such as diabetes mellitus, hypertension, hypercholesterolemia, kidney disease, obesity, and smoking (Payne et al 2010).

Noninvasive assessment of arterial stiffness is based on the measurement of indirect and intrinsically associated parameters, which can be related to stiffness. Generally, the methodologies can be divided into three groups: 1) direct stiffness estimation using measurements of diameter and distending pressure (local arterial stiffness estimation), 2) pulse wave velocity and pulse transit time (regional arterial stiffness estimation), 3) analysis of the pulse waveform.

3.1. Direct arterial stiffness estimation

Stiffness, which is the rigidity of an object, can be defined through the resistance of the body to the applied deformation force. The stiffness of the arterial wall is expressed through the stress σ (mechanical stress caused by applied mechanical force on unit area, measured N/m^2), which is applied from given direction, and strain ε (relative deformation of the body, measured in arbitrary units) ratio, which is the Young's elastic modulus (E) and measured in Pascal's (Pa) (Nichols and O'Rourke 2005, Cavalcante et al 2011). More detailed the Young's elastic modulus expresses the slope of the stress and strain linear relationship within the Hooke's limits in case the material is linear-elastic or "Hookean". Furthermore, the slope can be calculated by using any two points within the Hooke's limit range. In this way calculated slope is called incremental elastic modulus (E_{inc}) (Nichols and O'Rourke 2005).

The Young's modulus is independent from the direction, where the force was applied, in case the material is isotropic. The arterial wall is assumed to be isotropic in the calculations of most commonly used indices. However, the arterial wall is anisotropic and therefore the approximation is used for the estimation of vessel wall properties (Chirinos 2012).

The arterial wall consists of complex structure of the components that determines the stiffness of arterial wall. The main components are elastin, collagen fibers and smooth muscle cells. The elastin and collagen fibers are passive (without using biochemical energy) elastic components whereas smooth muscle cells are actively modulating the stiffness of the arterial wall (Bank et al 1996, Zulliger et al 2004). Furthermore, the elastic moduli of elastin and collagen fibers are different. Therefore, the arterial wall is not Hookean and the relationship between stress and strain is with a curved shape. The Young's modulus increases with the increasing

levels of stress. This means that the elastic modulus of artery is dependent on the distending pressure and it has to be taken into account while comparing results (Nichols and O'Rourke 2005).

It has to be also noted that the relationship between distending pressure and strain is not interchangeable with stress and strain relationship and law of Laplace has to be taken into account (Atlas 2008, Noordergraaf 1978). Relatively simple formulas can be derived for the calculation of local incremental elastic modulus of arterial wall by using the measurement of wall thickness in diastole and two measurements of diameters at two different pressure levels. This calculation can be done under assumptions that artery is with perfectly circular shape, there are no deformations in the longitudinal direction and the wall of artery is isotropic (Laurent et al 2006). In case the pressure and diameter is measured at the same location then these measurements can be related to the wall stiffness of artery in this location.

In addition the parameters related to the local stiffness of the artery are estimated through the pressure-volume and pressure-area relations. However, these relationships are influenced not only by the stiffness of the artery, but also vessel geometry (Chirinos 2012). Furthermore, the relationships are not linear, but within relatively narrow pressure ranges can be considered as linear for larger arteries (Meinders and Hoeks 2004). In case of smaller muscular arteries the error can be larger (Reneman et al 2005). Thus, the measurements are carried out mainly on larger arteries.

The compliance is the ratio between volume relative changes to the relative change in pressure and in addition to the stiffness the parameter is also dependent on diameter and wall thickness of artery. The reciprocal of compliance is called elastance. The compliance values for arteries with different diameters can not be compared between each other. Thus, the compliance is normalized with volume of artery and it is called distensibility (Nichols and O'Rourke 2005).

The volume of the artery is difficult to measure and in applications it is replaced by the vessel area or diameter. It has been done under assumptions that the cross-sectional vessel area is circular and volume increase of the artery is due to the radial expansion rather than due to deformations in the longitudinal direction (Chirinos 2012).

The non-linear relationship between pressure and lumen diameter is compensated in the calculation of stiffness index β (Hirai et al 1989). The stiffness index β has been used for the estimation of artery mechanical properties in earlier studies (Miyaki et al 2010, O'Rourke et al 2002).

The above described indices are used for local arterial stiffness estimation in number of different studies (O'Rourke et al 2002, Pahkala et al 2013, Ciftçi et al 2013, Oguri et al 2013). The blood pressure should be measured at the location where the mechanical changes of the artery are detected. The local blood pressure can be estimated through the registration of pressure waveform from the location of interest by using applanation tonometry (van Bortel et al 2001) or finger cuff (Boehmer 1987) and the calibration of the pressure waveform is carried out by

using measured blood pressure of brachial or radial artery (Verbeke et al 2005). The calibration can be carried out by using different techniques including general transfer function method.

For the determination of vessel diameter in vivo at diastole and stroke changes in diameter can be carried out by using any bi-dimensional ultrasound system. However, the ultrasound systems, which are equipped with high-resolution linear array transducers, should be used to obtain high quality ultrasound image of artery (Currie et al 2010, Nualnim et al 2011). With advanced image analysis software the mechanical parameters of vessel can be determined with high precision. It has to be taken account that this kind of diameter determination needs high degree of technical expertise and the procedure takes long time. Thus, it is not effective to use for example in large screening studies. The determination of diameters of deep arteries, such as aorta, has been carried out also in some studies by using MRI system (Franquet et al 2013). However, in most of the pathophysiological and pharmacological studies are carried out by using ultrasound system. Despite some of the disadvantages the ultrasound system is nowadays only non-invasive method, which can be used for the determination of local arterial stiffness (Young's modulus) through determination of diameter and IMT of artery (Laurent et al 2006). The IMT determination has been used in addition to the arterial stiffness calculation as separate parameter to monitor the inward or outward remodeling (van der Heijden-Spek 2000, Bussy et al 2000, Boutouyrie et al 2000) of arterial wall and as one risk factor of cardiovascular diseases (Molinari et al 2010).

3.2. Pulse wave velocity and pulse transit time

Pulse wave velocity is the speed at which the pulse wave propagates from the heart through the arterial system to the peripheral vessels. The pulse wave propagates through the arteries with finite speed and it is not constant for arterial system. The PWV depends on the viscoelastic properties of the artery. It has been generally accepted that the PWV is the most simple, non-invasive, robust, and reproducible method to determine regional arterial stiffness (Laurent et al 2006). In addition, aortic PWV, which is an index of aortic stiffness, has entered to the guidelines for hypertension of the European Society of Hypertension as providing extra cardiovascular risk prediction besides classical risk factors (Mancia et al 2007).

The pressure wave propagation without reflections along uniform artery can be described through transfer function. The transfer function is characterized by propagation constant, which is complex variable as it has magnitude and phase. The magnitude is determined by attenuation coefficient, which depends on viscosity of the blood and mechanical properties of arterial wall. The pulse wave propagation speed is finite and the propagation constant includes also the phase constant due to the viscoelasticity of arteries. The pulse wave velocity varies with frequency as the different harmonic components of pulse wave are travelling with different speed along the artery, which is also known as harmonic dispersion (Li et al 1981, Li 2004, Callaghan et al 1984).

PWV dependency on artery viscoelastic properties are expressed with Moens-Korteweg equation (Korteweg 1878, Moens 1878), which has been corrected by Bergel (Bergel 1960) and modified by Hughes (Hughes et al 1979):

$$PWV = \sqrt{\frac{E_0 \cdot \mathrm{e}^{\xi \cdot P} \cdot h}{2 \cdot r \cdot \rho \cdot \left(1 - \sigma^2\right)}}, \quad (1)$$

where E_0 is elastic modulus of the arterial wall at the zero intravascular pressure P (measured in mmHg), ξ is a constant that depends on the particular artery (typically between 0,016 and 0,018), h is wall thickness, r is lumen radius, ρ is blood density, and σ is Poisson ration. At first Moens-Korteweg equation was derived under assumption that the arterial wall has a thin wall, which means that $h/(2 \cdot r)$ is small. However, in order to decrease the error of that assumption the equation was corrected as a result of study by Bergel (Bergel 1960) and Poisson ratio σ was added to the relationship, which was taken equal to 0,5. Young's modulus of the artery depends non-linearly on the applied pressure. In the earlier study (Hughes et al 1979) was shown that the Young's modulus of the aorta increases exponentially with increasing intravascular pressure P. Then the incremental elastic modulus E_{inc} is calculated as follows (Hughes et al 1979):

$$E_{\mathrm{inc}} = E_0 \cdot \mathrm{e}^{\xi \cdot P}. \quad (2)$$

The other relationship for PWV calculation was derived from Moens-Korteweg equation by Bramwell and Hill (Bramwell and Hill 1922):

$$PWV = \sqrt{\frac{V \cdot \mathrm{d}P}{\rho \cdot \mathrm{d}V}}, \quad (3)$$

where V is the volume of artery segment, dV is the volume change due to the pressure change dP in artery.

Due to the difference in the Young's modulus and dimensions of the artery the PWV is changed according to the (1), while the pulse wave is propagating through the cardiovascular system. The Young's modulus is lower for proximal arteries and increases while moving towards periphery. In case of healthy subjects the PWV is around 4 up to 8m/s in elastic arteries (asc. aorta, abd. aorta, carotid artery) and 8 up to 15m/s in the muscular arteries, such as femoral, tibial and brachial artery (O'Rourke et al 2002, Nichols and O'Rourke 2005). In addition the PWV depends on the blood pressure according to the (1), which has to taken into account, when comparing the results between subjects and different studies. The blood pressure should be measured as well while carrying out the PWV measurements.

Although there are other methods for PWV estimation (Nichols and O'Rourke 2005, Zhang et al 2005, Khir et al 2001, Feng and Khir 2010) the widely used technique is based on measurement of the distance between two arterial sites and division with time it takes for pulse wave to travel through the path length. The pulse propagation time is also called as pulse transit time - PTT. The pulse waves can be recorded by using different techniques. The recorded waveform represents whether pressure (Asmar et al 1995), diameter (van der Heijden-Spek et al 2000), flow velocity (Blacher et al 2003, Cruickshank et al 2002) or volume changes (Nam et al 2013) in artery. Those waveforms are all expressing the pulse wave, but the nature each of them is different. However, it has been noted that the waveforms are in phase in the beginning of the cardiac cycle (Boutouyrie et al 2009a). Often the pressure signal recording has been carried out for PWV estimation, although this technique may cause the distortions in the waves if the pressure on transducer is applied incorrectly (Boutouyrie et al 2009a, Pilt et al 2010a).

The distance between recording sites of pulse waves are measured over the skin surface. It causes the error into measurements, because it is not true length of artery (Hamilton et al 2007). The error is smaller in case of relatively straight arterial segments. The measurement error becomes noticeably larger, when the two signal recording locations situates far away and the artery structure is more complex such as in the case of carotid-femoral PWV estimation (Karamanoglu 2003). It is also difficult to compare PWV measurement results between different research laboratories as the distance can be measured by using different methods (Xu 2003). The systematic overestimation of PWV can be up to 30% in case the distance measurement is carried out transcutaneously between signal recording sites of carotid and femoral artery (Rajzer et al 2008, Salvi et al 2008).

For PTT estimation the time difference is assessed between two equiphase points on recorded waveforms. The pulse waveform changes while propagating through the arteries. It has been explained through the influence of wave reflections appearing due to the branching of arteries and the changes of the arterial stiffness and dimensions along the artery (Nichols and O'Rourke 2005). In addition the arterial stiffness changes non-linearly with blood pressure, which also influences the PWV. Due to that the PWV is not constant within one cardiac cycle. The equiphase point is determined on propagating pulse wave, which represents the velocity of the whole pulse wave. It has been found that the early region of pulse wavefront remains its characteristics while propagating through the arterial system. Thus, it has been suggested to determine the PTT between the equiphase points on waveforms, which are located at the “foot” of the raising front. Different algorithms are used for the equiphase point detection and PTT estimation between synchronously measured pulse waves (Chiu et al 1991, Kazanavicius et al 2005, Temitski et al 2012). The results may differ between 5 up to 15% depending on the algorithm that is used for the PTT estimation (Millasseau et al 2005).

The “gold standard” method for arterial stiffness estimation is aortic PWV, which is assessed as carotid to femoral PWV (Mancia et al 2007). Due to the different methodologies and techniques for the distance and PTT estimation the

standardization has been carried out for carotid to femoral PWV estimation (Boutouyrie et al 2010). The largest amount of epidemiological studies has been conducted in order to prove the ability of aortic PWV to predict cardiovascular events in certain patient groups and in population at large (Laurent et al 2006).

The non-invasive estimation of the aortic PWV is difficult as the artery is hidden deep inside the body. However, the simultaneous recording of flow waves from left subclavian artery and from abdominal aorta just above its bifurcation by using Doppler ultrasound enables to estimate the aortic PWV. This method needs qualified expert skills in ultra sound Doppler measurements. The alternative method is the estimation of aortic PWV by using the pulse wave recordings from carotid and femoral arteries as those locations are closest to the aorta, where the pressure wave registration can be carried out from the surface of skin.

There are different devices, which are enabling the estimation of carotid to femoral PWV. The Complior System (Artech, Les Lilas, France) enables to record simultaneously pressure wave signals from carotid and femoral artery using two piezoelectric transducers. The other device is SphygmoCor system (ArtCor, Sydney, Australia) (Wilkinson et al 1998), which has been widely used in clinical studies. The pressure wave recordings are carried out successively from femoral and carotid artery by using the sensitive wide band piezoelectric sensor. Separately registered pressure waves are synchronized with the ECG signal and the PWV is estimated. The third device is PulsePen (Diatecne, Milano, Italy), which is similar to SphygmoCor system. All mentioned devices above require trained person and the reproducibility of the results depends on the skills of operator.

It has to be noted that the pressure waves are travelling to the opposite direction from the heart in case the carotid to femoral PWV is estimated. Thus, for the path length calculation the distance from heart to carotid artery is subtracted from the distance from heart to femoral artery. In addition it has been assumed that the wave propagation speeds from the heart to the pulse wave recording sites are equal, which is doubtful. The advantages and limitations of the first two devices are reviewed in the study by Boutouyrie et al (Boutouyrie et al 2009b).

There has been also proposed method, which estimates the PTT from the single pulse waveform (Westerhof et al 2006, Qasem and Avolio 2008). The aortic pressure waveform is decomposed into forward and backward travelling pressure waves and the time difference is measured, which corresponds to $2 \cdot PTT$ for the given segment of artery. By knowing the distance from the signal recording site to the reflection site the PWV can be calculated. However, in the latest study they have been reported the problem with this methodology as the reflection site is difficult to determine and it seems to change the location through aging (Westerhof et al 2008).

Similar methodology has been commercialized in the Arteriograph device (TensioMed, Budapest, Hungary) (Baulmann et al 2008). It has been assumed that there is one major pressure wave reflection site in the bifurcation of aorta. The forward and reflected waves are detected from the brachial artery by applying the cuff around the upper-arm. The cuff is pressurized to the supra systolic pressure

(systolic pressure + 35mmHg) and from the recorded waveform the time delay between incident and reflected waves are detected, which corresponds to 2·PTT. The distance is suggested to measure between jugulum (sternal notch) and the symphysis pubica (pubic symphysis), two characteristic anatomical points. There has been carried out invasive validations of Arteriograph for aortic PWV and AIx estimation and relatively high correlations were achieved (Horváth et al 2010). However, the working principle and validation is debated. Further investigations are suggested in order to provide an invasive validation of the working principle of Arteriograph in order to convince the medical society to introduce the device in clinical practice (Parati and De Buyzere M 2010). Lately, has been carried out number of clinical studies, where the Arteriograph has been used for the aortic PWV and AIx estimation (Mulders et al 2012, Gaszner et al 2012, Ikonomidis et al 2013).

The pulse wave propagation in other branches of arteries is studied in addition to the carotid-femoral PWV (Naidu et al 2005). The pulse wave starts to propagate, when blood is ejected from the left ventricle to the aorta. The arrival of pressure wave is detected from the artery of upper or lower limb. The pressure waves in the arteries were detected by using the pressurized cuffs, which were placed around the limbs. Thus, the exact detection point of the pulse wave on artery varied due to the cuff size. They found that all estimated PWVs in the branches from heart to higher and lower limb arteries and carotid to femoral artery were significantly increased in coronary artery disease patients.

Often the R-peak of the ECG signal is used for the starting point of the pulse wave propagation from the heart (Naschitz et al 2004). However, the R-peak shows only the electrical activity of the heart not the starting point of the wave propagation. There is short period between the heart activation and opening of the valves of left ventricle, which is called pre-ejection period. PEP is not constant and depends on the physical condition of subject. The ejection of the blood to the aorta can be detected from the phonocardiographic or transthoracic impedance signal. VaSera VS-1500N (Fukuda Denshi, Tokyo, Japan) vascular screening system registers simultaneously ECG, phonocardiographic and pressure wave signals from limb arteries. However the PWV values for each arterial branch is not given. Instead the Cardio-Ankle Vascular Index (CAVI) is calculated, which is based on the PWV estimation.

The aortic PWV is under major interest as it is a cardiovascular risk marker of advanced disease and may predict of morbid events in the next 5 up to 10 years (Mancia et al 2007). However, aortic PWV does not offer any insight into the condition of smaller blood vessels. All the arteries are stiffening and the atherosclerotic disease involves whole cardiovascular system. The assessment of peripheral arteries may enable earlier detection of atherosclerosis (Cohn J N 2006). It has been noted that lower limb arteries are particularly altered by atherosclerosis (Laurent et al 2006). However, currently there is no evidence that the PWV measured from peripheral arteries may predict the cardiovascular event (DeLoach and Townsend 2008).

3.3. Pulse waveform analysis

Pressure wave is generated by the left ventricle contraction and blood ejection into the aorta. The pressure in aorta increases due to the blood volume increase. The pressure increase in aorta is dependent on the ability of the arterial wall to stretch and on the blood volume decrease through peripheral beds of tissue. The blood volume change is related to the change in pressure through the arterial compliance. The arterial compliance is decreased due to the increase in arterial stiffness and in case of the same stroke volume the larger pressure wave is generated. (Avolio et al 2010)

The pulse wave propagation through vascular tree is complex process. The nature of wave propagation depends on the elastic properties and geometry of the arteries and blood viscosity. In addition, the pulse wave reflection appears at the location where the artery is branching. The wave reflection and reflected wave magnitude is explained through the wave transmission theory as a mismatch between impedances of branching arteries. The impedance is complex quantity and it is determined by the mechanical properties of arteries and blood. As a result the waveform of propagating pulse wave changes along the arterial tree. Therefore, the pressure waves at the two arterial locations with the same mean pressure can have different pulse pressure and shape. (Avolio et al 2010)

The pressure waveform at the aortic root depends on the contraction of left ventricle and the geometric and elastic properties of the arterial system. The distinctive features can be detected from the one cardiac cycle long pressure waveform (figure 2). In the ascending aorta the peak of the flow velocity wave appears before the peak of the pressure wave, because the stretch of the elastic artery segment. The inflection point (P_i) on aortic pressure waveform appears about at the same time with maximal point of the flow wave. The peak of the flow velocity wave situates at about 30% of the whole ejection duration (Westerhof et al 2006). The augmented component is described through augmentation index (*AIx*) and is defined as (Murgo et al 1980):

$$AIx = \frac{P_s - P_i}{P_s - P_d} = \frac{AP}{PP}, \qquad (4)$$

where P_s is systolic blood pressure (maximal value of pressure waveform), P_d is diastolic blood pressure (minimal value of pressure waveform), *AP* is augmentation pressure and *PP* is pulse pressure. The AIx has been found to change through the ageing (Kelly et al 1989). The AIx, calculated from aortic pressure waveform, is negative in young individuals and becomes positive for older subjects. The significant changes in the pressure wave morphology are explained through the changes in structural components of arterial system, which affects the pulse propagation. In addition it has been found that AIx is influenced by blood pressure and the values are higher in case of patients with type I diabetes (Wilkinson et al 2000a) and hypercholesterolemia (Wilkinson 2002), which can be explained

through premature vascular ageing (Ravikumar et al 2002, Cockroft and Wilkinson 2002).

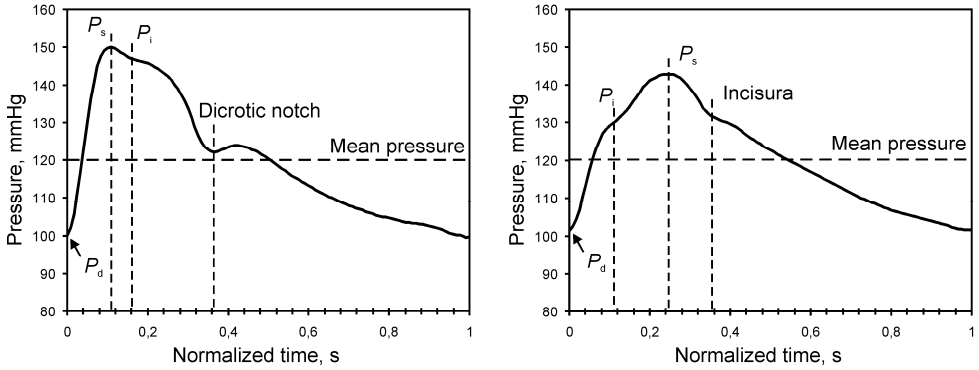

Figure 2. Averaged radial and aortic pressure waveforms normalized in time with characteristic points (reproduced according to Avolio et al 2010).

The radial pressure waveform includes similar features compared to the aortic waveform, which is registered from the same subject. However, the waveforms are significantly different. The minimal point of the radial artery pressure waveform corresponds to diastolic pressure similarly as in aortic waveform. The mean pressure of the radial artery waveform is lower from aortic waveform, but the difference is small and it can be considered equal in case of healthy subjects. The diastolic and mean pressures measured from radial or brachial arteries have been used as reference for the aortic waveform calibration. The maximal point in radial artery waveform corresponds to the systolic blood pressure, but it is situated within cardiac cycle at different location (Avolio et al 2010). This causes also the differences between simultaneously measured invasive radial and aortic systolic pressures (Pauca at al 1992).

Usually the inflection point (P_i) appears in radial artery pressure waveform after the first pressure peak, which is in this case systolic pressure peak. However, due to the ageing the P_i may become higher than first peak and form a systolic pressure peak (Kelly et al 1989). The formed systolic peak in radial artery waveform is then also related to the systolic peak in aortic waveform (Takazawa et al 2007). In some cases the late systolic peak can be visible in radial artery waveform as separate peak with local maximal point or it forms the convexity before dicrotic notch as it is visible in figure 2.

The incisura, which is visible after the systolic peak in aortic waveform, corresponds to aortic valve closure. The local minimum after the inflection point on radial artery waveform is called as dicrotic notch (Avolio et al 2010). The timing of incisura on aortic waveform correlates with dicrotic notch in radial artery waveform and thus the ejection duration can be obtained (Gallagher et al 2004).

Often the pulse waveform composition has been explained through the forward and backward travelling wave. The forward travelling wave is caused by left

ventricle ejection. The backward travelling wave is mainly caused due to the reflection of forward travelling wave from the branch points of arteries. It has been reported that the single reflection site is difficult to determine (Westerhof et al 2008). There are many reflection sites in the arterial system and the reflected waves can summate and act as a one wave arising from single reflection point (Nichols and O'Rourke 2005).

According to the theory the stiffness of the arteries is only one variable that determines the AIx. In addition the aortic pressure waveform depends on the wave characteristics of the left ventricle ejection profile, magnitude and timing of the reflected waves (Kingwell and Gatzka 2002, Nichols and O'Rourke 2005). The pulse waveform analysis allows the detection of changes in waveforms and it has been tried to interpret through the changes in the mechanical properties of arteries (Hamilton et al 2007).

The increase in aortic augmentation pressure is related to the increase in arterial stiffness. Due to the higher arterial stiffness the reflected wave propagates with higher velocity and arrives faster back to the aorta from reflection sites by augmenting the pressure wave and increasing the central systolic blood pressure. The reflected wave arrives back during the systolic phase by increasing the left ventricle afterload (Chirinos and Segers 2010). The earlier arrival of reflected wave also causes the decrease in diastolic pressure, which results in the reduction of the coronary artery perfusion pressure (Nichols and O'Rourke 2005). As the pressure waveform changes while travelling through arterial system it is important to record the central pressure waveform in order to define the effects on left ventricle and coronary artery.

The direct recording of aortic pressure wave is invasive. The aortic pressure waveform analysis can be carried out non-invasively by using SphygmoCor system. The pressure wave can be registered from carotid artery by using applanation tonometry. As the carotid artery situates close to the aorta the waveforms are similar and no transfer function is needed for the analysis. However, the recording of pressure wave from carotid artery needs highly trained person as the vessel is not supported. In addition the recording of pressure wave is difficult in case of subjects with obesity and carotid stenosis (Rhee et al 2008).

The other widely used technique, which is also applied on SphygmoCor system, involves the pressure wave registration from the radial artery and the aortic waveform is derived by using generalized transfer function (Pauca et al 2001). The pressure wave recording from radial artery is preferred as it is supported by bone and the applied pressure by tonometry is easier to handle. The AIx is determined from the derived aortic waveform and it has been used widely as an indicator of aortic stiffness (Rhee et al 2008). Nevertheless, the issues have been raised regarding the impreciseness of the generalized transfer function (Hamilton et al 2007). Transfer functions are generally constructed from the data of healthy subjects. It has been found that this approach may cause errors in case of type II diabetes patients and the AIx is over estimated (Hope et al 2004). In addition it has been suggested that for the aortic AIx estimation there is no need to use transfer

function at all. The AIx, which is estimated from radial artery, and AIx, which is estimated from derived aortic waveform, are highly correlated r=0,96 (Millasseau et al 2003). This approach has been applied in Arteriograph, where the aortic AIx estimated from brachial artery pressure waveform without using the generalized transfer function (Horváth et al 2010).

It has been found that aortic AIx depends on heart rate (Wilkinson et al 2000b). Therefore the AIx value in SphygmoCor system has been normalized for the heart rate of 75bpm and noted as AIx@75.

4. Photoplethysmographic signal and waveform analysis

PPG is a non-invasive optical technique, which can be used to monitor the circulatory changes in the cardiovascular bed of tissue. For the PPG signal recording the light source is placed towards the skin surface and light is emitted to the examined tissue. The light is absorbed and scattered in the tissue. Just a small fraction of emitted light intensity can be detected with the photodetector, which is placed on the skin adjacent to the light source (reflection mode) or opposite side of measured volume (transmission mode). In PPG probes the LEDs and photodiodes or phototransistors are often used, which makes the technology relatively cheap and reproducible. In PPG probes the LEDs are usually in the red or infrared wavelength range. However, the other wavelength rages are used as well and it is application dependent. (Allen 2007)

From the finger or forehead registered PPG signal generally consists of DC and AC components and noise. Amplitude of AC component can be ten times smaller than DC component. DC component depends on total blood volume in the examined tissue and it varies slowly in the time. The AC component of PPG signal is synchronous with the cardiac cycle and depends on blood volume and flow changes, blood vessel wall movement, pulsatile pressure and the orientation of red blood cells (Kamal et al 1989, Lindberg and Öberg 1993, Allen 2007). Though origins of the AC component waveform mechanism of the PPG signal have been studied; the phenomenon is still not fully understood (Allen 2007). Generally, it has been accepted that the AC component of the PPG signal can provide valuable information about the cardiovascular system and it corresponds to heart generated pulse wave. AC and DC components of the PPG signal are affected by respiration and factors that influence local perfusion, such as vasomotion and sympathetic nervous system activity (Johansson and Öberg 1999, Nitzan et al 1998).

PPG technology is widely used in the pulse oximeters, however other clinically important physiological parameters such as the breathing and heart rate, can be monitored as well. In addition the PPG technology has been used for the PTT measurements in order to estimate the vascular ageing (Allen and Murray 2002). Furthermore, the PTT measurement is widely used for the estimation of beat-to-beat blood pressure without cuff. This technique would enable to monitor the blood pressure changes over long periods (e.g. 24 hours) (Zheng et al 2013) and provide clinically important dynamical changes, which are predictors of cardiovascular events (Fagard et al 2008, Dolan et al 2005).

The PPG waveform is affected by the changes in the mechanical properties of arteries as the AC component of the signal corresponds to pulse wave. Therefore, this simple technique may have also potential for the identification of premature increase in the stiffness of arteries and may have considerable value in the prevention of cardiovascular disease. In all those applications the AC component carries important information. Therefore in the subsequent text the term "PPG signal" corresponds to the AC component of PPG signal.

Noise in the PPG signal can be originated from different sources (Sukor et al 2011). The power line interference causes the 50Hz or 60Hz noise. The ambient light may cause the blinding of the photodetector or modulate the signal. Often the PPG signals are affected by the motion caused noise, which is related to the movement of the sensor or the limb of the subject, where the signal is obtained. In addition the pulsating volume in the examined tissue is diminished due to the poor perfusion state and therefore amplitude of PPG signal is decreased. Consequently the SNR of the signal is decreased.

Similarly to the pressure wave, the foot of the PPG signal has been detected for PTT estimation (Nitzan et al 2002). Nevertheless, there has been also used 50% of the raising front level detection for PTT measurement, which has been found comparable with foot detection and it is more appropriate in case there is high probability for motion artifacts in signal (Lass et al 2004). Often the time delay between R-peak of the ECG signal and raising front of the PPG signal is detected for the PTT estimation (Naschitz et al 2004). In addition ECG signal R-peak has been used for the wave front detection in order to align the recurrences of PPG signal for the waveform analysis (Allen and Murray 2003). There has been found high correlations between blood pressure and PTT in case of physical exercise (Marcinkevics et al 2009). Furthermore, advanced models are proposed for the blood pressure estimation from PTT measurement and 24-hour monitoring (Poon and Zhang 2005). In addition for more accurate blood pressure estimation the PTT is measured without PEP. For that purpose the time delay is measured between opening of aortic valve and PPG signal raising front. The opening of aortic valve is detected from phonocardiographic or transthoracic impedance signals. In the mentioned applications the raising front of PPG signal has to be possible to accurately detect, which can be complicated in case of noise.

Different methods have been used to suppress the noise in the PPG signal. The simple FIR bandpass filter can be used in order to limit the unwanted high and low frequency components. However, the gross movement, coughing and breathing patterns, such as deep gasp or yawn, may cause the noise in PPG signal, which share the same frequency components, where the harmonic components of PPG signal are situated. One possibility is to detect the noisy recurrences of PPG signal and leave them out from the further analysis (Couceiro et al 2012). The other approach is to remove the noise by using different signal processing algorithms. Wavelet transforms (Lee and Zhang 2003) and independent component analysis (Stetson 2004, Kim and Yoo 2006) based techniques have been applied. Though, the studies have been shown that these methods fail in certain situations (Foo 2006,

Yao and Warren 2005). The motion artifacts can be removed from PPG signals using cycle by cycle basis Fourier series analysis (Reddy et al 2008). However, this approach is computationally complex. In addition the adaptive filters have been used for the suppression of motion caused noise under assumption that the expected PPG signal is statistical independent from the artifacts. The additional acceleration sensors have to be used with PPG probe for that purpose (Foo and Wilson 2006, Wood and Asada 2007, Comtois et al 2007).

The PPG signal has slowly changing nature and most of power of the PPG signal is concentrated into first 10 harmonic components. PPG waveform has similar characteristics as pressure waveform and the systolic phase and diastolic phase are separated with dicrotic notch (Chan et al 2007). The front of the PPG signal is the fastest changing part during one cardiac cycle.

The waveform analysis of PPG signal has been carried out since 1941. Dillon and Hertzman firstly described the PPG waveform through the crest time and dicrotic notch height (Dillon and Hertzman 1941). It was found that height of dicrotic notch from the baseline depends on the vasoconstriction and vasodilatation effects. In addition there is increase in crest time and disappearance of dicrotic notch in subjects with hypertension and arteriosclerosis.

The PPG signal waveform depends on the location, where the signal is obtained (Allen and Murray 2003). From the finger recorded PPG signal waveform is almost identical to the radial artery recorded pressure waveform. The relationship can be represented by a single transfer function (Millasseau et al 2000). Thus, the mechanical properties of arteries, which are determining the waveform of radial artery, are similarly affecting the waveform of finger PPG signal. The cardiovascular ageing has noticeable influence on PPG signal waveform through the mechanical changes in the arterial system. This change is visible in the PPG waveforms, which are recorded from different locations of body (Allen and Murray 2003). The increase in the age of the subject and consequent vascular ageing results with the triangulation of the curvy finger PPG waveform (Hlimonenko et al 2003). These changes are similar to the radial artery (Kelly et al 1989).

In recent studies the PPG waveform has been decomposed by using the Gaussian or log-normal functions in order to separate direct and reflected waves for the cardiovascular system assessment (Rubins 2008, Huotari et al 2009). In addition the PPG waveform has been analysed on frequency domain and the decrease of power in the harmonics are indicated due to the increase in age. This has been suggested as the useful noninvasive measure of aging and vascular disease (Sherebrin and Sherebrin 1990).

A number of parameters can be used to determine the waveform of the pulse wave on time domain, which can be applied as well for PPG waveform (Korpas et al 2009). On time domain the proportions of pulse wave can be measured, such as crest time of the pulse wave front, time from the foot of pulse wave until maximal point of the diastolic wave, total pulse duration, systolic and diastolic peak amplitude. From previously mentioned proportions the parameters related to arterial stiffness can be calculated (Millasseau et al 2002, Millasseau et al 2006).

In the systolic phase of PPG waveform can be seen similarly to the radial artery pressure waveform initial wave peak, inflection point, late systolic peak and dicrotic notch. Through triangulation of the waveform the distinctive points are difficult to distinguish. The derivatives of the PPG signal can be used for the detection of the mentioned characteristic points on waveform.

The SDPPG signal analysis was firstly introduced by Takazawa group to evaluate ageing and increase of arterial stiffness (Takazawa et al 1998). However, in this analysis the detection of distinctive points from PPG waveform is not in the scope. Instead the five distinctive wave peaks 'a', 'b', 'c', 'd', and 'e' from the SDPPG signal are detected and amplitudes of each wave are estimated. The amplitudes are normalized with wave 'a' as follows: *b*/*a*, *c*/*a*, *d*/*a*, *e*/*a*. It was found that with increase of age the value of *b*/*a* (r=0,75; P<0,001) increased and *c*/*a* (r=-0,67; P<0,001), *d*/*a* (r=-0,72; P<0,001), and *e*/*a* (r=-0,25; P<0,001) decreased. According to the results the ageing index was proposed as follows (Takazawa et al 1998):

$$AGI = \frac{b - c - d - e}{a}. \qquad (5)$$

It was found that the average *AGI* was elevated in case the subject had any of the following diseases: diabetes mellitus, hypertension, ischemic heart disease, and hypercholesterolemia. The average *AGI* for 474 healthy subjects was -0,22±0,36 and 126 subjects with history of disease had average *AGI* -0,06±0,41.

It was followed by studies, where the correlation relationship between SDPPG normalized amplitudes and other physiological parameters was analyzed in more detailed. The changes in the amplitudes of the SDPPG waves were analyzed in children and young people by Iketani et al (2000). They found that aging decreased the *b*/*a* ratio and *AGI* and increased the *c*/*a* and *e*/*a* ratios. Overall the *AGI* decreased with age between 3 and 18 years and then increased, forming a parabolic relationship.

In the study by Bortolotto the finger SDPPG amplitude ratios were compared with Complior measured carotid-femoral PWV concerning the influencing factors of age and atherosclerosis, in a large hypertensive population (Bortolotto et al 2000). It was found that the average values of PWV, AIx of PPG waveform and AGI were elevated in case of hypertensives with atherosclerotic alterations.

The relationship between the wave amplitudes of SDPPG and various cardiovascular risk factors among middle-aged men was analyzed by Otsuka et al (2007). They found that the *b*/*a* ratio increased with age, hypertension, dyslipidemia, impaired fasting glucose/diabetes mellitus, and lack of regular exercise. Similarly, the *d*/*a* ratio decreased with age, hypertension, and alcohol intake 6 up to 7 days per week. In addition from the femoral artery registered PPG signal has been used for the regional and local aterial stiffness estimation by using SDPPG analysis (Grabovskis et al 2011). It was found that *b*/*a* ratio correlated

(r=0,729; P<0,0001) with Young's modulus of femoral artery, which is measure of arterial stiffness.

In addition to the SDPPG parameters the AIx of invasive aortic pressure and finger PPG wavefrom was compared in the study by Takazawa group (Takazawa et al 1998). The AIx was estimated as a ratio between amplitudes of the late and early systolic component. They found high correlation between two measures of AIx (r=0,86; P<0,001). This shows the possibility to use finger PPG signal waveform to estimate the changes in aortic pressure wave. However, in the later studies the ratio between amplitudes of PPG signal and diastolic wave peak has been estimated for arterial stiffness estimation and it is called as reflection index. However, this measure differs from AIx.

The PPG signal has to be twice differentiated for SDPPG analysis. The differentiator works as a high-pass filter and as a result the higher frequency components are amplified (Proakis and Manolakis 2006). The amplified higher frequency components have to be suppressed, because it consists of unwanted noise.

It has been noted that in case of PPG waveform analysis it is important to apply appropriate filtering and it is principally essential when using second derivative analysis (Millasseau et al 2003). In the same study more detailed information about PPG signal band limiting filter has been given, where Parks-McClellan digital low-pass filter (aka Remez filter) has been used with following parameters: edge-frequency of 10 Hz, transition-band of 2Hz, pass-band ripple of 0.05 dB, stop-band attenuation of 100 dB. The edge-frequency of the pass band is the highest frequency of interest in the PPG signal. According to Millasseau et al (2003) the parameters of the filter were claimed to be chosen by unpublished observations, where the filter with given edge-frequency produced no loss of information. However, the suppression of the higher frequency components has to be enough in order to detect the distinct wave peaks from SDPPG signal.

The band limiting filter, similar to Millasseau et al (2003), for SDPPG analysis has been less detailed described in many studies including Takazawa et al (1998), Iketani et al (2000), and Otsuka et al (2007). The cut-off frequency of the low-pass filter has been used between 10 up to 10.6Hz from study to study. In addition the transition band of the filter, which plays an important role in the processing of the signal, has not been given in most of the studies (Bortolotto et al 2000, Hashimoto et al 2005, Otsuka et al 2006).

5. Experimental studies

5.1. Experimental measurement complex (Publication I)

A measurement complex for synchronous recording of pulse wave signals from different locations of arterial and peripheral sites as well as other physiological signals registered by different devices was developed (Publication I). The complex provides simultaneous estimation of PWV and pulse waveform parameters related to the arterial stiffness. The experiments were carried out in North Estonia Medical

Centre. The study was conducted in accordance with the Declaration of Helsinki and formally approved by the Tallinn Ethics Committee on Medical Research.

Two reference devices, SphygmoCor and Arteriograph, are used in the measurement complex for the aortic AIx and PWV estimation. As those devices are widely used in the clinical studies then it gives also possibility to compare the PWVs from other segment of arteries and pulse waveform analysis results.

The PWVs are measured from the segments of upper and lower limb arteries in addition to the aortic PWV. In publication I has been listed that the pulse wave signals are recorded from index finger, wrist, elbow, neck, earlobe, forehead, knee and the big toe. However, after the pilot studies some of the locations are changed. After corrections the pulse waves are recorded from index finger, wrist (radial artery), elbow (brachial artery), forehead, knee (popliteal artery), femoral artery, and the big toes.

The pulse waves are registered from index finger, big toe and forehead by using PPG technique. The PPG signals are obtained from the finger and big toe using the commercially available Envitec F-3222-12 clip sensors. The Masimo LNOP TF-I reflectance sensor is used for the recording of forehead PPG signal. The distance between LED and photodetector is 7mm. In both sensors the infrared LED is used, which has peak at 880nm. The PPG sensors are connected to the lab-built modules, which drives the LED and transforms the photoelectric current from photodiode into voltage signal. LED is working in pulsed mode, which enables to cancel the noise from ambient light. In addition the current of the LED can be adjusted manually from the module and optimized for the recording. Four PPG modules are built by the author of this thesis.

It is difficult to obtain the pulse wave signal from arteries by using the commercially available PPG sensors. The arteries are situated under other types of tissues and intensity of diffused light from the deeper layers of tissue can be low. For that purpose location specific reflectance sensors should be developed. The piezoelectric transducers are used for the pulse wave recording from radial, brachial, femoral and popliteal artery. Commercially available piezoelectric transducers MP100 (ADInstruments, USA) are used for the registration of mechanical pulsations of arteries. The piezoelectric transducers are placed above the artery and the additional pressure is applied with elastic bandage. It is ensured that the applied pressure is not affecting the signal quality (Pilt et al 2010a, Pilt et al 2010b). Two piezoelectric modules with two input channels are built by the author of this thesis in order to amplify the signals and convert them suitable for analog-to-digital converter.

In addition to the pulse waves the following signals are recorded simultaneously: phonocardiographic, ECG, peripheral pressure wave. For the PWV estimation in the arterial segments from the heart to the lower and upper limb arteries the phonocardiographic signals are recorded using the ADInstruments cardiomicrophone. From phonocardiographic signal it is possible to detect the opening of the left ventricle aortic valve and to leave out the PEP in the estimation of PTT. In addition the ECG signal is recorded simultaneously and used as a

reference signal for the signal processing. ECG signal is stable and less sensitive to motion caused noise. In addition it is easy to detect the beginning of heart contraction from the R-peak of the ECG signal. The ECG signal is recorded with commercially available ADInstruments PowerLab 4/20T device in order to ensure the safety of the patient. In addition the device enables to record the phonocardiographic signal. The ECG and phonocardiographic signals are digitized with sampling rate of 1kHz.

Beat-to-beat blood pressure wave is monitored from the right hand index finger by using Finapres system. The device enables analogue output from where the calibrated pressure wave can be obtained. The outputs of Finapres system, PPG and piezoelectric modules are connected to the National Instruments PCI MIO-16-E1 data acquisition card. The card digitizes the analogue signals with resolution of 12-bit and sampling rate of 1kHz.

The synchronization between two analog-to-digital converters is needed. It has been carried out by using the additional synchro signal connection between two devices. The synchronous recording of the signals was tested by using the generated sine wave with frequency of 5Hz. The signal from generator output was fed to the inputs of the PowerLab and data acquisition card. After the analysis it was found that two systems are recording the signals synchronously.

In addition the pilot study was carried out on four subjects in order to test the applicability of measurement complex. Firstly, the measurements were carried out with reference devices, while the subject was in supine position. As follows, all the signals were recorded synchronously with measurement complex. The signals were processed in MATLAB and PWVs were calculated for the limb arterial segments and compared with Arteriograph estimated aortic PWV. All measured PWVs were below the 9m/s. In addition the PWVs were lower than aortic PWV in the segments from elbow to index finger and from knee to big toe. Similar results were also achieved in the earlier study (Hlimonenko et al 2008).

In addition after the pilot studies the ultrasound system has been included to the measurement complex in order to obtain the thickness of the arterial wall and diameter of vessel lumen. This enables to estimate the Young's elastic modulus of the artery, which is the measure of stiffness.

5.2. Noise suppression in photoplethysmographic signal for PTT estimation (Publication II)

The registered pulse wave signals can be noisy in case the examined subject has to deal with some kind of physical activity or has during the recordings unintentional movements. Motion caused noise can overlap the the frequency components of the pulse wave signal. In publication II the algorithm for the suppression of motion caused noise from PPG signal has been developed and tested on simulated and recorded PPG signals from the subject. In addition the algorithm averaging effect on PTT calculation is analysed.

Comb filter has frequency response, where the main lobes are regularly spaced over the frequency domain. All the frequency components, which are situating

between main lobes, are suppressed. In case the frequency response of the filter is adjusted according to the harmonic components of the desired signal, the noise components between main lobes are suppressed. In case of discrete periodic signals $x[k]$ the comb filter is described as follows:

$$y[k] = \frac{x[k] + x[k - D]}{2}, \qquad (6)$$

where $y[k]$ is the output signal of filter, k is integer and refers to sample number in the signal, and D is coefficient, which determines frequency response of the filter. The output of the filter is averaging the two consecutive periods in case the filter is adjusted for the periodic signal frequency. The filter can be modified in order to average more than two consecutive periods.

The biosignals are recurring, but not periodic. Therefore, the comb filter has to be adapted for each recurrence of PPG signal. In publication II the adaption of the filter has been carried out based on the pulse frequency, which is calculated from the ECG signal. Generally, in MATLAB developed adaptive comb filter interpolates the r consecutive recurrences of PPG signal to the same length and calculates the average waveform. The attenuation between the main lobes is increased by enlarging the number of averaged recurrences r. However, using more than four (first side lobe attenuation 11.4dB) or five (first side lobe attenuation 12.1dB) recurrences will not lead to considerable advantage as with ten recurrences the first side lobe attenuation is 13.1dB.

Averaging of recurrences causes the decrease in signal waveform differences between the cardiac cycles. The recurrences are weighted for the output waveform calculation in order to reduce the effect of the more passed cardiac cycles to the output of the filtered signal. The weights were found for the adjusted adaptive comb filters, which are using for the output signal calculation 3 up to 5 recurrences.

The adaptive comb filters were tested on 24s long simulated PPG and ECG R-peak signals, which frequency varied from 1Hz up to 2Hz. The white noise was added to the signal. It was found that adaptive comb filter with r=3, r=4, r=5 attenuated noise 18dB, 24dB, and 32dB, respectively. With adjusted adaptive comb filter the attenuation of noise with the same numbers of r was lower compared to the non-adjusted comb filter. However, by comparing the amount of information taken from the previous recurrences for the output calculation the adjusted comb filter gives advantage in noise suppression. The 24dB noise attenuation was achieved in case the 228% of information was used from the previous 3 recurrences for adjusted adaptive filter output calculation. The same noise attenuation was achieved in case the 300% of information was used from the previous 2 recurrences. 100% of information corresponds to the situation, when selected recurrence is involved to the output calculation with weight 1.

In addition the adaptive comb filter was tested on PPG signals, which were recorded from forehead. The ECG signal was recorded synchronously. The subject was asked to make squat downs in order to decrease the SNR of the signal. The

recorded PPG signal was filtered with high- and low-pass filters with cut-off frequencies of 0.3Hz and 30Hz, respectively. As follows the adaptive comb filter was applied. By comparing the frequency spectrums before and after comb filtering it was visible that the frequency components were suppressed between harmonic components of the PPG signal. Furthermore, the fronts of the PPG signal were able to visually detect after the comb filtering.

The adaptive comb filter has averaging effect on signal waveform and due to that the influence on PTT estimation was analysed by using simulated PPG and ECG R-peak signals. The PTT in the first simulated test signal was changed between 0,25 and 0,35s. The PTT was estimated by using raw and comb filtered PPG signal. The comb filter used six recurrences r=6 for the output signal calculation. It was found that the PTTs, estimated using the comb filtered signal, are delayed about three periods from that of the raw generated PPG signal. Furthermore, in the second simulated test signal the PTT value was changed sharply from 0.35 to 0.25s. Six periods long reaction time was found in case the adaptive comb filter uses six recurrences for output signal calculation.

In addition the PTT delay effect was analysed in case from forehead recorded PPG signal. The change in the PTT was obtained with Valsalva maneuver. The similar PTT delay effect was visible in case the comb filtered PPG signal was used. However, the typical PTT changes of the Valsalva maneuver were mostly visible in case the four recurrences were used for the filter output signal calculation.

The developed adaptive comb filter is the simple method for the suppression of the motion caused noise in PPG signal. However, the output signal of the filter depends on the previous recurrences and due to that the small characteristic changes are reduced. The balance between noise suppression and allowable signal averaging effect has to be considered in the applications of the filter.

5.3. Second derivative photoplethysmographic signal analysis algorithm (Publication III)

From the finger SDPPG waveform analysis derived *AGI* can be a potential parameter for arterial stiffness estimation and the evaluation of cardiovascular ageing. In publication III the SDPPG analysis algorithm has been improved in order to achieve the minimal standard deviation of *AGI*. Lower standard deviation of *AGI* gives more effective differentiation between the levels of cardiovascular ageing.

In publication III has been shown that in case of healthy subject the *AGI* value may differ between the consecutive recurrences by using SDPPG analysis algorithm (Millasseau et al 2003). Although, the subject was in supine position and it was assumed that the cardiovascular system was not changing during short periods of time, the difference between maximal and minimal values of *AGI* constituted about 39% from the whole scale of *AGI*. It was visible that the detected peaks of SDPPG waveform were situated in the two consecutive recurrences of PPG signal at the different phases of cardiac cycle. The different detection of wave peaks in the consecutive reccurrences is due to the insufficient suppression of noise and higher harmonic components of PPG signal.

The differentiator works as high-pass filter and it amplifies the noise, which situates at higher frequency components. It has to be supressed with low-pass filter. The low-pass filter with static cut-off frequency supresses the frequency components of two consecutive recurrences differently as PPG signal frequency components are dependent on heart rate. New SDPPG signal analysis algorithm limits equally the number of harmonic components in each of the recurrence. The analysis algorithm is implemented in MATLAB.

For that purpose the raw SDPPG signal is resampled in such a way that one of the selected recurrence lengths is 1s long. As follows the Parks-McClellan low-pass filter with 1Hz wide transmission band is applied. The copy of the selected recurrence from the filtered SDPPG signal is place to the waveform matrix. As follows the next recurrence is selected from the raw SDPPG signal and resampling, filtering and copying process is carried out. The selected recurrence is placed to the next row in the waveform matrix. The described processing loop is carried out for all of the recurrences in the SDPPG signal. In addition, parallel with the SDPPG signal processing the PPG and fourth derivative of PPG signal are processed in the same way. As a result the three waveform matrices are constructed.

All the waveforms in the matrices are aligned according to the 50% level point of PPG signal raising front. As follows the distinct wave peaks ‘a’, ‘b’, ‘c’, ‘d’, and ‘e’ in the SDPPG waveforms are found between the zero crossing points of fourth derivative of PPG signal waveform and the amplitude ratios *b*/*a*, *c*/*a*, *d*/*a*, *e*/*a* and *AGI* were calculated.

The optimal edge frequency was found for Parks-McClellan low-pass filter in order to achieve the lowest standard deviation of the SDPPG wave amplitudes, which in the end minimizes the standard deviation of AGI. Furthermore, the variation in the placement of detected waves on time domain has to be minimal through out all the recurrences for on subject. For that purpose the 1 minute long PPG signals from index finger were obtain using in the publication I described measurement complex. The temperature of room was controlled and kept at 23±1 degrees Celsius. The PPG signals were recorded from 21 healthy and physically active subjects aged from 21 to 66 years. The subjects were grouped by the age as follows: 20-30, 30-40, 40-50, 50-60, 60-70. Each age group from 20 to 50 years comprised 5 subjects. The other two groups comprised three subjects. The recorded PPG signals were processed with new SDPPG algorithm and the edge frequency of Parks-McClellan filter was changed between 4 to 14Hz with step of 1Hz. For comparison the same signals were processed with the algorithm by group of Millasseau (Millasseau et al 2003).

It was found that the minimal standard deviation of amplitude ratios and minimal variations in the placement of detected waves on time domain was achieved in case the edge frequency of low pass filter was 6Hz. This edge frequency has been considered optimal for finger PPG signals. Compared to the previous algorithm the twice lower average standard deviation of *AGI* was achieved, which constitutes 5% of the whole scale of *AGI* (Takazawa et al 1998). The relatively high correlation (r=0,91) was found between the age and *AGI*, which

is in relation with previously published results (r=0,80) by Takazawa group (Takazawa et al 1998).

The algorithm was also tested on signals from the diabetes patient group. The diabetes patients may have increase in cardiovascular age and elevation in arterial stiffness due to the sclerotic processes. The diabetes patient group included 21 subjects.

The linear regression model was constructed in order to estimate the relation between age and AGI. The regression model was constructed based on the results of healthy subjects. The relatively high AGI values, compared to the regression line and healthy subjects, were found for diabetes patients. However, some of the diabetes patients had AGI values similar to the healthy subjects. It can be caused by the effective treatment of diabetes mellitus and active life style of the subject, which has stopped the premature stiffening of arteries. It was seen from Bland-Altman plot that the diabetes patient group average differece from regression line was 0,36. In addition the significant difference between two groups was found (P<0,0005).

Based on these results the improved SDPPG algorithm can be used for the estimation of cardiovascular ageing and the subjects with probable increase in arterial stiffness can be differentiated.

5.4. Forehead photoplethysmographic waveform indices for cardiovascular ageing estimation (Publications IV)

In publication IV the forehead PPG signal was analysed by using in publication III introduced SDPPG analysis algorithm. The aim was to investigate the cardiovascular ageing effect on forehead PPG signal and to find SDPPG indices for the differentiation of the subjects with increased arterial stiffness. In this study the forehead PPG signals were recorded from 22 supposedly healthy subjects aged from 21 to 50 years and from two diabetes patients with age of 33 and 27. As the finger and forehead PPG signal recordings were carried out simultaneously then almost half of the recordings were used from the study described in publication III.

The aortic PWV was estimated in this study as a reference for the cardiovascular system evaluation. Estimated PWV is related to the stiffness of the aorta through Moens-Korteweg equation. Elevated PWV indicates the increase in the stiffness of aorta and it is assumed that also the stiffness of blood vessels in the forehead has been increased due to the sclerotic processes. The PWV in aorta was estimated by using the Tensiomed Arteriograph.

It was found that the diabetes patients had PWV above 10m/s, which indicates the increase in the stiffness of aorta. Furthermore, one healthy subject had PWV of 15,4m/s. All the other subjects had PWV below 9m/s. However, compared to the earlier study (Ohmori et al 2000) no relationship between aortic PWV and age was found.

The optimal low-pass filter edge frequency in this study was found at 6Hz, which is similar to the study in publication III. The PPG signals were processed and the SDPPG signal amplitude ratios were estimated. It was found that the extracted amplitude ratios b/a (r=0,60), c/a (r=-0,24), d/a (r=-0,59), and e/a (r=-0,50) are

dependent on the age. Furthermore, the changes in the amplitude ratios are in the same direction compared to the finger signal amplitude ratios (Takazawa et al 1998). This means that the similar changes, compared to the finger waveform, can be seen in forehead signal, although the waveforms are not identical. In addition the absolute values of the amplitude ratios from forehead and finger signal are different due to the waveform differences.

The values of amplitude ratios *b*/*a* and *d*/*a* form the diabetes patients and from one healthy subject with elevated PWV were noticeably different from healthy subjects. In case of amplitude ratio *b*/*a* the values were elevated and in case of ampitude ratio *d*/*a* the values were lowered.

The changes in the forehead PPG waveform, which are caused by the cardiovascular ageing, can be characterized using the SDPPG amplitude ratios. Based on the results it can be assumed that the premature increase in cardiovascular ageing is more evident in case of amplitude ratios of *b*/*a* and *d*/*a*.

5.5. Finger photoplethysmographic waveform index for discrimination of subjects with higher arterial stiffness (Publications V)

In the publication V the finger PPG waveform index has been compared with SphygmoCor derived aortic AIx to show that PPGAI can be used for the detection of premature cardiovascular ageing. The PPGAI has been obtained using in the publication III described SDPPG analysis algorithm. The amplitudes of the PPG waveform have been obtained at the locations of wave peaks ‘b’ and ‘d’. The named amplitudes are normalized with the amplitude of PPG waveform and denoted as *PPGb* and *PPGd*. The PPGAI is calculated as follows:

$$PPGAI = \frac{PPGd}{PPGb}. \quad (7)$$

In this study the subject groups and participated subjects are the same as in the study of publication III. Furthermore, in this study the recorded signals for the publication III were used. During the experiments the pressure waves were obtained from left hand radial artery with SphygmoCor prior to the PPG signal recordings. The aortic pressure waveform was derived from radial artery waveform by using transfer function. The AIx@75 was estimated from aortic pressure waveform.

The strong linear correlation relationship was found between SphygmoCor derived aortic AIx@75 and PPGAI (r=0,85). All the datapoints from healthy subjects and diabetes patients were used in correlation coefficient calculation. Similarly, high correlation relation (r=0,86) between invasive aortic AIx@75 and PPG AIx was found by Takazawa group (Takazawa et al 1998). In addition the regression model was constructed for the aortic AIx@75 estimation from PPGAI.

The linear relationships between aortic AIx@75, PPGAI and age were investigated by using the datapoints from healthy subjects. Relatively high correlation relationship was found between age and PPGAI (r=0,75) and the

regression model was constructed. The datapoints from healthy subjects were situated close to the regression line. However, the PPGAI values from diabetes patients were noticeably higher from the regression line, which indicates the premature cardiovascular ageing and increase in arterial stiffness. Similarly, the positive correlation relationship (r=0,59) was found between age and arotic AIx@75. The datapoints were more dispersed, compared to PPGAI, around the regression line. However, the values of AIx@75 were higher than regression model line, which is similar to the PPGAI.

The datapoint differences from the regression lines were calculated for aortic AIx@75 and PPGAI. For both indices the significant differences between the healthy subject and diabetes patient groups were found. The average difference of diabetes patients from regression line was 0,26 and the regression model standard deviation was found 0,10 in case of PPGAI. Similarly, the average group difference form regression line was 14,4% and the regression model standard deviation was 12,11%. Based on the results the PPGAI provides, compared to the aortic AIx@75, better discrimination of the subjects with higher arterial stiffness as the standard deviation of the regression model constituted 39% from the average difference of the diabetes partient group. It has been shown that the relatively cheap PPG technology and developed SDPPG analysis algorithm can be applied to discriminate the subjects with premature increase in arterial stiffness from the healthy subjects.

Conclusions

The results of this study confirm the possibility to detect premature increase in arterial ageing using inexpensive and non-invasive optical method based on the developed novel SDPPG waveform analysis algorithm. The measurement complex provided synchronous recording of the pulse wave parameters in different sites and other physiological signals required for investigations. The adaptive comb filter was developed and tested for the motion caused noise suppression to increase the SNR of the PPG signal.

The main results of current study are following:

- The adaptive comb filter attenuated the white noise in PPG signal by 18dB, 24dB, and 32dB in case the filter used for output calculation 3, 4, and 5 recurrences, respectively. In addition the PPG signal SNR was possible to increase for the PTT calculation in case the signal was recorded from forehead and affected by motion caused noise. However, the filter has averaging effect on output signal waveform and PTT calculation. This effect has to be considered in the applications of the filter.
- Compared to the former algorithm, the standard deviation of *AGI* was twice lower using the new SDPPG algorithm for the finger PPG waveform analysis. This gives more effective differentiation between the levels of arterial ageing. Furthermore, the diabetes patients had elevated AGI values, which can be explained through increased arterial ageing. The significant difference was found between the groups of healthy subjects and diabetes patients.
- The arterial ageing caused changes in the forehead PPG signal can be characterized using the developed SDPPG signal analysis algorithm. Furthermore, the subjects with increased arterial stiffness had noticable increase in SDPPG signal amplitude ratio of *b*/*a* and decrease in amplitude ratio of *d*/*a*, which indicated the premature arterial ageing. In addition it was found that the arterial ageing caused changes in the forehead waveform are same directional with the finger waveform.
- Strong linear relationship was found between aortic AIx@75 and PPGAI. The AIx@75 and PPGAI values were elevated in case of diabetes patient group. The PPGAI enables better discrimination between healthy subjects and patients with higher arterial stiffness.

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Kokkuvõte

Optilise pulsilaine signaali analüüs arterite varase vananemise määramiseks diabeedihaigetel

Südame-veresoonkonna haigused on üheks peamiseks surmapõhjuseks maailmas. Vananedes arteri endoteel kulub ja kahjustub ning põhjustab ateroskleroosi ja naastude teket veresoone seinale. Erinevate haiguste korral, seal hulgas diabeedi puhul, on arterite vananemise protsess kiirenenud. Arterite lupjumise tulemusena suureneb nende jäikus, mis põhjustab südame koormuse tõusu, sest veresoonte poolt avaldatud suurema takistuse tõttu on verd raskem läbi soonte pumbata. See põhjustab omakorda erinevaid veresoonkonnaga seotud haiguseid nagu näiteks hüpertensiooni, südame isheemiatõve jne. Veresoonkonna seisundi muutuste varajase avastamise ning selle tulemusena rakendatud õige ravi korral on võimalik edasine haiguse süvenemine ära hoida.

Arterite jäikuse hindamiseks töötatakse välja ning võetakse kasutusele üha enam mitteinvasiivseid meetodeid. Enamus meetodeid on suhteliselt keerukad ja kallid ning protseduuride läbiviimiseks on vaja selleks spetsiaalse väljaõppe saanud operaatorit. Arterite seisundi hindamiseks oleks vaja meetodit, mis oleks mitteinvasiivne, odav ning lihtsalt teostatav. Uute ja mitteinvasiivsete meetodite esiletõusuga on hakatud aina tihedamini kasutama pulsilaine levikiirust ja pulsilaine kuju analüüsi.

Antud töö eesmärgiks oli uurida optilise meetodi abil salvestatud pulsilaine kuju ja leviaja analüüsi võimalusi varajase arterite jäikuse suurenemise ning sellest tuleneva veresoonkonna vanuse määramiseks. Selleks koostati uurimiskompleks pulsilainete ja teiste füsioloogiliste signaalide mitteinvasiivseks sünkroonseks salvestamiseks. Signaalide salvestused ning muud vajalikud protseduurid viidi läbi Põhja-Eesti Regionaalhaiglas tervetel ning diabeedihaigetel. Töö käigus uuriti ning koostati algoritm liikumisest tingitud mürade vähendamiseks salvestatud optilises pulsilaine signaalis. Arterite jäikuse erinevuste uurimiseks töötati välja optilise pulsilaine signaali kuju analüüsi algoritm, mis põhineb teise tuletise meetodil. Lisaks võrreldi väljatöötatud meetodi ning algoritmi efektiivsust kliinilises praktikas kasutatavate meetoditega, mis võimaldaks eristada normaalse ning suurenenud arterite jäikusega uuritavaid.

Töö tulemusena leiti järgmist:

- Koostatud uurimiskompleks võimaldab sünkroonselt salvestada pulsilaine ja teisi füsioloogilisi signaale.
- Koostatud algoritm eemaldab optilisest signaalist liikumisest tingitud müra, mille tulemusena on võimalik pulsilaine leviaega edukalt määrata.
- Väljatöötatud optilise pulsilaine signaali kuju analüüsi algoritm võimaldab eristada arterite jäikust ning seeläbi veresoonkonna vanust tervete ja diabeedihaigete grupi vahel.

Abstract

Optical pulse wave signal analysis for determination of early arterial ageing in diabetic patients

Cardiovascular diseases are one of the leading causes of death in the world. Through ageing the endothelium of artery abrase and get damage, this causes the atherosclerosis and generation of plaques to the vessel wall. Due to different diseases, as well with diabetes mellitus, the ageing process of arteries is accelerated. The stiffness of the arteries is increased as a result of calcification, which causes the increase in the load of the heart, because the blood is more difficult to pump throught the vessels with increased resistance. This in turn causes the different diseases connected to the cardiovascular system for example hypertension, ischemia etc. Further propagation of the disease can be prevented with premature detection of the changes in the cardiovascular system condition and with applied correct treatment.

Different non-invasive methods have been lately developed and applied to estimate arterial stiffness. However, most of the methods are relatively complex and expensive, furthermore the trained operator is needed for the measurements. There is need for a methods, which are non-invasive, inexpensive and easy to perform. The PWV and pulse wave analysis methods has been used more often in the novel non-invasive devices for the arterial stiffness estimation.

The aim of the current work was to investigate the possibilities to detect the premature increase in the arterial stiffness and consequent increase in the cardiovascular ageing using the pulse waveform and transit time analysis on optically recorded signal. The measurement complex was built for the non-invasive syncrhronous recording of pulse wave and other physiological signals. The recording of the signals and other necessary procedures were carried out on healthy subjects and diabetes patients in North Estonia Medical Centre. During the study the algorithm was investigated and developed for the supression of the motion caused noise in recorded optical signal. The optical pulse waveform analyisis algorithm was developed, which is based on the second derivative method. In addition the effectiveness of developed method was compared with recognized and in clinical practice used methods in differentiating the subjects with normal and higher arterial stiffness.

As a result the following was found:

- Compiled measurement complex enables to record synchronously pulse wave and other physiological signals.
- Constructed algorithm suppresses the motion caused noise from the optical signal and as a result it is possible successfully to estimate the pulse transit time.

- Developed optical pulse wave signal analysis algorithm enables to differentate the arterial stiffness and consequent cardiovascular system age between healthy and diabetes patient group.

APPENDIX 1

PUBLICATIONS

Publication I

Pilt K, Meigas K, Viigimaa M, Temitski K, Kaik J (2010) "An experimental measurement complex for probable estimation of arterial stiffness", *In: Proceedings of 30th Annual International Conference of the IEEE EMBS, Buenos Aires, Argentina, August 31 – September 4*, 194-197 (DOI: 10.1109/IEMBS.2010.5627925).

PUBLICATIONS

Publication II

Pilt K, Meigas K, Ferenets R, Kaik J (2010) "Photoplethysmographic signal processing using adaptive sum comb filter for pulse delay measurement", *Estonian Journal of Engineering*, 16: 78-94 (DOI: 10.3176/eng.2010.1.08).

PUBLICATIONS

Publication III

Pilt K, Ferenets R, Meigas K, Lindberg L-G, Temitski K, Viigimaa M (2013) "New photoplethysmographic signal analysis algorithm for arterial stiffness estimation", *The Scientific World Journal*, vol. 2013, Article ID 169035, 9 pages (DOI: 10.1155/2013/169035).

PUBLICATIONS

Publication IV

Pilt K, Meigas K, Temitski K, Viigimaa M (2012) "Second derivative analysis of forehead photoplethysmographic signal in healthy volunteers and diabetes patients", *In: IFMBE Proceedings of World Congress on Medical Physics and Biomedical Engineering, Beijing, China, May 26-31*, 410-413 (DOI: 10.1007/978-3-642-29305-4_109).

PUBLICATIONS

Publication V

V **Pilt K**, Meigas K, Ferenets R, Temitski K and Viigimaa M (2013) "Photoplethysmographic signal waveform index for detection of increased arterial stiffness", *Manuscript submitted*

ELULOOKIRJELDUS

1. Isikuandmed

Ees- ja perekonnanimi	Kristjan Pilt
Sünniaeg ja –koht	10.11.1981, Tallinn, Eesti
Kodakondsus	eestlane

2. Kontaktandmed

Aadress	Sõpruse pst. 255-36, 13414 Tallinn, Eesti
Telefon	+372 620 22 10
E-posti aadress	kristjan.pilt@cb.ttu.ee

3. Hariduskäik

Õppeasutus (nimetus lõpetamise ajal)	Lõpetamise aeg	Haridus (eriala/kraad)
Tallinna Saksa Gümnaasium	2000	Keskharidus
Tallinna Tehnikaülikool	2005	Elektroonika ja biomeditsiinitehnika, bakalaureusekraad
Tallinna Tehnikaülikool	2008	Elektroonika, magistrikraad

4. Keelteoskus (alg-, kesk- või kõrgtase)

Keel	Tase
Eesti	Emakeel, kõrgtase
Inglise	Kõrgtase
Vene	Algtase
Soome	Algtase
Jaapani	Algtase

5. Täiendõpe

Õppimise aeg	Täiendusõppe läbiviija nimetus
10.2003-09.2004	*University of Electro-Communications*, Tokyo, Japan
17-18.10.2011	Dr Richard M. Felderi koolitus „Mõjusa õpetamise õpituba“, Tallinna Tehnikaülikool
09.2011-02.2012	Linköpingi Ülikool, Rootsi
03.2007-09.2012	4 Rahvusvahelise doktorikooli iBioMEP täiendkursust
04.05.2012	Täienduskoolitus "Biooptika meditsiinitehnikas", Tallinna Tehnikaülikool

6. Teenistuskäik

Töötamise aeg	Tööandja nimetus	Ametikoht
06.2003-07.2003	AS Ecomatic	Automaatika kilpide komplekteerija
2005-2006	SA Põhja-Eesti Regionaalhaigla	Klienditeenindaja
2009-k.a.	Tallinna Tehnikaülikool	Teadur

7. Teadustegevus

Optiliste meetodite kasutamine ateroskleroosi varajasel diagnoosil

8. Loometöö

Loengumaterjalid aines "Mikrolaine- ja optiline tehnika", koostanud Kristjan Pilt ja Kalju Meigas, TTÜ, 2012, ISBN 978-9949-23-305-2

9. Tunnustused

Aasta Tehnikaüliõpilane - Eesti Inseneride Liidu aunimetus

10. Kaitstud lõputööd

- Sandra Silluta, MSc. Arterite elastsusmooduli määramine Moens-Korteweg'i valemi põhjal ning seoste leidmine ühise unearteri intima-media paksusega, TTÜ, 2013
- Jaana Lauri, MSc. Samafaasipunktide detekteerimise meetodite võrdlus pulsilaine viiteaegade määramiseks, TTÜ, 2012
- Argo Veide, MSc. Kunstlikult tekitatud peegelduste uurimine perifeerselt arterilt registreeritud rõhulaines, TTÜ, 2012
- Annika Mikola, BSc. Difuusse peegelduse uurimine tugevalt hajutavas ja neelavas keskkonnas ning võrdlus Monte Carlo meetodiga, TTÜ, 2012
- Mikk Viidebaum, MSc. Moens-Kortewegi võrrandi põhjal pulsilaine levikiiruse ja vererõhu vahelise seose eksperimentaalne uurimine käsivarrel, TTÜ, 2011
- Ester Jürgenson, MSc. Pulsilaine levikiiruse määramise võrdlus seadmetega Arteriograph ja SphygmoCor, TTÜ, 2011

11. Teadustöö põhisuunad

SF0140027s07, Biosignaalide interpreteerimine meditsiinitehnikas, 2007-2012
ETF5888, Koherentse fotodetekteerimise kasutamine kardiovaskulaarses diagnostikas - vererõhu ja arteri viskoelastsete parameetrite mitteinvasiivne monitoring, 2004-2007
AR13061, Kõrgtasemelisel signaalitöötlustehnoloogial põhinevad EEG algoritmid ajuhäirete automaatseks tuvastamiseks, 2013-2015
ETF6173, Mikrolainekiirguse mõju kognitiivsetele funktsioonidele, 2005-2008
ETF7506, Optilise koherentse fotodetekteerimise kasutamine ateroskleroosi varajasel diagnoosil, 2008-2011
ETF8621, Uudne optiline meetod ureemiliste toksiinide - alatoitumuse ja kroonilise põletiku ning SVH riski potentsiaalsete markerite, monitooringuks, 2011-2014
ETF6936, Uudne optiline multikomponent monitor neerupuudulikkusega patsientide ravi kvaliteedi hindamiseks, 2007-2010
VIR523, Töövõime ja sotsiaalne kaasatus, 2011-2013

APPENDIX 3

CURRICULUM VITAE

1. Personal data

Name	Kristjan Pilt
Date and place of birth	10.11.1981, Tallinn, Estonia

2. Contact information

Address	Sõpruse pst. 255-36, 13414 Tallinn, Eesti
Phone	+372 620 22 10
E-mail	kristjan.pilt@cb.ttu.ee

3. Education

Educational institution	Graduation year	Education (field of study/degree)
Tallinn German Gymnasium	2000	Secondary education
Tallinna University of Technology	2005	Electronics and biomedical technology, bachelor degree
Tallinna University of Technology	2008	Electronics, master degree

4. Language competence/skills (fluent, average, basic skills)

Language	Level
Estonian	Mother-tongue, fluent
English	Fluent
Russian	Basic skills
Finnish	Basic skills
Japanese	Basic skills

5. Special courses

Period	Educational or other organization
10.2003-09.2004	*University of Electro-Communications*, Tokyo, Japan
03.2007-09.2012	4 graduate courses in International Doctoral Programme – iBioMEP
17-18.10.2011	Dr Richard M. Felder's course „Effective College Teaching Workshop", Tallinn University of Technology
09.2011-02.2012	Linköping University, Sweden
04.05.2012	Complementary training „Bio-optics in medical technics", Tallinn University of Technology

6. Professional Employment

Period	Organization	Position
06.2003-07.2003	Ecomatic Ltd.	Automation control system replenisher
2005-2006	North Estonia Medical Centre	Client servant
2009-	Tallinn University of Technology	Research scientist

7. Scientific work

Application of optical methods in early diagnosis of atherosclerosis

8. Creative work

Lecture materials in "Microwave and optical technics", compiled by Kristjan Pilt and Kalju Meigas, TUT, 2012, ISBN 978-9949-23-305-2

9. Honours and awards

Technical Student of the Year 2008 - Estonian Association of Engineers title of honor

10. Defended theses

- Sandra Silluta, MSc. Assessment of elastic modulus of arteries using Moens-Korteweg equation and finding connections with intima-media thickness of common carotid artery, TTÜ, 2013
- Jaana Lauri, MSc. The comparison of the detection methods of the same phase points for the calculation of the pulse transit time, TTÜ, 2012
- Argo Veide, MSc. Investigation of artificially induced reflections in registered pressure wave from peripheral artery, TTÜ, 2012
- Annika Mikola, BSc. Study of diffuse reflectance in highly scattering and absorbing medium and comparison with Monte Carlo method, TTÜ, 2012
- Mikk Viidebaum, MSc. Experimental investigation of the relationship between pulse wave velocity and blood pressure on human arm based on Moens-Korteweg equation, TTÜ, 2011
- Ester Jürgenson, MSc. Comparison of pulse wave velocity measurement using Arteriograph and SphygmoCor devices, TTÜ, 2011

11. Main areas of scientific work/Current research topics

ETF6936, A novel optical multicomponent monitor estimating ESRD patients' treatment quality, 2007-2010
ETF8621, A novel optical technology for monitoring of uremic toxins - potential markers for malnutrition–inflammation syndrome and CVD risk, 2011-2014
AR13061, Algorithms for automatic detection of brain disorders based on advanced EEG signal processing techniques, 2013-2015
ETF7506, Application of Coherent Photodetection in Early Diagnosis of Atherosclerosis, 2008-2011
ETF5888, Application of Method for Coherent Photodetection in Cardiovascular Diagnostics - Non-Invasive Monitoring of the Blood Pressure and the Viscoelastic Parameters of Arteries, 2004-2007
SF0140027s07, Interpretation of Biosignals in Biomedical Engineering, 2007-2012
ETF6173, Microwave effects on cognitive functions, 2005-2008
VIR523, Work Ability and Social Inclusion, 2011-2013