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PULSE WAVE ANALYSIS FOR PREDICTING RISK OF A CARDIOVASCULAR EVENT

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ABSTRACT

Kalle Kinnunen: Pulse Wave Analysis for Predicting Risk of a Cardiovascular Event
(Pulssiaaltoanalyysimenetelmät sydän- ja verisuonitautikohtauksien ennakoimisessa)
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As cardiovascular diseases are the leading cause of death in the world with approximately 17.9 million related deaths in 2016 alone, there is a great need to improve the diagnosis of these diseases and to prevent the following events. This problem is particularly important as 85% of these cases could be preventable.

Pulse wave analysis has been studied for finding markers or risk of various abnormalities including overall cardiovascular risk and peripheral artery disease. Arterial pulse wave analysis is based on measuring and evaluating arterial pulse waves that are pulsatile changes of the blood pressure caused by pumping of the heart. These methods could be utilized to improve the diagnosis of cardiovascular diseases and thus result in lowered number of events. This is based on the fact that these methods are non-invasive and have the potential to be widespread.

In this thesis, arterial pulse wave analysis methods were evaluated for their impact on relieving this issue by evaluating the different variables and methods in question and their actual clinical relevance. Also, a brief overall look to commercial measurement devices was implemented. The study was performed by carrying out a thorough literature survey from the related study fields.

Based on the literature, carotid-femoral Pulse Wave Velocity (cfPWV) was found to be the most prominent variable for predicting overall cardiovascular risk. Cardiovascular risk is the overall risk to have any cardiovascular disease and it also pertains to the risk of cardiovascular mortality.

cfPWV has essential reliability and reproducibility with competent guidelines, devices and standardization process in place. However, the standardization still needs further efforts for effective and comparable widespread clinical use. The need for standardization is mainly caused by the fact that the methods and devices are still not uniformly used.

Utilization of pulse wave analysis variables for improving the diagnosis of peripheral artery disease specifically was found to be worthwhile but further studies are still needed. One important aspect related to this is that until these methods are included into peripheral artery disease guidelines, there is no relevant clinical benefit available from them.

As a whole, pulse wave analysis methods are intensively studied as a tool for diagnosis, but the varieties in measurement and on analysis methods at clinical circumstances as well as lack of validation continue to be major obstacles that prevent these methods from breaking through.

Keywords: pulse wave analysis, pulse wave velocity, cardiovascular diseases, peripheral artery disease, arterial stiffness

CONTENTS

LIST OF ABBREVIATIONS AND SYMBOLS

AAA	Abdominal aortic aneurysm
CAD	Coronary artery disease
CVD	Cardiovascular disease
PAD	Peripheral artery disease
ABI	Ankle-to-brachial (pressure) index
AIx	Augmentation index
ASI	Arterial stiffness index
cfPWV	Carotid-femoral pulse wave velocity
cPP	Central pulse pressure
cSBP	Central systolic blood pressure
DC	Diastolic rate constant
PRT	Pulse rise time
PWA	Pulse wave analysis
PWV	Pulse wave velocity
SC	Systolic rate constant
SEVR	Subendocardial viability ratio
AHA	American Heart Association
WHO	World Health Organization
BSN	Body sensor network
ECG	Electrocardiogram
EMFI	Electromechanical film
IPG	Impedance plethysmography
IPPG	Imaging photoplethysmography
MRI	Magnetic resonance imaging
PPG	Photoplethysmography
CO	Cardiac output
DBP	Diastolic blood pressure
DPTI	Diastolic pressure–time index
HR	Heart rate
LV	Left ventricular
MAP	Mean arterial pressure
SBP	Systolic blood pressure
SPTI	Systolic pressure–time index
SVR	Systemic vascular resistance
C	compliance
D	distensibility
ε	strain
P	pressure
ρ	blood density
R	resistance
s	distance
T	time
V	volume
Z	impedance

1. INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in the world. In 2016, approximately 17.9 million deaths were caused by CVD [1]. The incidents of CVD will only increase as a result of the rising prevalence of risk factors in low-risk countries [2]. But in fact, a great part of these fatalities and expenses could be avoided. World Health Organization (WHO) has estimated that 75% of premature CVD cases are preventable [3]. In addition to mortality, the health care expenses of CVDs are causing significant economic pressure on countries.

This study investigates whether arterial pulse wave analysis methods are able to relieve the vast amount of cardiovascular mortality by better prediction and diagnosing. Focus will be on the actual pulse wave analysis variables such as pulse wave velocity (PWV) and augmentation index (AIx) and on the measurement methods such as applanation tonometry and oscillometric measuring. Also, the actual clinical value of these variables and measurements methods for predicting overall CVD risk or for diagnosing peripheral artery disease (PAD) will be discussed. This study does not cover the implementation of pulse wave analysis methods on children.

Firstly, the related vascular diseases coronary artery disease (CAD), PAD and aortic aneurysms, will be introduced as these are conditions, which affect on the observed pulse waves. Then, the risk factors, such as high blood pressure and arterial stiffness causing CVDs will be discussed as these are conditions that are important part of predicting CVDs. The third chapter will address the basics of pulse waves, the variables that can be extracted from them and how they are measured. In the fourth chapter, the clinical value of pulse wave analysis for predicting overall cardiovascular risk is discussed. Subsequently, the possibilities for diagnosing PAD are considered. Lastly, in the fifth chapter, the most important observations and conclusions are combined together.

2. VASCULAR DISEASES

Vascular diseases are a sub-group of CVDs. Vascular diseases are specifically a condition of the circulatory system, where normal function of a blood vessel or of several blood vessels is deteriorated with a varying impact.

For this study, the focus will be on CAD, PAD and aneurysms amongst all cardiovascular diseases, since the changes in pulse waves caused by these diseases are best detected by arterial pulse wave analysis (PWA) methods. Hypertension and arterial stiffness will also be discussed as these are risk factors for cardiovascular diseases.

2.1 Coronary artery disease (CAD)

Coronary artery disease refers to a narrowing of coronary arteries. These essential arteries supply the heart with oxygen and are thus crucial for the functioning of the heart. In the case of CAD, where an artery has substantially narrowed or completely blocked, heart attack, heart failure or rhythm disorders of the heart can take place. Therefore, it is important to diagnose CAD in an early state to be able to treat it and prevent complications. [4]

Atherosclerosis, a hardening of arteries, is the cause of CAD. It is caused by minor inflammations that originate in the arterial walls and by substances such as cells and fats traveling in these arteries that stick to these sites and form plaques as seen in Figure 1. [4]

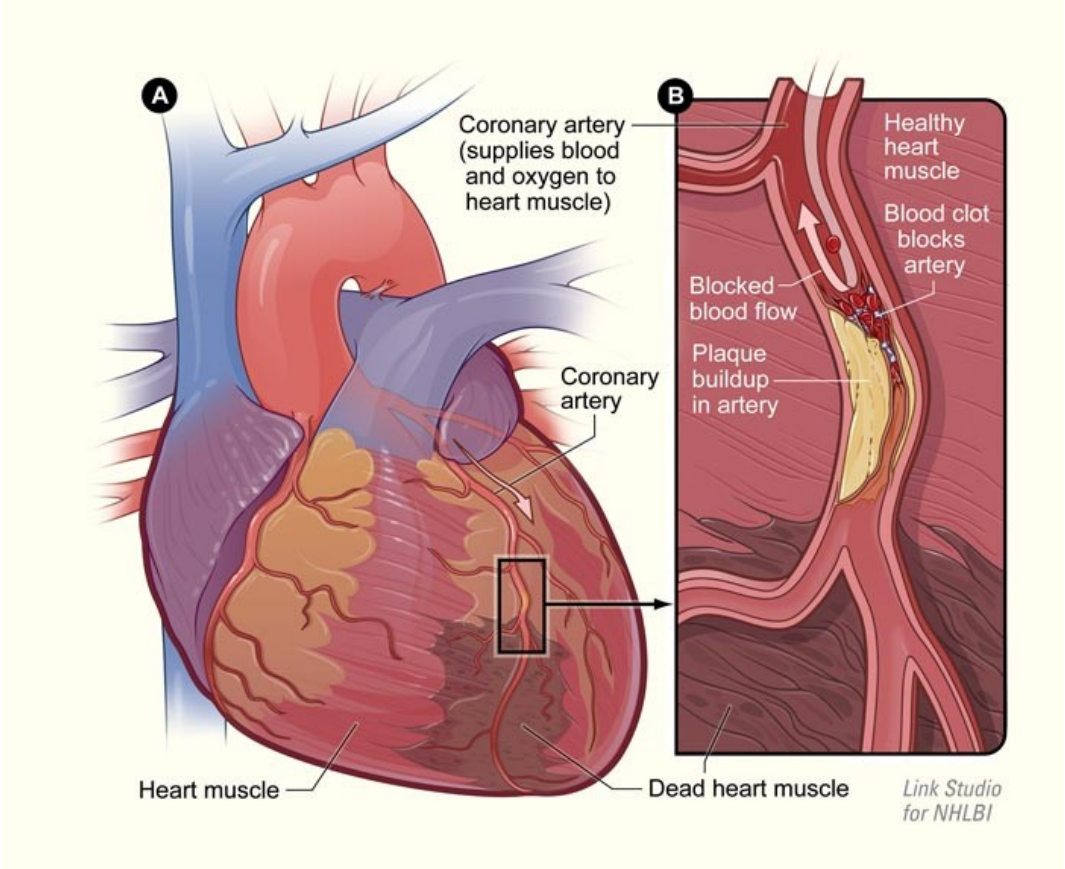

Figure 1. *Illustration of the plaque buildup in CAD and consequences [5].*

The risk factors for CAD are both affectable and unaffectable. The factors that can be affected at least partially are high blood pressure, high cholesterol levels, obesity, lack of exercising, unhealthy diet, stress, smoking, and diabetes. The factors that one cannot affect are sex, ethnicity and family history. Also, the risk of having coronary artery disease increases with aging. [4]

2.2 Peripheral artery disease (PAD)

Peripheral artery disease is a disorder where peripheral arteries have decreased perfusion caused by a buildup of plaques, as seen in Figure 2 [6]. It is a subtype of atherosclerosis. The peripheral arteries in question supply limbs and pelvis with oxygen-rich blood. [6]

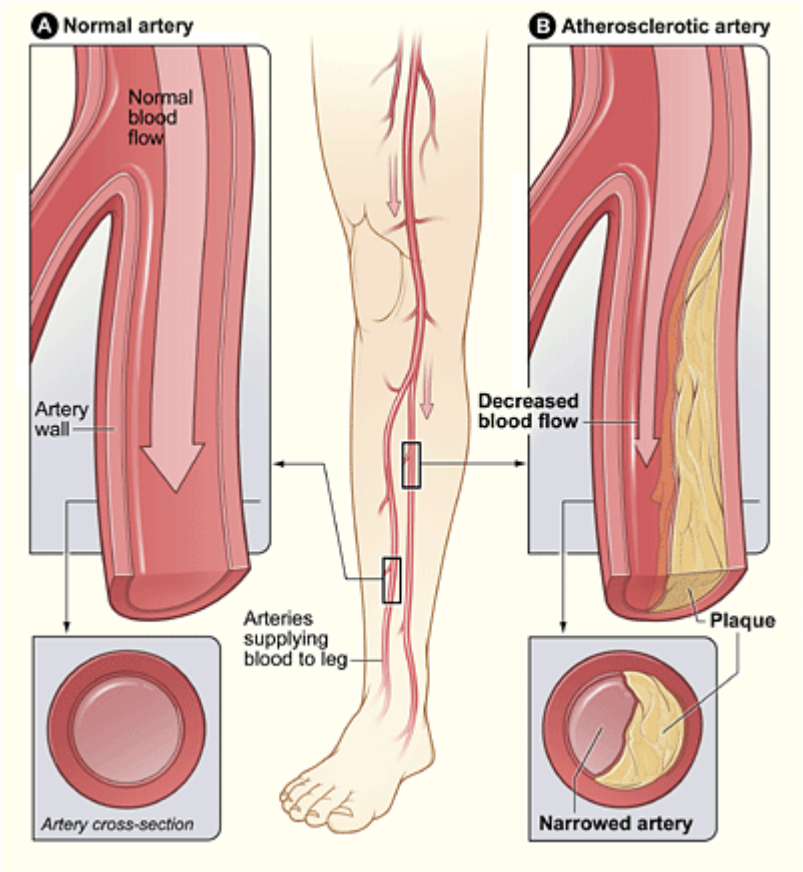

Figure 2. *Illustration of a normal artery (A) and an artery of a PAD patient (B). In Subfigure 2.B there is a deposit of plague in an artery and normal perfusion is disturbed [7].*

PAD can cause ischemia or insufficient blood supply for the tissue. If the arteries of the lower limbs have PAD lesions, this can cause intermittent claudication, rest pain or may even lead to an amputation of a limb due to necrosis [6, 8]. More importantly, J.W. Olin & B.A. Sealove have pointed out in [9] that PAD often progresses as undiagnosed and can result in poor quality of life or depression. It also increases the risk of having a heart attack or stroke.

Risk factors of PAD include diabetes, smoking, obesity, hypertension, high cholesterol levels, heart disease, stroke, aging and having a family history of PAD. Smoking increases the risk of having PAD by fourfold. [6]

2.3 Aneurysm

Aneurysm is a condition where an artery has an enlargement and it can rupture [10]. This type of abnormal balloon-like swelling, as illustrated in Figure 3, occurs as a result of a

weakened artery wall. Aortic aneurysms are either thoracic or abdominal. Abdominal aortic aneurysms (AAA) are the most common type of aneurysms. [11]

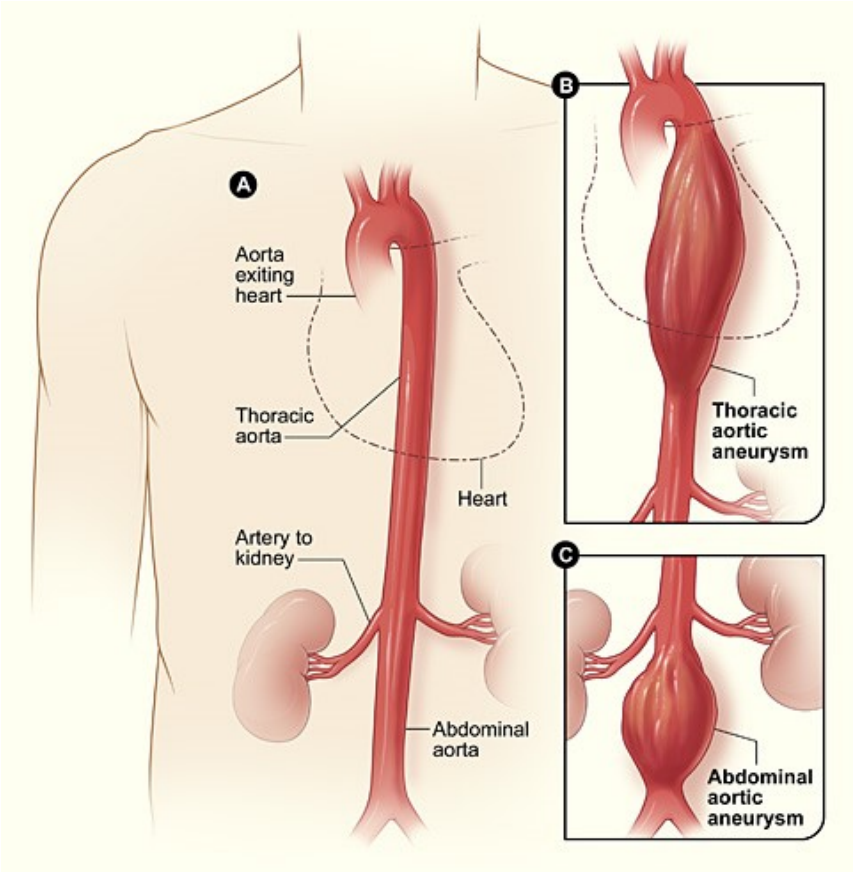

Figure 3. *Illustration of the difference between normal aorta (A) and aorta with an aneurysm (B) & (C) [12].*

Commonly, when a segment of abdominal aorta exceeds 3.0 cm in diameter, it is considered as an aortic aneurysm. However, most of AAAs are asymptomatic and minority detected by imaging of stomach that is done solely for treating another illness. This is critical as any AAA exceeding 5 cm in diameter is prone to rupture and in case of rupture, over 50% of the incidents are fatal due to patient not reaching emergency room in time. [13]

AAAs occur as the media of an artery degenerates whilst the lumen of the artery enlarges in a progressive manner. Risk factors for aneurysm include age over 65, smoking, being a Caucasian male, chronic obstructive pulmonary disease, CAD, prior aneurysm repair and high blood pressure. [13]

2.4 Risk factors

Risk factors for cardiovascular diseases are fairly similar and the two most significant ones for predicting CVDs are high blood pressure and arterial stiffness. Firstly, high blood pressure will be discussed and then arterial stiffness.

2.4.1 Hypertension (high blood pressure)

Hypertension is an important risk factor for cardiovascular diseases [14, pp. 1, 15]. It is a serious condition that has been attributed to 54% of strokes and 45% of CADs incidents that occur worldwide [16]. It is also linked with the development of aneurysms and PAD [17, 18].

Blood pressure is stated as a pair of systolic and diastolic value. For example, 130/80 mmHg informs that systolic value is 130 mmHg and diastolic 80 mmHg. However, the actual definition of high blood pressure is controversial. Commonly as a general guide, blood pressure is regarded as high if the systolic value exceeds 140 mmHg and/or the diastolic value exceeds 90 mmHg. [19]

The prevalence of hypertension increases with aging. It is mostly caused by lifestyle choices but there are also genetic causes. The affecting lifestyle choices are smoking, obesity, excessive salt usage, too low activity, use of painkillers, use of hormones, use of alcohol and stress are common causes of hypertension. [20]

2.4.2 Arterial stiffness

Arterial stiffness describes the diminished ability of an artery to correspond with pressure changes by expanding or contracting [21]. It varies in different regiments of the body. For example, a healthy subject has large arteries that are more elastic than the smaller arteries of the subject.

Stiffening of the arteries is one of the key factors affecting pulse pressure, left ventricular (LV) load and coronary perfusion pressure [22]. Most importantly, arterial stiffness is thought as one of the most critical risk factors for the incidence of a cardiovascular event [23]. It has been also suggested that it can precede and play a role in developing hypertension [24].

Physical variables of arterial stiffness are compliance (C) and distensibility (D). Compliance represents the change in the diameter of an artery depending on pressure. It can be presented in the following way

$$C = \frac{\Delta V}{\Delta P} \tag{1}$$

where ΔV is the change in volume and ΔP is the change in pressure. In a healthy artery, there is a significant change in volume with even a small pressure change. On the other hand, in a stiffened artery only a small change in volume will occur even with a significant pressure change. [21]

Distensibility describes the value of arterial compliance with respect to the initial diameter of an artery [21]. It can be presented in the following way:

$$D = \frac{\Delta V}{\Delta P} \cdot V \tag{2}$$

where ΔV is the change in volume, ΔP is the change in pressure and V is the initial volume. [21]

With increased arterial stiffness, the propagation velocity of a pressure pulse wave increases within the arterial tree. This is called pulse wave velocity (PWV), which pertains to arterial distensibility and in the simplest model it is presented as

$$\mathrm{PWV} = \frac{1}{\sqrt{\rho \cdot D}} = \sqrt{\frac{E_{inc} h}{2 r \rho}} \tag{3}$$

where ρ is the blood density, D is distensibility, E_{inc} is the elastic modulus of the artery, h is the wall thickness and r is the radius of the artery. [14, pp. 20, 21]

Due to ageing, arteries get stiffer and dilate. These changes are most visible in the aorta and its close-by branches. There are also changes in the structural layers of arteries The layers of the arteries are outer adventitia, tunica media and inner tunic intima. As the artery stiffens, individual elastin lamellae get thinner in the media and the tunic intima thickens.

The traditional cardiovascular risk factors can contribute to developing arterial stiffness. Notably, also chronic kidney disease can have a negative impact. [23]

Large arteries with atherosclerosis i.e. narrowing of the artery due to plaque build-up, for example in CAD and PAD, also show increased stiffness. Furthermore, hypertension can cause arterial stiffening as a result of increased pressure faced. [21] The genetic factors also play a role in arterial stiffness development. [24]

3. PULSE WAVES

This chapter will go over physiology of pulse waves, what variables are extracted from them and how pulse waves are measured with different methods. Lastly, the commercial pulse wave analysis devices are reviewed.

3.1 Pulse pressure waveform

Pulse wave is a recording presenting the pulsatile pressure changes of the blood pressure caused by pumping of the heart. It is composed of propagating forward waves and of reflecting backward waves from peripheral arteries. These waves travel along the arterial tree. The reflected backward waves are caused by arterial bifurcations (branching), atherosclerotic plagues and terminal arterioles. A demonstration of an aortic pulse waveform is provided in Figure 4. [14, pp. 9, 45-53]

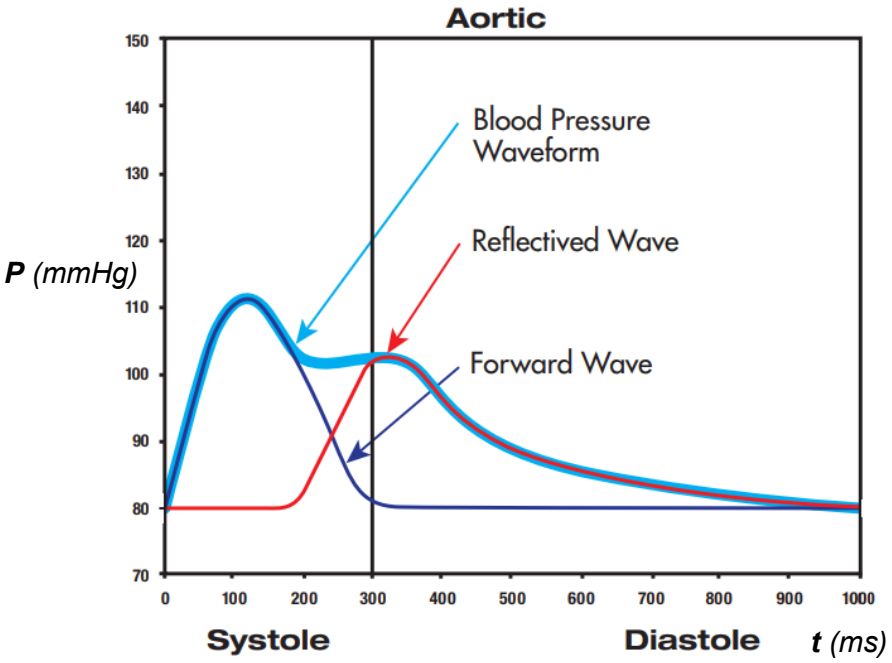

Figure 4. *Illustration of a pulse wave. The dark blue line is the forward propagating wave caused by systole. The red line is the combination of reflected waves and the light blue is a combination of these two, a pulse wave. Adapted from [25].*

In a young person with healthy arteries, the reflected wave returns in diastole. But with a person who has stiffened arteries, the reflected wave increases in speed and magnitude. This causes the reflected wave to return already in systole as seen in Figure 5.A. This results in increased pulse pressure, in increased LV afterload and in a decrease in

the myocardial perfusion pressure, as seen in Figure 5.B. These are significant changes as the circulation of the heart functions primarily during diastole and thus relies to a degree on the normal propagation of the reflected waves. [25]

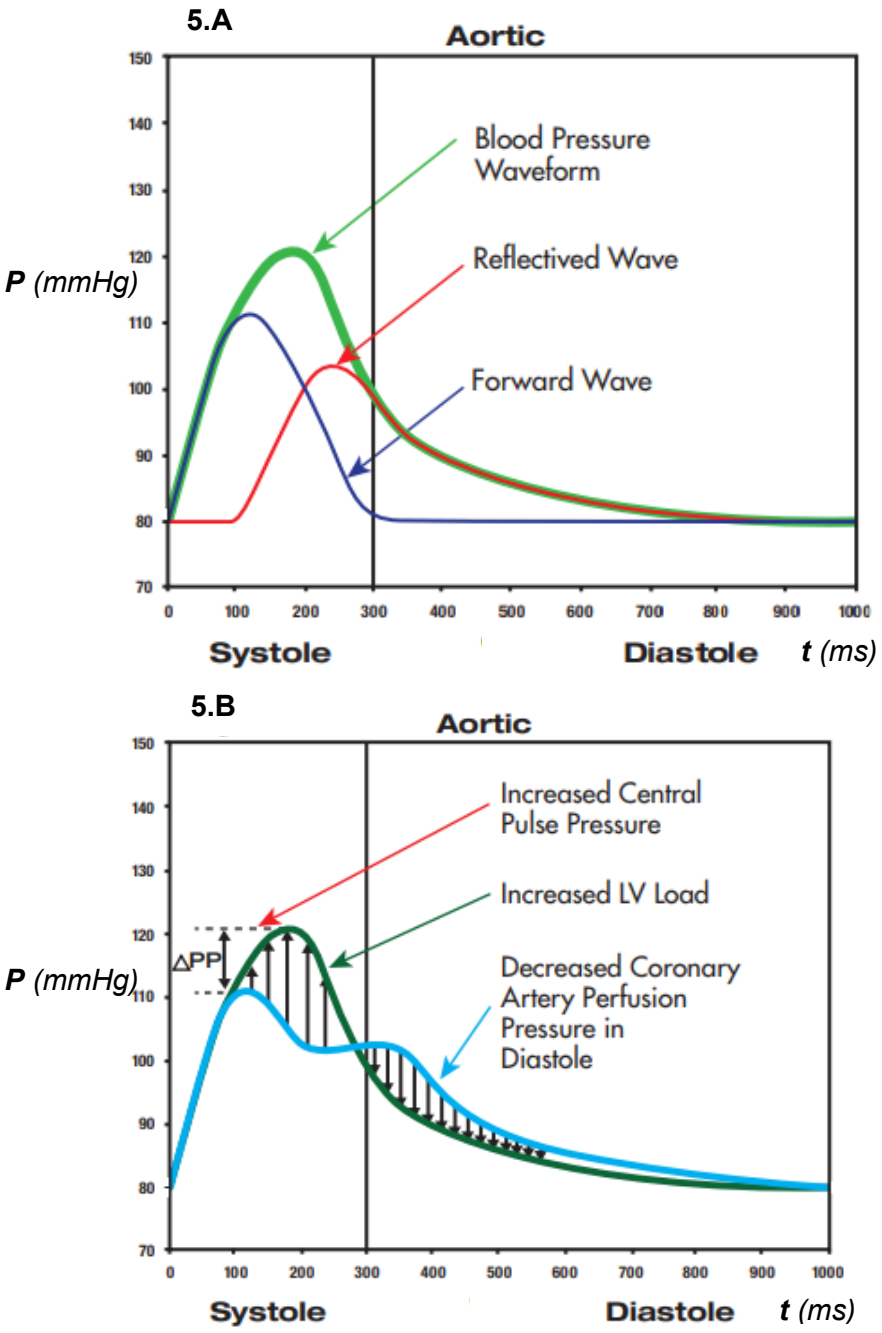

Figure 5. *Pulse waveform of a person with stiffened arteries (A). Changes in the pulse waveform highlighted, which were caused by the earlier arrival of the reflected wave (B). Adapted from [25].*

However, it is important to recognize that the pulse pressure waveform differs even both from person to person and even in the same person in different arteries. The waveform

depends on the left ventricular ejection, the viscoelastic properties of an artery, on the viscosity of the blood, as well as on the wave reflection and dispersion. [26]

PWA is needed as Mean Arterial Pressure (MAP) does not clarify the differences in differing blood pressures, since MAP only is determined as multiplication of three parameters: Heart Rate (HR), Cardiac Output (CO) and Systemic Vascular Resistance (SVR). An example below, in Figure 6, describes two subjects: (a) with normal blood pressure values and (b) with distinctive hypertension. While the other subject has hypertension, they both still have the same MAP. [14, pp. 3-7]

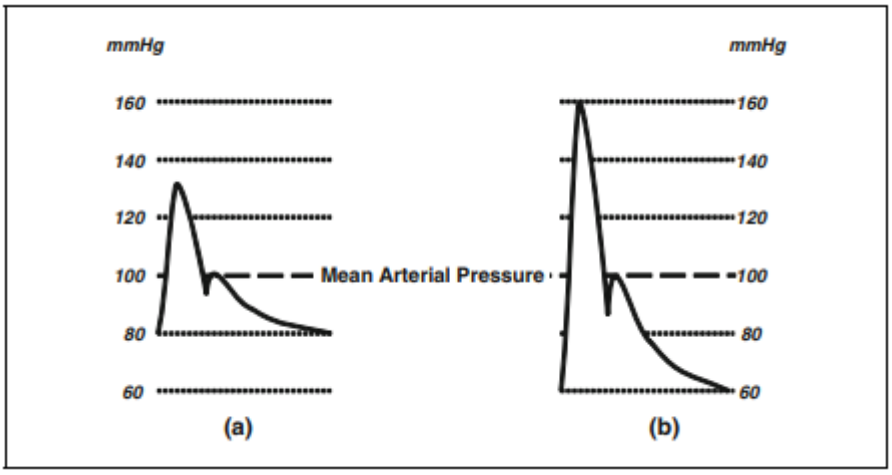

Figure 6. *An example of the insufficiency of the MAP. Subject (a) with regular blood pressure values and (b) with distinctive hypertension values. Still, both have the same MAP. [14, pp. 6, 24]*

Similarly, two subjects who have same systolic blood pressure (SBP) and diastolic blood pressure (DBP), can have substantially different pulse waveforms. These both examples express that critical information is possibly left undiscovered with traditional variables.

Important variables such as central Pulse Pressure (cPP), AIx and Subendocardial Viability Radio (SEVR) can be derived from a pulse waveform and have been widely researched for the analysis of the state of cardiovascular health.

However, these parameters are details of the central arterial system and they can only be acquired invasively or by extracting them from a peripheral measurement with a help of a transfer function [14, pp. 114, 27]. It is important to note that the application is not always focused on central circulatory system information and thus does not always require a transfer function.

The use of a transfer function causes error as it is a generalized function used to convert peripheral arterial information into central arterial information of the aorta. This type of function assumes that every subject has similar arterial properties, and this is not true.

The resulting error could be solved by use of an individually defined transfer function but defining such for every subject is too laborious. These transfer functions have been shown to have sufficient accuracy for generating the arterial properties of an aorta but still they are considered as an additional error factor. [27]

3.2 Pulse wave analysis (PWA)

Pulse wave is analysed by examining the waveform or the PWV or with a combination of both. [14, pp. 17; 69] The relevant variables for pulse wave analysis are currently: PWV, AIx, Arterial Stiffness Index (ASI), cPP, SEVR, Systolic rate Constant (SC) and Diastolic rate Constant (DC).

As arterial stiffness is an important independent key risk factor for developing a CVD and a possible event, most studies focus on analysing variables related to arterial stiffness. Such arterial stiffness related variables are PWV, AIx and ASI.

PWV (propagation of the wave along the arterial tree) is the current gold standard for predicting risk of cardiovascular disease. This is the most studied way of evaluating arterial stiffness [28]. PWV can be presented in the following way

$$\mathrm{PWV} = \frac{s}{\Delta T} \tag{4}$$

where s is the distance between two different measuring sites of pulse waves and ΔT is the time difference of the pulse wave arrivals at these two sites. The reproducibility and reliability of PWV have been confirmed by a vast amount of scientific literature [29-31]. [14, pp. 20]

There are extended reference values presented by many different studies for most of the continents excluding Africa. The lack of universal standardization and reference values with consensus is still a major problem for PWV. [32, 33] In related expert consensus document [34], a PWV value of 10 m/s was proposed in 2012 as a threshold value but use of such fixed thresholds is not advisable as all factors are not taken into consideration, for example, a transient increase in MAP can lead to deceived conclusions [34].

AIx is a variable presenting the increase in blood pressure caused by the early arrival of a pulse wave. AIx is measured in percentages and can be presented in the following way

$$AIx = \frac{SBP - P_i}{cPP} \times 100\% \tag{5}$$

where SBP is the central Systolic Blood Pressure, P_i is the inflection point it is the blood pressure value in the point where backward wave starts to superimpose with the forward wave and cPP is the central Pulse Pressure i.e. the change in systolic and diastolic blood

pressure, as seen in Figure 7. The inflection point is not always clear and may require analysis of the fourth derivate. Augmented pressure (AP), which can be seen in Figure 7, describes the same phenomenon, but in a unit of pressure instead of percentages. [14, pp. 70]

AIx relates both to arterial stiffness and pulse wave velocity. There are a significant amount of studies showing it to effectively predict cardiovascular events. However, it is not a generally accepted variable for evaluating arterial stiffness as there lies controversy on its credibility [14, pp. 73-80, 35, 36]. The largest issue is that heart rate affects AIx and thus it is not an independent measure of arterial stiffness [37].

Furthermore, AIx has limitations as a measure of wave reflection [38]. The mathematical equation of the variable has a clear issue meaning that earlier arrival of reflected waves may not be identified correspondingly. Basically, a rise in AP won't necessarily mean that there is an increase in AIx, unless cPP is stable. This is problematic as a rise in AP is commonly accompanied by an increase in cPP. [36]

Lastly, a transfer function is commonly used to derive AIx and this creates error. When compared with PWV this means that AIx includes an additional error factor. [14, pp. 28, 27]

Arterial stiffness index (ASI) is a variable originating from 24-hour ambulatory blood pressure monitoring. It has been proposed as a variable for evaluating cardiovascular risk in an easy manner. It can be presented in the following way:

$$ASI = \frac{\ln\frac{SBP}{DBP}}{\varepsilon} \tag{6}$$

where *SBP* is the systolic blood pressure, *DBP* is the diastolic blood pressure (Figure 7) and ε is the occurred arterial strain [39]. Where there are studies that show it to be linked with cardiovascular indices, it is in fact heavily affected by vascular resistance and decisively by heart rate in addition to arterial stiffness [40, 41]. This limits the use of it as a variable to evaluate arterial stiffness. Due to this it is also not recommended for the evaluation of cardiovascular risk. [42]

cPP as derived from pulse wave analysis, has as well been introduced as an independent variable for predicting CVDs. It can be presented in the following way

$$cPP = cSBP - DBP \tag{7}$$

where *cSBP* is central systolic blood pressure and *DBP* diastolic blood pressure as seen in Figure 7. [14, pp. 70]

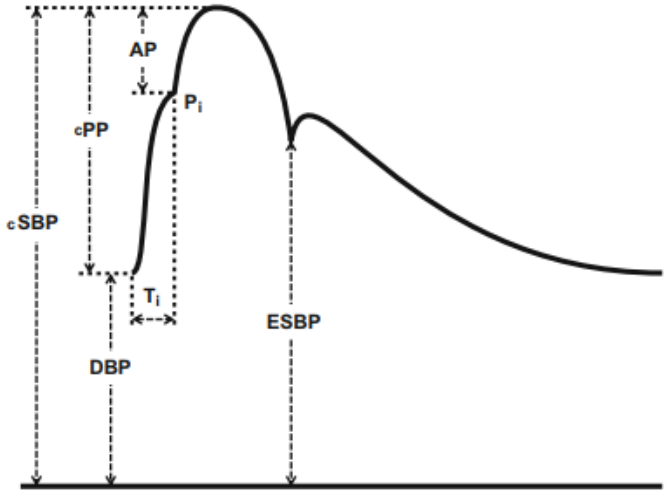

Figure 7. *Illustration of pulse waveform and related variables: cSBP, cPP, DBP, and AP [14, pp. 70].*

There have been studies that have found a relationship between cPP and cardiovascular mortality but overall the predictive impact is marginally better than traditional blood pressure measurements and is not a recommend variable. This is the consensus even if it could provide a bit better risk stratification. [40, 43] Also, use of transfer function is often needed to obtain cPP and this again causes error in the results.

SEVR is a variable derived from the waveform of a pulse. It is determinated by means of dicrotic notch, which is a small and brief increase in blood pressure that occurs after aortic valve closes, it can be seen in Figure 8 [44]. SEVR can be presented in the following way

$$SEVR = \frac{DPTI}{SPTI} \tag{8}$$

where *DPTI* is the diastolic pressure-time index, it withholds the area after the dicrotic notch, and SPTI is the systolic pressure-time index, the area before the dicrotic notch. This can be perceived in Figure 8, where the dicrotic notch divides these two areas. [14, pp. 71]

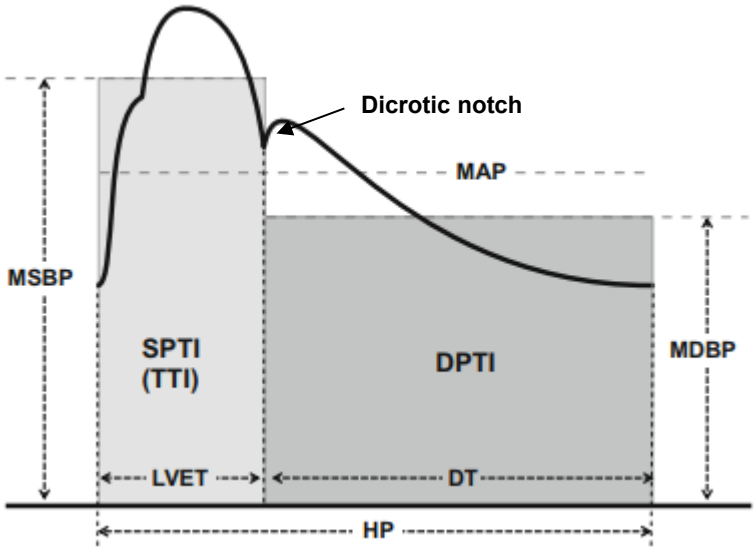

Figure 8. *Illustration of pulse waveform and SPTI, DPTI, and MAP* variables *[14, pp. 71]. The dicrotic notch separates SPTI and DPTI [44].*

Even though it is actually a variable that describes whether the heart is getting enough oxygen to function, there has been continuous research regarding its potential to be a CVD predictor. Correlations between SEVR and CVD cases have been observed and a critical value of 0.5 has been proposed for this variable [45]. SEVR below 0.5 is considered as an indicator of restricted subendocardial blood flow and oxygen supply. [14, pp. 92]

Most recently, H-M Cheng *et al.* in their study [46] studied variables SC and DC with a reservoir model. The reservoir model takes into consideration the systolic charging and diastolic discharging of the arterial system.

In the model, SC describes the filling of the reservoir. It can be presented in the following way

$$\mathrm{SC} = \frac{1}{Z_0 C} \tag{9}$$

where Z_0 is the characteristic impedance of the root of the aorta and *C* is total arterial compliance [47].

On the other hand, DC describes the draining of the reservoir. It can be presented in the following way

$$\mathrm{DC} = \frac{1}{RC} \tag{10}$$

where *R* is systemic arterial resistance and *C* is the total arterial compliance [47]. This connection of SC and DC with pulse wave can be seen in Figure 9 [46].

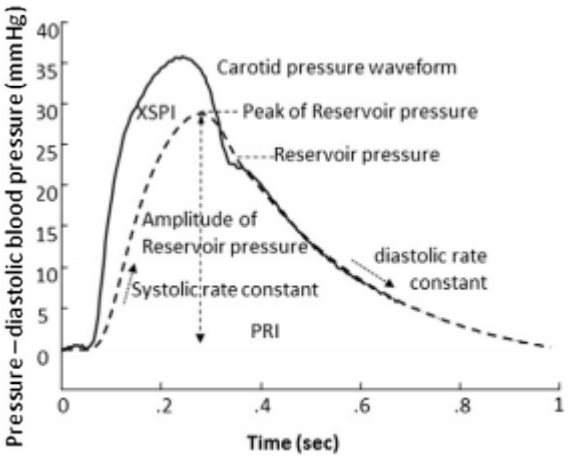

Figure 9. *Illustration of pulse waveform and relating variables, SC and DC [46].*

Study concluded that by studying the pulse waveforms of two cohorts that SC and DC were independent and consistent predictors of cardiovascular mortality. [46]

Limitations of the study were that a transfer function was used for deriving carotid pressure waveform and the study did have a disagreement with an earlier study [48]. Overall, more research is needed to confirm these findings and to resolve the disagreements. Also, for any actual clinical impact, the reference values for SC and DC must be determined and the measurement must be standardized. [46] Lastly, these variables should be only considered relevant if and when they are included into pulse wave analysis related guidelines.

Besides the aforementioned analysis methods, new pulse wave analysis variables are proposed continuously. However, they are often at least initially based on insufficient data. Such two proposed indexes are arterial velocity pulse index and arterial pressure volume index as stated in [49] by R. Sasaki-Nakashmia *et al.* Despite the fact that the indexes were stated promising independent factors these were actually compared with unreliable brachial-ankle pulse wave velocity (baPWV).

baPWV is unreliable and unsuitable measurement for cardiovascular risk evaluation as it is a peripheral measurement and thus does not consider arterial properties of an aorta [14, pp. 28]. For example, with subjects that have aortic diseases baPWV produces inaccurate measurements and it may underestimate the arterial stiffness of a subject with hypertension [50, 51]. There is a better measurement available that considers these arterial properties of the aorta and it is the aortic pulse wave velocity (cfPWV) [14, pp. 28].

3.3 Measurement of pulse waves

Pulse waves can be measured both invasively and non-invasively [14, pp. 107]. Due to the nature of invasive methods, non-invasive methods are preferred.

Present non-invasive methods are applanation tonometry, photoplethysmography (PPG), impedance plethysmography (IPG), electromechanical transducers, Magnetic Resonance Imaging (MRI) and oscillometric measurement. Body sensor network (BSN) systems have also been implemented [52].

As PWV is widely accepted as the gold standard method, most measuring methods focus on solely obtaining it, but naturally, the actual pulse waveform is acquired as well.

3.3.1 Applanation tonometry

In applanation tonometry, a probe that contains at least one force sensor is used for detecting the arrival of pulse waves at different sites [53]. In practice, one presses the arterial area against underlying bone for the recording of a pulse wave, as can be seen in Figure 10. For acquiring PWV, the pulse waves are recorded either simultaneously at two sites or separately with the help of an additional electrocardiograph. [14, pp. 20-23]

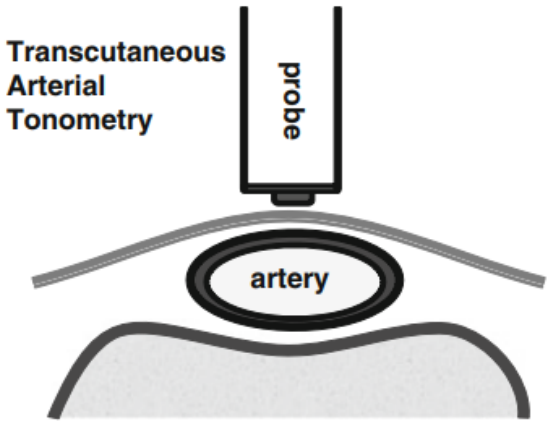

Figure 10. *Illustration of a probe being utilized in applanation tonometry for recording of an arterial pulse wave [14, pp. 110].*

The most common recording site combination is carotid-femoral, it is illustrated in Figure 11. This specific measurement and produced cfPWV are the current gold standard with the disadvantage of estimated distance instead of an exact one. The key advantage of this method is that the viscoelastic properties of an aorta are taken into consideration as the proximal sensor is measuring PWV along the aorta. [14, pp. 28]

Other combinations such as carotid-radial or carotid-brachial have as well been studied but these measurement methods are not suitable for clinical purposes. [14, pp. 36]

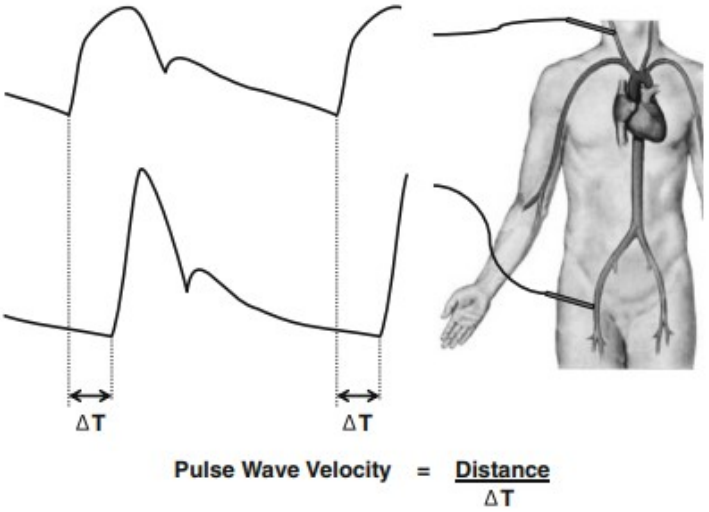

Figure 11. *Measuring of cfPWV by capturing carotid and femoral pressure waveforms simultaneously [14, pp. 21].*

In the first method, proximal and peripheral pressure waveforms are recorded simultaneously with transducers. With the proximal and peripheral pulse waveform, the time delay can be calculated. Then the cfPWV can be calculated by dividing the distance of transducers with the time delay. [14, pp. 20-21]

Alternatively, cfPWV can be acquired by measuring the pulse waves at different sites in separate times with only one transducer. In this method, electrocardiogram (ECG) is also recorded and time delay is calculated by examining the time delays of both pulse waves to the R waves of QRS complex. Again, cfPWV is formed by dividing the distance of transducers with the time delay. [14, pp. 21-23]

Overall, applanation tonometry is considered as easy, fast and as the most reliable method. However, it is also an expensive one and needs an experienced operator. With applanation tonometry, both pulse waveform and pulse wave velocity are acquired. [14, pp. 21; 28]

3.3.2 Photoplethysmography (PPG)

With photoplethysmography, the recorded signal is dependent on the peripheral blood volume and measurement is done by utilizing a light source and a light detector. It can be used for measuring blood pressure, blood oxygen saturation (use of at least two different wavelengths required) and the arterial condition of a patient. However, PPG for blood pressure measurement is not common due to limitations. The potential of PPG for an accurate pulse wave measuring has been pointed out by several studies [54, 55]. [56]

It has caught the interest of researchers due to it being an easy, simple and inexpensive measurement method. Basically, a through propagating cardiovascular pulse wave is detected via a probe that has a light source and a detector, as seen in Figure 12 where PPG finger clip sensor is used as an example. PPG reflects the blood volume changes occurring in an artery. The artery is either between heart and fingertip, if measured from a fingertip or between heart and toe if measured from a toe. [57]

Figure 12. *An example of a PPG finger clip sensor, which is using infrared light. Adapted from [58].*

Another proposed method to record PWV is with a collar and a bracelet by the Vicorder® device. A collar with a photoplethysmographic sensor is placed on the neck of a patient and a bracelet is placed on the root of the patient's thigh. However, measurement of distance and both the validity and relation to other measurements methods need further investigating. [14, pp. 128]

Additionally, video-based or imaging photoplethysmography (IPPG) has also been studied as a method for acquiring data of pulse waves. However, due to the lack of studies on obtaining information on the of central pulse waves, if at all possible, this method seems to be irrelevant. Furthermore, it is still in its infancy as low sample frequency and the feared inaccuracy caused by motion artifacts are a problem. [59, 60]

Overall, the traditional PPG is an easy and inexpensive measuring alternative. However, one must consider that pulse waves undergo an amplification phenomenon in the arterial tree and thus recording from a peripheral site cannot give the most accurate information of the central properties, as a transfer function is employed. Applications in obese subjects where other methods may fall short due to fatty deposits preventing signal acquisition could be a potential more frequent indication. [61]

3.3.3 Impedance plethysmography (IPG)

In impedance plethysmography, an alternating current with frequency typically between 20 kHz and 100 kHz is applied through electrodes to estimate inner arterial cross-sectional area of the arteries between the measurement sites. This method is based on the fact that blood has higher conductivity than other tissues. [62]

IPG is not recommended for pulse wave analysis as it is not clearly stated as such in the American Heart Association (AHA) scientific statement [33] or in the European expert consensus document [63]. Its accuracy might as well be hindered by the fact that it cannot separate an artery and vein from each other due to it being extracorporeal. Also, even the slightest change in the electrode positioning can cause prominent changes in the amplitude of the bioimpedance. Thus, the calibration must be very precise. [62]

However, if the measurements can be performed in a way that veins are not taken into account by accident, IPG could be a potential measuring method that also considers the viscoelastic properties of the aorta. There are several relevant studies published recently [64-66]. But, without a doubt extensive amount of studies will still be needed, also with cohorts, to decide the true usability of IPG.

3.3.4 Electromechanical transducers

Electromechanical transducers have been widely studied for acquiring data of pulse waves [67-69]. Measurement devices based on these sensors can be energy-efficient and inexpensive alternatives to capture pulse waves [70]. Also, their quality of being thin and flexible is a clear advantage. Suitable sensors are either acceleration, pressure or displacement sensors. [71] Significant limitation of these transducers is that they will not give information about the diastolic blood pressure as they are only sensitive to dynamic loading.

Often, a piezoelectric film is employed, and it is placed on top of an artery. As an artery vibrates the film is deformed proportionally to pressure. [71]

Another choice is an electromechanical film (EMFi), which is a permanently charged electret material. As external dynamic force is being applied to the EMFi, a displacement charge is caused to the surface electrodes due to a change in internal charge distribution. This all originates from changes in air void thicknesses, which separate the multiple polypropylene layers that form the film. [52]

For piezoelectric films, the sensor positioning, and noise vulnerability are key cornerstones to account for in order to make this method widely usable. Currently, this type of measuring system can only be used at a resting state. As any motion of a body artifact

movement greater than that of a pulse wave will be superimposed. [71] Also, for a force sensor it is key to use a fitting static force to flatten the artery but not to occlude it [52].

Limiting factor for both piezoelectric films and EMFis is the usual peripheral measurement, which does not give the most accurate information of the aortic pulse wave. However, a product on a market called The Complior System® is a promising example of this method as it uses two piezoelectric sensors that are in fact placed on carotid and femoral arteries [14, pp. 127-128].

3.3.5 Oscillometric methods

Oscillometric cuffs and bracelets have been employed for obtaining pulse waves. Oscillometric devices are mostly supposed to register pulsatile pressure changes in a brachial artery [61]. These devices are an easy and affordable method with a possibility of widespread use.

Oscillometric devices on the market include the ARCSolver system, the Arteriograph System, BPLab the VaSera System and Tel-O-GRAPH. The physiological hypotheses of these devices are often questioned [14, pp. 126; 129]. However, they perform acceptably in studies and Tel-O-GRAPH performed actually with excellent accuracy [72-74].

ARCSolver and Arteriograph have shown acceptable accuracy when compared with an intra-aortic catheter when analyzed as assayed with the Bland-Altman method [72]. Also, BPLab and the Arteriograph similarly performed with acceptable accuracy when compared with applanation tonometry [73-76].

Most importantly, Tel-O-GRAPH performed in an excellent manner in a recent study done in 2017, when compared with applanation tonometry. So, it seems that even when peripheral measurements are used, excellent correlation can be achieved. [77]

Overall, peripheral oscillometric measurement seems a fickle way for pulse wave velocity extraction due to the aortic stiffness and overall central pulse waveform being significantly different than that of radial, brachial or axillary regions [14, pp. 57]. However, these results suggest that oscillometric measurement could be a viable measurement method with high reproducibility and reliability. Naturally, more studies with a greater cohort are needed to confirm these findings.

3.3.6 Magnetic resonance imaging (MRI)

Magnetic resonance imaging is without a doubt the most high-end measuring method [78]. With MRI one can extract accurately aortic vascular parameters such as compliance, stiffness, ASI, and PWV. This is due to the possibility of assessing pretty much

any artery, getting an accurate PWV value from it and getting exact distance measurement. [32]

MRI proves to be especially useful for obese subjects. As with these subjects, the distance measurement is more prone to be a false one. [79] So, the direct imaging of thoracic and abdominal aorta is a clear advantage of this method. The limitations causing MRI not to be a widespread measuring method are mainly the costs and additionally lack of commercial software available that can be used for computing PWV. [80]

3.3.7 Devices on the market

There are devices on the market with different measuring approaches. The diagnostic quality of the devices varies deeply and some of the devices are rather just easy to use with a possibility of no plausible scientific background [14, pp. 129-130]. Most commonly, the measurement is based on applanation tonometry, but oscillometric methods are common as well. However, with oscillometric methods, there is still a lack of independent validation studies and of comparative data. [81] Relevant pulse wave measurement devices are presented in Table 1.

Table 1. *Devices on the market measuring cfPWV and/or cPP [14, pp. 125-130, 81].*

Instrument	Manufacturer	Method	cfPWV	cPP	Reference
Arterio-graph®	TensioMed Ltd.	Oscillometric		(x)	[14, pp. 129, 83]
BPLab®	OOO Petr Tele-gin	Oscillometric	x		[81]
CardioMon®	Medifina	Oscillometric		(x)	[14, pp. 128-129]
Complior®	Alarm Medical	Piezoelectric sensors	x	x	[14, pp. 127-128, 35, 81]
Mobil-O-Graph®	IEM	Oscillometric		(x)	[14, pp. 126, 80, 83]
Omron HEM-9000AI®	Omron Healthcare co. Ltd.	Tonometry		(x)	[14, pp. 127]
PulsePen ETT®	DiaTence srl	Tonometry	x	x	[14, pp. 126 ,81]
PulsePen ET®	DiaTence srl	Tonometry + ECG	x	x	[14, pp. 126, 81]
SphygmoCor®	AtCor Medical Pty. Ltd.	Tonometry + ECG	x	x	[14, pp. 127, 81]
VaSera®	Fukuda Denshi Co. Ltd.	Oscillometric	x		[14, pp. 128, 35, 82]
Vicorder®	Skidmore Medi-cal Ltd.	Photo-plethysmo-graphy	(x)	(x)	[14, pp. 128]

x validated device; (x) further studies are needed for validation

Arteriograph, BPLab, CardioMon, Mobil-O-Graph and VaSera devices use the oscillometric measuring. Arteriograph, CardioMon and Mobil-O-Graph can measure cPP. BPLab and VaSera are capable of measuring PWV [35, 82]. Arteriograph, CardioMon and Mobil-O-Graph have been considered to need further studies [83]. [14, pp. 126-129, 81]

The devices based on tonometry are Omron HEM-9000AI, PulsePen ETT, PulsePen ET and SphygmoCor. Tonometry is considered as the best measuring method and the devices can measure both cfPWV and cPP with the exception of Omron HEM-9000AI. [14, pp. 127] Omron HEM-9000AI was in fact considered to require further studies for true validation. [84]

Commercially available devices using other measuring methods are Complior and Vicorder as stated by P. Salvi in [14, pp. 126]. Complior utilizes two sensitive piezoelectric sensors for obtaining the carotid and femoral pulse waveforms simultaneously [35, 81].

Vicorder is a photoplethysmographic method using a collar and a bracelet. The collar with photoplethysmographic sensors is placed on a patient's neck to acquire carotid

pulse wave and the bracelet is placed on the root of the patient's thigh. The actual method, distance measurement and relationship with other devices still require further studies to be verified as credible and reproducible [85, 86]. [14, pp. 128]

The greatest aspect to understand with these devices is that the devices are based on different techniques and produce different results. This highlights the need for reference values and standards that consider the different circumstances related to the PWV measurement. These circumstances such as ethnicity and the varying device used will affect how the results should be interpreted.

4. CLINICAL VALUE OF PULSE WAVE ANALYSIS

In this chapter, focus will first be on the value of pulse wave analysis for detecting overall raised risk of a cardiovascular disease. Then, possibilities for diagnosing peripheral artery disease will be discussed.

Even though AAA patients have shown to have deviant AIx values, there are no prominent results currently for utilizing pulse wave analysis methods for the diagnosis of AAA [87]. Thus, pulse wave analysis methods for diagnosis of AAA will not be discussed.

4.1 Overall cardiovascular risk

Aortic stiffness is widely understood as an independent predictor of cardiovascular incidence [88]. Its evaluation with carotid-femoral pulse wave velocity, the gold standard method, improves the prediction of cardiovascular risk. [31] The nomination as gold standard was stated both in AHA scientific statement [35] and in European expert consensus document [63]. Furthermore, cfPWV meets most of the criteria that are expected from a surrogate endpoint [89].

On the other contrary, carotid-radial, carotid-brachial, femoro-tibial and brachial-ankle site combinations for PWV measurement are not considered suitable for general cardiovascular risk assessment [14, pp. 36-38].

Aortic pulse wave velocity is in theory ready for clinical use in Europe as there are widely recognized reference values published [90] that are based on European cohort. Intrinsically this requires use of a validated PWV measurement device and following of related guidelines in AHA scientific statement [35] and in European expert consensus document [63].

However, it should also be taken into consideration that the study of the reference values [90] was limited by 1) No information of PWV evolution over time, 2) Consensus needs to be reached whether to use these values as cut-off values, 3) Different techniques were used, and this was also compensated for.

For the other continents, the individual reference value studies should be verified and combined into continental specific reference value in order to produce similar guidelines. This is especially important so that different ethnic backgrounds are taken into consideration.

To accomplish widespread active clinical use of pulse wave velocity as a predictor of cardiovascular risk, aortic pulse wave velocity measurement must be standardized. There is a great need for studies and measurements to be more comparable and unambiguously interpretable. The key matters to standardize are PWV measurement device, distance measurement, MAP incorporation and measuring circumstances [32]. [29]

The measurement should be done with validated PWV measurement device and furthermore this validation process of a device should be standardized. With a validated device, one gets comparable results and has reference values to support the research. The validation of a device should be independent and comparable with the validation processes other devices have undergone. Ultimately, it would be ideal to have interchangeable devices. However, the devices must at least have fitting reference values that take under consideration continental differences. [29, 91]

In the carotid-femoral PWV measurement, the distance measurement can be conducted by two different approaches. First approach is to measure from suprasternal notch to the femoral site (b) minus the suprasternal notch-to-carotid distance (a), these path lengths are illustrated in Figure 13. The second approach is direct measurement from carotid site to femoral site and the direct measure should be multiplied by 0.8, this path length is illustrated in Figure 13 as well. [14, pp. 23-25, 29] The recommended equipment for distance measurement is calipers [35].

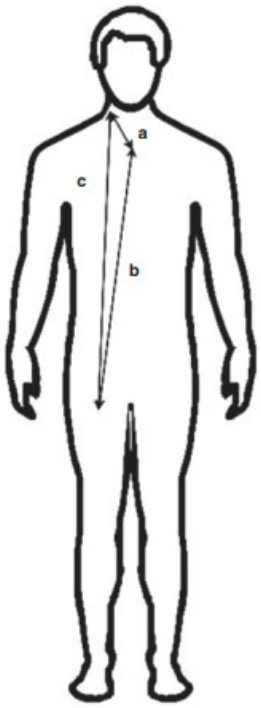

Figure 13. *Illustration of the two distance measurement approaches to acquire distance for PWV determination. Vector (a) is the suprasternal notch-to-carotid distance, vector (b) is the suprasternal notch-to-femoral distance and vector (c) is the carotid-to-femoral distance. Vector (b) – (a) is the first approach and vector (c) on its own is the direct distance measurement. [92]*

A single threshold value should not be used for interpreting the PWV value as impacting factors are not taken to consideration such as age and the association with MAP. The measurement sites and measuring process should also be reported in the studies. As distance has a great impact on the resulting PWV and falsely measured one can cause significant error. [29]

The MAP values should be measured and incorporated to the research papers, because interventions lowering MAP, will also lower PWV. Basically, this means that a decrease in PWV is not always a result of an improved arterial stiffness condition. In order to interpret that arterial stiffness condition has been improved there must be a decrease in PWV to a degree that is not justified by decrease of MAP alone. [29]

The measurement of PWV should be done while the patient is in fasted state. Duplicate PWV measurements should be conducted, after a 10-minute rest period and the patient should be laying down in supine position. Lastly, the operator should be familiar with the measuring device, is trained to perform measurements and accomplishes reproducible results. [29, 34]

Other potential variables to assess cardiovascular risk are SEVR and a combination of SC and DC. However, the local PWV measurement is always more accurate than PWV or another variable acquired as a result of PWA and a transfer function. SEVR currently has only a critical value of 0.5, below this subendocardial vascularization is deficient [14, pp. 92]. DC and SC still need further studies, including longitudinal ones, to determine their true accuracy, reproducibility, and appropriate reference values.

Oscillometric methods, EMFi, and piezoelectric sensors, and PPG are the inexpensive methods to make accurate PWV measurement broadly available. Success in such inexpensive devices would greatly increase the clinical value of pulse wave analysis.

4.2 Peripheral artery disease

Non-invasive diagnosis of PAD is commonly done with affordable ankle-brachial index (ABI). However, it is severely limited in case of calcification to a degree where an artery cannot be flattened and thus no reliable measurement can be acquired. [93] The accuracy of ABI also has variability and specificity, thus PWA-derived variables such as AIx, PWV, and pulse rise time (PRT) have been proposed as alternative methods to improve the accuracy [94, 95]. Out of the PWV-variables, AIx and PWV pertain to pulse waves of the aorta and PRT pertains to the peripheral pulse waves. So far, these PWA-derived variables are not an essential part of PAD guidelines.

AIx derived from applanation tonometry is independently associated with PAD and has clinical potential [96]. It has been shown that PAD is characterized with an increase in AIx with respect to controls. PWV is also increased with PAD patients. [97-98] However, with these variables, further studies are needed to validate them and acquire reference values. Also, separation of PAD from other abnormalities causing increased PWV or AIx might as well prove to be an issue. The advantage of AIx is that only a single measurement site is needed.

Another approach is cPP/PWV index that has been proposed as a risk factor for severe PAD. This has its basis on that PWV lowers with people with PAD [99], which is not in consensus with the previous PWV and AIx studies [96-98]. The cohort in the study was larger than in previous related studies. The decrease of PWV could be thought to result from increased flow resistance, where the increased flow resistance is caused by the occlusion of an artery.

In any case, the relationship of PWV and PAD should be confirmed. With confirmation and further research, a decrease in PWV and an increase in cPP could be an efficient way to predict increased risk of PAD [99].

PRT derived by means of PPG and measured from a toe is another potential approach. PRT is regarded as the time between a local minimum before pulse wave peak and the peak of the pulse wave. This PRT is measured and evaluated from a lower limb. It was an effective PAD marker in a recent study, but studies with larger sample size and different ethnic cohorts are needed to validate the method and the critical value. The advantages of PRT-based method are the inexpensive, convenient and easy measurement. [96]

5. CONCLUSION

PWA methods are intended for predicting cardiovascular diseases primarily by evaluating arterial stiffness. Optimized and standardized measurement with the right variable can be affordable widespread way of predicting CVDs with significant clinical value.

Notable pulse wave analysis variables are PWV, AIx, ASI, cPP, SEVR, and a combination of SC and DC. Out of these the most viable and recommended one is cfPWV. This is mainly based on the fact that PWA variables commonly depend on use of a generalized transfer equation.

The most common measuring methods currently for pulse wave analysis are applanation tonometry and oscillometric measurement. Even though tonometry with carotid-femoral site combination is the recommended method with the best accuracy and reproducibility, the results are operator dependent. The essential aspect of applanation tonometry with carotid-femoral site combination is that viscoelastic properties of an aorta are taken into consideration.

On the other hand, oscillometric methods can also have acceptable accuracy and sufficient reproducibility. The oscillometric measurement could be an easy and affordable method capable of widespread use. However, oscillometric devices need independent studies to confirm their validity. A main drawback of oscillometric measurement is that it is a peripheral measurement, which means that use of a transfer function is required in order to acquire the central pulse waveform.

Additionally, although electromechanical transducer and PPG measuring methods are still unpopular commercially, they possess a vast amount of potential to be affordable and easy measuring method that could become widespread, with extended measuring possibilities such as BSN applications. Whereas PPG can have extensive use with obese subjects, use of transfer equation can be a pitfall for these methods.

Currently, cfPWV is clinically relevant but the widespread impact needs standardization. The key aspects to be standardized are the usage of validated PWV measurement device with adequate reference values, distance measurement and incorporation of it to the related document, incorporation of MAP to the related document, using recommended measuring conditions and sufficient operator training.

PWA has utilization prospect in the diagnosis of PAD by enhancing the diagnosis made with ABI. However, they are not an established part of PAD guidelines and require further

research. The researched variables are AIx, PWV, cPP/PWV, and PRT. The conflicting findings on whether PWV increases or decreases with PAD need to be addressed prior to any clinical usage of PWV related variables for PAD diagnosing.

To conclude, pulse wave analysis methods are intensively studied as a tool for diagnosis, but the varieties in measurement and on analysis methods at clinical circumstances as well as lack of validation continue to be major obstacles that prevent these methods from breaking through. Eventually, success of standardization will decide the success and impact of these methods.

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