POLITECNICO DI TORINO

Master Degree Course in Biomedical Engineering

Master Degree Thesis

Venous Pulse Wave Velocity evaluation using innovative tonometers

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Chapter 1

Introduction

About 10% of patients entering the Emergency Department (ED) are subjected to an evaluation of their hydration conditions (volemic status) with the aim of evaluating and eventually improving their vital organ perfusion. For this purpose, different non-invasive techniques, like the measurement of inferior vena cava (IVC) pulsatility, are commonly adopted to understand the volemic status of patients. Unfortunately, these techniques proved to have some limitations, for example varying respiratory pattern in spontaneous breathing can affect IVC ultrasound reliability. Even though new methodologies to evaluate the vital organs perfusion have been developed, some studies about Venous Pulse Wave Velocity (vPWV) are still performed. vPWV, in fact, can be investigated as a new parameter to understand the patient's conditions and the management of fluid therapies. The first researches, dated back to 1967, have not been followed up, probably due to the ineffective adopted methodologies. vPWV has been investigated less than PWV of arteries for two different reasons: the lack of natural pulsatility in the veins and the strong dependence on the respiratory system. Recently, two researches have focused on vPWV overcoming the limits of the venous system; they generated an artificial compression from an extremity of upper or lower limbs in order to propagate the wave, synchronizing the impulse with both cardiac activity and the respiratory system. The evaluation of vPWV can be crucial: first, because veins are more compliant vessels than arteries, second they are a perfect fluid reservoir for our body. For these reasons, depending on the quantity of fluid in the venous district, venous vessels change their contraction and consequently blood's velocity. The aim of this work is the measurement and evaluation of vPWV replacing the previous device with a system based on tonometry (ATHOS designed by Politecnico di Torino for the detection of arterial velocity): the pulse wave has been generated artificially on a limb extremity by a pneumatic system and it has been detected with this new sensors. After some preliminary tests aimed to understand the best positioning of tonometers in order to detect the signal of interest, vPWV was detected placing two sensors on the left arm, where the signal-noise ratio is better detected, using two bands. An experimental protocol was created for healthy subjects and then, an algorithm has been implemented in MATLAB to measure the latency between the two waves. Finally, a statistical analysis was made comparing the results given by tonometers and the results of Echo-Doppler (obtaining an intraclass correlation coefficients (ICC>0,8 and an absolute mean error of 0.8 m/s).

The thesis is structured as follows: in the first chapter it will be explain some principles about cardiovascular system, venous vessels and the detection and mechanism of venous pulse wave velocity. Then, it will discuss methods and experiments done during the work. Finally, the results given by experimental protocol and the statistical analysis comparing the two different methods.

Chapter 2

Background

2.1 Cardiovascular system

The cardiovascular system is a complex system that consists of different parts: heart,blood vessels and blood. This parts work all together to give the correct quantity of nutrients to all cells of body. Thank to heart,blood that is pumped flowing through blood vessels to every part of the body and assures to the organs the correct supply of nutrients and oxygen.

2.1.1 The heart and cardiac cycle

The heart is the principle organ involved in the cardiovascular system.It is the cardiac muscle and is a dynamic pump of blood and brings the nutrients to tissues and cells.It has a dimension to the fist of an hand and it is inside a cavity called mediastinum that is placed under the sternum. It has three different layers:

1. Epicardium: it is the external layer and it consists of a monostratified epithelial tissue.

2. Myocardium: It consists of heart muscular tissue.

3. Endocardium: It is the tissue that covers the cardiac cavity.

As the figure below (figure 2.1), there are also ventricles and atria on both side: they are four and are the cavity of heart. The ventricles are in the downside of the cavity, while the atria in the upside.

As the fact that it has a left and right side, the heart has also a top and bottom side respectively called base (the top) and apex (the bottom).

Between the atria and ventricles there is the septum: it is a wall that prevents mixing the blood of the two separated side.Another important part are the valves. Four valves are present:

1. Atrioventricular valves: between the atrium and ventricles.

2. Semilunar valves: at the exit of pulmonary arteries and aorta.

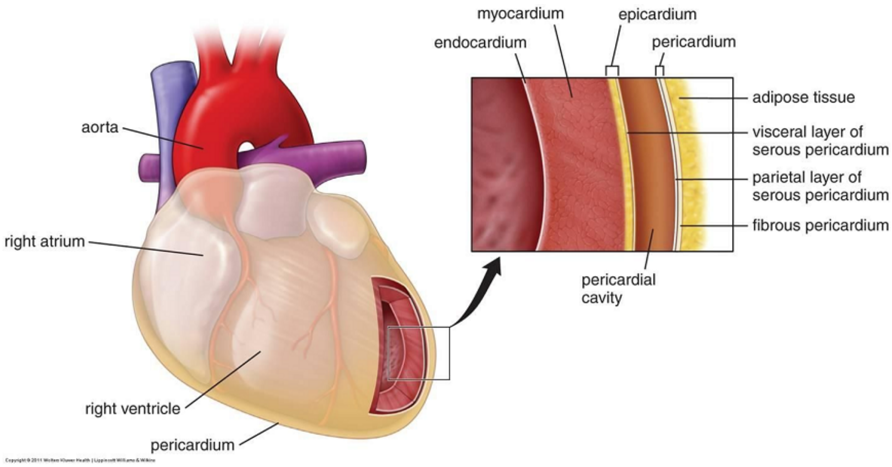

Figure 2.1: Heart with the different tissue
https://www.toppr.com/ask/en-ca/question/what-is-epicardium-endocardium-and-myocardium

At the same time,the heart pumps the blood full of oxygen and without through two different pathways in the entire body. The contraction and relaxation of the heart is called cardiac cycle. The figure 2.2 shows the cardiac cycle of the heart. Two principle phases are present: when the heart is completely relaxed, the phase is called diastole and when the phase is the contraction is called systole. The cardiac cycle has 4 different phases:

1. Ventricular filling: when blood returns from the veins to heart (called venous return).Due to the great pressure, the blood comes to the atria thank to AV valves [1]. At the end of this phase the atria contracts and the blood fills the atria cavity (at the end of diastole), while semilunar valves are closed because the pressure of ventricles is smaller than aorta and pulmonary arteries.

2. Isometric contraction: in this phase, the semilunar valves remain closed because the ventricle pressure is not enough high to open them, but at the same time the AV valves remain closed. This phase is the beginning of systole and finishes when the ventricles pressure is enough high to open the valves.

3. Ventricular ejection: after the reaching of ventricle pressure peak, the blood flows to aorta and pulmonary arteries and the ventricle pressure starts to decreasing. With this the systole phase ends and the diastole starts.

4. Isovolumetric relaxation:in this phase a small volume of blood remains inside the ventricles, but for the fact that the pressure is small, both the valves (semilunar and AV) remain closed in this phase[1].

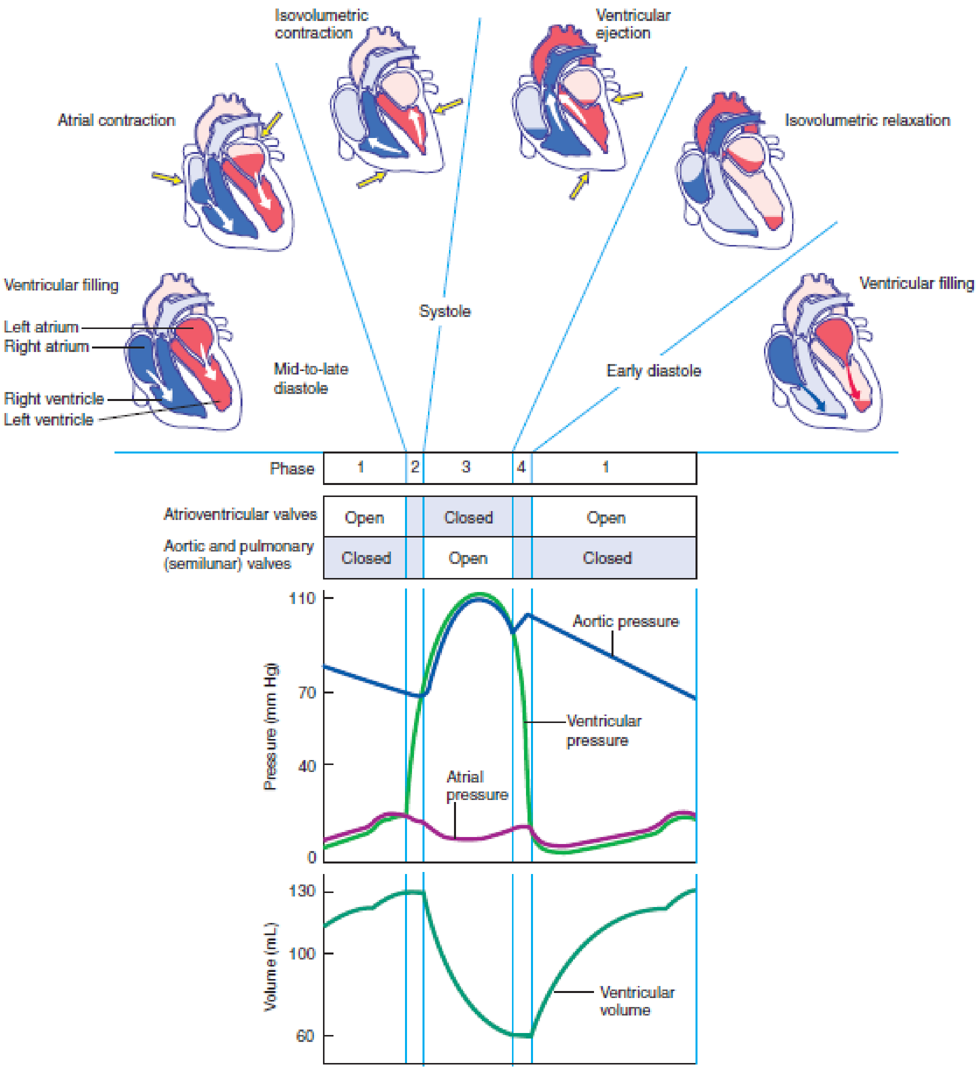

Figure 2.2: Cardiac Cycle [1]

In a more general vision, we can discuss in detail the pathway of the blood in the figure 2.2. The path of blood is divided in two different circuit: pulmonary circuit and systemic circuit [1].

The pulmonary circuit is the path that the blood performs from the right atrium where the blood is poor of oxygen to the left atrium, full of oxygen. Instead, the systemic circuit is the path where the blood flows to all tissue of the body changing oxygen and nutrients.

Starting from the right atrium, the right atrium pumps the blood poor of the oxygen to the pulmonary arteries that reaches the pulmonary tissues and fills up of oxygen. Through the pulmonary vein, the blood returns to heart in left atrium where then it passes to left ventricles. From the ventricles, the blood arrives to aorta that is the largest of all blood vessels. This has different branches called coronary arteries and other branches that reach the head,limbs ...

After exchanging the oxygen with the tissues, the blood (poor in oxygen) returns to rigth atrium through inferior vena cava.

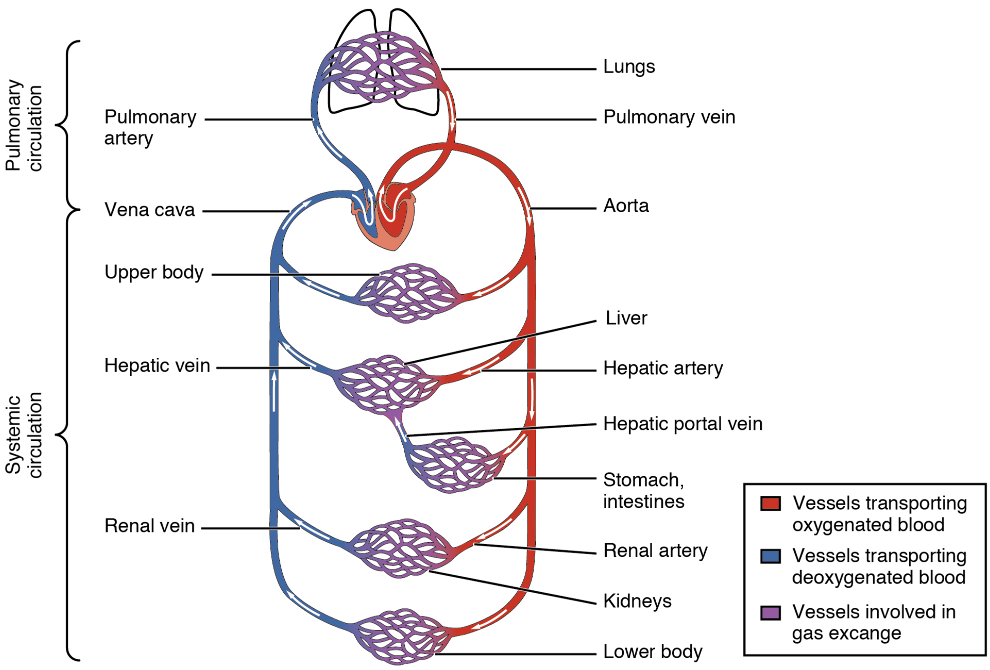

Figure 2.3: Systemic and pulmonary circulation
https://openstax.org/books/anatomy-and-physiology

An important parameter for the cardiovascular system and the heart is the cardiac output (CO): in fact the principle function of the heart is the pumping of the blood that arrives to left ventricles to arterial vessels.

The heart must generate sufficient pressure to propel blood from the left ventricles: each time left ventricle contracts, a volume of blood is ejected to aorta. The cardiac output referred to this and it is equal to:

$$CO = SV * HR \tag{2.1}$$

Where SV (stroke volume) is related to the volume ejected to aorta during the contraction of left ventricles [1] and HR is the heart rate, or the number of beats for minute. The variation of heart and volume changes the cardiac output.

The unit of measure for this parameter is millimeters for minutes (mL/minutes) or Liters for minute (L/min). In fact the value for SV is mL/beats and for heart rate beats/min. When a person is at the rest the left and right ventricles pump only 5 liters to the organs per minutes. For an adults at the rest, the normal heart rate is 75 beats per minutes and the stroke volume is around 70 mL. So for the fact that the blood volume cannot change during cardiac cycle through pulmonary and systemic circuit: the two volume pumping from the left and right ventricles must be the same and so also the cardiac output.

As said before, there are two different phases during the cardiac cycle : diastole and systole. The volume at the end of diastole is called End Diastolic Volume (EDV), while the volume present at the end of the systole is called End Systolic Volume (ESV). The difference between this two volumes is the stroke volume.

Another important parameter is the mean arterial pressure (MAP) that is related to CO. As the name said, it is the average of arterial pressure during one single cardiac cycle [2]. Preload depends on the compliance of veins and blood volume. In fact increasing blood volume, increasing also the preload and pressure,consequently increase also the cardiac output [2]. The value of MAP is typically of the order of 60 mmHg to maintain the organ perfusion.

2.1.2 Blood vessels

Both with the heart, the cardiovascular system has also different types of vessels. The blood flows through them during the pathway described. The main vessels are:

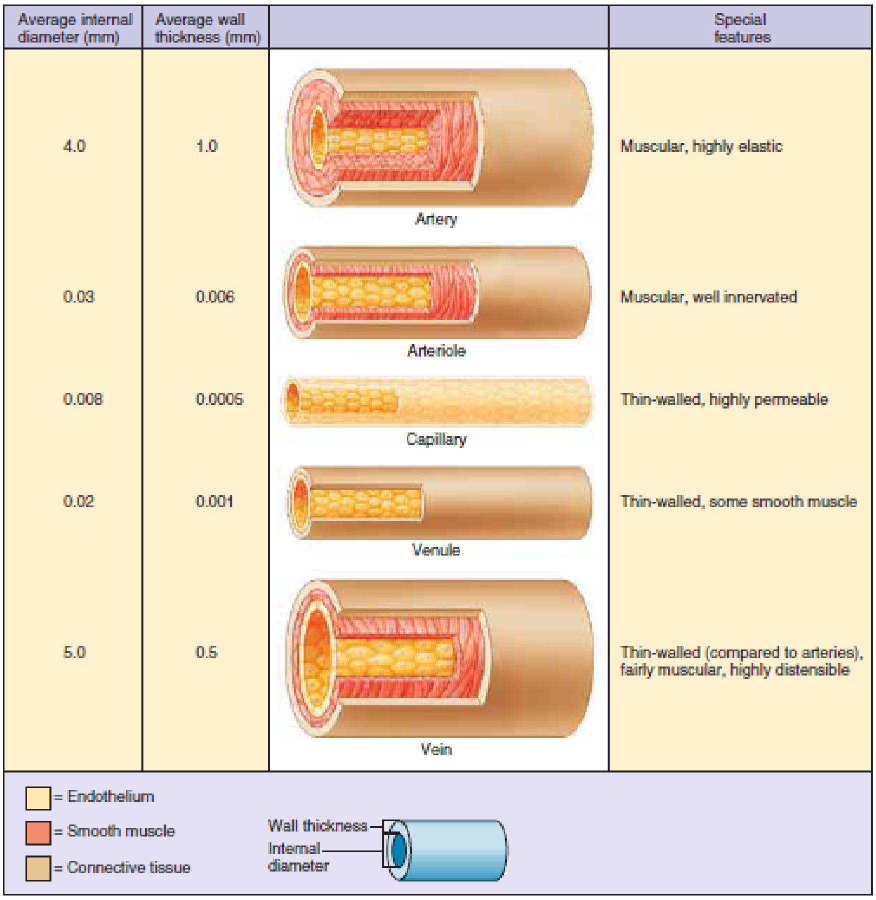

Figure 2.4: Structure of blood vessels [1]

1. Arteries: this kind carry blood away from heart.They are the elastic vessels having the largest diameter and a very thin wall. The typical example are the aorta, the artery that carry the oxygen blood form left ventricle to the tissue. This arteries have an elastic wall because in this part, the blood is pushed at high pressure [3].

2. Veins: the type of vessels that we are interested in that carry blood back to heart.

3. Arterioles: small arteries.The arterioles brings the blood full of oxygen to

capillaries where there are an exchange of oxygen.The number of elastic fibers present in arteries decreases when the size decreases.

4. Venules:this vessels collects the blood from capillaries.

5. Capillaries: the most important for exchange oxygen between tissue and blood.

Both the arteries and veins are composed of three layers [4]: intima, media and adventitia. The figure 2.5 shows the different kind of layer present.

Starting from the innermost layer (intima),it is composed of a single endothelium layer and it is separated from media by a basal lamina.

Media is the intermedium layer and it is composed of smooth muscles in a different kind of proteins like collagen and elastin. The different quantity of elastin depends also the type of vessel for example aorta has a great presence of this because it must be able to contract during cardiac cycle and elastin and collagen give it a certain of mechanical properties [4].

The outermost layer is the adventitia: it is separated from the media by the external elastic lamina and it has a great quantity of fibroblasts,collagen and also autonomic nerves.

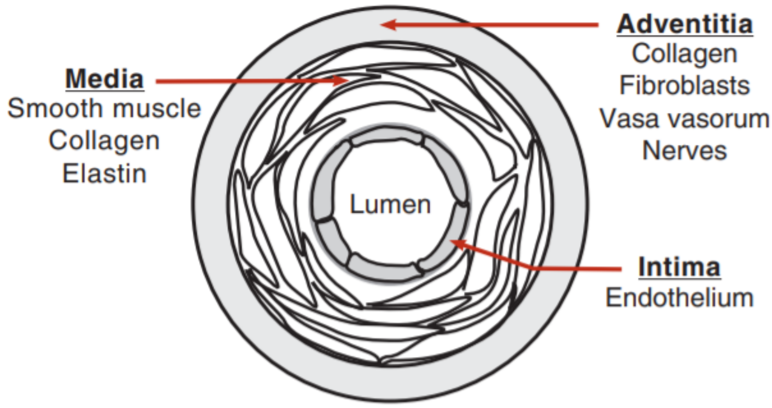

Figure 2.5: Intima,Media Adventitia [4]

I'll study in deep the structure of the veins that are the object of this study. The venules come together to form veins. The veins have larger diameter respect to arteries, but they have thinner thickness.

The diameter of venous cavity is of the order of 50 mm (the aorta only 12 mm), but they have a hall thickness of the order of 1.5 mm [4]. The structure of the tissue is similar to arteries: in fact it is formed of smooth muscle and elastic and fibrous connective tissue. For the fact of their narrow thickness, the pressure of the veins is smaller than arteries.

They are equipped of unidirectional valves and it is useful to avoid the blood flowing back to organ and tissue.

For their structure, different to arteries the veins are important compliant vessels: in rest conditions, they contain 70% of blood volume present in the body.With a variation of pressure they can host a great blood volume respect to arteries.

The veins is the volume reservoir of the body for their structure:the very thin walls and their elasticity makes the veins able to easily stretched and with a high compliance a low variation in pressure causes a large expansion. The pie chart 2.6 shows the different distribution of the blood volume in the various portion of the cardiovascular system.

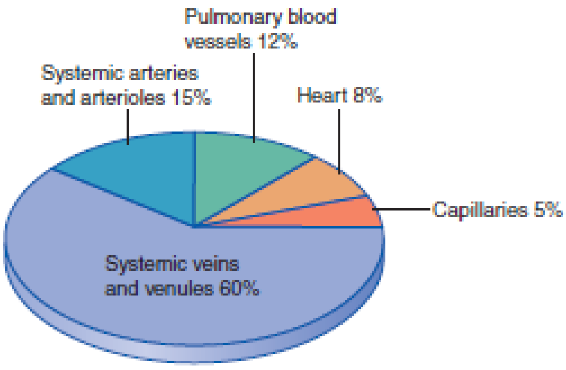

Figure 2.6: Pie chart of Pulmonary blood [1]

2.1.3 Vascular resistance and compliance

The circulation system can be considered as electric circuit with a total resistance that in this case resistance of the wall (R) and the current that in this case is represented by the flow rate (Q). The formula is equal to Ohm's law, but in this case the resistance is represented by the obstruction during the blood flow in the circulatory system [5]:

$$Q = \frac{\Delta P}{R} \tag{2.2}$$

P is the pressure and the different of pressure permits to blood to move in our body.

At the same time,the blood vessels can be assume as a large cylinder with a constant diameter and it can be described by Poiseulle's law that describes the resistance of a vases [6]:

$$R = \frac{8\pi\rho\nu l}{\pi^2 r^4} \tag{2.3}$$

Where r is the radius of vase, ρ is the density of the blood vessels and ν is the viscosity and it is related with hematocrit quantity. From this equation, it can be important to said that the resistance has a strong dependence on the radius in fact it is inversely proportional: with a low variation of radius, results a great variation of resistance.

Another important properties for a blood vessels is the compliance.

$$C = \frac{\Delta V}{\Delta P} \tag{2.4}$$

This equation described the compliance as the fraction between the volume (venous volume) and pressure (venous pressure).

The compliance described how much blood vessels expand after a variation of pressure.It is important to notice it because the veins have an high compliance. With a change in venous pressure, it is possible to change venous volume as a factor that depends on the venous structure and conformity.

As said before, for this reason in the venous system there is 75% of blood volume. With a small change in pressure, there is a significant accumulation of fluid for this property [7].

The arteries for their thick walls have a slow compliance respect to veins and for this reason they have a necessary to have a great difference of pressure and volume to expand them. We can schematically described this mechanism with the figure 2.7: the vertical axis is the volume, while the horizontal axis is the pressure. It is evident to notice that with a increasing of volume, there is an increasing of pressure. The slope of the curve is great at slow pressure because depend on the ration between volume and pressure. From point A and point B there is an increasing of pressure and volume. This increasing or decreasing depends on the slope that is related with the structure of veins and so with the compliance. For low value of pressure and volume, it is noticed that the values of compliance are higher, then the slope of curves reaches a plateau. It is important to say like the figure shows that with high values of pressure and volume, the compliance decreasing and so the veins are stiffer. The value of compliance depends also on the vascular tone: in fact there are varies curves depending on tone.The curve goes down if the tone increases: so with an increasing of vascular tone, there is a decreasing of compliance. In fact the vascular tone depends on smooth muscle and so with an increasing of it, there is a reduction on venous compliance and so a curve higher in the graph.

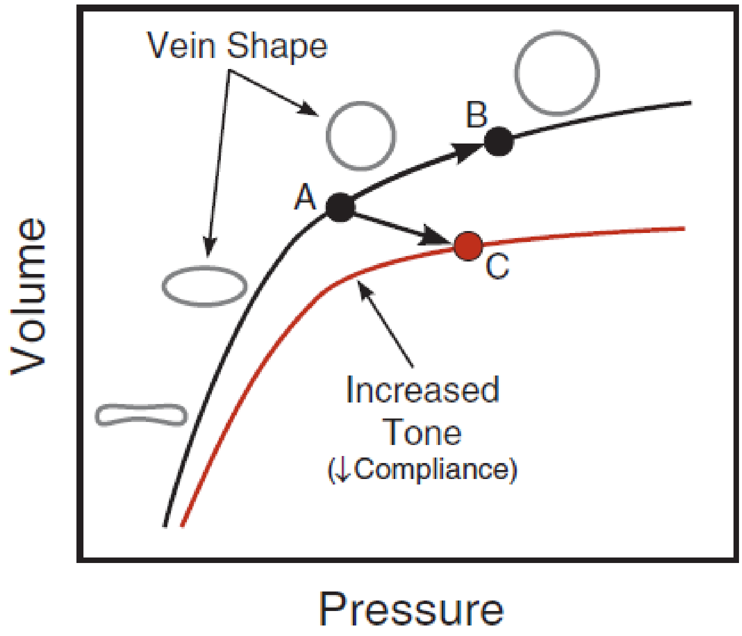

Figure 2.7: Compliance curves depending on tone. [4]

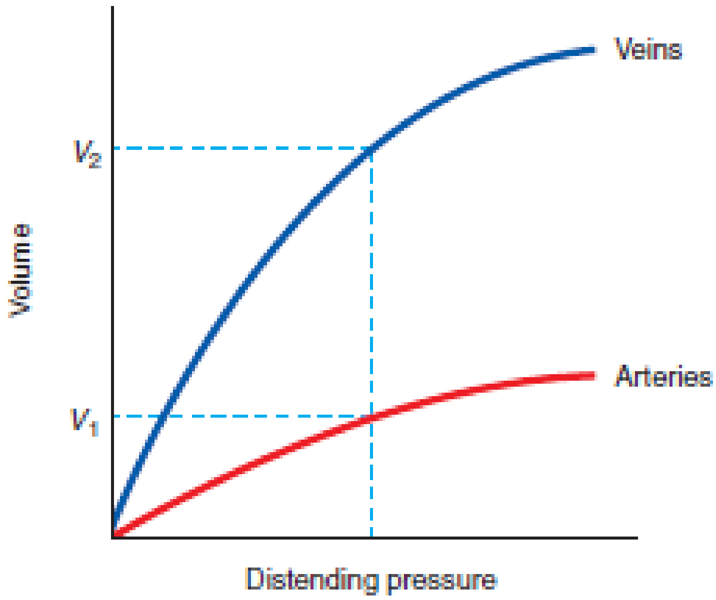

Figure 2.8: Compliance curve for arteries and veins [1]

2.1.4 Central venous pressure

The term venous blood pressure is a generic term that describes the pressure present in the venous compartment. A more specific term is the central venous pressure (CVP) and it is crucial because estimates the pressure that arrives in the right atrium through the inferior vena cava.

The venous pressure has a small values respect to arteries and it can be influenced by different factors.

The central venous pressure is the protagonist not only of the cardiac filling, but also of the ventricular stroke volume. This mechanism is regulated by Frank Starling mechanism. This law is based on the ability of the heart to change its force contraction and stroke volume to changes in venous return [6] and so the cardiac output in the right atrium.

The most important parameters that affectes the venous pressure are:

1. Gravity : when a person is in a supine position, the blood is uniformly distributed in all the organs of the body and the venous pressure is around 2 mmHg. While a person is in the standing position, the blood accumulates in the lower part and so for the high compliance of veins respect to arteries, this causes an increasing of pressure and volume in veins compartment (around 90 mmHg) and this reduces ventricular filling pressure in the right atrium (Frank Starling Mechanism). The reduced stroke volume causes a decreasing in cardiac output in the left ventricle and also arterial blood pressure [4].

   When the arterial blood pressure decreases, this is called postural hypotension in standing position and it can be a syncope because the person is in the state of loss consciousness [4]. The nervous system tries to restore the arterial pressure increasing heart rate and with vasoconstriction.For example when a person walks, the movement causes a increasing in venous return restoring the CVP (fig 2.9).

2. Muscles: it is the activity of skeleton muscles because the peripheral veins have one-way valves as described before and they serve to prevent the blood return. When the muscles contracts, this causes an increasing of venous pressure and the valves present upstream closes ,while the valves downstream opens: this causes a pumping mechanism that facilitates venous return. During a physic exercise, the contraction of the muscles can help venous return oovercoming the gravity. This mechanism is described in the figure 2.10.

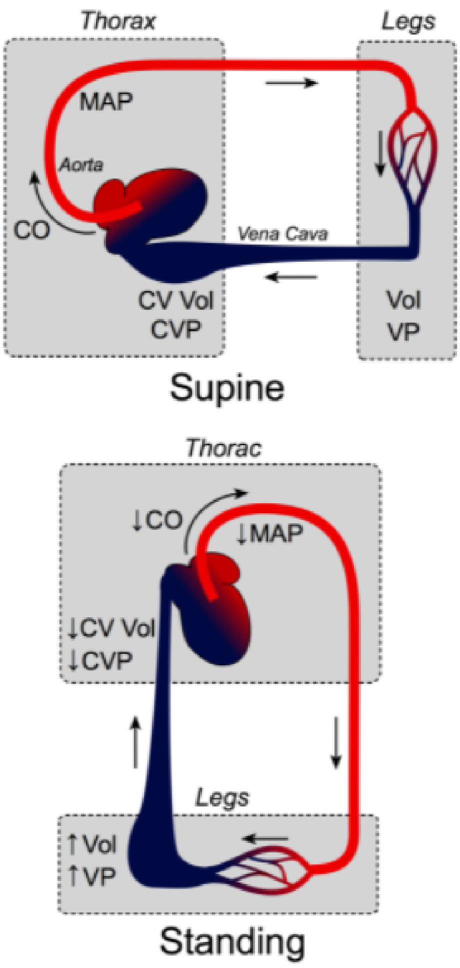

Figure 2.9: Gravity mechanism on CVP [4]

3. Respiratory system: the venous pressure varies with the inspiration and exhalation phases. Pressure and volume depends on intrapleural pressure [4]. The intrapleural pressure (the pressure between the thoracic wall and the lungs) is negative: during the inspiration the chest expands and the air enters in the lung, this pressure becomes more negative, although during the exhalation happens the opposite. During the inspiration, not only the chest and lung expand, but also the vena cava,atrium and ventricles so causing a decreasing of the pressure during inspiration in the atrial chamber (tipically - 2 mmHg), contrary an increasing of venous gradient and facilitates of venous return to right atrium [4]. This decreasing of atrial pressure is associated an expansion of cardiac chamber and so the increasing of trasmural pressure because the volume of atrial chamber increases (it is referred to atrial chamber expansion)

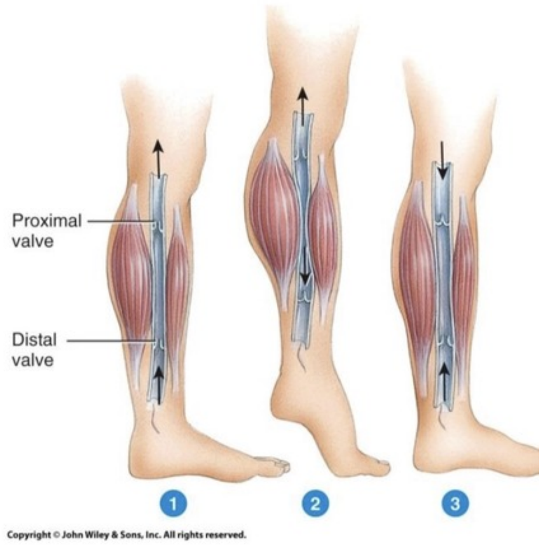

Figure 2.10: Muscles mechanism
https://quizlet.com/370653011/sap2-4c-cv-system-vessels-flash-cards

[4]. Increasing the rate of respiration, increases also the cardiac output and stroke volume.Finally, it is notice that increasing the central venous pressure, increases also heart rate and when the central venous pressure decreases,cardiac output decreases.

4. Blood volume: the relation between volume and pressure is very simple. With an increasing of volume corresponds a increasing of pressure.

5. Venomotor tone: with a contraction of smooth venous wall,there is a decreasing in venous compliance due to contraction of walls and so an increasing in venous pressure [1].

2.2 Pulse Wave Velocity

The Pulse Wave Velocity (PWV) is the speed in which pressure waves propagates inside the blood vessels.

The first study about the pulse wave velocity goes back to 1922 when Bramwall and Hill wrote about the stiffness of arterial vessels and the fact that the pulse wave depends on it [8]. The stiffness is defined as the pressure needed to have a certain value of diameter of vessels. For this reasons it is necessary to have invasive measure, so during the late decades new method non-invasive to measure the pulse wave velocity have born.Since this moment,the measure of pulse wave velocity became an important index of cardiovascular disease in arterial vessels. In fact the velocity in the blood vessels is related not only with fluid inside,but also with the structure of blood vessels and their stiffness. When the velocity is higher, this indicates the presence of more stiffness and so an index of cardiovascular disease.

The study of Pulse wave in artery is based on the fact that with the increasing of arterial stiffness increases also the velocity of the liquid in the vases and it is correlated with the arterial stiffness of the vessels. It is the easiest pulse wave to calculate because the pulsatility of an artery is more significant than venous pulsatility, but the equation on which the velocity is based ,is the same. The relation was studied by Moens and Korteweg in 1878 [9] and it is as follow:

$$PWV = \sqrt{\frac{Eh}{\rho d}} \tag{2.5}$$

E is the elastic module and it is referred to arterial stiffness, h is the thickness of artery, ρ is the density of blood and D is the diameter of it. Higher is the PWV, the stiffer the blood vessels walls. For the first time in 2007, it appeared as an index of cardiovascular diseases. The equation described the quadratic relation between the pulse wave velocity and the stiffness. It can be useful in the case for example of atherosclerosis.

The measure of pulse wave of arteries is often a local measurement because it is done in two different points of a subjects: the first is carotid site and the second is the femoral site and it is defined as a fraction of two different sites and the latency.

As the figure shows two different kinds of waves propagates from the ventricles to the aorta: a first wave that proceeds with a velocity of 1 m/s and a second wave that is the pulse wave velocity that propagates with a speed of 4-8 m/s.

As the figure below, the pulse wave velocity is defined as:

$$PWV = \frac{distance}{time} * 0.8 \tag{2.6}$$

Pulse wave velocity is a velocity and in order it is a fraction between the distance between the two selected sites and the time between the two wave. Often the pulse wave velocity is an indirect measure of PA (arterial pressure in mmHg).

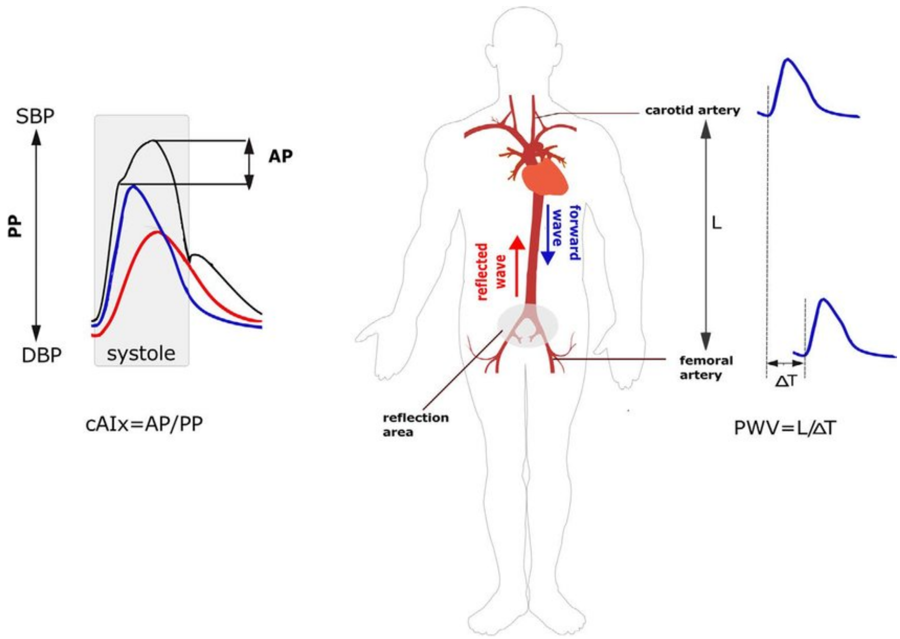

Figure 2.11: Measurement of PWV (artery)
https://doi.org/10.1038/srep27016

It is often calculated with the path between carotid artery and femoral artery (neck and femoral site), called cf-PWV or ba-PWV (brachial ankle). The typical measurement between the two wave of two sites is the method foot-to-foot: the foot indicates the feet of the two waveforms, but the time can be defined in different ways because it is difficult to defined the beginning of the wave. The two different types of waveforms described previously are widely used in clinical research. There are different method to measure it.

The time is also called Pulse Transit Time (PTT) and it is the time between the two spots. The value 0.8 indicates that the path where the blood flows trough veins isn't straight pathway. This is one limit of the typical PWV because it is an external measurement and a correct distance between the two sites are needed. The blood vessels have a curvature: this coarse approximation of it constitutes a coarse approximation of the distance and consequently an important disadvantage. The same method of PTT is applied for venous pulse wave velocity. This type has less attention for its difficult to measure.

2.2.1 PWV with Tonometry

In order to introduce the work done, numerous devices are present in literature to calculate PWV in artery. Several systems to calculate PWV are based on MRI (magnetic resonance) or doppler ultrasound and are often used in hospital, but for the difficulty to use this product, researches have been investigated new types of products, as tonometers that today represents the gold standard to this aim.

The term "applanation tonometry" derives from the use of this method for the ocular tonometry, in fact numerous measurement belong to intraocular pressure (IOP). For ths reason, the earliest study of this technique, date back to 1963 by Pressman and Newgard [10], found a relation between the tonometer and sphygomanometry. From this initial work, varies studies were made in order to understand the accuracy and reliability of the new sensors, as for example in 1971 and 1972 .

A tonometer is an instrument that measured the pressure of a objects for example the eyes or artery into a solid object (the bone) [11].

The typical scheme of tonometers is showed in the figure 2.12 , where the sensor is put in the proximity of blood vessels in this case the artery and with a sufficient force, derived from the artery, this causes a stress contact that is approximatly equal to intralumenar pressure [12].

At the same time, Pressman an Newgard were the first that starting from the model of ocular tonometry proposed by Schwartz in 1966 that approximated the eye as a spherical shell, have described a mathematical model for the artery, considering also the skin and layers between [10]. Under different simplifications, the mechanical model is presented in the figure 2.13, where the tissue and artery were approximated as a resistance parallel system and the only force considered was the perpendicular force while the tangential force is negligible. The measure of arterial pressure under this conditions are equal to the fraction between the force and a costant that is the spring rate of transducer structure [10].

There a two type of tonometers:devices with a single transducer that was introduced by Millar and tonometer with multi-array sensor [11]. Today the most used and widely popular in the market is one single tonometer.

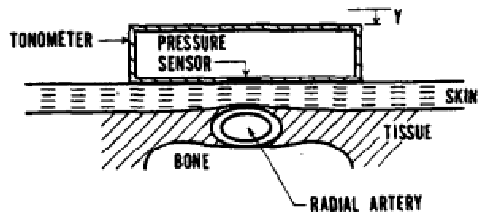

Figure 2.12: Tonometer functional scheme [12]

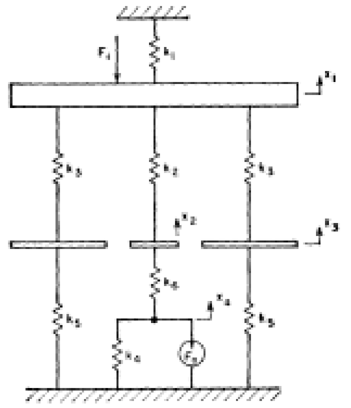

Figure 2.13: Arterial transducer scheme [10]

In the market, there are two different products that are based on applanation tonometry: SphygmoCor and PulsePen devices.

- SphygmoCor device [13]

  The first time that SphygmoCor (XCEL, Actomedical, Australia) appeared on the market was in 2008.It is based on the use of applanation tonometry and measures simultaneously the pulse wave between the carotid and femoral sites. [13]. As the image shows, the tonometry with SphygmoCor have some limitations: the first is related to the fact that in some subjects is difficult to see the typical wave related with pulse wave velocity and second is the user dependent because the operator put the tonometer where the artery is located [13].

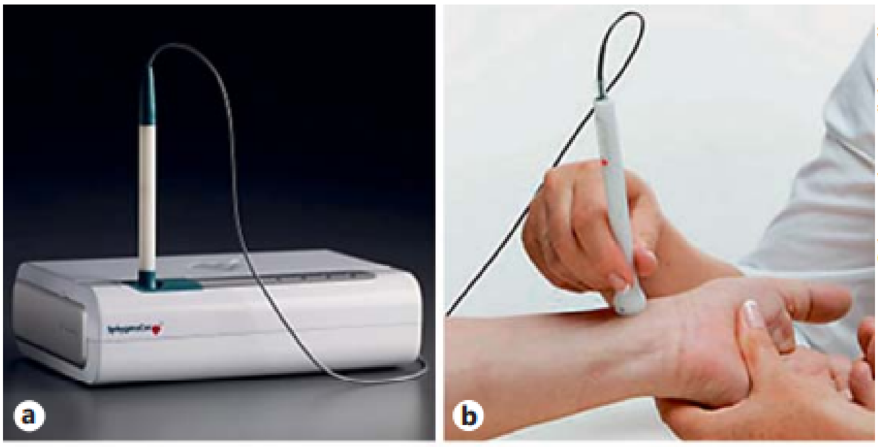

Figure 2.14: SphygmoCor device [13]

- PulsePen device [14]

  The PulsePen (Diatecne,Milan,Italy) is another type of device that is based on tonometry. The first article that show its validation appeared in 2004 [14]. It acquires simultaneously both electrocardiogram and the two wave signal. It is very small,portable and non-invasive device 2.15, that allows the acquisition also of absolute pressure value,an estimation of pressure wave and PWV with the help of one single tonometer.[14]

Figure 2.15: PulsePen device [14]

The measures of it are significant because it can be non-invasive,low cost,fast and in a reproducible way. However, there are still new researches to find new way to obtain it: from invasive wave to non invasive solution, from contact to non-contact devices.

The venous pulse wave velocity can be use for different aims respect to arteries. In fact, it is important to recognised the volemic status of patient during an emergency or also in intensive therapy for the correct perfusions of fluids. In this section, it will be described the new measurement that belong to veins and the possible application in clinical setting. The continuous monitoring of pulse wave velocity is considered a promising technique that is related to blood pressure.The measure of pulse wave velocity in veins has never been considered because the pulse of veins is really hard to recognised and so only in the last decades there are only several studies and new systems were designed for this purpose.

2.2.2 Pulse wave velocity in veins

The venous pulse wave velocity (vPWV) is related to venous stiffness and it is known that their compliance is different from arteries due to the wall structure of veins. Only in the last decade, vPWV has become to have attention in some researches, but the great difficulties is related to the fact that the venous flux has a great dependent from the respiratory system and the fact that there is a lack of pulsatility in the venous flux. For this reason the pulse wave velocity cannot be analyzed with the method of artery. The low pressure in venous compartment makes the measurement of vPWV more difficult.

The first researches was in 1967. In this study, a comparison between origin pulse of veins and with an artificial compression was made to understand the velocity[15], but for ineffective methodologies hasn't been taken into consideration [16].

Another study was done in 1971 [9] with the use of ultrasound in 10 healthy subjects at the level of two sites (femoral and subclavian sites), but there was also a strong dependence of respiratory system (during Varsavia manovre in fact the pulse velocity increases during the experiments).

Recent studies have tried to study the vPWV with the use of an artificial systems that increase the pressure of venous flux and increase the probability to catch the venous wave and detected by echo-Doppler system [17]. To overcome the limits about venous district, today there are two different systems that are able to synchronize the artificial compression (necessary to increase the pressure in the veins) and also cardiac activity:a system of compression is put on an extremity limb of the patient and an artificial wave is generated and then the wave propagates 2.16. This system will show better in the next section.

In this case there is a button and the subject presses at the end of expiratory phase. Recently, it was developed a new portable device for this aim implemented

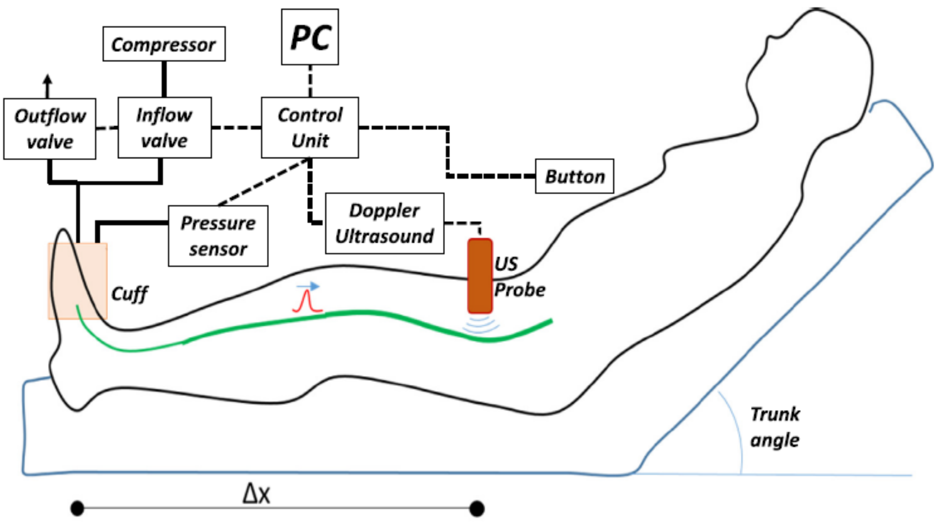

Figure 2.16: Experimental setup [18]

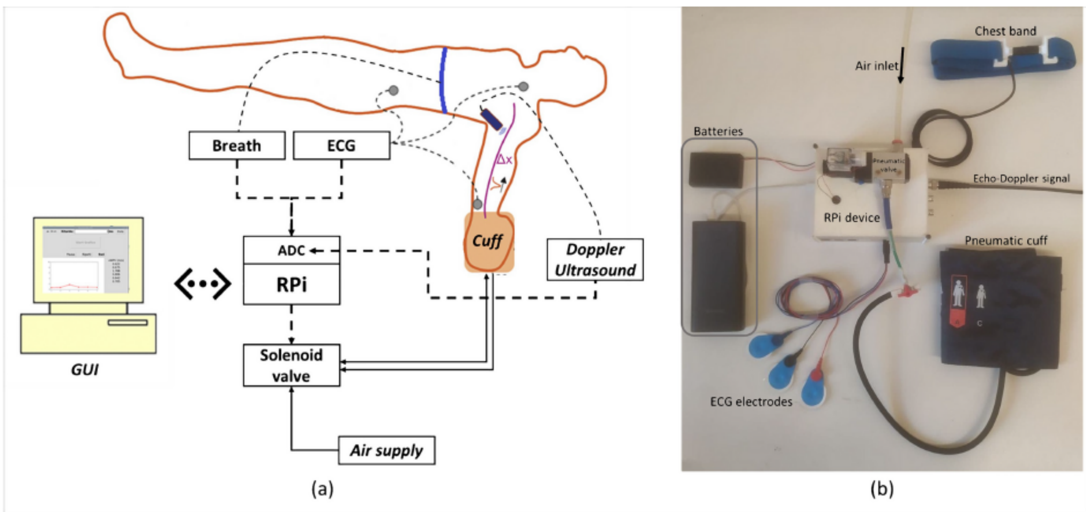

Figure 2.17: (a)Functional scheme of the device. (b)Prototype [19]

with PC board Raspberry, acquired both ECG signal and respiratory. [19], as in the figure 2.18. The only conditions that is different for venous compartment is the fact that an artificial compression in the extremity limb,arms or legs, is necessary.

The first study done in 1967 had the presence of a system of compression [16] and the other use the echo-doppler, but without the artificial compression [9]. It is based only on the natural pulsation of veins.

The new system has been developed recently using togheter this two methods

[18]: first, a system of compression tries to induce an artificial wave in a vein starting from an extremity for example a hand or foot and then the signal was recorded from the echo-doppler system in proximal sites. This proximal sites is on the proximity of the ankle or near the armpit.

2.2.3 Venous pulse wave velocity in clinical setting

In emergency department (ED), 10% of patients that enter in emergency are dehydrated and it is important to adopt the correct fluid therapy because the uncorrect dose of fluid injected to patient can be letal both in state of hypovolemia that in state of hypervolemia, respectively reduced and excessive quantity of vessel volume.

In clinical setting it is often necessary understand the correct volume that can be injected inside the patients and due to the fact that the correct somministration of fluid isn't immediate.

In patients undergoing hemodialysis, understanding proper fluid administration may be critical. In fact, following the administration of fluids, there would be an increase in cardiac output and consequently an increase in pressure. In some patients with heart failure, however, this increase would only lead to harmful consequences. The heart muscle would not be able to contain the new fluid supply.

To do this, it is necessary to understand which patients supported a good fluid intake and who did not respond correctly to fluid therapy. In this case, fluid respondent and fluid-non respondent are distinguished [20].Following an infusion of fluids, the cardiac output should increase and the patient would be able to contain new fluids. Static markers have been used for decades, meaning markers that consider only one point in the starling curve. In fact, the starling law relates venous return and cardiac preload: to an increase in stroke volume, cardiac preload also increases.

Different studies have been developed in order to abandon the old startegies based on static markers of preload [20]. This dynamic tests are described in the following table.

Table 2.1: Fluid challenge

Method	Description
Passive leg raising (PLR)	This method is based on the fact that with the change of position (legs or trunk), venous blood volume changes present in our body.
End expiratory occlusion tests (EEO) [21]	It is a test where the subjects stop the mechanical ventilation for few seconds.This could increase venous return and therefore an increase in cardiac preload.
Convention(or mini) fluid challenge [22]	As for, the conventional one consists of infusion of 300-500 mL of fluids, while the "Mini fluid challenge" consists of a rapid infusion of 100 mL of fluids.This could increase the preload,but it is not reversible.
Mechanical ventilation [20]	It is based on hemodynamics parameters variation . Changing intrathoracic pressure, there is a small changing in cardiac preload.

This methods are all based on the fact that with a changing of cardiac preload ,there is a changing in cardiac output. Consequently, depends on the responsiveness of fluid therapy, it is crucial understand the response of cardiac system, in order to avoid problems and with this we can understand the response of therapy [20].

The researches of the studied of this pulse wave velocity can be crucial for two different reasons: the first is that the venous compartment hosts the 75% of the total blood volume and the second is that the veins are compliant vessels. The venous pulse wave velocity is scanty due to the lack of natural pulsation in veins and for small associated blood pressure changes,but it can be fundamental for the detection of the volemic status of patients and the management of fluid therapy or to recognise the hydratation state of the patient. For this reasons, vPWV can be a

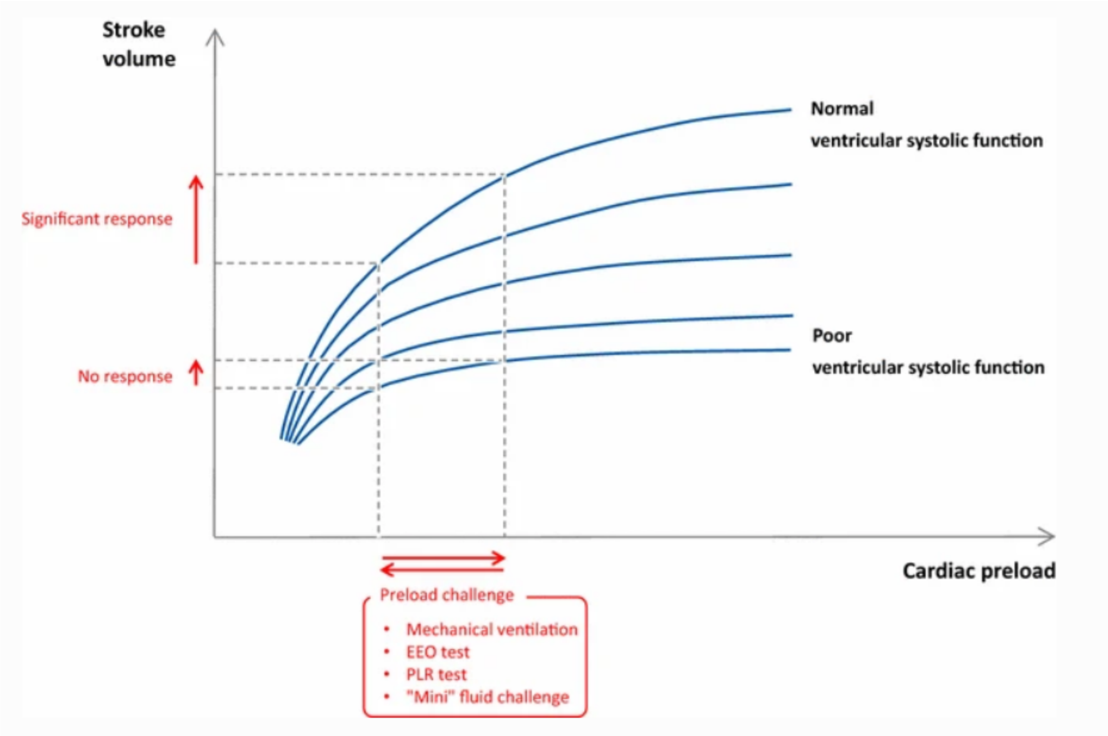

Figure 2.18: Starling curve [20]

good parameter to understand hemodynamic. In fact, with the change of position of leg there is an increasing of the velocity, consequently increasing of pressure in the arm.

vPWV could be a useful hemodynamic parameter to simplify the fluid challenge and predict from a small change in pressure, that is related with vPWV, a change of volume . This would lead to understand the subject's volume status in the clinical setting.

2.3 Employed devices and tools

In this section, it will talk about the two systems that are used and connected together for the work and the principle components.

2.3.1 Athos system and innovative tonometers

The tonometers has became the gold standard for the measurements of pulse wave velocity and in the market, SphygmoCor represents the gold standard. Although, another kind of devices have been developed for this aim to find new non invasive solution.

Politecnico di Torino has designed ATHOS, a low cost system for the detection of PWV. This device represents a low cost solution and have demonstrated a good agreement and accuracy with the comparison with SphygmoCor [23]. The term ATHOS stands for "Arterial sTiffness faitHull tOol aSsesment" [23]. The main scheme is showed in the figure below.

All the components cited are projected by STMicroelectronics,Shangai.

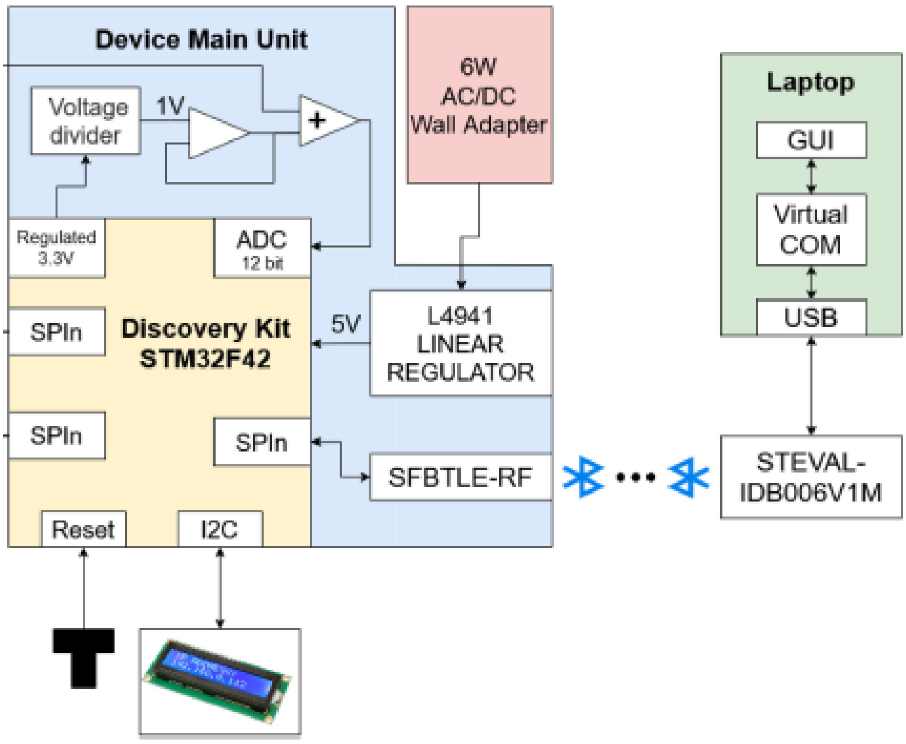

Figure 2.19: ATHOS scheme [24]

The hardware of ATHOS is composed of a main unit that synchronizes all the signal acquisition. An external laptop is connected wireless with the system where a graphical user interface shows the signal acquired. The three external input can acquired signal from two different tonometers and the other one can be processed signal coming from EDAN SE-1 electrocardigraph and so for ECG [24].

The device is powered with a supply of 6W AC-DC to fulfill the compliance with the medical normative where a double isolation is necessary. The 6W AC-DC adapter is connected with a linear voltage regulator that provides to the discovery kit the required voltage of 5V. When the discovery board works, the voltage of 3.3V is provided to MEMS sensors.

There is a reset button near the display that can be used to reset the system and also a button to turn on or off the system in the backside near the AC-DC adapter.

Fro wireless interconnection it is used SFBTLE-RF module that communicated with a STEVAL-IDB006V1M,plugged into the USB port in the external laptop of the operator. The SFBTLE-RF module integrates the BLE and works at a frequency of 2.4 GHz [24]. The data trasmission can operate up to distance of 10 m to ensure galvanic isolation and to guarantee the correct monitoring between the main unit and laptop.

In the top part of the figure, the presence of a conditioning circuit can be see. This circuitry serves to adapted the signal acquired from the ECG to the input of 12 bit ADC of the discovery kit. It works with an input range of 0-3.3 V.

The signals coming from tonometer are sampled with a frequency of 170 Hz, but to better synchronize the signal belong to ECG input (or in this case the trigger signal), the MCU takes 4 equal samples for tonometer because the maximum frequency is 170 HZ for MEMS sensors. The sampling frequency of the ACD is set at 680 Hz.Fro this reason to have signals synchronized,4 samples are repeated and saved (in fact 4x170 Hz=680 Hz) [24].

Then the data are captured and put on a buffer of 28 samples fro ECG(trigger) and 7 samples for tonometer. In the following paragraph, the main components of the system will be described.

- **STM32F429 Discovery kit and STM32F429ZIT6 microcontroller**

  Produced by STMicroeletronics,the STM32F429 Discovery Kit is showed in the figure below where the main important component is the microcontroller STM32F429ZIT6. It is 32 bit high performance Micro-controller unit (MCU) and it is based on ARM- Cortex-M4 core. It includes also a LCD display TFT 2.4". The LCD display gives information to the operator of the bluetooth low energy (BLE) status and the correct insertion of the two sensors. In fact the two different sensors communicate with the Discovery kit and the MCU with the two SPI (serial peripheral interface) ports that have previously configured with 3-wire communication protocol [24].

An external laptop is necessary due to the presence of wireless interconnection. The signals recorded are visualized through a graphical interface developed. This can be useful to real time recording and to understand the correct positioning of the sensors. The data are saved for offline analysis (MATLAB).

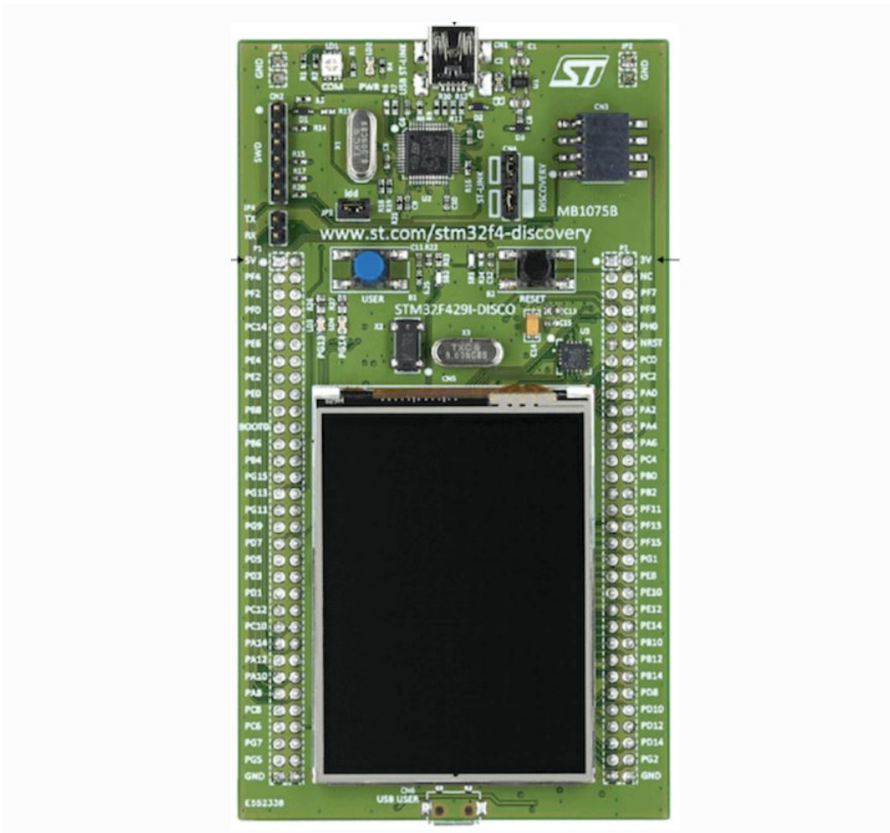

Figure 2.20: Discovery kit
https://docs.zephyrproject.org/latest/boards/arm/stm32f429i$_{d}isc1/doc/index.html$

- **LPS35HW sensors**

  This components are produced by STMicroeletronics. It is an ultra compact piezoresistive pressure sensor. For this specific application it was modified, but some details cannot be disclosed because it has not been patented [24].

  The pressure sensor on the left it's the commercial pressure sensors from STMicroelectronics, the metallic plate was removed and it was replaced with a resin (blue part in the figure) that simulated the movement to the gel (yellow part in the figure) in the bottom part. The modified sensor was soldered in a PCB of 1 cm diameter. It is near two bypass capacitor and give the information to SPI ports (24 bit sensor data output).

  The main features of the commercial sensors will be in the following list.

  – Absolute pressure range: 260 to 1260 hPa
  – Current 3 μA
  – 24 bit pressure data output
  – Supply voltage: 1.7 to 3.6

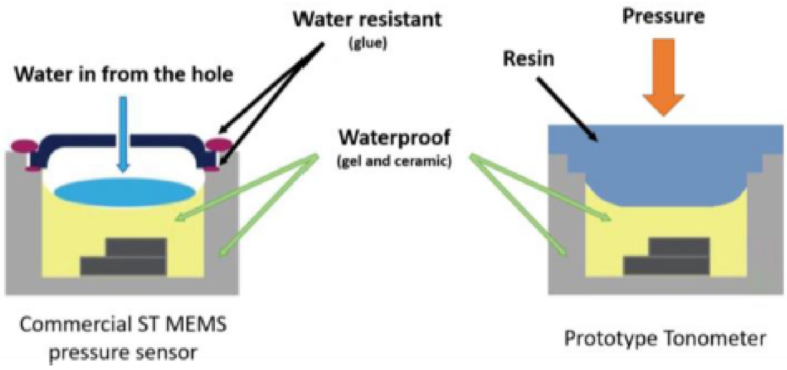

Figure 2.21: Prototype tonometer [24]

- **Graphical user interface**

  The ATHOS system is equipped with a graphical interface in real time thanks to which the acquired signals can be viewed in real-time.

  This interface will be used for the work done and slightly modified. There is also an algorithm capable of obtaining pulse wave velocity in the arteries.This window displays the signals of the two tonometers thanks to the USB dongle port connection which allows the data acquired by ATHOS to be transferred [24].

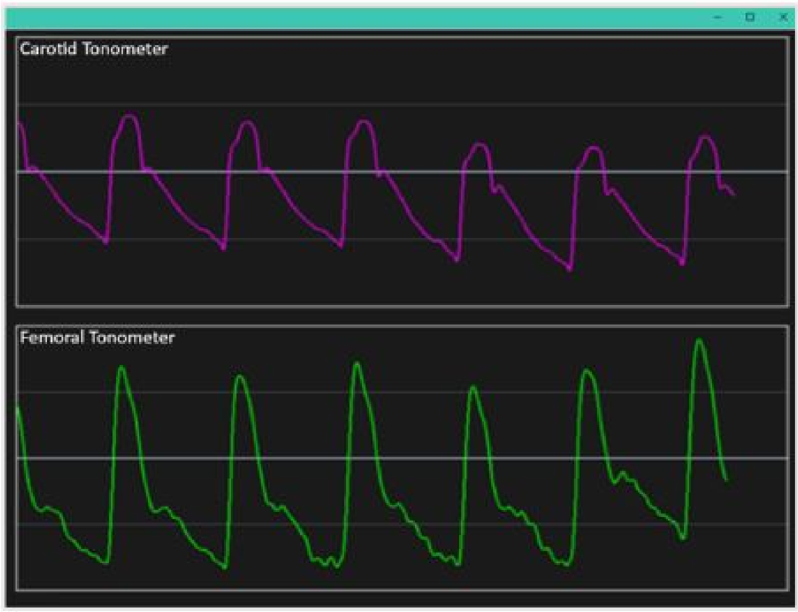

Fig. 8. "Acquisition window" with a refresh time of five seconds. It is noticeable how the pink signal (the carotid) is not big enough to be zoomed. Otherwise, the green (femoral), that is bigger than the white lines, does not saturate in the window.

Figure 2.22: GUI ATHOS [24]

2.3.2 Cuff compression system

In this section, it will talk about the artificial compression system used in the previous work to evaluate velocity of veins with the use of Echo-Doppler. The scheme is showed in the figure 2.23.

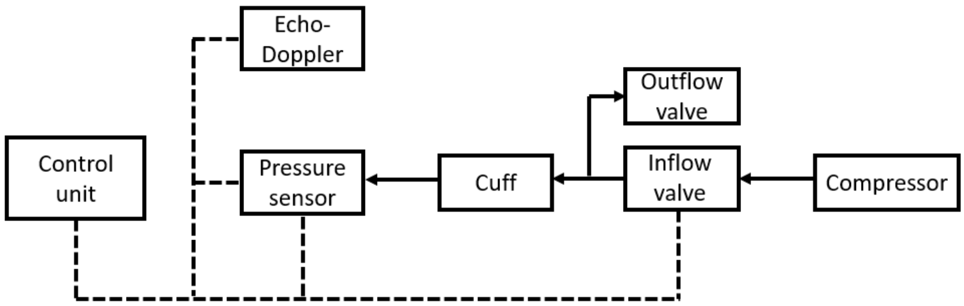

Figure 2.23: Cuff compression scheme

The main components are:

- **Cuff** (figure 2.24)

  This is wrapped around the feet or the arm of the subject. After pressing the specific button, this cuff fills with air and remains for some milliseconds in order to generate a sufficient pressure for wave.

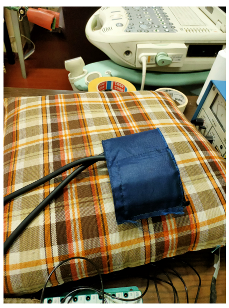

Figure 2.24: Cuff

- **Inflow and Outflow valves** (figure 2.25)

  This are two electro-digital valves.One valve serves to inject the air inside the gas (Inflow valve). The other (Outflow valve) injects the air externally.

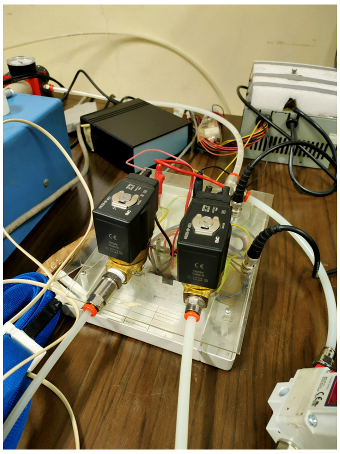

Figure 2.25: Inflow and Outflow valves

- **Compressor**

  It is mechanical device and the crucial aim is to elevate a gas pressure.

- **Pressure regulator**

  It allows to have a constant pressure compared to the upstream pressure value.

- **Pressure sensor**

  It is a sensor that is able to convert the pressure coming to the cuff in an analog signal.It serves to understand how much is the pressure inside the cuff, in fact we can visualize the value on the Spike computer interface (around 300 mmHg).

- **Control unit**

  The system of acquisition is CED (Cambridge Electronic Design), that allows the reading and recording of all signals of interest. The signal registered are: echo doppler audio signal, the time of trigger and pressure. It can also acquired the breath signal and ECG. It permits also the generation of signal of the two valves.

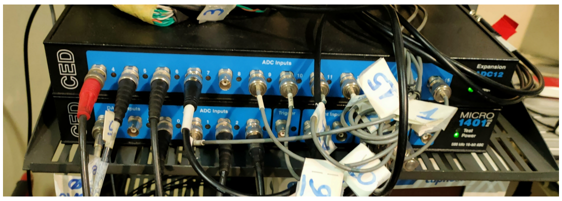

Figure 2.26: CED

- **Echo-Doppler ultrasound** (Mylab 25 XView, Esaote, Genova, Italy, with linear array LA 523).

  The device is based on the ultrasound. The ultrasound are generated by the probe, that is made of piezoelectric material.Waves ultrasound propagate inside the body and have a frequency higher than audible band (f>20 KHz) and when cross a tissue,so a change of impedance,they come back to receiver and can have 2D image.

  Another use of ultrasound is also as flow meter. With this modality, the device measures blood's velocity. The law behind it is Doppler effect: it is based on the fact that when a source is in motion relative to a receiver, the frequency coming to receiver varies according to the motion of the source. If the frequency is high, the motion is approaching, in the other way the motion is moving away. In this case the source and receiver is the same object.

  The blood consists two parts: liquid (that doesn't interact with US) and the corpuscular part, that is the part that interacts with US. When the corpuscular part moves inside the vessels interacts with US and for diffusion, the frequency coming back to the probe is different from the initial frequency. For this reason, we talk about the doppler frequency:

$$f_d = \frac{2 f_0 v}{c} cos\theta \tag{2.7}$$

  where f_0 is the initial frequency and f_d is the Doppler frequency. It is a additive or reductive quantity depending on whether the flow is approaching (f_0+f_d) or moving away (f_0-f_d).The formula has a sign according to the motion.

  In the case in which θ is equal to 0, it is not possible measuring the velocity. Normally, the angle values should be between 40°C and 60°C.

  The typical situation is showed in the following figure. In the case of blood vessel, the ultrasound image given by the device has two different color: blue vessels represents the blood moving away, while red color approaching.

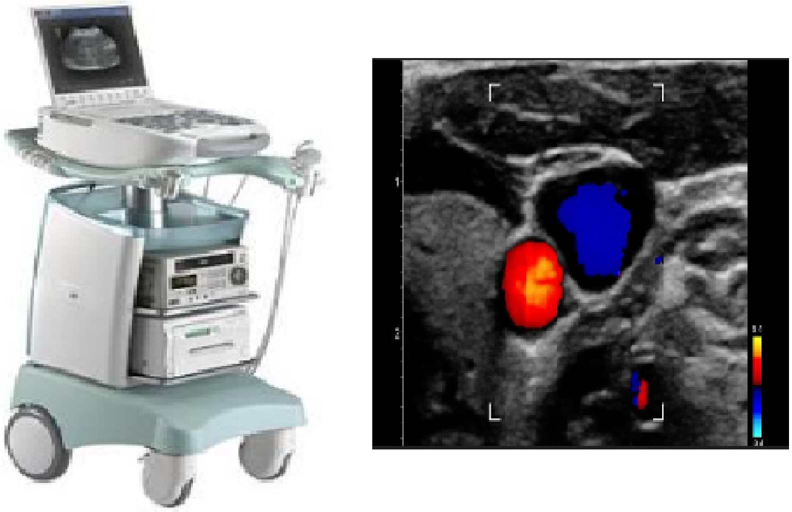

Figure 2.27: Figure (a): Device employed (b) Color image (https://esaote-mylab-five.weebly.com/esaote.html(a) https://www.siemens-healthineers.com/it/ultrasound/ultrasound-point-of-care/acuson-freestyle-ultrasound-machine(b))

Along with this system, an algorithm for venous pulse wave analysis has been implemented. After saving the Spike2 data,the signal are sampled at a frequency of 10000 Hz, then they are converted to .mat files for off-line analysis.

The signal is divided into 1 second epochs and subsequent is filtered with a band pass between 200-1000 Hz [25]. The algorithm uses the audio envelope of the doppler echo. After obtaining the envelope apply the threshold method to detect the footprint and then to calculate the latency.

The same algorithm will be used for the analysis of the data obtained with the echo-doppler and for the comparison with the tonometers.

Chapter 3

Materials and methods

3.1 Acquisition system

The aim of this thesis is the measurement and evaluation of vPWV with the replacement of the previous device with tonometers: the pulse wave is generated artificially on a limb extremity (arm) by a pneumatic system and it is detected with the use of tonometers.

The system used during this project was developed for the measurement of pulse wave velocity in the arteries.It has became a gold standard for this because it is low cost,non invasive,portable and clinical grade PWV device respect for example to SphygmoCor device that is more expensive. In the previous researches this device was validated with a group of 10 subjects and the results obtained are comparable with the gold standard present in the market.

Previously, vPWV was measured using Echo-Doppler. Connecting the two system, the system called "Cuff compression system" and ATHOS device, different experiments are lead to understand the capacity of tonometers to detect the velocity. vPWV hasn't a gold standard on the market and it is hardly to understand the results obtained. The researches are still in infancy and numerous researches must be done in order to obtained precise and accurate results. For our aim, we consider as gold standard the Echo-Doppler ultrasound for vPWV and then, it will be compare with the results given by tonometers. The whole system using for tests is showed in the figure in the following page 3.1.

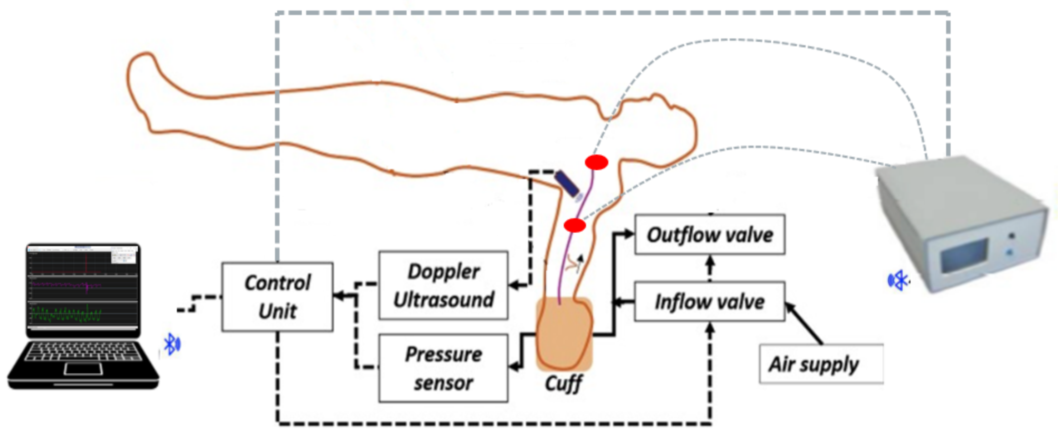

Figure 3.1: Scheme of new system: ATHOS [24] and Cuff compression system [25]

The laptop is connected through USB port to control unit of cuff compression system and through bluetooth with ATHOS and the tonometers.

In the ATHOS device there are three different input : two of them are used for the tonometers an the last,previosly used for ECG, in this case is used for another signal. The figure showed ATHOS device that is connected to trigger signal coming from CED of the other system (control unit) and then to the two tonometers. For this purpose, one access of Athos (the one connected to ECG in the prevISOUS works) was used for trigger, a digital signal that represents the time in which the compression is delivered.In the figure 3.2, the first inputs are used for the two tonometers and the last (on the rigth) for the trigger input.This trigger signal represents the time in which the artificial pneumatic pressure is generated. It is a kind of impulse wave that has a duration of some milliseconds (around 30 ms). It was useful during the measurements to understand the initial point of wave.

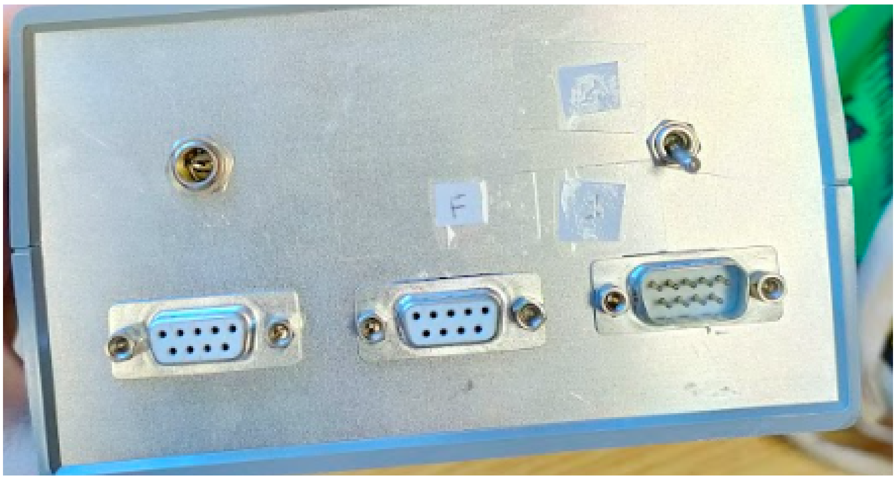

Figure 3.2: ATHOS back with 3 inputs

Two 3D supports are projected with SolidWorks in order to put the two PCB used during the experiments. Then, the two supports are put in two different bands. The two bands are used to bind the sensors on the arm.

The placement on the arm was chosen because compared to legs, the arm has more superficial veins and easy to find. The veins of the legs are deeper and for the aim of project, the location of this results more facilitated.

The figure shows the support designed with SolidWorks where the PCB is put. The shape is concave to easily rest it on the surface of the arm.

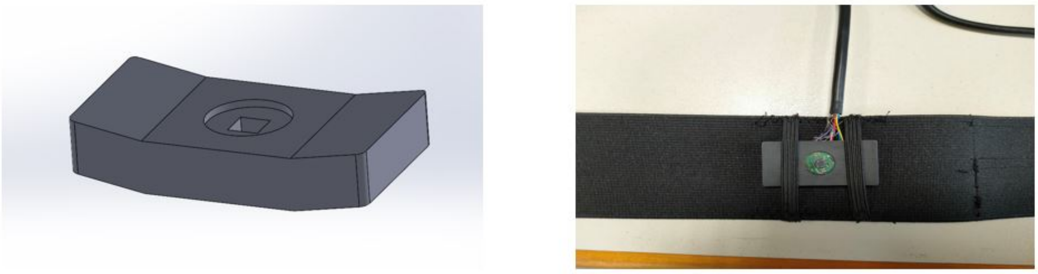

Figure 3.3: SolidWorks support

The hardware, software that included the graphical user interface and the sensors present in ATHOS are used to acquire the signals coming to veins together with the other system that included a system of compression in order to induced pulse wave and an increase of venous pressure. Then, the acquired signals are analyzed with a first algorithm to calculate the pulse transit time and the pulse wave velocity in the veins. The graphical user interface present in ATHOS was developed using Visual Studio ambient (C sharp).

In this thesis, it is modified in order to obtain a better signal visualization because the signal obtained putting the sensors on the skin to measure the pulse wave velocity in the artery have a bigger value, instead in this case it is necessary to do a zoom to recognize the signal and have a better recognition.

So, in the ATHOS system there is also the presence of an algorithm to elaborate the signal. In this case, it is not necessary because all the signal are elaborated with offline analysis in MATLAB. The GUI represents the three signal : in the upper part there is trigger signal and in the bottom part, in the last two blocks, the tonometers.

The button present are: algo,trigger,instant,dummy.

- Trigger: shows the trigger signal, in the other option it cannot be visualized in the interface.
- Log: save the signals in a file with a name that operator can decide.
- Algo: with the "algo" an algorithm that serves for pulse wave in arteries can start and then elaborate the signal..

On the right,the system shows if it is correct the bluetooth connection between the device and the laptop. The operator can show different options, but for this application the system doesn't needed the working of the algorithm of the ATHOS previous work because the signal analysis is done with MATLAB.

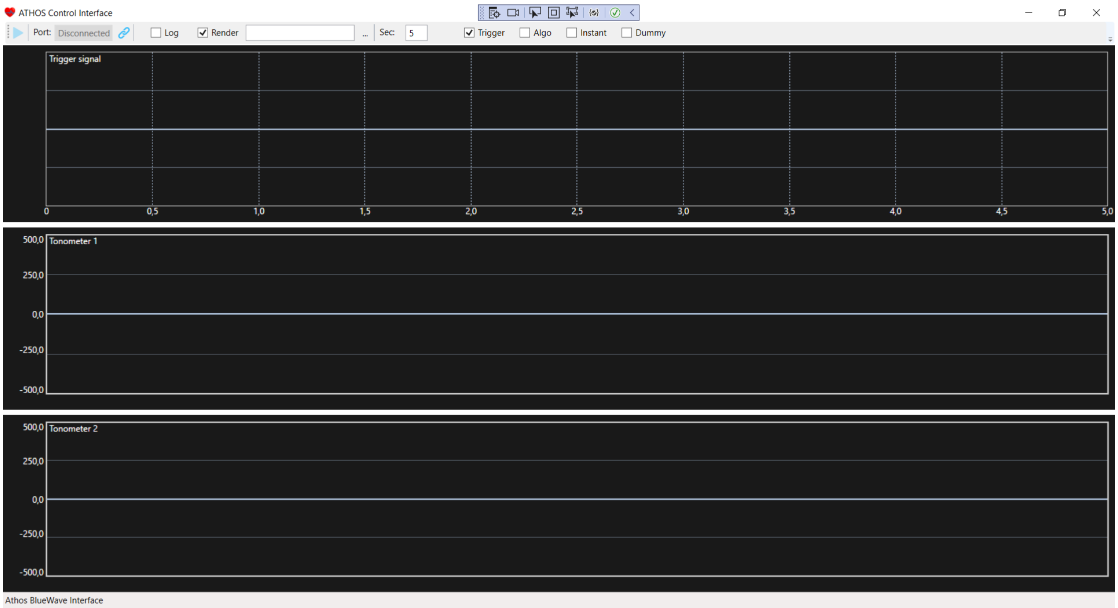

Figure 3.4: GUI ATHOS

EXPERIMENTAL PROTOCOL

The system described has worked together with the artificial compression system that was used for the study of vPWV. In order to understand the best location of the sensors on the arm different tests took place.

The subjects remained lying on the couch during the experiments.This must be done for one single reason: the pressure on the veins as said in the previous chapters when a person stand up is greater in the foot. To have an uniform distribution the pressure and so avoid that the pressure is too low during the experiments, the subject remain lying.

- Tests with one single tonometer

  During this tests only one tonometer is put in the proximity of armpit. The probe is placed also near armpit. The veins considered is basilic vein.

- Tests with double tonometers

  First of all, during the initial tests, the first tonometer was placed under the cuff and the second, one time on the fold and another near armpit. These tests were done to analyse the velocity with two distances.

  The final protocol provided placing the first tonometer on the fold of the arm and the second tonometer near the armpit,always on the basilic vein.

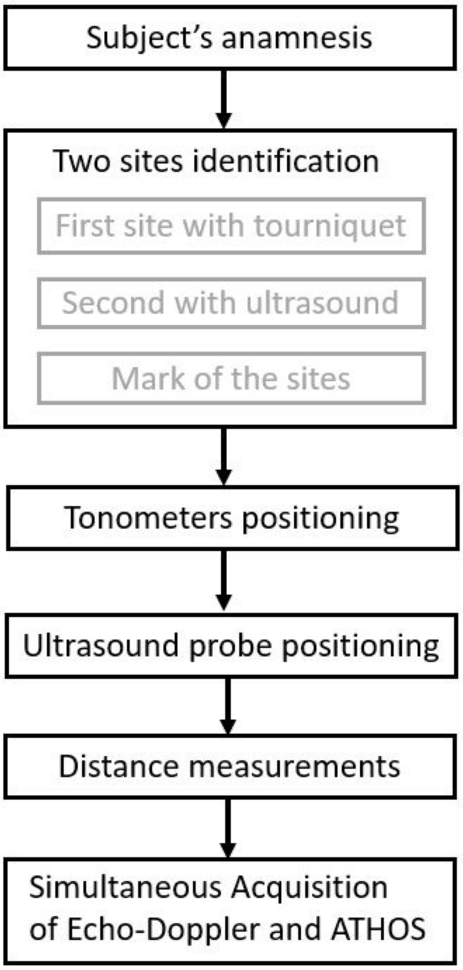

Figure 3.5: Protocol flowchart

For the placement of the first sensor, it needed the help of a tourniquet. It's necessary for a better visualization of the superficial vein of the fold. The tourniquet is a device that tighten around the arm gradually increase the volume of blood vessels in the site. To place the second sensor it was necessary the use of ultrasound because in this area, it's hard to understand where is located the vein.

The distances between the pneumatic artifical system on the extreme arm was taken with a tape measure by the operator.

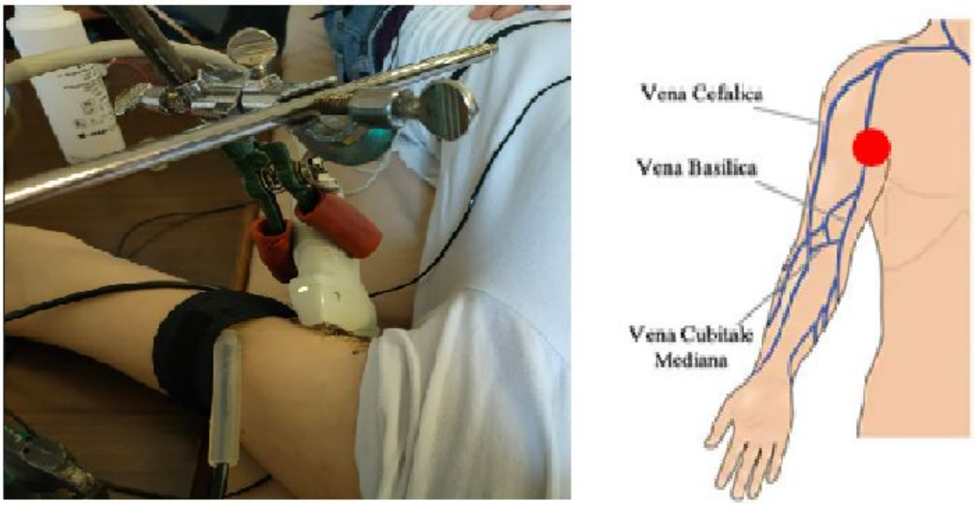

Figure 3.6: Experiment single tonometer
https://www.my-personaltrainer.it/salute-benessere/vene-braccio.html

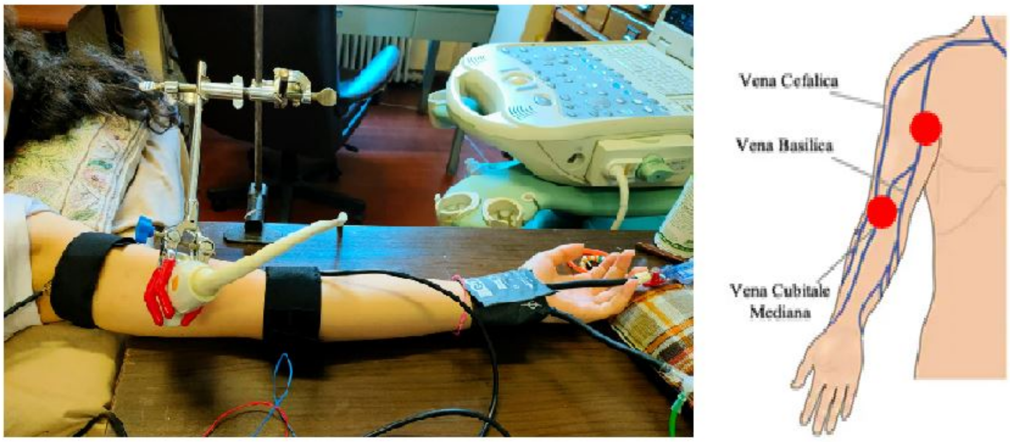

Figure 3.7: Experiment double tonometer
https://www.my-personaltrainer.it/salute-benessere/vene-braccio.html

The ultrasound probe is placed in the center between the tonometers.

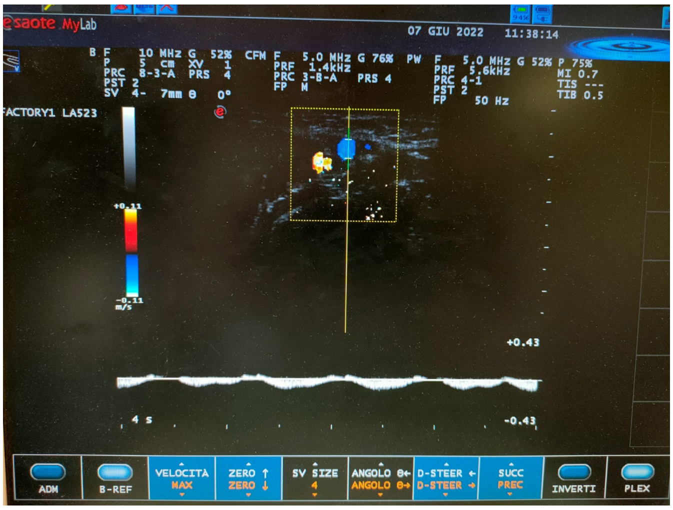

Figure 3.8: Color doppler and basilic veins

The artificial compression is generated from this system and the signal was recorded by ATHOS and showed in the graphical interface. The third input belonged to the ECG signal was substitued by trigger signal that it can be used to detected the correct time of the generated stimulus and to calculated the pulse transit time for our researches. The figure shows the system used for this application and the connection between the two system. The figure below shows the three different signals acquired during the experiments. They are saved in ".bin" format and then elaborate with matlab.

The signals on the top is the trigger signal and the other on the bottom are the signals in this case acquiring on the fold of the arm (pink) and near armpit (green). The peak in the proximity of the trigger is the signal of interest.

At the same time, connecting with USB, the signal of cuff's pressure and the Echo Doppler's signal are acquired also with the time of trigger of the compression system. The three output are connected to CED (Cambridge Eletronics Design) and with Spike2 software are visualised.

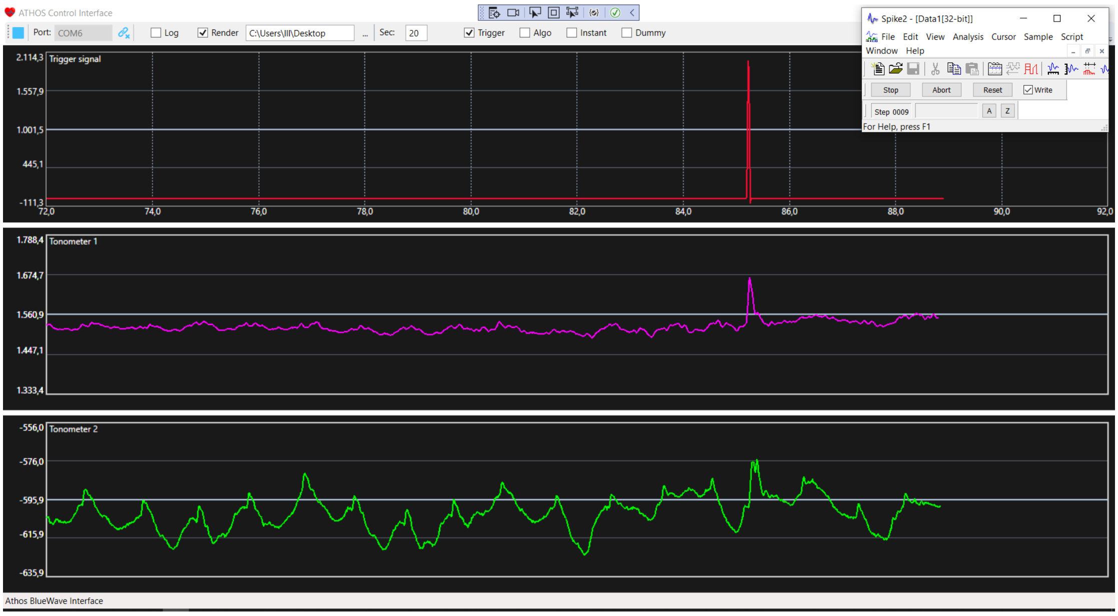

Figure 3.9: Interface with signals

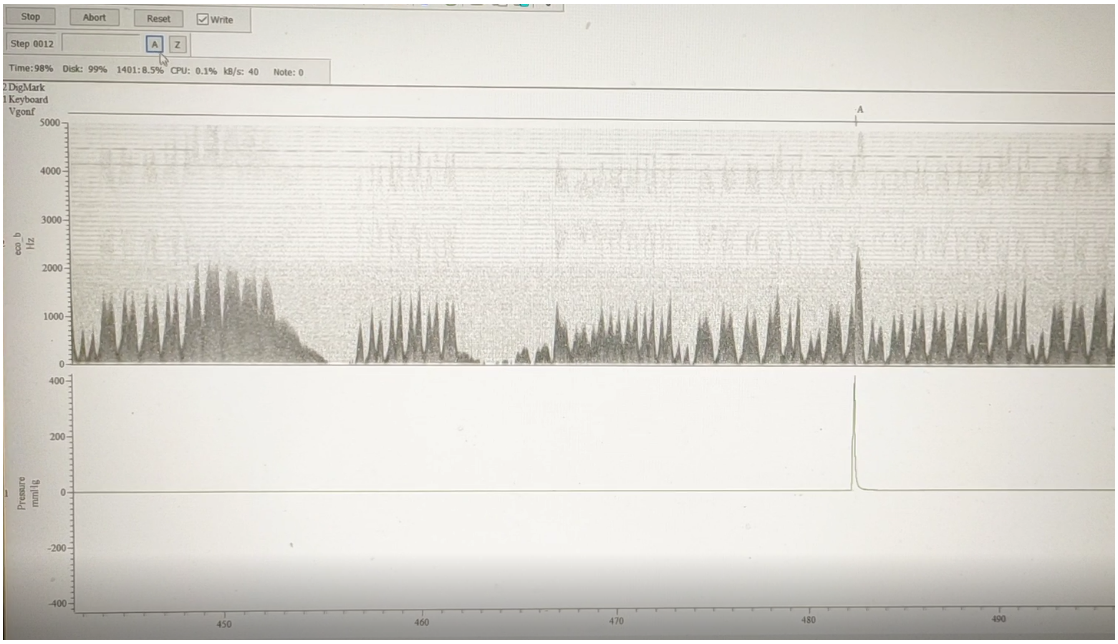

Figure 3.10: Spike Interface

This is the other graphical interface used during the work and it is more versatile because for the presence of real time zoom. An external operator press the button called A that give the compression to generate the wave. The other button (Z) can be used for the reset of the cuff.

3.2 Algorithm and signal analysis

The algorirthm developed consists of different blocks and it can improve in the future for pulse wave velocity in veins and the use of tonometers.

It takes inspiration from the algorithm using by Athos and the elaboration of the arterial signals. It can elaborate signal in order to extract the footprint and the pulse wave velocity.

First, after a visualization of Power Spectrum Density (PSD), the signals analyzed was filtered to obtain a better shape of it and to remove artifacts.

After this, the recognition of the footprint of the trigger was done in order to extract the exacting initial time of the artificial pressure made and then, after the division of the signal in epochs of 1 second (taking inspiration from the previous work), it was analysed in order to extract the footprint of the wave. The footprint of the wave was recognised with the algorithm to footprint extrapolation and then, the difference between the two time was done.

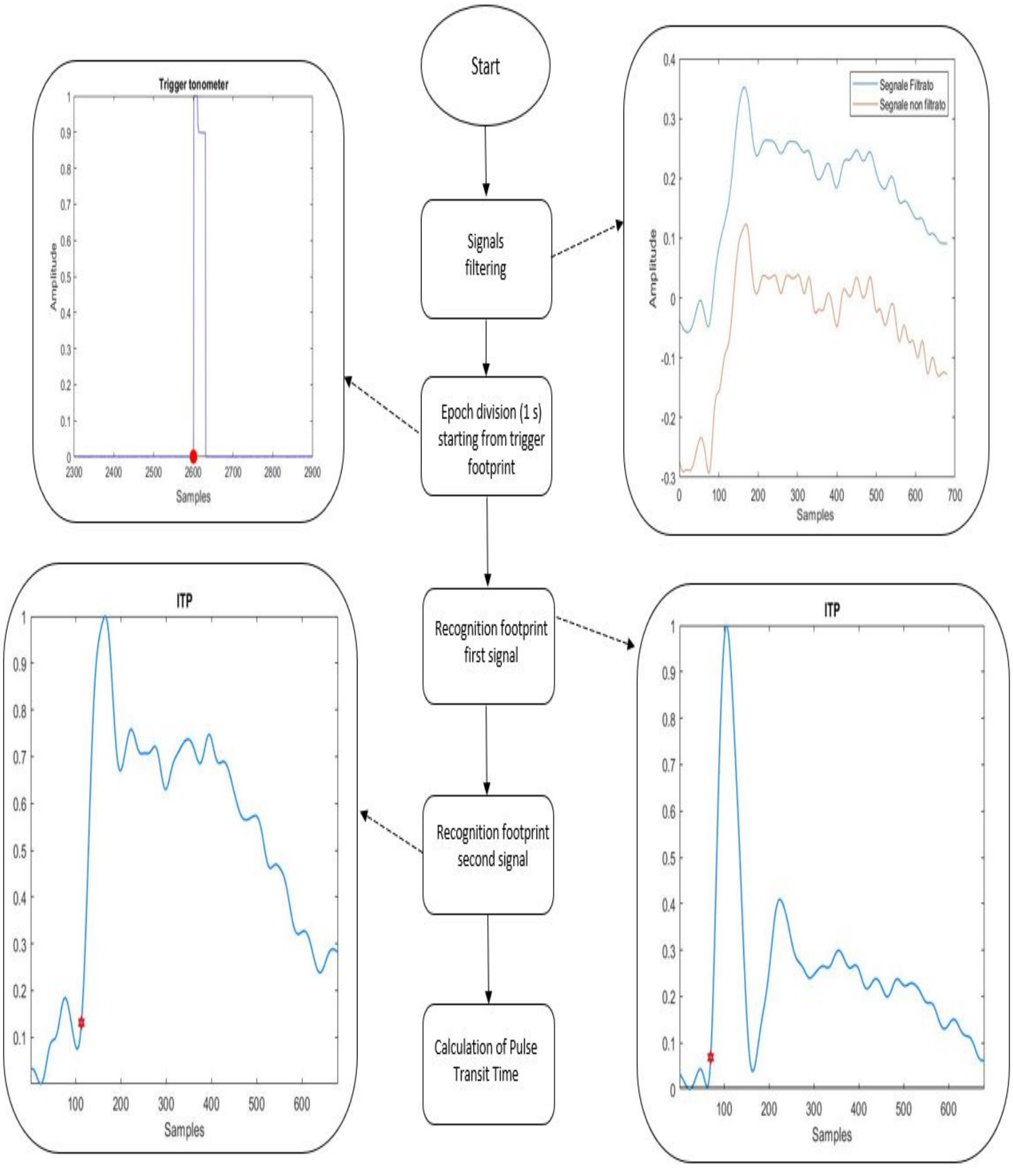

Figure 3.11: Flowchart

3.2.1 Signal filtering

The signal analysed is in time domain. Every signal picked up have to be elaborated in the best way to reduce the noise. The noise present in a signal is often an additive noise and the formula is in the follow:

$$x(t) = s(t) + n(t) \tag{3.1}$$

Where x(t) is the raw signal with noise acquired by the withdrawal system, n(t) is the noise and s(t) is the real signal. It is difficult to understand how eliminate the noise in the signal because it's always present and it's only possible to limit its presence. It's possible to differentiate two different signal:

1. Random signal: as EMG or EEG signals. In this case the shape isn't predictable.

2. Deterministic process: in this case like ECG the shape is known. It's important to say that the signal acquired in this thesis are all deterministic. The waveform is repeatable and it in the most of cases the same. So, the characteristic of the signal can be consider similar to ECG.

In order to better understand the studied wave forms the signal to noise ratio (SNR) must be reduced. The typical filters are:

- High pass filter: to eliminate frequencies that are lower than cutoff frequency and pass the frequency higher.

- Low pass filter:to eliminate frequencies that are higher than cutoff frequency and pass the frequency lower.

In order to reduce the noise for this work, the signal was filtered with a pass band filter between 0.1-20 Hz to reduce the trend and the most of the high frequency oscillations.

Then, starting from trigger's footprint, that represents the time in which the compression is delivered, the signal was divided in epoch of 1 s.

In this epoch of our interest, the recognition of footprint starts.

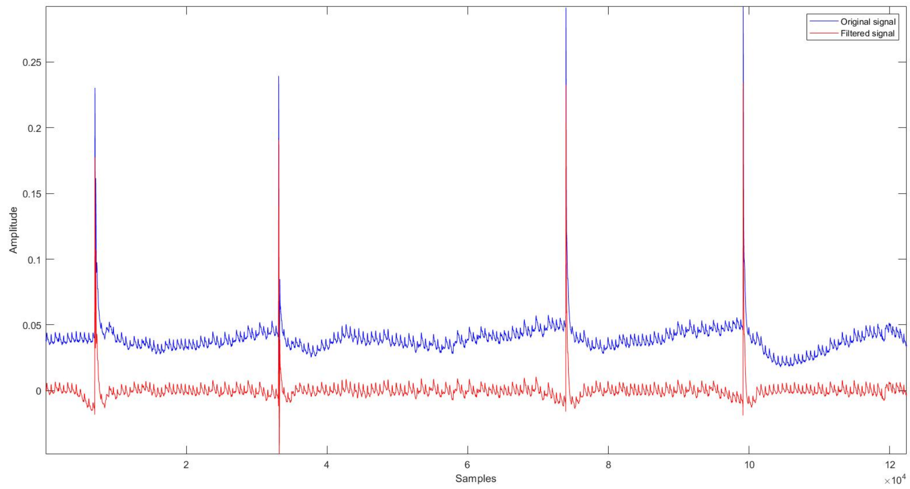

Figure 3.12: Signal filtered

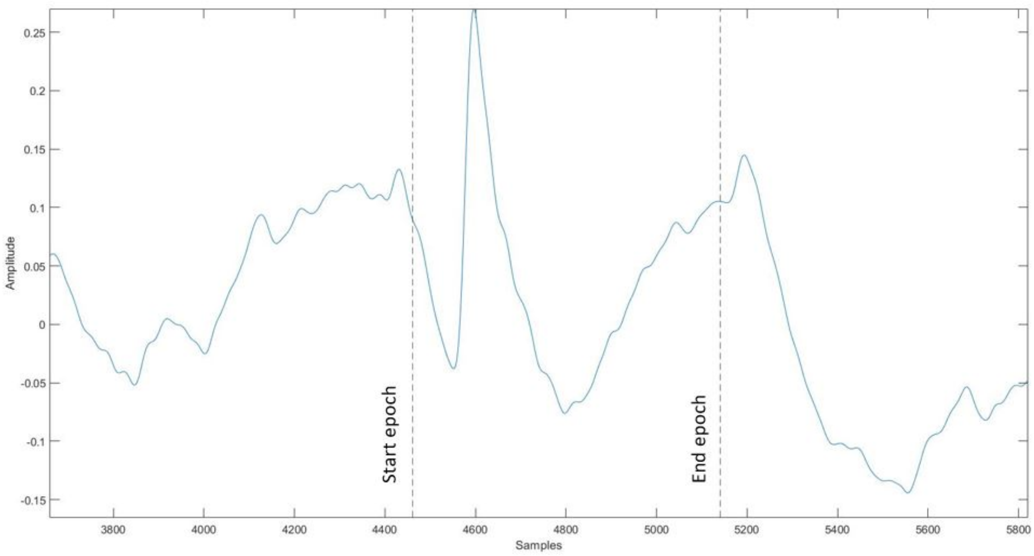

Figure 3.13: Epoch

3.2.2 Extraction of footprint and calculation of Venous Pulse Wave Velocity

In literature, there are three different methods to calculate the footprint of wave:

1. Second derivative

In this case, after the calculation of the second derivative of signal, the maximum upstroke of the second derivative represents the value of interest to find the corresponding value of time.

2. Threshold

   After finding the value of minimum and peak, a threshold is imposed (for example 5%) and then, the corresponding value of y-axis is found with the value of threshold imposed.

3. Intersecting tangent point (ITP)

   The footprint is given by the intersection of the two line and it is the most widely used in literature for this aim [26].

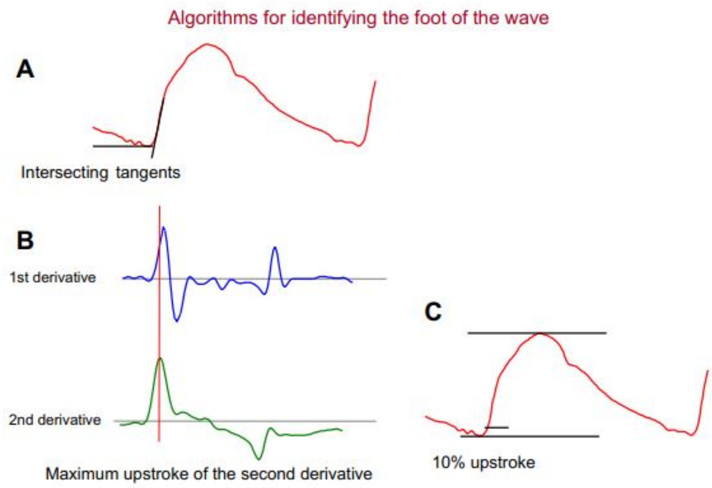

Figure 2 Different algorithms used to identify specific part of the pulse signal (here distension waveform of the carotid artery). Panel A: intersecting tangents; Panel B: maximum upstroke of the second derivative; Panel C: percentage of the full amplitude of the cycle.

Figure 3.14: Three methods for footprint [27]

To our purpose, the footprint was detected with ITP algorithm. It is the most widely used because depends on the inclination of tangent line adapting according to the peak.

First of all the peak of the possible wave is found imposing a threshold of the maximum height value. Often, the peak is before 300 ms.

After determining the value of the peak, the value of minimum falls between the time where the trigger is delivered and this value. So, the first derivative is calculated in order to find the larger inclination in the signal and it is between the value of maximum and the value of minimum. Then, an horizontal line crossing the minimum value is drawn and another line through the maximum of derivative. The intersection between the first horizontal line and the tangent line is the point of footprint.

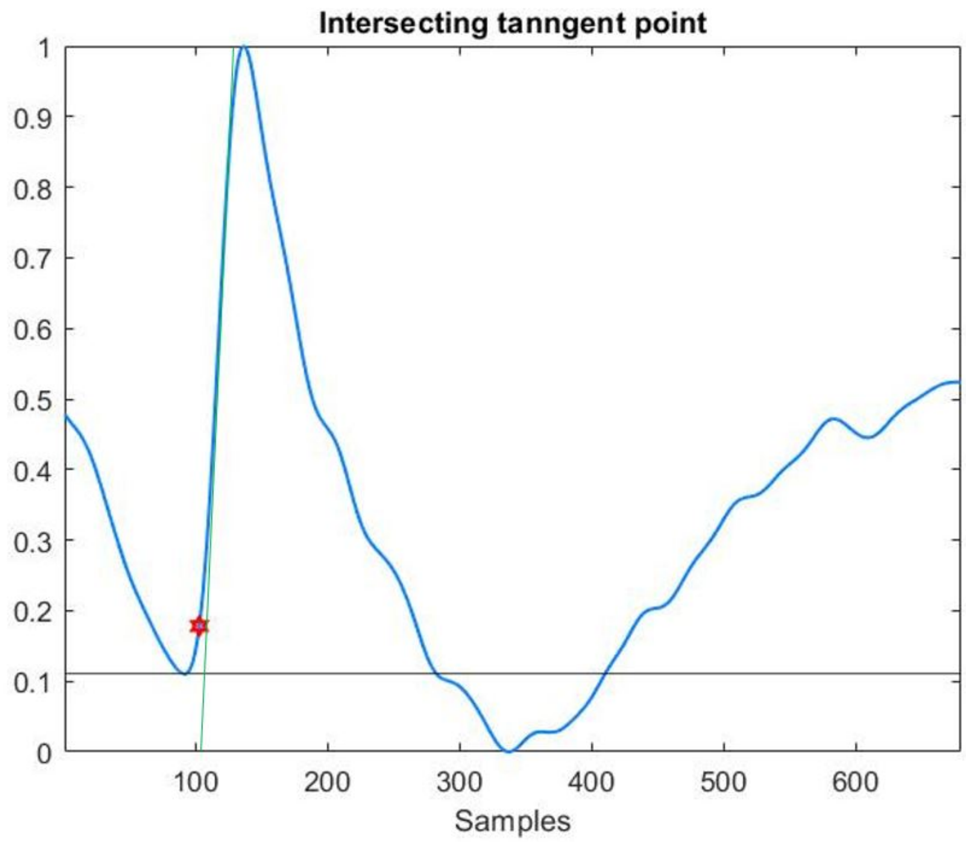

Figure 3.15: Intersection (ITP)

In some tests with two tonometers, one sensor was placed under the cuff.

In this case, a comparison between the signal from the tonometer under the cuff and the signal of pressure was done and it was found a similarity between the two signals.In fact, they present a similar shape.

For this reason, the footprint of the first signal in this case isn't found with ITP algorithm. The point detected was the value in which the analog pressure reached 2 mmHg and this value was the corresponding value for tonometer signal.

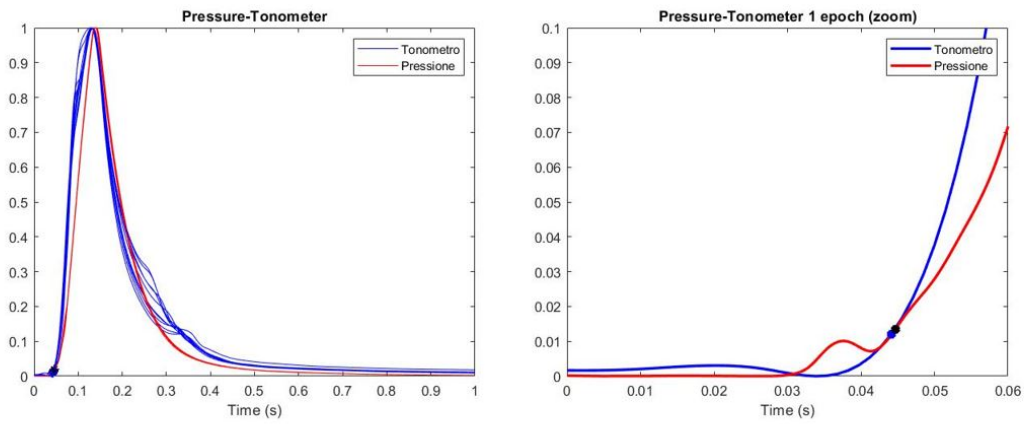

Figure 3.16: Tonometer and pressure signal similarity

Finally, after found the footprint of wave in the different cases, the time value was calculated, so the pulse transit time value.

For the different cases, the value of time corresponds to:

1. One tonometer
$$\Delta T = t_{f2} - t_t; \tag{3.2}$$
Where t_f2 is the footprint time of the wave detected near the armpit and t_t is the time of trigger footprint.

2. Two tonometers: (one under the cuff and the other on the arm)
$$\Delta T = t_{f2} - t_p; \tag{3.3}$$
Where t_f2 is the footprint time of the wave detected near the armpit and t_p is the time of trigger footprint.

3. Two tonometers(one on the fold of the arm and the other on the armpit)
$$\Delta T = t_{f2} - t_{f1}; \tag{3.4}$$
Where t_f2 and t_f1 are the footprint time of the waves detected near the armpit and fold .

At the end, the velocity is calculate as the fraction between the distance measured with the tape during the experiment and the latency calculated with the algorithm.

$$vPWV = \frac{distance}{latency} \tag{3.5}$$

Chapter 4

Results and discussion

4.1 Tests

In this section it will talk about the tests carry out during the work. The first experiment were done with the use of one tonometer and then, due to the fact that the aim of this work was finding two different points to measure the vPWV, at the end two points are used for this purpose.

The data obtained from different experiments were processed with the algorithm discussed above.

4.1.1 Test one tonometer

In this case, the tonometer was placed near armpit. Simultaneuosly, the probe of echo-doppler in the proximity of it. The data were obtained for three different subjects (25-35 ages). To compare the results obtained, the boxplot were calculated for the results given by tonometers and echo-doppler.

The signal from the sensors has a good reliability , in fact the shape for the different epochs are similar: they highlight a minimum for all epochs and a evident peak. Despite this, the waveform for the three subjects appears different. It can be caused by a bad positioning of the sensor in the proximity of the vein.

The basilic vein is often found near an artery and this could have caused unwanted oscillations of the signal.

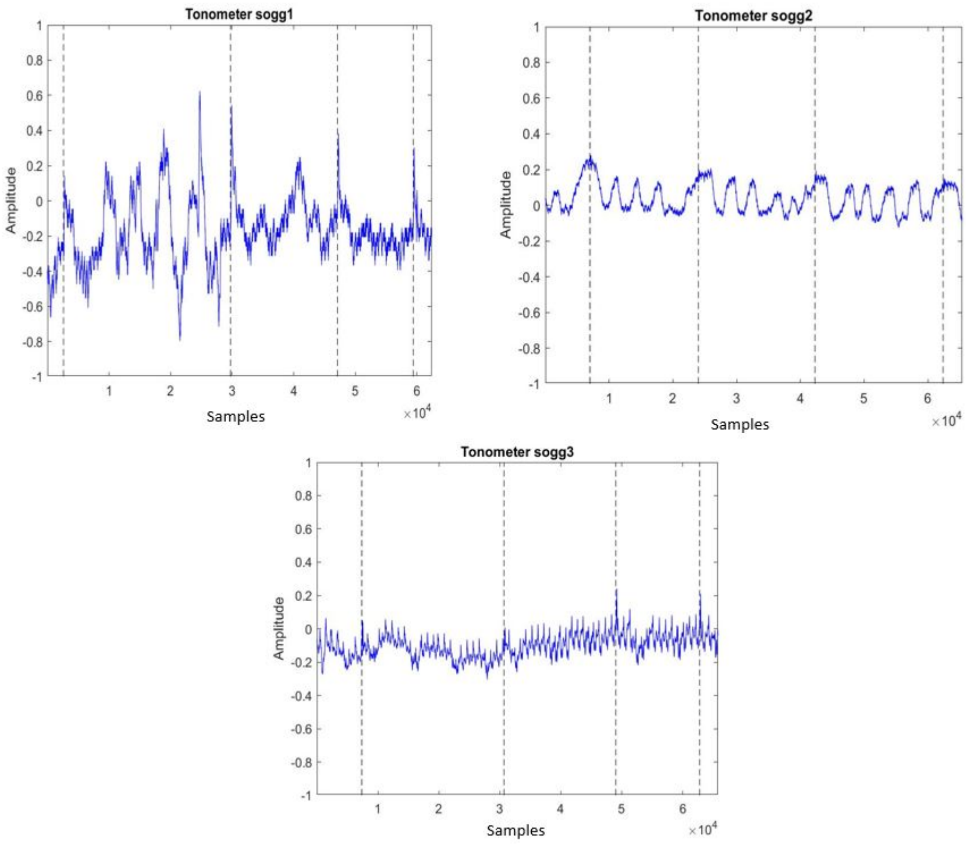

Figure 4.1: Signals for three subjects with only one tonometer. The dashed line is the trigger.

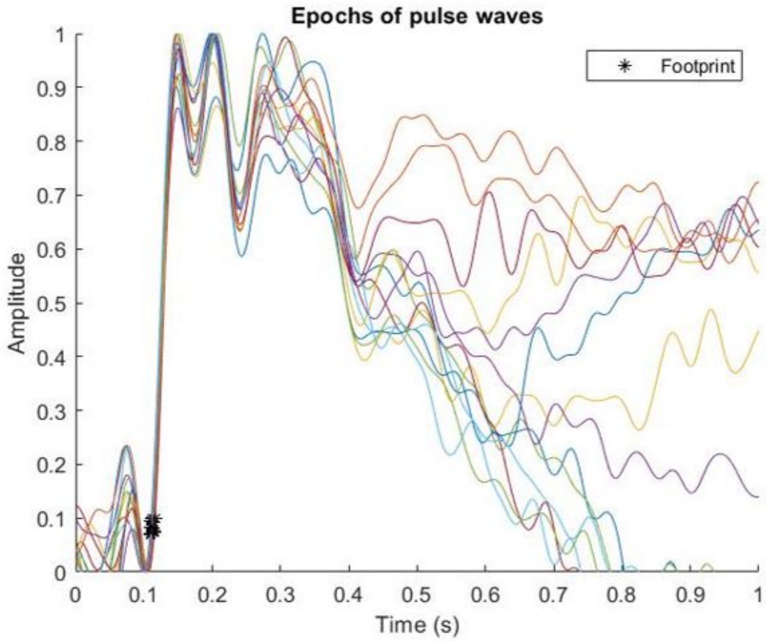

Figure 4.2: Epochs for one subjects

In the figure above, it can be seen that all epochs are stackable with a evident minimum for the identification of footprint.

The results in the boxplot for the three subjects showed values similar to those seen in the previous articles. The value of velocity depends on the subject and varies between 1 m/s to 4 m/s. The values of Echo-Doppler resulted higher and have higher standard deviation values. Since the probe and the tonometer have been placed in two different points, the results in the figure are reliable. In fact, the probe was placed in a more distal direction and so, a few centimeter away from the sensor.

Despite these first experiments, we have shown acceptable results, the use of a single sensor is not optimal for the search for attentive and precise results. In fact, the tonometers have filters inside that can delay or anticipate the measurements. For this reason, in the subsequent experiments the use of two sensors made it possible to cancel this latency.

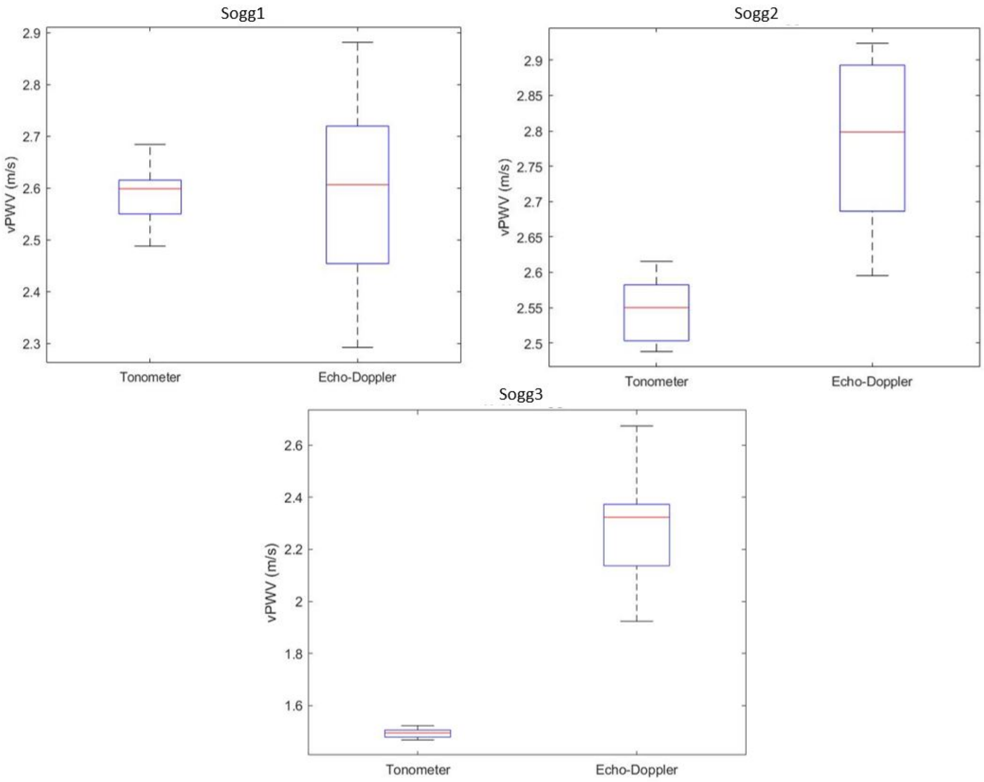

Figure 4.3: Results three subjects

4.1.2 Test double tonometers

Subsequently, the measurements involved the use of two tonometers.

From the results obtained with the use of a single tonometer, the basilica vein near the armpit was found to be a good point for positioning the sensor given the sufficiently high distance (> 30 cm) from the cuff.

Another point was found on the vein present on the fold of the arm, where the vein is sufficiently on the surface to be able to detect it. Using a tourniquet facilitated its placement. Despite the visibility, the use of echo-doppler was still necessary in some subjects.

With the algorithm illustrated above, the mean and standard deviation of the velocities of the epochs obtained for each individual subject were calculated.

The data showed a higher velocity value than the searches for the first 2 subjects (> 4 m/s), despite an acceptable value for the subjects 3,4,5. For these subjects, after taking the measurements between the fold and the sensor under the cuff, data was also taken between the cuff and the point near the armpit.

The results in this case were compared with the values previously taken between the cuff and the fold.

The values obtained were higher in the cuff-armpit case of 1-2 m/s.

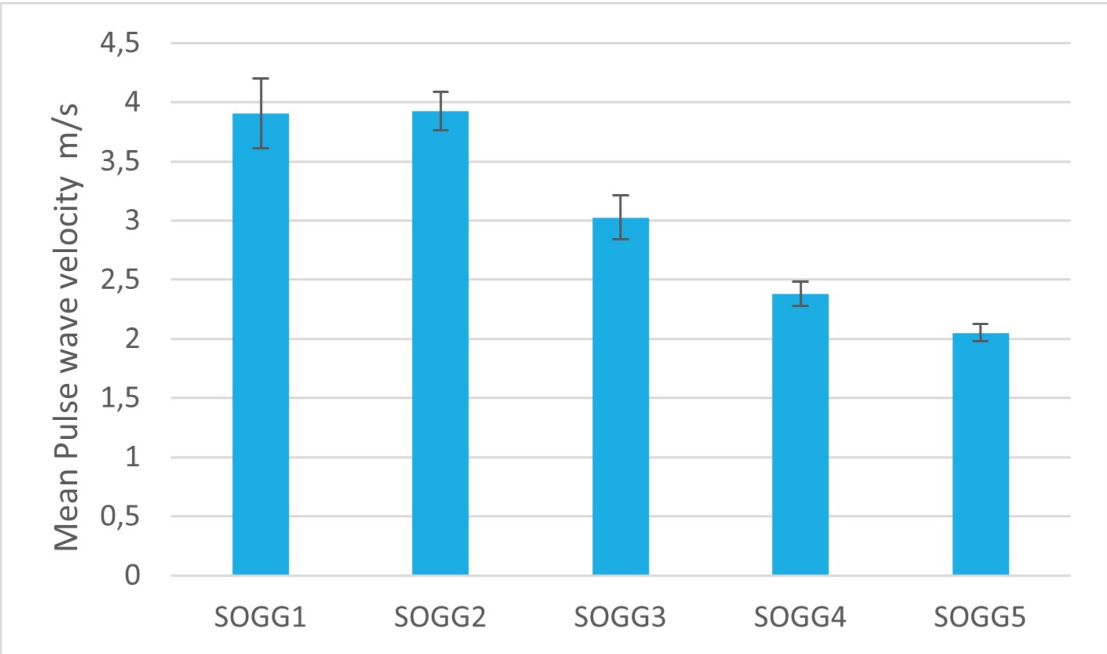

Figure 4.4: Bar chart of the signals between cuff and fold

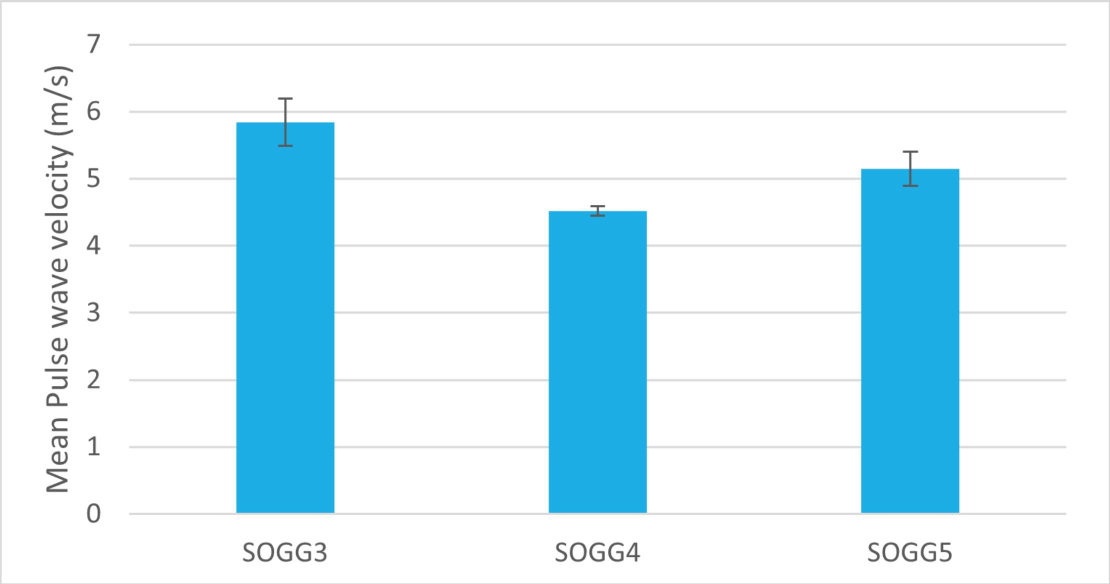

Figure 4.5: Bar chart of the signals between cuff and fold

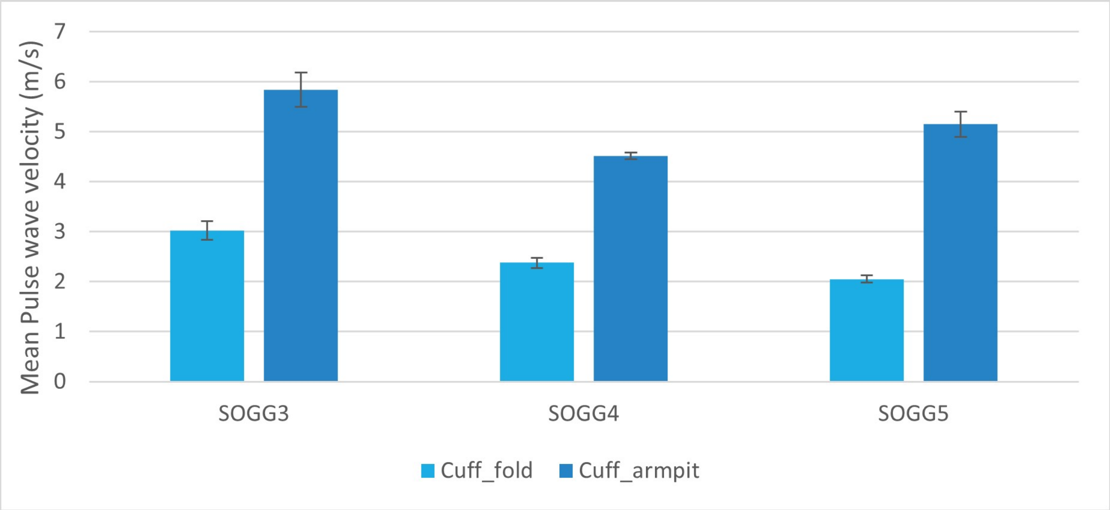

Figure 4.6: Bar chart of the signals between cuff and armpit

Since the analog pressure signal was similar to the signal under the cuff as mentioned above, these tests were repeated with the two sensors positioned on the fold and near the armpit at the same time and taking the cuff pressure as the first signal. In this way it was possible to better analyze the speeds between the two points, therefore the speed measured in the first path (cuff-fold) and in the second path (cuff-armpit).

For this purpose, the mean velocities and standard deviation for each subject (in this case five other subjects) were again calculated. The bar diagram shows the three speeds: cuff-fold, cuff-armpit and between the two sensors, placed at an average distance of about 10 cm.

It can be seen that the speed between cuff-fold is greater for 3 out of 5 subjects than that of cuff-armpit. This means that in the initial path the speed accelerates and then decreases in the second.

Some velocity values are still too high compared to the standard values, reaching values up to 6 m / s much more similar to the velocity values of the arteries.

At the same time the speeds between the two points were calculated and this showed reliable values. With values between 2 m/s -4 m/s.

The standard deviation values are always low, therefore shown a low variability of the measures.

A bar diagram was also calculated for the average of the speed differences, then the differences in the speeds given for the first stretch and that resulting from the speed between the two points and the difference between the speed in the second stretch and the speed were calculated between the two points. All expressed in absolute value.

This graph shows a greater speed difference between the first and the section between the two sensors, again as far as the subjects 3,4,5 are concerned. A minor difference in speed between the sleeve-armpit stretch and that between the two sensors.

Since the values obtained between the two sensors are similar to the standard ones, it was useful to design a measurement protocol and verify the effective quality of the measurements with the tonometers compared to the values obtained with the echo-doppler.

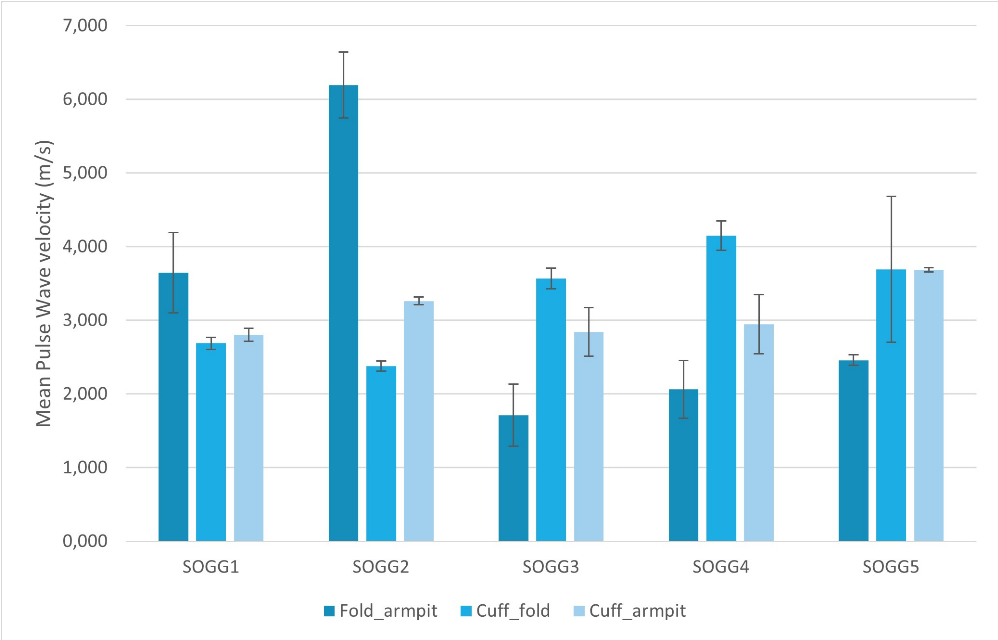

Figure 4.7: Bar chart of the signals between cuff and fold taken simultaneously

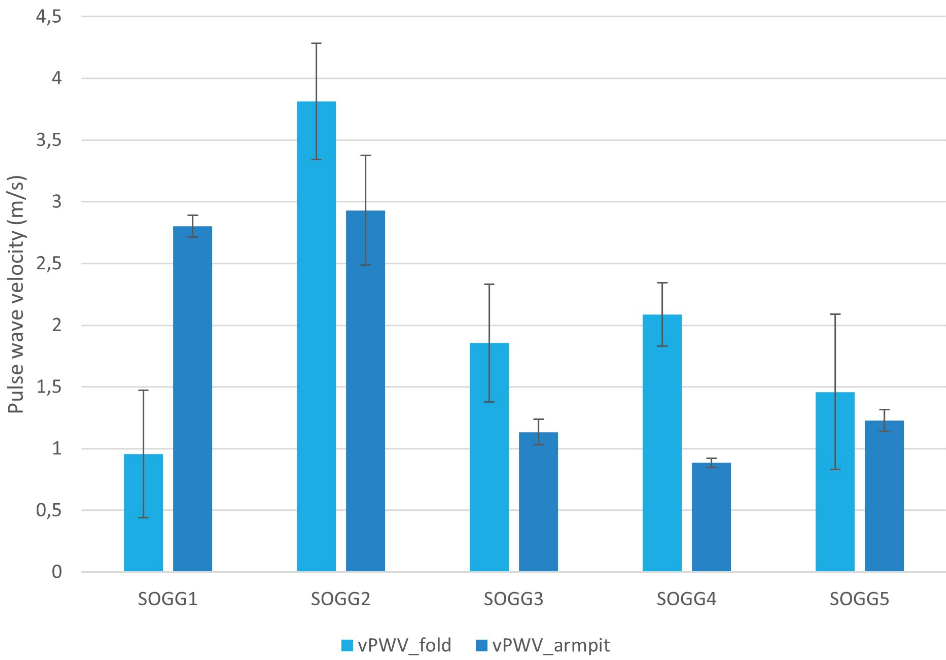

Figure 4.8: Bar chart of the differences

The last experimental protocol envisages comparing the measurements obtained with the two placed tonometers and the Doppler echo.

It was therefore performed on a sufficient number of subjects. In this case, 14 healthy volunteers aged 20-35 years were taken.

The protocol has already been described in the previous chapter and requires the subject to lie down on the couch with the two sensors positioned on the arm and the probe in the middle of them.

The button is pressed by an external operator. Each trigger is at least 20 seconds apart from the other.

The distance is measured with a meter. For our purpose, each subject was asked for height and weight, in order to have a more general clinical view and to obtain the body mass index (BMI). This is to take into account a possible correlation between BMI and acquisitions.

Table 4.1: Phisiologycal parameter of subjects

Subject	Gender	Height (cm)	Weight (kg)	Age	BMI(kg/m^2)
1	M	165	75	27	27,55
2	M	180	71	25	21,91
3	M	173	59	22	19,91
4	M	176	62	25	20,02
5	M	182	78	24	23,55
6	M	178	60	31	18,94
7	M	182	87	26	26,26
8	F	160	63	25	25,39
9	M	178	84	24	26,51
10	M	170	63	25	21,80
11	F	163	45	25	16,94
12	F	155	48	22	19,98
13	F	168	65	22	23,03
14	F	170	59	21	20,42

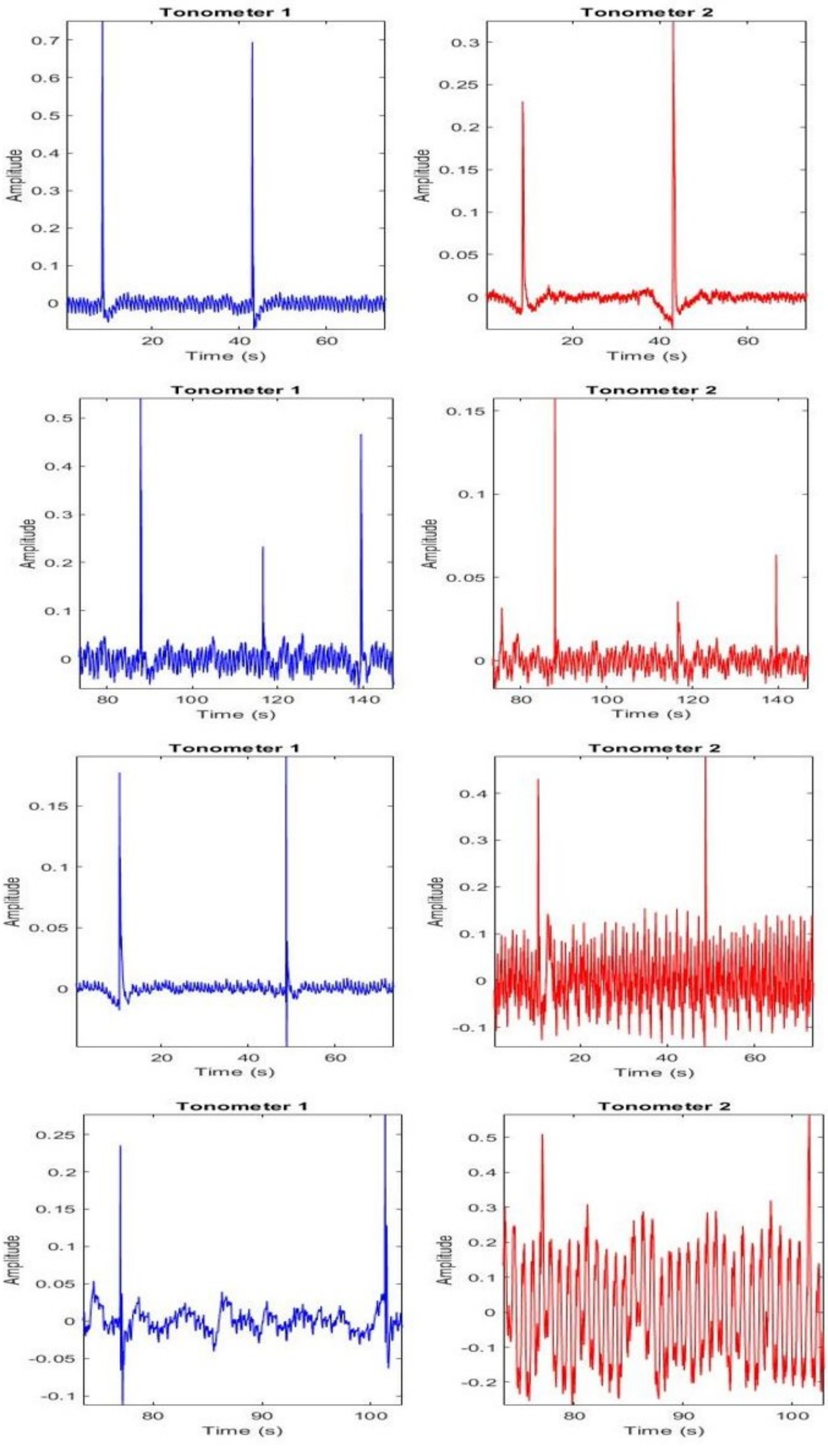

Figure 4.9: Examples of signals (Subjects 3,6,7,8)

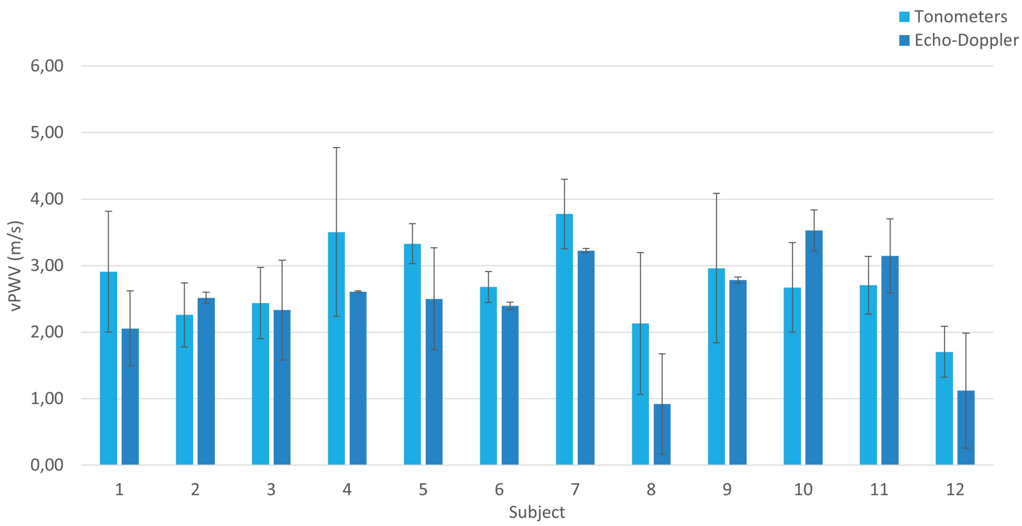

Figure 4.10: vPWV for the 12 subjects

Some epochs have been eliminated simply with a visual evaluation in order not to lead to a bad interpretation by the algorithm. Furthermore, subject 14 and subject 13 did not have good acquisition and were discarded in the comparison with the Doppler ultrasound.

As previously done, the bar graph was evaluated with the mean and standard deviation of 8 epochs of the 12 subjects taken in the study. The same epoch for the Doppler echo was evaluated and a comparison was made.

First of all, it can be clearly seen that there is no correlation between BMI and relative acquisition, as all the subjects taken into consideration showed, regardless of BMI, a vPWV value between 1-5 m / s. It is to be hypothesized that, at high values of vPWV, a bad positioning of the sensors and noise related to the nearby artery correspond.

The means and standard deviations were also taken into account for the Doppler echo algorithm. These showed slightly lower values than the tonometers and less variability.

Furthermore, it should be added that the Doppler ultrasound algorithm would lead to incorrect results as the probe was positioned at the most distal point. This would lead to an decrease in the signal-to-noise ratio.

A useful method for evaluating the agreement between two measures is the Bland-Altman graph. This is a widely used scatter plot to compare if two methods (in this case tonometry and echo doppler) are in agreement.

It is a scatter plot in which the average of the measures is present on the x-axis and the difference of the two measures on the y-axis .

In this case, the difference is the measurement made with the tonometers and the one with the echo-doppler.

The difference would be the measurement error and the mean of the measurements would be the best estimate of their value.

At the same time, the maximum and minimum values of the confidence interval of the two measures were calculated. The black center line represents the mean of the difference of the two measurements.

As can be seen from the graph, the points are all included in this range. Therefore the two methods represent congruent results,but at the same time, this means that the two measurements are not interchangeable.

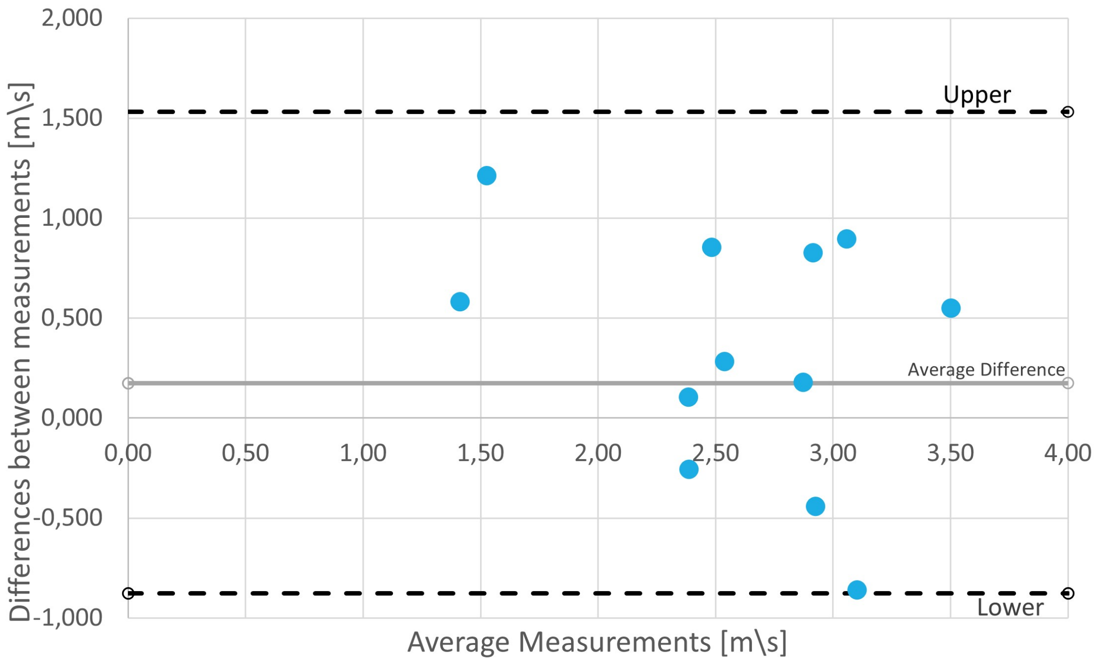

Figure 4.11: Bland-Altman plot

At the same time it can be useful to represent the scatter plot of 12 subjects. There is a fair linear regression between the two measures. The coefficient of determination is 0.3 and at the same time the correlation coefficient is 0.6.

For some subjects the two measurements have very high variability for tonometers and very low variability for Doppler echo, it is useful adopted another type of

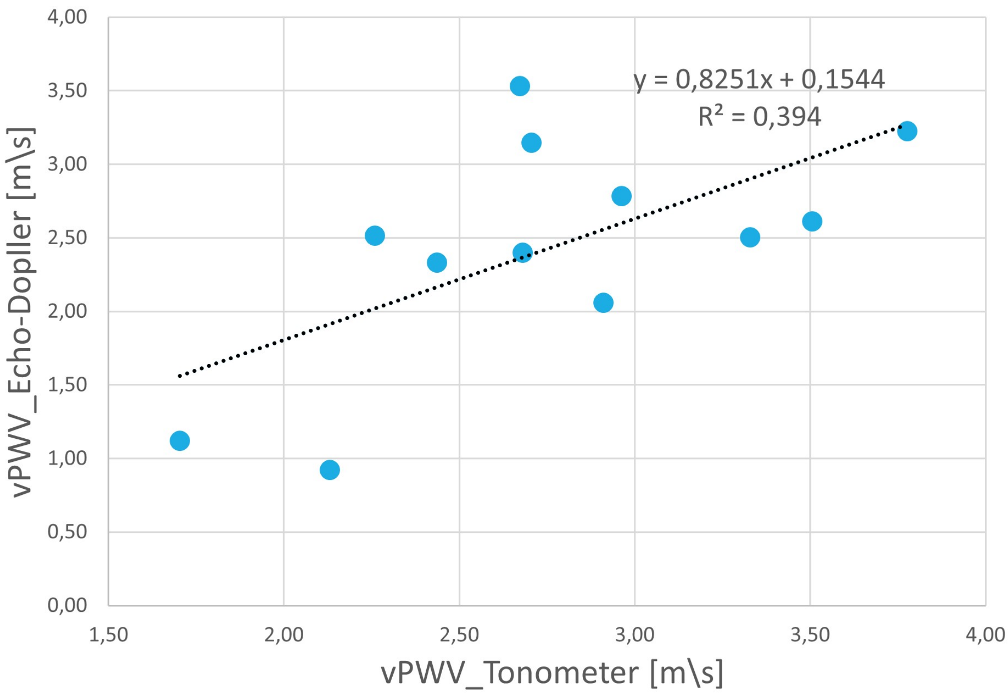

Figure 4.12: Regression plot

statistical test based on intra-class correlation (ICC). It can evaluate the level of agreement between the two measures. The value of ICC can be between 0-1, where 0 means no reliability and 1 reliability.

This value was calculated by considering both the estimate of the pulse wave velocity as:

- A function of three variables (subject, epoch and method). In this case, the intra-class coefficient of variation was equal to 0,87.
- A function of two variables (epoch and method). In this case, the intra-class coefficient of variation was equal to 0,95.

Another parameter calculated was mean error equal to 0,8 m/s. The error could be high due to the low resolution given by the tonometers which, even if it is wrong by a few samples, can be high (even 5 ms).

Chapter 5

Conclusion

The work uses a new methodology for the study of venous pulse wave velocity. Despite the few articles about vPWV, tonometers were able to calculate venous velocities in the order of magnitude of previous studies. The use of the Echo-Doppler ultrasound also allowed the comparison of the obtained measurements. The two algorithms showed comparable measurement values as analyzed from the results of the statistical tests (ICC>0,8).

From the present study, therefore, it was possible to obtain a measurement of the pulse wave velocity in the veins with:

- The use of innovative surface sensors. Easily positioned through the use of a band unlike the Echo-Doppler which is more uncomfortable. This could be useful for example for long-term monitoring of pulse wave velocity for subjects undergoing dialysis.
- An automatic algorithm able to find the points in the vicinity of the cuff impulse. The tonometers, in addition to being easy to place, are together with the system already implemented much less expensive than the ultrasound system.
- Union of the two systems to measure the pulse wave velocity: the cuff compression system, together with the use of ATHOS to be able to view the signals.

The use of two tonometers would also lead to a more precise measurement of speed than using a single system, such as the ultrasound system. Numerous studies have yet to be made to ensure that pulse wave velocity can be measured with tonometers and new improvements should be implemented in order to have more reliable and repeatable measurements.

First of all, the limits concern the sampling frequency of the tonometers (fc = 170 Hz) which is very low and therefore leads to very low resolutions to find the footprint of the wave of interest. Even a wrong sample would lead to pulse transit time values that can vary by about 5 ms, which would consequently lead to incorrect pulse wave velocity values.

The positioning of the sensors was not easy to decide: despite the practicality of the bands used (which could also be replaced by the use of a plaster), the ultrasound system must still be used to understand where the basilic vein is (usually in the proximity of the artery). The artery, as previously mentioned, has the flow moving in the opposite direction and creates oscillations that would lead to perturbing the wave of interest.

Another limitation is the non-synchronization with the breath and cardiac activity on which the venous system is strongly dependent. In the future, it would therefore be appropriate to analyze the results by automating the system with heart activity and breathing, in order to compare the results.

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